MELD 3.0 adequately predicts mortality and renal replacement therapy requirements in patients with alcohol-associated hepatitis

Authors

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Graphical abstract
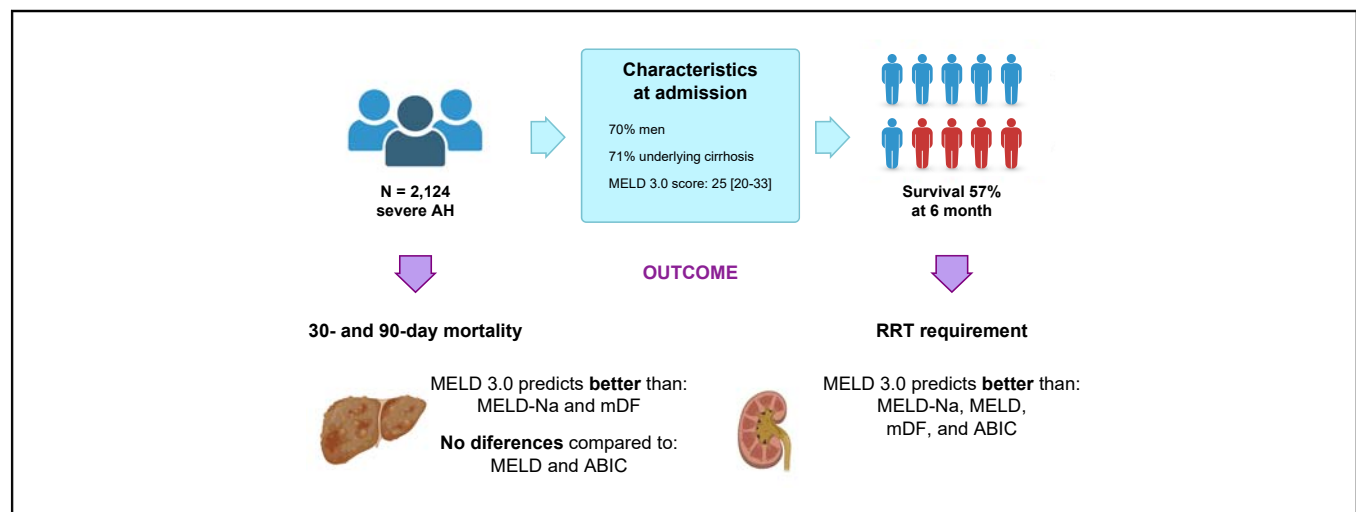
Highlights

- AH hepatitis is associated with multi-organ failure and high short-term mortality.
- MELD 3.0 predicted 30- and 90-day mortality better compared with the MELD-Na score and mDF.
- MELD 3.0 was not superior to MELD and ABIC scores in predicting mortality, but its classification accuracy was similar between countries.
- MELD 3.0 was the best predictor of renal replacement therapy requirements compared with other models.

Impact and implications

Severe AH has high short-term mortality. The establishment of treatments and liver transplantation depends on mortality prediction. We evaluated the performance of the new MELD 3.0 score to predict short-term mortality in AH in a large global cohort. MELD 3.0 performed better in predicting 30- and 90-day mortality compared with MELD-Na and mDF, but was similar to MELD and ABIC scores. MELD 3.0 was the best predictor of renal replacement therapy requirements. Thus, further prospective studies are needed to support the wide use of MELD 3.0 in AH.

MELD 3.0 adequately predicts mortality and renal replacement therapy requirements in patients with alcohol-associated hepatitis

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Background & Aims: Model for End-Stage Liver Disease (MELD) score better predicts mortality in alcohol-associated hepatitis (AH) but could underestimate severity in women and malnourished patients. Using a global cohort, we assessed the ability of the MELD 3.0 score to predict short-term mortality in AH.

Methods: This was a retrospective cohort study of patients admitted to hospital with AH from 2009 to 2019. The main outcome was all-cause 30-day mortality. We compared the AUC using DeLong's method and also performed a time-dependent AUC with competing risks analysis.

Results: A total of 2,124 patients were included from 28 centres from 10 countries on three continents (median age 47.2 ± 11.2 years, 29.9% women, 71.3% with underlying cirrhosis). The median MELD 3.0 score at admission was 25 (20–33), with an estimated survival of 73.7% at 30 days. The MELD 3.0 score had a better performance in predicting 30-day mortality (AUC:0.761, 95%CI:0.732–0.791) compared with MELD sodium (MELD-Na; AUC: 0.744, 95% CI: 0.713–0.775; $p = 0.042$) and Maddrey's discriminant function (mDF) (AUC: 0.724, 95% CI: 0.691–0.757; $p = 0.013$). However, MELD 3.0 did not perform better than traditional MELD (AUC: 0.753, 95% CI: 0.723–0.783; $p = 0.300$) and Age-Bilirubin-International Normalised Ratio-Creatinine (ABIC) (AUC:0.757, 95% CI: 0.727–0.788; $p = 0.765$). These results were consistent in competing-risk analysis, where MELD 3.0 (AUC: 0.757, 95% CI: 0.724–0.790) predicted better 30-day mortality compared with MELD-Na (AUC: 0.739, 95% CI: 0.708–0.770; $p = 0.028$) and mDF (AUC:0.717, 95% CI: 0.687–0.748; $p = 0.042$). The MELD 3.0 score was significantly better in predicting renal replacement therapy requirements during admission compared with the other scores (AUC: 0.844, 95% CI: 0.805–0.883).

Conclusions: MELD 3.0 demonstrated better performance compared with MELD-Na and mDF in predicting 30-day and 90-day mortality, and was the best predictor of renal replacement therapy requirements during admission for AH. However, further prospective studies are needed to validate its extensive use in AH.

Impact and implications: Severe AH has high short-term mortality. The establishment of treatments and liver transplantation depends on mortality prediction. We evaluated the performance of the new MELD 3.0 score to predict short-term mortality in AH in a large global cohort. MELD 3.0 performed better in predicting 30- and 90-day mortality compared with MELD-Na and mDF, but was similar to MELD and ABIC scores. MELD 3.0 was the best predictor of renal replacement therapy requirements. Thus, further prospective studies are needed to support the wide use of MELD 3.0 in AH.

Introduction

Alcohol-associated liver disease (ALD) constitutes a leading cause of alcohol-related deaths worldwide.[1–3] In fact, ~40% of all deaths resulting from liver disease are attributable to ALD.[4,5] Alcohol-associated hepatitis (AH) is a severe form of ALD and is caused by sustained and excessive alcohol consumption.[6,7] Among patients with severe forms of AH, the mortality at 6 months may be as high as 30–40%.[8,9] Corticosteroids are considered the first-line pharmacological therapy in severe cases and are recommended by clinical guidelines.[10–13]

The Model of End-Stage Liver Disease (MELD) and modified Maddrey's discriminant function (mDF) scores have been shown to accurately predict mortality, where a score of >20 or ≥32, respectively, is associated with lower 90-day survival.[14,15] A recent study demonstrated that the MELD score best predicted 90-day mortality in AH.[16] Since its original description in 2002, the MELD score has been modified in several aspects.[17] MELD sodium (MELD-Na) did not further improve the accuracy of MELD to predict mortality, whereas the mDF demonstrated the poorest performance as a static score to predict 90-day mortality in AH.[16] Despite the usefulness of MELD, it could underestimate severity in women and malnourished patients.[18,19] To overcome these limitations, a new version of MELD (MELD 3.0) was recently developed.[20] This version added female gender and albumin to the score, demonstrating a slightly more accurate mortality prediction compared with MELD-Na in patients with cirrhosis.[20]

Severe AH constitutes an acute decompensation and could be present across the ALD spectrum.[21] Most patients with AH are malnourished and have sarcopenia, which can also be worsened by corticosteroids and acute kidney injury (AKI).[22] In addition, it is not easy to estimate renal function, and AKI is strongly associated with mortality in AH.[22] Thus, it appears crucial to have a

score with high accuracy in predicting mortality in different scenarios and the need for renal replacement therapy (RRT) to facilitate decision-making. Therefore, we assessed the ability of the MELD 3.0 to predict 30- and 90-day mortality in AH in a worldwide cohort study, compared with other scoring systems. We also explored the performance of MELD 3.0 in predicting mortality, assessing different subgroups according to corticosteroid use, sex, and prediction of RRT requirements during hospitalisation.

Patients and methods

Study design and participants

We conducted a retrospective registry-based study of patients admitted to hospital with severe AH. We included patients who met the National Institute on Alcohol Abuse and Alcoholism (NIAAA) clinical criteria of severe AH.[23] The specific inclusion criteria were: (i) A history of alcohol use of >60 g/day in men and >40 g/day in women; (ii) aspartate aminotransferase (AST) <400 U/L with AST/alanine aminotransferase (ALT) ratio >1.5; (iii) serum γ-glutamyl transpeptidase (GGT) >80 mg/dl; (iv) abnormal coagulation tests (prolonged prothrombin time and/or International Normalised Ratio [INR] values); and (v) serum bilirubin levels >3 mg/dl. According to clinical criteria, those with uncertain AH diagnosis underwent a liver biopsy to confirm the diagnosis of AH. Only patients meeting all the clinical criteria (probable AH) or biopsy-proven AH (definite AH) independent of corticosteroid use were included.

The diagnosis of cirrhosis was based on prior medical history and imaging (ultrasound, transient elastography, computed tomography, or magnetic resonance imaging). Liver biopsy was performed in patients whose diagnosis was unclear (confounding factors) based on the attending physician's criteria.

Treatment with corticosteroids and their continuation or discontinuation following an assessment of response was based on the discretion of the treating physician. We excluded patients who: (i) were less than 18 years old; (ii) were pregnant; (iii) had AST and/or ALT levels >400 IU/ml; (iv) had had prolonged alcohol abstinence (>60 days) before admission; (v) had drug-induced liver injury (DILI), ischemic hepatitis, biliary duct obstruction, viral hepatitis, autoimmune hepatitis, or Wilson disease; (vi) had hepatocellular carcinoma beyond Milan criteria; (vii) had extrahepatic neoplasia with a life expectancy of less than 6 months; or (viii) had a history of severe extrahepatic disease that conferred a survival of less than 6 months. For patients with more than one admission, information was registered only for the first episode of AH.

Data collection

We performed a retrospective review of the records of patients hospitalised with a diagnosis of severe AH (from January 2009 to January 2019). We recorded laboratory results performed during admission, as well as the type of steroids and length of use. We also recorded the MELD, MELD-Na, mDF, and Age-Bilirubin-International Normalised Ratio-Creatinine (ABIC) scores at admission, infections, mortality, and causes of death at 90 days.[14,24–26] We calculated the MELD 3.0 score according to the formula described by Kim et al.:[20]

MELD 3.0 = 1.33 (if female) + 4.56*$\log_e$ (bilirubin) + 0.82*(137–Na) – 0.24*(137–Na)*$\log_e$ (bilirubin) + 9.09*$\log_e$ (INR) + 11.14*$\log_e$ (creatinine) + 1.85*(3.5–albumin) – 1.83*(3.5–albumin)*$\log_e$ (creatinine) + 6.

We assessed the Lille score at day 7 of patients who were treated with corticosteroids.[27]

The data collected were recorded in a confidential electronic case report form, which was used at all the centres collecting the data. The electronic database was only managed by the main researchers of the study. We requested an informed consent waiver at each participating centre, and data were de-identified before analysis.

Statistical analysis

The primary outcome was 30-day mortality in patients with severe AH. The secondary outcomes were 90-day mortality and RRT requirements during admission. As an exploratory analysis, we assessed the performance of scores to predict 30-day and 90-day mortality in patients stratified by sex and those who underwent corticosteroid treatment. We also evaluated response to corticosteroid treatment at day 7 using the Lille score. Categorical variables were summarised using frequencies and percentages. We assessed normal distribution in continuous data using the Kolmogorov–Smirnov test and histograms. Continuous variables with normal distribution were described by mean and SD. Variables without a normal distribution were summarised using the median and interquartile ranges. Analyses were completed using the Chi-square test for categorical variables, the Student's t test for normally distributed continuous variables, and non-parametric tests for continuous variables that were not normally distributed.

We constructed receiver operating characteristics (ROC) curves to assess the accuracy of prognosis scores, and we calculated the AUC. We used DeLong's method to test for statistically significant differences between ROC curves.[28] We specified a tie-corrected non-parametric estimate (trapezoidal approximation) because of the assumption that the true ROC curve was smooth. This means that the classifiers measured (i.e. MELD 3.0, MELD-Na, MELD, mDF, and ABIC) were a discretised approximation of a true latent and a continuous classifier. The SEs and CIs were estimated through bootstrapping. We also estimated mortality in time-dependent AUC with competing risk (liver transplantation) using the inverse probability of censoring weighted method.[29,30] We determined the optimal cut-off point to predict RRT requirements using the Youden index. We also assessed the sensitivity and specificity of each cut-off value. Those patients who were lost to follow-up were censored in the analyses. Heterogeneity among countries was assessed by comparing the AUC adjusted by country using the STATA 'comproc' command. With 'comproc', the Wald test results for marker comparisons are based on the bootstrap SEs for the difference between markers.[31,32] We evaluated the incremental value of each country by comparing the AUC for logistic models predicting 30-day mortality when including or not the country of each patient.[31,32]

We calibrated the probability of 30- and 90-day mortality in AH using calibration plots with the user-written STATA module 'calibrationbelt'.[33] A second logit regression model was formulated to assess the relationship of predictions to the true probabilities of the event, based upon a polynomial transformation of the predictions, the degree of the polynomial (beginning with second order) being forwardly selected based on a sequence of likelihood ratio tests. The deviation of the calibration belt from the identity line was reported with a p value. For all analyses, p <0.05 was considered significant. This manuscript adheres to the TRIPOD statement for reporting prediction models.[34] The analyses were performed with STATA software version 14 (StataCorp, College Station, TX, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the cohort

We included a total of 2,124 patients from 28 centres (10 countries on three continents). The median number of patients included per centre was 26 (10–72) (Table S1). The mean age was 47.2 ± 11.2-years old, 29.9% were women, and 71.3% had a previous history of cirrhosis. The median MELD, MELD-Na, and MELD 3.0 scores at admission were 25 (20–31), 28 (24–34), and 25 (20–33), respectively. In addition, the median mDF and ABIC scores were 58 (40–83) and 8.0 (6.9–9.0), respectively. Patients presented with median albumin of 2.6 (2.0–3.0) g/dl, bilirubin of 13.3 (7.0–23.7) mg/dl, and INR of 1.9 (1.6–2.3). At admission, median creatinine was 0.8 (0.6–1.5) mg/dl, blood urea nitrogen (BUN) of 13 (7–27) mg/dl, and plasma sodium of 132 (128–136) mEq/L; 12.1% of patients required RRT during the hospitalisation. The main characteristics of the cohort and the differences according to the previous history of cirrhosis are summarised in Table 1.

The median follow-up was 183 (27–799) days. A total of 167 (7.9%) and 254 (12%) patients were lost to follow-up at 30 and 90 days, respectively. The overall estimated survival since admission was 73.7% (95% CI: 71.5–75.8%) at 30 days, 62.5% (95% CI: 59.9–65.0%) at 90 days, and 57.2% (95% CI: 54.5–59.7%) at 180 days. Of the patients, 13% underwent liver transplantation, with a median time between admission and liver transplantation was 204 (65–437) days. The main attributed causes of death were multi-organ failure (37.2%), infections (17.6%), gastrointestinal bleeding (12.1%), and AKI (6.3%); several patients had more than

Table 1. Baseline characteristics of all patients in the study and according to the presence of cirrhosis[*],[†].

Characteristics	Global (n = 2,124)	Patients without cirrhosis (n = 475)	Patients with cirrhosis (n = 1,177)	p value[‡]
Age (yr)[†]	47.2 ± 11.2	44.9 ± 11.2	49.1 ± 11.0	<0.001
Female (%)	29.9	37.7	33.9	0.154
Race/ethnicity (%)				<0.001
White	51.3	54.7	66.0	
Asian	22.5	3.2	5.6	
Hispanic or Latino	13.3	21.3	14.1	
Black	6.5	12.4	6.5	
American-Indian	1.5	1.9	1.9	
Native Hawaiian/Pacific Islander	1.2	1.7	1.5	
Unknown	3.7	4.8	4.3	
Cirrhosis (%)	71.3	–	–	–
MELD at admission[§]	25 (20–31)	24 (19–30)	26 (22–31)	0.006
MELD-Na at admission[§]	29 (24–34)	28 (23–33)	29 (24–34)	<0.001
MELD 3.0 at admission[§]	25 (20–33)	24 (18–31)	26 (20–34)	<0.001
mDF at admission[§]	58 (40–83)	46 (31–67)	56 (40–83)	<0.001
ABIC at admission[§]	8.0 (6.9–9.0)	7.3 (6.2–8.7)	8.2 (7.1–9.2)	<0.001
Laboratory testing:[§]				
Total bilirubin (mg/dl)	13.3 (7.0–23.7)	11.1 (5.5–22.0)	12.3 (6.7–23.0)	0.114
INR	1.9 (1.6–2.3)	1.6 (1.3–2.0)	1.9 (1.6–2.3)	<0.001
Creatinine (mg/dl)	0.8 (0.6–1.5)	0.8 (0.6–1.4)	0.9 (0.6–1.6)	0.004
Sodium (mEq/L)	132 (128–136)	132 (128–136)	132 (128–136)	0.321
Albumin (g/dl)	2.6 (2.0–3.0)	2.8 (2.2–3.2)	2.7 (2.2–3.0)	0.030
Corticosteroid use (%)	45.7	52.1	48.9	0.243
Dialysis[¶] (%)	12.1	6.3	8.5	0.153

ABIC, Age-Bilirubin-International Normalised Ratio-Creatinine; INR, International Normalised Ratio; mDF, Maddrey's discriminant function; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease sodium.
[*] A total of 1,652 (77.8%) had data related to the presence of cirrhosis.
[†] Comparisons were performed using the Chi-square test for categorical variables, the Student's t test for normally distributed continuous variables, and non-parametric tests for continuous variables that were not normally distributed.
[‡] p value for patients without vs. with cirrhosis.
[§] Median and interquartile range (25–75).
[¶] At least twice over the previous week.

one cause of death (5%). In total, 46.3% of patients developed an infection during hospitalisation. The most common were the urinary tract infections (37.6%), respiratory tract infections (18.1%), and spontaneous bacterial peritonitis (6.0%). In total, 44.3% of infected patients had bacteraemia with positive blood cultures.

Performance MELD 3.0 and other models in alcohol-associated hepatitis

The median MELD 3.0 score at admission was 24 (19–30) in survivors and 34 (27–43) in patients who died at 30 days (p <0.001). The MELD 3.0 score had a better performance in predicting 30-day mortality (AUC 0.761, 95% CI: 0.732–0.791) compared with MELD-Na (AUC 0.744, 95% CI: 0.713–0.775; p = 0.042) and mDF (AUC 0.724, 95% CI: 0.691–0.757; p = 0.013) (Fig. 1A). MELD 3.0 was also superior (AUC 0.744, 95% CI: 0.718–0.771) to MELD-Na (AUC 0.721, 95% CI: 0.694–0.749; p = 0.003) and mDF (AUC 0.706, 95% CI: 0.677–0.735; p = 0.004) in predicting 90-day mortality (Fig. 1B). However, MELD 3.0 was similar to traditional MELD and ABIC in predicting 30- and 90-day mortality (Table 2). A MELD 3.0 score >20 had a sensitivity of 91.5% and a specificity of 32.6% in predicting 30-day mortality and was slightly better than the previous versions of MELD (Tables S2–S4). The sensitivity and specificity of mDF and ABIC are described in Tables S5 and S6. In patients deceased at 90 days, MELD 3.0 showed an increased score in 279 (54.2%) patients and a decreased score in 193 (37.5%) patients, with 43 (8.3%) patients not having any change compared with MELD-Na (Table S7). In addition, we performed a time-dependent AUC with competing risk analysis to better understand the performance of models in predicting mortality, weighting the benefit

in survival following a liver transplant. In this analysis assessing transplant as a competing risk, MELD 3.0 was also superior to MELD-Na and mDF in predicting 30- and 90-day mortality (Table S8).

We assessed the calibration of models in predicting 30- and 90-day mortality. Although most models had an acceptable calibration, the MELD 3.0 demonstrated the best calibration for predicting 30- and 90-day mortality, whereas mDF showed the poorest calibration. Of note, ABIC showed a regular calibration in patients with higher scores (Fig. S1). Heterogeneity between countries was also assessed by comparing AUC adjusted per country. The discriminatory accuracy of MELD 3.0 did not significantly differ by adjusting by country (Table S9). However, MELD and ABIC significantly improved their discriminatory accuracy adjusting by country (p = 0.047 and p = 0.012 for testing the incremental predicting value of the country, respectively) (Table S9).

In total, 45.7% of patients were treated with corticosteroids. Their mean age was 47.2 ± 10.9 years old, 29.8% were women, 69.7% had a prior history of cirrhosis, and they had a median MELD 3.0 score of 26 (21–32). In these patients, the overall performance of MELD 3.0 (AUC 0.728, 95% CI: 0.681–0.776) was only superior to mDF in predicting 30-day mortality (AUC 0.681, 95% CI:0.628–0.733; p = 0.048) (Table S10). However, MELD 3.0 demonstrated a better performance in predicting 90-day mortality (AUC 0.720, 95% CI: 0.679–0.760) compared with MELD-Na (AUC 0.687, 95% CI: 0.645–0.729; p = 0.013) and traditional MELD (AUC 0.693, 95% CI: 0.651–0.735; p = 0.049) (Table S10). Only 51.7% of patients who underwent corticosteroid treatment achieved the criteria of responders at day 7. ABIC demonstrated a superior performance (AUC 0.746, 95% CI: 0.708–0.784) in
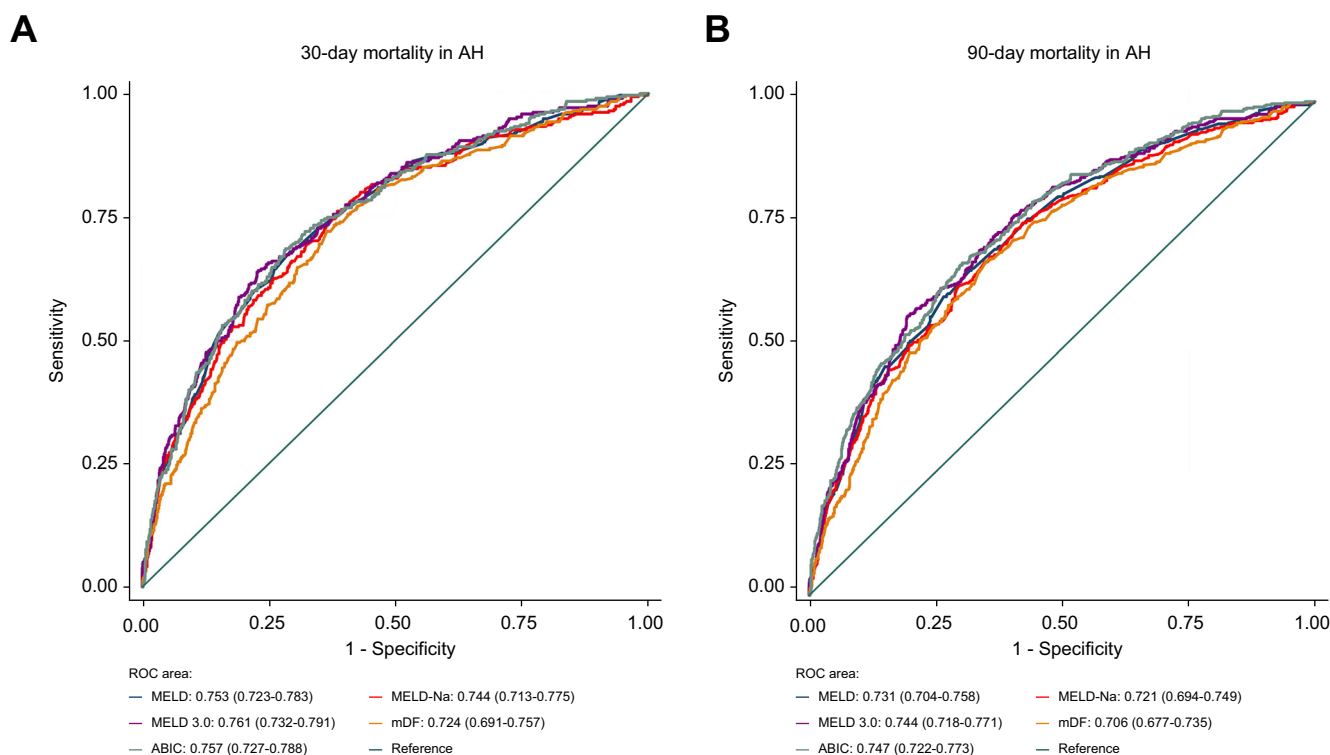
Fig. 1. Comparison of MELD-Na and MELD 3.0 in predicting mortality in AH. Receiver operating characteristic curves and AUC were generated, and MELD 3.0 score was superior to MELD-Na and mDF predicting (A) 30-day mortality and (B) 90-day mortality. The 95% CIs are given in parentheses. AH, alcohol-associated hepatitis; ABIC, Age-Bilirubin-International Normalised Ratio-Creatinine; MELD, Model of End-Stage Liver Disease; MELD-Na, MELD, Model of End-Stage Liver Disease-sodium.

predicting response to corticosteroid treatment *vs.* MELD 3.0 (AUC 0.685, 95% CI: 0.644–0.727; *p* = 0.002), whereas MELD 3.0 was superior to the other models (Table S11).

Impact of sex on survival prediction
The median MELD 3.0 score at admission according to sex was 26 (20–34) in men and 25 (18–32) in women (*p* = 0.012). MELD 3.0 did not perform better over the other models in predicting 30-day mortality for men or women exclusively (Table S12). However, it did demonstrate a better performance in predicting 90-day mortality compared with MELD-Na (AUC 0.724, 95% CI: 0.691–0.758; *p* = 0.013) in men, and mDF (AUC 0.686, 95% CI: 0.636–0.737; *p* = 0.031) in women (Table S12).

Renal replacement therapy requirements in AH
We also explored the performance of the scores in predicting RRT requirements during hospitalisation. The estimated survival was lower in patients who required RRT compared with those who did not at 30 days (47.7%, 95% CI: 40.6–54.5% *vs.* 78.2%, 95%

CI: 75.7–80.4%) and at 90 days (30.5%, 95% CI: 24.1–37.1% *vs.* 68%, 95% CI: 65.1–70.6%) (*p* <0.001) (Fig. 2A). MELD 3.0 demonstrated the best performance predicting RRT requirement during hospitalisation (AUC 0.844, 95% CI: 0.805–0.883) compared with all the other models (Fig. 2B; Table S13). A MELD 3.0 score of 35 or more had a sensitivity of 74.1% and a specificity of 81.6% for predicting RRT requirements during admission (Table S14).

Discussion
MELD and MELD-Na scores have previously demonstrated a higher accuracy in predicting short-term mortality in AH compared with other models.[16] However, there are several concerns about the use of MELD and MELD-Na scores because of potential disparities in women and malnourished patients. In this large cohort study, we evaluated the performance of the third iteration of the MELD score (MELD 3.0) for predicting mortality in severe AH. We identified a slight but significantly better performance of the MELD 3.0 score over MELD-Na and

Table 2. Performance of MELD 3.0, MELD-Na, MELD, mDF, and ABIC scores in predicting 30- or 90-day mortality in AH[*].

Model	30-day mortality (95% CI)	*p* value	90-day mortality (95% CI)	*p* value
MELD 3.0	0.761 (0.732–0.791)	Reference	0.744 (0.718–0.771)	Reference
MELD-Na	0.744 (0.713–0.775)	0.042	0.721 (0.694–0.749)	0.003
MELD	0.753 (0.723–0.783)	0.300	0.731 (0.704–0.758)	0.064
mDF	0.724 (0.691–0.757)	0.013	0.706 (0.677–0.735)	0.004
ABIC	0.757 (0.727–0.788)	0.765	0.747 (0.722–0.773)	0.825

ABIC, Age-Bilirubin-International Normalised Ratio-Creatinine; AH, alcohol-associated hepatitis; mDF, modified Maddrey's discriminant function; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease sodium; ROC, receiver operating curve.
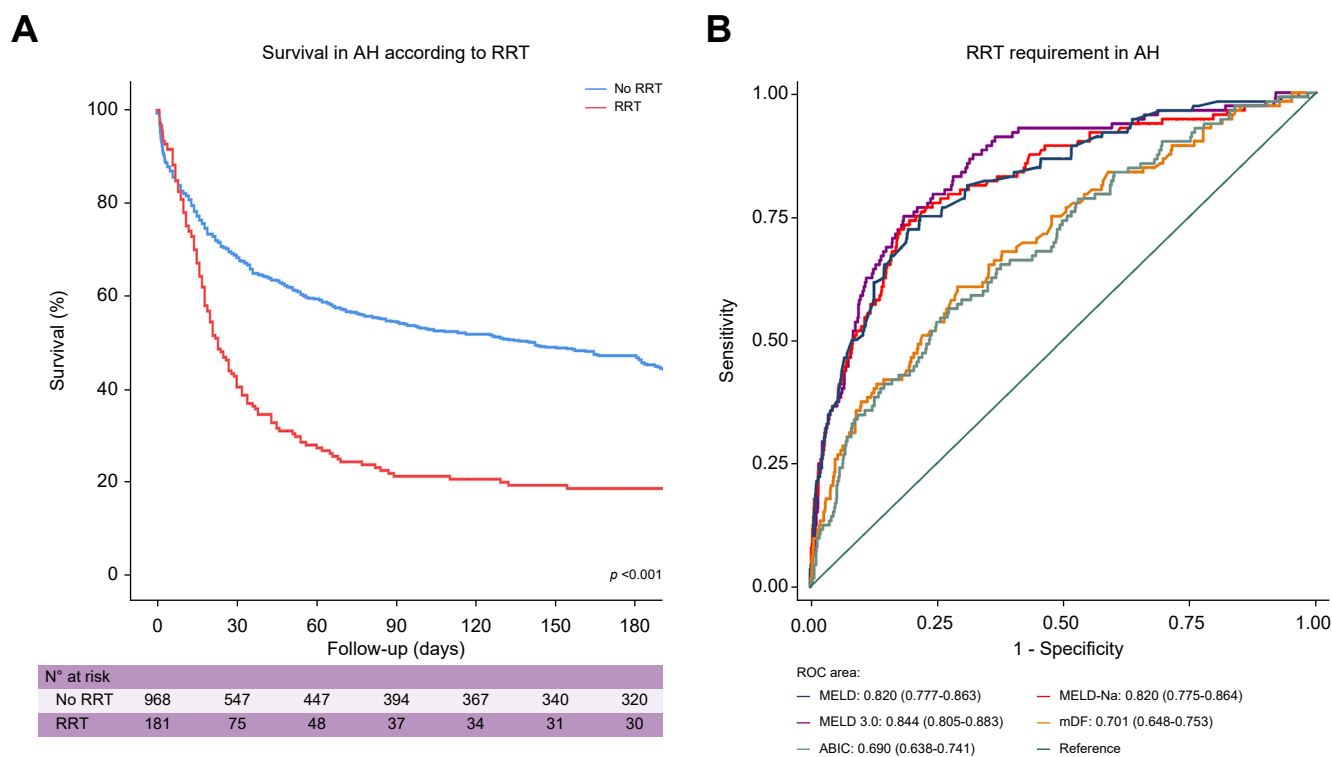* We performed comparisons between ROC AUC using DeLong's method.

Fig. 2. Short-term survival of patients with AH. (A) Per RRT requirement and (B) comparison of models in predicting RRT requirements. Survival was estimated using Kaplan–Meier curves, and comparisons were performed using log-rank tests. Receiver operating characteristic curves and AUC were generated to compare performance between models in predicting RRT requirement. The 95% CIs are given in parentheses. AH, alcohol-associated hepatitis; ABIC, Age-Bilirubin-International Normalised Ratio-Creatinine; MELD, Model of End-Stage Liver Disease; MELD-Na, MELD, Model of End-Stage Liver Disease-sodium; RTT, renal replacement therapy.

mDF in predicting 30-day mortality, although this was similar with all three models at 90 days. In addition, the MELD 3.0 score up-categorised 54.2% of deceased patients at 90 days over the MELD-Na score. Interestingly, we observed that MELD 3.0 had the highest performance in predicting RRT during admission compared with the other models (AUC 0.84, 95% CI: 0.81–0.88). Although MELD 3.0 did not demonstrate a better performance compared with traditional MELD and ABIC scores, its calibration was slightly better, especially in patients with higher scores, and its classification accuracy was similar among different countries.

Historically, mDF has been used as a predictor of mortality risk in patients with severe AH (with a score over 32) based on a retrospective analysis.[24] However, it requires the use of prothrombin time (PT), which has been largely replaced by the INR, and its reference value is not always reported by many clinical laboratories. In addition, mDF had the poorest performance in this study. Thus, a MELD score of 21 or higher demonstrated a better accuracy yield predicting mortality in severe AH.[35] Since 2016, the MELD-Na score has been used for liver allocation instead of MELD, because hyponatraemia was recognised as a prominent independent risk factor for mortality in end-stage liver disease.[25] MELD-Na has also been used in patients with AH, with a similar performance to MELD.[16] As a novel feature, MELD 3.0 includes the addition of two variables (female gender and serum albumin), demonstrating a more accurate mortality prediction compared with MELD in patients with cirrhosis and improving previous disparities in allocation for liver transplantation among patients with decompensated cirrhosis.[20]

The first MELD score included only three variables (serum bilirubin, serum creatinine, and INR), which could imply several shortcomings. For example, interlaboratory variability in the INR and creatinine measurements can contribute to an overall mean variation in calculated MELD of 4.8 points (range 2–11).[36] Likewise, hyperbilirubinaemia can substantially affect the result of a colorimetric assay used to measure creatinine. In addition, key factors that contribute to rising mortality are not assessed (e.g. hypoalbuminaemia). Some patients with AH have chronic liver disease, alcohol use disorder, or other causes that lead to malnutrition, which impacts mortality and transplant requirements.[19] As an acute phase reactant, there might be other reasons for alterations of albumin in these patients. Such differences in laboratory values can also be observed according to sex. Indeed, in a steady state, the main determinant of serum creatinine is its endogenous production, in which several factors, unrelated to renal function, have a role, mainly muscle mass, which, in turn, is influenced by sex.[37,38]

AKI is a common cause of death and can be observed in up to 30% of patients with severe AH.[22,39] A previous model described in the MELD-GRAIL-Na study showed that the addition of glomerular filtration rate (GFR) allows for improved discrimination among women and those with the highest risk of premature mortality caused by cirrhosis.[40] However, this model was designed for chronic patients with stable GFR, and multiple factors make it difficult to estimate renal function during an acute decompensation, discouraging its use in AH.[22] Our study is consistent with previous literature, observing a decreased

survival in patients with RRT requirements.[22,41] In addition, we found that MELD 3.0 better predicts the need for dialysis during hospitalisation. This better performance could be explained by several factors. First, the GFR is overestimated in women compared with men with the same creatinine level.[42] Second, women are disadvantaged by MELD and are estimated to receive 1–2.4 fewer creatinine-derived MELD points compared with men with the same renal function.[42] Third, the higher creatinine values add more points compared with previous versions, and the ceiling of serum creatinine was lowered from 4.0 mg/dl to 3.0 mg/dl.[20] In the future, a MELD 3.0 score cut-off could be determined to prevent and treat AKI early in severe AH, with potential clinical benefit in this population.

The mDF and MELD scores have been previously used to define corticosteroid therapy in severe AH.[10,11] Although the STOPAH study suggested a narrow therapeutic window, a recent study demonstrated a short-term benefit of corticosteroids even with higher MELD scores, where the highest effect was observed in patients with MELD scores between 25 and 39.[21] However, this benefit was lost in patients with the most severe liver disease.[21] Patients with severe AH are prone to infections, especially of bacterial and fungal origin.[43] A recent registry-based study in the USA demonstrated that malnutrition is an independent risk of infections and death in AH.[44] Therefore, an adequate selection of candidates for corticosteroids and the early detection of infections during treatment are key to decreasing death caused by infectious diseases.[45] MELD 3.0 could better represent malnourished patients and potentially impact a better selection of patients for corticosteroid treatment. Although a new model called the Mortality Index for Alcohol-Associated Hepatitis (MIAAH) was developed to predict short-term mortality, its performance was lower than that of traditional MELD in the validation cohort.[46] Thus, further studies should compare the performance of MIAAH and MELD 3.0 in this population.

Our retrospective cohort study includes numerous patients, ethnicities, and centres. However, it suffers several limitations related to its retrospective nature, including potential losses or errors in the data records. Another limitation was the diagnosis of cirrhosis because it was performed by the attending physician using clinical data, laboratory results, and imaging (mostly without a liver biopsy). Furthermore, the albumin serum levels in the blood could be elevated because of previous administration of albumin, which could modify the MELD 3.0 values. In addition, there are important differences in nutrition and muscle mass among ethnicities, which were not specifically assessed in this study. By contrast, we considered RRT requirements as an outcome, but some centres might not have had RRT available for patients with AH, and the criteria for establishing RRT could differ among centres. Future studies are needed to define the capacity of MELD 3.0 to determine the best candidates for treatments, such as corticosteroids or early establishment of RRT.

In conclusion, our large global cohort study demonstrated that MELD 3.0 predicts better 30-day and 90-day mortality in AH compared with MELD-Na and mDF. It also predicted better the RRT requirements during admission compared with other models, and MELD 3.0 scores were strongly associated with decreased survival. The MELD 3.0 has adequate calibration, and its classification accuracy did not differ between countries. Thus, our results suggest that MELD 3.0 is a promising approach for determining mortality risk and RRT in AH. However, further prospective studies are needed to validate our findings supporting MELD 3.0 score use.

Abbreviations

ABIC, Age-Bilirubin-International Normalised Ratio-Creatinine; AH, alcohol-associated hepatitis; AKI, acute kidney injury; ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; DILI, drug-induced liver injury; GGT, γ-glutamyl transpeptidase; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; INR, International normalised ratio; mDF, Maddrey's Discriminant Function; MELD, Model of End-Stage Liver Disease; MELD-Na, MELD, Model of End-Stage Liver Disease-sodium; MIAAH, Mortality Index for Alcohol-Associated Hepatitis; NIAAA, National Institute on Alcohol Abuse and Alcoholism; RRT, renal replacement therapy.

Conflicts of interest

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

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

LAD and JPA conceived and designed the study. All authors collected the data and contributed to data analysis and interpretation; JPA, LAD, EF, WD, AKS, and RB performed final analysis and drafted the manuscript. All authors had access to the study data, participated in drafting the article and revising it critically for important intellectual content, and gave final approval for the version submitted.

Data availability statement

The data sets generated and analysed during the study are not publicly available but are available from the corresponding author on reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://10.1016/j.jhepr.2023.100727.

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Author names in bold designate shared co-first authorship

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