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An algorithm based on immunotherapy discontinuation and liver biopsy spares corticosteroids in two thirds of cases of severe checkpoint inhibitor-induced liver injury

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Summary

Background: There are few data on corticosteroids (CS)-sparing strategies for checkpoint inhibitor (ICI)-induced liver injury (ChILI).

Aim: We aimed to assess the performance of a 2-step algorithm for severe ChILI, based on ICI temporary discontinuation (step-1) and, if lack of biochemical improvement, CS based on the degree of necroinflammation at biopsy (step-2).

Methods: Prospective study that included all subjects with grade 3/4 ChILI. Peripheral extended immunophenotyping was performed. Indication for CS: severe necroinflammation; mild or moderate necroinflammation with later biochemical worsening.

Results: From 111 subjects with increased transaminases (January 2020 to August 2023), 44 were diagnosed with grade 3 ($N=35$) or grade 4 ($N=9$) ChILI. Main reason for exclusion was alternative diagnosis. Lung cancer (13) and melanoma (12) were the most common malignancies. ICI: 23(52.3%) anti-PD1, 8(18.2%) anti-PD-L1, 3(6.8%) anti-CTLA-4, 10(22.7%) combined ICI. Liver injury pattern: hepatocellular (23,52.3%) mixed (12,27.3%) and cholestatic (9,20.5%). 14(32%) presented bilirubin >1.2 mg/dL. Overall, 30(68.2%) patients did not require CS: 22(50.0%) due to ICI discontinuation (step-1) and 8/22 (36.4%) based on the degree of necroinflammation (step-2). Biopsy mainly impacted on grade 3 ChILI, sparing CS in 8 out of 15 (53.3%) non-improvement patients after ICI discontinuation. $CD8^+$ HLA-DR expression ($p=0.028$), central memory ($p=0.046$) were lower in CS-free managed subjects, but effector-memory cells ($p=0.002$) were higher. Time to transaminases normalisation was shorter in those CS-free managed (overall: $p<0.001$, grade 3: $p<0.001$). Considering our results, a strategy based on ICI discontinuation and biopsy for grade 3 ChILI is proposed.

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Conclusions: An algorithm based on temporary immunotherapy discontinuation and biopsy allows CS avoidance in two thirds of cases of severe ChILI.

1 | INTRODUCTION

Immunotherapy based on immune checkpoint inhibitors (ICIs) has completely changed the scenario of patients with oncological diseases by increasing survival rates of many of the most common advanced cancers, such as lung cancer.[1] Since the approval of ipilimumab, an anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) agent,[2] there has been increasing evidence on the benefit of immunotherapy, and the number of tumours with approved indication for ICIs is growing exponentially.[3] Nevertheless, the widespread use of ICIs in daily clinical practice has been associated with a parallel rise in the number of immune-related adverse events (irAEs) due to these drugs.[4]

Checkpoint inhibitor-induced liver injury (ChILI) may occur in 2%–25% patients treated with ICIs.[5] Although this toxicity is normally mild, it can be life-threatening in the case of acute liver failure development.[6,7] As for the rest of severe irAEs, treatment with corticosteroids (CS) is the backbone of therapy for severe ChILI,[8,9] that is grade 3 or grade 4 hepatitis according to the Common Terminology Criteria for Adverse Events (CTCAE) system. However, results from two series of patients with ChILI have shown that some severe cases may not require CS, and liver injury may be resolved with just temporary discontinuation of immunotherapy.[10,11] Hitherto, there has been no data on predictive factors for good prognosis without need of CS. Liver biopsy has allowed to identify different histological patterns according to the type of ICI,[10,12] but there is scarce data on the potential relation between histological findings and prognosis of ChILI. In some cases, a potential link between a lower degree of necroinflammation and the spontaneous recovery of severe ChILI without CS has been suggested, though that was not the primary aim of that study.[10]

The primary aim of this study was to assess the performance of a 2-step algorithm for the management of patients with severe ChILI, based on temporary discontinuation of immunotherapy (first step) and then, indication of CS according to the degree of necroinflammation in liver biopsy (second step). A secondary aim was to evaluate analytical, histological and immunological predictors of spontaneous resolution of the severe ChILI without need of CS therapy.

2 | PATIENTS AND METHODS

2.1 | Study design and patients

This is a prospective study, conducted at a tertiary level University hospital, that included all consecutive subjects undergoing ICIs who presented with grade 3 or 4 increase of transaminases defined according to the CTCAEv4 system as an alanine aminotransferase (ALT) or aspartate aminotransaminase (AST) rising 5- to 20-fold over the upper limit of normality (ULN) (grade 3) or AST/ALT over 20-fold the ULN (grade 4) in subjects with previously normal values.

All patients on ICIs who presented grade 3 or 4 transaminases increase were referred to the Liver Unit and underwent a detailed study in order to rule out other causes of acute hepatitis, including viral infections, liver progression of the underlying oncological disease or presence of concomitant treatments that may trigger drug-induced liver injury (DILI). The latter was assessed by the Roussel Uclaf Causality Assessment Method (RUCAM) and patients undergoing any other drug scoring ≥6 points were excluded.[13] All patients with an alternative diagnosis for the acute hepatitis were excluded, as well as those with baseline transaminases values above twofold ULN (males 50 IU/mL; females 35 IU/mL) or prior or concomitant treatment with CS at the time of the grade 3 or grade 4 hepatitis. Inclusion criteria for the study encompassed grade 3 or 4 hepatitis; at least one dose of any ICI (anti-programmed cell death-1- anti-PD1-, or its ligand- anti-PD-L1-, anti-CTLA-4 or anti-lymphocyte-activation gene 3- anti-LAG-3).

A 2-step algorithm was designed in order to assess the rate of patients with severe ChILI who would improve without therapy with CS. The study protocol is summarised in Figure 1. Briefly, in all patients who met the inclusion criteria, ICIs were discontinued after exclusion of alternative diagnosis through liver ultrasound or computed tomography scan and serologies for viral hepatitis as well autoantibodies and peripheral extended immunophenotyping. 48–72 h after ICI discontinuation (step 1), a new blood sample was analysed. Those who showed a decrease of transaminases values, defined as a 20% drop in AST/ALT levels, were maintained without ICI until grade 1 hepatitis or ALT/AST normalisation, when ICIs were restarted.

In the case of lack of improvement in AST/ALT levels, a liver biopsy was performed within 24–48 h (step 2); a preliminary result was available on the same day. CS therapy at dose of 0.5 mg/kg/day (normal bilirubin) or 1 mg/kg/day (increased bilirubin) was indicated only for those patients with severe necroinflammation of liver tissue (see Section 3 for definition). In those individuals with mild or moderate necroinflammation at liver biopsy, CS were only initiated in case of progressive worsening in the following days, defined as progression to grade 4 hepatitis or increase in bilirubin values.

The rationale for the decision of CS for individuals with severe necroinflammation, was the low likelihood for spontaneous recovery, after ICIs discontinuation. Moreover, patients with severe necroinflammmation are at potential risk of acute liver injury or acute liver failure as demonstrated in those with autoimmune hepatitis.[14,15]

This study was approved by the Vall d'Hebron Hospital Ethics Committee (PR[AG]481/2018) and the Spanish Agency of Medicines and Medical Devices (AEMPS), and it was conducted in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines and local regulatory requirements. Informed

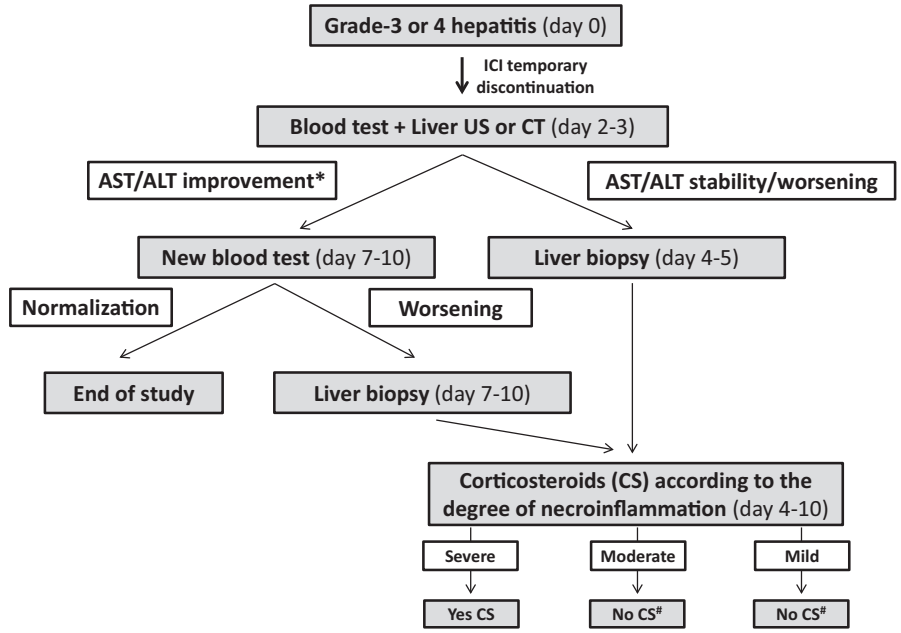

FIGURE 1 Summary of the study design. All patients with a grade 3 or grade 4 checkpoint inhibitor-induced liver injury were included in the study after ruling out an alternative diagnosis. ICIs were temporarily discontinued in all cases, and a new blood test and an imaging technique were carried out 48–72 h after the initial diagnosis. Those with analytical improvement were periodically followed up until normalisation or grade 1 hepatitis when ICIs were restarted. In those that worsened or remained stable despite ICI discontinuation, a liver biopsy was performed within 24–48 h (day 4–5 of study). On the same day, the decision to initiate corticosteroids was based on the degree of necroinflammation. *Improvement was defined as a 20% decrease in AST/ALT values and worsening as progression to grade 4 hepatitis or increase in bilirubin values. #Criteria for corticosteroids in patients with mild or moderate necroinflammation at liver biopsy was analytical worsening during follow-up defined as progression to grade 4 hepatitis or increase in bilirubin values. ALT, alanine aminotransferase; AST, aspartate transferase; CS, corticosteroids; CT, computed tomography; US, ultrasound.

consent forms were provided to all included subjects, and all data were anonymised.

3 | METHODS

Demographic and clinical variables were recorded at the time of the ChILI: gender, age, race, history of autoimmune disorders and previous liver diseases and dates of diagnosis. Consumption of other treatments including herbal supplements were also recorded. Data on the oncologic disease included: type, date and stage of cancer, presence of liver metastases. Previous cancer therapy lines were collected, including ICIs and history of previous irAEs, as well as their severity and the need for CS therapy.

Acute viral hepatitis was ruled out by serology (anti-HCV, HBsAg, anti-HEV, anti-HAV) and nucleic acid amplification tests (HBV DNA, HCV RNA and HEV RNA). In the case of any positive result, patients were excluded.

Laboratory parameters recorded at the time of the ChILI consisted of blood count, prothrombin time, bilirubin, creatinine, ALT, AST, gamma–glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin, gamma globulin and immunoglobulins-Ig (IgG, IgM, IgA) levels. Autoantibodies evaluation included antinuclear (ANA), anti-smooth muscle (SMA), anti-mitochondrial (AMA) and anti-neutrophil cytoplasmic antibodies (ANCA), anti-soluble liver antigen (anti-SLA), liver/kidney microsomal antibody type 1 (anti-LKM1) and liver cytosol antibody type 1 (anti-LC1).

Severity of ChILI was assessed by both the CTCAE system v4 and the DILI severity index (*mild* if bilirubin <2 × ULN, *moderate* if bilirubin ≥2 × ULN, *severe* if bilirubin ≥2 × ULN plus INR >1.5/ascites/hepatic encephalopathy/other organ failure).[16] Liver injury pattern was classified as hepatocellular, mixed or cholestatic according to the *DILI expert Working group* criteria.[16] The extended T, B and innate cells immunophenotyping was performed in all patients at diagnosis of severe ChILI by multiparameter flow cytometry panels as fully explained in the supplementary material S1.

Liver biopsy specimens were assessed in haematoxylin and eosin-stained slides. Necroinflammation was graded according to Ishak modification for hepatic activity index in chronic hepatitis and scored on a scale of 0–18 based on its three different items (interface hepatitis, lobular degeneration and portal inflammation) as summarised in Table 1.[17] Fibrosis was graded on a scale of 0–4 according to the Ishak system. Presence of plasma cell infiltrate was evaluated on immunostaining for CD138 (DAKO, monoclonal mouse anti-human CD138 (MI15) antibody) and graded from 0 to 3 as described elsewhere.[18] Distribution of $CD8^+$, $CD4^+$, $CD20^+$, $CD68^+$, $CD56^+$ cells; expression of PD1, PD-L1 and IgG4; presence of granulomas, eosinophils, endothelitis, ductal proliferation or damage and supurative cholangitis were also assessed. All biopsies were read by the same pathologist. At least 10 portal tracts were required.

TABLE 1 Necroinflammation items and scoring according to the Ishak grading system.

Score	Interface hepatitis	Score	Lobular degeneration[a]	Portal inflammation
0	Absence	0	Absence	Absence
1	Mild piecemeal necrosis	1	Mild (<1/3 of lobules or nodules)	Mild (sprinkling of inflammatory cells in <1/3 of portal tracks)
3	Moderate piecemeal necrosis (<50% of the circumference of most portal tracts)	3	Moderate (involvement of 1/3–2/3 of lobules or nodules)	Moderate (increased inflammatory cells in 1/3 to 2/3 of portal tracks)
4	Marked piecemeal necrosis (≥50% of the circumference of most portal tracts)	4	Marked (dense packing of inflammatory cells in >2/3 of portal tracts)	Marked inflammation (dense packing of inflammatory cells in >2/3 of portal tracks)
5	Moderate piecemeal necrosis plus bridging necrosis[b] Marked piecemeal			
10	Multilobular necrosis[c]			

Note: Necroinflammation degree grading: Mild: ≤3 points. Moderate: 4–10 points. Severe: ≥11 points.

[a]Degeneration: acidophilic bodies, ballooning; focal necrosis: scattered foci of hepatocellular necrosis.

[b]Bridging is defined as >2 bridges in the liver biopsy specimen; no distinction is made between portal–portal and portal–central linkage.

[c]Two or more contiguous lobules with panlobular necrosis.

3.1 | Statistical analysis

Quantitative variables were expressed as mean and standard deviation or median and interquartile range (IQR) or range and analysed with the Mann–Whitney *U*-test or the Student's *t*-test, as appropriate. Categorical variables were expressed as frequency and percentage and compared using the chi-squared or Fisher's exact test, when frequencies were less than 5%. The results were considered statistically significant when the *p*-value was lower than 0.05. All statistical analyses were performed using IBM SPSS, version 26.0 (SPSS Inc, Armonk, NY, USA).

4 | RESULTS

4.1 | Characteristics of patients at the severe checkpoint inhibitor-induced liver injury episode

From January 2020 to August 2023, 111 patients undergoing ICIs who developed a grade 3 or 4 hepatitis were assessed (Figure 2). Overall, 67 (60.4%) subjects were excluded, mainly due to an alternative diagnosis (48/67, 71.6%). Progression of underlying cancer was the most common reason for exclusion (21/67, 31.3%) followed by DILI (14/67, 20.9%) by an alternative hepatotoxic drug within the prior 3 months, including amoxicillin-clavulanate ($n=5$), isoniazid ($n=3$), herbal supplements ($n=2$), ciprofloxacin ($n=2$), non-steroidal anti-inflammatories ($n=1$) and antithyroid drugs ($n=1$).

Finally, 44 individuals with severe ChILI were included in the study. Women accounted for 56.8% of subjects, and median age was 62 years (Table 2). The most common underlying cancer was lung (29.5%) and melanoma (27.3%). In addition, 6 (13.6%) of the patients had history of an autoimmune disorder, and 12 (27.3%) had already received a prior line of therapy that included any ICI.

Patients were receiving an anti-PD1 (23, 52.3%) or anti-PD-L1 (8, 18.2%) agent, 10 (22.7%) a combination of anti-PD-1 plus either an anti-CTLA-4 or an anti-LAG-3 agent and 3 (6.8%) an anti-CTLA-4 agent in monotherapy. 19 (43.2%) patients were receiving ICI in combination with another treatment, either chemotherapy ($n=9$) or tyrosine-kinase inhibitors (TKI; $n=10$).

Prior to diagnosis of severe ChILI patients had received a median number of three doses of ICI. Time from ICI last dose to ChILI was 20 days (Table 3). Severity assessed by the CTCAE system classified 35 (79.5%) cases as grade 3 and 9 (20.5%) as grade 4 hepatitis, whereas classification by the DILI severity score was mild in 35 (79.5%), moderate in 7 (15.9%) and severe in 2 (4.5%). Overall, eight (18.2%) presented with jaundice and 14 (31.8%) with increased total bilirubin values. Concerning liver injury pattern, the most common was hepatocellular (23, 52.3%) followed by mixed (12, 27.3%) and cholestatic (9, 20.5%).

The oncological disease response at the time of severe ChILI was as follows: 4.5% complete response, 36.4% partial response, 38.6% stable disease and 20.5% non-liver progression. Five subjects presented with a concomitant irAE: thyroid involvement ($n=3$: 2 thyroiditis and 1 hypothyroidism; one of them with concomitant colitis), concomitant immune-mediated pneumonitis ($N=1$) and severe rash ($n=1$).

Altogether, 10 (22.7%) subjects had at least one detectable autoantibody, with ANAs as the most frequent (7/44, 15.9%), followed by SMA (2/44, 4.5%) and ANCA (1/44, 2.3%). No case tested positive for anti-LKM, AMA, anti-SLA, anti-LKM1, anti-LC1 or rheumatoid factor.

4.2 | Performance of the 2-step algorithm for identification of patients who would benefit from a CS-free management

Overall, 30 (68.2%) of the 44 did not require CS for the management of severe ChILI according to the 2-step algorithm (Figure 3). As a

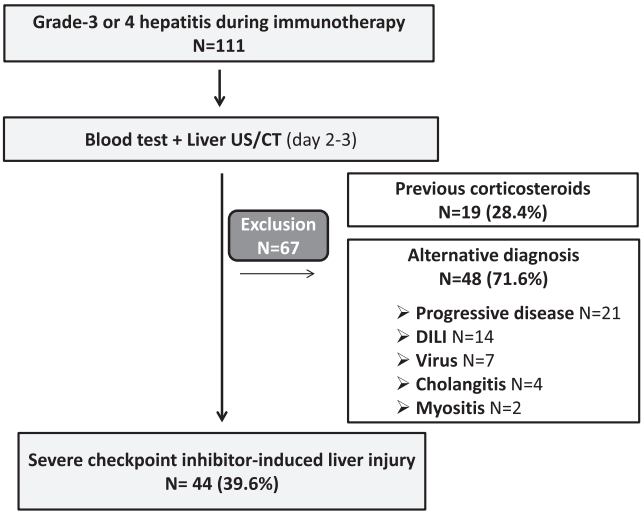

FIGURE 2 Flowchart of included patients. All subjects who developed grade 3 or grade 4 hepatitis when undergoing ICIs were assessed for inclusion in the present study. From 111 assessed cases, 67 (60.4%) were excluded, mainly due to presence of an alternative diagnosis for the increase of transaminases, with cancer progression as the most frequent (19/67, 28.4%). Finally, 44 patients without concomitant corticosteroid therapy were diagnosed with grade 3 or grade 4 checkpoint inhibitor-induced liver injury and were included in the study. ALT, alanine aminotransferase; AST, aspartate transferase; CT, computed tomography; US, ultrasound.

result of the first step (ICI temporary discontinuation), 22 (50.0%) subjects presented improvement of the transaminases values. Despite initial improvement, two patients with biochemical improvement were treated with CS at Days 9 and 14 of ChILI diagnosis due to the presence of a concomitant irAEs (colitis and pneumonitis).

In the 22/44 (50.0%) patients without improvement after ICI discontinuation a liver biopsy was performed (step 2). As summarised in Figure 3, degree of necroinflammation at liver biopsy was as follows: 5 mild, 9 moderate, 8 severe. According to the protocol, CS were started within 24 h from the biopsy in only the eight patients showing signs of severe necroinflammation. No CS were given initially to the 14 patients with either mild ($n=5$) or moderate ($n=9$) necroinflammation. All five subjects with mild necroinflammation experienced progressive transaminases normalisation, without CS therapy. However, 6 (66.7%) out of the nine patients with moderate necroinflammation required CS during follow-up due to later biochemical worsening. To note, the two patients with a severe scoring at the DILI severity score required CS due to the lack of improvement after ICI discontinuation and presence of severe necroinflammation at liver biopsy. These two patients also required the addition of mycophenolate mofetil for the management of the severe ChILI.

On the whole, 14 subjects received CS according to the 2-step algorithm. From them, 6 (42.9%) developed any related adverse effect: 3 infections, 1 decompensated diabetes, 1 osteoporotic fracture and 2 mood disturbances.

In summary, 30 (68.2%) of the 44 patients with severe ChILI benefited from sparing CS according to the 2-step algorithm: 22 (50.0%) due to the first step of the algorithm (ICI temporary discontinuation), and 8 (18.2%) more subjects in accordance with the second step based on the degree of necroinflammation at liver biopsy.

Overall, at the time of severe ChILI 35 subjects did not have progressive cancer disease. The risk of developing progressive disease afterwards was not modified according to CS therapy for severe ChILI (PD: 54.2% CS-free vs. 45.5% CS, $p=0.454$).

After recovery from the severe ChILI, 24 (54.5%) individuals restarted ICIs. Reasons for no rechallenge in the remaining 20 subjects

TABLE 2 Baseline characteristics of patients with grade 3 or 4 checkpoint induced-liver injury (ChILI).

	Overall ($N=44$)
Female sex	25 (56.8%)
Age (years)	62 (53–71)
Age ≥70 years	13 (29.5%)
Autoimmune disorder	6 (13.6%)
Underlying cancer	
Lung cancer	12 (27.3%)
Melanoma	13 (29.5%)
Urinary tract cancer	5 (11.4%)
Gastrointestinal cancer	5 (11.4%)
Breast cancer	4 (9.1%)
Gynaecologic cancer	2 (4.5%)
Others[a]	3 (6.8%)
Cancer status at the beginning of ICIs	
SD	2 (4.5%)
PD	41 (93.2%)
PR	1 (2.3%)
Liver metastasis	10 (22.7%)
Liver tests at the beginning of ICI (IU/mL)	
AST	22 (18–29)
ALT	21 (15–32)
ALP	90 (79–108)
GGT	49 (22–75)
Previous lines of therapy including ICI	12 (27.3%)
Type of ICI	
Anti-PD1	23 (52.3%)
Anti-PD-L1	8 (18.2%)
Anti-CTLA-4	3 (6.8%)
Combined ICIs[b]	10 (22.7%)
Other concomitant oncological therapy	19 (43.2%)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; anti-CTLA-4, anti-cytotoxic T-lymphocyte antigen 4; anti-PD1, anti-programmed cell death-1; anti-PD-L1, anti-programmed cell death-1 ligand; AST, aspartate aminotransferase; ChILI, checkpoint inhibitor-induced liver injury; GGT, gamma glutamyl transpeptidase; ICI, immune checkpoint inhibitor; NED, no evidence of disease; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Others included: orbital carcinoma ($n=1$), mesothelioma ($n=1$) and tyroid ($n=1$).

[b]Combined ICI includes anti-PD1 plus either anti-CTLA-4 or anti-LAG3.

TABLE 3 Characteristics of patients at diagnosis of the grade 3 or 4 checkpoint induced-liver injury (ChILI).

	Overall ($N=44$)
Doses of ICI to severe ChILI	3 (1–5)
Days from last ICI dose to ChILI	20 (12–22)
CTCAE severity	
Grade 3	35 (79.5%)
Grade 4	9 (20.5%)
Cancer status at severe ChILI	
SD	17 (38.6%)
PD	9 (20.5%)
PR	16 (36.4%)
NED	2 (4.5%)
Concomitant irAE at severe ChILI	5 (11.4%)
Jaundice	8 (18.2%)
Liver injury pattern	
Hepatocellular	23 (52.3%)
Mixed	12 (27.3%)
Cholestatic	9 (20.5%)
Lymphocyte count	1300 (1025–2075)
Creatinine (mg/dL)	0.79 (0.60–0.93)
Total bilirubin (mg/dL)	0.88 (0.55–1.75)
AST (IU/mL)	288 (190–494)
ALT (IU/mL)	404 (287–671)
ALP (IU/mL)	187 (124–345)
GGT (IU/mL)	205 (91–554)
IgG (mg/dL)	894 (766–1230)
ANA ≥1/80	7 (15.9%)
Any autoantibody[a]	10 (22.7%)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; ChILI, checkpoint inhibitor-induced liver injury; GGT, gamma glutamyl transpeptidase; ICI, immune checkpoint inhibitor; IgG, immunoglobulin G; NED, no evidence of disease; PD, progressive disease; PR, partial response; SD, stable disease.

[a]This factor included detection of ANA, SMA, ANCAs, anti-LKM, AMA, anti-SLA, anti-LKM1 and anti-LC1.

were as follow: discontinuation of treatment due to partial or complete oncological response ($n=8$), irAE ($n=5$: 3 severe ChILI and 2 non-liver irAE) and change of oncological therapy for non-liver progressive disease ($n=7$).

At last follow-up (September 2023), 14 (31.8%) out of 44 patients had died, all of them due to cancer progression at a median time of 17 (8–27) months after the severe ChILI episode.

4.3 | Factors associated with resolution of severe ChILI without need of CS therapy

Demographic, clinical and analytical data were explored in search of factors associated with spontaneous resolution of severe ChILI without need of CS (Table 4). Patients who did not require CS tended to be younger ($p=0.082$) and they presented a less severe hepatitis as demonstrated by the lower values of AST ($p<0.001$), ALT ($p<0.001$), total and conjugated bilirubin ($p=0.027$ and $p=0.009$, respectively). Previous treatment with ICI was more common among those with spontaneous resolution of severe ChILI ($p=0.040$). None of them had history of prior liver injury, although 3 out of these 12 subjects had presented a prior irAE (all hypothyroidism).

The underlying cancer and the pattern of liver toxicity had no impact on the performance of the 2-step algorithm ($p=0.178$ and $p=0.116$), with all groups benefiting from any of the steps for of the CS-sparing algorithm (Supplementary figures S1 and S2).

The scheme of ICI impacted on the need for CS, since most patients who avoided this therapy were on monotherapy with an anti-PD1 agent, whereas combined ICIs was more commonly associated with further need of CS ($p=0.037$). Presence of ANAs or any other antibody was not associated with need of CS ($p=0.270$ and 0.606, respectively).

Extended immunophenotyping on T cells performed at diagnosis of severe ChILI revealed a significant decrease ($p=0.028$) in the expression of HLA-DR in $CD8^+$ lymphocytes among those who did not require CS. Furthermore, $CD3^+$ T response was lower ($p=0.090$), as well as $CD3^+$ $CD4^+$ cells ($p=0.085$) and central memory (CM) ($CD3^+$ $CD4^+$ $CD45RA\text{-}CCR7^+$; $p=0.046$), though the relative number of effector-memory (EM) ($CD3^+CD4^+CD45RA^-CCR7^+$; $p=0.002$) was higher (Figure 4). When studying the polarisation of effector $CD4^+$ T lymphocytes, both CM and EM, we found a trend to higher Th1 ($CD3^+CD4^+CXCR3^+CCR6^-$) in those who benefited from CS sparing ($p=0.060$), though Th17 cells were similar ($p=0.809$ and $p=0.268$ respectively for $CD3^+CD4^+CXCR3^+CCR6^+$ and $CD3^+CD4^+CXCR3\text{-}CCR6^+$). At the liver biopsies, no differences were observed except for the degree of necroinflammation.

To note, the results of the algorithm varied according to the severity of the ChILI when severity was assessed by the CTCAE system. Up to 28 (80.0%) out of the 35 patients with grade 3 avoided CS by means of the algorithm, whereas this was only possible in two (22.2%) out of nine subjects with grade 4 ChILI ($p=0.002$). This difference was not observed when severity was evaluated by the DILI severity score ($p=0.171$), as shown in Figure 5.

On the whole, time to transaminases normalisation was greater in those who required CS (21 vs. 76, $p<0.001$), even when only grade 3 ChILI subjects were analysed (21 vs. 83, $p<0.001$).

4.4 | Proposed protocol for the management of severe checkpoint inhibitor-induced liver injury based on the results of the 2-step algorithm

Considering the results of our study, we suggest a strategy for managing patients with severe ChILI, as summarised in Figure 6. In all subjects presenting with severe ChILI, ICI discontinuation is recommended regardless of transaminases values since all grade subjects

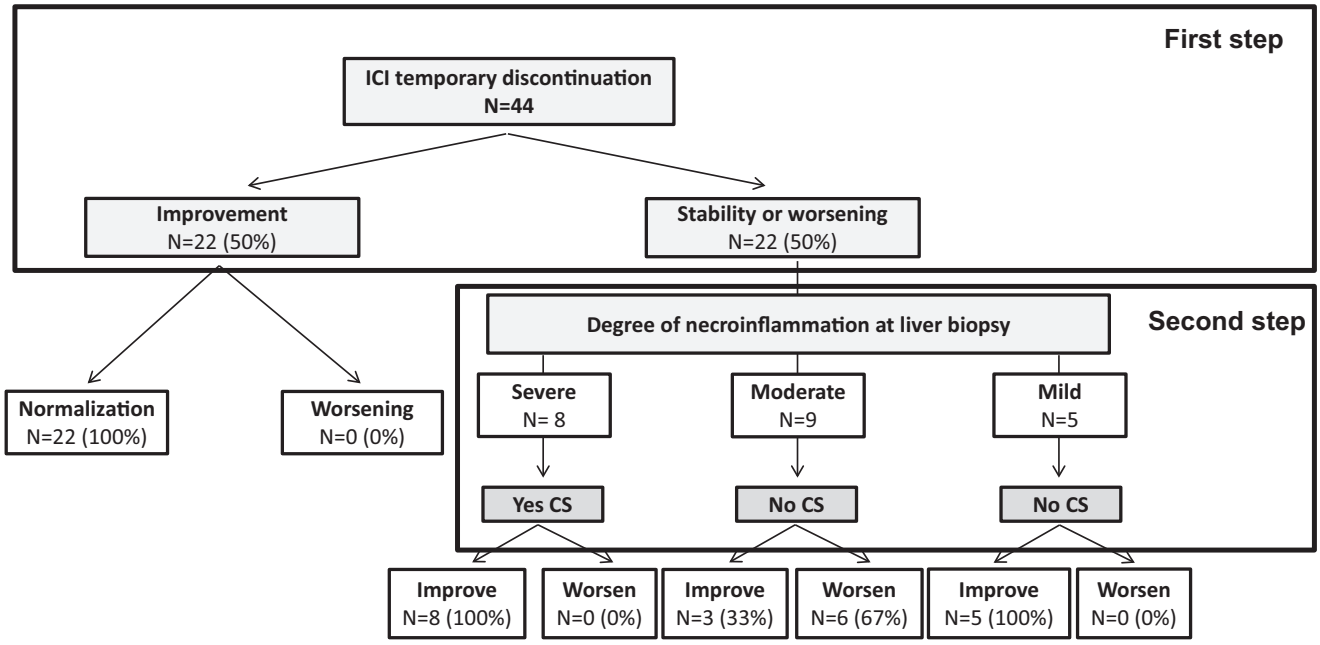

FIGURE 3 Results from the 2-step algorithm for the management of patients with severe checkpoint inhibitor-induced liver injury. The first step of the algorithm based on ICI discontinuation led to avoidance of corticosteroids in 22 (50.0%), whereas indication based on the histological degree of necroinflammation prevented corticosteroids in 8 (36.4%) out of the 22 individuals without improvement despite ICI discontinuation. CS, corticosteroids; ICI, immune checkpoint inhibitors.

benefited from this step. In those with improvement, close analytical follow-up is endorsed without need of CS.

In case of lack of improvement or even worsening despite ICI discontinuation, a liver biopsy is recommended in only those with grade 3 ChILI in order to identify subjects with mild and moderate necroinflammation and, therefore, candidates for avoidance of CS.

As summarised in Figure 5, liver biopsy had a positive impact on grade 3 ChILI, leading to avoidance of CS in 8 out of the 15 non-improvement subjects after ICI discontinuation. However, no grade 4 patient benefited from the results of biopsy. Therefore, in our proposed protocol, in patients with grade 4 ChILI who do not improve after ICI discontinuation, CS may be initiated without performing a liver biopsy. Moreover, due to the lack of benefit from the 2 steps of this algorithm and the risk of acute liver failure development, for patients presenting with a severe scoring at the DILI severity score, exclusion from this algorithm and prompt beginning of CS are recommended.

5 | DISCUSSION

This is the first prospective study to provide evidence supporting a CS-free management of subjects with severe checkpoint inhibitor-induced liver injury. Herein, we bring to light the results from a 2-step algorithm based on temporary ICI discontinuation and liver biopsy that led to avoidance of CS therapy in more than two thirds of patients with severe ChILI.

Although CS are the treatment of choice for most irAEs, they may potentially mitigate the effects of ICIs, compromising their activity in controlling the underlying cancer.[19] Moreover, CS may increase the risk of reactivation of latent infections such as tuberculosis or viral hepatitis.[20] Therefore, avoidance of this therapy for patients with severe irAEs may have a potential benefit beyond their classic and frequent adverse events such as hyperglycaemia, bone loss or arterial hypertension.

The first step of our algorithm based on temporal discontinuation of ICIs led to avoidance of CS in 50% of patients. These results are in line with a prospective study focused on the histological description of ICI toxicity, which also revealed the possibility of recovery from a severe ChILI without need of immunosuppression.[10] Interestingly, although grade 3 ChILI was clearly the group with the greatest benefit from this step, it should be highlighted that two out of the nine patients with grade 4 hepatitis and two of the seven with moderate severity according to the DILI severity score, also improved with just ICI temporary discontinuation.

Regarding the second step, the performance of a liver biopsy led to sparing CSs in 8 (36.4%) out of the 22 subjects who did not improve despite ICI discontinuation. Patients with mild necroinflammation, were managed with ICI discontinuation only, and none required CS due to progressive analytical improvement. Liver biopsy step had a remarkable impact on patients with grade 3 ChILI, sparing CS in 8 out of the 15 (53.3%) non-improvement patients with just ICI discontinuation (Figure 5). In contrast, all subjects with grade 4 ChILI candidates to biopsy presented a severe degree of necroinflammation and, in consequence, they received CS according to the 2-step algorithm. For this reason and despite the relatively small number of cases, the suggested protocol based on our results skips the performance of liver biopsy for patients with

TABLE 4 Factors associated with the need of CS according to the 2-step algorithm.

	Avoidance of CS (*N* = 30)	Need of CS (*N* = 14)	*p*-value
Female sex	17 (56.7%)	8 (57.1%)	0.618
Age (years)	59.9 (52.0–69.0)	69.7 (55.1–76.4)	0.082
Age ≥70 years	6 (20.0%)	7 (50%)	0.049
Autoimmune disorder	4 (13.3%)	2 (14.3%)	0.633
Underlying cancer			
Melanoma	6 (20.0%)	6 (42.9%)	0.237
Lung cancer	10 (33.3%)	3 (21.4%)	
Urinary tract cancer	2 (6.7%)	3 (21.4%)	
Gastrointestinal cancer	4 (13.3%)	1 (7.1%)	
Breast cancer	4 (13.3%)	0 (0%)	
Gynaecologic cancer	1 (3.3%)	1 (7.1%)	
Others[a]	3 (10.0%)	0 (0%)	
Liver metastasis	9 (30.0%)	1 (7.1%)	0.093
Previous lines of therapy including ICI	11 (36.7%)	1 (7.1%)	0.040
Type of ICI			
Anti-PD1	19 (63.3%)	4 (28.6%)	0.037
Anti-PD-L1	4 (13.3)	4 (28.6%)	
Anti-CTLA-4	3 (10.0%)	0 (0%)	
Combined ICIs	4 (13.3%)	6 (42.9%)	
Other concomitant oncological therapy	13 (43.3%)	6 (42.9%)	0.618
ICI doses to severe ChILI	3 (1–6)	3 (2–4)	0.458
Days from last ICI dose	18 (7–20)	21 (15–27)	0.059
Cancer status at ChILI			
SD	13 (43.3%)	5 (35.7%)	0.905
PD	5 (16.7%)	3 (21.4%)	
PR	11 (36.7%)	5 (35.7%)	
NED	1 (3.3%)	1 (7.1%)	
Concomitant irAE at severe ChILI	4 (13.3%)	2 (14.3%)	0.633
Lymphocyte count	1300 (900–2000)	1800 (1175–2550)	0.053
INR	0.94 (0.90–1.05)	1.04 (0.95–1.16)	0.159
Creatinine (mg/dL)	0.75 (0.60–0.93)	0.80 (0.59–1.10)	0.641
Total bilirubin (mg/dL)	0.81 (0.48–1.31)	1.05 (0.84–4.38)	0.027
Conjugated bilirubin (mg/dL)	0.23 (0.15–0.53)	0.45 (0.29–3.31)	0.009
AST (IU/mL)	227 (140–335)	710 (365–1119)	<0.001
ALT (IU/mL)	352 (265–486)	719 (488–1488)	<0.001
ALP (IU/mL)	186 (116–329)	233 (156–472)	0.326
GGT (IU/mL)	164 (61–581)	266 (103–582)	0.268
IgG (mg/dL)	993 (781–1258)	879 (730–1199)	0.551
ANA ≥1/80	6 (20.0%)	1 (7.1%)	0.270
Any autoantibody[b]	7 (23.3%)	3 (21.4%)	0.606

Abbreviations: ANA, antinuclear antibodies; ALP, alkaline phosphatase; ALT, alanine aminotransferase; Anti-PD1, anti-programmed cell death-1; anti-PD-L1, anti-programmed cell death-1 ligand; anti-CTLA-4, anti-cytotoxic T-lymphocyte antigen 4; AST, aspartate aminotransferase; ChILI, checkpoint inhibitor-induced liver injury; CS, corticosteroids; GGT, gamma glutamyl transpeptidase; ICI, immune checkpoint inhibitor; IgG, immunoglobulin G; NED, no evidence of disease; PD, progressive disease; SD, stable disease; PR, partial response.

[a]Others included: orbital carcinoma (*n* = 1), mesothelioma (*n* = 1) and tyroid (*n* = 1).

[b]This factor included detection of ANA, SMA, ANCAs, anti-LKM, AMA, anti-SLA, anti-LKM1 and anti-LC1.

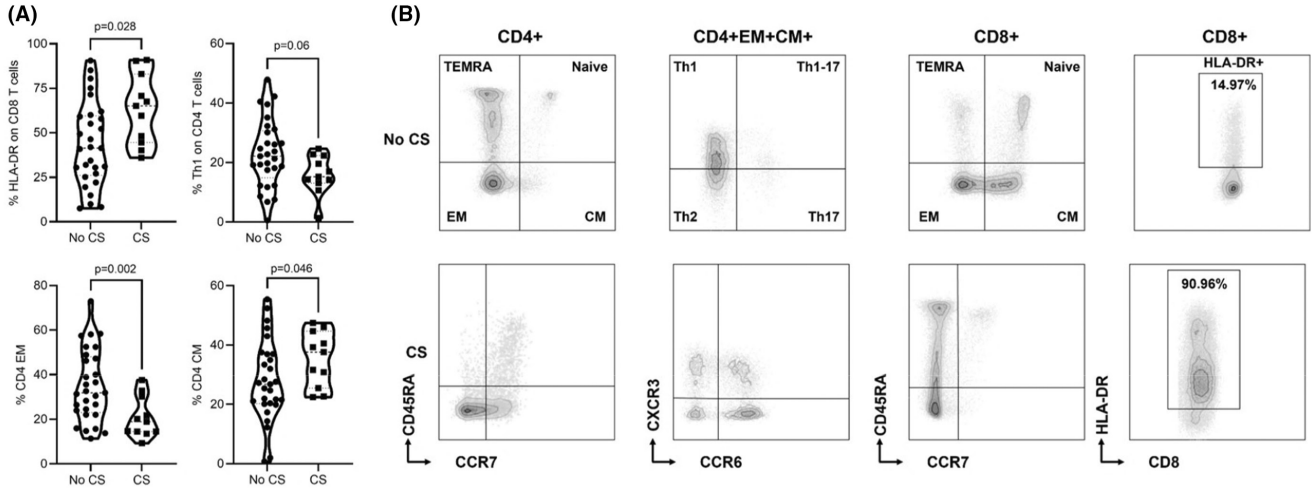

FIGURE 4 Immunophenotype analysis of peripheral blood cells in patients with severe ChILI. (A) Violin plots illustrating the percentage of the following populations: HLA-DR expression on CD8 T cells; effector memory (EM) CD4 T cells; CD4 Th1 T cells; and central memory (CM) CD4 T cells, in patients who required and did not require CS for the management of severe ChILI according to the 2-step algorithm. (B) Flow cytometry dot plots of extended immunophenotypes in a single patient from each group. CD4 differentiation (naïve: $CD45RA^{+}CCR7^{+}$; TEMRA: $CD45RA^{+}CCR7^{-}$; TEM: $CD45RA^{-}CCR7^{-}$; and TCM: $CD45RA^{-}CCR7^{+}$); Th polarisation (Th1: $CXCR3^{+}CCR6^{-}$; Th1-17: $CXCR3^{+}CCR6^{+}$; Th17 $CXCR3^{-}CCR6^{+}$ and Th2: $CXCR3^{-}CCR6^{-}$); CD8 T cells differentiation and HLA-DR expression.

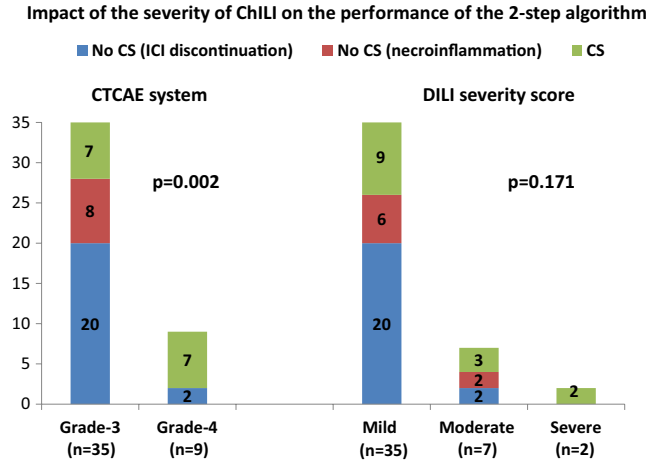

FIGURE 5 Performance of the 2-step algorithm according to the severity of the checkpoint inhibitor-induced liver injury. Notable differences were observed based on the severity of the ChILI, with a greater impact on patients with grade 3 hepatitis compared with those with grade 4. CTCAE, common terminology criteria for adverse events; CS, corticosteroids; DILI, drug-induced liver injury; ICI, immune checkpoint inhibitors.

grade 4 ChILI who do not respond to ICI temporary discontinuation (Figure 6). Moreover, for those presenting with severe grading at the DILI severity score this algorithm should be obviated due to the lack of benefit of the 2-step algorithm and the potential risk of acute liver failure development. Unexpectedly, CTCAE criteria proved to be more useful than DILI severity score for identification of patients who may not benefit from the performance of the liver biopsy step.

In our study patients treated with CS presented a good prognosis despite the relatively low doses proposed in our algorithm (0.5 mg/kg if normal bilirubin and 1 mg/kg/day if increased levels). These results are in line with the retrospective study by Li et al. that reported that therapy with CS at doses over 1.5 mg/kg/day had no impact on the prognosis of severe ChILI.[21]

Interestingly, patients who recovered from severe ChILI without CS presented a shorter time to transaminases normalisation ($p < 0.001$). This association remained when only grade 3 patients were analysed ($p < 0.001$), precluding the bias of the greater AST/ALT values among patients who required CS in the overall cohort. This finding is in line with a previous study that also observed a shorter time to normalisation of aminotransferases levels among subjects with severe ChILI who did not receive CS (3 vs. 7 weeks, $p = 0.007$), although the included number of patients was low (4 subjects managed without CS and 19 with CS).[22] Noteworthy, other factors such as the type of liver injury pattern or the concomitant use of other oncological therapies, including both chemotherapy and TKI, have no impact on the need of CS for the management of severe ChILI.

Importantly, our proposed strategy for management includes only patients with severe ChILI, after ruling out alternative diagnosis. In our study, a substantial percentage of patients assessed for inclusion were excluded, mainly due to progression of the underlying cancer. These results are in line with previous reports where among individuals undergoing pembrolizumab therapy, an anti-PD1 agent, the most common cause for liver injury was the development of hepatic metastases,[23] or a recent retrospective cohort where 19.1% were excluded following causality assessment, mainly due to progressive liver metastases.[7] It is also relevant to highlight the importance of ruling out the concomitant use or recent history of hepatotoxic drugs such as antibiotics or, more striking and novel, simultaneous prophylaxis with isoniazid for latent tuberculosis due to the potential risk of reactivation associated with immunotherapy, as recommended by some guidelines.[20]

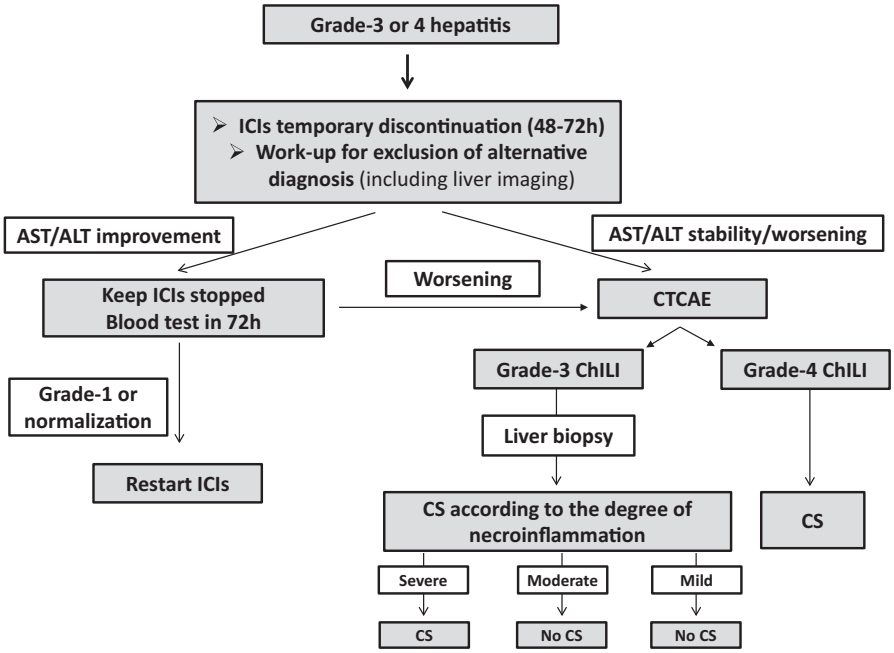

FIGURE 6 Proposed strategy for the management of patients with severe checkpoint inhibitor-induced liver injury based on our results. All subjects with severe ChILI may benefit from ICI temporary discontinuation, regardless of the transaminases values. In case of lack of improvement, a liver biopsy is recommended in those with grade 3 ChILI in order to identify those with mild and moderate necroinflammation and, therefore, candidates for avoidance of CS. For individuals with grade 4 ChILI who do not improve after ICI discontinuation, CS may be initiated without need of liver biopsy. ALT, alanine aminotransferase; AST, aspartate transferase; ChILI, checkpoint inhibitor-induced liver injury; CS, corticosteroids; CTCAE, Common Terminology Criteria for Adverse Events; ICI, immune checkpoint inhibitors.

Notably, and in accordance with previous reports citing the favourable outcomes of patients who developed severe or concomitant irAEs,[24,25] in our cohort up to 80% of subjects presented a good response in terms of the underlying cancer at the time of the severe ChILI. This finding supports the concept of a higher efficacy of immunotherapy in patients with severe irAEs, probably due to a more enhanced immune response. In this line, HLA-DR$^+$CD8$^+$ T cells expansion after ICI has been described as a predictor of treatment response.[26] However, excessive activation can lead to adverse effects. Herein, we observe that an excess expression of HLA-DR in cytotoxic T lymphocytes identified those patients with later requirement of CS. Interestingly, in a previous cohort including 22 cases of ChILI, 13 of them severe, an increased CD8$^+$ HLA-DR expression was also observed when these subjects were compared with those undergoing ICI without developing liver injury.[27] Although more extensive studies are needed, monitoring of this biomarker in patients with irAEs may help towards early identification of the need for immunosuppressive treatment for irAEs management. In our cohort, the CD4 lymphocyte differentiation phenotype showed a significant decrease in the EM/CM balance in patients who require CS. This observation could potentially indicate the proliferation of CM T cells following repeated antigen exposure. Although we lack baseline distribution data of patients prior to ICIs, previous studies have demonstrated a pre-therapy expansion of CD4$^+$ EM T cells in cytomegalovirus-infected patients with metastatic melanoma as a prognostic marker of ChILI.[28] More recently, a potential key role of IL-17 and therefore, Th17 cells, has been suggested in patients with ChILI, though no prognostic events were explored.[29] In our cohort, no differences were observed in either CD3$^+$CD4$^+$CXCR3$^+$CCR6$^+$ or CD3$^+$CD4$^+$CXCR3$^-$CCR6$^+$ cells in terms of CS avoidance.

Our study has some limitations. The study protocol excluded all patients with a severe ChILI that were undergoing CS for any reason, leading to the exclusion of 19 patients. The main reason for this decision was the influence of CS on the degree of necroinflammation,[15] which is the pillar for CS indication in patients who undergo a liver biopsy. The performance of a liver biopsy may be considered a limitation of our algorithm, especially taking into account the timeline for both its performance and the description of its findings for selection of patients who would benefit from a CS-sparing management. This step was chosen in view of the potential impact of the degree of necroinflammation on spontaneous recovery from severe ChILI reported in a previous study.[10] Although invasive, the positive impact of necroinflammation assessment in grade 3 ChILI, leading to the avoidance of CS in 53.3% of non-improvement patients with just ICI discontinuation, supports the inclusion of liver biopsy in the suggested strategy expounded in Figure 6. Moreover, some patients were undergoing concomitant oncological treatment such as chemotherapy and TKI, although its relative low rate of hepatotoxicity and the cholestatic pattern associated with some TKI such as lenvatinib reduces the impact of these drugs on DILI causality.

Although the number of patients included is relatively low and our algorithm has not been validated in an external cohort and lacks a comparative arm, to our knowledge ours is the first prospective study focused on reporting a CS-sparing strategy for patients with

severe ChILI, revealing, moreover, interesting histological and immunological data on patients with severe ChILI. Though noteworthy, our results need validation from an external cohort including a greater number of patients with severe ChILI.

6 | CONCLUSIONS

In summary, this algorithm based on temporary immunotherapy discontinuation and liver biopsy allows avoidance of CSs in two thirds of patients with severe checkpoint-induced liver injury.

AUTHOR CONTRIBUTIONS

Mar Riveiro-Barciela: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; validation; visualization; writing – original draft; writing – review and editing. **Ana Barreira-Díaz:** Conceptualization; data curation; formal analysis; investigation; methodology; validation; writing – original draft; writing – review and editing. **María-Teresa Salcedo:** Data curation; formal analysis; investigation; writing – review and editing. **Ana Callejo-Pérez:** Data curation; formal analysis; investigation; writing – review and editing. **Eva Muñoz-Couselo:** Data curation; formal analysis; investigation; writing – review and editing. **Patricia Iranzo:** Data curation; formal analysis; investigation; writing – review and editing. **Carolina Ortiz-Velez:** Data curation; formal analysis; investigation; writing – review and editing. **Susana Cedrés:** Data curation; formal analysis; investigation; writing – review and editing. **Nely Díaz-Mejía:** Data curation; formal analysis; investigation; writing – review and editing. **Juan Carlos Ruiz-Cobo:** Data curation; formal analysis; investigation; writing – review and editing. **Rafael Morales:** Data curation; formal analysis; investigation; writing – review and editing. **Juan Aguilar-Company:** Data curation; formal analysis; investigation; writing – review and editing. **Ester Zamora:** Data curation; formal analysis; investigation; writing – review and editing. **Mafalda Oliveira:** Data curation; formal analysis; investigation; writing – review and editing. **María-Teresa Sanz-Martínez:** Data curation; formal analysis; investigation; writing – review and editing. **Lluis Viladomiu:** Data curation; formal analysis; investigation; writing – review and editing. **Mónica Martínez-Gallo:** Data curation; funding acquisition; investigation; writing – review and editing. **Enriqueta Felip:** Data curation; formal analysis; investigation; writing – review and editing. **María Buti:** Conceptualization; data curation; formal analysis; investigation; methodology; supervision; validation; writing – original draft; writing – review and editing.

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AUTHORSHIP

Guarantor of the article: Mar Riveiro-Barciela.

PATIENT CONSENT STATEMENT

All patients signed informed consent for inclusion in the study.

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SUPPORTING INFORMATION

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

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