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Liver Stiffness Measurement by Magnetic Resonance Elastography is not associated with Developing Hepatocellular Carcinoma in Subjects with Compensated Cirrhosis

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Abstract

Background—Liver stiffness assessed by transient elastography is described as a potential risk factor for hepatocellular carcinoma (HCC) in cirrhosis. However, the strict assessment of hepatic parenchymal areas uninvolved with HCC has not been investigated.

Aims—To determine if liver stiffness of non-malignant hepatic parenchyma by MR elastography (MRE) is higher in patients with HCC compared to controls.

Methods—Cases were defined by compensated cirrhosis with a Child-Turcotte-Pugh (CTP) score < 7 and HCC by radiological criteria or histology. Control subjects with compensated cirrhosis were frequency matched to cases by sex and disease etiology. Overt manifestations of portal hypertension and previous therapy for liver disease or HCC were exclusion criteria. Region of interest analyses were performed on hepatic parenchyma regions distant to HCC location among cases.

Results—30 patients with HCC and 60 matched controls comprised the study cohort. The mean age for cases was 64 ± 10 years (range, 45–85) with 70% men. Major disease etiologies were chronic viral hepatitis (57%), nonalcoholic fatty liver disease (33%), and alcohol (10%). Twenty-eight (93%) patients had solitary HCC lesions with a mean size of 5.2 cm (range, 2–14 cm). However, patients with HCC had similar liver stiffness among uninvolved areas distant to HCC lesions as compared to controls without HCC (mean, 6.1 ± 2.0 kPa vs. mean, 6.3 ± 2.5 kPa, p=0.7).

Conclusion—In contrast to previous studies with transient elastography, we did not observe a systematic association between liver stiffness assessed by MRE and the presence of HCC in patients with compensated cirrhosis.

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Statements of Interest

Jayant A. Talwalkar has received royalties from GE Healthcare for activities not related to the present article.

Meng Yin has intellectual property rights related to MR elastography, including rights involved in a paid-up license between Mayo Clinic and General Electric. Dr. Yin has also received royalties from GE Healthcare for activities not related to the present article.

Richard L. Ehman has intellectual property rights related to MR elastography, including rights involved in a paid-up license between Mayo Clinic and General Electric. Dr. Ehman has also received royalties from GE Healthcare for activities not related to the present article. Furthermore, Mayo Clinic may establish a company to assist MR elastography manufacturers to develop it as a product.

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Hepatocellular carcinoma is the fifth most common cancer worldwide and the third most common cause of cancer mortality (1). Recent trends show a rising incidence of hepatocellular carcinoma in developed countries including United States (2,3). This is probably a reflection of the increasing rate of hepatitis C associated cirrhosis and the epidemics of obesity and diabetes (3,4). The presence of cirrhosis constitutes an important predisposing factor for development of hepatocellular carcinoma (5). In 80 to 90% of the cases, hepatocellular carcinoma arises in a background of cirrhosis (6). The annual incidence of hepatocellular carcinoma in patients with compensated cirrhosis ranges from 2–6% (7), while the incidence in non cirrhotic livers is 0.4% (8). HCC is also the leading cause of death in cirrhotic patients.. The five year survival rate for treated populations is estimated between 50–75% whereas survival rates of 20–50% are observed for untreated patients (9).

While the current practice guidelines recommend screening for HCC in patients with cirrhosis by ultrasonography every six to twelve months, the verification of HCC requires the presence of arterial hypervascularity and delayed venous washout for 2 cm lesions by computerized tomography or magnetic resonance imaging (10). However, the use of these modalities may not have a significant impact on early detection as compared to ultrasound. Recent cross-sectional studies using transient elastography suggest that increased liver stiffness value may be a potential risk factor for HCC among individuals with cirrhosis as compared to disease controls without HCC (11,12). However, the strict assessment of hepatic parenchymal areas uninvolved with HCC may be difficult to perform with transient elastography, as this method can only assess a fractional component of total hepatic parenchyma involving the right lateral liver (13). Furthermore, the relationship between increased liver stiffness and presence of HCC in patients with moderate to severe obesity remains unknown (14,15). The influence of portal hypertension and hepatic decompensation on liver stiffness may also complicate determining the level of association between liver stiffness value thresholds and risk for developing HCC.

Magnetic resonance elastography (MRE) is a novel technique that can provide in vivo measurements of tissue elasticity in various organs including the liver. Recent studies have demonstrated systematic associations between mean liver stiffness value and degree of hepatic fibrosis assessed by liver histology (16–18). In addition, malignant hepatic lesions have significantly greater mean liver stiffness values as compared to benign tumors in patients with and without chronic liver disease. Notably, the liver stiffness of HCC lesions can be even higher in value than parenchymal areas involved with histological cirrhosis (19).

The main aim of our study was to determine if liver stiffness values of non-malignant hepatic parenchyma assessed by MRE were higher in subjects with compensated cirrhosis and HCC as compared to matched controls without HCC. The rationale for pursuing these objectives is based on the ability of MRE to assess hepatic parenchymal areas distant to HCC lesions including areas medial to the right liver.

Materials and Methods

Patient Population

This study was approved by the Mayo Institutional Review Board. Verbal and written consent was obtained from all subjects after the nature of the procedure had been fully explained to them and documented in the medical records.

Between February 2007 and January 2008, 30 subjects with a suspected or confirmed diagnosis of HCC and cirrhosis were recruited for this case-control study. The inclusion criteria for cases were: 1) compensated cirrhosis by clinical or histologic criteria defined by

a Child-Turcotte-Pugh (CTP) score < 7 and 2) HCC defined by consensus radiological criteria and/or histology (6,10) The exclusion criteria are: 1) absolute contraindications to MRI including pacemaker, implanted cardiac defibrillator, cochlear implant, ventriculo-peritoneal shunt, aneurysm clip, deep brain stimulator, and severe claustrophobia; 2) history of decompensated cirrhosis complicated by one or more of the following: esophageal variceal hemorrhage, ascites, hepatic encephalopathy, or spontaneous bacterial peritonitis; 3) history of liver transplantation or hepatic resection; and 4) previous therapy for underlying chronic liver disease.

Control subjects were also identified during the same time period as cases. Inclusion criteria for controls were: 1) compensated cirrhosis by clinical or histologic criteria defined by a Child-Turcotte-Pugh (CTP) score < 7 and 2) no evidence for HCC by cross-sectional imaging within 6 months of study recruitment. Exclusion criteria were the same as for cases. Frequency matching was used to match controls with cases by sex and liver disease. Due to the strict adherence for matching by cirrhosis and liver disease etiology, the matching of cases and controls by age within 5 years was not feasible.

Contrast-enhanced MRI Abdomen Technique

MR abdominal examinations were performed on a 1.5 T MR Scanners (Signa, General Electric Medical Systems, Milwaukee, WI) with a phased-array torso coil. The standard liver imaging protocol included the following sequences: coronal single shot fast spin echo T2 weighted sequence, respiratory triggered fast spin echo T2-Weighted sequence and/or axial breath hold fast recovery fast spin-echo T2 weighted sequence, axial dual echo in- and out-of phase spoiled gradient echo sequence, axial dynamic 3D fat saturated spoiled gradient echo sequence (LAVA, liver acquisition with volume acceleration) before and after administration of contrast agent, and delayed 2D axial fast spoiled gradient echo sequence. Gadodiamide (Omniscan, Amersham Health) 0.1mmol/kg or Gadobenate dimeglumine (Multihance, Bracco) 0.05mmol/kg was injected intravenously at a rate of 2–3ml/s using an automated injector (MedRad, Pittsburgh, PA) and was followed by a 30mL saline flush. Arterial, portal venous and delayed phase images were obtained in all patients. A 2ml test bolus was performed to determine the scan delay following contrast injection to optimize the arterial phase acquisition. All the sequences were performed with patient holding breath in end-inspiration.

MR Elastography Technique

At the end of each conventional abdomen examination, MR elastography was then performed using a transmit/receive body coil. All volunteers and patients were imaged in the supine position with a 19-cm diameter, 1.5-cm – thick cylindric passive longitudinal shear wave driver placed against the anterior body wall. The driver was placed over the right lobe of the liver on the chest wall below the breast. Continuous longitudinal vibrations at 60 Hz were generated by varying acoustic pressure waves transmitted from an active driver device via a vinyl tube (2.5-cm inside diameter, 7.6-m length).

A 2-dimensional gradient echo MR elastography sequence was used to collect axial wave images with the following parameters: 60-Hz continuous sinusoidal vibration, field of view = 32–42 cm, matrix = 256 × 64, flip angle = 30°, slice thickness = 10 mm, repetition time/echo delay time = 50/23 ms, 4 evenly spaced phase offsets, and 1 pair of 60-Hz trapezoidal motion-encoding gradients with zeroth and first-moment nulling along the through-plane direction. Two spatial presaturation bands were applied on each side of the selected slice to reduce motion artifacts from blood flow. To obtain a consistent position of the liver for each phase offset, individual subjects were asked to hold their breath at the end of expiration.

Quantitative images displaying shear stiffness (elastograms) were generated by processing the acquired images of propagating shear waves with a previously described automated local frequency estimation (LFE) inversion algorithm (17,18). The stiffness values of tumor-free hepatic parenchyma from an entire cross-sectional image were calculated by placing between 2–3 regions of interest (ROI) in the parenchyma 2–3 cm away from the tumors. Every attempt was made to use the values in the image that showed mostly tumor-free liver parenchyma, preferably a slice that did not show any tumor. The ROIs were circular and 1–3 cm in diameter and were placed in the region of the parenchyma excluding major blood vessels such as hepatic veins, main portal veins, and branches that have a width greater than 6 pixels (approximately 8 mm). The mean value from multiple ROIs was calculated and results were expressed in kiloPascals (kPa) for each subject. MR elastography interpretation was performed in a blinded fashion without knowledge of clinical information for all subjects..

Data Collection

Relevant demographic and clinical information was abstracted from the electronic medical record in consenting subjects. Variables of interest for cases and controls included age, sex, height, weight, body mass index, and etiology of chronic liver disease. Serum laboratory tests including complete blood count, INR, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and albumin were measured within 6 months of liver stiffness measurement. Data on HCC size (in cm), number of lesions, presence or absence of vascular invasion, and stage of disease.

Statistical Analysis

Continuous variables were expressed as mean (standard deviation) unless otherwise noted. Categorical variables were expressed as a proportion or percentage. Univariate logistic regression analysis was used to determine the relationship between mean liver stiffness value and the presence or absence of HCC. The relationship between HCC and other demographic and clinical parameters was also evaluated with univariate logistic regression analysis. The association between mean liver stiffness value and clinical variables of significance was assessed by Spearman's correlation coefficient test. The overall level of statistical significance was set at an alpha value of 0.05. All statistical analyses were performed with using JMP 6.0 (Statistical Discovery From SAS Institute, Cary, NC, USA).

Results

Thirty subjects with HCC and compensated cirrhosis (cases) and 60 subjects with compensated cirrhosis alone (controls) comprised the study cohort. The mean age for patients with HCC was 65 ± 11 years (range, 45–85) and 73% were men. The mean body mass index (BMI) was 27.7 ± 5.8 kg/m². For control subjects, the mean age was 59 ± 12 years (range, 27–82) and 60% were men. The mean BMI in this group was 30.7 ± 6.6 kg/m². Liver disease etiologies among cases were chronic viral hepatitis (57%), nonalcoholic fatty liver disease (33%), and alcohol (10%). For controls, the etiologies of liver disease were chronic viral hepatitis (55%), nonalcoholic fatty liver disease (26%), and alcohol (14%) (Table 1)

At initial diagnosis, 28 (93%) patients had single HCC lesions with a mean size of 5.2 cm (range, 2–14 cm). Eleven subjects (37%) were found with single HCC lesions < 3 cm. No subject had radiographic evidence of portal vein invasion by tumor. However, two subjects were affected by occlusion of the right portal vein suspicious for tumor invasion. Three patients underwent TACE (n=1), RFA (n=1), and surgical resection (n=1), respectively, as treatment for HCC prior to assessment with MRE. The diagnosis of hepatocellular

carcinoma was established with biopsy or surgery in 16 cases, with the remaining 12 cases verified by validated radiologic criteria.

Association between Clinical Variables and HCC

Univariate analysis demonstrated that HCC was positively associated with age ($p=0.02$) serum AST level ($p=0.0016$), and serum albumin level ($p=0.002$). BMI was significantly higher in controls as compared to cases ($p=0.03$). There were no differences between cases and controls in terms of sex, ALT, alkaline phosphatase, INR, total bilirubin, and platelet count. (Table 1).

Association between Liver Stiffness of Uninvolved Hepatic Parenchymal Regions and HCC

MRE was successfully performed in all cases and controls with out any technical difficulty, including those individuals with moderate to severe obesity (Figure 1). Among individuals with HCC, the mean liver stiffness values within hepatic parenchymal regions distant from tumor involvement was 6.3 ± 2.1 kPa. In controls, the mean liver stiffness value was similar to cases with HCC (6.1 ± 2.3 kPa, $p=0.7$). Subgroup analysis of subjects with chronic viral hepatitis did not identify any significant differences between cases and controls (data not shown). Figure 2 shows the individual mean liver stiffness values from cases and controls.

Relationship between Clinical Variables and Liver Stiffness of Uninvolved Hepatic Parenchymal Regions

The correlation between age, BMI, AST, albumin, and mean liver stiffness was assessed for cases and controls. While statistically significant relationships between individual variables and the presence of HCC were observed, there was no strong association between these variables and mean liver stiffness in cases or controls (Figure 3).

Discussion

The results of our preliminary study show that mean liver stiffness assessed by MRE in hepatic parenchymal regions uninvolved with tumor is not significantly higher in patients with early to intermediate stage HCC as compared to control subjects without HCC, adjusting for age, etiology of liver disease, and the presence of compensated cirrhosis. This relationship persisted when examining a subgroup of patients with moderate to severe obesity who might be at higher risk for HCC. Furthermore, the mean liver stiffness of uninvolved hepatic parenchyma was not influenced by sex, AST, total bilirubin, albumin, or platelet count values in both patient groups.

In 80–90% of cases, the development of HCC occurs in the setting of advanced histological fibrosis (1,5,6,10,). Hence, there is great interest in recognizing novel factors that may improve the ability to facilitate early detection of HCC in patients with cirrhosis.. The noninvasive assessment of chronic liver injury by ultrasound-based transient elastography provides excellent diagnostic accuracy for identifying the presence of advanced fibrosis and cirrhosis (11, 20–22) primarily among individuals with chronic viral hepatitis. Subsequently, these investigations also examined the potential relationship between liver stiffness measurement and presence of HCC. Foucher et al (11) demonstrated that patients stage 3 and 4 hepatic fibrosis and mean liver stiffness values ≥ 53 kPa were more likely to present with HCC as compared to similar patients with lower mean stiffness values. At a diagnostic cutoff value of 53.7 kPa, the sensitivity for detecting HCC was 37%, specificity 87%, positive predictive value 30%, and negative predictive value 90%. Masuzaki et al (12) demonstrated that the stratum-specific likelihood ratio for the presence of HCC was 5 when a mean liver stiffness value ≥ 25 KPa was observed among patients with chronic hepatitis C. Notably, there may have been some patients developing HCC in the absence of cirrhosis

which suggests that inflammation may have been the dominant histological explanation for increased liver stiffness. Nahon et al (14) also reported that patients with HCC had significantly higher liver stiffness measurement values by transient elastography compared to subjects without HCC. Recently, a prospective cohort study of 866 patients demonstrated an independent relationship between liver stiffness and the probability for developing HCC over time (15). However, some cases developing HCC lacked evidence for cirrhosis while others may have had elevations in liver stiffness because of decompensated liver disease (23).

The results of our study are divergent from previous case-control studies using ultrasound-based transient elastography to assess the association between liver stiffness and HCC (11,12,14,15). Several caveats about our study need to be emphasized. Only 1 study looked at subjects with underlying chronic liver diseases other than viral hepatitis (14). In all of the reported studies, the strict assessment of liver stiffness in multiple areas of hepatic parenchyma uninvolved with tumor was not performed based on limitations with transient elastography for examining areas beyond the lateral right liver lobe. In contrast, MRE has the ability to calculate liver stiffness over the entire cross-sectional area of hepatic parenchyma visualized on imaging. In addition, it remains possible that liver stiffness values measured by ultrasound transient elastography could have been influenced by peritumoral edema and thus resulting in a higher than actual liver stiffness measurement in some instances.

Subjects with obesity have not been systematically assessed with TE to determine the relationship between liver stiffness value and probability for HCC. Earlier investigations have shown the role of obesity in the development of HCC due to its association with metabolic syndrome which is a risk factor for NAFLD (24–26). There is accumulating evidence that hepatic steatosis increase the risk of HCC in patients with hepatitis C (27,28). To date, there has not been a significant obstacle for MRE based on the presence of obesity. In our study, the mean BMI of all patients was 29.65 ± 6.43 kg/m² and no technical difficulties were encountered secondary to BMI. In contrast, the study by Foucher et al. (11) examined patients with a mean BMI between 24 and 25 kg/m². Although prior investigations have shown that obesity is an independent risk factor for development of HCC (24–26), our study was not designed or powered to specifically address this question.

Age at presentation and sex are important risk factors for the development of chronic liver disease (29). Serum ALT elevation has also been previously shown to be associated with an increased risk for HCC independent of liver disease etiology (30). In this study, we found that patients with cirrhosis and HCC were older, and had increased AST with reduced albumin values compared to controls with cirrhosis alone. However, there was no correlation was found between liver stiffness and the variables age, body mass index, AST, and albumin.

The lack of correlation between liver stiffness and BMI supports prior studies which have shown that degree of steatosis does not significantly affect liver stiffness. However, several studies have shown that liver stiffness value can be significantly influenced by hepatic inflammation described indirectly by elevated serum aminotransferase levels (31,32). Although the cases in our study had higher serum AST values than controls, the correlation between serum AST and liver stiffness value was not found to be significant in this study .

Several questions were raised by our study. As with other case-control studies, we are not able to establish a cause and effect relationship between HCC and liver stiffness. Our sample size was relatively small, and not all of the known etiologies of liver disease were represented. For example, the precision for assessing statistical significance of correlations

between age and AST levels with liver stiffness could have been improved with a larger sample size. However, an increase in case:control ratio beyond 1:3 or 1:4 would not result in any further appreciable gains in study power. Furthermore, we intentionally recruited individuals with compensated cirrhosis to eliminate the confounding effect of decompensated cirrhosis on liver stiffness. Of note, there were some baseline differences between cases and controls in our study. While cases were 6 years older on average than controls, we pre-specified that matching on age would occur within 5 years as the number of available controls was limited in our study. The average BMI was lower in cases with HCC than for controls. The clinical significance of this difference, however, is not felt to be highly influential as we have previously reported that BMI does not independently affect or influence liver stiffness measurement by MRE (17). Mean serum AST levels were higher for cases as well, yet the average background liver stiffness was not significantly higher than for controls. We would have expected higher average liver stiffness values for cases if the serum AST values reflected moderate to severe hepatic inflammation which does not appear to be the case. The lower mean serum albumin levels in cases is of interest. Although there was no evidence for ascites in these subjects, it raises a question about the unique contribution of albumin as a marker of hepatic function and its potential effect on liver stiffness. Future studies are planned to examine this association. While histological confirmation was not available for each tumor nodule, the remaining patients without a previous biopsy had accepted radiological criteria for a diagnosis of HCC in the setting of cirrhosis.

Planar wave imaging for MRE was performed with a 2-dimensional wave inversion. The inversion process does not take into account propagation of waves at an angle relative to the plane of section. With reference to small structures, this problem can potentially yield liver stiffness values that may be incorrectly low owing to partial volume and edge effects in the inversion algorithm. This problem generally occurs whenever a lesion is smaller than the wavelength of the shear wave used. Therefore, one may have to use a higher frequency and smaller-wavelength acoustic waves to accurately estimate the stiffness of smaller structures. High-frequency waves, however, are more attenuated than lower-frequency waves in the liver.

In contrast to previous studies with ultrasound transient elastography, we did not observe a systematic association between liver stiffness assessed by MRE and the presence of HCC in patients with compensated cirrhosis. Furthermore, these results suggest that using elastography imaging in clinical practice for patients with compensated cirrhosis to individualize screening and surveillance for HCC cannot be strongly recommended at the present time.

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Abbreviations

CTP	Child-Turcotte-Pugh
MELD	Model for End-Stage Liver Disease
MRE	magnetic resonance elastography
HCC	hepatocellular carcinoma

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Figure 1. MR Elastography of the liver in patients with cirrhosis and cirrhosis with HCC

Anatomic images of a patients with cirrhosis and a patient with cirrhosis and hepatocellular carcinoma (HCC) are shown in the far left column. The middle column shows wave image data in the liver, superimposed on the corresponding anatomic images. The resulting elastograms are shown in the far right column. The elastograms show that the mean liver stiffness of corresponding areas of hepatic parenchyma not involved with HCC are similar (6.5 kPa versus 6.4 kPa, respectively). Note the stiffness of the HCC lesion is 12.6 kPa,

Figure 2. Mean liver stiffness values in patients with HCC and cirrhosis (cases) and patients with cirrhosis alone (controls)
Liver stiffness is not significantly higher in cases than in the control group.

Figure 3.

No correlations were observed between mean liver stiffness and a) age, b) BMI, c) AST, or d) albumin among cases and control groups.

Table 1

Demographic and clinical features cases and controls

	Cirrhosis with HCC N= 30	Cirrhosis without HCC N= 60	P value
Age (years)	65±11	59±12	0.02
Males (%)	73	60	ns
BMI (kg/m ²)	27.7± 5.8	30.6±6.6	0.03
ALT (U/L)	79±60.	83±74	ns
AST (U/L)	112±79	68±42	0.0016
Albumin (mg/dL)	3.6±0.5	4.6±0.5	0.022
Bilirubin (mg/dL)	2.2±4.9	1.3±1.2	ns
Platelet (10 ⁹ /L)	170.7±167	124.58±66.9	ns
INR	1.2±0.3	1.1±0.1	ns
Etiology (%)			
Viral Hepatitis	68	55	ns
NAFLD	20	26	ns
Alcohol	10	14	ns
Others	17	9	ns

ns; non significant