Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Role of magnetic resonance elastography in compensated and decompensated liver disease

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Background & Aims: Non-invasive predictors identifying subjects with compensated liver disease at highest risk for transitioning to a decompensated state are lacking. We hypothesized that liver shear stiffness as measured by magnetic resonance elastography is an important non-invasive predictor of hepatic decompensation.

Methods: Among patients with advanced fibrosis undergoing magnetic resonance elastography (2007–2011), a baseline cohort and follow up cohort (compensated liver disease) were established. Cause specific cox proportional hazards analysis adjusting for competing risks was utilized to determine the association between elevated liver shear stiffness and development of decompensation (hepatic encephalopathy, ascites, variceal bleeding).

Results: In the baseline cohort (n = 430), subjects with decompensated liver disease had a significantly higher mean liver shear stiffness (6.8 kPa, IQR 4.9–8.5) as compared to subjects with compensated liver disease (5.2 kPa, IQR 4.1–6.8). After adjustment for Model for End Stage Liver Disease score, hepatitis C, age, gender, albumin, and platelet count, the mean liver shear stiffness (OR = 1.13, 95% CI 1.03–1.27) was independently associated with decompensated cirrhosis at baseline. Over a median follow up of 27 months (n = 167), 7.2% of subjects with compensated disease experienced hepatic decompensation. In the follow up cohort, the hazard of hepatic decompensation was 1.42 (95% CI 1.16–1.75) per unit increase in liver shear stiffness over time. The hazard of hepatic decompensation was 4.96 (95% CI 1.4–17.0, $p = 0.019$) for a subject with compensated disease and mean LSS value $\geqslant$5.8 kPa as compared to an individual with compensated disease and lower mean LSS values.

Conclusion: Baseline liver shear stiffness assessed by magnetic resonance elastography is independently associated with decompensated liver disease.

Introduction

Patients affected by compensated and decompensated cirrhosis are known to have disparate clinical outcomes. As compared to the general population, individuals with compensated cirrhosis have a 5 fold increase, whereas patients with decompensated disease have a 10 fold increase in mortality [1]. Overall survival is lower at 1 year (75% *vs.* 87%) and 5 years (45% *vs.* 67%) for persons with decompensated cirrhosis as compared to compensated cirrhosis. The probability of transitioning from a compensated to decompensated state varies from 4% to 12% per year [2–4]. Given that a majority of deaths in patients with compensated cirrhosis are due to progression to a decompensated state and the development of its ensuing complications, the ability to predict decompensation is important. If patients with compensated liver disease at the highest risk of decompensation can be identified, it may be possible to institute enhanced surveillance and prophylactic measures for this patient subset.

However, objective tests that predict the risk of transition to a decompensated state are lacking. Hepatic venous pressure gradient (HVPG), as an indirect measure of portal pressure across the liver, is a potential marker of this transition [5,6]. However, the measurement of HVPG is invasive, subject to operator variability and not readily available in clinical practice. Furthermore, it is unclear whether it completely captures the risk of decompensation [7]. Non-invasive methods that assess liver stiffness, namely ultrasound based transient elastography (TE) or magnetic resonance elastography (MRE), are

Keywords: Non-invasive; Outcomes; Natural history; Prognosis; Cirrhosis.
Received 12 June 2013; received in revised form 27 November 2013; accepted 9 December 2013, available online 19 December 2013
☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2014.01.018.
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Abbreviations: LSS, Liver shear stiffness; MRE, magnetic resonance elastography; HCV, hepatitis C; MELD, model for end stage liver disease; CI, confidence interval; OR, Odds ratio.

predictive of cirrhosis and the presence of clinically significant portal hypertension at baseline [8]. However, it is unclear whether these methods can identify compensated patients at risk for clinical decompensation [9].

The role of liver stiffness as a potential predictor of hepatic decompensation as measured by TE has been recently examined [10–12]. However, to date a heterogeneous group of patients with variable degrees of underlying fibrosis has been studied, with concomitant liver biopsies available in only a minority of patients. Hence, the role of elastography in the group at highest risk (namely persons with advanced fibrosis) is unknown [10,11]. The technical specifications of TE may also limit its utility in patients that are obese or among individuals with ascites [13].

The use of magnetic resonance elastography (MRE) as a predictor of hepatic decompensation has not been studied. In a recent analysis, MRE had a significantly higher diagnostic accuracy as compared to ultrasound based elastography for staging liver fibrosis [14]. The presence of ascites or obesity is also not a limiting factor with MRE and the frequency of complete examinations may be higher as compared with ultrasound-based approaches. Thus, we hypothesized that liver stiffness as measured by MRE is an important non-invasive predictor of hepatic decompensation in patients with compensated liver disease.

Patients and methods

The aims of the study were to (1) assess the baseline relationship between elevated liver shear stiffness and presence of decompensated liver disease and (2) assess whether elevated liver shear stiffness among persons with compensated liver disease can predict the development of future decompensated cirrhosis.

Magnetic resonance elastography

MRE is a commercially available technique for quantitatively assessing liver shear stiffness. The premise of the examination is based on the observation that fibrosis is associated with elevated liver stiffness and significantly different from normal liver parenchyma. It is analogous to physical examination where a "stiff or hard" liver on palpation potentially signifies the presence of advanced fibrosis. It typically adds less than 5 min when incorporated as part of a standard abdominal MRI exam. MRE measures the mechanical property of liver tissue by transmitting mechanical waves into the parenchyma and quantifying stiffness based on wave propagation and velocity. A pneumatic passive driver is placed over the lower chest and upper abdomen overlying the right lobe of the liver at the level of xiphisternum. This driver transmits mechanical waves at 60 Hz, which are transferred from an active driver component placed outside the scanning room. The active and passive drivers are connected to each other by a 7.6 m long plastic tube. The mechanical waves induce propagating shear waves within the liver and are imaged by using a specialized MRI sequence (MR Elastography sequence). The data is processed using inversion algorithms to generate quantitative images or elastograms that are representative of the liver's mechanical properties. Mean stiffness values (in kilopascals, kPa) are measured in regions of interest within the liver [15,16].

Subjects

We examined all consecutive patients that underwent an MRE at Mayo Clinic Rochester between 2007 and 2011 with follow up through September 2012. Though the database was created and outcomes registered concurrent with subjects getting MRE, the analysis was a retrospective analysis. A majority of the examinations took place in the outpatient setting and occurred at the physician's discretion and was not based on a priori clinical decision rules. The most common reasons for MRE included follow up of known cirrhosis, exploration of abnormal liver function tests, follow up of fibrosis status after initial diagnosis and/or initiation of disease-specific treatment, and evaluation of liver mass.

Of all patients that underwent MRE, subjects with either a clinical diagnosis of cirrhosis or biopsy proven advanced fibrosis (stage 3 or 4) were examined. This group formed the baseline cohort for determining the level of association between LSS and the presence of compensated or decompensated disease. The clinical stage of cirrhosis for individual subjects was assigned using an accepted classification system as proposed by D'Amico: stage 1 (absence of esophageal varices and of ascites), stage 2 (presence of non-bleeding esophageal varices without ascites), stage 3 (ascites with or without non bleeding esophageal varices) and stage 4 (variceal bleeding with or without ascites) [3].

From all patients in the baseline cohort, we then selected subjects with biopsy proven advanced fibrosis (stage 3 or 4) and excluded patients based on the following criteria: (a) presence of HCC and (b) hepatic decompensation or liver transplantation at baseline to create a cohort of patients with compensated liver disease (follow up cohort). The follow up cohort was limited to persons with biopsy proven advanced fibrosis to enrich the group with those at highest risk of decompensation. In patients with multiple examinations over the 4 years study period, only the baseline examination was considered and examinations/patients without paired biopsies were excluded.

Statistical analysis

The primary variable of interest was liver shear stiffness (LSS) as measured by MRE. The primary outcome was either the presence (baseline cohort) or development (follow up cohort) of hepatic decompensation, defined as the presence of ascites, hepatic encephalopathy, or variceal bleeding. A diagnosis of decompensation was based on clinical assessment and not simply on radiological findings (e.g., trace ascites on imaging). Though more than one complication was possible in an individual patient (e.g., variceal bleeding and hepatic encephalopathy), each subject was only counted once for having an event of interest. The follow up cohort was followed until the last clinical visit, development of decompensated disease, death, liver transplantation, or end of the study period (September 2012).

Comparisons between continuous variables were made using Student's *t* test or Wilcoxon two sample test while dichotomous variables were compared using Chi square or Fisher's exact test. Differences in liver stiffness among persons with compensated and decompensated liver disease in the baseline cohort were compared. In the baseline cohort, logistic regression analysis was used to assess the association between elevated LSS and the presence of hepatic decompensation adjusted for age, sex, diagnosis, Model for End Stage Liver Disease (MELD) score, albumin, ALT, body mass index (BMI) and platelet count.

In the follow up cohort, given that death or liver transplantation may be competing events and the occurrence of either event may preclude or alter the probability of decompensation, competing risks analysis was utilized to assess the association between elevated LSS and development of hepatic decompensation [17,18]. Cumulative incidence estimates for decompensation were generated. Cause specific Cox proportional hazards analysis was utilized to assess the association between elevated LSS and the time to developing hepatic decompensation after accounting for competing events. Time dependent ROC analysis were completed using the nearest neighbor estimation method with a span of lambda(n) = 0.05. To select an optimal threshold value for liver stiffness, we considered the Younden J index to optimize the predictive ability of the cut-off points by time point while giving equal weights to sensitivity and specificity. Subsequently, cumulative incidence curves of decompensation where death and liver transplantation are competing risks were generated stratified by the optimal cut-off point. A non parametric estimation of cumulative incidence function and the comparison between the two groups in the presence of competing risks was considered and tested using the Gray's test [19]. Time-dependent ROC curve analysis was performed with R software, version 3.0.1 and with the "survivalROC" package. The rest of the analysis with SAS 9.3. The study was approved by the Mayo Clinic Institutional Review Board.

Results

Baseline cohort

Between 2007 and 2011, there were 430 patients with advanced fibrosis and/or a clinical diagnosis of cirrhosis and comprised the baseline cohort. Of these individuals, a total of 230 (53.4%) subjects had biopsy-proven advanced fibrosis. In a majority of the cases the biopsy was performed before the MRE (median 11 months, interquartile range, IQR 0.03–46.7). In 36 cases, the