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Alcoholic hepatitis histological score has high accuracy to predict 90-day mortality and response to steroids

Patrícia Andrade[a,*], Marco Silva[a], Susana Rodrigues[a], Joanne Lopes[b], Susana Lopes[a], Guilherme Macedo[a]

[a] Gastroenterology Department, Centro Hospitalar São João, Porto, Portugal
[b] Pathology Department, Centro Hospitalar São João, Porto, Portugal

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ABSTRACT

Introduction/objectives: A histological classification system (AHHS) has been recently proposed to predict 90-day mortality in patients with alcoholic hepatitis (AH). We analyzed the spectrum of histological features in patients with AH and assessed the ability of AHHS for predicting both response to steroids and 90-day mortality.
Methods: Retrospective study of patients admitted to our tertiary centre between 2010 and 2014 with biopsy-proven AH. Histological features were analyzed and AHHS value was calculated. Kaplan–Meyer curves were calculated to assess the ability of AHHS to predict response to steroids and 90-day mortality.
Results: We included 34 patients (70.6% men, mean age 48.5 ± 8.9 years). Transjugular liver biopsy was performed 3.5 ± 2.9 days after admission. Presence of bilirubinostasis ($p = 0.049$), degree of bilirubinostasis ($p < 0.001$), absence of megamitochondria ($p < 0.001$) and degree of polymorphonuclear infiltration ($p = 0.018$) were significantly associated with higher mortality at 90 days. Patients who responded to steroids had a significantly lower AHHS value than non-responders (5.4 ± 0.9 *vs* 8.1 ± 1.1, $p = 0.003$). AAHS value was significantly higher in patients who died compared to patients who survived at 90 days (9.0 ± 0.7 *vs* 5.0 ± 0.9, $p < 0.001$). AHHS predicted response to steroids [AUROC 0.90 ($CI_{95\%}$ 0.742–1.000), $p = 0.004$] and 90-day mortality [AUROC 1.0 ($CI_{95\%}$ 1.0–1.0), $p < 0.001$] with high accuracy.
Conclusions: In this cohort of patients, presence and degree of bilirubinostasis, absence of megamitochondria and degree of PMN infiltration were significantly associated with 90-day mortality. AHHS had a high accuracy for predicting response to steroids and 90-day mortality in this cohort of patients.

1. Introduction

Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease in developed countries and is the leading cause of death among adults with excessive alcohol consumption [1,2]. Alcoholic hepatitis (AH) is the most severe form of ALD and often occurs on the background of cirrhosis in patients with high alcohol intake (alcohol consumption of >80 g alcohol/day for men and >60 g/day for women). Short-term mortality of AH remains high (20–40%), probably because of poor patient characterization and the need for modern targeted therapies [3–5].

A presumptive diagnosis of AH may be based on clinical (jaundice, coagulopathy and an appropriate history of heavy alcohol consumption) and biochemical data but, to date, there are no reliable non-invasive diagnostic tools for AH and a definite diagnosis still requires histological confirmation [6].

Previous studies suggested a relationship between single histological parameters and patient's outcome [7–11]. However, AH was probably the only prevalent liver disease that lacked a well-validated histological classification providing both prognostic and clinically meaningful data. Recently, Altamirano et al. developed a novel histological scoring system (the alcoholic hepatitis histological score (AHHS)) capable of predicting short-term survival in patients with AH [12].

* Corresponding author at: Department of Gastroenterology, Faculty of Medicine, Centro Hospitalar São João, Alameda Prof. Hernani Monteiro, 4200-319 Porto, Portugal. Tel.: +351 22 551 3600; fax: +351 22 551 3601.
E-mail address: anapatriciarandrade@gmail.com (P. Andrade).

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The aim of this study was to analyze the spectrum of histological features in a cohort of patients with AH and assess the ability of AHHS to predict both response to therapy and 90-day mortality.

2. Material and methods

2.1. Population

This was a retrospective study conducted at our tertiary referral centre (Centro Hospitalar São João, Porto, Portugal) between January 2010 and December 2014. All patients with clinical and biochemical parameters suggestive of AH were reviewed. Inclusion criteria were: (i) age > 18 years; (ii) excessive alcohol consumption (alcohol consumption >80 g/day for men and >60 g/day for women) before admission; (iii) moderate elevation (5–10 times upper limit of normal) of transaminases with aspartate aminotransferase higher than alanine aminotransferase; (iv) high gamma-glutamyl transpeptidase and bilirubin levels; (v) absence of additional aetiology for liver disease; (vi) histologic diagnosis of AH.

Demographic, clinical and laboratory parameters were obtained from electronic medical records. All liver samples were obtained by transjugular approach between days 1 and 7 of admission after written informed consent. Liver specimens were formalin fixed and paraffin embedded, and 3-mm slides were stained with H&E and Masson trichrome. Only specimens with a minimum of 6 portal tracts were analyzed. Two expert liver pathologists analyzed all biopsy specimens and upon agreement the following histologic features were recorded, at the time of the original liver biopsy report: (i) presence of hepatocellular damage/ballooning (absent or present); (ii) presence of Mallory bodies (absent or present); (iii) degree of polimorphonuclear (PMN) infiltration (absent, mild, moderate, severe); (iv) degree of steatosis (absent, mild, moderate, severe); (v) presence of megamitochondria (absent or present); (vi) presence and location of bilirubinostasis (absent, hepatocellular bilirubinostasis; canalicular or ductular bilirubinostasis; hepatocellular plus canalicular or ductular bilirubinostasis); (vii) stage of fibrosis (no fibrosis; portal fibrosis; expansive fibrosis; bridging fibrosis; cirrhosis). After analyzing and recording histological features individually, the AHHS value was calculated for each patient. AHHS included the stage of fibrosis, degree of bilirubinostasis, degree of polymorphonuclear infiltration and presence/absence of megamitochondria. The outcomes analyzed were the ability of AHHS to predict response to steroids and 90-day mortality.

All patients received supportive therapy including nutrition and vitamin supplementation. Patients who developed complications during hospitalization were treated according to international guidelines and local protocols: spontaneous bacterial peritonitis (empirical antibiotics started immediately following the diagnosis and targeted antibiotics after culture plus albumin 1.5 g/kg at diagnosis and 1 g/kg on day 3) and hepatorenal syndrome (terlipressin 0.5–2 mg intravenously, up to six times daily with 60 g salt-poor albumin). Patients with a Maddrey's discriminant function >32 were treated with prednisone 40 mg orally for 4 weeks. The response to corticosteroid treatment was assessed at day 7 using the Lille model.

2.2. Statistical analysis

SPSS 22.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis. Categorical variables were described as absolute frequencies (n) and relative frequencies (%); continuous variables were described as mean ± standard deviation (parametric distributions) or as median and percentiles (non-parametric distributions). The normality of the continuous variables was tested using the Kolmogorov–Smirnov test and the respective histogram. Student's t test was used to compare quantitative variables with a normal distribution, and the Mann–Whitney U test was used to compare the quantitative variables without a normal distribution. Any groups with more than two quantitative variables were compared using the Kruskal–Wallis test. A Pearson Chi-square test was used to compare categorical variables. Spearman's rank order correlation test (r_s) was used to assess correlation between AHHS and clinical scoring systems. The statistical significance of survival data using the Kaplan–Meyer curves was tested using the log-rank test. Statistical significance was set at p value <0.05.

3. Results

3.1. Patients

Thirty-four patients with biopsy-proven AH met the inclusion criteria and were included in this study. Mean age of patients was 48.5 ± 8.9 years, and 24 (70.6%) were men. Mean time between admission and transjugular liver biopsy was 3.5 ± 2.9 days. No major complications related to procedure were recorded. Demographic, clinical and biochemical data are summarized in Table 1.

Eighteen patients (52.9%) were treated with steroids; of these 11 (61.1%) responded to therapy according to Lille score, and completed four weeks of treatment with prednisone 40 mg/day. Overall, 21 patients (61.8%) developed a complication during hospitalization: 15 patients (44%) developed infection, 12 patients (35%) had an episode of overt hepatic encephalopathy, 9 patients (26%) developed renal failure patients and 4 patients (12%) had gastrointestinal bleeding. The overall 90-day mortality was 29.4% (Table 1). All patients died during hospital admission (8 during the first hospitalization and two after hospital readmission). Patients were closely followed at our outpatient clinic after hospital discharge. Median follow-up time was 28.5 (IQR 15.7–37.2) months. During follow-up, three other patients died (46, 56 and 90 weeks after initial

Table 1
Baseline demographic, clinical and laboratorial characteristics of patients (n = 34).

Age, years, median (SD)	48.5 ± 8.9
Male, n (%)	24 (70.6)
Time until TJLB	3.5 ± 2.9
Major complications related-TJLB	0 (0.0)
Laboratory parameters, mean (SD)	
Haemoglobin (g/dL)	10.5 ± 2.7
Leucocyte count (g/dL)	9.5 ± 7.4
Platelet count ($\times 10^9$/L)	94.0 ± 62.4
Aspartate aminotransferase (U/L)	146.5 ± 73.8
Alanine aminotransferase (U/L)	74.5 ± 45.2
Serum bilirubin (mg/dL)	10.3 ± 7.1
Serum albumin (g/dL)	27.3 ± 5.3
Serum creatinine (mg/dL)	0.8 ± 0.5
Serum Na^+ (mEq/L)	134.0 ± 5.0
International normalized ratio	1.7 ± 0.4
Clinical severity scoring systems at admission, points, mean (SD)	
MELD score	20.6 ± 6.2
ABIC score	7.4 ± 1.8
GAHS score	7.6 ± 1.5
Maddrey discriminant function	62.3 ± 46.4
Lille score	0.5 ± 0.4
Therapy with steroids, n (%)	18 (52.9)
Response to steroids, n (%)	11 (32.4)
Complications during hospitalization, n (%)	
Infection	15 (44)
Hepatic encephalopathy	12 (35)
Renal failure	9 (26)
Gastrointestinal bleeding	4 (21)
Overall mortality rate at 90-days, n (%)	10 (29.4)

ABIC: age-bilirubin-INR-creatinine; GAHS: Glasgow alcoholic hepatitis score; MELD: model for end-stage liver disease; SD: standard deviation; TJLB: transjugular liver biopsy.