Research Article
NAFLD and Alcohol-Related Liver Diseases

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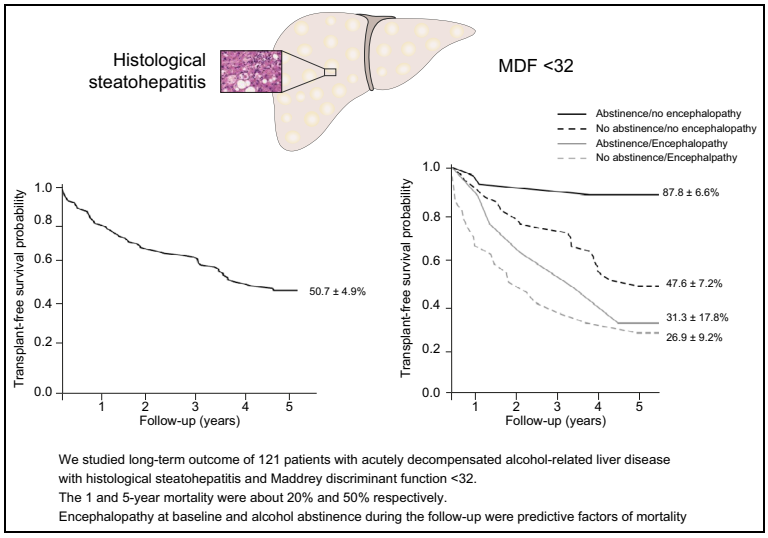
Long-term outcomes in patients with decompensated alcohol-related liver disease, steatohepatitis and Maddrey's discriminant function <32

Graphical abstract



Highlights

- Patients with non-severe alcoholic hepatitis have a low risk of short-term mortality.
- The 5-year mortality of decompensated patients with alcoholic steatohepatitis and an mDF <32 is about 50%.
- Hepatic encephalopathy and lack of alcohol abstinence impair long-term prognosis.

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Lay summary

Patients with alcoholic hepatitis that is of intermediate severity have a low risk of short-term mortality but not much is known regarding long-term outcomes for these patients. This study clearly indicates that patients with intermediate disease characteristics have poor long-term outcomes. The presence of hepatic encephalopathy at the time of diagnosis and the absence of alcohol abstinence during follow-up are factors that predict poor long-term mortality.

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NAFLD and Alcohol-Related Liver Diseases

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Long-term outcomes in patients with decompensated alcohol-related liver disease, steatohepatitis and Maddrey's discriminant function <32

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Background & Aims: Patients with alcoholic hepatitis and a modified Maddrey's discriminant function (mDF) <32 have a low risk of short-term mortality. However, few data exist concerning long-term outcomes. The aims of this study were to evaluate 5-year survival rates and to identify predictive factors for long-term prognosis in this patient population.

Methods: We studied patients from 2 centers who were admitted for hepatic decompensation (ascites, hepatic encephalopathy, or jaundice) and who had histological findings of steatohepatitis and an mDF <32. Clinical and biological parameters were recorded at the time of liver biopsy and alcohol consumption was recorded during follow-up. We performed Cox proportional hazard survival analysis to identify factors associated with 5-year survival.

Results: One hundred and twenty-one patients were included (male: 64%, mean age: 51.5 ± 10.3 years, presence of cirrhosis: 84%). The median model for end-stage liver disease and mDF scores were 14 (IQR 11.7–16.1) and 19 (IQR 11.1–24), respectively. During follow-up, 30% of the patients remained abstinent. Survival rates at 1, 6, 12, 24, and 60 months were 96.7 ± 1.6%, 90.1 ± 2.7%, 80.8 ± 3.6%, 69.9 ± 4.3%, and 50.7 ± 4.9%, respectively. The majority of deaths (80%) were liver related. In multivariable analysis, encephalopathy at baseline and alcohol abstinence were predictive of 5-year survival. The 5-year survival rates of patients without and with encephalopathy at baseline were 60.5 ± 5.8% and 29.7 ± 8.0%, respectively, and the 5-year survival rates of abstinent and non-abstinent patients were 74.0 ± 8.0% and 40.9 ± 5.8%, respectively.

Conclusions: The mortality rate of patients with alcoholic hepatitis and an mDF <32 is around 50% at 5 years. Hepatic encephalopathy at baseline and lack of alcohol abstinence impair long-term prognosis. New treatment strategies, including measures to ensure abstinence, are required.

Lay summary: Patients with alcoholic hepatitis that is of intermediate severity have a low risk of short-term mortality but not much is known regarding long-term outcomes for these patients. This study clearly indicates that patients with intermediate disease characteristics have poor long-term outcomes. The presence of hepatic encephalopathy at the time of diagnosis and the absence of alcohol abstinence during follow-up are factors that predict poor long-term mortality.

Introduction

Excessive alcohol consumption is a major public health problem and alcohol-related liver disease (ALD) is the most common cause of cirrhosis in the Western world.[1] ALD presents as a broad spectrum of disorders including simple steatosis, alcoholic hepatitis (AH), and cirrhosis. Patients with severe AH, defined as modified Maddrey's discriminant function (mDF) >32, have high short-term mortality[2] and may benefit from specific therapies, such as corticosteroids, that improve short-term survival.[3–6] It has been previously shown that severity scores, including the model for end-stage liver disease (MELD) and the Lille score, predict short-term mortality in patients with severe AH treated with corticosteroids and that alcohol abstinence is the main predictor of long-term survival.[7–9] Patients with AH and an mDF <32 have less than a 10% risk of 1-month mortality[3] and are typically not considered for specific therapy. However, the definition of AH severity is based on old studies and the evolution of non-severe forms of AH is still uncertain. Indeed, the long-term outcomes for these patients and the factors influencing their long-term survival remain largely unknown. The few studies that have evaluated the survival of these patients beyond 1 month reported 3-month mortality rates between 5% and 15%[10–13] and a 1-year mortality rate of about 15%.[13,14] Nevertheless, in these studies, prognostic factors for mortality were not evaluated and new data are needed to guide patient care.

Keywords: Non-severe; Alcoholic hepatitis; Long-term survival; Encephalopathy; Abstinence; ASH.
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The present study aimed to evaluate the long-term (5-year) survival of patients admitted with symptomatic AH and an mDF <32 and to identify prognostic factors of long-term mortality in these patients. For this purpose, we analyzed predictive factors of long-term mortality in a unique cohort of patients with biopsy-proven alcohol-related steatohepatitis (ASH) from 2 centers, admitted for recent liver decompensation, who had an mDF <32.

Patients and methods

This was a retrospective study using prospective databases of patients consecutively admitted to either the Department of Gastroenterology and Hepatology of CUB Hôpital Erasme, Brussels, Belgium, or to the Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Austria. Patients considered for inclusion in this study were admitted for recent liver decompensation with biopsy-proven ASH and had an mDF<32.

Indications for liver biopsy in the 2 centers were occurrence of recent liver decompensation to demonstrate or exclude ASH, the need for staging of fibrosis when there was a suspicion of advanced fibrosis or cirrhosis without obvious morphological or biological signs of cirrhosis, or when the diagnosis of alcoholic liver disease was not clear-cut to exclude other causes of liver disease.

In the Brussels cohort, between 2003 and 2014, 473 patients with recent liver decompensation underwent a liver biopsy, including 396 patients with histological ASH (332 had an mDF ≥32 and 64 had an mDF <32) and 77 patients without histological ASH. Among the patients without histological ASH, 21 patients had an mDF <32 and were included in the control group.

In the Graz cohort, during the 14-year inclusion period (1995-2009), a total of 411 patients were admitted for decompensation of ALD. Among those, 121 underwent a liver biopsy, which revealed the presence of histological ASH in 86 patients. Among the 86 patients with histological ASH, 57 had an mDF <32 and 29 had an mDF ≥32. Among the 35 patients without histological ASH, 17 had an mDF <32 and were included in the control group, while 18 had an mDF ≥32.

All patients had biopsy-proven ASH and an mDF <32 at the time of biopsy. All were admitted for acute decompensation defined as recent onset of jaundice and/or ascites and/or encephalopathy with or without coagulopathy. mDF scores were consistently <32 throughout the admission in all but 1 patient. This patient had an mDF >32 at the time of admission that decreased to <32 at the time of biopsy and thereafter. This patient was thus considered to have “non-severe” AH.

The presence of ASH was defined by the presence of hepatocytes with ballooning degeneration with or without Mallory-Denk bodies and lobular infiltration by polymorphonuclear neutrophils.[15] In 116 patients with enough remaining stored liver tissue for additional histologic evaluation, we performed histological analysis to assess fibrosis stage, presence and site of bilirubinostasis, degree of polymorphonuclear infiltration and presence of megamitochondria, as previously described, to calculate the alcoholic hepatitis histological score (AHHS).[16]

The diagnosis of cirrhosis was based on liver biopsy findings and/or an unequivocal clinical and biochemical profile, a highly suggestive endoscopic exam, or typical imaging finding in agreement with current guidelines.[17]

Hepatic encephalopathy was defined by the presence of an overt encephalopathy with a minimum West Haven grade 2.[18] All patients had a history of excessive alcohol intake of 40 g/day or more for many years and other causes of liver disease such as viral hepatitis, autoimmune hepatitis, or hemochromatosis were excluded. Clinical, biological, endoscopic, morphological, and histologic parameters were recorded at the time of liver biopsy.

To assess the role of AH on patient prognosis, we compared the cohort of patients with ASH and an mDF <32 to a control group of patients with recent liver decompensation with an mDF <32 and without histological ASH.

The majority of patients underwent regular follow-up and alcohol consumption was recorded during each consultation. For other patients, relatives or general practitioners were contacted to obtain the missing information. Abstinence was defined by total cessation of alcohol use during the year after liver biopsy without any relapse, as previously reported.[19] Written informed consent was obtained from all patients and this study was approved by the local ethics committee at each institution.[20,21]

Statistical analysis

Continuous variables are expressed as mean ± SD and as median (IQR) for normal and skewed variables, respectively. Data were compared between groups using Student's *t* test or the Mann-Whitney *U* test, as appropriate. Categorical variables were studied using a 2-sided Chi-square test. The transplant-free survival of patients expressed as a percentage was assessed by the Kaplan-Meier method and differences between subgroups were assessed by log-rank test. Cox proportional hazard survival analysis was performed to identify factors associated with long-term mortality in patients with ASH admitted for recent liver decompensation with an mDF <32, and in the control group. Thereafter, we performed subgroup analysis to identify prognostic factors of long-term mortality in patients with ASH admitted for jaundice. Parameters with a p value <0.05 in univariate analysis were selected for inclusion in a multivariable Cox regression model. A p value <0.05 was considered statistically significant. Calculations were performed using SPSS 18.0 software (Chicago, IL, USA).

Results

Patient characteristics

The baseline features of the patients are shown in Table 1. Most patients were male (63.6%) with a mean age of 51.5 ± 10.3 years. The median MELD and mDF scores were 14 (11.7–16.1) and 19 (11.1–24), respectively. The majority of patients had cirrhosis (84.3%). Causes of decompensation were jaundice in 56.2%, and/or prothrombin time <50% in 7.4%, and/or clinical ascites in 59.5%, and/or clinical encephalopathy in 32.2%. After 3 months, 44.3% of the patients relapsed and 69% had relapsed after 5 years.

The histological characteristics of the patients are shown in Table 2. The median AHHS score was 6 [5-7]. Sixty-four patients had an AHHS score ≥6.

Survival

Patients were followed for a median time of 40 (12.3–77.2) months. During the 5 years of follow-up, 54 patients died after a median time of 467 (202–1,064) days. Among them, 43 patients died of liver-related complications including liver decompensation, sepsis related to liver failure, variceal bleeding, and hepatocellular carcinoma, while 8 patients died of non-hepatic causes

Table 1. Characteristics of patients with acutely decompensated alcohol-related liver disease, with histological steatohepatitis and mDF <32.

Parameters	Erasme center (n = 64)	Graz center (n = 57)	*p* value	Total population (n = 121)
Age (years)	55.1 ± 8.1	47.5 ± 11.2	<0.001	51.5 ± 10.3
Sex (F/M)	20/44	24/33	0.258	44/77
Cirrhosis (Y/N) (%)	57/7 (89.06)	45/12 (78.9)	0.141	102/19 (84.3)
MELD score	13.4 (11.6–15.4)	15.0 (12–18.8)	0.105	14 (11.7–16.1)
mDF	19.2 (12.8–24.7)	19.0 (7.5–24.0)	0.083	19.0 (11.1–24.0)
WBC (×10^3 cells/mm^3)	7.5 (6.1–10.4)	8.3 (5.8–11.4)	0.878	8.0 (6.0–11.0)
Neutrophil count (×10^3 cells/mm^3)	5.0 (3.9–7.4)	4.5 (3.6–8.6)	0.663	4.9 (3.8–8.0)
Platelet count (×10^3/mm^3)	164 (113.5–245)	153 (121–251.5)	0.995	161 (117.5–246)
Total bilirubin (mg/dl)	2.8 (1.8–4.5)	4.5 (1.8–8.5)	0.046	3.2 (1.9–6.4)
INR	1.3 (1.1–1.4)	1.2 (1.1–1.4)	0.035	1.3 (1.1–1.4)
Prothrombin time (%)	61 (53–76)	74 (63–90.5)	<0.001	70 (57–84.5)
Albumin (g/L)	32 (27–36)	33 (29–38)	0.124	32 (28–37)
Creatinine (mg/dl)	0.7 (0.6–0.9)	0.9 (0.7–1.0)	<0.001	0.8 (0.6–1.0)
ALT (IU/L)	36.5 (26.3–52)	40 (26–66)	0.511	37 (26–60)
AST (IU/L)	80.5 (59–121)	75 (48.5–139.5)	0.640	77 (55.5–129)
Sodium (mmol/L)	137 (134.5–140.5)	137 (135–139)	0.645	137 (135–140)
Ascites (Y/N) (%)	40/24 (62.5)	32/25 (56.1)	0.578	72/49 (59.5)
Encephalopathy (Y/N) (%)	24/40 (37.5)	15/42 (26.3)	0.243	39/82 (32.2)
Bilirubin >3 mg/dl (Y/N) (%)	30/34 (46.9)	38/19 (66.7)	0.043	68/53 (56.2)
PT <50% (Y/N) (%)	8/56 (12.5)	1/56 (1.8)	0.035	9/112 (7.4)
Abstinence during FU (Y/N) (%)	15/43 (25.8)	21/36 (36.8)	0.232	36/79 (31.3)
Follow-up (days)	1,047 (360–2,112)	1,414 (400–2,960)	0.061	1,218 (374–2,349)

Continuous variables are expressed as mean ± SD and as median (IQR) for normal and skewed variables. Data were compared using Student's *t* test or Mann-Withney *u* test. Categorical variables were studied using a 2-sided Chi-square test.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FU, follow up; INR, international normalized ratio; MDF, Maddrey's discriminant function; MELD, model for end-stage liver disease; PT, prothrombin time; WBC, white blood count. *p* = *p* value comparing variables of the 2 centers.

(4 neoplasia, 2 cranial trauma, and 2 cardiovascular disease). The cause of death was unknown for 3 patients. Five patients underwent a liver transplantation during follow-up after a median time of 272 (173–903) days.

Survival rates at 1, 3, 6, 12, 24 and 60 months were 96.7 ± 1.6%, 94.2 ± 2.1%, 90.1 ± 2.7%, 80.8 ± 3.6%, 69.9 ± 4.3%, and 50.7 ± 4.9%, respectively (Fig 1A).

Prognostic factors of 5-year mortality in patients with acutely decompensated ALD, histological steatohepatitis and mDF <32

Table 3 shows the results of the univariate analysis for identification of predictive factors of 5-year mortality in these patients.

Table 2. AHHS of patients with acutely decompensated alcohol-related liver disease, with histological steatohepatitis and mDF <32.

Characteristics	Points	Number of patients (%)
Fibrosis score		
No fibrosis or portal fibrosis	0	6 (5.2)
Expansive fibrosis	0	8 (6.9)
Bridging fibrosis or cirrhosis	+3	102 (87.9)
Bilirubinostasis		
No	0	68 (59.1)
Hepatocellular only	0	4 (3.5)
Canalicular or ductular	+1	26 (22.6)
Canalicular or ductular plus hepatocellular	+2	17 (14.8)
PMN score		
No/mild	+2	79 (68.1)
Moderate/severe	0	37 (31.9)
Megamitochondria score		
None	+2	77 (66.4)
Present	0	39 (33.6)
AHHS score		
0-3 points		6 (5.2)
4-5 points		45 (39.1)
6-9 points		64 (55.7)
Median AHHS score		6 [5-7]

AHHS, alcoholic hepatitis histological score; PMN, polymorphonuclear neutrophils.

Parameters associated with 5-year mortality were female sex, prothrombin time, platelet count, the presence of encephalopathy at baseline, and abstinence from alcohol during the follow-up. AHHS score was not predictive of long-term mortality. The 5-year mortality was 31.3 ± 24.5% for patients with AHHS between 0 and 3, 54.1 ± 7.9% for patients with AHHS 4 or 5, and 50.4 ± 6.7% for patients with AHHS between 6 and 9 ($p = 0.899$). After multivariable analysis, encephalopathy at baseline and alcohol abstinence remained associated with 5-year mortality (Table 4).

Five-year survival rates according to the presence of encephalopathy at baseline and/or abstinence during follow-up are shown in Fig. S1. The 5-year survival rates of patients with and without encephalopathy at inclusion were 29.7 ± 8.0% and 60.5 ± 5.8%, respectively ($p < 0.001$) and the 5-year survival rates of abstinent and non-abstinent patients during follow-up were 74.0 ± 8.0% and 40.9 ± 5.8%, respectively ($p = 0.003$).

Subgroup analysis of patients with AH and mDF <32 admitted for jaundice

In a second step, we studied prognostic factors of 5-year mortality in the subgroup of 68 patients with a clinical syndrome of AH characterized by jaundice (bilirubin level >3 mg/dl) in the 8 weeks prior to admission. The baseline characteristics of patients admitted with jaundice compared to patients without jaundice are shown in Table S1. Overall, MELD score, aminotransferase levels, and white blood counts were higher in patients with bilirubin >3 mg/dl. In contrast, the presence of coagulopathy, cirrhosis, and ascites were more frequent in patients without jaundice. mDF scores, the percentage of patients with encephalopathy, and abstinence rates were similar in the 2 groups. Concerning histological characteristics, there was no difference in median AHHS between patients with bilirubin level <3 mg/dl and those with bilirubin level ≥3 mg/dl. Bilirubinostasis was higher and megamitochondria were more frequent in patients

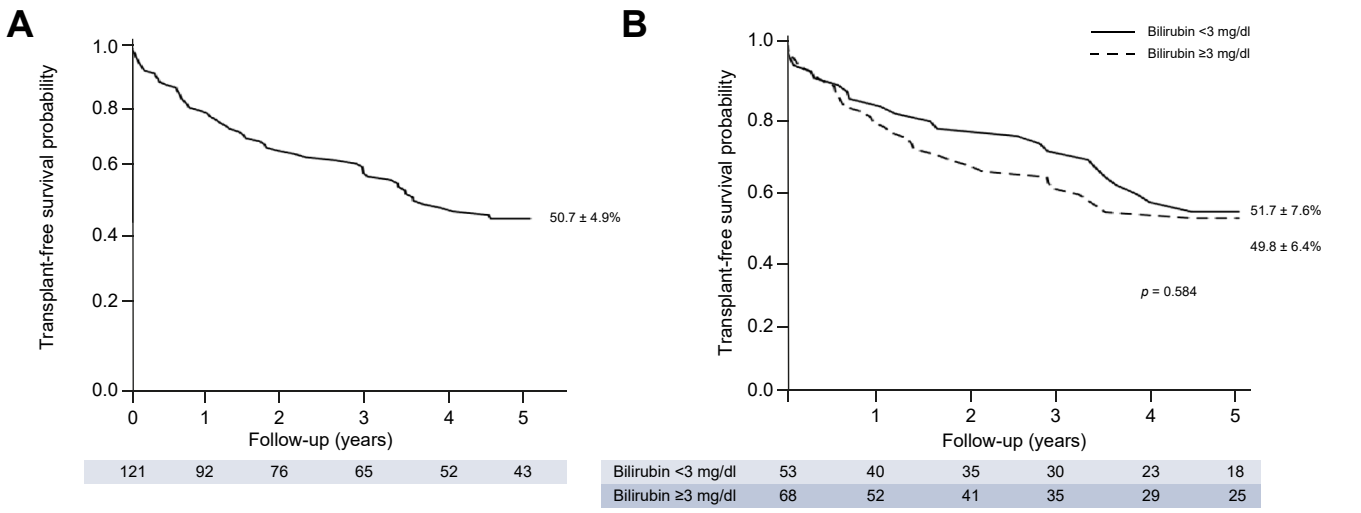

Fig. 1. Kaplan-Meier curves showing the probability of 5-year survival. (A) Kaplan-Meier curves showing the probability of 5-year survival in patients with acutely decompensated alcohol-related liver disease, with histological steatohepatitis and mDF <32. (B) Kaplan-Meier curves showing the probability of 5-year survival in patients with acutely decompensated alcohol-related liver disease, with histological steatohepatitis and mDF <32, with and without jaundice. The transplant-free survival of patients expressed as a percentage was assessed by the Kaplan-Meier method and differences between subgroups were assessed by log-rank test. A *p* value less than 0.05 was considered statistically significant. mDF, Maddrey's discriminant function.

with bilirubin ≥3 mg/dl. The 5-year survival of patients admitted with and without jaundice was similar (49.8 ± 6.4% *vs.* 51.7 ± 7.6%, $p = 0.584$) (Fig 1B).

Univariate analysis showed that abstinence from alcohol during follow-up (hazard ratio [HR] 0.38; 95% CI 0.14–0.98; $p = 0.046$) and presence of encephalopathy at baseline (HR 3.59; 95% CI 1.78–7.26; $p < 0.001$) were predictive factors of 5-year mortality in this population (Table S2). After multivariable analysis, abstinence (HR 0.39; 95% CI 0.15–1.00; $p = 0.050$) and encephalopathy (HR 3.84; 95% CI 1.89–7.82; $p < 0.001$) remained independently associated with 5-year mortality in patients with the clinical syndrome of AH (Table S3). The 5-year survival rates of these patients with and without encephalopathy at inclusion were 21.4 ± 9.3% and 62.8 ± 7.5%, respectively ($p < 0.001$), and the 5-year-survival rates of abstinent and non-abstinent patients during follow-up were 71.7 ± 10.9% and 39.2 ± 7.4 %, respectively ($p = 0.038$).

Table 3. Factors associated with 5-year mortality in patients with acutely decompensated alcohol-related liver disease, with histological steatohepatitis and mDF <32.

Variables	HR	95% CI	*p* value
Age	1.01	0.99–1.04	0.360
Female sex	1.74	1.02–2.97	0.043
Cirrhosis	1.75	0.75–4.09	0.198
MELD score	1.05	0.98–1.13	0.195
mDF	1.03	0.99–1.06	0.084
WBC	1.00	1.00–1.00	0.152
Neutrophil count	1.00	1.00–1.00	0.322
Platelet count	0.99	0.99–0.99	0.027
Total bilirubin	0.97	0.91–1.04	0.416
INR	4.63	0.94–22.74	0.059
Prothrombin time	0.98	0.97–0.99	0.027
Albumin	0.97	0.93–1.01	0.185
Creatinine	1.55	0.82–2.92	0.177
ALT	0.99	0.99–1.00	0.517
AST	1.00	0.99–1.00	0.921
Sodium	0.99	0.92–1.06	0.683
Ascites	1.26	0.72–2.19	0.414
Encephalopathy	2.75	1.61–4.72	<0.001
Abstinence during FU (Y /N)	0.34	0.16–0.73	0.005
AHHS score(continuous)	1.03	0.86–1.24	0.750
AHHS 0–3/4–5/6–9 score(categorical)	1.06	0.66–1.68	0.818

Cox proportional hazard survival analysis was performed to identify factors associated with 5-year mortality.

AHHS, alcoholic hepatitis histological score; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FU, follow-up; INR, international normalized ratio; MELD, model for end-stage liver disease; mDF, Maddrey's discriminant function; MM, megamitochondria; PMN, polymorphonuclear neutrophil; PT, prothrombin time; WBC, white blood count.

Patients with ASH and mDF <32 compared to control group with mDF <32 without ASH

The characteristics of patients in the control group are shown in Table S4. There was no difference between the ASH group and the control group with regard to age, sex, MELD score, presence of cirrhosis, ascites, encephalopathy, or abstinence. Five-year survival rates for patients with or without ASH were 50.7 ± 4.9% *vs.* 60.9 ± 9%, respectively ($p = 0.250$). Among patients without histological ASH, 9 patients died of liver-related complications, while 2 patients died as a result of cardiovascular events. The cause of death was unknown for 1 patient. Independent predictive factors of 5-year mortality in the control group were age (HR 1.096; 95% CI 1.021–1.176; $p = 0.011$) and presence of encephalopathy (HR 3.463; 1.092–10.983; $p = 0.035$).

Discussion

While the short-term prognosis for patients with AH and an mDF <32 is favorable,[3] data regarding the long-term outcomes for these patients are scarce, emphasizing the need for this study. The present study confirms that the risk of death at 1 and 3 months is about 5%, which is comparable to the limited data available in the literature, including a recent meta-analysis demonstrating the paucity of high-quality studies in patients with non-severe AH.[10–13] In contrast, the 1- and 5-year survival rates for patients with biopsy-proven ASH and an mDF <32 who were admitted for recent liver decompensation were only 80% and 50%, respectively. Therefore, the term “non-severe alcoholic hepatitis” is not appropriate for patients with symptomatic AH

Table 4. Multivariable analysis of predictive factors of 5-year mortality in patients with acutely decompensated alcohol-related liver disease, with histological steatohepatitis and mDF <32.

Variable	HR	95% CI	*p* value
Female sex	1.59	0.89–2.84	0.116
Platelet count	0.99	0.99–1.01	0.094
PT	0.99	0.98–1.01	0.762
Encephalopathy at baseline	2.33	1.30–4.18	0.004
Alcohol abstinence	0.38	0.17–0.86	0.020

Cox proportional hazard survival analysis was performed to identify factors associated with 5-year mortality.
HR, hazard ratio; mDF, Maddrey's discriminant function; PT, prothrombin time.

and an mDF <32 and we suggest using the term "alcoholic hepatitis of intermediate severity" to define this entity.

We identified the presence of hepatic encephalopathy at baseline as a predictive factor of long-term mortality and patients with encephalopathy have a risk of death at 5 years as high as 70%. It was previously shown that the presence of signs of liver decompensation such as ascites, encephalopathy, or variceal bleeding increases the risk of mortality in cirrhotic patients.[22,23] Moreover, in a Danish cohort of patients with alcohol-related cirrhosis, the 1-year mortality was 64% after clinical episodes of encephalopathy, worse than after other types of complication, such as ascites or variceal bleeding.[24] Interestingly, encephalopathy was used in some studies as a criterion of severity for patients with AH; patients with encephalopathy were treated with corticosteroids independently of their mDF score.[2,3,25]

We also identified alcohol abstinence as another predictive factor of long-term mortality in these patients. Patients who continue to drink alcohol after a diagnosis of "non-severe" AH had a risk of death at 5 years of about 60%. The persistence of alcohol consumption is well known as a predictive factor of death in patients with alcoholic cirrhosis.[26–29] Moreover, while scores of liver disease severity such as the MELD and Lille scores are prognostic of short-term mortality in patients with severe AH, alcohol relapse is a key factor of long-term mortality in this population.[7–9] The definition of abstinence varies in different studies. We defined abstinence as complete abstinence from alcohol within the year after liver biopsy without any relapse thereafter. In this study, about 45% of the patients relapsed after 3 months, and about 70% of the patients relapsed during follow-up. This result underlines the fact that recurrent alcohol intake occurs early after the initial episode of AH and emphasizes the need for a multidisciplinary approach to prevent alcohol relapse. Furthermore, the causes of non-liver-related death in our cohort were mostly due to cardiovascular disease, neoplasia, or cranial trauma, all factors that may themselves be related to alcohol consumption.

The presence of cirrhosis was not associated with the risk of death. This result, which may appear surprising, is likely related to the limited number of patients without cirrhosis in this study. In addition, we showed that AHHS was not predictive of long-term mortality. This score was developed to predict 3-month mortality in patients with more severe AH and its utility for predicting long-term outcomes has not been demonstrated. It should be noted that AHHS was also not predictive of 90-day mortality (data not shown), a result likely related to the low short-term mortality rate in our study population.

Our study is subject to several limitations. First, patients with non-severe AH constitute a heterogeneous population. We decided to study symptomatic patients with non-severe AH, defined as patients with histological steatohepatitis with an mDF <32 and with signs of liver decompensation. This definition may be debatable but is probably the most relevant to clinical practice. A potential selection bias of this study is related to the fact that some patients with an mDF <32 and signs of liver decompensation may have not had a liver biopsy. However, both cohorts were prospective and included patients with ALD consecutively admitted for acute decompensation, which makes us confident regarding the representativeness of our study population.

Since the common definition of AH includes the recent onset of jaundice,[30] we performed a subgroup analysis among patients with acute onset of jaundice. We showed that patients with jaundice had higher MELD scores, aminotransferase levels, and white blood counts. Coagulopathy, cirrhosis and ascites were more frequent in patients without jaundice, which was anticipated as these criteria were used to define acute decompensation of ALD. mDF, frequency of encephalopathy, and rates of abstinence were similar between patients with and without jaundice. Moreover, AHHS and 5-year survival of patients with and without jaundice at admission were similar. In this subgroup analysis, lack of alcohol abstinence and hepatic encephalopathy remained independently associated with the risk of death at 5 years, providing further confidence in the study results.

Another unsettled issue is whether the prognostic factors of long-term mortality identified in this population are specific to patients with ASH lesions or also apply to all patients with ALD, irrespective of the presence of ASH. We tried to assess this point by comparing our study population to a similar control group without histological ASH. However, defining a perfect control group is a difficult task. We have chosen to include patients with recent liver decompensation, an mDF <32, and no histological ASH. These patients were scarce because the majority of patients with decompensated ALD who underwent a liver biopsy either had histological ASH or had an mDF >32. We did not find any significant differences in 5-year survival rates among patients with "non-severe" AH and the control group. The presence of encephalopathy was also predictive of death at 5 years in the control group as was the case in our study population. These results do not allow us to conclude whether the presence of histological ASH impacts long-term prognosis of patients admitted for recent liver decompensation with an mDF <32. Future studies should be designed to evaluate long-term survival in patients with and without AH matched for parameters of liver disease severity.

In conclusion, this study demonstrates that the presence of steatohepatitis in patients with recent liver decompensation and an mDF <32 should not be considered a benign disease as the 1-year mortality rate is 20% and the 5-year mortality rate is 50%. Thus, we advocate for discontinuation of the use of the term "non-severe alcoholic hepatitis" for these patients and would suggest using the term "alcoholic hepatitis of intermediate severity" to define this entity. The presence of hepatic encephalopathy at the time of diagnosis and alcohol abstinence are predictive factors of long-term mortality. Patients with symptomatic AH and an mDF <32 should be closely followed and new treatment strategies, including measures to ensure abstinence, are required in order to improve long-term prognosis.

Abbreviations

AH, alcoholic hepatitis; AHHS, alcoholic hepatitis histological score; ALD, alcohol-related liver disease; ALT, alanine

aminotransferase; ASH, alcohol-related steatohepatitis; AST, aspartate aminotransferase; FU, follow-up; HR, hazard ratio; INR, international normalized ratio; mDF, Maddrey's discriminant function; MELD, model for end-stage liver disease; MM, megamitochondria; PMN, polymorphonuclear neutrophil; PT, prothrombin time; WBC, white blood count.

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Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions
Delphine Degré: acquisition of data; analysis and interpretation of data; statistical analysis; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Rudolf E Stauber: acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Gaël Englebert: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Francesca Sarocchi: Pathological analysis; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Laurine Verset: Pathological analysis; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Florian Rainer: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Walter Spindelboeck: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Hassane Djimi: statistical analysis; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Eric Trépo: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Thierry Gustot: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Carolin Lackner: pathological analysis; analysis and interpretation of data; critical revision of the manuscript for important intellectual content, study supervision. Pierre Deltenre: analysis and interpretation of data; statistical analysis; drafting of the manuscript; critical revision of the manuscript for important intellectual content; study supervision. Christophe Moreno: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; study supervision.

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