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CLINICAL—LIVER

A Histologic Scoring System for Prognosis of Patients With Alcoholic Hepatitis

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This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of this CME activity, successful learners will understand and apply a new scoring system to assess the prognosis of patients with alcoholic hepatitis.

See editorial on page 1156.

BACKGROUND & AIMS: There is no histologic classification system to determine prognoses of patients with alcoholic hepatitis (AH). We identified histologic features associated with disease severity and created a histologic scoring system to predict short-term (90-day) mortality. **METHODS:** We analyzed data from 121 patients admitted to the Liver Unit (Hospital Clinic, Barcelona, Spain) from January 2000 to January 2008 with features of AH and developed a histologic scoring system to determine the risk of death using logistic regression. The system was tested and updated in a test set of 96 patients from 5 academic centers in the United States and Europe, and a semiquantitative scoring system called the Alcoholic Hepatitis Histologic Score (AHHS) was developed. The system was validated in an independent set of 109 patients. Interobserver agreement was evaluated by weighted κ statistical analysis. **RESULTS:** The degree of fibrosis, degree of neutrophil infiltration, type of bilirubinostasis, and presence of megamitochondria were independently associated with 90-day mortality. We used these 4 parameters to develop the AHHS to identify patients with a low (0–3 points), moderate (4–5 points), or high (6–9 points) risk of death within 90 days (3%, 19%, and 51%, respectively; $P < .0001$). The AHHS estimated 90-day mortality in the training and test sets with an area under the receiver operating characteristic value of 0.77 (95% confidence interval, 0.71–0.83). Interrater agreement values were 0.65 for fibrosis, 0.86 for bilirubinostasis, 0.60 for neutrophil infiltration, and 0.46 for megamitochondria. Interestingly, the type of bilirubinostasis predicted the development of bacterial infections. **CONCLUSIONS:** We identified histologic features associated with the severity of AH and developed a patient classification system that might be used in clinical decision making.

Keywords: Alcoholic Hepatitis; Alcoholic Liver Disease; Histologic Classification; Liver Biopsy.

Alcoholic hepatitis (AH) is the most severe form of alcoholic liver disease.[1] The short-term mortality of AH remains high (20%–30%), probably because of poor patient characterization and the need for modern targeted therapies.[2]

Abbreviations used in this paper: **ABIC, age/bilirubin/international normalized ratio/creatinine; AH, alcoholic hepatitis; AHHS, Alcoholic Hepatitis Histologic Score; CI, confidence interval; HVPG, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease; PMN, polymorphonuclear.**

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Current therapies (ie, corticosteroids and pentoxifylline) fail in many patients, and there is a clear need to develop new pathophysiologically oriented approaches. Although the presence of AH can be suspected based on clinical and biochemical data, a definitive diagnosis requires histologic confirmation.[3] Regretfully, there are no well-validated noninvasive methods to establish the diagnosis of AH.

Despite the huge burden of alcoholic liver disease and the prevalence of AH, research into this disease has been limited.[4] Although prognosis can be estimated based on biochemical parameters,[2,5–7] AH is probably the only prevalent liver disease that lacks a well-validated histologic classification that can provide both prognostic and clinically meaningful data. Identifying key histologic parameters associated with patient outcomes can inform translational studies and also reveal key disease drivers. Histologic classification schemes exist for other prevalent liver diseases, such as chronic viral hepatitis, nonalcoholic steatohepatitis, autoimmune hepatitis, and primary biliary cirrhosis.[8–12] The present study attempts to fill an important gap in the field of AH. We performed a large multicentric study, including some of the main experts in this field, to develop a novel histologic classification. Study, testing, and validation cohorts of patients with biopsy-proven AH were included.

Some reports show that isolated histologic findings can reflect disease severity in patients with AH.[13–17] However, no studies have integrated these parameters to develop a meaningful histologic classification. Thus, the aims of this study were to investigate how the interaction of individual histologic features of AH predicts survival and if it can be used to generate and validate a novel histologic scoring system.

Subjects and Methods

Study Cohort

A total of 181 consecutive patients admitted to the Liver Unit (Hospital Clinic, Barcelona, Spain) from January 2000 to January 2008 with clinical and analytical parameters suggesting an episode of AH were studied. The inclusion criteria were excessive alcohol consumption (>60 g/day) before admission, moderately elevated aminotransferase levels with the aspartate aminotransferase level greater than the alanine aminotransferase level, high γ-glutamyl transpeptidase and serum bilirubin levels, and a histologic diagnosis of AH characterized by the presence of hepatocellular damage (hepatocellular ballooning and presence of Mallory bodies), inflammatory infiltrate (predominantly polymorphonuclear cells), and pericellular fibrosis.[2,18] All patients who gave informed consent underwent a liver biopsy within 48 hours of admission as part of our clinical protocol. Sixty patients were not included because of other causes of liver disease (concomitant hepatitis C virus, n = 16; concomitant hepatitis C virus/human immunodeficiency virus coinfection, n = 3; drug-induced hepatotoxicity, n = 4; hemochromatosis, n = 1; military tuberculosis, n = 1; and syphilitic hepatitis, n = 1) or incomplete histologic criteria of AH (n = 34). After histologic confirmation and a strict evaluation of inclusion and exclusion criteria, 121 patients with biopsy-proven AH were included in the training set.

Severe AH was defined as a Maddrey's discriminant function >32 and/or an age/bilirubin/international normalized ratio/creatinine (ABIC) score ≥6.71 at admission.[2] Patients with a Maddrey's discriminant function >32 were treated with prednisone orally for 4 weeks, followed by a 2-week taper period. During hospitalization, patients with clinical complications such as ascites, spontaneous bacterial peritonitis, renal dysfunction, overt hepatic encephalopathy, or gastrointestinal bleeding associated with portal hypertension were treated according to current international guidelines.[19–22] The Ethics Committee of the Hospital Clinic Barcelona approved the study, and all patients gave written informed consent.

Histologic, Clinical, and Hemodynamic Assessment

Demographic, clinical, and analytical parameters were collected for creation of a comprehensive database as described previously.[2,23] The response to corticosteroid treatment was assessed at 7 days using the Lille model.[24] All liver biopsy specimens in the training set were obtained by the transjugular approach within 48 hours of admission. Liver specimens were formalin fixed and paraffin embedded, and 3-μm slides were stained with H&E and Masson trichrome. An expert liver pathologist (R.M.) reviewed all biopsy specimens and was blinded. A detailed histologic analysis was prospectively performed and included the following: (1) degree of hepatocellular damage/ballooning (0, mild; 1, marked), (2) presence of Mallory bodies (0, absent; 1, present), (3) degree of polymorphonuclear (PMN) infiltration (0, mild; 1, moderate/severe), (4) degree of steatosis (0, <33%; 1, 33%–66%; 2, >66%), (5) lobular fibrosis (0, no fibrosis or zone 3; 1, fibrosis in zones 2 and 3; 2, panlobular fibrosis), (6) fibrosis stage (0, no fibrosis or portal fibrosis; 1, expansive periportal fibrosis; 2, bridging fibrosis and cirrhosis), (7) megamitochondria (0, no; 1, yes); and (8) presence and site of bilirubinostasis (0, none; 1, hepatocellular bilirubinostasis; 2, canalicular or ductular bilirubinostasis; 3, hepatocellular plus canalicular or ductular bilirubinostasis).[25] See the Supplementary Methods for a detailed explanation of histologic evaluation. Hepatic hemodynamic assessment was performed within 48 hours of admission. The portal pressure was estimated based on the hepatic venous pressure gradient (HVPG), as described in detail previously.[26]

Test and Validation Sets

Five international academic centers contributed 205 consecutive additional patients with AH (University Hospital Gasthuisberg, KU Leuven, Belgium; Mayo Clinic, Rochester, MN; Hospital General Universitario Gregorio Marañón, Madrid, Spain; Hôpital Huriez, Lille, France; and Royal Free Hospital, London, England). These patients constituted the test set and validation cohort (see details in the Supplementary Methods). All participant centers followed the same inclusion/exclusion criteria outlined in the preceding text for the training set. In all of these centers, most of the biopsies were performed within 48 hours of admission and were processed and analyzed in the same way as in the training set (see Statistical Analysis for details).

The histologic assessment of liver specimens was performed by expert liver pathologists. Liver specimens from Lille (France) were fixed with alcohol/formalin/acetic acid, and the rest of the liver specimens were fixed as in the study cohort. Importantly, to ensure a homogeneous histologic assessment of all biopsy specimens, a detailed training plan was performed between the central pathologist (R.M.) and all local