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Relationship between updated MELD and prognosis in alcohol-associated hepatitis: Opportunities for more efficient trial design

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Abbreviations: AH, alcohol-associated hepatitis; GAHS, Glasgow alcoholic hepatitis score; InTeam, Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis; MELD, Model for End-Stage Liver Disease; NIAAA, National Institute on Alcohol Abuse and Alcoholism; NIH, National Institutes of Health; RCT, randomized controlled trial.

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Abstract

Background: Alcohol-associated hepatitis (AH) is associated with significant mortality. Model for End-Stage Liver Disease (MELD) score is used to predict short-term mortality and aid in treatment decisions. MELD is frequently updated in the course of AH. However, once the most updated MELD is known, it is uncertain if previous ones still have prognostic value, which might be relevant for transplant allocation and trial design. We aimed to investigate the predictive performance of updated MELDs in a prospectively collected cohort of patients with AH by the InTeam consortium.

Methods: Three hundred seven patients (with 859 MELD values within 60 d of admission) fulfilled the inclusion criteria. The main endpoint was time to death or transplant up to 90 days. We used a joint model approach to assess the predictive value of updated MELDs.

Results: Updated MELD measurements had a strong prognostic value for death/transplant (HR: 1.20, 95% CI: 1.14–1.27) ($p < 0.0001$). Previous MELD values did not add predictive value to the most current MELD. We also showed that MELD at day 28 (MELD28) had a significant predictive value for subsequent mortality/transplant in a landmark analysis (HR: 1.18, 95% CI: 1.12–1.23). We show that the use of an ordinal scale including death, transplant, and MELD28 as a trial outcome could substantially reduce the sample size required to demonstrate short-term benefit of an intervention.

Conclusion: We show that updated MELDs during the trajectory of AH predict subsequent mortality or the need for transplant. MELD28 inclusion in an ordinal outcome (together with death or transplant) could increase the efficiency of randomized controlled trials.

INTRODUCTION

Alcohol-associated hepatitis (AH) is associated with significant morbidity and mortality.[1,2] Several prognostic risk scores have been developed to assess disease severity and mortality, and determine candidates who might benefit from pharmacological intervention, such as corticosteroids.[3–8] Static models, including Maddrey's modified discriminant function, the ABIC (age, bilirubin, international normalized ratio, and creatinine score) score, the Glasgow alcoholic hepatitis score (GAHS), and the Model for End-Stage Liver Disease (MELD), are assessed at baseline for predicting short-term mortality and selecting candidates for treatment.[3–6] In contrast, dynamic models may afford more subtle differentiation in the predicted outcome of AH. We have shown previously that serial estimation of serum bilirubin stratifies patients and identify those likely to recover, in whom corticosteroids confer no benefit.[9] Following treatment with corticosteroids, the dynamic Lille model calculated at days 4 or 7 is used to evaluate treatment response.[10,11] Furthermore, a model using both baseline MELD and 7-day Lille score proved to be superior to models using only baseline data to predict prognosis in AH.[11]

MELD score is increasingly used to select patients for treatment, and current guidelines suggest a threshold of >20 points to start steroids.[12] Indeed, recent observational data suggest that corticosteroids reduce short-term mortality in patients with MELD scores ranging from 21 to 51, with the greatest impact observed in individuals with MELD scores between 25 and 39 while offering no significant mortality benefit with MELD values below 20.[2]

In day-to-day practice, MELD is measured repeatedly during the first few weeks after the onset of an AH episode to reassess the prognosis of the patient and to make therapeutic decisions regarding liver transplant. However, the value of updated MELD measurements in predicting survival has not been thoroughly assessed. Furthermore, it is unclear if the change in MELD (or rate

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of change) captures the risk of death better than the most up-to-date value (or "current" value). Understanding the prognostic value of MELD during the first few weeks of the AH episode could also help optimize the design of randomized controlled trials (RCTs) by using MELD as a surrogate measure of outcome (death/transplant). Indeed, designs focused on short-term (28 d) mortality as a binary primary outcome have shown insufficient power to detect the benefit of pharmacological interventions.[13–15] In this context, the use of MELD at 28 days (MELD28) in those alive without a transplant could markedly improve the power of such trials.

Therefore, in this study, we aimed at evaluating, in a prospective cohort of patients admitted with AH, (a) the value of updated MELD scores during the first 60 days after presentation to predict mortality up to 90 d, (b) whether the predictive value of a given MELD at any time point during follow-up depends on the previous trajectory of MELD (or, on the contrary, the only predictive MELD is the current MELD), (c) what is the value of MELD28 to predict subsequent mortality, and (d) the impact of using MELD28 as part of an ordinal outcome in the power of randomized trials for AH.

METHODS

Data on 341 patients hospitalized with AH between 2014 and 2018 were collected from the prospective InTEAM central database. InTeam was an NIH-supported consortium of 13 centers across the United States, Canada, Mexico, France, Spain, and the United Kingdom. All centers were tertiary-care liver transplant centers. AH was defined by the InTEAM members according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria, and patients with *probable* or *definite* AH were eligible for inclusion.[16] The inclusion criteria were as follows: age between 18 and 70, all patients had excessive alcohol use in the 3 months before admission, aspartate aminotransferase $>$ alanine aminotransferase , and total bilirubin >3 mg/dL. A liver biopsy was performed as per the standard of care in each center. The exclusion criteria were other or multiple etiologies, including autoimmune, viral, HCC, complete PVT, pregnancy or breastfeeding, terminal extrahepatic diseases, and specific treatment for AH (ie, corticosteroids and/or pentoxifylline) 3 or more days before study inclusion. For the purpose of this study, only patients with a minimum follow-up period of 7 days were included. Thus, the final sample size for the present study was 307 patients. Patients were managed according to the standard of care at each center. Previous results from this cohort have been reported.[17]. Severe AH was defined by MELD >20. MELD score was capped at 40. The endpoint for the present substudy of the InTeam cohort was *time to death or transplant* (up to 90 d).

All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. The InTeam consortium study (clinical bio-repository) was approved by the institutional review committee of each center and each patient provided informed consent.

Statistical analysis

Analyses were conducted using R statistical software (R Foundation for Statistical Computing) with packages JMbayes2,[18] survival,[19] rms,[20] Hmisc.[21]

To assess the value of the updated MELD score in the dynamic prediction of mortality/transplant, we used a joint modeling approach with JMbayes2 R package.[18] This consists of 2 linked submodels, the longitudinal submodel (a linear mixed model) that predicts the "instantaneous" MELD value for every patient during the first 60 days and a Cox proportional hazard model of transplant-free survival. The main difference between this approach and a Cox model introducing MELD as a time-dependent covariate is that the latter uses only the "measured" values of MELD. For example, in a patient who had a MELD of 30 at day 7, and the next measured MELD was at day 28 and had a value of 20, the Cox model with time-dependent MELD would consider that the patient had a constant MELD of 30 between day 7 and day 27, and then abruptly dropped to 20 on day 28. In the joint model, the MELD trajectory is first modeled for every patient with the linear mixed model, and takes into account the irregular time points at which MELD was measured and the censoring of the patients. The joint model includes the subject-specific linear predictors of the mixed-effects models as time-varying covariates in the Cox survival model. Therefore, it uses the modeled MELD, which better represents what happened to MELD between days 7 and 28 in a given patient. The accuracy of the model was assessed using the c-statistic (discrimination) and integrated Brier score (overall performance).[22]

The joint model also allows testing whether the previous slope of MELD trajectory or the cumulative exposure to MELD adds predictive value to the current MELD (ie, if at a given time point and once the most up-to-date MELD is known, whether previous values added any additional prognostic information).[23] We additionally tested the potential modifying effect of age, sex, and severity of AH with an interaction test.

Since the 28-day time point has been used as the primary outcome for randomized trials,[13,24–31] we conducted a landmark analysis as a complementary approach to the joint model, setting time zero of follow-up at day 28. In this analysis, we used a Cox model to assess the predictive value of MELD28 (in those alive, not transplanted, and still at follow-up at 28 d) on the risk of death or transplant up to 90 days from the initial presentation. Since not all patients still at risk (not dying before 28 d and not lost to follow-up) had MELD measured exactly at day 28, we used the predicted MELD28 (using the linear mixed model).

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Finally, and based on the distribution of MELD values in those patients alive and not transplanted (and still at follow-up) at day 28, we estimated the sample size for potential randomized trials using either a binary outcome (death/transplant *vs* alive at 28 d) or an ordinal outcome. This ordinal outcome is based on a scale that has death as the worst outcome, transplant as the next worst, and then the ordered distribution of MELDs. The thresholds to define MELD categories were chosen for illustration purposes. We provide sample sizes for the assumptions of proportional odds[32] and a power 0.8, using the function *posamsize* in the Hmisc package.[21] In addition, we provide in the Supplemental Methods, http://links.lww.com/HC9/A976, a function to estimate the power based on trial simulations with an ordinal outcome as described.

RESULTS

Baseline characteristics of the cohort

For the present study, 307 patients with AH fulfilled our inclusion criteria. Supplemental Figure S1, http://links.lww.com/HC9/A976, shows the disposition of the patients, and Table 1 shows their baseline characteristics. The overall risk of death or transplantation was markedly different between patients with severe (15.7%, 27.2%, and 29.5% at 30, 60, and 90 d) and moderate AH (3.6%, 6.3%, and 6.3%, respectively) (Supplemental Figure S2, http://links.lww.com/HC9/A976).

TABLE 1 Baseline characteristics of the patients in the study cohort

Variable (Units)	Total
Total number of patients (%)	307 (100)
Sex, n (%)	
Female	106 (34.5)
Male	201 (65.5)
Age (y)	49.0 (40.0–57.0)
Albumin (g/dL)	2.5 (2.1–3.0)
Bilirubin (mg/dL)	12.3 (6.3–20.5)
INR (unit)	1.8 (1.5–2.1)
Platelet (10^9/L)	125 (79–206)
AST (U/L)	128.0 (96.0–193.0)
ALT (U/L)	45.0 (31.8–66.3)
ALP (U/L)	173.0 (120.8)
GGT (U/L)	555.0 (115.5–669.0)
Creatinine (mg/dL)	0.7 (0.6–1.1)
MELD	23.0 (20.0–27.0)
Severity of AH, n (%)	
Moderate	84 (27.4)
Severe	223 (72.6)

Note: Values of continuous variables represent the median (25–75 percentiles).
Abbreviations: AH, alcohol-associated hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; INR, international normalized Ratio; MELD, Model for End-Stage Liver Disease.

Serial MELD and prognosis (joint model approach)

Figure 1A shows the available MELD data points (n = 859) within 60 days of inclusion in the study. To assess the value of serial MELD measurements on prognosis, we constructed a joint model as described in the Methods section. Details of the longitudinal model to predict current MELD are provided in Supplemental Table S1, http://links.lww.com/HC9/A976. Figure 1B provides examples of how this model approximates individual MELD trajectories for each patient.

The joint model showed a significant association between the current MELD value and the risk of death/transplant ($p < 0.0001$) with an HR of 1.20 (95% CI: 1.14–1.27). Thus, at any time during the first 60 days of follow-up, a unit difference in MELD was associated with a 20% relative difference in the rate of death/transplant. Figure 2 summarizes graphically the results of the joint model predictions, showing how the probability of death/transplant is updated over time. The performance of the MELD-based joint model at different time points is shown in Supplemental Table S2, http://links.lww.com/HC9/A976, showing how the accuracy of prediction increases as MELD values are updated.

We also assessed if once the most updated or current MELD value is known, the previous trajectory of MELD provides prognostic information. As discussed in the Methods section, the joint model allows to introduce different parameterizations, including the slope of the predictor (which reflects previous MELD trajectory) and the total cumulative MELD exposure. Neither the MELD slope ($p = 0.776$) nor the cumulative MELD exposure ($p = 0.538$) significantly added prognostic value to the current MELD value (Supplemental Table S3, http://links.lww.com/HC9/A976), indicating that once the current MELD is known, previous MELD values do not add additional predictive information for the risk of death/transplant.

Finally, to understand potential modifiers of the predictive value of MELD, we tested, in the joint model, the interactions of MELD with age, sex, and corticosteroid treatment (Supplemental Table S4, http://links.lww.com/HC9/A976). Only age, but not sex or corticosteroids, significantly interacted with MELD.

MELD value at 28 days (MELD28) and prognosis (landmark analysis approach)

To further test the robustness of the joint model predictions, we used a landmark approach to assess

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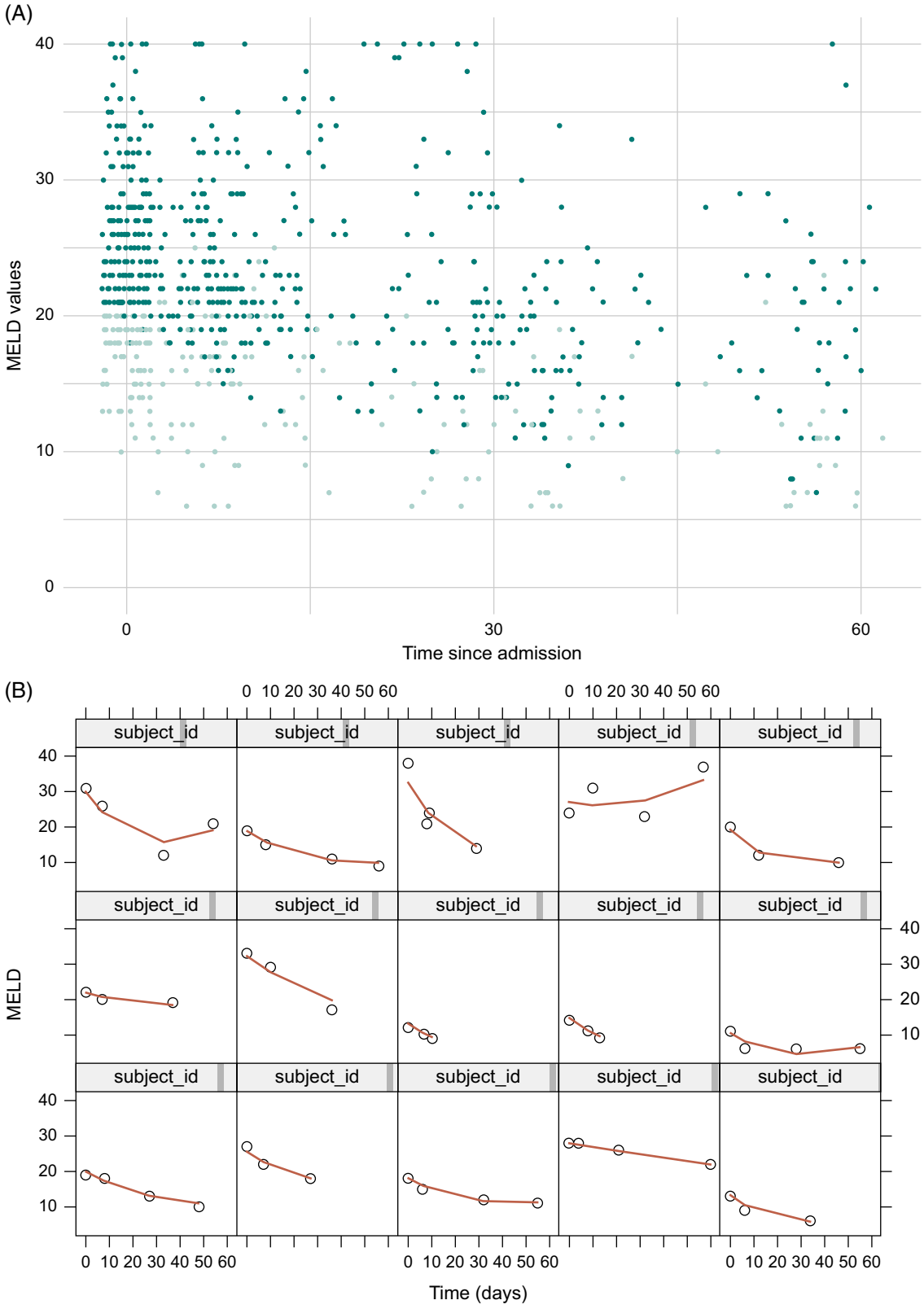

FIGURE 1 (A) Available MELD data points within 60 days of inclusion in the study (n = 859). Clear green points represent values of MELD from patients classified at baseline as moderate AH (MELD ≤20 at baseline), while dark green points are from patients classified as severe AH at baseline. (B) Examples of how the longitudinal model fits predicted MELD trajectories in 15 of the patients from the study cohort. Abbreviation: MELD, Model for End-Stage Liver Disease.

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the predictive ability of the MELD-28 score for mortality within the 90-day period (62 d after the landmark). Since not all patients had MELD measured on day 28, in those patients who were alive and still on follow-up on day 28, we used the longitudinal model to predict the MELD-28 value. The MELD-28 value was introduced in a Cox model that had day 28 as time zero of follow-up. There were 33 events (4 transplants and 29 deaths) between day 28 and day 90). MELD-28 was strongly predictive of subsequent mortality ($p < 0.0001$) with excellent discrimination and calibration (Supplemental Table S5, http://links.lww.com/HC9/A976). The HR for transplant-free survival for every unit of MELD was 1.18 (95% CI: 1.12–1.23). Figure 3 shows a nomogram with mortality predictions based on MELD-28. To test whether baseline MELD would add prognostic information to MELD-28, we introduced the baseline MELD as a predictor together with 28-day MELD. Baseline MELD did not add predictive value to MELD-28 ($p = 0.716$) (Supplemental Table S6, http://links.lww.com/HC9/A976). This is in line with the results obtained with the joint model, showing that once the MELD at a given time point is known, previous MELD scores do not add predictive value.

Severity of AH and MELD prediction

To further assess the impact of AH severity (moderate AH vs. severe AH) on MELD predictions, we conducted 2 analyses. We first showed that the association between MELD across all levels of severity and death/transplant does not significantly depart from linearity (Supplemental Figure S3, http://links.lww.com/HC9/A976). Second, the interaction between MELD and the severity of AH on the joint model was tested. We found the interaction was nonsignificant (Supplemental Table S4, http://links.lww.com/HC9/A976), suggesting the association between the current MELD and prognosis is not affected by how the patient was classified at admission in terms of the severity of AH.

Implications for trial design and the use of an ordinal outcome to assess efficacy in RCTs

Since MELD28 is strongly predictive of subsequent mortality, it would have the potential to be used as part of an ordinal outcome to assess the efficacy of new treatments for AH. Since current mortality rates of AH are decreasing, it will be difficult to power a study to demonstrate benefit with a binary endpoint death/transplant as the primary outcome. We, therefore, provide an example of the impact of including MELD28 as part of an ordinal scale that would include mortality as the most severe category, transplant as the next most severe, and the distribution of MELD28 values in those patients still alive and not transplanted at day 28. Table 2 shows the distribution of this ordinal scale in our cohort, both for the subset of patients with severe AH and moderate AH, and the potential distribution of the patients across the ordinal scale for different effect sizes of a new experimental treatment. In Table 3, we show the sample sizes required to demonstrate a benefit in an RCT for severe AH, using a binary endpoint as compared to the use of an outcome based on the ordinal scale. As shown in the table, the needed number of patients would markedly decrease by incorporating the distribution of MELD28 into the outcome. We present similar data for trials for moderate AH in Supplemental Tables S7, http://links.lww.com/HC9/A976 and S8, http://links.lww.com/HC9/A976.

DISCUSSION

In this study, we assessed the value of serial MELD measurements during the first 60 days in patients admitted with AH to predict mortality for up to 90 days. First, we showed that updated MELD scores were strongly associated with the risk of death or transplantation in patients with AH. We showed a significant improvement in the prediction accuracy when the predictions were made closer to the time horizon to evaluate the outcome. This is relevant for patient care because it reflects the current practice in which blood tests are repeated serially in patients with AH both during hospitalization and after discharge.

Second, we showed that adding the previous MELD did not enhance the predictive value of the current MELD. This supports the current general strategy of MELD use in transplant allocation and prioritization (where only the most up-to-date value is used for ranking purposes) and also for patients with AH. We confirmed this concept in 3 ways. The joint model allows testing the effect of the previous slope and the previous cumulative exposure to the variable under assessment. We found that neither the slope nor the previous total MELD exposure added significant predictive value to the current MELD. As a confirmatory approach, we conducted a landmark analysis to test the predictive value of MELD at 28 days, confirming that the MELD28 value is strongly predictive of subsequent mortality. Again, once the MELD28 value is known, the baseline MELD does not add predictive value, confirming the results of the joint model approach.

The strong prognostic value of MELD in the first few weeks of AH suggests that the distribution of MELD values at a given time point during the trajectory of AH (in those patients not dying or not getting a transplant) could be used to enhance the design of RCTs. As we show in Table 3, the sample size needed to demonstrate efficacy with a binary endpoint (death or transplant) in the current

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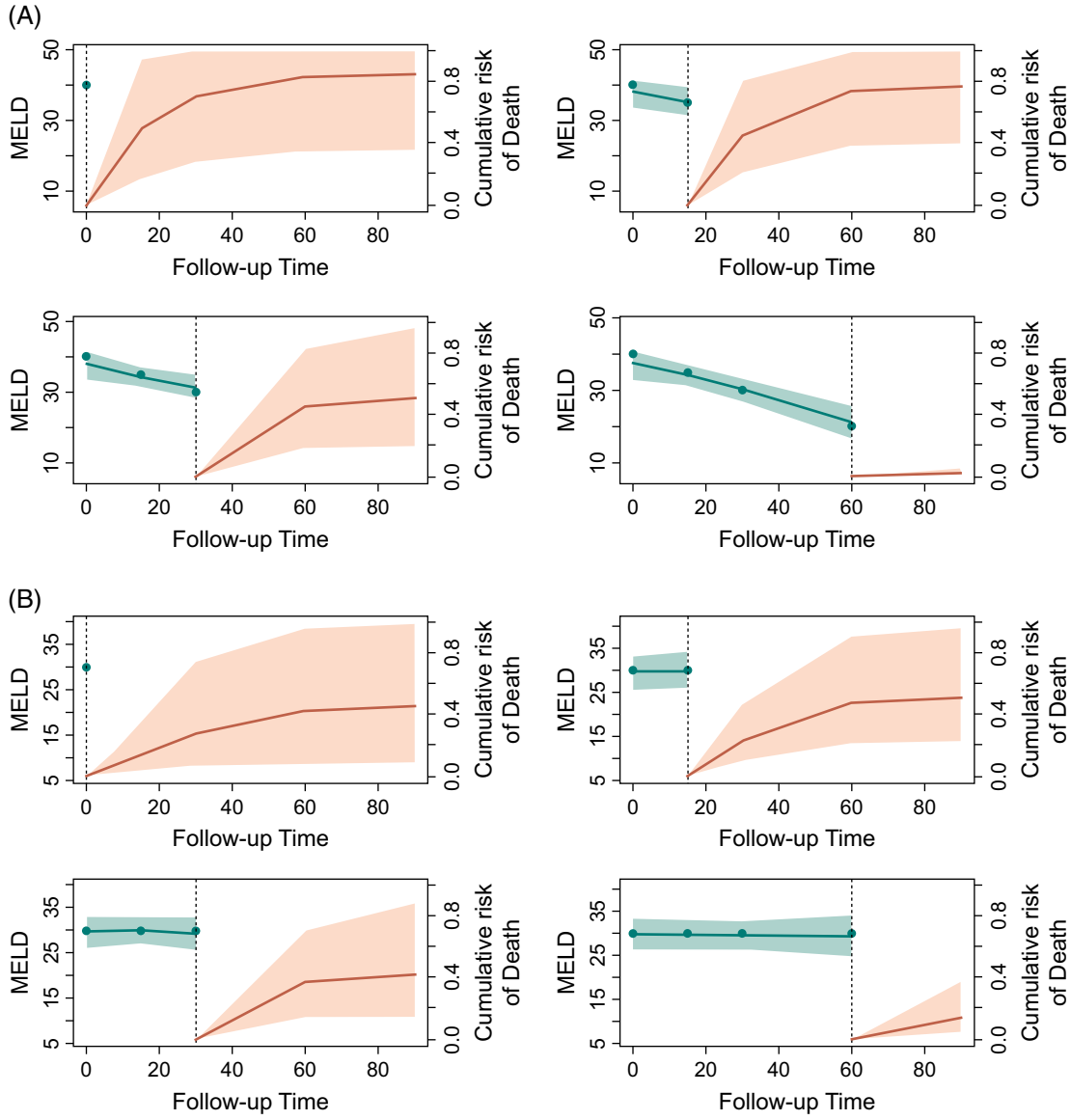

FIGURE 2 Dynamic MELD prediction in patients with progressive serial MELD measurement at baseline, day 15, day 30, and day 60. The mortality risk portion of the graph represents the risk of transplant/death with the 95% prediction interval. (A) Example of a patient with decreasing MELD from 40 to 20. (B) Example of a patient with a stable MELD of 30. Abbreviation: MELD, Model for End-Stage Liver Disease.

context of AH trials makes the logistics of these trials difficult. Several fields have incorporated the use of ordinal outcomes as the primary endpoint to demonstrate efficacy, with recent examples in stroke,[33] COVID-19,[34] and pulmonary hypertension.[35] An ordinal outcome for AH trials could include death as the worst category,

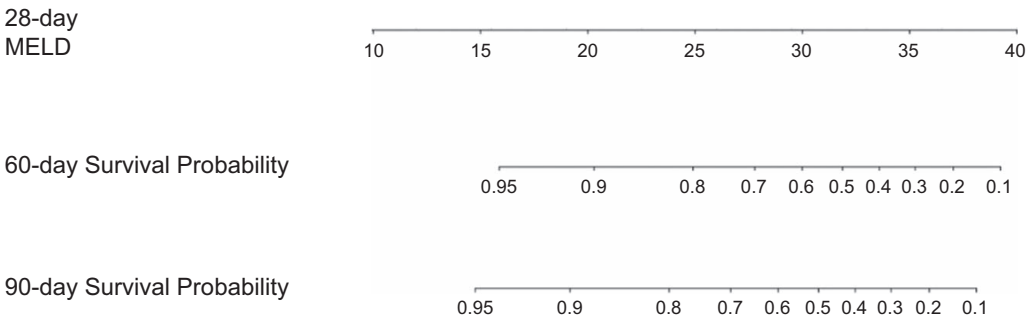

FIGURE 3 Nomogram showing the 60-day and 90-day transplant-free survival probability based on the 28-day MELD score. Abbreviation: MELD, Model for End-Stage Liver Disease.

TABLE 2 Distribution of the patients with severe AH at 28 days according to the ordinal scale in the InTeam cohort, and after applying different effect sizes

		Distribution of patients according to the ordinal scale at day 28				
			Expected distribution in a treatment arm applying different ORs			
Ordinal scale		InTeam (%)	OR: 0.77 (%)	OR: 0.72 (%)	OR: 0.65 (%)	OR: 0.50 (%)
8	Death	12.4	9.8	9.2	8.4	6.6
7	Transplant	1.9	1.6	1.5	1.4	1.1
6	MELD = > 30	7.1	5.9	5.7	5.3	4.3
5	MELD 30–25	13.3	11.7	11.3	10.6	9.0
4	MELD 25–20	16.2	15.4	15.1	14.6	13.1
3	MELD 20–17.5	20.5	21.4	21.5	21.6	21.4
2	MELD 17.5–15	17.6	20.4	21.1	22.2	24.7
1	MELD < 15	11	13.8	14.6	15.9	19.8

Note: The distribution of MELDs applies to those patients alive, not transplanted, and still in follow-up at day 28.
Abbreviations: AH, alcohol-associated hepatitis; MELD, Model for End-Stage Liver Disease.

transplant as the second worst, and the distribution of MELDs in those not having death or transplant. For illustration purposes, we chose the distribution across 6 categories of MELD, but MELD-28 could also be used as a continuous variable. The use of such an outcome would substantially increase power and decrease the sample size for a given effect size (Table 3). Since it is highly unlikely that an improvement in creatinine, bilirubin, or international normalized ratio induced by an experimental treatment would be followed by a worsening (or lack of improvement) in patient outcomes, such an ordinal scale would likely have high credibility for regulatory agencies. Indeed, the most up-to-date MELD in a given patient is already used in one of the most critical decisions in hepatology, such as when indicating a transplant and when ranking a given patient on the waiting list. Furthermore, the trial itself could incorporate analyses to document that the effect on the harder outcomes (death or transplant) is consistent with the effect on the milder outcomes (MELD distribution) by checking the proportional odds assumption.

TABLE 3 Potential impact of the use of an ordinal outcome on the sample size in patients with severe AH

Sample size for an RCT in severe AH (assuming a distribution of outcomes at day 28 in the placebo arm as in the InTeam cohort)		
	Endpoint at day 28	
Effect size (OR)	Dichotomous (Death/transplant vs. alive)	Ordinal scale 8 categories (Death, transplant, MELD distribution in those alive)
0.77[a]	3750	1413
0.72[b]	2374	895
0.65	1381	520
0.5	533	201

Note: There was a marked decrease in the needed sample size when using an ordinal scale as the primary outcome, as compared to the dichotomous outcome. Sample size calculations were for a proportional odds model with 80% power.
[a]0.77: approximate effect size (HR) observed in Louvet et al.[14]
[b]Effect size (unadjusted OR) observed in Thursz et al.[13]
Abbreviations: AH, alcohol-associated hepatitis; MELD, Model for End-Stage Liver Disease; RCT, randomized controlled trial.

Our study has several strengths. The information was collected prospectively in 13 centers across 6 different countries, which enhances the study's external validity and generalizability to diverse populations. Second, our modeling strategy used a single variable (MELD), so there is minimal risk of overfitting in our analysis. Finally, we used complementary approaches to address the study

The additional advantage of an ordinal outcome would be the possibility of testing efficacy at earlier time points. It is well established that in AH, the drivers of short-term and long-term outcomes differ, and hence the therapeutic targets might be different.[36] Indeed, after a few weeks, the prognosis of AH is mostly dependent on whether the patient continues/resumes using alcohol.[36,37] In addition, patients with AH are frequently lost to follow-up, which makes it difficult to have complete trial data in long trials. Therefore, trials with a short time horizon to assess an acute intervention early in the trajectory of AH (such as it was done, eg, in the STOPAH trial[13]) would be an important step forward for drug development.

Finally, an ordinal outcome seems the only feasible option for trials in moderate AH, in which short-term mortality is exceedingly low. An alternative that has been proposed for these trials is the assessment of MELD change. However, change from baseline is difficult to interpret since higher values tend to have higher chances of change, and a similar change might have a very different meaning according to the baseline. In the framework of ordinal outcomes, the baseline MELD can be easily incorporated into the analysis as a covariate, allowing a direct and easy interpretation of the resulting OR as "for patients that were equally sick at baseline what were the chances of an improvement in outcome with the new treatment."

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question (joint model and landmark analysis), showing consistent results. The main limitation of the study is the lack of standardized time points for measuring MELD. This is difficult to fulfill in a cohort of patients with AH. There was indeed a substantial proportion of patients lost to follow-up. Fifteen percent of the patients in the original cohort were lost to follow-up by day 90. Another limitation is that the transplant landscape for AH has substantially changed, especially after 2018.[38] Still, since the main driver for transplant indication and prioritization is MELD, the impact of an increased rate of transplant on the interpretation of our findings would be low. Finally, we acknowledge that we used MELD in its original iteration in this study. Over time, newer iterations of MELD, designed to improve accuracy and limit unintended bias against women, have been introduced.[39,40] We suspect that our findings here would be replicated by MELD 3.0, but this would have to be tested.

In conclusion, we show here that updated MELDs during the trajectory of AH are strongly associated with prognosis. This suggests that incorporating MELD scores as part of an ordinal outcome may be a sound approach to improve efficiency in therapeutic trials for AH.

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CONFLICTS OF INTEREST

Juan G. Abraldes reports consulting for Boehringer Ingelheim, AstraZeneca, Advanz, 89Bio, and Boston Pharmaceuticals. He received research grants from Cook and Gilead paid to the University of Alberta. Bernd Schnabl consults for Ambys Medicines, Ferring Research Institute, Gelesis, HOST Therabiomics, Intercept Pharmaceuticals, Mabwell Therapeutics, Surrozen, Patara Pharmaceuticals, and Takeda. Bernd Schnabl is the founder of Nterica Bio. UC San Diego has filed several patents with Bernd Schnabl as an inventor. Bernd Schnabl's institution, UC San Diego, has received research support from Artizan Biosciences, Axial Biotherapeutics, BiomX, CymaBay Therapeutics, NGM Biopharmaceuticals, Prodigy Biotech, Intercept, Chromologic, and Synlogic Operating Company. Robert S. Brown Jr consults for Abbvie, Gilead, eGenesis, Intercept, and Mallinckrodt. He received grants from Durect. Philippe Mathurin consults for Agomab Therapeutics and Intercept. Debbie Shawcross consults, advises, is on the speakers' bureau, and has received grants from EnteroBiotix. She consults, is on the speakers' bureau, and has received grants from Norgine. She consults and advises Satellite Bio and MRM Health. She consults for Apollo Therapeutics. Victor Vargas advises Ipsen. Elizabeth Verna received grants from Salix. Ramon Bataller consults for GlaxoSmithKline Novo Nordisk, and Boehringer Ingelheim. He is on the speakers' bureau for Abbvie and Gilead. Juan G. Abraldes consults for 89Bio, Boehringer Ingelheim, AstraZeneca, Advanz, Boston Pharmaceuticals, and Novo Nordisk. He received grants from Cook and Gilead. Joan Genesca consults for Boehringer Ingelheim and is on the speakers' bureau for Echosens. The remaining authors have no conflicts to report.

ETHICS APPROVAL

Each participating center obtained approval from their institutional ethics committee (IRB from the University of Pittsburgh as a coordinator center PRO17040075)

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