The MELD score is superior to Maddrey's discriminant function score to predict short-term mortality in alcohol-associated hepatitis: a global study

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Abstract

Background and aims: Several scoring systems predict mortality in alcohol-associated hepatitis (AH), including the Maddrey's discriminant function (mDF) and MELD score developed in the USA, Glasgow Alcoholic Hepatitis Score (GAHS) in the UK, and ABIC in Spain. To date, no global studies have examined the utility of these scores, nor has the MELD-Na been evaluated for outcome prediction in AH. In this study, we assessed the accuracy of the different scores to predict short-term mortality in AH and investigated additional factors to improve mortality prediction.

Methods: Patients admitted to hospital with a definite or probable AH were recruited by 85 tertiary centers in 11 countries and across three continents. Baseline demographic and laboratory variables were obtained. The primary outcome was all-cause mortality at 28 and 90 days.

Results: In total 3,101 patients were eligible for inclusion. After exclusions (n=520), 2,581 patients were enrolled (74.4% male, median age 48, IQR 40.9–55.0 years). The median MELD score was 23.5 (IQR 20.5–27.8). Mortality at 28 and 90 days was 20% and 30.9%, respectively. The AUROC for 28 day mortality ranged from 0.776 for MELD-Na to 0.701 for mDF, for 90 day mortality it ranged from 0.773 for MELD to 0.709 for mDF. The AUROC for mDF to predict death were significantly lower than all other scores. Age added to MELD obtained only a small improvement of AUC.

Conclusions: These results suggest that mDF score should no longer be used to assess AH's prognosis. MELD score has the best performance in predicting short-term mortality.

Keywords

alcohol-associated hepatitis; prognostic scores; severity; mortality

Introduction

Alcohol-associated hepatitis (AH) is the most severe acute form of alcohol-related liver disease. AH portends a poor prognosis with high short-term mortality between 20–50% [1]. Prognostic scores are used in clinical practice to assess the severity of the disease and identify high-risk patients for consideration of corticosteroid treatment [2]. The Maddrey's discriminant function (mDF) has been traditionally used in guidelines and clinical trials to define severe disease (mDF > 32) [3]. However, mDF has some limitations, such as it does not include creatinine, a widely recognized prognostic factor in AH [4], and measurement of the prothrombin time varies significantly between laboratories [5]. Several studies have reported the model for end-stage liver disease (MELD) is a better predictor of mortality in AH than the mDF [6, 7]. Other validated prognostic scores in AH are the age, bilirubin, international normalized ratio and creatinine (ABIC) score [8] and Glasgow alcoholic hepatitis

score (GAHS) [9]. The mDF and MELD scores were initially derived and validated in the USA, the ABIC in a cohort from Spain and the GAHS in Glasgow, UK. These scores have not been validated globally despite the expected influence of genetic, socioeconomic, climatic, and local diagnostic and technical laboratory factors [1, 10, 11].

Serum Na is an independent predictor of mortality in patients with cirrhosis[12]. Both the MELD score and the MELD-Na score which incorporates serum Na into the MELD score are currently used to prioritize allocation of organs for liver transplantation in patients with cirrhosis [13] but MELD-Na has been validated in patients with AH only in a small study[14]. Moreover, around 30% of patients with AH do not have cirrhosis [15].

Therefore, we aimed to assess the predictive accuracy of MELD-Na in a global cohort of patients with AH as well as other prognostic score such as the mDF, MELD, GAHS, and ABIC scores in determining mortality at 28 and 90 days. We also determined whether there were other parameters that could improve mortality prediction.

Methods

Study design and population

We analyzed individual patient data of well-characterized patients hospitalized with AH in 85 tertiary centers in 11 countries. The diagnosis of AH was determined across all centers using the standardized definition, as described below. All participant centers followed the same inclusion/exclusion criteria. Institutional review boards from each center approved the study.

A diagnosis of AH made following epidemiological, clinical, and biological criteria according to the Standard Definitions of the National Institute on Alcohol Abuse and Alcoholism NIAAA [16]. According to clinical criteria, patients with uncertain of AH diagnosis had undergone a liver biopsy, which must confirm the diagnosis of AH. Only patients with biopsy proven AH (definite AH); and patients with history of alcohol use and liver test abnormalities as described below without confounding factors (probable AH) were included.

Specific inclusion criteria were a) a history of alcohol use of >60 g/day in men and >40 g/day in women, b) an aspartate aminotransferase <400 U/l with AST/ALT ratio >1.5, c) Serum γ-glutamyl transpeptidase –GGT– levels >80 mg/dl, d) altered coagulation tests (prolonged prothrombin time and/or INR values), and e) serum bilirubin levels >3 mg/dl. For patients with more than one admission, information was collected only for the index episode. Exclusion criteria were a) other identifiable causes of liver disease: hepatitis B or C virus infection, autoimmune hepatitis, hemochromatosis, Wilson's disease, suspicion for drug induced liver injury disease, or alternative diagnosis on liver biopsy, b) complete portal vein thrombosis, c) hepatocellular carcinoma and other malignancies, d) human immunodeficiency virus infection, e) other extrahepatic severe illness with low life expectancy according to investigators' criteria.

Data collection

Age, sex, alcohol consumption (g/day), mortality status (including date of death), and the presence clinical complications at admission (*viz.* systemic inflammatory response syndrome (SIRS), infection, gastrointestinal (GI) bleeding, acute kidney injury (AKI) and encephalopathy) were collected. AKI was defined as serum creatinine ⩾ 1.5 mg/dL and/or AKIN criteria [17]. Baseline laboratory variables were also collected and the MELD, MELD-Na, mDF, GAHS, and ABIC scores derived using these data.

Regarding socioeconomic determinants of health, we obtained data from Human Development Reports of United Nations from 2019 to include surrogate inequality and economic parameters (Addendum, Supplemental Digital Content 9). We focused on the Human Development Index (HDI), a summary measure of a long and healthy life, being knowledgeable and have a decent standard of living, and the Inequality-adjusted HDI (IHDI) that takes into account not only the average achievements of a country in health, education and income, but also how those achievements are distributed among its population by "discounting" each dimension's average value according to its level of inequality as parameters reflecting inequality and the economy of each country.

Statistical analysis

Baseline characteristics are expressed as percentages and median and interquartile range (IQR). The primary endpoint was all-cause mortality at 28 and 90 days. The prognostic scores' accuracy was evaluated using receiver operating characteristics (ROC) curves, and the area under the curves (AUROC) was calculated. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratio (LR) were calculated for each score. The DeLong method [18] was used to test for statistically significant differences between ROC curves. Cox regression analysis was used to identify risk factors for mortality at 28 and 90 days. The variables demonstrating statistically significant association on both 28 and 90-day mortality univariate analysis (p<0.001) were included in the multivariate analysis. Logistic regression was performed to generate equations.

P<0.05 was considered statistically significant.

We performed all statistical analyses with IBM SPSS software (Version 26) and MedCalc Statistical Software version 16.4.3 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2016) for AUROC comparison.

Results

Baseline characteristics of included patients

A total of 3,101 patients with AH were recruited from 85 tertiary centers in 11 countries (Table, Supplemental Digital Content 1). After exclusions (n=520), 2,581 patients (74.4% male, median 48, IQR 40.9–55 years) were finally included (Figure 1). Global and by country baseline characteristics of included patients are shown in Table 1, and baseline laboratory variables are shown in Table, Supplemental Digital Content 2. The majority of

patients were white (57.7%), followed by Indians (14.1%), Asians (12%), Latin Americans (9%), and Blacks (1.8%). Regarding sex distribution, Anglo-Saxon countries (USA, UK, and Canada) had a higher percentage of women with a diagnosis of AH (38.6% vs. 10.0%, p<0.001). Globally, women compared with men were younger, with less alcohol consumption, and lower mortality at 28 and 90 days, similar than Anglo-Saxon countries (Table 2).

Overall, 28 and 90-day mortality was 20% and 30.9%, respectively. Mexico showed the highest rates of short-term mortality at 28 (37.8%, p<0.001) and 90 days (56.8%, p<0.001) than the entire cohort. Other countries with higher mortality than the entire cohort were Colombia at 28 days (27.5%, p=0.008), Canada at 90 days (32.1%, p=0.009), Brazil at 28 (22.2%, p<0.001) and 90 days (33.3%, p<0.001), and India at 28 (23.2%, p<0.001) and 90 days (35%, p<0.001); whereas UK and Korea showed a lower mortality rate at 28 (15.9%, p<0.001; 16.1%, p<0.001; respectively) and 90 days (26.2%, p<0.001; 22.3%, p<0.001; respectively). The median (IQR) MELD score, MELD-Na, mDF, GAHS, and ABIC scores were 23.5 (20.5–27.8), 26.8 (23.4–31.3), 55.6 (41.4–78.9), 9 (7–10), and 7.9 (6.9–9) respectively. Mexico exhibited substantially higher scores, median MELD 30.9 (24.9–37.4) vs, 23.1 (20.3–27.9), p<0.001. By contrary, Korea obtained lower scores, median MELD 20.3 (17–26) vs, 23.7 (20.8–28), p<0.001. The rest of significant differences between the different countries and the entire cohort are shown in Table, Supplemental Digital Content 3.

Performance of existing prognostic models and MELD-Na

AUROCs for the accuracy to predict mortality at 28 and 90 days for the different scores are shown in Figures 2 and 3. The AUROCs for prediction of mortality at 28 days ranged from 0.776 for MELD-Na and 0.775 for MELD to 0.701 for mDF, whereas for 90 days, mortality predictions ranged from 0.773 for both MELD-Na and MELD to 0.709 for mDF. mDF had the lowest AUROC to predict death, with significant differences between all other scores and mDF (Figure 2 and 3). ABIC score was inferior to MELD and MELD-Na but superior to mDF and without significant difference with GAHS that globally had not significant differences with MELD and MELD-Na but it was also superior than mDF.

Since the 42% of included patients were from UK (Addendum, Supplemental Digital Content 10), an analysis was performed excluding UK patients; MELD and MELD-Na scores showed the highest AUROCs predicting mortality (Table, Supplemental Digital Content 4 and 5). Table 3 shows the AUROC of all scores by country. ABIC score significantly predicted mortality at 28 and 90 days in all countries, and in France was the only score that significantly predict mortality. Particularly, Glasgow score was not useful predicting mortality in Colombia and France, and mDF was not useful in Spain and France.

The optimal baseline cut-off values for predicting death at 28 and 90 days using this global cohort was 25 for MELD, 28 for MELD-Na, 51 and 52 for mDF, 9 and 8 for GAHS, and 9 for ABIC. The receiver operating characteristic for each cut-off value is shown in Table 4.

Figure 4 represents the equivalence between the different values of the scores in relation to the probability of death.

Identification of independent predictors of short-term mortality

The variables associated with mortality in the univariate analysis are displayed in Table, Supplemental Digital Content 6.

On multivariate analysis the independent predictors of death were bilirubin (p<0.001), age (p<0.001), leucocytes (p<0.001), international normalized ratio (INR) (p<0.001), creatinine (p<0.001), sodium (p<0.001), and aspartate aminotransferase (AST) (p=0.005 for 28 days and p=0.024 for 90 days) (Table, Supplemental Digital Content 7).

The AUC for 28 and 90 days for age added to the MELD score (Age-MELD score = −6.031+0.033*lnAGE+0.141*lnMELD) compared to MELD alone was 0.761 vs. 0.750, p<0.001, and 0.760 vs. 0.749, p<0.001, respectively. Fifty-five years or over was associated with an increased risk of death (AUC 0.567, p<0.001; sensitivity 34.5%, specificity 77%).

A novel score combining all the independent predictors of mortality [0.445+0.042*ln(bilirubin)+0.041*ln(age)+0.039*ln(leukocytes)+0.460*ln(INR)+0.002*ln(AST)+0.452*ln(Cr)+(−0.041)*ln(Na)] was marginally more accurate than MELD score in predicting 28 mortality (AUC for 28 days 0.795 vs. 0.779, p=0.026), but not 90 day mortality 0.779 vs. 0.775, p=0.570).

Considering socioeconomic factors, IHDI was significantly associated with mortality at 28 (p<0.001) and 90 days (p<0.001) (Figure, Supplemental Digital Content 8); not associated with mortality in a multiple regression analysis considering all independent predictors of mortality analyzed previously (data not shown).

Discussion

Although many studies have assessed the performance of different scoring systems in AH, this is the first global study including patients from 3 continents that addresses this question. Also, this is the first large study that evaluates the performance of MELD-Na in AH, the previous study including only 26 patients [14]. Our results showed that the MELD score is the best prognostic score to predict short-term mortality in AH, whereas mDF showed a significantly lower prediction capacity than all previously validated scores. MELD-Na score did not significantly improve the accuracy of the MELD score. Interestingly, age is a relevant independent predictive factor of mortality.

We included well-characterized AH cohorts from different countries in Europe, North America, South America, and Asia. There were no patients from Africa, Oceania, large parts of Asia, and Eastern Europe. In addition to the currently available prognostic scores, different variables that may influence the short-term prognosis in AH were evaluated [19,] including those associated with treatment, socioeconomic, cultural, and behavioral factors such as sex and age that may influence the amount of alcohol intake [10, 20].

This study found global interesting demographic differences in patients with AH across different world regions. Almost half of the patients with AH in the USA, UK, and Canada were women, unlike the other countries where AH was more frequent in men. It is believed that globally AH is more common in men [1]. In the USA, the reported percentage of

hospitalized men with AH is lower than in other countries, but still around 69.7% using inpatient databases from 2010 to 2014 among 56,973 registered patients [21]. Similarly, 63% of patients recruited to the STOPAH trial were men [22]. This data maybe be explained by an increased alcohol consumption and admissions related to alcohol misuse among young women in these countries [23]. Finally, we demonstrate that the reported alcohol intake in patients with AH in countries such as Mexico and Brazil is somewhat greater than in other countries and, furthermore, is associated with higher mortality. This corroborates our previously published data indicating that the quantity of alcohol intake influences survival in Mexican patients with AH [24].

In the current study, MELD was the best score to predict short-term mortality, and mDF had a significantly worse prediction capacity than all the previously validated scores. We also provide evidence that the performance of MELD-Na is not predictively superior to MELD alone in this patient population. Whereas other scoring systems (i.e. ABIC and GAHS), performed similar to MELD but inferior to mDF; this study strongly suggests that mDF should not be used to assess the prognosis in patients with AH. An analysis of the STOPAH trial data by Forrest EH et al. reported a similar conclusion but lacked the global scale of these findings [25]. Indeed, mDF is one of the most commonly used scores to determine prognosis and determine need for steroids in clinical trials [26]. In recent studies, mDF has shown a lower accuracy for mortality prediction than the others prognostic scores [6, 27, 28]. This is probably because mDF does not include renal function, an important prognostic factor in AH [29]. Therefore, the MELD score, rather than the mDF score, should be used to identify patient at high risk of mortality in the clinical practice, and should be used to assess prognosis in multicentric international clinical trials.

In addition, the performance of each score was analyzed in individual countries showing that the ABIC score significantly predicted mortality at 28 and 90 days in all countries being the only score that predicted mortality in France. However, the cohort from France was relatively small and had less mortality than the other countries. Therefore, the finding that MELD does not predict mortality in France should be taken cautiously.

We also attempted to improve upon the performance of the MELD score to predict short term survival. First, we assessed the performance of the MELD-Na score, which is widely used in patients with decompensated cirrhosis [30]. We provide evidence that the performance of MELD-Na was not superior to MELD alone in this patient population besides its similar AUC.

Moreover, we identified bilirubin, leucocytes, INR, AST, creatinine, sodium, and age as independent predictors of mortality in our series. In several studies age has been shown to be a predictive factor of survival in AH and it is included within the ABIC and GAHS scores calculations [8,9]. When we generated a predictor combining MELD and age it resulted in a statistically significant but small improvement in the AUC. No increase of MELD accuracy was observed, neither with the calculation of a global score taking into account all the predictive factors of mortality in our cohort.

Interestingly, we also found that inequality in socioeconomic factors between countries influences AH mortality at 28 and 90 days.

Of note, dynamic factors other than baseline parameters could influence the outcome of patients with AH. Two recent meta-analysis including patients from the STOPAH study, confirmed that prednisolone improves 28-day survival in these patients. However, this effect is not significant at later time points [31,32]. Moreover, alcohol relapse negatively impacts medium and long-term survival [33]. Finally, a recent report indicates that early referral to an addiction specialist improves short-term survival [34]. Therefore, the patients' outcome is influenced not only by baseline parameters reflecting liver and renal dysfunction but also specific therapy, abstaining from alcohol, and comorbid conditions [35].

The major strength of this study is that a global cohort has been analyzed. However, there are some limitations of this study. First, all included AH were not biopsy-proven. However, current clinical guidelines suggest performing a liver biopsy only when the diagnosis of AH (unclear alcohol use history; atypical laboratory data, or suspicion of another etiology of liver disease) [36]. In fact, patients were included in the analysis if they did not meet all restrictive exclusion criteria. Second, data on genetic factors such as PNPLA3 polymorphisms were not available in many of the countries included in the study since PNPLA3 polymorphisms failed to influence mortality in AH [37]. In fact, some of the countries with higher mortality (i.e. Mexico) have shown a higher prevalence of the most unfavorable PNPLA3 genotype [38]. Third, the utility of these scores in predicting survival beyond 3 months is not clear.

In conclusion, our study demonstrates that in AH, MELD is the best scoring system to globally predict short-term survival and that mDF has the lowest predictive capability of the scores analyzed. Future studies should define optimal MELD cut-offs to determine not only treatment benefit but also when all treatment might be futile and analyze other biomarkers as predictors of severity and mortality in AH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial support:

Abbreviations:

AH   alcohol-associated hepatitis

mDF	Maddrey's discriminant function
MELD	model for end-stage liver disease
ABIC	age, bilirubin, international normalized ratio, and creatinine score
GAHS	Glasgow alcoholic hepatitis score
NIAAA	national institute on alcohol abuse and alcoholism
INR	international normalized ratio
AST	aspartate aminotransferase
ALT	alanine aminotransferase
GGT	serum γ-glutamyl transpeptidase
SIRS	systemic inflammatory response syndrome
GI	gastrointestinal
AKI	acute kidney injury
IQR	interquartile range
ROC	receiver operating characteristics
AUROC	area under receiver operating characteristics curves
PPV	positive predictive value
NPV	negative predictive value
LR	likelihood ratio

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Study highlights

What is Known

- The MELD and mDF scores have been assessed to predict mortality in AH in several countries. However, the GAHS and ABIC scores have only been examined in the UK and Spain, respectively. Global validation of these scores is necessary to determine whether regional variables could influence their utility in AH.

- Furthermore, the predictive accuracy of the MELD-Na score in AH, previously examined in cirrhosis, and other predictive variables to improve the prediction of existing scores, are unknown.

What is new here

- MELD was the best score to predict short-term mortality in AH.

- The mDF score had significantly less accurate than all previously validated scores.

- MELD-Na did not further improve the accuracy of MELD.

- There were no other independent predictors that could be added on to significantly increase the mortality prediction of MELD.
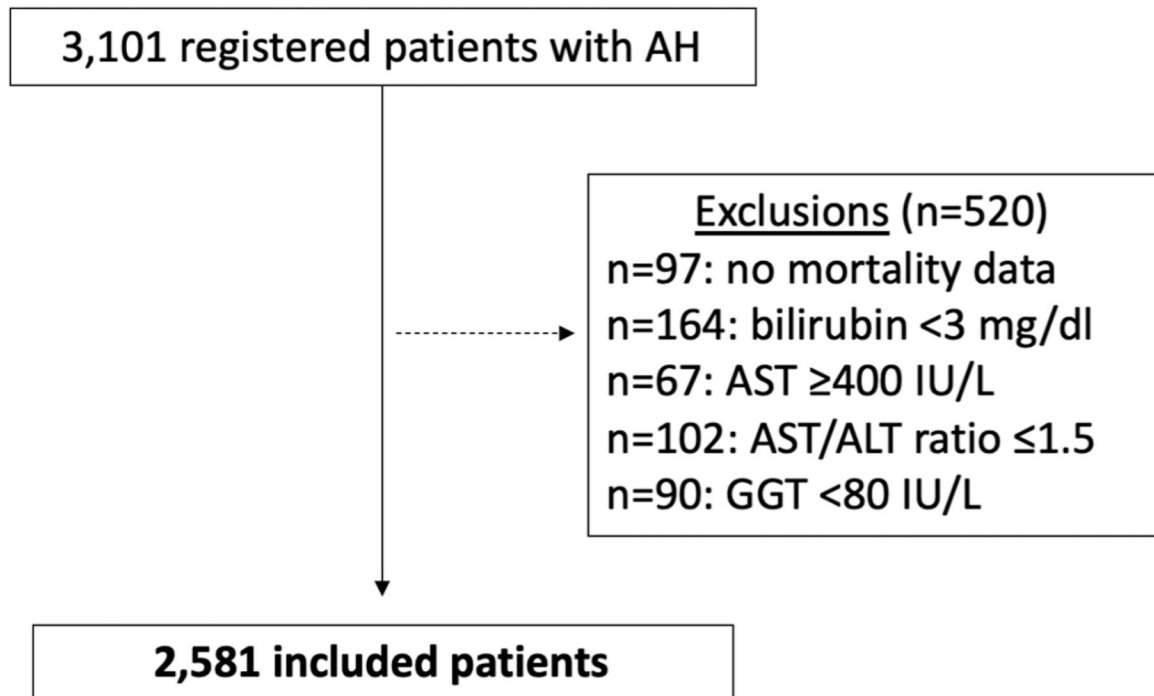
Figure 1.
Flow-chart of patient inclusion.
AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase
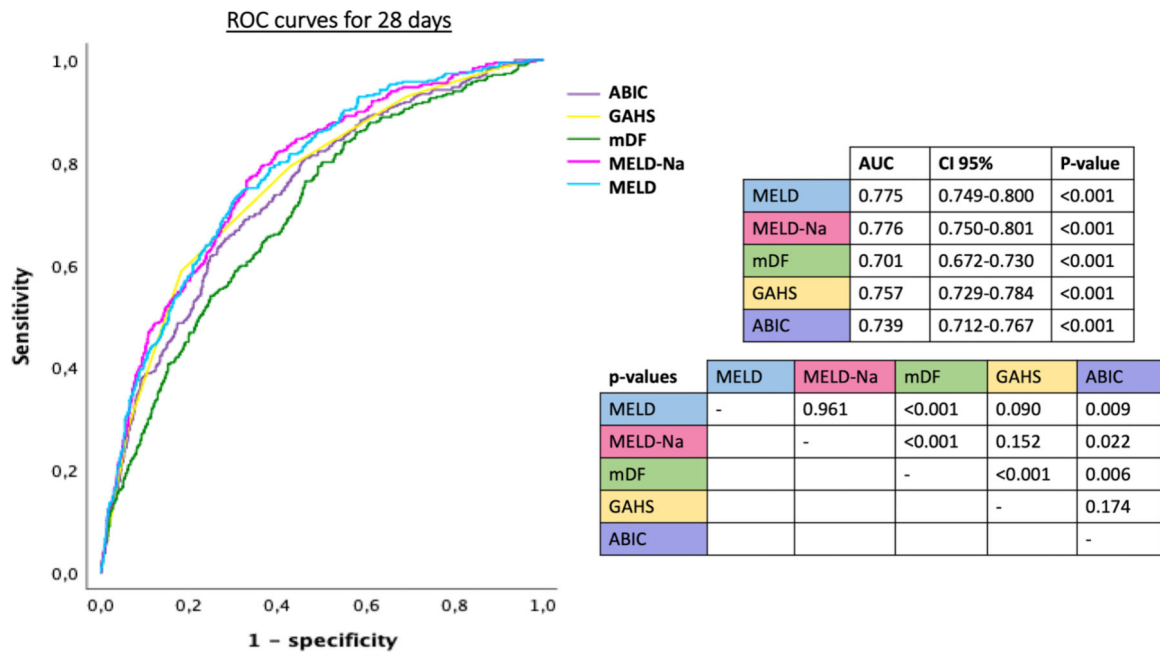
Figure 2.
ROC curves of the different prognostic scores for alcohol-associated hepatitis calculated baseline, used to predict mortality at 28 days, and p-values comparing scores.
MELD: model for end-stage liver disease, mDF: Maddrey's discriminant function, GAHS: Glasgow alcoholic hepatitis score, ABIC: age, bilirubin, international normalized ratio and creatinine score, AUC: area under curve, CI: confidence interval

ROC curves for 90 days

	AUC	CI 95%	P-value
MELD	0.773	0.750-0.795	<0.001
MELD-Na	0.773	0.750-0.795	<0.001
mDF	0.709	0.684-0.734	<0.001
GAHS	0.756	0.733-0.780	<0.001
ABIC	0.737	0.713-0.762	<0.001

p-values	MELD	MELD-Na	mDF	GAHS	ABIC
MELD	-	0.930	<0.001	0.092	0.009
MELD-Na		-	<0.001	0.142	0.018
mDF			-	<0.001	0.004
GAHS				-	0.142
ABIC					-
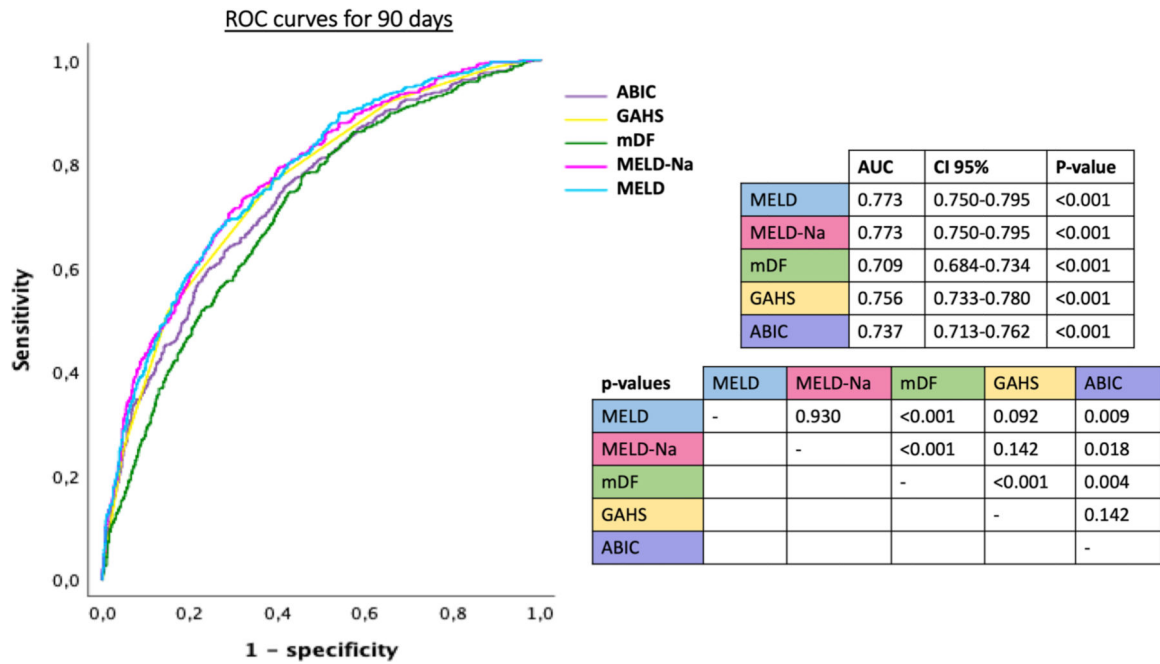
Figure 3.
ROC curves of the different prognostic scores for alcohol-associated hepatitis calculated baseline, used to predict mortality at 90 days, and p-values comparing scores.

MELD: model for end-stage liver disease, mDF: Maddrey's discriminant function, GAHS: Glasgow alcoholic hepatitis score, ABIC: age, bilirubin, international normalized ratio and creatinine score, AUC: area under curve, CI: confidence interval

Figure 4.
Equivalence between the different prognostic scores according to the probability of death.
MELD: model for end-stage liver disease, mDF: Maddrey's discriminant function, GAHS:
Glasgow alcoholic hepatitis score, ABIC: age, bilirubin, international normalized ratio and
creatinine score

Baseline characteristic of included patients.

Table 1.

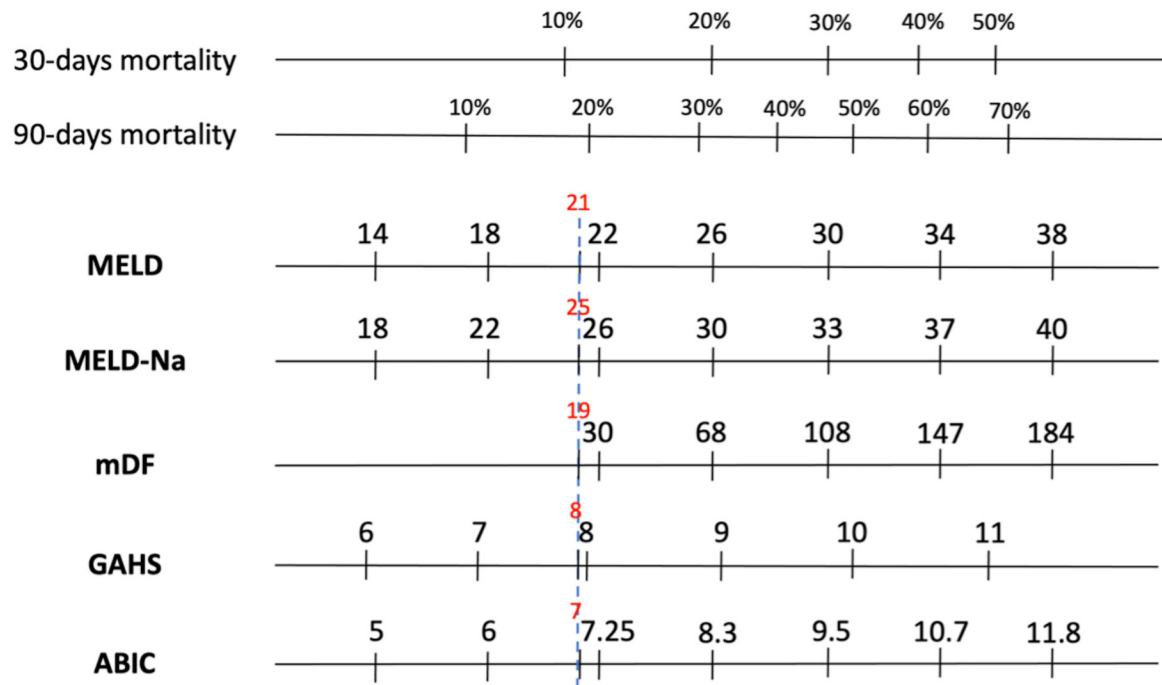|	Spain n=84	Mexico n=222	Korea n=274	USA n=291	Colombia n=40	France n=66	Brazil n=90	India n=366	Chile n=28	UK n=1,092	Canada n=28	Total n=2,581
Sex (male, %)	76.2	87.8	87.6	57.4	82.5	92.4	90	97.5	78.6	62.6	53.6	74.4
Age (years)	47 (43–55)	43 (35–50)	51 (45–58)	48 (38–55)	52 (48–60)	55 (49–61)	43.5 (37–50)	45 (39–51)	54.5 (47–64)	48.8 (42–56)	51.5 (38–58)	48 (41–55)
Race												
White (%)	77.4	0	0	79.7	0	89.4	67.8	0.3	0	96.1	78.6	57.7
Black (%)	0	0	0	12.7	0	3	2.2	0	0	0.5	0	1.8
Asian (%)	2.4	0	100	0	0	7.6	0	0	0	2.5	3.6	12
Latin American (%)	8.3	70.7	0	5.8	0	0	28.9	0	85.7	0	0	9
Indian (%)	0	0	0	0	0	0	0	99.7	0	0	0	14.1
No registered (%)	11.9	29.3	0	1.7	100	0	1.1	0	14.3	0.9	17.9	5.4
Deaths at 28 days (%)	14.3	37.8	16.1	24.1	27.5	15.2	22.2	23.2	14.3	15.9	7.1	20
Lost to follow-up 28d	2.4	3.2	10.9	5.5	15	0	17.8	16.7	0	0	7.1	5.4
Deaths at 90 days (%)	20.2	56.8	22.3	36.8	27.5	25.8	33.3	35	17.9	26.2	32.1	30.9
Lost to follow-up 90d	11.9	6.3	27	11	22.5	7.6	27.8	29.8	3.6	0	28.6	11.1
MELD	22.7 (18–27)	30.9 (25–37)	20.3 (17–26)	24.7 (21–31)	25.5 (19–31)	22.3 (19–26)	26.5 (21–36)	22.6 (19–26)	21.2 (18–27)	23.4 (21–26)	21.8 (20–26)	23.5 (20–28)
MELD-Na	21.2 (19–24)	32.7 (28–38)	23.5 (20–30)	28.4 (25–33)	27.5 (22–33)	25.3 (23–29)	30.7 (25–38)	-	22.6 (19–32)	26.3 (24–30)	25.8 (23–30)	26.8 (23–31)
mDF	56.3 (40–87)	71.6 (50–103)	38 (21–61)	52.5 (37–72)	51.6 (25–77)	47.3 (35–68)	53.9 (46–91)	66.1 (47–97)	40.9 (22–52)	55.4 (43–74)	-	55.6 (41–79)
GAHS	9 (8–10)	10 (9–11)	8 (7–9)	9 (8–10)	9 (8–11)	-	9 (8–10)	7.5 (7–8)	8 (7–9)	8 (7–9)	8 (7–9.7)	9 (7–10)
ABIC	7.6 (7–9)	8.5 (7–10)	7.5 (7–9)	7.9 (7–9)	8.8 (7–10)	8.2 (7–9)	8.3 (7–11)	7.5 (7–8)	8.2 (7–9)	8 (7–9)	8.1 (7–9)	7.9 (7–9)

	Spain n=84	Mexico n=222	Korea n=274	USA n=291	Colombia n=40	France n=66	Brazil n=90	India n=366	Chile n=28	UK n=1,092	Canada n=28	Total n=2,581
Alcohol consumption (g/day)	100 (80–140)	180 (118–320)	113 (60–150)	120 (45–229)	100 (100–180)	100 (75–150)	227.5 (125–584)	-	130 (92–181)	131.5 (84–210)	160 (85–200)	126 (84–210)
Corticosteroid treatment (%)	67.9	52.7	2.2	41.9	12.5	-	50	-	46.4	50.1	60.7	36.3

MELD: model for end-stage liver disease, mDF: Maddrey's discriminant function, GAHS: Glasgow alcoholic hepatitis score, ABIC: age, bilirubin, international normalized ratio and creatinine score

Table 2.

Baseline characteristics by country according to gender.

		Age (years)	P*	Deaths at 28 days (%)	P*	Deaths at 90 days (%)	P*	Alcohol consumption (g/day)	P*
Spain n=84	**Male n=64**	48 (43–55)	0.152	14.1	0.670	18.8	0.816	100 (80–140)	0.387
	Female n=20	45 (39–53)		15		25		80 (64–90)	
Mexico n=222	**Male n=195**	43 (35–50)	0.991	42.1	0.002	61.5	<0.001	196 (116–320)	0.307
	Female n=27	40 (38–52)		7.4		22.2		160 (120–240)	
Korea n=274	**Male n=240**	51 (45–59)	0.030	16.3	0.966	22.9	0.782	113 (60–150)	0.029
	Female n=34	45 (40–54)		14.7		17.6		60 (50–115)	
USA n=291	**Male n=167**	49 (40–56)	0.004	28.7	0.016	43.1	0.007	140 (45–246)	0.088
	Female n=124	44 (35–53)		17.7		28.2		100 (34–186)	
Colombia n=40	**Male n=33**	51 (48–60)	0.770	27.3		27.3	0.842	52 (51–61)	0.089
	Female n=7	52 (51–61)		28.6		28.6		100 (90–100)	
France n=66	**Male n=61**	55 (49–61)	1.000	16.4	1.000	26.2	0.547	55 (40–60)	0.589
	Female n=5	55 (40–60)		0		20		97 (71–123)	
Brazil n=90	**Male n=81**	44 (37–50)	1.000	22.2	0.850	33.3	0.909	43 (30–49)	0.482
	Female n=9	43 (30–49)		22.2		33.3		500 (150–723)	
India n=366	**Male n=357**	45 (39–51)	0.521	22.7	0.311	34.7	0.809	-	-
	Female n=9	37 (35–49)		44.4		44.4		-	
Chile n=28	**Male n=22**	52 (48–64)	0.648	9.1	0.191	13.6	0.488	140 (100–200)	0.317

		Age (years)	P*	Deaths at 28 days (%)	P*	Deaths at 90 days (%)	P*	Alcohol consumption (g/day)	P*
	Female n=6	62 (42–66)		33.3		33.3		100 (85–135)	
UK n=1,092	**Male n=684**	49 (42–57)	0.012	16.7	0.442	28.7	0.019	140 (100–218)	<0.001
	Female n=408	47 (41–55)		14.7		22.1		105 (70–181)	
Canada n=28	**Male n=15**	53 (46–59)	0.449	6.7	0.393	33.3	0.755	160 (96–200)	0.695
	Female n=13	51 (36–57)		7.7		23.1		120 (72–200)	
Total n=2,581	**Male n=1,919**	49 (41–56)	0.005	21.5	<0.001	33.3	<0.001	140 (98–224)	<0.001
	Female n=662	47 (40–54)		15.6		23.9		101 (68–180)	

*Global and by country gender differences in age, mortality and alcohol consumption

Table 3.

ROC curves to predict mortality at 28 and 90 days per country.

Mortality at 28 days

	Spain	Mexico	Korea	USA	Colombia	France	Brazil	India	Chile	UK	Canada
MELD	0.740 #	0.748 *	0.810 *	0.727 *	0.759 #	0.698	0.775 *	0.640 *	0.967 *	0.739 *	0.909 *
AUC, 95% CI	(0.550–0.929)	(0.684–0.812)	(0.745–0.875)	(0.650–0.803)	(0.597–0.920)	(0.414–0.981)	(0.648–0.902)	(0.577–0.703)	(0.877–1.057)	(0.699–0.780)	(0.749–1.069)
MELD-Na	0.875 *	0.749 *	0.802 *	0.718 *	0.721 #	0.673	0.759 *	-	0.967 *	0.742 *	0.932 *
AUC, 95% CI	(0.762–0.988)	(0.685–0.813)	(0.735–0.870)	(0.640–0.797)	(0.547–0.895)	(0.431–0.914)	(0.637–0.881)		(0.877–1.057)	(0.701–0.783)	(0.696–1.077)
mDF	0.656	0.677 *	0.744 *	0.654 *	0.702 #	0.679	0.753 *	0.624 *	0.767 #	0.679 *	-
AUC, 95% CI	(0.468–0.845)	(0.606–0.748)	(0.661–0.828)	(0.570–0.738)	(0.503–0.901)	(0.399–0.959)	(0.629–0.877)	(0.559–0.688)	(0.553–0.980)	(0.636–0.723)	
GAHS	0.807 #	0.718 *	0.760 *	0.653 *	0.633	-	0.820 *	-	0.867 *	0.759 *	0.830 #
AUC, 95% CI	(0.608–1.007)	(0.649–0.786)	(0.685–0.834)	(0.568–0.738)	(0.427–0.839)		(0.696–0.943)		(0.695–1.038)	(0.719–0.799)	(0.584–1.075)
ABIC	0.802 *	0.665 *	0.737 *	0.727 *	0.743 #	0.802 #	0.701 #	0.601 #	0.967 *	0.751 *	0.886 *
AUC, 95% CI	(0.644–0.961)	(0.594–0.735)	(0.655–0.819)	(0.646–0.808)	(0.562–0.923)	(0.589–1.016)	(0.569–0.834)	(0.533–0.669)	(0.877–1.057)	(0.711–0.792)	(0.696–1.077)

Mortality at 90 days

	Spain	Mexico	Korea	USA	Colombia	France	Brazil	India	Chile	UK	Canada
MELD	0.847 *	0.765 *	0.836 *	0.766 *	0.759 #	0.694	0.748 *	0.645 *	0.967 *	0.709 *	0.914 *
AUC, 95% CI	(0.701–0.992)	(0.700–0.829)	(0.784–0.889)	(0.698–0.834)	(0.597–0.920)	(0.478–0.911)	(0.624–0.871)	(0.587–0.703)	(0.877–1.057)	(0.674–0.745)	(0.803–1.025)
MELD-Na	0.867 *	0.771 *	0.831 *	0.766 *	0.721 #	0.708 #	0.736 *	-	0.967 *	0.709 *	0.898 *
AUC, 95% CI	(0.726–1.007)	(0.707–0.835)	(0.775–0.888)	(0.699–0.834)	(0.547–0.895)	(0.516–0.900)	(0.613–0.860)		(0.877–1.057)	(0.673–0.744)	(0.772–1.025)
mDF	0.693	0.686 *	0.764 *	0.696 *	0.702 #	0.519	0.673 #	0.619 *	0.767 #	0.673 *	-
AUC, 95% CI	(0.495–0.902)	(0.613–0.759)	(0.693–0.836)	(0.622–0.770)	(0.503–0.901)	(0.265–0.772)	(0.535–0.912)	(0.560–0.678)	(0.553–0.980)	(0.637–0.710)	
GAHS	0.897 *	0.729 *	0.802 *	0.724 *	0.633	-	0.791 *	-	0.867 *	0.718 *	0.941 *

	Spain	Mexico	Korea	USA	Colombia	France	Brazil	India	Chile	UK	Canada
Mortality at 28 days											
AUC, 95% CI	(0.760–1,033)	(0.662–0.797)	(0.743–0.861)	(0.652–0.796)	(0.427–0.839)		(0.675–0.906)		(0.695–1,038)	(0.682–0.753)	(0.852–1,031)
ABIC	**0.880** *	**0.701** *	**0.739** *	**0.789** *	**0.743** #	**0.736** #	**0.694** #	**0.599** #	**0.967** *	**0.726** *	**0.945** *
AUC, 95% CI	(0.760–1,000)	(0.631–0.772)	(0.669–0.809)	(0.724–0.854)	(0.562–0.923)	(0.538–0.934)	(0.561–0.827)	(0.539–0.659)	(0.877–1,057)	(0.691–0.761)	(0.856–1,035)

#
p<0.05

*
p<0.001

MELD: model for end-stage liver disease, mDF: Maddrey's discriminant function, GAHS: Glasgow alcoholic hepatitis score, ABIC: age, bilirubin, international normalized ratio and creatinine score, AUC: area under curve, CI: confidence interval

Table 4.

Receiver operation characteristic analysis for different cut-off values of the different prognostic scores to predict death at 28 and 90 days.

Mortality at 28 days					
	MELD	**MELD-Na**	**mDF**	**GAHS**	**ABIC**
Cut-off value	25	28	51	9	9
Sensitivity, 95% CI	68 (64–72)	77 (73–81)	81 (77–84)	59 (54–64)	57 (53–61)
Specificity, 95% CI	70 (68–72)	67 (65–69)	48 (45–50)	81 (79–83)	77 (75–79)
Positive LR, 95% CI	2.3 (2.1–2.5)	2.3 (2.1–2.5)	1.5 (1.5–1.6)	3.1 (2.7–3.5)	2.5 (2.2–2.8)
Negative LR, 95% CI	0.4 (0.4–0.5)	0.3 (0.3–0.4)	0.4 (0.3–0.5)	0.5 (0.4–0.6)	0.6 (0.5–0.6)
PPV, 95% CI	36 (34–38)	36 (34–38)	29 (27–30)	43 (40–46)	38 (36–41)
NPV, 95% CI	90 (89–91)	92 (91–94)	90 (89–92)	89 (88–90)	88 (87–89)
Mortality at 90 days					
	MELD	**MELD-Na**	**mDF**	**GAHS**	**ABIC**
Cut-off value	25	28	52	8	9
Sensitivity, 95% CI	63 (60–67)	71 (67–74)	76 (72–79)	77 (73–80)	55 (51–58)
Specificity, 95% CI	73 (71–76)	71 (69–73)	54 (52–57)	60 (57–63)	77 (75–79)
Positive LR, 95% CI	2.4 (2.2–2.6)	2.4 (2.2–2.7)	1.6 (1.5–1.8)	1.9 (1.8–2.1)	2.4 (2.2–2.7)
Negative LR, 95% CI	0.5 (0.5–0.6)	0.4 (0.4–0.5)	0.4 (0.4–0.5)	0.4 (0.3–0.4)	0.6 (0.5–0.6)
PPV, 95% CI	52 (49–54)	51 (49–54)	43 (41–45)	46 (44–48)	52 (49–54)
NPV, 95% CI	82 (80–83)	85 (83–86)	83 (81–85)	85 (83–87)	79 (78–81)

MELD: model for end-stage liver disease, mDF: Maddrey's discriminant function, GAHS: Glasgow alcoholic hepatitis score, ABIC: age, bilirubin, international normalized ratio and creatinine score, CI: confidence interval, LR: likelihood ratio, PPV: positive predictive value, NPV: negative predictive value