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ORIGINAL ARTICLE

Presence of multilobular necrosis on liver biopsy identifies corticosteroid responsiveness in acute indeterminate hepatitis

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Abstract

Background and Aims: Treatment of patients with severe indeterminate hepatitis (IAH) is an unmet need. Corticosteroids are often used in the management of these patients but criteria for the selection of patients for this intervention are arbitrary. The aims of this study were to analyse the clinical and pathological features of patients with IAH to define predictors of corticosteroid responsiveness.

Methods: This study included consecutive patients with acute indeterminate hepatitis admitted to a single hospital and underwent a liver biopsy. The clinical manifestation and histopathological features of steroid and non-steroid groups were compared and their relationship with corticosteroids response was evaluated.

Results: Forty-eight patients were included, 24 (50%) recovered and the other half underwent liver transplantation or died within 3-months. Of the 48 cases, 24 received corticosteroids (initial dose of 45 ± 12 mg prednisolone). Corticosteroids were initiated 2.7 ± 3.8 days after admission. Liver biopsy was performed 2-days (median, IQR

Abbreviations: ALF-OFs, Acute Liver Failure-Organ Failure Score; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IAH, indeterminate hepatitis; IgG, immunoglobulin G; INR, international normalised ratio; MELD score, model for end-stage liver disease score; MELD-Na score, end-stage liver disease-sodium score.

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1-3) after admission. Fifteen (62.5%) patients receiving corticosteroids survived without transplantation compared with 9 (37.5%) that did not receive steroids ($P = .149$). In those with multilobular necrosis, 50% reduction in the death/transplantation rate was observed after steroid treatment ($P = .018$). In patients without multilobular necrosis and with or without perivenulitis, corticosteroids did not impact the outcome. Response to corticosteroids was independent of the MELD score.

Conclusions: The presence of multilobular necrosis on liver biopsy helps identify a subgroup of IAH cases who may benefit from the administration of corticosteroids.

KEYWORDS

biopsy, corticosteroid, indeterminate hepatitis, necrosis, pathology

1 | INTRODUCTION

Indeterminate acute hepatitis (IAH) refers to an acute hepatitis illness in which the aetiology cannot be determined despite an exhaustive search for the cause. This condition has been referred to as 'non A, non B, non C', 'non A-E', or 'seronegative' acute hepatitis.[1] IAH is clinically challenging due to its inherent complexity, lack of diagnostic criteria, poor prognosis and its treatment is an unmet need. Approximately 10%-12% of acute liver failure cases are due to IAH.[2]

Although administration of corticosteroids has been demonstrated to improve the outcome of severe IAH in paediatric patients,[3] its role in adult patients is not clear.[4,5] In patients with severe acute hepatitis of mixed etiologies, short-term use of corticosteroids was suggested to be beneficial and not accompanied by increased infectious complications.[4] Urgent liver transplantation was required for those that did not respond. However, there are no criteria that define which patients with IAH may benefit from the administration of corticosteroids.

Liver biopsy to determine the aetiology of patients with IAH is rarely performed because of the risk of bleeding. Our previous study showed that multilobular necrosis may be a predictive factor for poor prognosis in severe IAH.[6] In this clinicopathological study, we explored the clinical and pathological features that may be used to select patients with IAH that may benefit from corticosteroids.

Lay Summary

1. Corticosteroids are often used in the management of patients with indeterminate hepatitis (IAH) but criteria for selection of patients for this intervention are arbitrary.
2. In this clinicopathological study of IAH, 50% reduction in the death/transplantation rate was observed after steroid treatment in those with multilobular necrosis.
3. In patients without multilobular necrosis, corticosteroids did not impact the outcome.

2 | METHODS

2.1 | Ethics

The study was approved by the London–Hampstead Research Ethics Committee (07/Q0501/50) and was in compliance with the Declaration of Helsinki.

2.2 | Patients

This study is part of the CARNATION study, which is a retrospective-prospective project that aims to explore clinicopathological characteristics of patients with acute hepatitis.[6] Histological records from January 2010 to October 2019 were screened to find eligible cases at the Royal Free Hospital, London using the following texts: 'acute hepatitis' or 'acute liver failure'. The clinical record was then reviewed to select eligible cases of IAH. IAH was diagnosed if all the other known causes of liver disease were excluded after an extensive liver database (Supplementary material 1) and histopathological analysis.

Patients were excluded if they (i) had no liver biopsy on admission; (ii) had missing baseline data for key parameters; (iii) had chronic liver disease; (iv) histology was referred for second opinion from another hospital; (v) had previous liver transplantation; (vi) had missing original glass slides and (vii) insufficient remaining tissue for histology review.

In this study, the decision to use corticosteroids was left to the judgement of the hepatologist who oversaw the management of the patient.

2.3 | Data collection

The following data were obtained from patients: sex, age, date of histopathology examination, medical history of chronic disease, corticosteroid therapy and the response, patients outcome, as well as the results

of biochemical tests, such as serum levels of alanine aminotransferase (ALT), aspartate transaminase (AST), bilirubin, alkaline phosphatase (ALP), international normalised ratio (INR) and creatinine.

The following liver specific scores were calculated in all cases on admission: model for end-stage liver disease (MELD) score,[7] MELD-sodium (MELD-Na) score,[8] and Acute Liver Failure-Organ failure (ALF-OF) score.[9]

2.4 | Histopathological review

All the biopsies were performed through the transjugular route. In general, we obtained four cores of liver tissue providing adequate material for histopathological examination. Two histopathologists who specialized in liver disease (CA and AQ) and were blinded to the clinical data reviewed the liver pathology independently. The following histological features were recorded systematically: ductular and canalicular cholestasis. The inflammatory cell infiltrate was assessed in terms of overall inflammatory burden and then according to distribution (portal, interface, lobular) adapting the Ishak system[10] as follows: portal, interface and lobular. Individual cell populations were also assessed, including plasma cells, neutrophils, macrophages and eosinophils. The other pathological features included central perivenulitis,[11,12] ductular reaction,[13] lymphocytes aggregates, lymphocytes follicles. Definition of the above terms was listed in Supplementary material 2. Multilobular necrosis was defined as loss of hepatocytes affecting multiple lobules as described by Lefkowitch.[11] Examples of multilobular necrosis are shown in Figure 1.

2.5 | Statistical analysis

SPSS software (version 24.0, SPSS Inc, Chicago, USA) was used to manage and analyse data in this study. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) and analysis with Student *t* test (for variables normally distributed) or Mann–Whitney U-test (for variables non-normally distributed). Categorical variables were expressed as percentages and examined with the chi-squared test or Fisher's exact test. A *P*-value <.05 was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of patients

We identified 294 consecutive patients with acute hepatitis during the study period. After reviewing the clinical history, 246 patients were excluded (Figure S1). The mean age of the included 48 cases was 44.4 ± 14.9 years and 43.8% of them were male. The liver biochemistry tests showed mean total bilirubin of 328.1 ± 196.9 μmol/L, ALT of 1306.6 ± 949.8 U/L, AST of 1206.9 ± 1203.9 U/L, and INR of 2.1 ± 1.09. Hepatic encephalopathy was present in four patients (8.3%) and ascites in four (8.3%). The mean MELD score was 23.5 ± 7.4 and the ALF-OF was 2.9 ± 0.6. Thirteen (27.1%) patients were positive for one autoimmune antibody and 7 (14.6%) were positive in two.

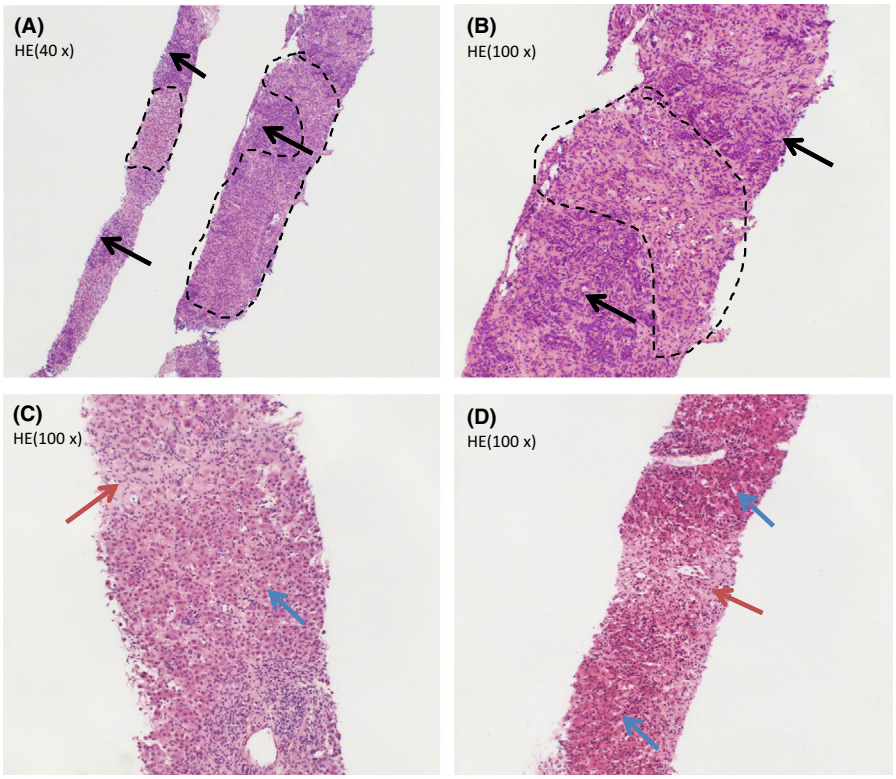

FIGURE 1 Examples of multilobular necrosis (A and B) and confluent zonal necrosis (C and D). Complete hepatic plate loss spanning multiple adjacent lobules delineated by dash line in A. High magnification view of area of complete hepatic loss spanning the area of a lobule in B. Black arrow: ductular reaction; blue arrow: preserved hepatic plates; red arrow: confluent zonal (perivenular) necrosis

3.2 | Comparison between survivors and non-survivors

Of 48 patients, 17 (35.42%) underwent liver transplantation and 7 (14.6%) died (5 in hospital and 2 in the community) within 3-months. They were defined as non-survivors. Twenty-four patients (50%) who recovered were defined as survivors (Table 1). Sex, age, hepatic encephalopathy, ascites, ALT, AST, platelet count and CRP levels were comparable between two groups. Bilirubin, INR, MELD and ALF-OF levels were significantly higher in non-survivors compared with the survivors ($P < .05$ for all). The histopathological analysis of liver biopsies revealed a higher frequency of multilobular necrosis (62.5% vs. 16.7%, $P = .003$) and perivenulitis (50% vs. 20.8%, $P = .07$) in non-survivors than in survivors.

3.3 | Association between pathological features and biochemical parameters

Liver biopsy was performed a median of 2-days (interquartile range 1-3) after admission. We explored the relationship between the pathological features and the results of biochemical tests on admission. Multilobular necrosis was found in 19 patients (39.6%). These patients had higher INR (2.7 ± 1.3 vs. 1.7 ± 0.8, $P = .008$) and lower albumin levels (31.1 ± 4.8 vs. 37.5 ± 7.5, $P < .001$) compared with those without. The liver specific scores, such as MELD, MELD-Na score and ALF-OF were higher in the patients with multilobular necrosis. As for the pathological feature, ductular reaction (89.5% vs. 51.7%, $P = .016$) and ductular cholestasis (31.6% vs. 6.9%, $P = .045$) were more common in those with multilobular necrosis. (Table S1).

Seventeen patients (35.4%) had perivenulitis on biopsy liver. The presence of perivenulitis was not associated with any biochemical parameter or pathological feature. (Table S2).

3.4 | Comparison between groups that received corticosteroids with those that did not

Twenty-four patients (50%) received treatment with corticosteroids (initial dose of 45 ± 12 mg prednisolone) during hospitalization. Corticosteroids were initiated 2.7 ± 3.8 days after admission. The comparison of baseline characteristics of patients treated with or without corticosteroids is presented in Table 2. No difference in the baseline characteristics was observed between the groups treated with or without corticosteroids. The autoimmune antibody positive rate was similar between the two groups. Bilirubin and the INR levels were similar between the groups. Liver histopathology results were also similar between the groups ($P > .05$ for all parameters).

3.5 | Clinicopathological characteristics of corticosteroid responders

Fifteen (62.5%) patients who received corticosteroids survived without transplantation compared with 9 (37.5%) that were not treated ($P = .149$). As shown in Table 3, MELD score, MELD-Na score and ALF-OF were significantly higher in non-responders ($P < .05$ for all). As for other baseline characteristics and pathological features, no difference was found between two groups. The autoimmune antibody profile was similar between steroid responders and non-responders. No difference in the immunoglobulin G (IgG) level was found between responders and non-responders.

3.6 | Outcomes of corticosteroid therapy in specific subgroups

The outcome of patients in different subgroups is shown in Table 4 and Figure 2. In those without multilobular necrosis, administration of corticosteroid did not improve survival rates ($P = 1$). However, 50% reduction in the death/transplantation rate was observed after steroid treatment in those with multilobular necrosis ($P = .018$, Figure 2A). The presence of perivenulitis did not predict the response of corticosteroids (Figure 2B).

We used AUROC to find the best threshold of MELD score for the outcome and the results showed the best cutoff was 25. Patients were categorized into higher MELD group (≥25) and lower MELD group (<25). Although higher MELD score was significantly associated with worse outcomes in the overall cohort, the use of corticosteroids did not improve the outcome in either MELD group (Figure 2C).

3.7 | Side effect corticosteroid therapy

The most common side effect of steroids was infection. During hospitalization, three patients developed nosocomial infection, with two in steroid group and one patient in non-steroid group. Of these three infected patients, two survived through 3-months, one in steroid group and one in non-steroid group. One patient developed steroid-associated pancreatitis and died.

3.8 | Long-term outcome of survivors

Four of the survivors who initially responded to steroid treatment developed autoimmune hepatitis during follow-up. Three had a relapse of acute hepatitis after withdrawal of steroids and developed severe fibrosis in the follow-up biopsies. All four patients required long-term immunosuppression (details in Table S3).

TABLE 1 Comparison between survivors and non-survivors (death/transplantation)

	Survivors (n = 24)	Death/transplantation (n = 24)	*P* value
Steroid treatment, n (%)	15 (62.5)	9 (37.5)	.149
Age (years)	44.96 ± 16.14	43.79 ± 13.95	.79
Male, n (%)	10 (41.67)	11 (45.83)	1
Hepatic encephalopathy, n (%)	2 (8.33)	2 (8.33)	1
Ascites, n (%)	1 (4.17)	3 (12.5)	.609
MELD	19.09 ± 7.56	27.72 ± 4.17	<.001
MELD-Na	20.44 ± 8.06	28.48 ± 4.06	<.001
ALF-OFs	2.56 ± 0.55	3.19 ± 0.39	<.001
Total bilirubin (μmol/L)	252.04 ± 200.07	404.21 ± 164.69	.006
INR	1.58 ± 0.75	2.59 ± 1.15	<.001
Creatinine (μmol/L)	112.92 ± 185.35	97.21 ± 80.9	.706
ALT (U/L)	1238.42 ± 976.13	1374.71 ± 938.55	.624
AST (U/L)	1159.5 ± 1343.85	1254.21 ± 1072.92	.789
ALP (U/L)	179.92 ± 104.97	164.58 ± 71.7	.558
GGT (U/L)	141.25 ± 80.46	128.33 ± 69.64	.754
Albumin (g/L)	37.38 ± 7.99	32.61 ± 5.65	.023
CRP (mg/L)	18.26 ± 36.97	11.64 ± 8.21	.41
Sodium (mmol/L)	137.04 ± 3.43	137.38 ± 2.53	.704
White blood cell ($\times 10^9$/L)	8.23 ± 6.25	8.6 ± 3.15	.798
Neutrophil ($\times 10^9$/L)	5.49 ± 4.44	5.66 ± 3.03	.879
Lymphocyte ($\times 10^9$/L)	1.53 ± 0.83	1.52 ± 0.75	.962
Platelets ($\times 10^9$/L)	243 ± 96.2	214.33 ± 93.72	.301
IgG (g/L)	15.28 ± 5.65	14.45 ± 7.06	.666
Hepatocyte preserved, n (%)	21 (87.5)	18 (75)	.461
Multilobular necrosis, n (%)	4 (16.67)	15 (62.5)	.003
Perivenulitis, n (%)	5 (20.83)	12 (50)	.07
Ductular reaction, n (%)	14 (58.33)	18 (75)	.358
Ductular cholestasis, n (%)	2 (8.33)	6 (25)	.245
Acidophilic body n (%)	17 (73.91)	13 (72.22)	1
Canalicular cholestasis, n (%)	9 (39.13)	8 (44.44)	.981
[a]Lobular inflammation, n (%)			.107
Mild	10 (43.48)	5 (27.78)	
Moderate	12 (52.17)	9 (50)	
Severe	1 (4.35)	4 (22.22)	
Portal inflammation, n (%)			.183
Mild	11 (45.83)	8 (33.3)	
Moderate	12 (50)	12 (50)	
Severe	1 (4.17)	4 (16.67)	
Interface inflammation, n (%)	18 (81.82)	16 (88.89)	.673
Lymphoid aggregate, n (%)	4 (16.67)	2 (8.33)	.666
Lymphoid follicle, n (%)	1 (4.17)	1 (4.17)	1
Neutrophil, n (%)	5 (20.83)	10 (41.67)	.213
Plasma cell, n (%)	6 (25)	11 (45.83)	.227
Macrophages, n (%)	21 (87.5)	20 (83.33)	1
Eosinophil, n (%)	6 (25)	5 (20.83)	1

Abbreviations: ALF-OFs, Acute Liver Failure-Organ Failure Score; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; INR, international normalised ratio; MELD score, model for end-stage liver disease score; MELD-Na score, end-stage liver disease-sodium score.

[a]In some patients without hepatocyte preserved, the lobular inflammation was not able to assess.

TABLE 2 Comparison between steroid and non-steroid groups

	Non-steroid (n = 24)	Steroid (n = 24)	*P* value
Survival, n (%)	9 (37.5)	15 (62.5)	0.149
Age (years)	44.79 ± 17.31	43.96 ± 12.5	0.849
Male, n (%)	10 (41.67)	11 (45.83)	1
Hepatic encephalopathy, n (%)	3 (12.5)	1 (4.17)	0.609
Ascites, n (%)	3 (12.5)	1 (4.17)	0.609
MELD	24.01 ± 9.02	23 ± 5.65	0.649
MELD-Na	24.76 ± 9.23	24.33 ± 5.48	0.85
ALF-OFs	2.96 ± 0.66	2.79 ± 0.47	0.283
Total bilirubin (μmol/L)	302.17 ± 199.49	354.08 ± 195.01	0.367
INR	2.3 ± 1.29	1.88 ± 0.8	0.179
Creatinine (μmol/L)	122.75 ± 189.08	87.38 ± 68.02	0.396
ALT (U/L)	1174.75 ± 875.68	1438.38 ± 1019.96	0.342
AST (U/L)	1033.25 ± 720.84	1380.46 ± 1542.48	0.325
ALP (U/L)	176.38 ± 86.58	168.12 ± 93.55	0.753
GGT (U/L)	165.25 ± 56.13	123.9 ± 78.74	0.303
Albumin (g/L)	34.87 ± 8.26	35.21 ± 6.37	0.876
CRP (mg/L)	17.09 ± 35.89	13.04 ± 14.7	0.627
IgG (g/L)	14.06 ± 6.78	15.66 ± 5.89	0.404
Sodium (mmol/L)	137.5 ± 2.62	136.92 ± 3.35	0.505
White blood cell ($\times 10^9$/L)	7.95 ± 3.57	8.88 ± 5.99	0.517
Neutrophil ($\times 10^9$/L)	5.07 ± 3.16	6.08 ± 4.28	0.358
Lymphocyte ($\times 10^9$/L)	1.65 ± 0.76	1.4 ± 0.8	0.268
Platelets ($\times 10^9$/L)	234.29 ± 84.41	223.04 ± 106.18	0.686
Total bilirubin on day 0 after steroid therapy (μmol/L)	302.17 ± 199.49[a]	362.12 ± 197.5	0.301
INR on day 0 after steroid therapy (μmol/L)	2.3 ± 1.29[a]	1.86 ± 0.86	0.171
ALT on day 0 after steroid therapy (U/L)	1174.75 ± 875.68[a]	1335.62 ± 938.68	0.542
Hepatocyte preserved, n (%)	18 (75)	21 (87.5)	0.461
Multilobular necrosis, n (%)	11 (45.83)	8 (33.33)	0.555
Perivenulitis, n (%)	7 (29.17)	10 (41.67)	0.546
Ductular reaction, n (%)	13 (54.17)	19 (79.17)	0.126
Ductular cholestasis, n (%)	4 (16.67)	4 (16.67)	1
Acidophilic body n (%)	13 (65)	17 (80.95)	0.424
Canalicular cholestasis, n (%)	7 (35)	10 (47.62)	0.615
[a]Lobular inflammation, n (%)			0.954
Mild	9 (45)	6 (28.57)	
Moderate	7 (35)	14 (66.67)	
Severe	4 (20)	1 (4.76)	
Portal inflammation, n (%)			0.375
Mild	9 (37.5)	10 (41.67)	
Moderate	11 (45.83)	13 (54.17)	
Severe	4 (16.67)	1 (4.17)	
Interface inflammation, n (%)	16 (80)	18 (90)	0.661
Lymphoid aggregate, n (%)	4 (16.67)	2 (8.33)	0.666
Lymphoid follicle, n (%)	1 (4.17)	1 (4.17)	1
Neutrophil, n (%)	7 (29.17)	8 (33.33)	1

TABLE 2 (Continued)

	Non-steroid (n = 24)	Steroid (n = 24)	*P* value
Plasma cell, n (%)	8 (33.33)	9 (37.5)	1
Macrophages, n (%)	21 (87.5)	20 (83.33)	1
Eosinophil, n (%)	5 (20.83)	6 (25)	1
Fibrosis, n (%)			1
No	19 (79.17)	18 (75)	
Mild (F1)	5 (20.83)	6 (25)	
ANA			0.501
Negative	17 (70.83)	16 (66.67)	
1:80-1:100	3 (12.5)	8 (33.33)	
>1:1000	4 (16.67)	0	
SMA			0.609
Negative	23 (95.83)	21 (87.5)	
Positive	1 (4.17)	3 (12.5)	
LKM			1
Negative	23 (95.83)	24	
Positive	1 (4.17)	0	
Other Autoimmune disease			1
Psoriasis	0	1 (4.17)	
Myasthenia gravis and Behcet's syndrome	0	1 (4.17)	
Hypothyroidism	1 (4.17)	0	

Abbreviations: ALF-OFs, Acute Liver Failure-Organ Failure Score; ANA, antinuclear antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; INR, international normalised ratio; LKM, anti-liver-kidney microsomal antibody; MELD score, model for end-stage liver disease score; MELD-Na score, end-stage liver disease-sodium score; SMA, anti-smooth muscle antibody.

[a]In some patients without hepatocyte preserved, the lobular inflammation was not able to assess.

4 | DISCUSSION

This study focused on the role of liver histopathology in the guidance of corticosteroid therapy in patients with IAH. Overall, we did not find any independent predictor of response to administration of corticosteroids. However, in post hoc analyses, the results showed a reduction of 50% in the death/transplantation rate after treatment with corticosteroids in IAH patients with multilobular necrosis. This result indicates a potential role of liver biopsy in patients with IAH in selecting patients for treatment with corticosteroids. The use of corticosteroids for the treatment of adult patients with IAH is controversial and there are no clear data supporting its use. In our study, the decision to use corticosteroids was left to the judgement of the hepatologist in charge of the patient and it is interesting to note that 50% of patients received corticosteroids attesting to the controversy around the usefulness of this treatment in patients with IAH. The baseline characteristics of the groups administered corticosteroids or not were comparable. This apparently random use of corticosteroids allowed us to perform analyses to assess its potential usefulness.

The efficacy of corticosteroids varied with the severity of liver injury. Although the risk of death/transplantation with corticosteroids was lower in the patients with multilobular necrosis, no differences were observed in those without. Multilobular necrosis is a severe parenchymal injury in the form of loss of hepatocytes spanning multiple lobules. Higher liver specific prognostic scores were found in patients with multilobular necrosis, indicating severe impairment of liver function. It was, therefore, not surprising that patients with multilobular necrosis had a worse outcome. Patients with MELD >25 had a poor outcome but we did not observe any benefit of steroids in this group.

The mechanism why patients with multilobular necrosis benefit from corticosteroids is unclear. Massive hepatic necrosis (present 42% of sections), central perivenulitis (65%), presence of lymphoid follicles (32%), and plasma cell-enriched inflammatory infiltrate (63%) are four features suggestive of autoimmune acute liver failure[12] though they are also observed in association with massive hepatic necrosis due to other causes. Several studies have shown the potential usefulness of corticosteroids in some groups of patients with severe acute hepatitis such as those with unidentified autoimmune hepatitis as a cause of presumed IAH.[14-16] Moreover, the four patients with confirmed autoimmune hepatitis on follow-up did not all present as typical autoimmune hepatitis on admission. However, the long-term follow-up of four survivors suggests that these patients may have had acute autoimmune hepatitis at presentation or

TABLE 3 Comparison between steroid responder and non-responder

	Responder (n = 15)	Non-responder (n = 9)	*P* value
Age (years)	44.47 ± 12.89	43.11 ± 12.52	.803
Male, n (%)	7 (46.67)	4 (44.44)	1
Hepatic encephalopathy, n (%)	1 (6.67)	0 (0)	1
Ascites, n (%)	0 (0)	1 (11.11)	.375
MELD	21.28 ± 6.39	25.86 ± 2.37	.021
MELD>=25, n (%)	3 (20)	8 (88.89)	.002
MELD-Na	23.03 ± 6.36	26.52 ± 2.61	.075
ALF-OFs	2.69 ± 0.52	3.00 ± 0.28	.084
Total bilirubin (μmol/L)	328.47 ± 200.99	396.78 ± 188.03	.412
INR	1.71 ± 0.89	2.16 ± 0.56	.144
Creatinine (μmol/L)	73.67 ± 14.71	110.22 ± 109.47	.348
ALT (U/L)	1407.8 ± 1045.8	1489.33 ± 1035.48	.855
AST (U/L)	1460.8 ± 1572.63	1246.56 ± 1574.82	.751
ALP (U/L)	178.13 ± 111.36	151.44 ± 54.39	.441
GGT (U/L)	140.12 ± 86.84	86.00 ± 46.87	.348
Albumin (g/L)	35.73 ± 6.63	34.33 ± 6.2	.608
CRP (mg/L)	14.2 ± 18.04	10.88 ± 4.45	.508
Sodium (mmol/L)	136.20 ± 3.53	138.11 ± 2.80	.181
White blood cell ($\times 10^9$/L)	8.99 ± 7.62	8.69 ± 1.17	.882
Neutrophil ($\times 10^9$/L)	6.05 ± 5.29	6.14 ± 1.92	.953
Lymphocyte ($\times 10^9$/L)	1.54 ± 0.95	1.16 ± 0.4	.181
Platelets ($\times 10^9$/L)	256.53 ± 111.2	167.22 ± 71.88	.026
IgG (g/L)	16.49 ± 6.29	14.09 ± 5.04	.363
Hepatocyte preserved, n (%)	14 (93.33)	7 (77.78)	.533
Multilobular necrosis, n (%)	4 (26.67)	4 (44.44)	.412
Perivenulitis, n (%)	4 (26.67)	6 (66.67)	.092
Ductular reaction, n (%)	12 (80)	7 (77.78)	1
Ductular cholestasis, n (%)	1 (6.67)	3 (33.33)	.13
Acidophilic body n (%)	5 (71.43)	12 (85.71)	.574
Canalicular cholestasis, n (%)	6 (42.86)	4 (57.14)	.659
Lobular inflammation, n (%)	10 (71.43)	5 (71.43)	1
Portal inflammation, n (%)	10 (71.43)	4 (44.44)	.383
Interface inflammation, n (%)	12 (92.31)	6 (85.71)	1
Lymphoid aggregate, n (%)	2 (13.33)	0 (0)	.511
Lymphoid follicle, n (%)	0 (0)	1 (11.11)	.375
Neutrophil, n (%)	4 (26.67)	4 (44.44)	.412
Plasma cell, n (%)	4 (26.67)	5 (55.56)	.212
Macrophages, n (%)	13 (86.67)	7 (77.78)	.615
ANA			1
Negative	10 (66.67)	6 (66.67)	
1:80-1:100	5 (33.33)	3 (33.33)	
>1:1000	0	0	
SMA			.615
Negative	13 (86.67)	7 (77.78)	
Positive	2 (13.33)	2 (22.22)	

TABLE 3 (Continued)

	Responder (n = 15)	Non-responder (n = 9)	*P* value
LKM			NA
Negative	15	9	
Positive	0	0	

Abbreviations: ALF-OFs, Acute Liver Failure-Organ Failure Score; INR, international normalised ratio; ANA, antinuclear antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; CRP, C-reactive protein; IgG, immunoglobulin G; LKM, anti-liver-kidney microsomal antibody; MELD score, model for end-stage liver disease score; MELD-Na score, end-stage liver disease-sodium score; SMA, anti-smooth muscle antibody.

TABLE 4 The efficacy of steroid in different subgroups

		Non-steroid		Steroid		
Subgroup	Number of case	Survival	Death/ transplantation	Survival	Death/ transplantation	*P* value
Multilobular necrosis						
No	29	9/13 (69.23%)	4/13 (30.77%)	11/16 (68.75%)	5/16 (31.25%)	1
Yes	19	0	11/11 (100%)	4/8 (50%)	4/8 (50%)	.018
Perivenulitis						
No	31	8/17 (47.06%)	9/17 (52.94%)	11/14 (78.57%)	3/14 (21.43%)	.138
Yes	17	1/7 (14.29%)	6/7 (85.71%)	4/10 (40%)	6/10 (60%)	.338
MELD score						
<25	23	8/10 (80%)	2/10 (20%)	12/13 (92.31%)	1/13 (7.67)	.56
≥25	25	1/14 (7.144%)	13/14 (92.86%)	3/11 (27.33%)	8/11 (72.67%)	.288

they developed it following severe acute liver injury as a secondary phenomenon. This is not surprising as it is known that autoimmune hepatitis can manifest acutely and may be undistinguishable both clinically and histologically from other causes of acute liver injury. Its diagnosis is difficult and rests on a full set of clinicopathological features that become available later in the course of the disease. We also found the presence of perivenulitis was associated with higher death/transplantation rate. Although a slight reduction in death/transplantation rate was observed after steroid therapy in those with perivenulitis (85.7%-60%), the difference did not reach statistical significance. Plasma cell infiltration and lymphoid follicles were also not found to be associated with steroid responsiveness. Taken together, these results suggest that in the patients with IAH with multilobular necrosis, early corticosteroid treatment is possibly indicated with clear stopping rules to prevent the risk of complications such as infection.

There are some limitations of this study. First, the sample size of this study was relatively small. This is not surprising as the disease condition being addressed here is rare especially with liver biopsy on admission. Second, some patients who were diagnosed as having IAH at first developed autoimmune hepatitis during follow-up and might have been misclassified. This may reflect real-world difficulties in diagnosing acute autoimmune hepatitis or propose that the IAH is predisposed to its subsequent development. Given the recruitment period for this study, anti-soluble liver antigen or human leukocyte antigen status were not routinely measured in our centre, which may have pointed to a diagnosis of AIH. Third, according to the EASL practice guidelines,[17] it is possible that 8 patients may have been misclassified as having IAH rather than acute autoimmune hepatitis. However, even in this subpopulation of patients, response to corticosteroids remained uncertain questioning the usefulness of the diagnostic criteria in the selection of patients for administration of corticosteroids. Fourth, the presence or absence of massive hepatic necrosis in a liver biopsy sample depends on sampling. The predictive value of massive hepatic necrosis in our series could reflect the extent of the liver parenchyma injury increasing the chance that areas of multilobular necrosis are represented in a core biopsy sample but sampling variation is a limiting factor when interpreting liver biopsies in this context.[6]

In conclusion, the results of this study suggest that although corticosteroids cannot be recommended for routine use in patients with IAH, a subgroup of patients with multilobular necrosis on liver biopsy may benefit from a trial of steroids. Large multicenter studies are needed to develop new algorithms for the management of this rare but clinically devastating condition.

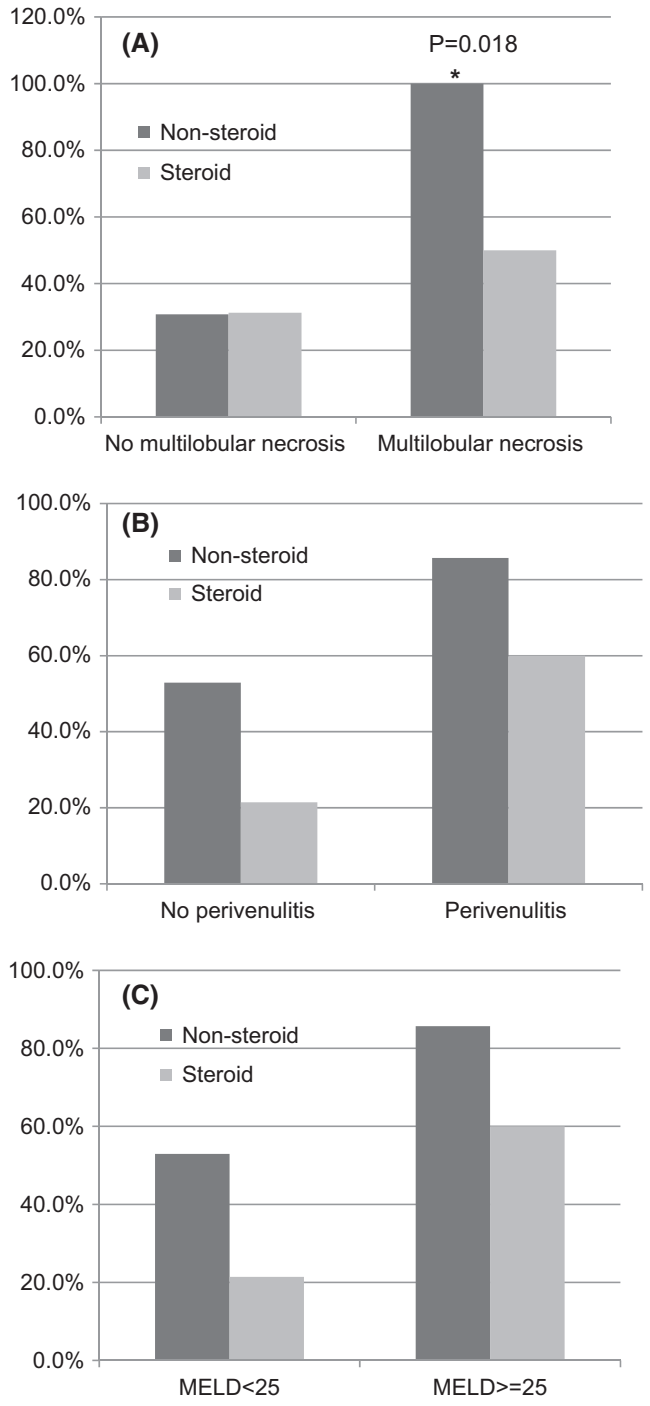

FIGURE 2 The death/transplantation rate in different subgroups

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CONFLICT OF INTERESTS

Rajiv Jalan has research collaborations with Takeda, and Yaqrit, and consults for Yaqrit. Rajiv Jalan is the founder of Yaqrit Limited, which is developing UCL inventions for the treatment of patients with cirrhosis. Rajiv Jalan is an inventor of ornithine phenylacetate, which was licensed by UCL to Mallinckrodt. He is also the inventor of Yaq-001, DIALIVE and Yaq-005, the patents for which have been licensed by his University into a UCL spinout company, Yaqrit Ltd. Cornelius Engelmann has ongoing research collaboration with Merz Pharmaceutical and Novartis. He has received speaker fees from Novartis, Gilead and Merz Pharmaceuticals.

AUTHORS' CONTRIBUTIONS

Study concept and design: Rajiv Jalan and Alberto Quaglia. Acquisition, cleaning and analysis of data: Su Lin and Alexandra Phillips. Histology staining: Andrew Hall and Mohsin Hassan. Histopathology review: Alberto Quaglia, Catarina Araujo and Andrew Hall. Drafting of the manuscript: Su Lin and Rajiv Jalan. Critical revision: Alberto Quaglia, Rahul Kumar and Cornelius Engelmann. Study supervision: Rajiv Jalan. All authors contributed to the manuscript for important intellectual content and approved the submission.

DATA AVAILABILITY STATEMENT

Anonymised raw data can be made available for scrutiny or future collaboration.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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