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# Magnetic resonance elastography for non-invasive evaluation of liver fibrosis in southern Brazil

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## ABSTRACT

**Introduction:** The assessment of the degree of liver fibrosis is essential for prognosis, treatment strategies and effectiveness evaluation of drugs related to chronic liver disease. The aim of this study was to determine the prevalence of significant and advanced liver fibrosis evaluated by magnetic resonance elastography.

**Methods:** This was a retrospective cross-sectional study. Adult patients who were referred for elastography magnetic resonance of the abdomen evaluation were included in this research.

**Results:** 119 patients were enrolled in the study, with a mean age of 52.5 ± 12.8 years. Significant and advanced fibrosis were found in 9.2% and 20.2% patients, respectively. Readers R1 and R2 had an excellent agreement for measured liver stiffness values (k=0.929; p<0.001). In the multivariate analysis, diabetes mellitus was associated with liver stiffness only in model 1. In the other models, no associations were found between liver stiffness and comorbidities.

**Conclusion:** Magnetic resonance elastography detected a significantly high prevalence of advanced liver fibrosis in a southern Brazilian population. Diabetes mellitus was considered an independent factor associated with increased liver stiffness.

**Keywords:** *liver cirrhosis; elasticity imaging techniques; prevalence*

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## INTRODUCTION

Liver fibrosis, characterized by excessive accumulation of extracellular matrix in response to injury and inflammation, is a primary risk factor for cirrhosis and hepatocellular carcinoma, increasing liver-related mortality[1,2]. The liver has substantial regenerative capacity and can support blood flow without a significant increase in intrahepatic pressure. However, chronic damage can lead to increased vascular pressures and to remodeling of the liver parenchyma, therefore influencing tissue stiffness and, consequently, contributing to the development of liver fibrosis[3].

The assessment of the degree of liver fibrosis is essential to evaluate the prognosis, the treatment strategies and the effectiveness of drugs related to chronic liver disease[4,5]. Liver biopsy is currently considered the gold standard for staging liver fibrosis; however, it is an invasive, high-cost method, with complication risks and often rejected by patients. In addition, it can be inefficient in early stages[6,7].

Current studies have shown that fibrosis can be detected early even when suggestive anatomical features are absent[8-10]. Elastography techniques have recently emerged as non-invasive alternative tests for the assessment of liver fibrosis and are routinely incorporated into clinical practice[11-15]. Magnetic resonance elastography (MRE) can differentiate normal livers from fibrotic livers with 89 to 99% accuracy, 80 to 98% sensitivity and 90 to

100% specificity[13,16,17], and appears more accurate than sonographic elastography. Moreover, MRE is not operator-dependent or affected by clinical conditions, such as ascites or obesity, and can evaluate the stiffness of a large portion of the liver parenchyma[18-22].

Studies show that non-invasive markers have identified a clinically significant prevalence of liver fibrosis in the general population of 0.7% to 25.7%[23,24]. However, despite the validation of this method and the importance of early detection of liver fibrosis, few studies have used MRE to determine the prevalence of this pathology.

Thus, the aim of this study was to determine the prevalence of significant and advanced liver fibrosis evaluated by MRE. Secondarily, this research aims to assess factors associated with liver stiffness in southern Brazil.

## METHODS

### *Study design*

This was a retrospective cross-sectional study. The study protocol was approved by the Research Ethics Committee of the Pontifical Catholic University of Rio Grande do Sul (Reference no. 94804318.5.0000.5336), in the city of Porto Alegre, Brazil. All the authors signed a confidentiality agreement to ensure the anonymity of the data obtained from the electronic medical records of the hospital. The study was conducted in accordance with the guidelines set forth in the Declaration of Helsinki, and the article was prepared in accordance with The Strengthening the Reporting of Observational Studies in Epidemiology statement[25].

### *Setting and Participants*

The study included adult patients who referred for magnetic resonance imaging of the abdomen evaluation with elastography values at São Lucas Hospital in Southern Brazil in 2018.

Since iron overload is the most common cause of technical failure of hepatic MRE[19], patients with high iron concentrations were excluded. Patients whose images were inadequate to quantify the elastography, either because of difficulty in positioning on the machine or performing apnea, were also excluded.

### *Data measurements*

Demographic (gender, age, ethnicity) and clinical (weight, body mass index - BMI, comorbidities such as diabetes mellitus and hypertension, and laboratory tests) data were collected.

All patients underwent MRE examination to assess liver stiffness. The findings were evaluated independently by two board-certified radiologists, with at least five years of experience, who were blinded to the clinical and biochemical profiles of the patients.

The degree of hepatic iron and steatosis were evaluated by MRI. To evaluate the hepatic iron, R2-relaxometry technique was used, and it classified results as normal liver (< 2 mg/g), mild iron overload (2.0 – 6.9 mg/g), moderate iron overload (7.0 – 14.9 mg/g), and severe iron overload (≥ 15 mg/g)[26]. Hepatic steatosis was evaluated using chemical shift technique, and findings were classified as normal (fat fraction < 5 %), mild steatosis (fat fraction 5.1 – 14.9 %), moderate steatosis (fat fraction 15 – 29.9 %), and severe steatosis (fat fraction ≥ 30 %)[27].

### *Magnetic Resonance Elastography*

MRE examinations were performed at 1.5 T by using a gradient-recalled-echo pulse sequence (Model Optima MR450w, GE Medical Systems LLC, Wisconsin, USA). The waves used to determine liver stiffness were created by an active driver located outside de scanning room, continuously generating vibrations at a fixed frequency (60 Hz). These mechanical waves were then transmitted through a flexible plastic tube to a passive driver located anteriorly on the abdominal wall of the participant. The vibrations were then converted to shear waves within the liver and their propagation was mapped by the gradient-recalled echo MRE sequence acquired images (Figure 1), which encoded the tissue motion into magnitude and phase images. These images were subsequently analyzed with an inversion algorithm to produce a two-dimensional displacement map called the “wave image,” and a two-dimensional color-coded map of liver stiffness in units of kilopascals (kPa) called “elastogram”. A confidence mask was automatically created for each elastogram image by using a confidence algorithm to place a checkerboard pattern over all but the highest regions of statistical confidence. Finally, the mean liver stiffness was measured by drawing a ROI on each of four axial elastogram images, in the largest possible area of liver parenchyma exempt of major bloods vessels, liver margins, fossae and fissures, and artifacts. The mean liver stiffness values (in kPa) were calculated using the mean value of the four drawn ROI.

The fibrosis stages were defined as ≥ F2 (significant fibrosis) and ≥ F3 (advanced fibrosis), with thresholds of 3.0 and 3.6 kPa, respectively[16,28-31].

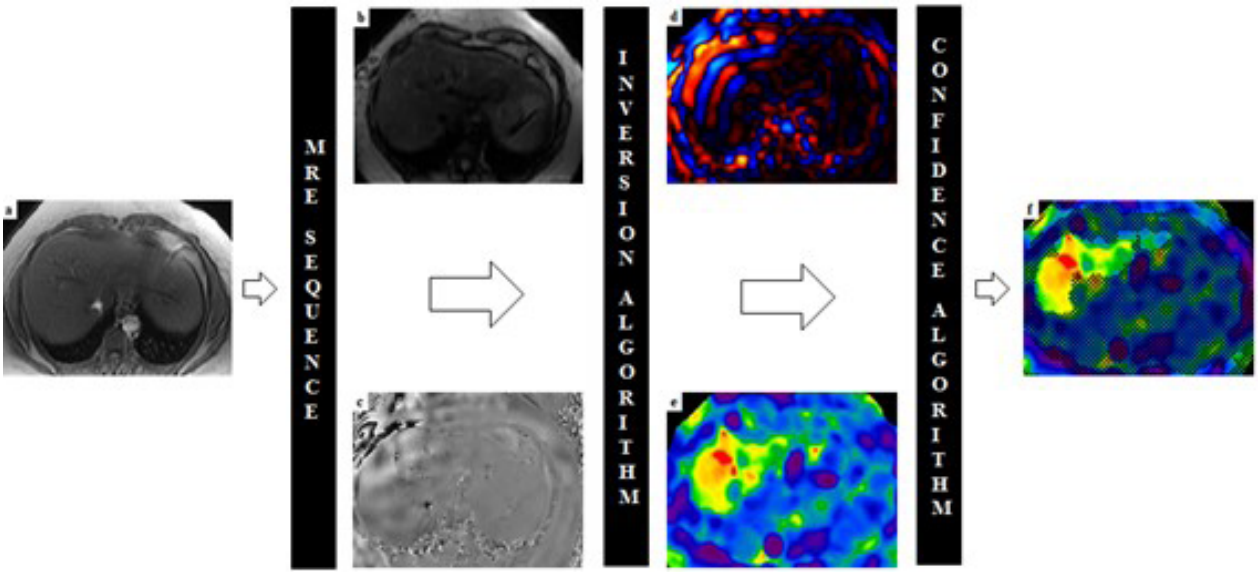


**FIGURE 1:** Review of production of MR elastographic images. Firstly, anatomic MRI liver images (a) are selected, then the applied shear waves coursing through the patient's liver cause displacement, which is detected and measured by the MR elastography (MRE) sequence to generate the magnitude (b) and phase images (c). These images are analyzed afterwards with an inversion algorithm to produce a set of wave images (d) to show propagation of shear waves through the liver and an elastogram (e) that is color coded to represent stiffness in kilopascals. (f)Finally, a confidence algorithm is used to form the confidence map.

### *Statistical analysis*

The statistical analysis was performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA).

The Shapiro-Wilk test verified the normal distribution for all parameters. The results were presented as case (proportion), mean ± standard deviation (SD), or by the median and interquartile range (P25-P75) for asymmetric distributions.

The Cohen kappa coefficient between the two abdominal radiologists was calculated, and classified according to the following designation: values between 0.81 and 1.0 were defined as almost perfect concordance; between 0.61 and 0.8, as strong concordance; between 0.41 and 0.6, as moderate; between 0.21 and 0.4, as reasonable; between 0 and 0.2, as weak; and less than zero as insignificant[32].

A multivariate analysis was performed by using generalized linear models to identify the independent variables associated with liver stiffness. Causal diagrams were used to guide the selection of variables for the multivariate models. These diagrams are directed acyclic graphs that encode hypotheses about the causal processes that generate Dice. Four models were tested, starting with the crude model, including hepatic steatosis, diabetes mellitus, and hepatitis C, followed by inclusion of the variable suggested by the causal diagram. In the present study, based on a literature review and the investigators' expertise, the variables were identified and are presented in Figure 2.

The tests were bidirectional and the differences were considered significant with $p < 0.05$.

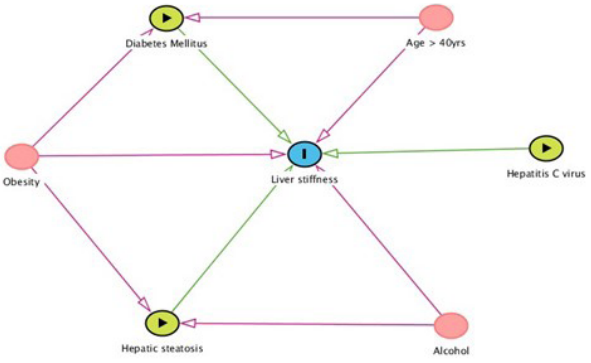


**FIGURE 2:** Causal diagram showing the association between alcohol use, obesity, age, diabetes, hepatitis c virus, and hepatic steatosis and liver stiffness as outcome in adult patients. The diagram represents the variables used in the multivariate analysis. The predictor variables (hepatitis C virus, diabetes mellitus, and hepatic steatosis) can be identified as the yellow circle and the outcome (liver stiffness) in the center, on blue circle. The remaining variables were used for adjustment, with obesity, alcohol use and age being pointed out by the diagram as a potential confounding factor for diabetes and hepatic steatosis.

## RESULTS

Between January and July 2018, 119 patients were enrolled in the study. The baseline characteristics

of the study population are summarized in Table 1. There was a predominance of males (58.8%), and the mean age was 52.5 ± 12.8 years. The mean body mass index (BMI) was 29.0 ± 5.6 kg/m2 and 77.0% had overweight/obesity (BMI ≥ 25.0); 8 patients (6.8%) had significant alcohol use; 32 (27.1%) had positive serologic markers or history of hepatitis B/C; 10 (8.4%), had diabetes mellitus; and 10 (8.4%), had hypertension. The mean liver stiffness value was 2.9 kPa (95% CI 2.7 – 3.1).

**Table 1**: General characteristics of patients

| Variables | N= 119 |
|---|---|
| Age (years), mean ± SD | 52.5 ± 12.8 |
| Sex, n (%) | |
| Male | 70 (58.8) |
| Body mass index (kg/m²), mean ± SD | 29.1 ± 5.6 |
| Nutritional Status, n (%) | |
| Normal weight | 25 (22.9) |
| Overweight / obesity | 84 (77.0) |
| Comorbidities, n (%) | |
| Alcoholism | 8 (6.8) |
| HCV | 28 (23.7) |
| HBV | 4 (3.4) |
| HIV | 5 (4.2) |
| Cirrhosis | 7 (5.9) |
| DM | 10 (8.4) |
| SAH | 10 (8.4) |
| Pancreatitits | 2 (1.7) |
| Acute Hepatitits | 2 (1.7) |
| Focal Liver Injury | 10 (8.5) |
| Others | 7 (5.8) |
| Degree of hepatic iron by MRI, n (%) | |
| Normal liver | 104 (87.4) |
| Mild iron overload | 15 (12.6) |
| Moderate iron overload | 0 |
| Severe iron overload | 0 |
| Hepatic steatosis, n (%) | |
| Normal | 63 (52.9) |
| Mild | 32 (26.9) |
| Moderate | 17 (14.3) |
| Severe | 6 (5.0) |

N= sample size; SD = standard deviation; MRI = magnetic resonance imaging.; HCV= hepatitis c virus; HBV= hepatitis b virus; HIV= human immunodeficiency virus; DM= diabetes mellitus; SAH= systemic arterial hypertension.

Prevalence of liver steatosis and fibrosis is demonstrated in Table 2. 55 patients (46.2%) presented fatty liver (of any etiology), of which 32 (26.9%) were classified as mild, 17 (14.3%), as moderate, and 6 (5.0%), as severe. Significant and advanced fibrosis were present in 9.2% and 20.2% of patients, respectively.

Readers R1 and R2 had an excellent agreement for measured liver stiffness values (k=0.929; p<0.001).

In the multivariate analysis (Table 3), diabetes mellitus was associated with liver stiffness only in model 1. In model 2, 3 and 4, no independent variable an association was observed between liver stiffness and comorbidities.

**Table 2:** Magnetic Resonance Elastography

| Imaging characteristics | N= 119 |
|---|---|
| MR elastography, n (%) | |
| Normal (<2.5 kPa) | 54 (45.4) |
| Normal or chronic inflammation (2.5 - 2.9 kPa) | 30 (25.2) |
| Fibrosis stage 1 – 2 (2.9 - 3.5 kPa) | 11 (9.2) |
| Fibrosis stage 2 – 3 (3.5 - 4.0 kPa) | 4 (3.4) |
| Fibrosis stage 3 – 4 (4.0 - 5.0 kPa) | 10 (8.4) |
| Fibrosis stage 4 (> 5.0 kPa) | 10 (8.4) |
| Mean liver stiffness (kPa), mean ± SD | 2,9 ± 1.2 |

N = sample size; MR = magnetic resonance; SD = standard deviation. MR elastography. Abnormal was considered all the patients with morphological alteration of the hepatic parenchyma.

**Table 3:** Multivariate analysis of the association between hepatic steatosis, diabetes mellitus, hepatitis C virus, and liver stiffness in adult patients.

| Adjustment of variables | OR | 95%IC | P-value |
|---|---|---|---|
| **Model 1 – raw analysis** | | | |
| Hepatic steatosis | 0.996 | 0.990 – 1.002 | 0.163 |
| Diabetes mellitus | 1.270 | 1.022 – 1.579 | **0.031*** |
| Hepatitis C vírus | 1.154 | 0.977 – 1.363 | 0.091 |
| **Model 2 – Adjusted for alcohol use** | | | |
| Hepatic steatosis | 0.996 | 0.990 – 1.001 | 0.131 |
| Diabetes mellitus | 1.211 | 0.964 – 1.523 | 0.100 |
| Hepatitis C vírus | 1.106 | 0.931 – 1.315 | 0.252 |
| **Model 3 – Adjusted for alcohol use and age > 40 years** | | | |
| Hepatic steatosis | 0.996 | 0.990 – 1.001 | 0.119 |
| Diabetes mellitus | 1.200 | 0.954 – 1.509 | 0.119 |
| Hepatitis C vírus | 1.081 | 0.912 – 1.281 | 0.370 |
| **Model 4 – Adjusted for alcohol use, age > 40 years, and obesity** | | | |
| Hepatic steatosis | 0.996 | 0.990 – 1.003 | 0.252 |
| Diabetes mellitus | 1.134 | 0.862 – 1.493 | 0.369 |
| Hepatitis C vírus | 1.106 | 0.913 – 1.340 | 0.305 |

OR = odds ratio. *p<0.05.

## DISCUSSION

This research investigated the prevalence of liver fibrosis and associated risk factors for increased liver stiffness in a reference radiological center in Southern Brazil.

The present study found a high prevalence of participants classified with advanced liver fibrosis, despite the mean liver stiffness being 2.9kPa. A healthy liver has a mean stiffness value from 1.54 to 2.87kPa[29,33-35] and the cut-off liver stiffness measurement for detection of liver fibrosis varies from 2.4 to 2.93kPa[28,34,36,37]. Currently, there is no consensus regarding the optimal cut-off point for liver fibrosis evaluated by MRE. The cut-offs for significant and advanced fibrosis are variable and depend of the etiologies and the inclusion of multiple causes of chronic liver disease[36,38]. Therefore, the interpretation of the measurement of liver stiffness must always be made considering the clinical context.

The MRE-defined prevalence of significant and advanced fibrosis in this study was 9.2% and 20.2%, respectively, whereas in the few studies that previously assessed this matter, values ranged from 5.1% to 13.8% and from 1.3% to 8%, respectively[24,30,39,40]. This data shows a gap between the current and previous studies regarding the prevalence of advanced fibrosis, which may be due to differences in diagnostic modalities or due to the presence of comorbidities that may be associated with fibrosis.

One reason for this disparate result could be the inherent difference between the accuracy of elastography techniques. MRE can be performed on different MRI machine models and tesla strengths and has robust reproducibility between radiologists[41,42]. Also, another reason for the high prevalence demonstrated in this study is the possible inclusion of more severe individuals.

Additionally, comorbidities may also corroborate with the increased prevalence of liver fibrosis: previous

studies have demonstrated a positive association between prevalence of liver fibrosis and fatty liver, metabolic syndrome, nonalcoholic fatty liver disease, and diabetes mellitus[43-45].

In this context, the main risk factor for increased liver stiffness demonstrated in this research was diabetes mellitus, a result that is consistent with previous studies that considered diabetes type 2 as the leading cause of liver disease[19]. The present study showed slightly higher values of patients with diabetes (8.4%) when compared to the Kang[38] and Hong Kong cohort[46], which also may be an explanation for the difference in advanced fibrosis prevalence. In this context, this study also found that patients with diabetes increased liver stiffness by 27%, corroborating the findings in the literature[38,47], that suggested that the prevalence of advanced fibrosis was three[47] and five[38] times higher in diabetics.

Some limitations of the present study must be considered. First, owing to ethical reasons, liver biopsy for diagnostic confirmation of MRE findings was not performed. Second, there is no universal cut-off guideline for stiffness. Third, the retrospective design has inherent limitations. Despite these concerns, the study of non-invasive methods for the assessment of liver fibrosis and its relationship with the main risk factors is important as it has a significant impact on the management and early treatment of liver disease.

In conclusion, MRE detected a high prevalence of significant and advanced liver fibrosis in a population in southern Brazil, suggesting it's important clinical implication for this diagnosis as an alternative for liver biopsy[48]. Also, diabetes mellitus was found to be a factor independently associated with increased liver stiffness. Future studies should explore different MRE cut-off points to better diagnose patients at risk for advanced fibrosis, in order to start early treatment to prevent the progression of liver disease and consequently poor prognosis.

### Competing interests

The authors declare no conflicts of interest.

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