Model for End-Stage Liver Disease Na Score Predicts Incident Major Cardiovascular Events in Patients With Nonalcoholic Fatty Liver Disease

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Cardiovascular disease (CVD) is the leading cause of mortality among adults with nonalcoholic fatty liver disease (NAFLD); however, accurate tools for identifying NAFLD patients at highest CVD risk are lacking. Using a validated algorithm, we identified a retrospective cohort of 914 NAFLD patients without known CVD. Fibrosis severity was estimated using the fibrosis-4 index. Patients were followed for 5 years for the development of a major adverse cardiovascular event (MACE); a composite of cardiovascular death, myocardial infarction, or unstable angina; urgent coronary revascularization; or stroke. Using an adjusted Cox proportional hazard regression model, NAFLD-specific biomarkers of CVD risk were identified. Discrimination was compared to that of the Framingham Risk Score (FRS) using the area under the receiver operating characteristic curve. Among 914 patients, the mean age was 53.4 years and 60.6% were female. Over 5 years, 288 (31.5%) experienced MACE. After adjustment for traditional cardiometabolic risk factors and underlying FIB-4 index score, each 1-point increase in the model for end-stage liver disease integrating sodium (MELD-Na) was associated with a 4.2% increased risk of MACE (hazard ratio, 1.042; 95% confidence interval, 1.009-1.075; $P = 0.011$). Compared to patients in the lowest MELD-Na quartile (<7.5), those in the highest quartile (≥13.2) had a 2.2-fold increased risk of MACE (adjusted hazard ratio, 2.21; 95% confidence interval, 1.11-4.40; $P = 0.024$; P trend = 0.004). Incorporating MELD-Na with the FRS significantly improved discrimination of future CVD risk (combined C-statistic 0.703 versus 0.660 for the FRS alone; $P = 0.040$). *Conclusion*: Among patients with NAFLD, the MELD-Na score accurately stratifies the risk for patients according to future CVD event risk. The addition of the MELD-Na score to the FRS may further improve discrimination of NAFLD-related CVD risk. (*Hepatology Communications* 2017;1:429–438)

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the United States, affecting an estimated 30 million adults.[1,2] Although hepatic complications are frequent in NAFLD, cardiovascular disease (CVD) represents the most common cause of mortality, accounting for 25% of deaths.[3,4] In epidemiologic studies, NAFLD has been shown to contribute independently to the development of CVD[5] and is associated with an increased prevalence of high-risk coronary

Abbreviations: AUROC, area under the receiver operating curves; BMI, body mass index; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; EMR, electronic medical records; FIB-4, fibrosis-4; FRS, Framingham Risk Score; HR, hazard ratio; ICD-9, International Classification of Diseases, Ninth Revision; INR, international normalized ratio; KM, Kaplan-Meier; MACE, major adverse cardiovascular event; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease integrating sodium; NAFLD, nonalcoholic fatty liver disease.

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plaques, aortic atherosclerosis, and increased carotid intima-media thickness and coronary artery calcium scores.[6-8] More recently, advanced NAFLD has also been linked to fatal and nonfatal ischemic CVD events, including acute coronary syndrome.[6,7]

Despite this, few validated tools exist for the stratification of CVD risk in patients with NAFLD. This is in stark contrast to the general population where considerable efforts have focused on identifying biomarkers of future CVD risk. Commonly applied risk assessment tools are based on the Framingham equation, which identified traditional cardiovascular (CV) risk factors, including hypertension, dyslipidemia, and diabetes, from a large community-based cohort of adults.[9] Through targeted efforts, interventions, such as smoking cessation, blood pressure control, and aggressive lipid-lowering therapy, have become the cornerstone of preventive cardiology and have significantly reduced the incidence of CV events in developed countries.[10,11]

Little is known about individual biomarkers in NAFLD that reflect future risk of ischemic CV events. One published longitudinal study focusing on NAFLD has demonstrated that the composite Framingham Risk Score (FRS) accurately predicts 10-year NAFLD-associated CVD risk[12]; however, in that analysis no individual biomarkers were evaluated or compared to the FRS. With such a paucity of data, there are currently no CV risk assessment tools validated for populations with NAFLD. The development of such models would provide clinicians with an important and practical means to stratify their patients who have NAFLD according to the future risk of adverse CV events and determine who might be most likely to benefit from targeted interventions.

The model for end-stage liver disease (MELD) was originally developed for the assessment of short-term mortality in patients with cirrhosis who were waiting for transjugular intrahepatic portosystemic shunts,[13] and its clinical utility has since extended to include prioritization of liver transplantation[14] and the prediction of operative mortality in cirrhosis.[15] More recently, data have emerged suggesting that the MELD scoring system may also serve as a novel biomarker of clinical and CV risk, even in patients without known liver disease.[16,17] It has been shown in a large unselected population admitted to an intensive care unit that MELD accurately predicts both short- and long-term mortality.[16] In addition, an elevated MELD predicts perioperative mortality and transfusion requirements[18] as well as a 1-year risk of requiring mechanical support or heart transplantation[17] in longitudinal cohorts with heart failure. Finally, our group recently reported that the MELD score is associated with prevalent CVD in a large cross-sectional NAFLD cohort.[19] Despite these lines of evidence, no longitudinal study has assessed the ability of the MELD or the MELD integrating sodium (MELD-Na) to predict the long-term risk of ischemic CV events in patients with NAFLD.

Using a validated[20] and well-characterized longitudinal electronic medical record (EMR)-based cohort of 914 individuals with NAFLD free of known underlying CVD, we assessed the ability of the MELD-Na score to predict of the risk of incident major ischemic CV events.

Patients and Methods

COHORT CREATION

Patients and data for the present study were drawn from a previously validated retrospective cohort created from the Partners HealthCare EMRs using the Partners Research Patient Data Registry.[19] Briefly, the Research Patient Data Registry is a centralized clinical data registry containing data from all institutions in

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the Partners HealthCare system. It includes data on ~10 million patients with ~2.3 billion EMR facts obtained from the Massachusetts General Hospital and Brigham and Women's Hospital, large tertiary-care referral centers serving the New England region of the United States.

NAFLD was defined using an algorithm that our group has previously validated for the identification of NAFLD from within this set of EMRs.[19,20] This algorithm calculates an NAFLD probability per patient based on the most recent triglycerides measurement, the total number of billing codes for NAFLD (International Classification of Diseases, Ninth Revision [ICD-9] 571.8 or 571.9), and the total number of mentions of NAFLD in clinical narrative notes, using text-based processing. Application of this algorithm to the EMR database yielded 3,284 patients over the age of 18, with probability > 0.85 of underlying NAFLD. Patients with cirrhosis, viral hepatitis, or those with a history of ethanol abuse were excluded as were patients who were currently taking or who had ever previously received anticoagulation with warfarin, to avoid confounding by indication or the misclassification of patients due to medication-related elevations in the international normalized ratio (INR). Finally, patients were excluded if they had any prior diagnosis of CVD, which was defined as one or more ICD-9 or Current Procedural Terminology (CPT) codes for myocardial infarction, CVD, ischemic heart disease, angina, stroke, transient ischemic attack, congestive heart failure, or peripheral vascular disease. Comorbidities were defined by the presence of one or more ICD-9 or CPT codes for that comorbidity over the patient's lifetime prior to the diagnosis of CVD. The remaining 914 adult patients without known CVD and who exceeded the NAFLD probability threshold of 0.85 were included in this analysis. From these 914 patients, a randomly selected subset (n = 50) underwent validation of baseline comorbidities, including CV disease status, by a manual physician review of the EMRs.

BASELINE MEASURES

Clinical, demographic, and laboratory variables were assessed at baseline. For laboratory parameters, the closest available value obtained within 24 months of study entry was used, and the date of that laboratory testing was recorded as the subject's baseline date. If multiple values were present for a given time point, then the average of available values was used. In addition to ICD-9 diagnosis codes, expressions from the notes were extracted to determine an individual's most recent smoking status (past, present, never), comorbid conditions, and to assess relevant medication use. Family history of CVD was identified through extraction from clinical narrative notes by the mention of one or more family members reported to have had a prior myocardial infarction, angina requiring hospitalization, percutaneous coronary intervention, coronary artery bypass graft, stroke, or sudden death.

Predicted values for CVD risk were calculated using the Framingham Risk Score (FRS), which employs a standard sex-specific score sheet comprised of the following variables: age, blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking history, and history of diabetes.[21,22] In each patient, the FRS was used to estimate the 10-year probability of incident CVD. The fibrosis-4 (FIB-4) score was calculated according to the following published algorithm[23]: FIB-4 = (age [years] × aspartate aminotransferase [U/L])/(platelets [109/L] × alanine aminotransferase$^{1/2}$ [U/L]). The MELD and the MELD-Na scores were calculated according to the following published algorithm[24,25]: MELD-Na = MELD + 1.59(135–[Na]), where MELD = 11.2ln(INR) + 3.78ln(total bilirubin) + 9.57ln(creatinine) + 6.43.

FOLLOW-UP AND ASSESSMENT OF OUTCOMES

Follow-up time was calculated beginning at the time of the captured baseline MELD-Na score. Patients were followed for a total of 5 years from baseline until the development of the primary outcome, death, or loss to follow-up. The primary outcome was major adverse CV events (MACE), a composite defined by CV death, nonfatal myocardial infarction, angina requiring hospitalization, intervention with percutaneous coronary intervention and/or coronary artery bypass graft, stroke, or transient ischemic attack. All clinical outcomes were defined by the presence of one or more ICD-9 codes as well as one or more associated relevant hospital admission diagnosis codes and/or procedure-related billing codes where relevant (Supporting Table S1). Patients were considered lost to follow-up if they had no documented contact within the Partners system for ≥12 consecutive months; for these cases, the date of last contact with the Partners system was documented. Finally, a randomly selected subset of 50 patients who achieved the primary endpoint was validated by manual physician review of the EMR.

STATISTICAL ANALYSIS

Data are expressed as mean ± SD or medians with interquartile ranges. Continuous variables were analyzed with the Student *t* test; the Mann-Whitney U test was used for nonparametric measures. The Pearson χ^2 test was used to test for differences in proportions. Continuous variables were evaluated as such and, when relevant, as categories to increase the potential clinical utility of any future risk model. Age was categorized in 10-year increments (age < 40, 40 < age ≤ 50, 50 < age ≤ 60, and age > 60). Body mass index (BMI) was categorized as underweight (BMI < 19), normal (19 < BMI < 25), overweight (25 < BMI < 29), or obese (BMI > 29). The FIB-4 score was used as a surrogate estimate of underlying hepatic fibrosis and was assessed both as a continuous variable and according to a threshold cut-off score of FIB-4 > 1.45 versus FIB-4 ≤ 1.45.[23] MELD-Na was assessed both as a continuous variable and in quartiles based on its baseline distribution.

Cox proportional hazards regression modeling was used to identify all candidate traditional and nontraditional risk factors associated with the outcome of interest. No violations of the Cox proportionality assumption (assessed by scale Schoenfeld residuals) were detected. Goodness of fit of the model was evaluated by plotting the observed number of failures in the data and the number predicted by residuals. Cumulative overall time-to-event data were calculated using Kaplan-Meier (KM) analysis with log-rank testing to compare differences in the primary endpoint across MELD-Na quartiles. Time at risk was assessed from the date of baseline MELD-Na score to the date of outcome, death, or last follow-up, whichever came first. A series of individual sensitivity analyses were conducted excluding patients over the age of 50, those who were obese, those with diabetes, those taking statin medications, or those with a baseline FIB-4 score > 1.45. We also conducted a stratified analysis by FIB-4 categories (FIB-4 ≥ 1.45 versus FIB-4 < 1.45) to test whether the relationship between MELD-Na and incident MACE varied according to severity of the underlying fibrosis.

In exploratory analyses, the prognostic strength of the MELD-Na score, the FIB-4, and the FRS were compared by calculating each area under the receiver operating curve (AUROC) for the clinical endpoint of interest. AUROCs were then quantitatively compared by computation of Harrell C-statistics,[26,27] and differences between models were assessed using bootstrapping. Calibration was tested by the Hosmer-Lemeshow goodness of fit test. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

BASELINE CHARACTERISTICS

Table 1 outlines the baseline clinical, demographic, and laboratory characteristics of the 914 included patients with NAFLD, all of whom were free of known CVD at baseline. The mean overall age was 53.4 years, and 60.6% were female. Hypertension was noted in 31.5%, diabetes in 22.8%, and 38.8% of patients had a diagnosis of metabolic syndrome. One quarter of the patients had diagnosed dyslipidemia, and among them, 35% were prescribed statin medications through the EMR prescription system. Comorbidities, including underlying CVD, were validated by a physician-led manual chart review in a randomly selected subset of 50 patients; none had prior evidence of underlying CVD in the EMRs.

BIOMARKERS OF NAFLD SEVERITY AND CORRELATIONS WITH 10-YEAR-CALCULATED CVD RISK

The mean baseline MELD-Na score was 11.2 ± 5.4, and the mean FIB-4 score was 1.11 ± 0.76 (Table 1). Patients were distributed evenly by quartiles of MELD-Na (category 1, MELD-Na < 7.50; category 2, 7.51-9.20; category 3, 9.21-13.10; category 4, ≥ 13.2), and those in the highest and lowest quartiles were compared. Patients in the highest MELD-Na quartile also had significantly increased mean FIB-4 scores (1.21 ± 0.47 vs. 1.03 ± 0.38; $P = 0.01$), increased creatinine (mean 1.32 ± 0.45 vs. 0.95 ± 0.23; $P < 0.001$), and to have increased 10-year-calculated CVD risk according to the FRS (21.4 versus 17.1; $P < 0.0001$), compared to those in the lowest quartile. Compared to the lowest quartile, patients in the highest MELD-Na quartile also had significantly increased mean FIB-4 scores (1.21 ± 0.47 versus 1.03 ± 0.38) as well as increased creatinine (mean 0.95 ± 0.23 versus 1.32 ± 0.45; $P <$ 0.001) and lower levels of sodium (mean 136.7 ± 3.9 versus 139.3 ± 2.7; $P = 0.040$), albumin (mean 3.6 ± 0.42 g/dL versus 4.2 ± 0.47 g/dL; $P < 0.001$), and platelets (mean 242.6 ± 84.4 versus 255.1 ± 79.7; $P = 0.005$). No significant differences were found in baseline

TABLE 1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF INCLUDED NAFLD SUBJECTS, WITH NO PRIOR HISTORY OF CORONARY ARTERY DISEASE (n = 914)

Variable*	N, %
Age category, %	
• Age < 40 (ref.)	372 (40.70%)
• 40 ≤ age < 50	244 (26.70%)
• 50 ≤ age < 60	173 (18.93%)
• Age ≥ 60	125 (13.68%)
Female sex, %	554 (60.61%)
Race, %	
• White (ref.)	584 (63.89%)
• African American	125 (13.68%)
• Asian	16 (1.75%)
• Hispanic	147 (16.08%)
• Other	42 (4.59%)
Family history CAD, %	122 (13.35%)
Current smoking, %	82 (22.47%)
Obesity, %	141 (15.43%)
Hypertension, %	288 (31.51%)
Diabetes, %	208 (22.76%)
Dyslipidemia, %	252 (27.57%)
Metabolic syndrome, %	355 (38.84%)
Laboratory variables	
Sodium, mEq/L	139.00 (137.0, 141.0)
Creatinine, mg/dL	1.10 (0.87, 1.30)
Albumin g/dL	4.10 (3.70, 4.40)
Alanine aminotransferase, U/L	23.00 (16.00, 41.00)
Aspartate aminotransferase, U/L	22.00 (16.00, 31.00)
International normalized ratio	1.10 (1.00, 1.20)
Platelets × 1000/mm^3	254.00 (209.00, 309.00)
Total cholesterol, mg/dL	219.00 (184.50, 252.00)
Low-density lipoprotein cholesterol, mg/dL	126.50 (97.5, 154.00)
High-density lipoprotein cholesterol, mg/dL	41.00 (34.00, 50.00)
Triglycerides, mg/dL	248.00 (193.00, 299.00)
CV and NAFLD risk scores	
Framingham risk score (mean, SD)	18.88 (8.03, 26.87)
FIB-4 score (mean, SD)	1.11 (0.76)
MELD-Na score (mean, SD)	11.17 (5.41)
MELD-Na category (quartiles) [median]	
• 1: ≤ 7.50	199 (21.77%) [6.40]
• 2: 7.51-9.20	258 (28.22%) [8.20]
• 3: 9.21-13.10	229 (25.05%) [10.70]
• 4: ≥ 13.20	228 (24.94%) [13.20]

Results expressed as median (interquartile range) unless otherwise stated.
Abbreviation: CAD, coronary artery disease.

alanine aminotransferase (mean 24 ± 9 IU/L versus 23 ± 13 IU/L; $P = 0.42$) or in levels of total bilirubin (mean 0.75 ± 0.31 versus 0.69 ± 0.46; $P = 0.56$) between groups.

ASSESSMENT AND VALIDATION OF CLINICAL EVENTS

The mean overall length of follow-up was 4.1 ± 1.5 years. Over this time, 288 NAFLD patients (31.5%) developed incident MACE, 88 patients (9.6%) died, and 161 (17.6%) were lost to follow-up. A randomly selected subset of 50/288 MACE events was validated by physician review of the EMRs; of these, 47 (94%) were confirmed to be true-positive cases.

TRADITIONAL CV RISK FACTORS FOR MACE

In univariable analysis, multiple traditional CV risk factors were associated with MACE, including age > 50 years, male sex, Hispanic and African American race, current smoking, family history of coronary disease, hypertension, diabetes, dyslipidemia, metabolic syndrome, and the FRS (Table 2). In the fully adjusted Cox proportional hazards regression model (Table 3), the following variables were associated with an independent risk of incident MACE: age > 50 (adjusted hazard ratio [HR], 2.62; 95% confidence interval [CI], 1.36-4.52; $P = 0.003$), prior or current smoking (adjusted HR, 1.69; 95% CI, 1.07-2.67; $P = 0.024$), family history of coronary artery disease (adjusted HR, 3.26; 95% CI, 1.28-8.27; $P = 0.013$), and dyslipidemia (adjusted HR, 2.94; 95% CI, 1.11-7.76; $P = 0.02$). When the FRS was included in the model with its constituent variables excluded to avoid collinearity, the FRS was also significantly associated with MACE (adjusted HR, 1.048; 95% CI, 1.019-1.077; $P = 0.0009$).

NONTRADITIONAL CV RISK FACTORS FOR MACE

Serum sodium, albumin, continuous FIB-4, and the MELD-Na score were each associated with an elevated risk of MACE in univariable analysis (Table 2). Patients in the highest MELD-Na quartile had a significantly higher 5-year cumulative incidence of MACE compared to the lowest quartile (5-year KM rate 54.0% versus 27.6%; $P < 0.0001$; Fig. 1). In contrast, we found no significant differences in the 5-year rates of the primary endpoint in patients with elevated FIB-4 ≥ 1.45 versus low FIB-4 < 1.45 (KM rate = 37.4% versus 33.7%; $P = 0.086$; Supporting Fig. S1).

In the fully adjusted Cox proportional hazards regression model, accounting for age, sex, race, obesity, hypertension, dyslipidemia including statin use, high-density lipoprotein level, diabetes, family history of coronary disease, metabolic syndrome, Na, albumin, smoking history, and FIB-4, MELD-Na was the only nontraditional CVD biomarker associated with a

TABLE 2. UNIVARIATE PREDICTORS OF MAJOR CARDIOVASCULAR EVENTS (MACE) AMONG PATIENTS WITH NAFLD (N=914) AND NO PRIOR HISTORY OF CARDIOVASCULAR DISEASE, MODELED BY UNIVARIATE COX PROPORTIONAL HAZARDS REGRESSION ANALYSIS

Variable*	Crude HR (95% CI)	P-value
Age category		
• Age < 40 (ref.)	Reference	–
• 40 ≤ age < 50	1.118 [0.799-1.564]	0.515
• 50 ≤ age < 60	2.695 [1.997-3.637]	<0.0001
• Age ≥ 60	2.516 [1.798-3.521]	<0.0001
Female sex	0.739 [0.586-0.932]	0.0107
Race		
• White	Reference	–
• African American	0.689 [0.481-0.986]	0.0418
• Asian	1.466 [0.604-3.561]	0.7152
• Hispanic	0.498 [0.339-0.731]	0.0004
• Other	0.997 [0.569-1.747]	0.992
Family History CAD	1.622 [1.035-2.812]	0.0450
Current smoking	1.610 [1.112-2.329]	0.0116
Obesity	1.390 [0.851-2.269]	0.188
Hypertension	1.668 [1.257-2.213]	0.0004
Diabetes	1.573 [1.118-2.213]	0.0093
Dyslipidemia	3.112 [2.062-4.697]	<0.0001
Metabolic syndrome	1.418 [1.115-1.802]	0.0044
Laboratory variables		
Sodium	0.983 [0.968-0.998]	0.0282
Albumin	0.766 [0.609-0.965]	0.0238
High-density lipoprotein cholesterol	0.976 [0.958-0.994]	0.0110
CV and NAFLD risk scores		
Framingham risk score	1.030 [1.019-1.040]	<0.0001
FIB-4 score (continuous)	1.151 [1.012-1.309]	0.0316
FIB-4 score > 1.45	1.527 [1.104-2.112]	0.0105
MELD-Na score (continuous)	1.041 [1.022-1.060]	<0.0001
MELD-Na Category (quartiles)		<0.0001*
• 1: ≤ 7.50	Reference	–
• 2: 7.51 – 9.20	1.316 [0.899-1.928]	0.158
• 3: 9.21 – 13.10	1.476 [1.011-2.155]	0.044
• 4: ≥ 13.20	2.290 [1.598-3.283]	<0.0001

Abbreviations: HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; CV, cardiovascular; NAFLD, nonalcoholic fatty liver disease

significantly increased risk of MACE (adjusted HR per each 1-point increase in MELD-Na,1.042; 95% CI, 1.009-1.075; $P = 0.011$) (Table 3). When the highest versus lowest MELD-Na quartiles were compared, those with MELD-Na ≥ 13.2 had a 2.2-fold increased adjusted risk of incident MACE (adjusted HR, 2.211; 95% CI, 1.111-4.399; $P = 0.024$ with $P_{trend} < 0.0001$) (Table 3). When the model was further adjusted for the FRS, each 1-point increase in MELD-Na remained associated with a 3.2% increased risk of MACE (adjusted HR, 1.032; 95% CI, 1.010-1.075; $P = 0.011$). In contrast, FIB-4 was not associated with an increased risk of MACE (adjusted HR per each 1-SD increase in FIB-4, 1.04; 95% CI, 0.87–1.14; $P = 0.23$). To test whether the relationship between MELD-Na score and MACE varied according to fibrosis severity, we stratified the cohort according to the FIB-4 category (FIB-4 ≥ 1.45 versus FIB-4 < 1.45), and the strength of the association between continuous MELD-Na and risk of incident MACE did not vary (for FIB-4 ≥ 1.45, HR, 1.046; 95% CI, 1.010-1.064; for FIB-4 < 1.45, HR, 1.041; 95% CI, 1.013-1.070; $P_{trend} < 0.0001$ in both strata).

Estimated effects of each risk factor were consistent across race but not sex. When estimates of effect were evaluated across sex, we observed a significant interaction ($P = 0.012$) between age and sex on the risk of incident MACE. We also stratified patients according to age above or below 50 years as this represents the average age of menopause in the United States. Among patients < age 50, men had a 1.8-fold increase in adjusted risk of incident MACE compared to women. Conversely, after age 50, women were no longer protected from the risk of MACE (adjusted HR

TABLE 3. MULTIVARIATE COX PH REGRESSION ANALYSIS OF TRADITIONAL RISK FACTORS FOR INCIDENT CVD AMONG PATIENTS WITH NAFLD

Risk Factor	# Cases/person-years of follow-up	Adjusted HR* [95% CI]	P-value
Age category			
• <40 (reference)	83/1,626.2	1.00	n/a
• 40-50	58/1,043.2	0.667 [0.359-1.241]	0.201
• 50-60	89/618.8	2.615 [1.571-4.352]	0.0002
• >60	58/472.1	2.482 [1.363-4.517]	0.0029
Female sex	157/2,338.2	0.713 [0.472-1.077]	0.108
Race			
• White (reference)	203/2,312.4	1.00	n/a
• African American	35/560.3	0.773 [0.413-1.447]	0.420
• Asian	5/61.4	1.709 [0.525-5.558]	0.374
• Hispanic	30 / 655.04	0.742 [0.403-1.366]	0.338
• Other	13/126.6	1.446 [0.414-5.058]	0.563
Smoking (any)	29/330.3	1.692 [1.071-2.674]	0.0242
Metabolic syndrome	183/1,519.8	1.050 [0.669-1.647]	0.814
Family History CAD	50/477.8	3.259 [1.284-8.269]	0.0129
Dyslipidemia	73/786.9	2.938 [1.113-7.756]	0.0295
Diabetes	92/767.8	1.816 [0.868-3.801]	0.113
Hypertension	81/703.9	1.853 [0.971-3.536]	0.062
MELD-Na Category (quartiles)			
• 1: ≤7.50	42/877.3	1.00	n/a
• 2: 7.51 – 9.20	71/1,085.7	1.477 [0.726-3.005]	0.2815
• 3: 9.21 – 13.10	74/916.8	1.607 [1.103-3.256]	0.0188
• 4: ≥13.20	101/882.1	2.211 [1.111-4.399]	0.0238

Abbreviations: PH, proportional hazards; CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease
*Cox PH regression model adjusted for age category, sex, ethnicity, obesity, hypertension, dyslipidemia, diabetes, the metabolic syndrome, any current or prior smoking history and family history of coronary artery disease (CAD).

among men versus women ≥ age 50, 1.02; 95% CI, 0.88–1.14; $P = 0.37$). The addition of an interaction term to the final multivariable model did not materially change the relationship between the MELD-Na score and the risk of MACE. Interactions between age and BMI, smoking or diabetes, and between statin medication use and MELD-Na score were not significant and therefore were not included.

In the AUROC analysis, the addition of the MELD-Na to the FRS improved discrimination of

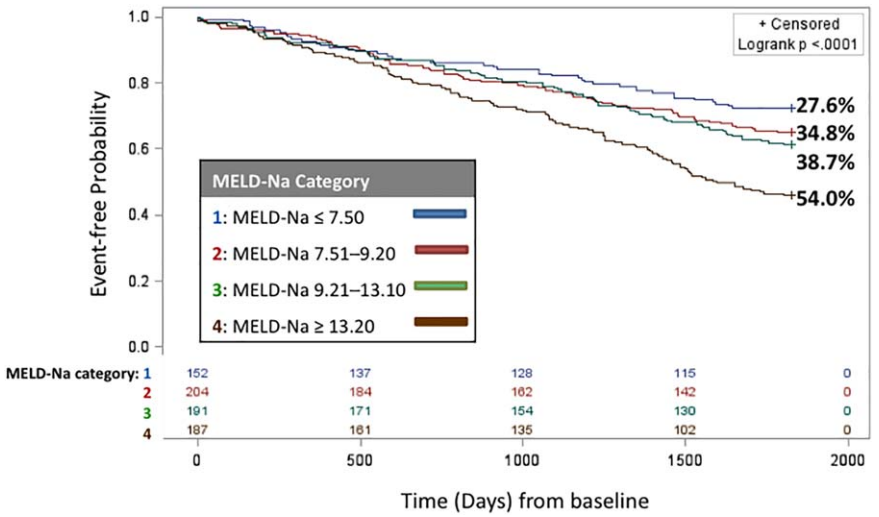

FIG. 1. Five-year KM rates of incident MACE according to the MELD-NA score category.

MACE risk. Used alone, the FRS correctly classified 65% of the study cohort (95% CI, 0.602-0.718), while the MELD-Na score correctly classified 62% of individuals (95% CI, 0.57-0.75). When combined, the new calculated score correctly classified 70% of the population (95% CI, 0.64-0.80), which was significantly enhanced compared to the FRS alone ($P = 0.040$) (Supporting Fig. S2). Calibration was adequate by the Hosmer-Lemeshow test, with χ^2 $P = 1.00$. In contrast, the FIB-4 correctly classified only 56% of individuals (95% CI, 0.51-0.62), and when combined with the FRS, it did not significantly impact the prognostic utility of that score (combined C-statistic, 0.66; 95% CI, 0.60-0.72; $P = 0.585$) (Supporting Fig. S3).

In a series of five sensitivity analyses, excluding subjects with (1) diabetes (n = 208), (2) obesity (n = 141), (3) those over the age of 50 (n = 298), (4) those with baseline FIB-4 > 1.45 (n = 245), or (5) statin medication users (n = 84) did not materially impact our estimated effects of MELD-Na on incident risk of MACE. Finally, we limited the cohort only to those with available baseline MELD-Na obtained within 12 months of study entry (n = 827). The demographics, baseline MELD-Na, and FIB-4 scores did not significantly differ between this group and the main study cohort (all $P > 0.05$), and the association between MELD-Na and risk of incident MACE was unchanged from the main analysis (adjusted HR, 1.045; 95% CI, 1.015-1.080; $P = 0.001$).

Discussion

In patients with NAFLD, available tools for CV risk assessment include only models created and validated in the general population, and these may not provide accurate risk stratification in this population. In the present study, we demonstrate that the integrated MELD-Na score accurately stratifies NAFLD patients according to their future risk of ischemic CV events. This simple serum-based score established a clear gradient of CV risk that added significant prognostic value to traditional measures for CV risk assessment, including the FRS. Notably, this relationship was consistent even in patients with low FIB-4, suggesting utility of the MELD-Na score for predicting CV risk in those with limited underlying fibrosis. If validated, this approach could provide clinicians with an accessible and practical strategy for identifying NAFLD patients at highest risk of adverse ischemic CV events.

Although the MELD and more recent MELD-Na scores were validated specifically in populations with established cirrhosis,[24,25] the MELD-based scoring system has recently emerged as a novel biomarker of clinical and CV risk in populations without end-stage liver disease.[16-18] Individual components of the MELD-Na (sodium, total bilirubin, creatinine, and INR) each reflect important downstream complications of cardiometabolic or nutritional disarray and have been shown to predict CV outcomes in the general population.[28-30] Recently, it was reported that a modified MELD-XI (i.e., MELD score excluding INR) > 12 confers an increased risk of short-term (HR, 4.82; 95% CI, 3.93-5.93; $P < 0.001$) and long-term (HR, 3.69; 95% CI, 3.20-4.25; $P < 0.001$) mortality in a cohort of 4,381 unselected patients admitted to an intensive care unit.[16] In patients with heart failure but without known chronic liver disease, an elevated MELD significantly increases the 1-year risk of cardiac decompensation requiring advanced mechanical therapy or heart transplantation.[17] Such data suggest that the constellation of risk factors captured by the MELD could offer novel prognostic value that extends to a wide range of individuals, including those without cirrhosis.

Until recently, ischemic heart disease was felt to be rare in chronic liver diseases[31] as such patients often manifest decreased lipid synthesis and systemic vasodilatation, particularly in advanced disease.[32,33] However, in this manner NAFLD is unique, with close ties to arterial hypertension, systemic inflammation, endothelial dysfunction, and lipid peroxidation, each of which contribute to atherogenesis[34,35] and overall CVD risk.[36,37] Advanced NAFLD is accompanied by hypercoagulability, impaired fibrinolysis,[38] and increased levels of circulating inflammatory cytokines, including interleukin-6, tumor necrosis factor alpha, C-reactive protein, and monocyte chemoattractant protein 1,[39] which are known to promote lipid deposition, vascular smooth muscle proliferation, and vessel plaque formation.[40,41] Indeed, epidemiologic studies have shown that progressive NAFLD fibrosis may be an important long-term contributor to overall CVD risk.[7,42] Despite this, no study has identified accurate serologic biomarkers that could be used to help clinicians effectively predict which of their NAFLD patients are at highest risk of experiencing an adverse CV event.

In this cohort, the MELD-Na score outperformed the FIB-4 for predicting future ischemic CV events, and of the two indices, only the MELD-Na added

prognostic value to the FRS. While this may be contrary to expectation, our population had a low mean FIB-4 score (1.1 ± 0.76), and without a sufficient population with advanced fibrosis, we had limited ability to characterize the direct relationship between FIB-4 and MACE. On the other hand, stratified analyses demonstrated that the relationship between MELD-Na and MACE did not vary by underlying FIB-4 category, and the linear trend across continuous MELD-Na scores was consistent in both high and low FIB-4 groups. Given the low overall FIB-4 scores in our study population, these results suggest that the observed relationship between MELD-Na and incident MACE was not mediated by undiagnosed cirrhosis or decompensated liver disease. Rather, it is possible that the MELD-Na could provide important prognostic information regarding future NAFLD-associated CV risk that is particularly applicable to patients with early stages of disease and limited underlying fibrosis. This hypothesis warrants investigation in other populations with well-characterized NAFLD of varying histological severity. In addition, we look forward to future validation studies that will define the relative added clinical benefit derived from including the MELD-Na in an existing CV risk calculator, such as the FRS.

The MELD-Na score benefits from accessibility and ease of use; if validated, it could offer clinicians a practical noninvasive tool to accurately stratify NAFLD patients according to CV risk and guide the implementation of targeted personalized risk reduction programs. However, before MELD-Na can be incorporated into NAFLD-specific CV prognostication models, prospective validation studies will be needed in well-characterized populations with radiographic or histologically defined NAFLD. We will eagerly await the validation of our findings in other NAFLD populations as well, including those needing secondary rather than primary CV prevention and in those already on therapy for whom the MELD-Na score could potentially offer a means to monitor longitudinal treatment response.

We acknowledge several limitations to this analysis. First, our retrospective cohort was derived from a historical EMR-based population with comorbidities defined by diagnosis codes. This rendered it susceptible to both selection and misclassification bias and potentially unmeasured confounders despite manual validation of comorbidities and clinical endpoints in the medical chart. Second, our population was comprised primarily of Caucasian patients whose low FIB-4 scores suggested minimal underlying fibrosis, and both of these factors could limit generalizability. Third, the use of baseline MELD-Na scores obtained within 24 months of study entry could have introduced uncertainty and measurement error into our analyses; to address this, we conducted a sensitivity analysis limiting our cohort to those with MELD-Na obtained within 12 months of baseline, and the estimated effects were unchanged.

Finally, it is important to emphasize that, although well-validated and widely used, surrogate serum indices, such as the FIB-4, may not accurately capture fibrosis stage nor does it allow for an estimation of steatohepatitis. Particularly given the low mean FIB-4 scores in our population, it will be important in future studies to carefully assess the prognostic utility of the MELD-Na for CV risk in well-phenotyped NAFLD populations, including those with advanced fibrosis and/or cirrhosis.

In this longitudinal cohort of patients with NAFLD, we confirm that the MELD-Na score accurately stratifies patients with NAFLD according to their future risk of major ischemic CV events. The addition of the MELD-Na score to the FRS may improve discrimination of NAFLD-related CV risk and help identify those NAFLD patients at highest risk of adverse CV events.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1051/suppinfo.