Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Collagen proportionate area predicts long-term mortality in patients with alcoholic hepatitis

Mads Israelsen[a,b,1,*], Marta Guerrero Misas[a,1], Anastasios Koutsoumourakis[a], Andrew Hall[c], Claudia Covelli[d], Elena Buzzetti[a], Laura Iogna Prat[a], Davide Roccarina[a], Tu Vinh Luong[c], Alberto Quaglia[c], Massimo Pinzani[a], Emmanuel A. Tsochatzis[a,**]

[a] UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, UK
[b] Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark
[c] Department of Cellular Pathology, Royal Free London NHS Foundation Trust and UCL Institute for Liver and Digestive Health, University College of London, London, UK
[d] Pathology Unit, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy

ARTICLE INFO

Article history:
Received 13 April 2021
Accepted 26 August 2021
Available online xxx

Keywords:
Alcoholic hepatitis
Alcohol-related liver disease
Liver
MELD
Prognosis
Survival

ABSTRACT

Background and aims: There are several short-term prognostic scores for alcoholic hepatitis (AH) that combine demographical and biochemical parameters. The extent of liver fibrosis may also be relevant to the prognosis of AH with potential added value. We evaluated collagen proportionate area (CPA) as a predictor of short and long-term mortality in AH.

Methods: We retrospectively included patients with biopsy-verified AH. Clinical, laboratory and outcome data were collected. CPA and five AH scores were calculated: Maddrey's DF, MELD, GAHS, ABIC, and the Lille Model. Predictors of short and long-term all-cause mortality were assessed using Cox regression analysis.

Results: We included 140 patients with AH. In total, 67 (48%) patients died after a median follow-up of 66 (IQR 102) months, with 17 (12%) dying within the first 90-days. CPA was not a predictor of 90-days mortality and had no additional value to the prognostic AH scores on short-term mortality. However, CPA predicted long-term mortality independently of prognostic AH scores. Importantly, CPA and abstinence from alcohol were independent predictors of long-term mortality in patients alive 90 days after the biopsy.

Conclusion: CPA predicts long-term mortality in patients with AH independently of abstinence from alcohol but has no prognostic value on short-term mortality.

Lay summary

Alcoholic hepatitis is an acute liver inflammatory condition caused by drinking excessive amounts of alcohol over many years and is associated with a one-month death rate up to 30%. We tested if applying computer-assisted analysis of digitalized microscopic slides (collagen proportionate area or CPA) to measure the amount of scar tissue could predict death in patients with alcoholic hepatitis. We found that although CPA did not predict mortality during the acute event, it was associated with higher risk of death in patients who recovered from alcoholic hepatitis. Therefore, the technique is a promising add-on to traditional histopathological evaluation of liver biopsies, which can be used during clinical follow-up after recovery from alcoholic hepatitis.

* Corresponding author at: Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark.
** Co-corresponding author at: Sheila Sherlock Liver Unit and UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, UK.
E-mail addresses: mads.egerod.israelsen@rsyd.dk (M. Israelsen), andrewhall1@nhs.net (A. Hall), tuvinh.luong@nhs.net (T.V. Luong), a.quaglia@ucl.ac.uk (A. Quaglia), m.pinzani@ucl.ac.uk (M. Pinzani), e.tsochatzis@ucl.ac.uk (E.A. Tsochatzis).
[1] Shared co-first authorship. These authors contributed equally to the work.

https://doi.org/10.1016/j.dld.2021.08.021

1. Introduction

Alcoholic hepatitis (AH) has 30-days mortality of up to 30% [1] and five-year mortality of around 50% [2]. Several short-term prognostic AH scores exist. They all use similar biochemical parameters, which may explain why their accuracy is almost equivalent [3,4]. However, 1-year mortality is as high as 13% in patients classified as having non-severe AH according to these biochemical parameters [5], and alcohol abstinence after an admission with severe AH remains the only prognostic marker for long-term mortality [6–8]. This emphasises a lack of tools to prediction of short and long-term mortality in AH.

The necessity of a liver biopsy in AH is controversial [9], but a histological assessment is considered additional prognostic value [10], and a liver biopsy is recommended for inclusion in clinical trials [11]. A biopsy-controlled study demonstrated that the presence of advanced fibrosis or cirrhosis was a strong predictor of 90-days mortality independent of other prognostic scores [10], and indeed prevalence of cirrhosis has been associated with increased short-term and long-term mortality in patients with AH in population-based studies [2]. This indicates that the extent of liver fibrosis predicts the outcome of AH and may have added value to the established prognostic AH scores for short-term mortality.

Collagen proportionate area (CPA) is a technique that provides a quantitative measurement of liver fibrosis using digital assessment of collagen and has been correlated with disease severity and prognosis in chronic liver disease across different aetiologies [12–16]. Recently, we showed that CPA strongly correlates with fibrosis stage in alcohol-related liver disease (ALD) and CPA is an independent predictor of clinical outcomes [17]. However, CPA has never been evaluated in patients with AH.

The primary aim of this study was to assess CPA alone and in combination with established prognostic AH scores to predict short-term and long-term mortality in patients with AH. Our secondary aim was to compare the correlation between established AH prognostic scores and CPA at the time of liver biopsy.

2. Methods

This was a single centre in patients with biopsy-proven alcoholic hepatitis. The primary outcome was all-cause mortality at 90 days and maximum follow-up. Patients were followed retrospectively until death, liver transplantation or the last clinical follow-up. Data collection was censored in June 2017.

2.1. Patients

Patients with suspected alcoholic hepatitis routinely undergo a liver biopsy at the Royal Free and all biopsies were performed before treatment with steroids. Consecutive patients with a clinical and histological diagnosis of alcoholic hepatitis and longitudinal follow-up were included from the Royal Free Hospital. The patients' clinical and biochemical features on admission were compatible with a diagnosis of AH, according to the following criteria: a) history of alcohol misuse in the last months preceding the hospital admission (>40 gr day for men; >20 gr/day for women), b) total serum bilirubin exceeding 2x upper limit of normality c) aspartate to alanine aminotransferase ratio exceeding 1.5 with aspartate aminotransferase over 45 U/L d) absence of a concomitant primary cause of liver disease and e) liver histology compatible with alcoholic hepatitis.

Demographic, biochemical, and data on daily alcohol consumption were recorded at the time of liver biopsy. Treatment with corticosteroids and pentoxifylline were recorded in relation to the hospitalisation.

Patients were classified as abstinent if abstinence was consequently stated in medical records after the time of the liver biopsy. Patients were classified as drinking if subsequent alcohol consumption was reported in the records. Patients were classified as "unknown status of alcohol abstinence" if there were ambiguous statements in the medical records.

2.2. Histological assessment

Liver biopsy were performed before steroid treatment samples were assessed centrally by a single liver pathologist blinded to all clinical data.

2.3. Measurement of collagen proportionate area

CPA was measured on the paraffin-embedded liver biopsies using standard magnification. Biopsies were stained centrally in one batch with picroSirius red, and digital images were obtained using a digital camera. CPA was hereby measured by image analysis software, with a step of manual elimination of structural collagen and artifacts. The method has previously been described in detail [14,18]. All CPA measurements were performed centrally by the same operator (MGM) in a blinded manner.

2.4. Prognostic AH scores

Five prognostic AH scores were calculated: Maddrey's DF [1], MELD [19], GAHS [20], ABIC [21], and the Lille Model [22]. Low and high-risk groups were categorised according to established cut-offs: Maddrey DF ≥32, MELD ≥21, GAHS ≥9, ABIC >9, Lille Model >0.45 [23].

2.5. Statistics

Descriptive data are reported as counts with frequencies, means with standard deviations and medians with interquartile ranges (IQR) according to data distribution. Categorical data were compared using the Chi-square test. All comparisons between two groups in regard to continuous and categorical data were assessed with the Wilcoxon rank-sum test. Spearman's rank-order correlation was used to test the association between CPA and the five prognostic AH scores (Maddrey's DF, MELD, GAHS, ABIC, and Lille Model). Univariable Cox regression analyses were performed to determine predictors of all-cause mortality at 90-days follow up, and maximum follow up. The variables were age at the time of biopsy, sex, abstinence from time of biopsy, presence of cirrhosis, CPA, and the five prognostic AH scores. Abstinence was dichotomised, and "unknown status of alcohol abstinence" was handled as subsequent drinking. To assess robustness of abstinence as a predictor of mortality, we also performed sensitivity analyses by including only patients with known drinking status. To assess the additional value of CPA, we build five models by inputting CPA together with each prognostic AH score using multivariable Cox regression analysis. To assess long-term follow up in patients who were alive 90 days after liver biopsy, variables with p-value <0.10 from a univariable analysis were included in multivariable analysis, where stepwise backward elimination was applied. Only the best performing prognostic AH score was inputted. All calculations were performed using STATA 16 (College Station, TX, US).

3. Results

3.1. Patients

We included 140 patients with biopsy-proven alcoholic hepatitis. Baseline characteristics of the patients are summarised in

Table 1
Baseline patient characteristics.

Variable	n=140
Age, years	46±12
Ethnicity, Caucasian n	104 (74%)
Males, n	82 (59%)
BMI#, kg/m^2	25 ±7
Alcohol intake, g/day	173 ±108
Diabetes, n	12 (9%)
Cirrhosis at time of biopsy, n	106 (76%)
Bridging fibrosis or cirrhosis at time of biopsy, n	120 (86%)
Previous decompensation, n	68 (49%)
CPA, %	29 (23)
Prognostic AH scores	
Maddrey's DF ≥ 32, n	100 (75%)*
Maddrey's DF	54 (41)
MELD ≥ 21, n	94 (72%)*
MELD score	24 (7)
MELD-Na score	26 (8)
GAHS ≥ 9, n	50 (38%)*
GAHS	8 (2)
ABIC > 9, n	29 (21%)
ABIC	7.7 (2.2)
Lille Model (at day 7) > 45	34 (27%) #
Lille model	0.19 (0.46)
Biochemistry*	
White blood cell count	11.5 (8.1)
INR	1.8 (0.8)
Bilirubin, μmol/L	254 (255)
Albumin, g/L	29 (8)
Platelets, 10^9/L	156 (148)
ALT, U/L	39 (44)

Values are reported as mean±standard deviation, counts (proportion) and median (IQR).
ABIC, age, bilirubin, INR and creatinine score; ALT, alanine aminotransferase; BMI, body mass index; CPA, collagen proportionate area; DF, discrimination function; GAHS, Glasgow alcoholic hepatitis scores; INR, international normalised ratio; MELD, the Model for End-Stage Liver Disease.
* Data available on 132 patients #Data on 124 patients.

Table 1. The median age was 46±12 years, and 83 (59%) were males. At the time of the biopsy, 106 (76%) patients had cirrhosis, and 68 (49%) had a history of prior hepatic decompensation. The median CPA was significantly higher in patients with cirrhosis compared to non-cirrhotics (36.2% (IQR=18) vs. 11.7% (IQR=8), P<0.0001) (Supplementary Figure 1). In patients with a histological diagnosis of cirrhosis, CPA values ranged from 9% to 65%. One-hundred (75%) patients had Maddrey's DF ≥32, and 94 (72%) patients had a MELD-score ≥21 with a high concordance correlation coefficient between the two scores (r =0.67). Fifty (38%) patients had GAHS ≥9, and 29 (21%) patients had ABIC >9. On day seven, we were able to calculate the Lille score in 124 patients, of which 34 (27%) had a score >0.45 (two patients were dead). The group of patients with high mortality risk according to GAHS, ABIC, and the Lille Model were mainly a subgroup of high-risk patients according to Maddrey's DF and the MELD-score (Fig. 1).

3.2. Correlation of CPA values with prognostic scores for AH

CPA was significantly increased in patients with poor prognosis according to Maddrey's DF and MELD (DF ≥32 and MELD ≥21), while there was no difference in the CPA in patients with poor prognosis according to GAHS, ABIC, and the Lille Model (Fig. 2 A-E). Increasing CPA values were also correlated to Maddrey's DF (r = 0.32) and the MELD score (r = 0.26), but there was no significant correlation with GAHS, ABIC, and the Lille Model (Fig. 2 F-J).

3.3. Treatment of AH and alcohol abstinence

Corticosteroids were used to treat AH in 71 (51%) patients, of which 11 also received pentoxifylline (Supplementary Table 1).

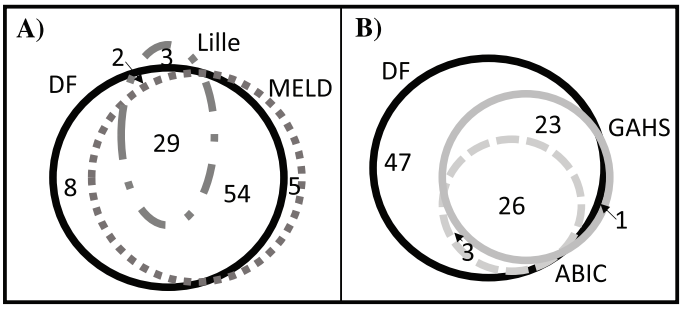

Fig. 1. Venn diagram showing the concordance of patients with high mortality risk according to the different prognostic scores.
100 (75%) patients had Maddrey's DF ≥32, 94 (72%) patients had a MELD-score ≥21, 50 (38%) patients had GAHS ≥9 and 29 patients (21%) had ABIC >9.
ABIC, age-bilirubin-INR-creatinine score; DF, discriminant function; GAHS, Glasgow alcoholic hepatitis score; Lille, Lille Model; MELD, Model of end-stage liver disease.

Forty-eight (34%) patients did not receive corticosteroids nor pentoxifylline, while seven patients (5%) participated in the double-blind STOPAH trial [24] and 13 (9%) patients had no treatment data available. The group who received steroid treatment had higher CPA values (29%, IQR=22) compared to the group receiving no treatment (24%, IQR=30), but it was not significant (p=0.07) (Supplementary Table 1). From the time of the biopsy and onwards, 56 (40%) patients continued drinking alcohol, 47 (33%) patients reported that they were abstaining from alcohol, while subsequent alcohol intake was classified as unknown in 38 (27%) patients.

3.4. CPA does not predict 90-days mortality

Six (4%) patients died within 30-days, and 17 (12%) patients died within 90-days (Supplementary Table 2). CPA was not a predictor of 90-days mortality (Tables 2 and 3). In the univariable analysis, predictors of 90-days mortality were increasing Maddrey's DF, ABIC, and Lille Model (Table 2). CPA did not have an independent prognostic value for 90-days mortality when combined with the prognostic AH score separately in five multivariable models (Table 3). Maddrey's DF, ABIC, and Lille Model were the significant predictors of 90-days mortality in such models. ABIC >9 (p-value = 0.019) and a Lille score >0.45 (p-value < 0.001) at day seven where the only significant predictors of 90-days mortality, when using the established cut-offs (Supplementary Figure 2)

3.5. CPA and abstinence are independent predictors of long-term mortality

In total, 67 (48%) patients died after a median follow-up of 66 (IQR 102; range 0.03-312) months. In the univariable analysis CPA predicted mortality at maximum follow-up (HR=1.02, 95% CI 1.004-1.039, P-value = 0.015) (Table 2). Other variables from the univariable analysis associated with increased long-term mortality were the presence of cirrhosis and increasing prognostic AH scores, while abstinence from the time of biopsy reduced long-term mortality (Table 2). The five models combining CPA with the prognostic AH scores showed that increasing CPA was an independent predictor of long-term mortality when combined with MELD score, GAHS, ABIC, and the Lille Model (Table 3). The same trend was observed when CPA was combined with Maddrey's DF, but it did not reach the significance level (Table 3). There was a major overlap of patients in which the different prognostic scores and CPA predicted long-term mortality (Supplementary Figure 3).

To further separate predictors of short- and long-term mortality, we subsequently focused on the patients who survived the index hospitalisation and were alive 90 days after the biopsy. Among these 123 patients, the median follow-up of was 6.3 (IQR

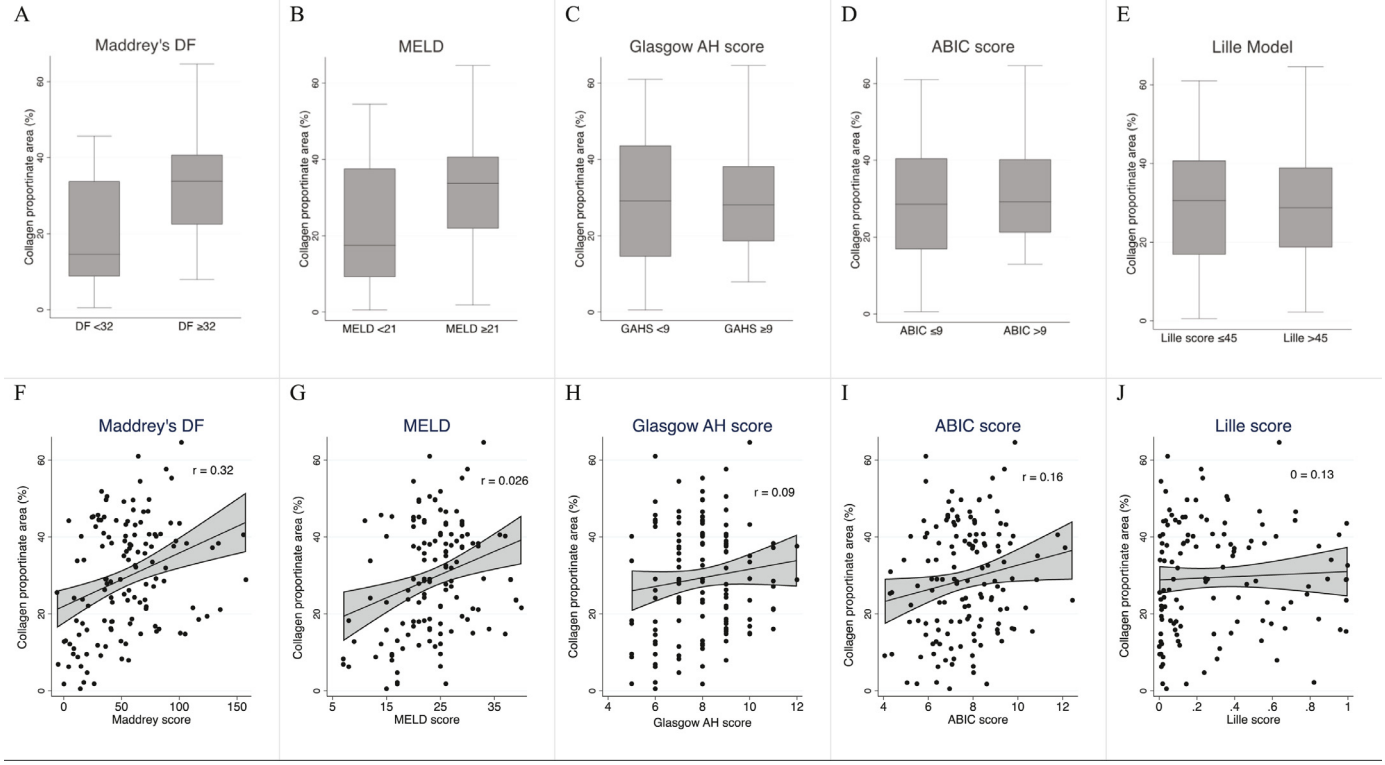

Fig. 2. Correlation of CPA values with prognostic AH scores. **A-E**) Box-plots showing median CPA with 25th-75th in low versus high risk groups according to each prognostic AH scores. **F-J**) Correlations between specific CPA values and prognostic AH scores. ABIC, age-bilirubin-INR-creatinine, AH, alcoholic hepatitis, MELD, Model of end-stage liver disease.

Table 2
Predictors of all-cause mortality in univariable Cox regression analysis at 90-days and maximum follow-up.

Variable	90-days follow-up		Maximum follow-up	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (female)	0.76 (0.28-2.05)	0.584	0.75 (0.45-1.23)	0.248
Age at biopsy	1.01 (0.97-1.05)	0.705	1.01 (0.99-1.03)	0.358
Abstinence	0.51 (0.16-1.66)	0.262	**0.38 (0.20-0.73)**	**0.003**
Cirrhosis at time of biopsy	2.44 (0.56-10.69)	0.235	**1.90 (1.01-3.57)**	**0.045**
Bridging fibrosis or cirrhosis at time of biopsy	2.73 (0.33-20.53)	0.331	1.86 (0.85-4.09)	0.121
CPA	1.01 (0.98-1.05)	0.506	**1.02 (1.004-1.039)**	**0.015**
Maddrey	**1.02 (1.003-1.028)**	**0.018**	**1.01 (1.004-1.018)**	**0.002**
Maddrey ≥32	5.69 (0.76-42.94)	0.092	1.83 (0.99-3.41)	0.055
MELD	1.05 (0.98-1.13)	0.143	**1.04 (1.01-1.08)**	**0.019**
MELD ≥21	3.12 (0.71-13.63)	0.131	**2.68 (1.38-5.18)**	**0.003**
GAHS	1.34 (0.996-1.809)	0.053	**1.17 (1.01-1.36)**	**0.038**
GAHS ≥9	2.00 (0.77-5.18)	0.154	1.44 (0.87-2.39)	0.154
ABIC	**1.57 (1.18-2.10)**	**0.002**	**1.31 (1.11-1.55)**	**0.001**
ABIC >9	**3.01 (1.14-7.91)**	**0.026**	1.66 (0.94-2.93)	0.080
Lille	**21.08 (5.24-84.78)**	**<0.001**	**3.11 (1.40-6.91)**	**0.005**
Lille >45	**7.79 (2.74-22.15)**	**<0.001**	**2.37 (1.38-4.08)**	**0.002**

ABIC, age, bilirubin, INR and creatinine score; CPA, collagen proportionate area; DF, discrimination function; GAHS, Glasgow alcoholic hepatitis scores; MELD, the Model for End-Stage Liver Disease.

8.1) years. In the univariable analysis predictors of long-term survival where CPA, alcohol abstinence and Maddrey's DF (Table 4). When these factors were combined in a multivariable analysis, CPA (HR = 1.03, 95% CI 1.01-1.05, P-value = 0.003) and abstinence (HR = 0.28, 95% CI 0.13-0.58, P-value = 0.001) were independent predictors of long-term mortality (Table 4).

We repeated the analysis after excluding 38 (27%) patients with unknown status of alcohol abstinence to test robustness of the results. In this sensitivity analysis CPA and abstinence were still significant (HR = 1.03, 95% CI 1.01-1.06, P-value = 0.011; HR = 0.30, 95% CI 0.14-0.65, P-value = 0.002) despite the smaller sample size. High CPA predicted mortality significantly among patients who continued drinking alcohol, while alcohol abstinence significantly reduced mortality in both low and high CPA (Supplementary Figure 4). In patients with high CPA who continued drinking alcohol five years mortality was 60% despite surviving index hospitalisation, whereas five years mortality was 11% in patients with low CPA and who abstained from alcohol after index hospitalisation.

4. Discussion

In this study of 140 patients with AH, we evaluated for the first time CPA as a potential predictor of mortality in AH. We found that

Table 3
Predictors of all-cause mortality in multiple Cox regression analysis – five models using CPA combined with each prognostic score of AH.

Variable	90-days follow-up		Maximum follow-up	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Model 1				
Maddrey	**1.02 (1.002-1.03)**	**0.019**	**1.01 (1.002-1.017)**	**0.001**
CPA	1.00 (0.97-1.04)	0.975	1.02 (1.000-1.037)	0.051
Model 2				
MELD	1.05 (0.98-1.13)	0.159	1.04 (0.998-1.078)	0.066
CPA	1.00 (0.97-1.04)	0.795	**1.02 (1.002-1.039)**	**0.032**
Model 3				
GAHS	1.34 (0.99-1.81)	0.057	1.15 (0.99-1.34)	0.075
CPA	1.01 (0.97-1.04)	0.687	**1.02 (1.005-1.041)**	**0.017**
Model 4				
ABIC	**1.56 (1.17-2.09)**	**0.003**	**1.29 (1.08-1.53)**	**0.004**
CPA	1.01 (0.97-1.04)	0.723	**1.02 (1.001-1.037)**	**0.044**
Model 5				
Lille	**7.82 (2.75-22.25)**	**<0.001**	**3.06 (1.36-6.87)**	**0.007**
CPA	1.01 (0.98-1.05)	0.585	**1.02 (1.005-1.044)**	**0.014**

Numbers of patients included in the models: Model 1 (n=134), Model 2 (n=132), Model 3 (n=133), Model 4 (n=140), Model 5 (n=124). ABIC, age, bilirubin, INR and creatinine score; CPA, collagen proportionate area; DF, discrimination function; GAHS, Glasgow alcoholic hepatitis scores; MELD, the Model for End-Stage Liver Disease.

Table 4
Prognostic scores as continues variables
Predictors of all-cause mortality in patient who were alive 90 days after liver biopsy.

Variable	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at biopsy	1.01 (0.99-1.03)	0.401		
Abstinence	**0.32 (0.15-0.66)**	**0.002**	**0.28 (0.13-0.58)**	**0.001**
Cirrhosis at time of biopsy	1.78 (0.88-3.59)	0.106		
CPA	**1.03 (1.005-1.046)**	**0.015**	**1.03 (1.01-1.05)**	**0.003**
Maddrey	**1.01 (1.000-1.017)**	**0.039**		NS
MELD	1.04 (0.997-1.085)	0.064		
Glasgow	1.12 (0.94-1.33)	0.203		
ABIC	1.21 (0.99-1.47)	0.065		
Lille	1.05 (0.34-3.23)	0.939		

The best performing prognostic AH score (Maddrey) was inputted in the multivariable analysis. ABIC, age-bilirubin-INR-creatinine, AH, alcoholic hepatitis, NS, not significant, MELD, Model of end-stage liver disease.

the CPA independently predicted long-term mortality but could not predict short-term mortality. Interestingly, CPA and abstinence from alcohol were the only independent predictors of long-term mortality in patients who survived the index hospitalisation and were alive 90 days after presentation. Finally, we observed that the CPA correlated with Maddrey's DF and MELD score.

Our results highlight that CPA is a useful prognostic marker of long-term outcome. This is noteworthy because abstinence has previously been considered the only independent predictor of long-term survival [7]. Here, we chose to do separate analysis on long-term mortality in patients alive 90 days after biopsy assuming that the acute episode of AH was resolved. Then we found that only CPA and alcohol abstinence independently predicted all-cause mortality. This indicates that the severity of the underlying ALD determines the outcome in patients who recover from AH. With a median follow-up exceeding 6 years it validates that CPA and alcohol abstinence are independent predictors of all-cause mortality in patients ALD [17]. It also suggests, that patients recovering from AH should be managed like other patients with ALD, where the prognosis is mainly determined by abstinence and the severity of fibrosis. Therefore, when a liver biopsy is performed for clinical reasons, CPA should be routinely measured, as it provides valuable prognostic information that can be used in tandem with the traditional semi-quantitative fibrosis staging. Furthermore, CPA sub-classifies cirrhosis and provides a refinement of prognosis even in this patient group [15]. Our analysis showed 3% increase of mortality per 1% increase in CPA – this would provide a huge refinement of prognosis in patients with cirrhosis, where CPA values ranged from 9% to 65%.

The extent of fibrosis as a predictor of short-term mortality in AH is controversial. While one small sample size study found no relation between fibrosis and clinical outcome [9], one larger study found that the magnitude of liver fibrosis predicted short-term mortality in AH [10]. This multicentre study by Altamirano et al. of 121 patients showed that bridging fibrosis or cirrhosis was an independent predictor of 90-days mortality. This information was integrated into a histological score that was subsequently validated in an external cohort of 205 patients. Surprisingly, we did not find that the presence of bridging fibrosis or cirrhosis was associated with significantly increased 90-days mortality. An explanation could be the relatively low 90-days mortality of 12% in our study compared to the 29% reported by Altamirano et al., thus raising the possibility of a type II error. The substantial difference in the 90-days mortality rate cannot be attributed to the prevalence of bridging fibrosis or cirrhosis, which was very comparable between the two studies (82% vs. 86%) and Altamirano et al. report lower MELD score (18 vs. 24), ABIC score (7.3 versus 7.7) and white blood cell count (8.9 vs. 11.5 $\times$ 10^9/L). However, there has been a large variation in clinical practice and threshold for performing a liver biopsy in AH. A less restrained approach to perform early liver biopsy could explain the low 90-days mortality in our study. Indeed, it has been the practice for a long time at the Royal Free Hospital to perform a confirmatory liver biopsy in all patients with suspected alcoholic hepatitis. Nevertheless, the impact of liver fibrosis on short term survival in AH remains unclear.

In this study, we also assessed five prognostic scores for AH and showed a significant overlap of patients categorised as high-risk for mortality. Therefore, it was not surprising that all scoring systems predicted mortality equally well, and this is in accordance with previous studies that have demonstrated that none of them is superior [3,4]. It has been demonstrated that combining these scoring systems may increase the predictive power [25]. However, when using overlapping biochemical parameters, assumingly the synergistic power is limited, and therefore it is necessary to identify other independent prognostic factors to significantly increase the predictive power of the established scores.

Our results indicate that the severity of fibrosis is a key prognostic factor for long-term survival in patients who recover from an episode of AH. Although in our unit a liver biopsy is routinely performed in patients with suspected alcoholic hepatitis, we recognize that there is no consensus on whether liver biopsy should be performed in this context [9,26]. However, if a liver biopsy is performed for clinical reasons, CPA should be routinely calculated and reported as it can be utilised to guide advance care planning.

Our study has limitations to consider. Due to the retrospective design, there were no predefined criteria for performing a liver biopsy. This may have caused a selection of patients in a relatively good condition where a liver biopsy was clinically meaningful, which may explain the relatively low short-term mortality rate. The limited number of events did not make it possible to analyse predictors of 30-days mortality. It should also be noted that only 34 patients in this study did not have cirrhosis, thus the sample size did not allow for additional analysis in this subgroup. However, CPA does most likely also predict long-term mortality in non-cirrhotic patients who recover from AH, as we have recently shown that it does predict decompensation and liver-related death in patients with early/compensated ALD [17].

To conclude, the CPA predict long-term clinical outcomes in patients with AH independently of alcohol abstinence, but it has no prognostic value for short-term mortality. Therefore, CPA assessment can be used during clinical follow-up after recovery from AH.

Authors contribution

MM and ET study concept and design; MM, AK, AH, CC, EB, LP, DR, and TVL data collection; MI, MM, and ET data analyses; MI and ET drafted the manuscript; all authors contributed to the manuscript with important intellectual content and approved the final version.

Declaration of Competing Interest

None declared.

Funding

Mads Israelsen's salaries were supported by Odense University Hospital and The University of Southern Denmark. Massimo Pinzani is supported by the National Institute for Health Research (NIHR) UCLH/UCL Biomedical Research Centre (BRC). Anastasios Koutsoumourakis was supported by an educational scholarship from the Hellenic Society of Gastroenterology.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.08.021.

References

[1] Maddrey WC, Boitnott JK, Bedine MS, Weber FL Jr, Mezey E, White RI Jr. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 1978;75(2):193–9.
[2] Sandahl TD, Jepsen P, Thomsen KL, Vilstrup H. Incidence and mortality of alcoholic hepatitis in Denmark 1999-2008: a nationwide population based cohort study. J Hepatol 2011;54(4):760–4.
[3] Forrest EH, Atkinson SR, Richardson P, et al. Application of prognostic scores in the STOPAH trial: discriminant function is no longer the optimal scoring system in alcoholic hepatitis. J Hepatol 2018;68(3):511–18.
[4] Papastergiou V, Tsochatzis EA, Pieri G, et al. Nine scoring models for short--term mortality in alcoholic hepatitis: cross-validation in a biopsy-proven cohort. Aliment Pharmacol Ther 2014;39(7):721–32.
[5] Bennett K, Enki DG, Thursz M, Cramp ME, Dhanda AD. Systematic review with meta-analysis: high mortality in patients with non-severe alcoholic hepatitis. Aliment Pharmacol Ther 2019;50(3):249–57.
[6] Altamirano J, Lopez-Pelayo H, Michelena J, et al. Alcohol abstinence in patients surviving an episode of alcoholic hepatitis: prediction and impact on long-term survival. Hepatology 2017;66(6):1842–53.
[7] Potts JR, Goubet S, Heneghan MA, Verma S. Determinants of long-term outcome in severe alcoholic hepatitis. Aliment Pharmacol Ther 2013;38(6):584–95.
[8] Louvet A, Labreuche J, Artru F, et al. Main drivers of outcome differ between short term and long term in severe alcoholic hepatitis: a prospective study. Hepatology 2017;66(5):1464–73.
[9] Mookerjee RP, Lackner C, Stauber R, et al. The role of liver biopsy in the diagnosis and prognosis of patients with acute deterioration of alcoholic cirrhosis. J Hepatol 2011;55(5):1103–11.
[10] Altamirano J, Miquel R, Katoonizadeh A, et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology 2014;146(5):1231–9 e1231-1236.
[11] Crabb DW, Bataller R, Chalasani NP, et al. Standard definitions and common data elements for clinical trials in patients with alcoholic hepatitis: recommendation from the NIAAA alcoholic hepatitis consortia. Gastroenterology 2016;150(4):785–90.
[12] Calvaruso V, Dhillon AP, Tsochatzis E, et al. Liver collagen proportionate area predicts decompensation in patients with recurrent hepatitis C virus cirrhosis after liver transplantation. J Gastroenterol Hepatol 2012;27(7):1227–32.
[13] Manousou P, Burroughs AK, Tsochatzis E, et al. Digital image analysis of collagen assessment of progression of fibrosis in recurrent HCV after liver transplantation. J Hepatol 2013;58(5):962–8.
[14] Calvaruso V, Di Marco V, Bavetta MG, et al. Quantification of fibrosis by collagen proportionate area predicts hepatic decompensation in hepatitis C cirrhosis. Aliment Pharmacol Ther 2015;41(5):477–86.
[15] Tsochatzis E, Bruno S, Isgro G, et al. Collagen proportionate area is superior to other histological methods for sub-classifying cirrhosis and determining prognosis. J Hepatol 2014;60(5):948–54.
[16] Buzzetti E, Hall A, Ekstedt M, et al. Collagen proportionate area is an independent predictor of long-term outcome in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2019;49(9):1214–22.
[17] Israelsen M, Guerrero Misas M, Koutsoumourakis A, et al. Collagen proportionate area predicts clinical outcomes in patients with alcohol-related liver disease. Aliment Pharmacol Ther 2020.
[18] Calvaruso V, Burroughs AK, Standish R, et al. Computer-assisted image analysis of liver collagen: relationship to Ishak scoring and hepatic venous pressure gradient. Hepatology 2009;49(4):1236–44.
[19] Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33(2):464–70.
[20] Forrest EH, Evans CD, Stewart S, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. Gut 2005;54(8):1174–9.
[21] Dominguez M, Rincon D, Abraldes JG, et al. A new scoring system for prognostic stratification of patients with alcoholic hepatitis. Am J Gastroenterol 2008;103(11):2747–56.
[22] Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007;45(6):1348–54.
[23] Papastergiou V, Burroughs AK, Tsochatzis EA. Prognosis and treatment of patients with acute alcoholic hepatitis. Expert Rev Gastroenterol Hepatol 2014;8(5):471–86.
[24] Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372(17):1619–28.
[25] Louvet A, Labreuche J, Artru F, et al. Combining data from liver disease scoring systems better predicts outcomes of patients with alcoholic hepatitis. Gastroenterology 2015;149(2):398–406 e398; quiz e316-397.
[26] Forrest EH, Gleeson D. Is a liver biopsy necessary in alcoholic hepatitis? J Hepatol 2012;56(6):1427–8 author reply 1428-1429.