

Nine scoring models for short-term mortality in alcoholic hepatitis: cross-validation in a biopsy-proven cohort

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SUMMARY

Background

Several prognostic models have emerged in alcoholic hepatitis (AH), but lack of external validation precludes their universal use.

Aim

To validate the Maddrey Discriminant Function (DF); Glasgow Alcoholic Hepatitis Score (GAHS); Mayo End-stage Liver Disease (MELD); Age, Bilirubin, INR, Creatinine (ABIC); MELD-Na, UK End-stage Liver Disease (UKELD), and three scores of corticosteroid response at 1 week: an Early Change in Bilirubin Levels (ECBL), a 25% fall in bilirubin, and the Lille score.

Methods

Seventy-one consecutive patients with biopsy-proven AH, admitted between November 2007–September 2011, were evaluated. The clinical and biochemical parameters were analysed to assess prognostic models with respect to 30- and 90-day mortality.

Results

There were no significant differences in the areas under the receiver operating characteristics curve (AUROCs) relative to 30-day/90-day mortality: MELD 0.79/0.84, DF 0.71/0.74, GAHS 0.75/0.78, ABIC 0.71/0.78, MELD-Na 0.68/0.76, UKELD 0.56/0.68. One-week rescoring yielded a trend towards improved predictive accuracies (30-day/90-day AUROCs: 0.69–0.84/0.77–0.86). In patients with admission DF ≥ 32 ($n = 31$), response to corticosteroids according to ECBL, 25% fall in bilirubin and the Lille model yielded AUROCs of 0.73/0.73, 0.78/0.72 and 0.81/0.82 for a 30-day/90-day outcome respectively. All models showed excellent negative predictive values (NPVs; range: 86–100%), while the positive ones were low (range: 17–50%).

Conclusions

MELD, DF, GAHS, ABIC and scores of corticosteroid response proved to be valid in an independent cohort of biopsy-proven alcoholic hepatitis. MELD modifications incorporating sodium did not confer any prognostic advantage over classical MELD. Based on excellent NPVs, the models are best to identify patients at low risk of death.

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INTRODUCTION

Alcoholic hepatitis (AH) is an acute inflammatory hepatic syndrome occurring in patients with alcohol misuse.¹ However, the clinical phenotype of AH is very variable. There are mild forms, likely to improve with conservative management, while severe cases have a high risk of death even if treated.² Currently, corticosteroids, pentoxifylline and N-acetylcysteine are the therapeutic options,^{3–6} although treatment of AH remains controversial.⁷ A survival benefit conferred by steroids is indeed disputed in standard meta-analysis,^{8, 9} but supported in individual patient data analysis.¹⁰ An ongoing, adequately powered, UK randomised controlled trial will probably answer such therapeutic controversies.¹¹ Due to the potential adverse events associated with corticosteroids (mainly occurrence of sepsis), AH is currently managed on a risk-benefit basis. Thus, prognostic stratification according to short-term mortality is paramount both for disease management and to enable clinical trials targeting new treatments in AH.

For over 3 decades, the Maddrey discriminant function (DF)¹² has been the standard surrogate for the assessment of disease severity and to guide treatment in AH. A cut-off value of ≥ 32 identified patients who had greater than 50% mortality at 30 days and therefore this was instituted as the threshold for corticosteroid therapy. Over the years, alternative prognostic scores have been developed: the Glasgow alcoholic hepatitis score (GAHS)¹³ and the age, bilirubin, international normalised ratio, creatinine score (ABIC).¹⁴ Alongside these disease-specific formulas, previous studies (including 34,¹⁵ 73¹⁶ and 202¹⁷ patients) have outlined the utility of the model for end-stage liver disease (MELD) for predicting mortality in AH, whereas the utility of the MELD including sodium (MELD-Na) has been also assessed in a small study.¹⁸ A further refinement has been to assess the response to corticosteroid treatment. In this context, the Lille score¹⁹ with a threshold of 0.45 has been developed to identify patients with severe AH who might benefit from corticosteroids, whereas also use of GAHS with a threshold of 9 has been proposed.²⁰ Previously, any fall in serum bilirubin levels after 1 week of corticosteroid therapy (Early Change in Bilirubin Levels: ECBL),²¹ or more specifically a 25% fall,²² have been proposed as simple indicators of corticosteroid response.

In recent years, several prognostic models have become available in AH, all of them advocated as best by their respective authors. External validation and model comparisons are therefore required to guide

selection among the models for use in routine clinical practice. However, diagnosis of AH is challenging and patients with other forms of hepatic decompensation (such as decompensated cirrhosis with severe jaundice and acute alcoholic steatosis) may be erroneously classified as AH. This is more likely to happen when liver biopsy is not performed, including a transjugular approach which can obviate clotting problems.²³ Indeed, diagnosis of AH based on clinical grounds has been associated with a 10–50% risk of misclassification.^{24–26} Thus, in the present study, we aimed to cross-validate nine prognostic indices for short-term mortality using an independent cohort of patients with AH confirmed by transjugular liver biopsy. This is standard practice in our centre whenever AH is suspected.

PATIENTS AND METHODS

Study population

Consecutive patients with a histological diagnosis of AH by liver biopsy, between November 2007 and September 2011, were identified through a computerised pathology register. All patients were referred for transjugular liver biopsy by their treating physician (who was a hepatologist in all cases) due to the clinical suspicion of AH. The patients' clinical and biochemical features on admission were compatible with a diagnosis of AH, according to the following criteria: a) history of alcohol abuse within the last 2 months (>40 g/day compatible with or men; >20 g/day for women), b) total serum bilirubin exceeding $2 \times$ upper limit of normality (ULN = $17 \mu\text{mol/L}$), c) aspartate to alanine aminotransferase ratio exceeding 1.5 with aspartate aminotransferase over 45 U/L and c) absence of concomitant primary cause of liver disease. Patients with pre-existing viral hepatitis ($n = 9$) were not excluded because the clinical basis of their hospital admission was due to AH. Demographical and laboratory data were extracted by reviewing the electronic medical charts. Survival at 30- and 90-days following hospital admission was established by chart review or phone contact, if necessary. Therapy for AH was also assessed. According to local protocol, patients with a severe AH (DF ≥ 32) were given a single daily dose of oral prednisolone 40 mg for 28 days, in addition to supportive therapy including gastric acid suppressors, high dose vitamin B and C, vitamin K, dietary supplements often by enteral feeding, and chlordiazepoxide if there were alcohol withdrawal symptoms. In those unable to take oral medication, 32 mg/day of methylprednisolone were

administered intravenously. Patients placed on steroids, presence of contraindications to steroid treatment and the exact date of initiation of steroid therapy were all recorded by retrospectively reviewing medical charts.

Derivation of prognostic models

For each patient, laboratory values obtained on the day of hospital admission were used to calculate prognostic

models according to their formulas (Table 1). MELD,²⁷ MELD-Na,²⁸ UKELD,²⁹ GAHS,¹³ ABIC¹⁴ and DF¹² were all re-calculated using laboratory data from day 7 after admission to establish whether 1-week rescoring could be associated with an improved predictive performance, as outlined previously.^{13, 17, 30, 31} The Lille score is a combination of six reproducible variables incorporating a dynamic one (i.e. the 1-week evolution in bilirubin).¹⁹

Table 1 | Formulas and included variables in prognostic models for alcoholic hepatitis

	Bilirubin	Creatinine	PT/ INR	Age	Albumin	Urea	Leucocytes	Na	Δ Bilirubin
MELD²⁷ 9.57 × log _e (creatinine, mg/dL) + 3.78 × log _e (bilirubin mg/dL) + 11.20 × log _e (INR) + 6.43	+	+	+	-	-	-	-	-	-
DF¹² 4.6 × (patient's PT – control PT) + bilirubin (mg/dL)	+	+	+	-	-	-	-	-	-
*GAHS¹³ Age (<50 years = 1, ≥50 years = 2) + Leucocytes (10 ⁹ /L) (<15 = 1, ≥15 = 2) + Urea (mmol/L) (<5 = 1, ≥5 = 2) + PT ratio (<1.5 = 1, 1.5–2.0 = 2, >2.0 = 3) + bilirubin (mmol/L) (<125 = 1, 125–50 = 2, >250 = 3)	+	-	+	+	-	+	+	-	-
ABIC¹⁴ (Age in years × 0.1) + (bilirubin mg/dL × 0.08) + (creatinine mg/dL × 0.3) + (INR × 0.8)	+	+	+	+	-	-	-	-	-
MELD-Na²⁸ MELD – Na – [0.025 × MELD × (140 – Na)] + 140 (where the serum sodium concentration is bound between 125 and 140 mmol per litre)	+	+	+	-	-	-	-	+	-
UKELD²⁹ 5 × [1.5 × log _e (INR) + 0.3 × log _e (creatinine mmol/L) + 0.6 × log _e (bilirubin mmol/L) – 13 × log _e (Na) + 70]	+	+	+	-	-	-	-	+	-
Lille¹⁹ R-Lille model = 3.19 – 0.101 × (age in years) + 0.147 × (albumin day 0 in g/L) + 0.0165 × (bilirubin-day 0 – bilirubin-day 7 (mmol/L)) – 0.206 × (renal insufficiency [^]) – 0.0065 × (bilirubin-day 0 mmol/l) – 0.0096 × (PT in seconds); Lille model = exp (–R)/ (1 + exp (–R))	+	+	+	+	+	-	-	-	+

PT, prothrombin time; INR, international normalised ratio; MELD, model for end-stage liver disease; DF, Maddrey's discriminant function; GAHS, Glasgow alcoholic hepatitis score; ABIC, age, bilirubin, international normalised ratio and creatinine score; MELD-Na, modified MELD including sodium; UKELD, United Kingdom model for end-stage liver disease.

* Rather than a formula, GAHS is based on a scoring system.

This model, as well as ECBL²¹ and a 25% fall in bilirubin levels,²² do not have the same prognostic basis and so cannot be compared to other models, as they were specifically developed for the assessment of corticosteroid response. Thus, these three scores were validated separately in a subgroup of patients with severe AH (admission DF ≥ 32) treated with corticosteroids, using clinical and biochemical parameters obtained on the day before treatment start and the evolution in bilirubin at day 7 of treatment with steroids.

Statistical analyses

Baseline characteristics of the study population were compared by using Chi-squared test for categorical data and Student *t*-test or Mann–Whitney *U* test for continuous data, as appropriate. Occurrence of death due to any cause within 30 or 90 days from the hospital admission was the study endpoint. Mortality rates were calculated as the proportion of patients that died within these time intervals. In patients with severe AH (admission DF ≥ 32), a Cox proportional hazards model was evaluated to assess the crude and adjusted effect of corticosteroid therapy with respect to either 30- and 90-day mortality. The utility of each model to predict 30- or 90-day mortality was evaluated using receiver operating characteristics (ROC) curves, and the area under the receiver operating characteristics curves (AUROCs) was calculated. In this analysis, a model with an AUROC between 0.7 and 0.8 was considered clinically useful and between 0.8 and 0.9 as having very good diagnostic accuracy. If the AUROC approaches 1.0, the model approaches 100% sensitivity and specificity, indicating a perfect diagnostic test.³² Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the models were calculated using originally published cut-offs: 32 for DF, 9 for GAHS, 21 for MELD, 28 for MELD-Na, 6.71 and 9 for the ABIC and 0.45 for the Lille score.^{12, 14, 16, 18–20} As no disease-specific calibration has been reported for UKELD, we calculated optimised predictive performances using the best cut-off within our cohort (point nearest to the top left corner of the ROC curve, yielding the best relationship between sensitivity and specificity). Comparison between AUROCs was performed by the method of Hanley and McNeil³² and the *P*-values obtained were considered indicative of nonsimilarity if below 0.05. All analyses were performed using the SPSS version 22 (SPSS, IBM, Chicago, IL, USA) except for the comparisons between AUROCs which were performed using MedCalc version 12.2.0 (Medisoftware, Mariakerke, Belgium).

RESULTS

Study cohort, biochemical data and scores of the different predictive models

Seventy-one consecutive patients with a biopsy-proven diagnosis of AH who met the inclusion criteria, comprised the study population. The baseline clinical data and prognostic score values are shown in Table 2. There were 47 males and 24 females with a median age of 49 years. Median admission MELD and DF were 18.8 and 47.5 respectively. The median interval between admission and the date of liver biopsy was 1.5 days (range: 0–6 days). This time interval was comparable between survivors and patients who died either within 30 days (*P* = 0.28) and 90 days (*P* = 0.76) from hospital admission. Overall, the 30-day mortality was 14.1% (10/71), whereas the 90-day mortality was 19.7% (14/71). The differences between survivors and nonsurvivors at 30 and 90 days from admission are shown in Table 2. With respect to 30-day mortality, patients who died had a higher admission median bilirubin, urea, creatinine, prothrombin time and INR, higher prognostic score values, lower albumin and were more frequently females as compared to patients who survived (Table 2a). Similar differences were detected with respect to 90-day mortality (except there were no significant gender differences and there was a trend for higher admission leucocyte count in those who died), and when comparisons were repeated by taking into account the 1-week biochemical values and scores (Table 2b). Considering the subgroup of patients with severe AH (admission DF ≥ 32 ; *n* = 49), patients who died at 30 days (*n* = 10) had a lower median albumin (26 vs. 30 g/L; *P* = 0.04) and were marginally more frequently of female gender (6/10 vs. 11/39; *P* = 0.07). With respect to 90-day mortality, patients with a severe AH who died (*n* = 14) had a lower admission median albumin (27 vs. 30 g/L; *P* = 0.05) and a higher median creatinine (74.5 vs. 53 mmol/L; *P* = 0.05) as compared to those who survived, whereas no other differences were detected between the two groups considering all 30-/90-day variables included in Table 2 (data not shown).

Data on corticosteroid treatment

Overall, 49 (69%) patients had a DF ≥ 32 at presentation and 34 (69.4%) were treated with corticosteroids, whereas no patient received pentoxifylline or other specific treatment for AH. Contraindications for corticosteroid treatment included variceal bleeding in 3 patients and infection in 5 patients, including 2 patients with

Table 2 | Comparison of admission and 1 week variables and scores between patients who survived at 30- and 90-days and those who died. All quantitative variables are given as medians (range)

Variable	Total cohort (n = 71)	30-day survivors (n = 61)	30-day nonsurvivors (n = 10)	P-value	90-day survivors (n = 57)	90-day nonsurvivors (n = 14)	P-value
a, Admission							
Age (years)	49 (26–75)	49 (26–75)	50 (30–57)	0.69	49 (26–72)	50 (30–75)	0.79
Male Gender n (%)	47 (66.2)	43 (70.5)	4 (40)	0.08	39 (68.4)	8 (57.1)	0.53
Bilirubin (µmol/L)	212 (44–827)	187 (44–827)	241 (144–711)	0.09	178 (44–827)	356 (144–711)	0.006
Albumin (g/L)	30 (19–42)	32 (19–42)	26 (20–34)	0.006	32 (19–42)	27 (20–34)	0.005
Creatinine (µmol/L)	57 (31–292)	54 (31–240)	74.5 (31–292)	0.02	53 (31–240)	74.5 (31–292)	0.03
Urea (mmol/L)	3.5 (0.8–17.3)	3.4 (0.8–17.3)	6.7 (2.8–15)	0.04	3.4 (0.8–12.8)	5.4 (2.3–17.3)	0.08
Sodium (mmol/L)	133 (121–155)	136 (131–155)	133 (121–144)	0.09	134 (121–155)	133 (121–144)	0.72
Prothrombin time (s)	22.2 (12.2–45.4)	21.8 (12.2–45.4)	26.1 (16.1–39.6)	0.03	21.7 (12.2–45.4)	24.5 (16.1–39.6)	0.02
INR	1.8 (0.9–4)	1.7 (0.9–4)	2.2 (1.3–3.2)	0.02	1.7 (0.9–4)	2.2 (1.3–3.2)	0.009
Leucocytes (10 ⁹ /L)	11.2 (2.8–34.7)	11.2 (2.8–25.2)	11.8 (9.2–34.7)	0.21	11.2 (2.8–25.2)	11.8 (9.2–34.7)	0.08
DF	47.5 (2.2–157.7)	42.3 (2.2–157.7)	57.4 (34–150.1)	0.04	40.1 (2.2–157.7)	58.3 (34–150.1)	0.007
GAHS	8 (5–12)	8 (5–12)	10 (7–12)	0.009	8 (5–12)	10 (7–12)	0.001
ABIC score	7.8 (4.4–12.1)	7.6 (4.4–11.6)	9.4 (6.9–12.1)	0.03	7.5 (4.4–11.6)	9.5 (6.9–12.1)	0.001
MELD score	18.8 (7.9–40.3)	18.7 (7.9–36.9)	25.6 (15.4–40.3)	0.004	18.2 (7.9–36.9)	25.4 (15.4–40.3)	0.0001
MELD-Na score	21.2 (6.3–40.2)	20.3 (6.3–38.2)	23.6 (15.4–40.2)	0.08	20.2 (6.3–38.2)	26.4 (15.4–40.2)	0.003
UKELD score	57.7 (48.7–72.8)	57.7 (48.7–72.8)	57.5 (52.7–69.2)	0.52	56.8 (48.7–72.8)	59.6 (52.7–69.2)	0.04
	(n = 63)	(n = 56)	(n = 7)		(n = 52)	(n = 11)	
b, Day 7 from admission							
Bilirubin (µmol/L)	146 (25–647)	128 (25–647)	214 (165–568)	0.01	120.5 (25–647)	420 (165–568)	0.0001
Creatinine (µmol/L)	55 (26–343)	54 (26–101)	154 (36–343)	0.02	54 (26–101)	95 (36–343)	0.007
Urea (mmol/L)	4.1 (1.6–22.3)	4.1 (1.6–20.8)	9 (2.8–22.3)	0.04	4.1 (1.6–20.8)	8.9 (2.8–22.3)	0.07
Sodium (mmol/L)	136 (111–161)	137 (125–161)	136 (111–149)	0.51	136.5 (111–149)	133 (125–161)	0.25
Prothrombin time (s)	20 (1.5–55.5)	19.8 (16–35.1)	23.9 (17.1–55.5)	0.009	19.8 (16–35.1)	23.2 (17.1–55.5)	0.02
INR	1.6 (0.9–16)	1.6 (0.9–3.1)	2.1 (1.4–4.8)	0.004	1.6 (0.9–3.1)	1.9 (1.4–4.8)	0.01
Leucocytes (10 ⁹ /L)	11 (3.6–34.1)	10.9 (3.6–34.1)	11.8 (5–31.1)	0.66	10.9 (3.6–34.1)	11.9 (5–31.1)	0.46
DF	28.2 (1.46–194.2)	27.6 (1.5–125.7)	50.9 (34.4–194.2)	0.002	27.2 (1.5125.7)	48.6 (34.4–194.2)	0.001
GAHS	8 (5–12)	7 (5–12)	9.5 (8–11)	0.01	7 (5–12)	9 (8–11)	0.003
ABIC score	7.2 (4.1–17.4)	7.1 (4.1–17.4)	8.3 (6.9–11)	0.04	7 (4.1–17.4)	7.9 (6.9–11)	0.02
MELD score	15.7 (1.38–46.5)	15.1 (1.4–34.1)	28.7 (13.9–46.5)	0.002	14.6 (1.4–34.1)	25.6 (13.9–46.5)	0.0001
MELD-Na score	18.5 (–7.3–44.1)	18.4 (–7.3–34.4)	27.8 (14.8–44.1)	0.01	17.9 (–7.3–34.4)	25.6 (14.8–44.1)	0.001
UKELD score	55.5 (43.2–72.8)	55.4 (43.2–68.3)	60.6 (48.4–72.8)	0.08	55 (43.2–68.3)	61.7 (48.4–72.8)	0.006

INR, international normalised ratio; DF, Maddrey discriminant function; GAHS, Glasgow alcoholic hepatitis score; ABIC, age, bilirubin, INR, creatinine score; MELD, model for end-stage liver disease; MELD-Na, modified MELD including sodium; UKELD, United Kingdom model for end-stage liver disease.

spontaneous bacterial peritonitis (diagnosed by a neutrophil count ≥ 250 cc/mm³ in the ascitic fluid), whereas another two patients refused corticosteroid treatment. In five patients, the decision for not treating with corticosteroids was based on the clinical judgment of the treating physician, despite no obvious treatment contraindications. Mean time between admission to Royal Free Hospital and start of corticosteroid treatment was 2.44 ± 1.88 days (range: 0–8 days). That time interval was comparable between patients who survived at 30 (2.64 ± 1.98) and 90 days (2.61 ± 1.88) and those who did not (1.5 ± 0.84 ; $P = 0.19$ and 1.87 ± 1.88 ; $P = 0.21$, respectively). Considering 49

patients with an admission DF ≥ 32 (i.e. those expected to benefit from corticosteroids²²), the 30-day survival rate was 28/34 (82.4%) in steroid-treated patients vs. 11/15 (73.3%) in nontreated ($P = 0.47$). At 90 days, the survival rate was 26/34 (76.5%) in patients receiving corticosteroids vs. 9/15 (60%) in nontreated ($P = 0.31$). In patients with a severe AH (admission DF ≥ 32), the crude hazard ratio (HR) for corticosteroid treatment was 0.57 [95% confidence interval (CI): 0.16–2.05; $P = 0.40$] with respect to 30-day mortality and 0.55 (95% CI: 0.19–1.58; $P = 0.27$) with respect to 90-day mortality. Lack of a significant corticosteroid effect on mortality persisted after adjustment for admission

variables differing ($P < 0.1$) between survivors and non-survivors (i.e. gender and bilirubin with respect to 30-day mortality; creatinine and albumin for 90-day mortality), yielding for 30-day mortality: HR = 0.69 (95% CI: 0.19–2.50; $P = 0.57$) and for 90-day mortality: HR = 0.56 (95% CI: 0.18–1.71; $P = 0.31$).

Use of the MELD, DF, GAHS, ABIC, MELD-Na and UKELD for the assessment of 30- and 90-day mortality

The ROC curves of the models with respect to 30-day and 90-day mortality are shown in Figure 1. The AU-ROCs for the prediction of 30-day mortality ranged from 0.56 for UKELD to 0.79 for MELD and for the prediction of 90-day mortality between 0.68 (UKELD) and 0.84 for MELD (Table 3A). No significant differences were found in pairwise comparisons between the AUROCs of the different models (data not shown). Re-calculation of the scores at day 7 from admission was possible for 63 patients; three patients died before day seven, and five patients (all of whom survived) did not have all the required biochemical data available at this time point. Re-scoring on day 7 generally yielded a trend towards increased AUROCs, ranging to 0.69–0.85 for

30-day and 0.75–0.86 for 90-day mortality (Table 3B). However, none of the differences reached statistical significance, and there were no statistically significant differences in the pairwise comparisons between models (data not shown). Figure S1 shows scatter plots of admission score values related to 30- and 90-day mortality, including representation of both originally published and optimal cut-off points within our cohort. The later were 44 for DF, 28 for MELD-Na and 56 for UKELD. A high ABIC cut-off of 9.5 resulted in increased specificity as compared to the originally suggested value of 9 (90% vs. 80% and 95% vs. 84% for a 30- and 90-day outcome respectively). Previously suggested MELD (21), GAHS (9) and low ABIC (6.7) cut-off points performed optimally within our cohort.^{13, 14, 16} Using originally proposed cut-points, the negative predictive values (NPV) for ruling out short-term mortality were high (mostly exceeding 90%), whereas ability of the models to correctly predict occurrence of death (positive predictive value; PPV) was substantially lower, in most cases less than 50% (range: 17–57%) (Table 3a). These properties remained largely unchanged when the predictive performances of the models were re-assessed 1 week from admission (NPV: 0.85–1.00, PPV: 0.20–0.57; Table 3b).

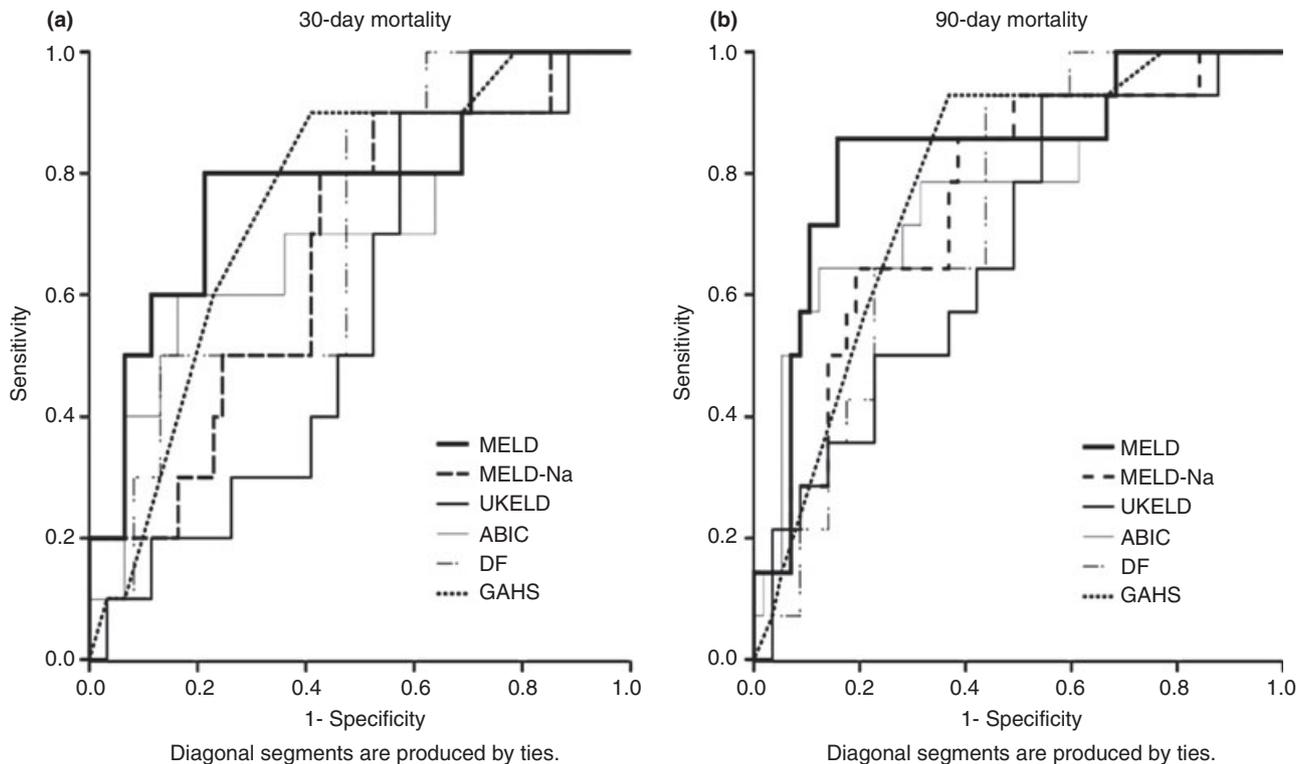


Figure 1 | Receiver operating characteristic curve of the different prognostic scores for alcoholic hepatitis calculated on admission, used to predict 30-day (a) and 90-day (b) mortality.

Table 3 | The AUROC and optimal operational characteristics in predicting 30- and 90-day mortality for the different prognostic scores calculated on the day of admission (a) and re-calculated after 7 days (b)

Score	AUROC	Std. err	95% CI	Sensitivity*	Specificity*	PPV*	NPV*
a, Admission (n = 71)							
30-day mortality							
MELD	0.79	0.085	0.62–0.95	0.80	0.79	0.38	0.96
DF	0.71	0.092	0.53–0.89	1.00	0.36	0.20	1.00
GAHS	0.75	0.073	0.61–0.89	0.90	0.59	0.27	0.94
ABIC	0.71	0.079	0.55–0.86	1.00/0.60	0.20/0.80	0.17/0.33	1.00/0.92
MELD-Na	0.68	0.087	0.50–0.84	0.30	0.82	0.22	0.88
UKELD	0.56	0.087	0.39–0.73	0.90	0.43	0.21	0.96
90-day mortality							
MELD	0.84	0.064	0.71–0.96	0.86	0.84	0.57	0.96
DF	0.74	0.062	0.61–0.86	1.00	0.39	0.29	1.00
GAHS	0.78	0.060	0.67–0.90	0.93	0.63	0.38	0.97
ABIC	0.78	0.072	0.64–0.92	1.00/0.64	0.21/0.84	0.24/0.50	1.00/0.91
MELD-Na	0.76	0.069	0.62–0.89	0.43	0.86	0.43	0.86
UKELD	0.68	0.076	0.53–0.83	0.93	0.46	0.30	0.96
b, Day 7 from admission (n = 63)							
30-day mortality							
MELD	0.84	0.084	0.68–1.00	0.60	0.87	0.43	0.93
DF	0.85	0.058	0.74–0.96	1.00	0.48	0.24	1.00
GAHS	0.77	0.070	0.63–0.91	0.60	0.70	0.25	0.91
ABIC	0.74	0.092	0.54–0.90	0.80/0.30	0.46/0.93	0.20/0.43	0.94/0.89
MELD-Na	0.78	0.090	0.61–0.96	0.40	0.93	0.40	0.92
UKELD	0.69	0.106	0.48–0.89	0.50	0.69	0.21	0.89
90-day mortality							
MELD	0.86	0.062	0.73–0.98	0.50	0.88	0.50	0.88
DF	0.84	0.054	0.73–0.94	1.00	0.51	0.33	1.00
GAHS	0.79	0.061	0.67–0.91	0.64	0.74	0.37	0.89
ABIC	0.75	0.077	0.58–0.88	0.79/0.29	0.49/0.95	0.28/0.57	0.90/0.57
MELD-Na	0.83	0.068	0.69–0.96	0.36	0.91	0.50	0.85
UKELD	0.77	0.084	0.60–0.93	0.57	0.72	0.33	0.87

AUROC, area under the receiver operating characteristics curve; Std. err, standard error; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; MELD, model for end-stage liver disease; DF, Maddrey discriminant function; GAHS, Glasgow alcoholic hepatitis score; ABIC, age, bilirubin, international normalised ratio and creatinine score; MELD-Na, modified MELD including sodium; UKELD, United Kingdom model for end-stage liver disease.

* Cut-off values used: MELD: 21, DF: 32, GAHS: 9, ABIC: 6.71/9, MELD-Na: 28, UKELD: 56.

Models proposed to assess corticosteroid responsiveness

Calculation of the ECBL, a fall in serum bilirubin by 25% and the Lille score was possible for 31 of 34 patients with severe AH (admission DF ≥ 32) receiving corticosteroids; two patients died before day 7 of corticosteroids, whereas an additional patient did not have all the required biochemical data. Comparisons in biochemical and clinical parameters between corticosteroid-treated patients who survived and those who died (six patients by day 30 and eight patients by day 90) are shown in Table 4. After 1 week of corticosteroids, 14 (45.2%) patients had a 25% fall in bilirubin from baseline, 22 (71%) had an ECBL, and 22 (71%) achieved a

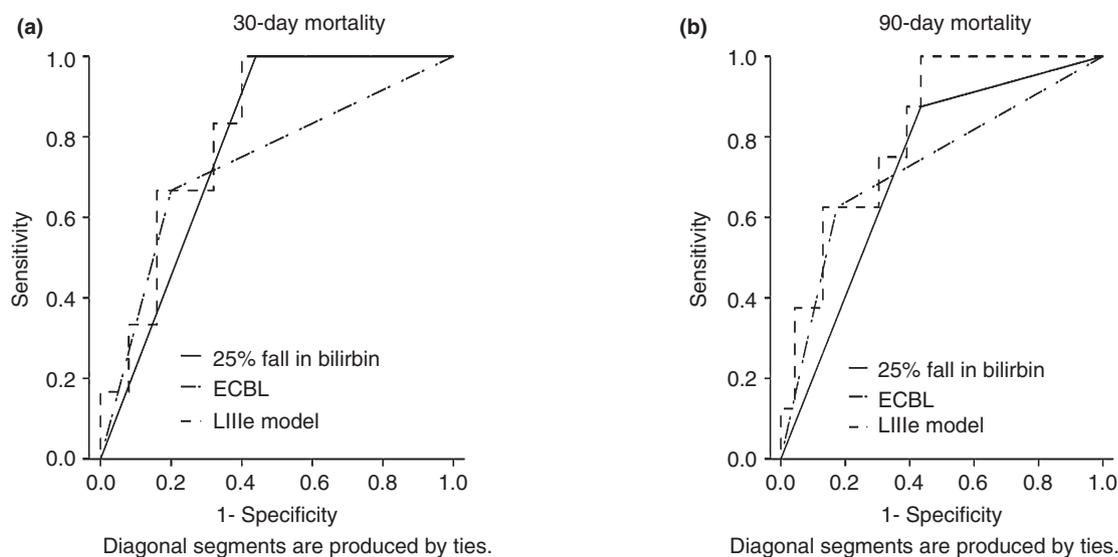
Lille response using the proposed cut-point of 0.45. The AUROC analysis and operational characteristics of the three models with respect to 30- and 90-day mortality are shown in Figure 2. Overall, no statistically significant differences were found in AUROC comparisons between the different models relative to either a 30- and 90-day outcome. Notably, a good response to corticosteroids according to all three criteria yielded an excellent NPV for excluding short-term mortality (>85%), whereas the PPVs were substantially lower, in all cases <60%.

DISCUSSION

The present study is an external evaluation of nine prognostic models of AH using a 100% biopsy-proven

Table 4 | Clinical and biochemical parameters used for the calculation of the Lille score in patients with severe alcoholic hepatitis (admission Maddrey ≥ 32) treated with corticosteroids ($n = 31$). Comparisons regard patients who survived at 30- and 90-days and those who died. Quantitative variables are given as medians (range)

Variable	30-day survivors ($n = 25$)	30-day nonsurvivors ($n = 6$)	P-value	90-day survivors ($n = 23$)	90-day nonsurvivors ($n = 8$)	P-value
Age (years)	49 (26–59)	50 (30–54)	0.88	49 (26–59)	49 (26–59)	0.96
Male gender n (%)	21 (84)	3 (50)	0.11	19 (82.6)	5 (62.5)	0.33
Bilirubin-day 0 ($\mu\text{mol/L}$)	328 (87–786)	397 (176–647)	0.63	318 (87–768)	456.5 (176–647)	0.31
Bilirubin-day 7 ($\mu\text{mol/L}$)	209 (45–768)	368 (175–851)	0.09	202 (45–768)	427.5 (175–851)	0.03
Δ Bilirubin ($\mu\text{mol/L}$)	64 (–117–286)	–31.5 (–204–87)	0.03	64 (–117–286)	–31.5 (–204–129)	0.03
Albumin (g/L)	30 (18–41)	28.5 (20–36)	0.25	30 (18–41)	28.5 (20–36)	0.25
Creatinine ($\mu\text{mol/L}$)	53 (29–209)	103.5 (26–267)	0.05	52 (29–209)	90 (26–267)	0.03
Prothrombin time (s)	23 (18.7–35.6)	26 (18.3–50.5)	0.09	23.8 (18.7–35.6)	23.5 (18.3–50.5)	0.23
INR	2 (1.4–3.1)	2.25 (1.4–4.7)	0.12	2 (1.4–3.1)	2.15 (1.4–4.7)	0.16
Lille score	0.14 (0.01–0.91)	0.75 (0.18–0.99)	0.02	0.09 (0.01–0.91)	0.75 (0.14–0.99)	0.009



Score	AUROC	Std. err	95% CI	Sensitivity	Specificity	PPV	NPV
30-day mortality							
ECBL	0.73	0.123	0.49-0.98	0.67	0.80	0.44	0.91
25% fall in bilirubin from baseline	0.78	0.084	0.62-0.94	1.00	0.56	0.35	1.00
Lille score*	0.81	0.019	0.66-0.97	0.67	0.80	0.44	0.91
90-day mortality							
ECBL	0.73	0.113	0.50-0.95	0.63	0.83	0.56	0.86
25% fall in bilirubin from baseline	0.72	0.099	0.53-0.91	0.88	0.57	0.41	0.93
Lille score*	0.82	0.079	0.66-0.97	0.63	0.83	0.56	0.86

AUROC, area under the receiver operating curve; ECBL, early change in bilirubin levels; CI, confidence interval;

PPV, positive predictive value; NPV, negative predictive value.

*Using a Lille score cut-point of 0.45¹⁹.

Figure 2 | AUROC analysis and operational characteristics for three different indicators of response to corticosteroid treatment, used to predict 30-day (a) and 90-day (b) mortality.

cohort, including the first disease-specific assessment of the UKELD used for prioritizing liver recipients in UK.³³ Overall, MELD, DF, GAHS and the ABIC proved to be clinically useful scores, performing comparably and with an acceptable accuracy (AUROCs exceeding 0.70) for both 30- and 90-day mortality. Our findings are congruent with those of previous validation studies in which, however, diagnosis of AH was based solely on clinical grounds. In a Danish study including 274 patients, MELD, MELD-Na, GAHS, Lille score and the ABIC also performed comparably in predicting 28-, 84- and 180-day mortality.³⁰ Similarly, in another study, MELD, DF, ABIC and GAHS performed equally in predicting short-term (30- and 90-day) survival, although all models were uniformly poor in predicting longer-term (6-month and 1-year) outcome.³⁴ In a prospective comparison of 182 patients, DF, GAHS, MELD and ABIC performed well with no statistically significant difference for either 28 or 90 days mortality after admission.³⁵ We observed a tendency towards better prognostic accuracies with respect to 90-day mortality (90-days AUROCs: 0.68–0.86 vs. 30-days AUROCs: 0.56–0.79), and when assessment of prognosis was repeated 1 week from admission (90-days AUROCs: 0.75–0.86 and 30 day AUROCs: 0.69–0.85). This is consistent with previous observations on the utility of repeated scoring, 6–9 days from hospital admission.^{13, 17, 30, 31}

DF was developed several decades ago based on patient cohorts that might have had different supportive care than in current patients. Our study, in agreement with previous observations, indicates an inadequate specificity (<40%) for mortality of DF: 39/49 (79.6%) of patients with DF ≥ 32 were alive by day 30 and 35/49 (71.4%) by day 90. Obsolescence of the cut-point of 32 may account, at least partially, for the inaccuracy of DF, and higher cut-offs have been proposed: 37 in the study by Dunn *et al.*,¹⁶ and 42 in the study by Sheth *et al.*¹⁵ Optimal cut-off within our cohort corresponds to 44, although even by using this value, specificity of DF would be still less than 60%. This inaccuracy of DF has been suggested as the basis of the long-standing debate on the efficacy of corticosteroid treatment.¹³ Moreover, poor standardisation of PT across different laboratories represents another limitation affecting the reproducibility of this index.³⁶

Previous studies^{15–17} have proposed use of MELD as an alternative model, more specific for mortality, as compared to DF. As well as INR which has problems in reproducibility of measurement,³⁶ MELD includes creatinine, a relevant prognostic indicator in AH, but which

measurement in a context of hyper-bilirubinemia is also problematic.³⁷ Our data, consistent with these older reports, shows sensitivity/specificity of 0.80/0.79 (30-days) and 0.86/0.84 (90-days) for the MELD vs. 1.00/0.36 (30-days) and 1.00/0.39 (90-days) for the DF. In a study by Srikureja *et al.*, 1-week MELD has been shown to be more accurate, as compared to admission MELD, for the prediction of in-hospital mortality.¹⁷ Our results are further validating this observation with respect to both the prediction of 30-day (AUROC: 0.84 for 1 week MELD vs. 0.79 for admission MELD) and 90-day risk of death (AUROC: 0.86 for 1 week MELD vs. 0.84 for admission MELD). However, in contrast to this last study, we could not identify any advantage in 1-week re-testing of MELD over DF, as re-calculation of the DF 1 week from admission also yielded excellent prognostic accuracies (AUROC >0.80), comparable to those obtained by recalculating MELD. Disease-specific calibration of MELD is an issue: in our cohort the optimal cut-off value was 21, similar to the study by Dunn *et al.*¹⁶ However, lower thresholds such as 11 reported by Sheth *et al.*¹⁵ and 18 reported by Shrikureja *et al.*¹⁷ have been proposed, probably reflecting differences in the grade of severity of disease between different cohorts. Neither MELD-Na nor UKELD, both modifications of MELD incorporating sodium, were prognostically superior to classical MELD within our cohort. Previously, MELD-Na was shown a stronger predictor of 180-day mortality (vs. MELD) when patients with clinically diagnosed AH and ascites were considered. However, the small sample size in this study (26 patients, 13 with ascites) precludes definitive conclusions.¹⁸

GAHS and ABIC are disease-specific formulas which also include creatinine^{14, 20} but are easier to calculate at the bedside in comparison to MELD. The ABIC score includes similar parameters as the MELD score, except for patient's age, whereas GAHS is the only index to consider an inflammatory parameter (white cell count) (Table 1). Although GAHS and ABIC have been shown to perform significantly better than DF within their internal validation cohorts, our results suggest comparable predictive accuracies of these three models. In a head to head comparison of GAHS and ABIC using 181 patients from the GAHS validation cohort, the two models also performed equally.³¹ ABIC is a dual cut-off model which generates a trichotomous classification into low, intermediate and high risk of death.¹⁴ Critically, such ability was questioned in a recent study in which the 3 stages did not result in differences in 90-day outcomes between the 'low' and 'intermediate' groups,

although there was a clearly worse outcome in those with ABIC >9.³⁵ Unfortunately, the relatively small number of events precluded us from undertaking a similar analysis.

The Lille score is a combination of six reproducible variables including a dynamic one, i.e. the evolution in bilirubin following 1 week of corticosteroid treatment.¹⁹ Within our biopsy-proven cohort, use of the Lille model proved an accurate predictor of both 30- and 90-day outcome (AUROC 0.81/0.82). However, our data do not justify its complexity over the much easier bedside calculation of ECBL and 25% fall in bilirubin, both performing with an acceptable grade of accuracy within our cohort (AUROC 0.72–0.78). Our findings are congruent with those of a recent prospective assessment, in which, however, diagnosis of AH relied solely on clinical criteria.³⁵ As availability of 7-day biochemical data are necessary in order to calculate the Lille score, it is interesting to note that re-calculation at 7 days of either the MELD or DF, also provided excellent predictive accuracies (AUROCs >0.80). However, their dynamic evolution (i.e. Δ MELD and Δ DF) has been reported to have less prognostic power in comparison with changes in Lille score.¹⁹ Thus, the Lille model represents the best currently validated dynamic criterion for the assessment of mortality in AH, and the only one linked to specific stopping rules for corticosteroid management: in poor responders (Lille >0.45) discontinuation of corticosteroids is recommended,¹⁹ particularly when Lille >0.56 (i.e. considered null responders).^{4, 10}

Importantly, all prognostic models and in particular DF, MELD, GAHS, ABIC and the Lille score showed excellent NPV, in most cases exceeding 90%. This is in contrast with PPV which were low, in most instances lower than 50% (Table 3). This finding suggests that the paradigm in clinical decision making and the designation of clinical trials targeting specific treatments in AH, should be to exclude low-risk patients, rather than to identify those with high death risk, using these models. Clearly, some patients identified at high risk may receive futile treatment but evaluating different thresholds or different weighting or new variables may refine prognosis.

The present study has limitations. We did not perform a sample size calculation, and our study cohort was based on the available patients but it does reflect a 4-year single-centre experience of histologically diagnosed AH. Therefore, although our sample size is comparable¹⁶ and more than double¹⁵ than that of previous publications, our study may be underpowered to detect a

significant difference in the predictive performances between models. This is more likely to be true in the analysis of the Lille score and its variants, which was restricted to 31 patients receiving corticosteroids. Treatment with corticosteroids may have led in underestimation of the predictive ability of general prognostic scores, although a survival benefit conferred by this treatment remains in some dispute^{8, 9} and corticosteroid-treated patients have been previously included for the development and/or validation of the models.^{14, 16} Despite adjustment for confounding variables there was no demonstrable corticosteroid effect on survival, which is unsurprising, considering that our study was not designed nor powered to detect a therapeutic effect. However, this may indicate that treatment effects are not a significant source for biasing predictive performances in the present study. Transjugular liver biopsy²³ is routinely performed in our institution whenever AH is suspected. Although inclusion of less severe cases by this institutional policy (and thus changes in predictive accuracies of the models) could be possible, the admission MELD in our series is comparable to that of other cohorts in which diagnosis of AH relied solely on clinical criteria.^{16, 30} Congruently, the 30- and 90-day mortality in our cohort was 14.1% and 17.9% respectively, which is consistent with previous studies reporting short-term mortality ranging to 14.4–27%.^{15–17, 30}

In conclusion, the negative predictive values of MELD, DF, GAHS and the ABIC as well as those of three different scores to assess corticosteroid response, proved to be valid for prognostication when assessed in an independent cohort of patients with biopsy-proven AH. In our series, both MELD-Na and UKELD did not confer any prognostic advantage in comparison with classical MELD. The choice of prognostic model thus depends on other factors including ease of use, routine use of corticosteroids according to institutional practice and the personal preferences of the treating physician. However, there is still room for further refinement, and efforts for improved prognostic models should continue, as there is increasing need for accurate prognostic stratification in AH, particularly with the possibility of early liver transplantation.^{35, 38} Thus, it is important currently to rely on response criteria to corticosteroids, or non-improvement at 7-days if liver transplantation is considered, as the PPV of all models is insufficient to establish a poor prognosis at admission.

AUTHORSHIP

Guarantor of the article: Andrew K. Burroughs.

Author contributions: VP, GP, ET, AD, SB, TVL collected data. VP, EAT, AKB designed the study and review each draft of the publication. VP performed statistical analyses and wrote the manuscript. VP, EAT, GP, SK, JOB, DP, DT contributed to interpretation and analyses of data. SK, TVL, JOB, DP, DT, AKB critically revised the article for important intellectual content. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Scatter plots of admission score values for prognostic scores in alcoholic hepatitis correlated with 30- (a) and 90-day (b) mortality.

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