



ARTIGOS ORIGINAIS

Magnetic resonance elastography and morphological alteration of the hepatic parenchyma

Elastografia por ressonância magnética e alteração morfológica do parênquima hepático

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Abstract

Background and Aim: Magnetic resonance elastography has been shown to be an effective non-invasive method for detecting liver fibrosis. The aim of this study was to evaluate the relationship between demographic and clinical data, liver stiffness and morphological alteration of the hepatic parenchyma and the predictive factors associated with the morphological alteration of the hepatic parenchyma. **Methods:** This is a cross-sectional study. Data from the electronic medical records of these patients were evaluated. Magnetic resonance elastography was performed at 1.5 Tesla by using a gradient-recalled-echo pulse sequence and analyzed by two blind independent readers. Generalized linear model analysis, adjusted by age, was performed to assess the potential predictive factors of morphological alteration of the hepatic parenchyma. **Results:** One hundred twenty-three subjects were retrospectively evaluated, with mean age of 52.8±12.7 years, and there was a predominance of males, 73 (59.3%). The mean liver stiffness value was 2.9 kPa (95% CI 2.7–3.1 kPa). The Cohen's *kappa* coefficient showed an excellent agreement of 0.931 (95% CI 0.95–0.97) for measured liver stiffness values between readers R1 and R2. Subjects with hepatic morphological alteration showed a mean liver stiffness significantly higher (4.1±1.4 kPa) compared to those without morphological alteration of the hepatic parenchyma (2.4±0.5 kPa, $p < .001$). **Conclusions:** Our results found a significant relationship between morphology of the hepatic parenchyma and alcoholism, hepatic comorbidities and liver stiffness. In addition, we observed alcoholism, hepatitis C, and cirrhosis as independent factors associated with morphological alterations of the hepatic parenchyma.

Keywords: Elastography. Liver. Hepatic fibrosis.

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Resumo

Introdução e Objetivo: A elastografia por ressonância magnética demonstrou ser um método não invasivo eficaz para a detecção da fibrose hepática. O objetivo deste estudo foi avaliar a relação entre dados demográficos e clínicos, rigidez hepática e alteração morfológica do parênquima hepático, bem como os fatores preditivos associados às alterações morfológicas do parênquima hepático. **Métodos:** Trata-se de um estudo transversal. Foram avaliados os dados dos prontuários eletrônicos desses pacientes. A elastografia por ressonância magnética foi realizada em aparelho de 1,5 T, utilizando uma sequência de pulso gradient-recalled-echo, e analisada por dois avaliadores independentes e cegos. Foi realizada uma análise de modelo linear generalizado, ajustada por idade, para avaliar os possíveis fatores preditivos de alteração morfológica do parênquima hepático. **Resultados:** Cento e vinte e três (123) indivíduos foram avaliados retrospectivamente, com média de idade de 52,8±12,7 anos, predominando o sexo masculino, com 73 indivíduos (59,3%). O valor médio de rigidez hepática foi de 2,9 kPa (IC 95%: 2,7–3,1 kPa). O coeficiente kappa de Cohen demonstrou excelente concordância de 0,931 (IC 95%: 0,95–0,97) entre os leitores R1 e R2 para os valores de rigidez hepática mensurados. Os indivíduos com alteração morfológica hepática apresentaram média de rigidez hepática significativamente maior (4,1±1,4 kPa) em comparação com aqueles sem alteração morfológica do parênquima hepático (2,4±0,5 kPa, $p < 0,001$). **Conclusões:** Nossos resultados encontraram uma relação significativa entre a morfologia do parênquima hepático e o alcoolismo, comorbidades hepáticas e a rigidez hepática. Além disso, observamos que o alcoolismo, a hepatite C e a cirrose foram fatores independentes associados às alterações morfológicas do parênquima hepático.

Palavras-chave: Elastografia. Fígado. Fibrose hepática.

Introduction

Mortality from liver disease has been growing at an alarming rate in recent decades, accounting for about 2 million deaths annually (1). Among the numerous causes involved, the complications of cirrhosis are highlighted on the world stage, with more than 1 million annual deaths reported (2).

Recently, studies have shown concern with early screening for liver disorders, in order to avoid more advanced stages (1, 3, 4). Liver fibrosis can be reversible with specific treatments and its early detection causes treatment to begin before reaching an irreversible degree (5, 6).

Liver biopsy, despite being considered the gold standard for detecting fibrosis, is an invasive method, subject to possible complications such as bleeding, pneumothorax, puncture of biliary trees and death (7, 8). In addition, it can present

some interobserver variability in the interpretation of results. Therefore, numerous non-invasive techniques have been tested to diagnose liver fibrosis, including magnetic resonance imaging (9–12) and, more recently, elastography (6, 12–13).

Currently, the magnetic resonance imaging (MRI) is one of the most used imaging tests to assess liver changes (12, 14). By this method, hepatic fibrosis is characterized by indirect signals such as increased caudal sludge, heterogeneous enhancement of the parenchyma, smaller liver size due to atrophy of the right lobe, parenchymal nodularity, portal venous hypertension, sign of the enlarged gallbladder fossa, among others (9, 10). However, these changes are advanced and, in many cases, irreversible.

On the other hand, magnetic resonance elastography (MRE) has shown to be an effective non-invasive method for detecting and grading liver fibrosis (15–17). This technique quantifies the deformity suffered by the parenchyma, at the cellular level, by a mechanical stimulus, based on the premise that a more rigid tissue presents less deformity. However, few studies have been published exploring the relationship between liver stiffness and hepatic morphological alteration (18, 19).

Therefore, the aim of this study was to evaluate the relationship between demographic and clinical data, liver stiffness and morphological alteration of the hepatic parenchyma. Secondly, to evaluate the predictive factors associated with the morphological alteration of the hepatic parenchyma.

Methods

The present study followed the guidelines for writing observational articles STROBE Statement (20). This is a cross-sectional study. The study protocol was approved by the Research Ethics Committee of the Hospital São Lucas (No. 2,828,116), and all the researchers signed the data confidentiality term. All examinations of patients undergoing magnetic resonance imaging of the abdomen, with elastography values, were performed at the São Lucas Hospital of the Pontifical

Catholic University of Rio Grande do Sul, from January to December 2018.

The study excluded patients who, due to difficulty in positioning or performing apnea, were unable to obtain valid images for the quantification of elastography, as well as those with moderate and severe iron overload were excluded.

Data from the electronic medical records of these patients were evaluated, such as clinical indication for the exam, age, sex, weight, body mass index, average liver stiffness (evaluated by MRE), liver iron concentration and liver fat fraction (evaluated by MRI), in addition to the complete evaluation of the morphology of the liver parenchyma and adjacent structures.

Two radiologists independently evaluated the MRE and were blinded to clinical information and morphological scoring. They had less than five years' experience in interpreting MRE, because it is a new technique used in this center.

MRI were performed by using 1.5-T with adjustments of the coils and field of view (Model Optima MR450w, GE). MRI protocols had to include at least the following: one T1-weighted sequence prior to gadolinium chelate administration, one T2-weighted sequence with or without fat-suppression techniques (fat-saturation, fluid-sensitive, or short tau inversion-recovery sequences), and one T1-weighted with fat suppression. Section thickness ranged from 3 mm to 5 mm.

Degree of hepatic iron was evaluated by MRI, using R2* relaxometry technique, and classified 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 (\geq 15 mg/g), according Labranche *et al.* (21).

Hepatic steatosis was also evaluated by MRI, using chemical shift technique, and 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 \geq 30%), according Szczepaniak *et al.* (22).

We used the two-dimensional real-time MRE to estimate liver stiffness. MRE was performed at 1.5 T by using a gradient-recalled-echo pulse sequence. A region of interest is typically drawn

on each of four axial images, and the mean stiffness is reported. A region was determined to have adequate wave quality if the propagating waves had both good amplitude and the presence of a clear dominant propagation direction. Thereafter, the region of interest was drawn manually in the largest possible area of liver parenchyma, which excluded major blood vessels seen on image. Mean liver stiffness values (in kPa) were calculated.

Calculations of liver stiffness with MRE are highly reproducible and show excellent interobserver agreement (23, 24). Liver stiffness was graded and correlated with the METAVIR fibrosis classification, in normal parenchyma (< 2.5 kPa), normal parenchyma or with chronic inflammation (2.5–2.9 kPa), fibrosis stage 1–2 (2.9–3.5 kPa), fibrosis stage 2–3 (3.5–4.0 kPa), fibrosis stage 3–4 (4.0–5.0 kPa), fibrosis stage 4 (> 5.0 kPa) (25). The fibrosis stages were defined as \geq fibrosis stage 2–F2 (significant fibrosis) and \geq fibrosis stage 3–F3 (advanced fibrosis), with thresholds of 3.5 and 4 kPa respectively.

Statistical analysis of the data was performed with the IBM SPSS Statistics 18. A Shapiro-Wilk test verified the normal distribution for all parameters. The results were presented as cases (proportion), mean \pm standard deviation, or by median and interquartile range (P25–LP75) for asymmetric distributions. The Cohen kappa coefficient between the two specialties was calculated, and classified according to the following classification: between 0.8 and 1.0 as almost perfect concordance, values between 0.6 and 0.8 as strong concordance, between 0.4 and 0.6, as moderate, between 0.2 and 0.4, as reasonable, between 0 and 0.2, as weak, and less than zero as insignificant (26).

For analysis purposes, the patients were categorized according to the architecture of the hepatic parenchyma: normal (without morphological alteration of hepatic parenchyma) and abnormal (with morphological alteration). Categorical comparisons were performed by the chi-square test with adjusted standardized residuals, using Yates's correction if indicated or by the Fisher

exact test. Student t-test or the Mann-Whitney U-test was used for comparison between groups for continuous variables.

Generalized linear model analysis, adjusted by age, was performed to assess the potential predictive factors of morphological alteration of the hepatic parenchyma. The tests were bidirectional, and the differences were considered significant with $p < .05$.

Results

From January to December 2018, 123 subjects were evaluated. The mean age of the patients was 52.8 ± 12.7 years, and the mean body mass index (BMI) was 29.1 ± 5.6 kg/m². General characteristics of the study population are presented in **Table 1**.

Table 1. General characteristics of patients (n= 123).

Variables	n(%)
Male sex	73(59.3)
Alcoholism	9(7.4)
Nutritional status	
Normal weight	25(22.3)
Overweight	43(38.4)
Obesity	44(39.3)
Normal degree of iron	104(84.6)
Hepatic steatosis	
Normal	64(52.5)
Mild	34(27.9)
Moderate	18(14.8)
Severe	6(4.9)
Comorbidities	
Hepatitis C	28(22.7)
Systemic arterial hypertension	11(8.9)
Focal Liver Injury	10(8.1)
Diabetes Mellitus	10(8.1)
Cirrhosis	8(6.6)
Human Immunodeficiency Virus	5(4.1)
Hepatitis B	4(3.3)
Pancreatitis	2(1.6)
Acute Hepatitis	2(1.6)
Others	7(5.7)

The Cohen's kappa coefficient showed an excellent agreement of 0.93 (95% CI= 0.95–0.97) for measured liver stiffness values between readers R1 and R2.

Table 2 showed the imaging characteristics.

The mean liver stiffness value was 2.9 kPa (95% CI= 2.7–3.1 kPa). The prevalence of F2 and \geq F3 in the overall cohort was 3.4% and 16.8% respectively. The imaging of hepatic parenchyma and liver stiffness are demonstrated in **Figure 1**.

Table 2. Resonance magnetic elastography and resonance magnetic imaging characteristics.

Imaging characteristics	n(%)
MR elastography	
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)
Abnormal MR imaging	35(28.5)

Abnormal was considered all the patients with morphological alteration of the hepatic parenchyma.

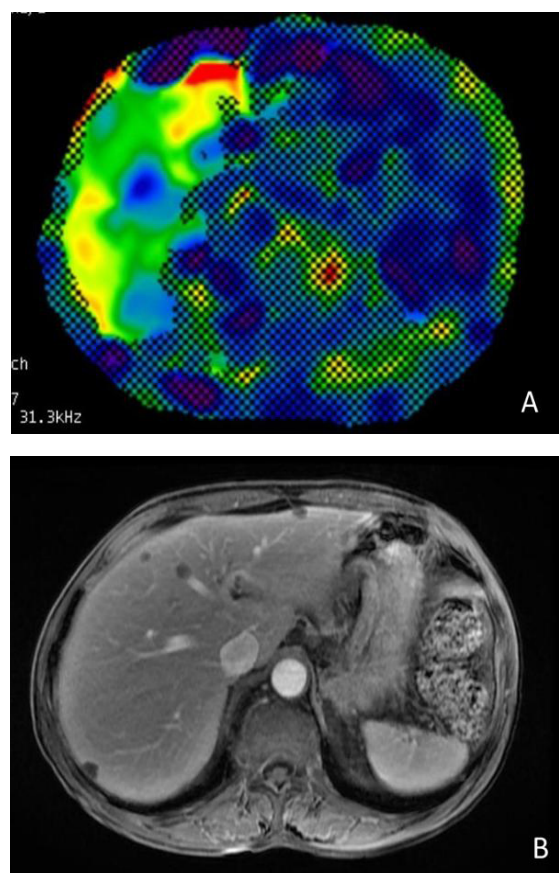


Figure 1. Hepatic parenchyma and liver stiffness. (A) Magnetic resonance imaging shows the liver with a normal hepatic parenchyma. (B) Magnetic resonance elastography shows the stiffness map (elastogram) produced by an inversion algorithm that processed the information in the wave image.

Table 3 shows a significant association between morphological alteration of the hepatic parenchyma and alcoholism, cirrhosis and hepatitis. However, no significant association was found for age, sex, body mass index and diabetes mellitus.

Table 3. Demographic and clinical characteristics according to the architecture of hepatic parenchyma.

Variables	Normal (n = 88)	Abnormal (n=35)	p-value
Age (years), mean±SD	51.8±13.7	55.3±9.7	.11†
Male Sex, n(%)	49(55.7)	24(68.6)	.13*
Alcoholism, n(%)	2(2.3)	7(20.6)	.002*
Body mass index (kg/m ²), mean±SD	28.9±5.7	29.7±5.4	.53†
Comorbidities, n(%)			
Cirrhosis	1(1.1)	(20.6)	.001*
Hepatitis C	13(14.8)	15(44.1)	.001*
Diabetes Mellitus	5(5.7)	5(14.3)	.12*

Patients with morphological alteration of the hepatic parenchyma was considered abnormal. *Chi-square test; †Student t-test.

In addition, subjects "abnormal" showed a mean liver stiffness significantly higher compared to those without morphological alteration of the hepatic parenchyma (**Figure 2**).

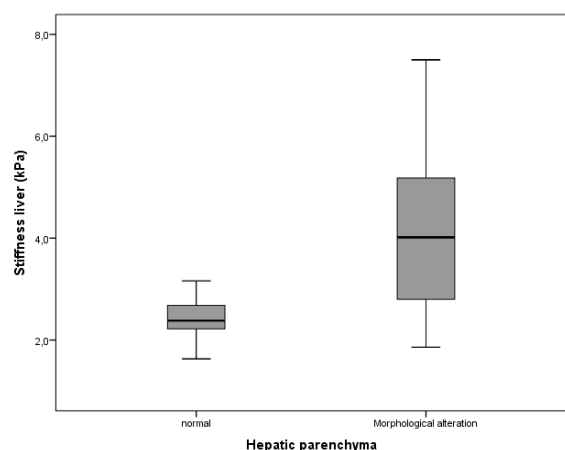


Figure 2. Mean liver stiffness in patients with (4.1±1.4 kPa) and without (2.4±0.5 kPa) morphological alteration of the hepatic parenchyma (p < .001).

Generalized Linear Model, adjusted by age, identified alcoholism, hepatitis C and cirrhosis as independent factors associated with morphological alterations of the hepatic parenchyma (**Table 4**).

Table 4. Multivariate analysis for identify the factors associated with morphological alteration of the hepatic parenchyma.

Variables	OR	95% CI	P-value*
Age, years	1.02	0.98–1.05	.22
Alcoholism	7.39	1.05–51.85	.04
Hepatitis C	4.39	1.46–13.21	.008
Cirrhosis	26.40	1.83–379.14	.02

*Generalized linear model, adjusted by age.

Discussion

Our results showed a significant relationship between morphological alteration of the hepatic parenchyma and alcoholism, hepatitis C, cirrhosis, and liver stiffness. In addition, we observed alcoholism, hepatitis C, and cirrhosis as independent factors associated with morphological alterations of the hepatic parenchyma.

Cirrhosis recognition is essential for the characterization of focal liver lesions, and it is commonly caused by alcohol abuse, hepatitis B or C virus infection, liver steatosis, biliary disease, autoimmune and genetic disease, among others (19). Pathologically, it is defined by distortion of hepatic architecture due to extensive hepatic fibrosis and nodular regeneration. In images studies, cirrhosis is characterized by alterations in the morphology and parenchyma as demonstrated by our results (27). Thus, recognition of these morphological changes in imaging tests, even if subtle, allows us to suggest the continuation of the investigation of liver disease, with elastography and other laboratory tests, if they have not yet been done.

Our study showed that approximately 10% of patients with abnormal liver morphology had associated cirrhosis. Mamone et al. (27) have shown that cirrhosis is the most common chronic liver disease, but other liver diseases may have a pseudo-cirrhotic appearance on the image.

Therefore, adequate interpretation of morphological hepatic alterations can provide vital clues towards establishing a differential diagnosis in patients with chronic liver disease.

Liver stiffness increases occurs gradually and asymptotically, corroborating with diagnosis in the final stages, in which the progression to cirrhosis becomes inevitable (28, 29). Thus, since MRE may allow measurements of liver stiffness while the morphological changes yet are minor, its use becomes attractive (30). Besides, MRE has significant advantages such as sampling multiple liver cross-sections, which is far more representative of the hepatic parenchyma than a single liver biopsy (7). Other advantage of this technique is that it is not affected by the presence of ascites and obesity, as shear waves generated in vivo have good hepatic penetration (6, 13).

Regarding the potential predictive factors of hepatic morphological alterations, as expected, a positive association was observed between alcoholism, hepatitis C, cirrhosis and hepatic morphological alteration. Alcoholism may explain the significant increase of the liver stiffness in patients with morphological alterations, given that it directly affects the hepatocytes (17). In addition, hepatitis C and cirrhosis are among the most prevalent diseases in the world that compromise hepatocytes (27). Kang et al. found similar mean liver stiffness using MRE (2.4 ± 0.4 kPa), but less prevalence of advanced fibrosis (1.3%), compared to 16.8% of advanced fibrosis found in our results (31).

The present study has some limitations to consider. First, it was a cross-sectional study, and it does not allow the establishment of causality. Second, we did not evaluate the inflammation status, which could be involved with more liver stiffness. Third, although our study population is homogeneous, our results are difficult to project for the general population, given the limited sample size. However, to the best of our knowledge, this study is the first to explore the liver stiffness in patients with morphological alteration of the hepatic parenchyma, among our population.

In conclusion, we found a significant rela-

tionship between architecture alteration of hepatic parenchyma and alcoholism, hepatic comorbidities and liver stiffness. In addition, we observed alcoholism, hepatitis C, and cirrhosis as independent factors associated with morphological alterations of the hepatic parenchyma. Future population-based studies, with a large sample size, assessing the relationship between liver stiffness and hepatic biopsy should be performed.

Notes

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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