Research Article

JOURNAL OF HEPATOLOGY

Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease

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Background & Aims: Few data exist on predictors of long-term prognosis in patients with alcoholic liver disease (ALD). Most studies have only assessed short-term prognosis in patients with advanced ALD. We aimed to assess the prognostic impact of clinical, biochemical and histological parameters on long-term prognosis in patients with early/compensated and decompensated ALD.

Methods: Consecutive patients (n = 192) with biopsy-proven liver disease due to alcohol abuse were analyzed retrospectively. Prognostic factors were evaluated in patients with early/compensated ALD (n = 60) and in patients with decompensated ALD (clinical decompensation and/or bilirubin >3 mg/dl at entry) (n = 132). Factors that predict long-term survival were identified using Cox regression models.

Results: Liver-related mortality at 5 years was 13% in early/compensated and 43% in decompensated ALD. In early/compensated ALD patients, long-term prognosis was determined by fibrosis stage, but not by clinical or biochemical variables. Severe fibrosis (F3/4) was present in 52% and had a major impact on 10-year mortality (F3/4: 45% *vs.* F0-2: 0%, p <0.001). In contrast, in decompensated patients, a combination of clinical features (sex), biochemical markers of liver failure (bilirubin, international normalized ratio [INR]), and histological features (pericellular fibrosis) predicted long-term survival. During follow-up, abstinence from alcohol was an important predictor of survival in both early/compensated and decompensated ALD.

Conclusion: Fibrosis stage is the main predictor of long-term survival in patients with early/compensated ALD, while clinical, biochemical and histological parameters predict survival in patients with decompensated disease. Promoting abstinence may improve survival in patients with both early and advanced ALD.

Lay summary: In this study, we evaluated long-term outcome in 192 patients with alcoholic liver disease who underwent liver biopsy: 60 patients with early disease (no symptoms) and 132 patients with advanced disease (jaundice, complications of cirrhosis). Importantly, half of the patients with 'early' disease already had severe fibrosis or cirrhosis on liver histology and dismal outcome (45% mortality at 10 years). Abstinence from alcohol improved the prognosis in both early and advanced stages of the disease.

Introduction

Alcoholic liver disease (ALD) is a substantial burden on public health and is responsible for half of the cases of cirrhosis worldwide [1,2]. Despite its health and socioeconomic burden, there have not been major advances in the management of these patients. There are no widespread programs for early detection and the current therapy for its more severe form (i.e., prednisolone for alcoholic hepatitis) has not evolved since 1971 [3,4]. The complex pathogenesis of ALD, influenced by host and environmental factors, is only partially understood. ALD comprises a spectrum of diseases, which is classified histologically as alcoholic fatty liver, alcoholic steatohepatitis (ASH) and alcoholic cirrhosis. ASH paves the way for the development of cirrhosis and eventually hepatocellular carcinoma (HCC) [5]. In addition, patients with underlying ALD and heavy alcohol drinking can develop a form of acute-on-chronic liver failure called alcoholic hepatitis (AH).

Most patients with ALD are diagnosed at late stages when liver-related decompensation develops. As a consequence, most research attention has been focused on late phases of the disease associated with high short-term mortality. In contrast, very few

Keywords: Liver diseases; Alcoholic; Hepatic fibrosis; Biopsy; Liver failure; Retrospective studies.
Received 3 May 2016; received in revised form 6 November 2016; accepted 9 November 2016; available online 25 November 2016

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studies have assessed clinical and histological parameters that predict disease progression in patients with early fully compensated ALD [6]. This fact is heavily influenced by the reluctance to perform liver biopsies in patients with a "self-inflicted" disease such as ALD. The low level of early clinical diagnosis, together with the rare utilization of liver biopsy, may be responsible for the under diagnosis and limited histological characterization of early ALD. In clear contrast, many large studies have characterized the histological parameters that influence the prognosis of patients with non-alcoholic fatty liver disease (NAFLD), another disease caused by an unhealthy lifestyle that shares many pathogenic and histological features with ALD [7].

In patients with advanced ALD, most studies have assessed factors that predict short-term mortality, while determinants of long-term outcome are largely unknown. Mortality from ALD mostly results from complications of cirrhosis and/or HCC. While some patients develop liver-related decompensation in a slowly progressive manner, others show an abrupt onset of jaundice and complications leading to early mortality. These latter patients often suffer from an episode of AH, a unique syndrome of patients with ALD [8,9]. A number of non-invasive prognostic models have been developed mainly to stratify patients with decompensated ALD and superimposed AH in groups with low and high short-term mortality risk at 1–3 months [10–16]. Similarly, a recent study identified histological parameters that predict short-term survival in patients with AH [17]. Whether these analytical and histological parameters also impact long-term survival is unknown.

The present study aimed to fill this gap and to identify the biochemical, clinical and histological parameters that predict the outcome of patients with early/compensated as well as decompensated ALD.

Patients and methods

Study cohort

In this retrospective study, we investigated consecutive patients treated at the Division of Gastroenterology and Hepatology, Medical University of Graz, between 1995 and 2009 with clinically suspected ALD based on heavy drinking (>60 g/day for men and >30 g/day for women) [1,18]. Part of this cohort underwent liver biopsy to establish the diagnosis and/or to assess the stage of the disease according to clinical practice guidelines [19,20]. Specifically, indications for liver biopsy included classification of the ALD types, i.e., alcoholic steatosis, ASH, and alcoholic cirrhosis and/or differentiation from other etiologies of liver disease. The study cohort comprised patients with early/compensated ALD (fully compensated liver disease, bilirubin <3 mg/dl) as well as decompensated ALD with clinically suspected AH defined as presence of liver-related decompensation (i.e., ascites, variceal bleeding) and/or an abrupt increase in bilirubin $\geqslant$3 mg/dl. Liver biopsy was obtained within one week after admission in decompensated and within 4 weeks in early/decompensated ALD. Percutaneous liver biopsy was performed in most cases, while in some patients with severe coagulation impairment, a transjugular procedure with three passes was preferred. Patients with concomitant clinical etiologies of liver disease, other histological diagnoses than ALD, or lack of a representative liver biopsy (fragmentation and/or artificial alteration of the biopsy core rendering the material unsuitable for assessing lobular architecture) were excluded. Concomitant liver diseases included: chronic hepatitis B virus or hepatitis C virus (HCV) infection, predominantly NAFLD, hemochromatosis, chronic pancreatitis, HCC, extrahepatic malignoma.

Clinical and biochemical data at the time of liver biopsy were carefully obtained from the medical charts and included demographic data, alcohol consumption, ascites, gastrointestinal bleeding, hepatic encephalopathy, routine parameters of liver and kidney function as well as hematological parameters. Non-invasive short-term prognosis scores for advanced ALD including Maddrey's discriminant function [10,11] and model for end-stage liver disease (MELD) [12] were calculated. In addition, the Child-Pugh score [21] was assessed.

All patients were advised to abstain from alcohol. In patients surviving their index admission, alcohol abstinence was evaluated based on the patients' self-report, as well as interviews of family members and primary care doctors. Hospitalized patients received standard care, including intensive care support when indicated. According to our local policy during the study period, none of the patients with severe AH received corticosteroids or pentoxifylline.

Patients were followed until death or censoring using follow-up data collected in the liver clinic as well as data from a national registry of deaths with patients censored as per 31st of December 2009. Patients who underwent liver transplantation during follow-up were censored at the time of transplantation.

The primary outcome variable of liver-related death comprised the diagnoses "alcoholic cirrhosis", "hepatorenal syndrome", "liver failure", "hepatic encephalopathy", "hepatic decompensation", "hepatocellular carcinoma" and "esophageal variceal bleeding".

The study was approved by the Ethics Committee of the Medical University of Graz and performed in accordance with the Declaration of Helsinki.

Histological assessment

Dewaxed sections (3 μm thick) were stained with hematoxylin and eosin (H&E), chromotrope aniline blue (CAB; connective tissue stain) or prussian blue (iron stain), respectively using standard procedures. All slides were reviewed by two expert pathologists (CL and JH) in consensus using a multiheaded microscope, and blinded to patient characteristics and outcome. Morphological features of ALD, macro- and microvesicular steatosis, portal inflammation, lobular inflammation, ductular reaction, canalicular cholestasis, ductular cholestasis, hepatocellular ballooning, Mallory-Denk bodies, apoptosis, megamitochondria as well as fibrosis stage and pericellular fibrosis were assessed semi-quantitatively by application of numerical scores. Cirrhosis was diagnosed in cases with regenerative parenchymal nodules surrounded by fibrous septa. The histological diagnosis of ASH was based on the minimal criteria of presence of steatosis (any degree), hepatocellular ballooning and lobular inflammation [22].

Statistical analysis

The statistical analyses were performed separately for the early/compensated and decompensated ALD groups. For continuous variables, median and range (minimum to maximum) are displayed, categorical data are presented as relative frequencies. The effect of prognostic variables on liver-related mortality was analyzed by the Kaplan-Meier method and compared by log-rank test. Furthermore, univariate Cox regression analysis was performed. Multicollinearity was checked using the variance inflation factors (VIF). Apart from histological ASH, hepatocellular ballooning and Mallory-Denk bodies, no multicollinearity could be identified (VIF <4). Therefore, histological ASH but neither hepatocellular ballooning nor Mallory-Denk bodies were entered in subsequent multivariate analyses. Baseline variables that were associated with liver-related mortality in univariate analysis ($p \leqslant 0.20$) were included as potential covariates in a Cox proportional hazards regression analysis using forward selection. For statistical analyses, SPSS Statistics 23 software (IBM® Corporation, USA) was used.

Results

Clinical, biochemical and histological characteristics of the patients

Between 1995 and 2009, 780 consecutive patients with a clinical diagnosis of ALD were seen at our institution. Of these, 250 patients underwent liver biopsy mostly for staging of fibrosis, classification of the histological ALD types, alcoholic steatosis and ASH, respectively and/or differential diagnosis. Patients with clinical, biochemical or serological evidence of another potential cause of chronic liver disease (n = 49, mainly concomitant HCV infection), other histological diagnosis than ALD (n = 3), and cases with insufficient biopsy material (n = 6) were excluded. Thus, the final study cohort consisted of 192 patients with histologically confirmed ALD (Fig. 1). Patients were followed-up for a median