Magnetic Resonance Elastography-Based Prediction Model for Hepatic Decompensation in NAFLD; a Multi-Center Cohort Study

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ABBREVIATIONS

MRE: Magnetic resonance elastography; IPDMA: individual participant data pooled meta-analysis; NAFLD: nonalcoholic fatty liver disease; LS: liver stiffness; BMI: body mass index; AASLD: American Association for the Study of Liver Diseases; LI-RADS: Liver Reporting and Data Systems; LSM: liver stiffness measurement, SD: standard deviation, IQR: interquartile range; MELD: model for end-stage liver disease; HCC: hepatocellular carcinoma

ABSTRACT

Background and Aims: Magnetic resonance elastography (MRE) is an accurate, continuous biomarker of liver fibrosis, however, the optimal combination with clinical factors to predict the risk of incident hepatic decompensation is unknown. Therefore, we aimed to develop and validate an MRE-based prediction model for hepatic decompensation for patients with nonalcoholic fatty liver disease (NAFLD).

Approach & Results: This international multi-center cohort study included participants with NAFLD undergoing MRE from six hospitals. The primary endpoint was hepatic decompensation, defined as the first occurrence of varices needing treatment or ascites or hepatic encephalopathy. Covariates associated with hepatic decompensation on Cox-regression were combined with MRE to construct a risk prediction model in the training cohort then tested in the validation cohort. Among 1,316 participants (52% women) the median age was 60 years (interquartile range [IQR] 19) and the median MRE was 3.49 (IQR 2.5) kPa. The training set consisted of 728 U.S. participants and the validation set consisted of 588 non-U.S. participants. The multivariable model included age, MRE, albumin, AST and platelet count with excellent discrimination, c-statistic of 0.90 and 0.88 for hepatic decompensation at 3- and 5-years respectively. The diagnostic accuracy of the multivariable model remained consistent in the validation cohort with a c-statistic of 0.88 and 0.90 for hepatic decompensation at 3- and 5-years respectively and was superior to FIB-4 in training and validation cohorts (P<.0001).

Conclusions: An MRE-based prediction model including allows for accurate prediction of hepatic decompensation and assists in the risk stratification of patients with NAFLD.

Keywords: nonalcoholic fatty liver disease, hepatic decompensation, ascites, varices, non-invasive, prediction

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) affects over 25% of the general population worldwide (1-3) and its prevalence has been increasing as the number of patients with obesity and metabolic syndrome continues to rise (4-6). Patients with NAFLD, particularly the subset with non-alcoholic steatohepatitis (NASH) can develop cirrhosis, hepatocellular carcinoma (HCC), and may have an increased risk for extra-hepatic malignancy and cardiovascular disease (7-11).

Fibrosis stage is the strongest predictor of future outcomes among patients with NAFLD (12), however, histologic staging among the entire affected population is impractical, due to its invasive nature, risk of complications, sampling error, and inter- and intra-observer variability (13). Among non-invasive surrogate markers, magnetic resonance elastography (MRE) has excellent diagnostic accuracy for fibrosis, including at earlier fibrosis stages (14-19). Recent longitudinal studies have demonstrated that higher liver stiffness on MRE is associated with liver-related outcomes including hepatic decompensation and mortality (20-24). Other clinical and demographic data may complement MRE and the combination may provide increased clinical utility in predicting the risk of liver related events, however the optimal combination is unknown.

Therefore, using an international multi-center multi-ethnic cohort, we aimed to develop and validate an MRE-based prediction model to provide accurate prognostic information regarding liver-related outcomes among patients with NAFLD.

MATERIALS AND METHODS

This is a retrospective cohort study with data from six centers from the United States, Europe and Asia; The University of California San Diego, Mayo Clinic Rochester, Cedars Sinai, Musashino Red Cross Hospital, Yokohama City University, and Ankara University School of Medicine with cohort development as previously described (20).

Key inclusion criteria were adults age ≥ 18 years with NAFLD and liver stiffness (LS) measurement by MRE who were assessed for hepatic decompensation, HCC, and death. NAFLD was defined as hepatic steatosis on imaging or a historical liver biopsy in the absence of significant alcohol consumption. Secondary causes of hepatic steatosis and other chronic underlying liver disease include viral hepatitis, consistent with the American Association for the Study of Liver Diseases NAFLD Practice Guidance as previously published (25).

Key exclusion criteria were a previous history of hepatic decompensation or HCC before enrollment or within 7 days of enrollment, follow-up duration of < 7 days, and incomplete critical laboratory data (Figure 1). The study was approved by the Institutional Review Board at each site.

Magnetic Resonance Elastography

Liver stiffness assessment was performed using 2-dimensional MRE. The stiffness values of the hepatic parenchyma were measured by drawing regions of interest (ROI) within the region of highest confidence on confidence maps avoiding the liver capsule, major vessels, gall bladder, and fissures. When reporting estimates of liver fibrosis, mean stiffness in kilopascals was calculated by averaging the values from the ROIs for each patient.

Covariates

Covariates selected *a priori* to be evaluated in a combined model included age, sex, body mass index (BMI), a diagnosis of hypertension (HTN), a diagnosis of type 2 diabetes mellitus (T2DM), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and platelet count. Each variable was available for the entire dataset per inclusion/exclusion criteria.

Outcome Measures and Follow up

The ***primary outcome*** measure was hepatic decompensation, defined as a composite endpoint including ascites, hepatic encephalopathy, or varices needing treatment at 3- and 5-years. ***Secondary outcomes*** include incident HCC defined by histology or Liver Reporting and Data Systems (LI-RADS) for definite HCC, i.e. LI-RADS 5 and all-cause mortality at 3- and 5-years.

Patient Follow-up

Follow-up time started at the time of the MRE. Participants were followed until development of hepatic decompensation, HCC, death, or the last clinical encounter. Follow-up assessment was performed by a retrospective chart review.

Statistical Analysis

Patient characteristics, including demographic, laboratory, imaging and outcome data are reported as median (interquartile range) for continuous variables and N (%) for categorical variables.

The distribution of liver stiffness on MRE and other non-normally distributed covariates were log or exponentially transformed. Univariable cox proportional hazards regression was used to factors associated with the primary and secondary outcomes. For the primary outcome the cohort was split into derivation (US cohort N=728) and validation cohorts (non-US cohort N=588). A multivariable cox proportional hazards model including all identified factors from the univariable model was applied in the training set and final model was identified using backwards stepwise removal of variables with P > .10. The diagnostic accuracy of the model was evaluated in the derivation and validation cohorts.

Univariable and multivariable cox proportional hazards regression were performed in the combined cohort for secondary outcomes and a final model was established using backwards stepwise removal of variables with P > .10. The diagnostic accuracy of the models was compared to FIB-4 using the method by DeLong (26).

All statistical analyses were performed using R version 4.0.5 or SAS, version 9.2 (SAS Institute), and a two-tailed *P* value less than 0.05 was considered statistically significant.

RESULTS

Patient Selection and Characteristics of Study Population

The study population included 1,316 participants (Figure 1). The population was divided into a training set of 728 patients from US Cohorts (53.2% women) and a validation set of 588 patients from European and Asian cohorts (51.5% women) Participants in the training cohort had a median (IQR) age of 58.0 (18) years and BMI of 32 (10.2) kg/m^2. The validation cohort had a median (IQR) age of 64.0 (19) years and BMI of 26.1 (5.5) kg/m^2. Median (IQR) liver stiffness on MRE for training and validation cohorts was 3.3 (±2.2) and 3.8 (±3.0) kPa, respectively (Table 1). The median (IQR) follow-up time in the training and validation cohorts was 3.3 (3.9) years and 2.3 (3.3) years, respectively.

Predictors of Hepatic Decompensation

Among 1,316 patients, 85 (6.5%) met the composite primary outcome of hepatic decompensation including varices needing treatment, ascites, or hepatic encephalopathy. There were 30 patients who developed varices needing treatment (2.3%), 62 who developed ascites (4.7%), and 38 developed hepatic encephalopathy (2.9%) (Table 2). In univariable analysis in the training set, age, sex, hypertension, diabetes, log (MRE), square (albumin), log (AST), and platelet count were significantly associated with hepatic decompensation (Table 3). In multivariable adjusted models, age [HR= 1.04 (95% CI: 1.01-1.06, p=.0077)], square (albumin) [HR=0.91 (95% CI: 0.84-0.98, p=.0091)], log (AST) [HR= 1.79 (95% CI: 1.13-2.84, p= .0126)], platelet count [HR= 0.99 (95% CI: 0.99-0.99, p=.0039)], and log (MRE) [HR= 5.89 (95% CI: 3.21-10.,82, p<.0001)] remained statistically significant (p<.05) (Table 3). The final multivariable model was equal to 0.035 x Age + 1.773 x ln(MRE) – 0.098 x sq(Albumin) + 0.585 x ln(AST) – 0.006 x Platelets. The equation

parameters and risk calculation information are shown in Supplemental Table 1. The equation derived in the validation cohort was evaluated in quintiles and stratified the risk of hepatic decompensation in the validation cohort (p<.0001) (Figure 2).

Diagnostic performance of MRE-based prediction model for hepatic decompensation at 3- and 5-years

The diagnostic accuracy of the MRE-based multivariable model including age, MRE, albumin, AST, and platelets for hepatic decompensation at 3-years was c=0.895 in the training set, which was statistically significantly better than the c-statistic of the FIB-4, c= 0.775 (P< .0001) (Table 4). The results remained consistent in the validation set for the three-year risk of hepatic decompensation with the MRE-based multivariable model, c=0.882, which was superior to FIB-4 c=0.739, (P<.0001).

The diagnostic accuracy of the MRE-based multivariable model including age, MRE, albumin, AST, and platelets for hepatic decompensation at 5-years was c=0.880 in the training set, which was statistically significantly better than the c-statistic of the FIB-4, c= 0.752 (P< .0001) (Table 4). The results remained consistent in the validation set for the five-year risk of hepatic decompensation with the MRE-based multivariable model, c=0.896, which was superior to FIB-4 c=0.755, (P<.0001).

Diagnostic performance of MRE-based prediction model for HCC

Among the study population (N=1,316), 20 patients (1.5%) developed incident HCC. A univariable Cox proportional hazards regression model demonstrated age, square (albumin), diabetes, log (MRE), and platelets as significant predictors of HCC (p<.0.05) (Supplemental Table 2). In a multivariable model only age HR=1.05 (95% CI:1.00-1.10, p=.0330), platelet count HR=0.99 (95% CI: 0.98-0.99, p=.0036) and log (MRE) HR=6.93 (95% CI: 2.32-20.71, p=.0005) remained associated with incident HCC. A multivariable model with age, platelet count and log(MRE)

demonstrated high diagnostic accuracy for HCC at 3- and 5-years, c=0.862 and 0.894 respectively (Supplemental Table 3). The MRE-based multivariable models were superior to FIB-4 at 3- and 5-years (P=.0017 and P=.0002).

Diagnostic performance of MRE-based prediction model for all-cause mortality

Among the study population (N=1,316), 90 participants died (6.9%) over the study period and 24 died after having hepatic decompensation or HCC. A univariable Cox proportional hazards regression model demonstrated age, log (MRE), square (albumin), log(ALT), and platelet count were associated with death (P<0.05) (Supplemental Table 4). In a multivariable model, age HR= 1.03 (95% CI: 1.01-1.05, p=.0034), log (MRE) HR= 2.98 (95% CI: 0.99-2.44, p=.0550), albumin HR= 0.83 (95% CI: 0.78-0.87, p<.001.), and log (ALT) HR=0.73 (95% CI: 0.53-0.99, p=.0493) remained associated with death. A multivariable model with age, square (albumin), platelet count, log (ALT) and log(MRE) demonstrated good diagnostic accuracy for death at 3- and 5-years, c=0.805 and 0.760 respectively (Supplemental Table 5). The MRE-based multivariable models were superior to FIB-4 at 3- and 5-years (P<.0001 and P<.0001).

DISCUSSION

In this multi-center, international study of adults with NAFLD, we found that a multivariable MRE-based model with age, AST, albumin, and platelets best predicted the risk of hepatic decompensation in training and validation cohorts. The diagnostic accuracy of the MRE-based multivariable model for the 3- and 5-year risk of decompensation remained between 0.88-0.90 in training and validation cohorts and was superior to FIB-4. The combination of clinical parameters widely available in routine practice with MRE may offer more refined risk prediction for patients with NAFLD. Applying the multivariable regression model as an online calculator can quickly yield the 3- and 5-year risk of hepatic decompensation to guide clinical management and patient counselling. In

addition, models to predict HCC and all-cause mortality outperformed FIB-4, had good diagnostic accuracy and warrant validation in external cohorts.

In Context with Published Literature

Fibrosis stage on liver biopsy has been adopted as a surrogate marker for future liver-related outcomes in clinical trials based on longitudinal studies demonstrating its association with liver-related outcomes and death. (8, 12) Recently, studies have demonstrated the direct association of non-invasive tests (NITs) such as FIB-4 index (27, 28), liver stiffness on vibration-controlled transient elastography (29), and MRE (20, 22, 30, 31) on liver-related events. The combination of NITs may offer enhanced risk prediction for liver-related events and to date, this has been evaluated with the MEFIB index, combining MRE and FIB-4, which had a high negative predictive value (20). Boursier et al.(32) reported on the sequential combination of FIB-4 and VCTE and demonstrated a strong association with liver-related events. Here, we evaluated a candidate set of variables and then formed a multivariable model for hepatic decompensation that retained excellent diagnostic accuracy in a multi-ethnic validation cohort. Using the multivariable model, the estimated 3- and 5-year risk of hepatic decompensation can be provided in clinical care, presenting a more granular understanding of a patient's individual risk. This approach resembles risk stratification in cardiovascular disease through Framingham (33) and ASCVD (34) risk scores and if validated, may inform the need for treatment in patients with NAFLD.

Importantly, MRE-based models for HCC and all-cause mortality also demonstrated good diagnostic accuracy and outperformed FIB-4. As the utilization of liver biopsy in NAFLD decreases, the ability to predict HCC risk and determine the need for screening without overt evidence of cirrhosis remains an unmet need. In our study, T2DM was associated with hepatic decompensation and HCC on univariable analysis but did not remain a significant predictor in multivariable models. In our cohort, there T2DM was collinear with age and MRE, which resulted in T2DM not remaining in the multivariable model.

Strengths and Limitations

This study has several notable strengths. First, our international multi-center, multi-ethnic cohort included a large sample size of > 1,300 patients who underwent baseline MRE and laboratory tests, making this one of the largest studies of NAFLD-related outcomes. Furthermore, the high number of incident hepatic decompensation events (n=85, 6.5%) allowed for adequate power to assess multivariable models in a training and validation cohort. However, this was a retrospective study of patients at academic medical centers. Nevertheless, future, multicenter, prospective studies will be required to validate the prognostic role of an MRE-based prediction model.

In addition, MRE was only assessed at a single time point in this study. So far, only a few studies demonstrated an association between change in MRE and change in liver histology in cohorts of 50-100 patients.(19, 35) A recent study evaluated the impact of change in MRE on liver-related outcomes and demonstrated that progression in liver stiffness on MRE in 29 patients with compensated cirrhosis was associated with hepatic decompensation or death (36). Future studies may evaluate if serial MRE measurements over time can refine the prediction of future liver-related events, however, the clinical value of accurate risk prediction with a single MRE value remains significant.

Implications for future research and clinical practice

Future studies will need to include head-to-head comparisons with other non-invasive tests, including VCTE, to compare performance and identify the optimal context of use. However, for patients with MRE assessment, an MRE-based model including age, AST, albumin, and platelets has excellent diagnostic accuracy to predict hepatic decompensation in adult patients with NAFLD and may be used to predict the 3- and 5-year risk of hepatic decompensation to counsel patients and inform treatment decisions.

FIGURE LEGEND

Figure 1: Study Cohort Derivation Diagram

Figure 2: Cumulative Incidence of Hepatic Decompensation by Quintiles of Risk on MRE-Based Multivariable Model

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