PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA E CIÊNCIAS DA SAÚDE

JOÃO PAULO LEAL SCHAMBECK

RESSONÂNCIA MAGNÉTICA POR ELASTOGRAFIA NO DIAGNÓSTICO DE FIBROSE HEPÁTICA

PÓS-GRADUAÇÃO - *STRICTO SENSU*

Pontifícia Universidade Católica
do Rio Grande do Sul

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Dissertação apresentada como requisito para a obtenção do grau de Mestre pelo Programa de Pós-Graduação em Medicina e Ciências da Saúde da Pontifícia Universidade Católica do Rio Grande do Sul.

Orientador: Prof. Dr. Bruno Hochhegger

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Resumo

Introdução: A fibrose hepática pode ser reversível com tratamentos específicos e sua detecção precoce faz com que o tratamento comece antes de atingir um grau irreversível. A biópsia hepática, apesar de ser considerada o padrão ouro para a detecção de fibrose, é um método invasivo, sujeito a possíveis complicações como sangramento, pneumotórax, perfuração de vias biliares e morte. Por outro lado, a ressonância magnética por elastografia (MRE) demonstrou ser um método não invasivo eficaz para detectar fibrose hepática.

Objetivo: avaliar a relação entre dados demográficos e clínicos, rigidez hepática e alteração morfológica do parênquima hepático. Segundo, avaliar os fatores preditivos associados à alteração morfológica do parênquima hepático.

Métodos: Este é um estudo transversal e duplo-cego. Os dados dos prontuários eletrônicos desses pacientes foram avaliados. A MRE foi realizada com 1,5 Tesla, usando uma sequência de pulso de eco de recordação de gradiente e analisado por dois leitores independentes, cegos para informações clínicas e pontuação morfológica.

Resultados: Cento e vinte e três sujeitos foram avaliados retrospectivamente, com idade média de 52,8 ± 12,7 anos, e houve predomínio do sexo masculino, 73 (59,3%). O valor médio da rigidez hepática foi de 2,9 kPa (IC 95% 2,7 - 3,1). O coeficiente kappa de Cohen mostrou uma excelente concordância de 0,931 (IC 95% 0,95-0,97) para rigidez hepática entre os leitores R1 e R2. Os indivíduos "anormais" apresentaram rigidez média do fígado significativamente maior (4,10 ± 1,45 kPa) em comparação com aqueles sem alteração morfológica do parênquima hepático (2,48 ± 0,53 kPa, $p < 0,001$). Além disso, identificamos o alcoolismo ($p = 0,044$), hepatite C ($p = 0,008$) e cirrose ($p = 0,016$) como fatores independentes associados a alterações morfológicas do parênquima hepático.

Conclusão: Nossos resultados encontraram uma relação significativa entre a arquitetura do parênquima hepático e alcoolismo, comorbidades hepáticas e rigidez hepática. Além disso, observamos o alcoolismo, hepatite C e cirrose como fatores independentes associados a alterações morfológicas do parênquima hepático.

Palavras-chave: fibrose hepática; fibrose hepática; elastografia; imagem de ressonância magnética

Abstract

Background: Liver fibrosis can be reversible with specific treatments and its early detection causes treatment to begin before reaching an irreversible degree. 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. On the other hand, magnetic resonance elastography (MRE) has been shown to be effective non-invasive method for detecting liver fibrosis.

Objective: 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: This is a cross-sectional and double blind study. Data from the electronic medical records of these patients were evaluated. MRE was performed at 1.5 T by using a gradient-recalled-echo pulse sequence, and analyzed by two independent readers, blinded to clinical information and morphological scoring.

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). 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 "abnormal" showed a mean liver stiffness significantly higher (4.10 ± 1.45 kPa) compared to those without morphological alteration of the hepatic parenchyma (2.48 ± 0.53 kPa, $p < 0.001$). In addition, we identified alcoholism ($p = 0.044$), hepatitis C ($p = 0.008$) and cirrhosis ($p = 0.016$) as independent factors associated with morphological alterations of the hepatic parenchyma.

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

Keywords: hepatic fibrosis; liver fibrosis; elastography; magnetic resonance imaging

Folha de Aprovação

JOÃO SCHAMBECK

RESSONÂNCIA MAGNÉTICA POR ELASTOGRAFIA NO DIAGNÓSTICO DE FIBROSE HEPÁTICA

Dissertação apresentada como requisito à obtenção do título de Mestre em Medicina pela Pontifícia Universidade Católica do Rio Grande do Sul.
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Dedico essa dissertação de mestrado à minha esposa Marcelle Morais dos Santos e ao meu filho, Gabriel dos Santos Schambeck, pois ambos são a razão de todo esforço e dedicação em minha vida.

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Lista de Abreviaturas

MRI - magnetic resonance imaging

MRE - magnetic resonance elastography

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

ROI - region of interest

SD - standard deviation

CI – confidence interval

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1. Introdução

A doença hepática é um dos principais problemas de saúde pública no mundo (TSOCHATZIS; BOSCH; BURROUGHS, 2014). Existem várias etiologias, as mais comuns são doenças relacionadas ao abuso de álcool, doença hepática gordurosa não alcoólica, hepatite viral, hepatite biliar, metabólica, vascular, auto-imune, fibrose cística, medicamentos e criptogênicos (ASRANI *et al.*, 2019; PINZANI; ROSSELLI; ZUCKERMANN, 2011; ZHOU; ZHANG; QIAO, 2014). Através de um dano celular constante e regeneração, essas morbidades geralmente levam a uma fibrose progressiva, potencialmente a um estágio final(PINZANI; ROSSELLI; ZUCKERMANN, 2011).

A lesão hepática é caracterizada pelo processo inflamatório sofrido pelos hepatócitos que se regeneram e apresentam tecido fibroso após a resolução do quadro, evoluindo para uma fibrose difusa do parênquima hepático, resultando em regeneração nodular, desorganização arquitetural e disfunção (AYDIN; AKCALI, 2018; KOYAMA; BRENNER, 2017).

Contudo, a fibrose hepática é reversível com tratamentos específicos, e sua detecção precoce faz com que se inicie o tratamento antes de um grau irreversível. Complicações da cirrose são a causa de 1 milhão de mortes anuais, sendo atualmente a 11^{o} causa mais comum de morte no mundo (ASRANI *et al.*, 2019; TSOCHATZIS; BOSCH; BURROUGHS, 2014).

A biópsia hepática é considerada o padrão ouro para a detecção de fibrose. Entretanto, é um método invasivo, sujeito a possíveis complicações como sangramento, pneumotórax e morte (CAREY; CAREY, 2010; SUMIDA; NAKAJIMA; ITOH, 2014). A biópsia apresenta um erro amostral significativo ao determinar a presença de fibrose assim como se identifica uma variabilidade nos escores de cirrose e fibrose, além de apresentar uma variação interobservador com a interpretação (RATZIU *et al.*, 2005).

Desse modo, inúmeras técnicas não invasivas têm sido testadas para diagnosticar a fibrose hepática (ASRANI; TALWALKAR, 2018; BANERJEE *et al.*, 2014; MARTÍNEZ *et al.*, 2011; PETITCLERC *et al.*, 2017; TALWALKAR *et al.*, 2008; VENKATESH; YIN; EHMAN, 2013). Alterações na textura do parênquima hepático resultante de fibrose precoce ou leve pode não ser facilmente detectado em técnicas convencionais (CAREY; CAREY, 2010).

Inúmeros achados no estudo da ressonância magnética indicam a fibrose hepática (FUCHS *et al.*, 2013; IMAJO *et al.*, 2016; TALWALKAR *et al.*, 2008). São caracterizados pelo aumento do lodo caudado, realce heterogêneo do parênquima, tamanho pequeno do fígado devido à atrofia do lobo direito, nodularidade parenquimatosa, hipertensão venosa portal (sinais como varizes, ascite, esplenomegalia), sinal da fossa da vesícula biliar aumentada, entre outros (PAVLIDES; COBBOLD, 2019; PINZANI; ROSSELLI; ZUCKERMANN, 2011; ZHOU; ZHANG; QIAO, 2014). No entanto, essas alterações já pertencem a graus de fibrose mais avançados, os quais muitas vezes não são mais reversíveis (PETITCLERC *et al.*, 2017; TALWALKAR *et al.*, 2008).

A elastografia por ressonância magnética tem se mostrado o método não invasivo mais eficaz na detecção de fibrose hepática (MARIAPPAN; GLASER; EHMAN, 2010; VENKATESH; YIN; EHMAN, 2013; YIN *et al.*, 2007). Este método quantifica a deformidade sofrida pelo parênquima, a nível celular, por um estímulo mecânico, partindo da premissa de que um tecido mais rígido apresenta menor deformidade, e assim se calcula o grau de fibrose (GODFREY *et al.*, 2013; VENKATESH *et al.*, 2015).

2. Referencial Teórico

Title: Diagnostic accuracy of magnetic resonance elastography and acoustic radiation force impulse for screening hepatic fibrosis: Systematic Review and Meta-analysis

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Abstract

Objective: The aim of this systematic review and meta-analysis was to compare the diagnostic performance of acoustic radiation force impulse and magnetic resonance elastography in the hepatic fibrosis diagnostic.

Methods: A meta-analysis was carried out based on articles published until October 2019. The articles are available at following databases: MEDLINE (via PUBMED), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), Scientific Electronic Library Online (SciELO), LILACS, Scopus, and CINAHL. Assessment of the methodological quality of the incorporated papers by the QUADAS-2 tool for US elastography and MR elastography.

Results: A total 2.153 studies articles were evaluated and 44 studies, comprising 6.081 patients with individual data, were included in the meta-analysis: 28 studies for US elastography and 16 studies for MRI elastography. The pooled sensitivity and specificity were 0.86 (95%IC 0.80 – 0.90) and 0.88 (95%IC 0.85 – 0.91), respectively, for US elastography, compared with 0.94 (95%IC 0.89 – 0.97) and 0.95 (95%IC 0.89 – 0.98) respectively, for MRI elastography. The pooled SROC curve for ultrasound elastography (figure 5) shows in the area under the curve (AUC) of 0.93 (95%IC 0.90 – 0.95), whereas the AUC for MRI elastography was 0.98 (95%IC 0.96 – 0.99). The diagnostic odds ratio for US and MRI elastography were 41 (95%IC 24 – 72) and 293 (95%IC 86 – 1000), respectively. There was statistically significant heterogeneity for US elastography sensitivity (I^2=85.26, P<0.001) and specificity (I^2=89.46, P<0.001). The heterogeneity for MRI elastography also was significant for sensitivity (I^2=73.28, P<0.001) and specificity (I^2=87.24, P<0.001).

Conclusions: our meta-analysis shows that acoustic radiation force impulse elastography and magnetic resonance elastography seems to be a good method for assessing liver fibrosis. In addition, MRE is a more accurate imaging technique than ARFI and can be used as alternative to invasive biopsy. These results should be confirmed with large studies comparing different ultrasound elastography techniques and various etiologies.

Keywords: meta-analysis; acoustic radiation force impulse elastography; magnetic resonance elastography; magnetic resonance elastography

Introduction

The hepatic diseases are extremely common in the clinical practice(ASRANI et al., 2019). There are several etiologies, which the most common are diseases related to alcohol abuse, non-alcoholic fatty liver disease, viral hepatitis, biliary, metabolic, vascular, autoimmune hepatitis, cystic fibrosis, medications, and cryptogenic. Through a constant cellular damage and regeneration, these morbidities often lead to a progressive fibrosis, potentially to a final stage (cirrhosis)(TSOCHATZIS et al., 2011).

The right grading is extremely important, in the view that the amount of fibrosis influences the therapy and predicts the diseases outcomes(ASRANI; TALWALKAR, 2018; CASTERA; FORNS; ALBERTI, 2008). Some of the consequences include portal hypertension, liver failure, ascites, hepatic encephalopathy, hepatorenal syndrome, and hepatocellular carcinoma. Even in the final stage, the patient may remain "compensated" for months or years. However, after the cirrhosis is established, it is estimated that the annual mortality rates can reach 57%(PAVLIDES et al., 2016).

For the impairment grading of liver parenchyma and diagnosis of fibrosis, liver biopsy is still considered the reference standard. However, it is an invasive technique that requires some considerations. The indication for this painful procedure involves patients, which presents higher risk of complications, due the basal diseases (bleeding and death). Hospitalization for several hours is needed(PAVLIDES et al., 2016). It is estimated that the fragment acquired represents only 1/50,000 of entire liver weight(DEGOS et al., 2010; GUO et al., 2014) Although the fibrosis commitment tends to be diffuse, frequently it is not uniform(PALMERI et al., 2011; SCHWENZER et al., 2009). Intra- and inter observer variability in specimen analysis, associated with sampling error is another limitation which may lead to misdiagnosis and incorrect staging(MERRIMAN et al., 2006; RATZIU et al., 2005). Considering the stated, these limitations implicate an uncertain accuracy, feasibility, reliability and responsiveness of treatments(DULAI; SIRLIN; LOOMBA, 2016). Consequently, non-invasive techniques are tempting for avoid iatrogenic difficulties, and safer approach for the follow-up monitoring(DULAI; SIRLIN; LOOMBA, 2016).

Among the alternatives, we emphasize the elastography techniques, which is based on the measurement of mechanical properties of interested tissues(ASRANI; TALWALKAR, 2018; GENNISSON et al., 2013; VENKATESH; YIN; EHMAN, 2013). The higher inelasticity may represent more advanced fibrosis/cirrhosis staging. Acoustic radiation force impulse (ARFI) is an ultrasound-based evaluation with easy access, quick attainment and low

cost. It is able to measure shear wave velocity estimating the tissue stiffness, as well a simultaneous evaluation of liver inner and surrounding structures (vessels, gallbladder) (ASRANI; TALWALKAR, 2018; BOTA et al., 2013). The equipment is becoming progressively more compact, which allow inpatient and outpatient evaluation. However, this method has some limitations like ultrasound studies are operator dependent, which also may lead to inter and intra-observer variance, and the evaluation is considerably impaired in patients with ascites and obesity(FIERBINTEANU-BRATICEVICI et al., 2009).

Magnetic resonance elastography (MRE) technique is another attractive approach as non-invasive assessment(ASRANI; TALWALKAR, 2018; VENKATESH; YIN; EHMAN, 2013). Beyond the stiffness measurement using complex algorithms, it offers the possibility of morphological study of the completely liver and upper abdomen. Furthermore, it allows evaluating the amount of liver fat, iron quantification, helping to appoint the disease etiology, as well the assessment of other focal lesions. The measurement is operator independent and allows two- and three-dimensional liver evaluation. MRE is becoming more assessable, although the cost is relatively higher than the ultrasound based study.

The aim of this systematic review and meta-analysis was to compare the diagnostic performance of acoustic radiation force impulse and magnetic resonance elastography in the hepatic fibrosis diagnostic.

Material and methods

This systematic review and meta-analysis were performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines(MOHER et al., 2009). A protocol was designed a priori and registered at PROSPERO: International prospective register of systematic reviews.

Search strategy

MEDLINE (via PUBMED), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), Scientific Electronic Library Online (SciELO), LILACS, Scopus, and CINAHL database were searched until October 2019. Reference list of identified studies and reviews were also hand-searched. The search strategy included the descriptors (MeSH terms and other entry terms) related to US elastography, MRE, METAVIR, and hepatic fibrosis (supplement 1).

Eligibility criteria

Full papers without language restrictions that evaluated ARFI or MRE in the diagnosis

of liver fibrosis (stage 2), using liver biopsy as the reference standard and classified according to METAVIR score were included.

The following exclusion criteria were used: (a) duplicated publications or studies additional to those already included; (b) biopsy proven which uses other than METAVIR score; (c) study not published; (d) case reports, letters to the editor, reviews, abstracts and meta-analysis; (e) study not available; (f) study with other outcomes than hepatic fibrosis (stage 2 or higher); (g) study with insufficient data for 2x2 table; (h) studies with nonalcoholic fatty liver disease.

Study selection

All data were analyzed by two independently researches. Two investigators (G.S. and G.T.) reviewed the titles and abstracts of each article identified in the literature search. All articles that clearly did not meet the inclusion criteria were excluded. The selected articles were retrieved for full-text analysis and eligible articles were identified. In case of disagreement, the articles were reviewed aiming at a consensus position, and if no consensus could be achieved, the matter was referred to a third investigator (G.C.F.).

Data extraction

Extraction of data from each study included in this review was also conducted independently by two investigators (J.B.F.K and L.M.G.), using a standardized instrument. The following data were extracted: country of study's origin, year of publication, study design, patient number, patient age, sex and body mass index, technical failures in undertaking liver elastography, histological score used, true positive, true negative, false positive, and false negative ARFI and MRE results.

Methodological Quality Assessment

Two reviewers independently performed the quality assessment of the RCTs according to Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool(WHITING et al., 2011). The patient selection, index test, reference standard, and flow and timing domains were evaluated. This tool classify studies as low-risk (if most of the information is classified as having a low risk of bias), uncertain-risk (if reporting is insufficient to allow assessment), or high-risk (if the proportion of high-risk information is sufficient to affect interpretation of study results). A third reviewer (J.P.L.S.) resolved discrepancies between the two reviewers.

Statistical Analysis

The pooled sensitivities, specificities, and 95% confidence intervals (CIs) were calculated by using random-effect analysis. The pooled positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratios (DORs) were also obtained. Summary receiver operating characteristic curves were constructed, and the areas under the curve were obtained. To assume an approximate normal distribution, we used the distribution of logit-transformed sensitivity and specificity and the natural logarithm of DOR. The Deeks funnel plot was used to display possible publication bias. Interstudy heterogeneity was also evaluated by using Galbraith plots. Studies outside the 95% boundaries of the regression line may be considered outliers accounting for interstudy heterogeneity. All analyses were performed by using Stata, version 12.0 (Stata, College Station, Tex).

Results

The initial search returned 2.153 studies, from which 468 were duplicate. We screened the remaining 1.685 titles and abstracts, of with 1.460 were excluded. Of 225 articles full-text articles assessed for eligibility, we excluded 180 studies. Finally, 44 studies, comprising 6.081 patients with individual data, were included in the meta-analysis: 28 studies for US elastography and 16 studies for MRI elastography (figure 1).

The Table 1 contain the main features of the US elastography studies included in this systematic review and meta-analysis. The majority of the studies were conducted in in European countries (three in Italy(COLOMBO et al., 2012; PISCAGLIA et al., 2011; RIZZO et al., 2011), four in Romania(SPOREA et al., 2011a, 2011b, 2011c, 2012), two in France(CASSINOTTO et al., 2013, 2014), one in Spain(CRESPO et al., 2012), one in Indonesia(GANI et al., 2017), and two German(FRIEDRICH-RUST et al., 2009; KARLAS et al., 2011), two in Brazil(RAGAZZO et al., 2017; SILVA JUNIOR et al., 2014), one in United State(DHYANI et al., 2018), seven in China(CHEN et al., 2012, 2015; LIN et al., 2016; LIU et al., 2016, 2017, 2015; TAI et al., 2015), three in Japan(NISHIKAWA et al., 2014; TAKAHASHI et al., 2010; TOMITA et al., 2013), one in Egypt(ELHOSARY et al., 2016), and one in South Korea(CHUNG et al., 2013). Twenty-six (92.8%) were prospective and performed in single center. The mean age of the 4465 patients was 52.8 years (SD 2.8), with a predominance of men (n=2331, 52.2%), and a mean body mass index was 24.9 kg/m² (SD 1.1).

The general characteristics of the selected studies by MRI elastography were summarized in Table 2. The investigating centers were located in Netherlands (n = 1)(BOHTE et al., 2014), in Belgium (n = 1)(HUWART et al., 2007), in United State (n =

4)(BATHEJA et al., 2015; BESA et al., 2018; WANG et al., 2011), in China (n=2)(SHI et al., 2014, 2016), in Taiwan (n = 2)(WU et al., 2015, 2017), in Singapore (n = 2)(HENNEDIGE et al., 2017; VENKATESH et al., 2014), in South Korea (n = 2)(B.H. et al., 2011; YE et al., 2012), and in Japan (n = 2)(ICHIKAWA et al., 2015; TOGUCHI et al., 2017). Eight studies (50%) were prospective and fifteen were performed in single center. Twelve studies (75%) were performed with MRI elastography 1.5 Tesla. Taken together, the studies reported data from 1616 subjects. The mean age was 52.8 years (SD 7.6), with majority men (n = 1.000, 61.8%). The mean body mass index was 24.5 kg/m² (SD 1.5).

Quality appraisal

Assessment of the methodological quality of the incorporated papers by the QUADAS-2 tool for US elastography and MR elastography is depicted in Figure 2, respectively. In the "patient selection" domain, 31 studies were considered to be at relatively low risk of bias and 13 unclear. In "index test" domain, all studies were at low risk of bias. In "reference standard", 42 studies were regarded as low risk and two were unclear. In terms of "flow and timing, 24 studies were scored with low risk of bias, seven, high risk, and 13 unclear.

Diagnostic Accuracy of hepatic fibrosis

Diagnostic performances were analyzed per fibrosis (METAVIR F = 2) in all studies included. Forest plots for the sensitivities and specificities with theirs corresponding 95% confidence intervals (CI) of US and MRI elastography are shown in Figure 3 and 4, respectively. The pooled sensitivity and specificity were 0.86 (95%IC 0.82 – 0.90) and 0.88 (95%IC 0.85 – 0.91), respectively, for US elastography, compared with 0.94 (95%IC 0.89 – 0.97) and 0.95 (95%IC 0.89 – 0.98) respectively, for MRI elastography.

The pooled SROC curve for ultrasound elastography (figure 5) shows in the area under the curve (AUC) of 0.93 (95%IC 0.90 – 0.95), whereas the AUC for MRI elastography was 0.98 (95%IC 0.96 – 0.99) (figure 6). The solid circle presenting the studies is positioned near the desirable upper left corner, indicating a relatively high level of overall accuracy in hepatic fibrosis evaluated by ultrasound or MRI elastography.

Heterogeneity Analysis

There was statistically significant heterogeneity for US elastography sensitivity (I^2=85.26, P<0.001) and specificity (I^2=89.46, P<0.001). The heterogeneity for MRI elastography also was significant for sensitivity (I^2=73.28, P<0.001) and specificity (I^2=87.24,

P<0.001). The diagnostic odds ratio for US and MRI elastography were 41 (95%IC 24 – 72) and 293 (95%IC 86 – 1000), respectively.

The funnel plots for US and MRI elastography are shown in Figure 7 and 8.

Discussion

In the present meta-analysis, it was evaluated the diagnostic performance of ultrasound elastography, evaluated by ARFI, and magnetic resonance elastography in the staging 2 of liver fibrosis, as reported in 45 studies (29 for ARFI and 16 for MRE).

Our results showed that ARFI and MRE could be used to diagnose liver fibrosis. Both imaging methods provide excellent diagnostic accuracy for staging 2 liver fibrosis, with AUROC of 0.93 and 0.98 for ARFI and MRE, respectively. However, the sensibility and specificity of MRE shows superior results compared to ARFI for the diagnosis of stage two of liver fibrosis. ARFI and MRE showed probability of 86% and 94%, respectively, correctly to diagnose liver fibrosis following a “positive” measurement.

Previous meta-analysis demonstrated inferior sensitivity and specificity compared to the present study, for both ultrasound elastography and resonance elastography. Tsochatzis et al.(TSOCHATZIS et al., 2011) demonstrated accuracy of transient elastography for diagnose the severity of fibrosis in chronic liver disease. The summary sensitivity and specificity detected in stage F = 2 (31 studies) was 0.79 and 0.78, respectively. Su et al.(SU et al., 2014) when assessing the accuracy of MRE for stage F = 2 liver fibrosis, showed results of sensitivity and specificity, respectively, 0.87 and 0.92. Guo et al.(GUO et al., 2014) show sensitivity 0.76 for ARFI and 0.87 for MRE, and significance was found in AUROC between ARFI (0.85) and MRE (0.97) for the diagnosis of stage 2 liver fibrosis.

Although in the study by Guo et al.(GUO et al., 2014) considerable heterogeneities were not observed in the MRE and ARFI studies; in our meta-analysis, we observed significant heterogeneity in the both imaging method for the evaluation of significant liver fibrosis. Tsochatzis et al.(TSOCHATZIS et al., 2011) showed results similar to the present meta-analysis finding statistically significant heterogeneity for stage 2 (I^2 = 67%, p<0.001), but not for the others. Therefore, interpretation about these results should be cautious.

Although the liver biopsy yet is the reference standard for evaluating and classifying stage of liver fibrosis, it has several limitations. It is invasive method and can cause minor complications including temporary pain until major complications, such as bleeding, hemothorax and even death(BARR et al., 2015; DIETRICH et al., 2017). Accurate staging of

liver fibrosis is very important, since hepatic fibrosis has a potential for reversal when in initial stages(SIGRIST et al., 2017). Therefore, the presence of significant fibrosis (F = 2) is already considered an important finding of progressive disease and needs special attention(SOHRABPOUR; MOHAMADNEJAD; MALEKZADEH, 2012).

We adopted a systematic search and analysis strategy to assess the accuracy of ARFI and MRE for diagnose of significant liver fibrosis. However, there are still limitations in our meta-analysis. First, we did not performed subgroup analysis for etiologies of liver disease and we did not evaluate the inflammation, which may be associated with the heterogeneity of studies. However, regarding of the inflammatory factors, no significant differences were observed in others studies(TSOCHATZIS et al., 2011). Second, we have only included full-text analysis with histopathological score METAVIR. Third, we not evaluate the others stages of liver fibrosis. Hence, our analysis was limited because there is not studies assessing joint ARFI and MRE in the same population. There is a single study that evaluated MRE and ultrasound by elastography, but it used the transient elastography, not ARFI. Despite the heterogeneity and limitations found in this study, the meta-analysis results reported non-invasive clinical practice for the diagnosis of liver fibrosis. Furthermore, our study included 45 studies with a large sample size and most prospective design studies.

In conclusion, our meta-analysis shows that acoustic radiation force impulse elastography and magnetic resonance elastography seems to be a good method for assessing liver fibrosis. In addition, MRE is a more accurate imaging technique than ARFI and can be used as alternative to invasive biopsy. These results should be confirmed with large studies comparing different ultrasound elastography techniques and various etiologies.

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Table 1. General characteristics of the US elastography selected articles.

Author, year	Country	Study design	Center	Sample size	Mean age (yrs)	Male sex	BMI (kg/m^2)	US Elastography
Dhyani, 2018	USA	Prospective	Single	20	54	12	ND	ARFI
Karlas, 2011	Germany	Prospective	Single	97	42.7	68	24.0	ARFI
Nishikawa, 2014	Japan	Prospective	Single	108	59.5	56	22.5	ARFI
Liu, 2015	China	Prospective	Single	108	40.8	81	21.9	ARFI
Liu, 2017	China	Retrospective	Single	174	36.8	107	ND	ARFI
Liu, 2016	China	Prospective	Single	187	34.9	111	ND	ARFI
Lin, 2016	Taiwan	Prospective	Single	60	51.8	40	26.7	ARFI
Silvia, 2012	Italy	Prospective	Single	54	55	38	25.8	ARFI
Hirofumi, 2015	Japan	Prospective	Single	22	6.3	13	ND	ARFI
In, 2015	Taiwan	Prospective	Single	204	52.9	48	ND	ARFI
Gani, 2017	Indonesia	Prospective	Single	43	47.3	31	ND	ARFI
Rust, 2009	Germany	Prospective	Single	86	48	46	26	ARFI
Elhosary, 2016	Egypt	Prospective	Single	190	53.3	142	ND	ARFI
Crespo, 2012	Spain	Prospective	Single	146	54	90	25.5	ARFI
Chung, 2013	South Korea	Prospective	Single	74	47.3	35	ND	ARFI
Chen, 2015	China/Taiwan	Prospective	Single	137	54	63	24.1	ARFI
Chen, 2012	China/Taiwan	Prospective	Single	142	51.6	59	24.6	ARFI
Cassinotto, 2014	France	Prospective	Multiple	349	54.8	188	27.4	ARFI
Cassinotto, 2013	France	Prospective	Single	321	54.4	192	27	ARFI
Takahashi, 2009	Japan	Prospective	Single	55	59.9	30	23.5	ARFI
Sporea, 2010	Romania	Prospective	Single	114	46.9	53	ND	ARFI
Sporea, 2011	Romania	Prospective	Multiple	197	50	78	ND	ARFI
Sporea, 2012	Romania	Retrospective	Multiple	914	55.7	423	24.7	ARFI
Sporea, 2011	Romania	Prospective	Single	233	48	90	ND	ARFI
Silva, 2014	Brazil	Prospective	Single	51	53.8	18	25.1	ARFI
Rizzo, 2011	Italy	Prospective	Single	139	55	83	26	ARFI
Ragazzo, 2017	Brazil	Prospective	Single	107	49.1	53	24.9	ARFI
Piscaglia, 2010	Italy	Prospective	Single	133	58	83	ND	ARFI

Legend: BMI = body mass index; US = ultrasound; ND = not described.

Table 2. General characteristics of the MR elastography selected articles.

Author, year	Country	Study design	Center	Sample size	Mean age (yrs)	Male sex	BMI (kg/m^2)	US Elastography
Kim, 2011	South Korea	Prospective	Single	55	58.3	46	22.3	1.5
Huwart, 2007	Belgium	Prospective	Single	88	54	37	25	1.5
Ye, 2013	South Korea	Retrospective	Single	173	57.2	129	22.7	1.5
Tiffany, 2016	Singapore	Retrospective	Single	63	50.1	44	24.9	1.5
Shintaro, 2014	Japan	Retrospective	Single	182	66.4	127	ND	3.0
Yu, 2014	China	Prospective	Single	113	42	48	21.7	3.0
Toguchi, 2017	Japan	Retrospective	Single	51	59.9	ND	ND	1.5
Venkateshl. 2013	Singapore	Prospective	Multiple	63	50	44	24.8	1.5
Sudhakar. 2015	USA	Retrospective	Single	62	54.6	31	ND	1.5
Wen-Pei, 2017	Taiwan	Retrospective	Single	104	60.6	87	24.5	1.5
Bohte, 2012	Netherlands	Prospective	Single	85	45	55	25.5	3.0
Besa, 2018	USA	Retrospective	Single	83	58.4	59	25.7	1.5
Batheja, 2015	USA	Prospective	Single	54	38.5	0	30	1.5
Wu, 2015	Taiwan	Retrospective	Single	185	53.2	135	24	1.5
Wang, 2011	USA	Prospective	Single	76	55	50	ND	1.5
Shi, 2016	China	Prospective	Single	179	42.9	108	23	3.0

BMI = body mass index; US = ultrasound; ND = not described.

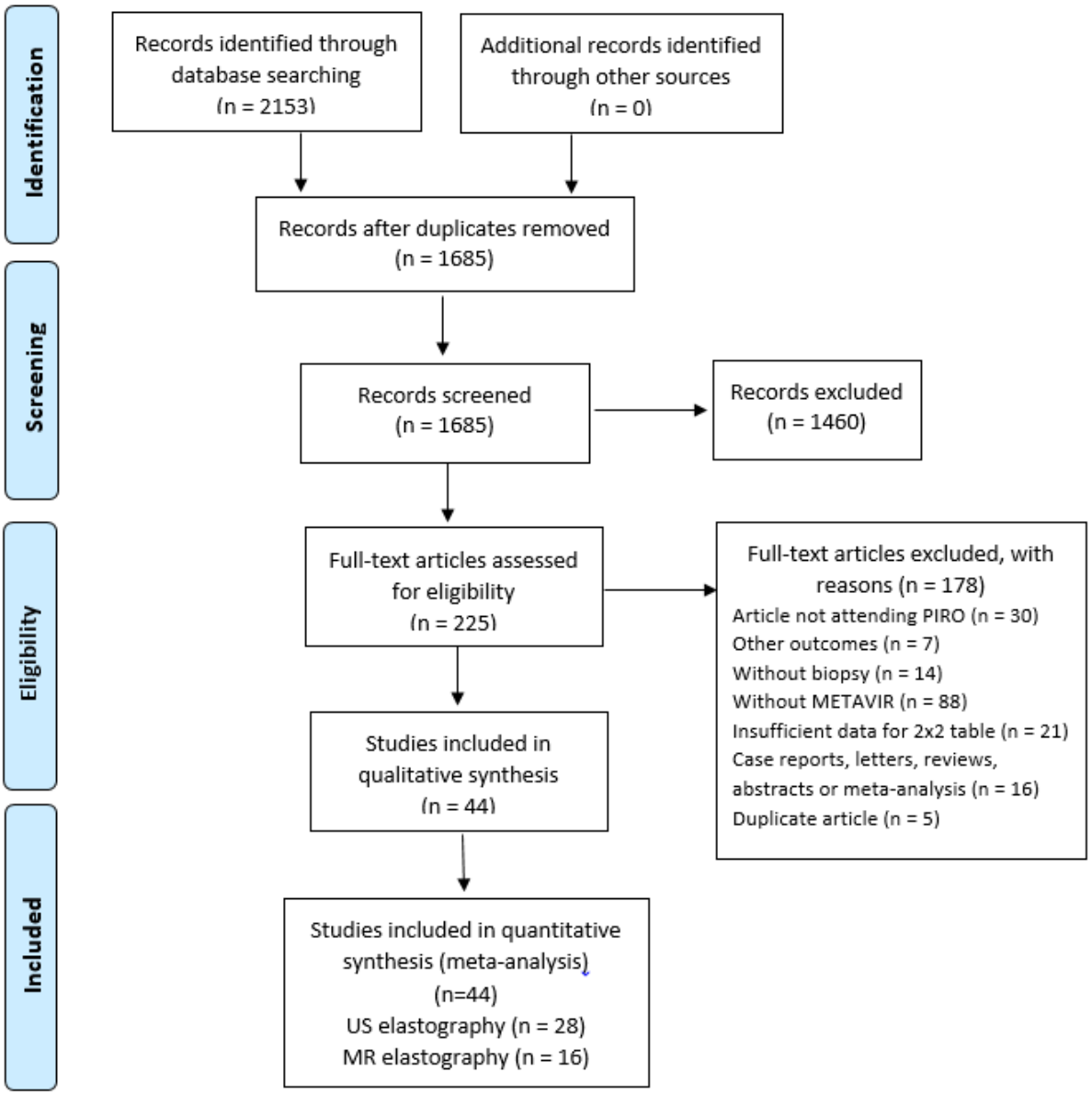

Figure 1. Study selection for meta-analysis

US = ultrasound. MRI = magnetic resonance imaging

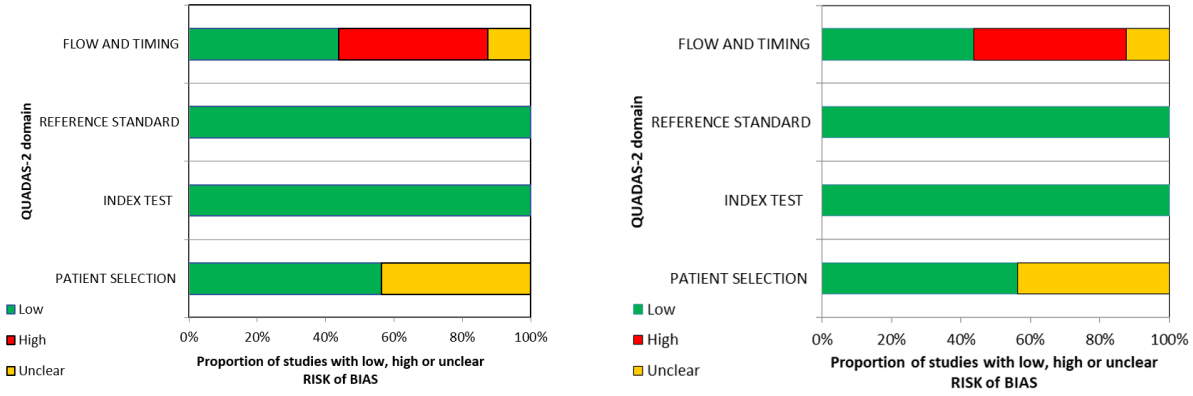

Figure 2. Proportion of studies by US elastography and MR elastography, respectively, with low, high and uncertain risk of bias according to the domains of the QUADAS-2 quality tool.

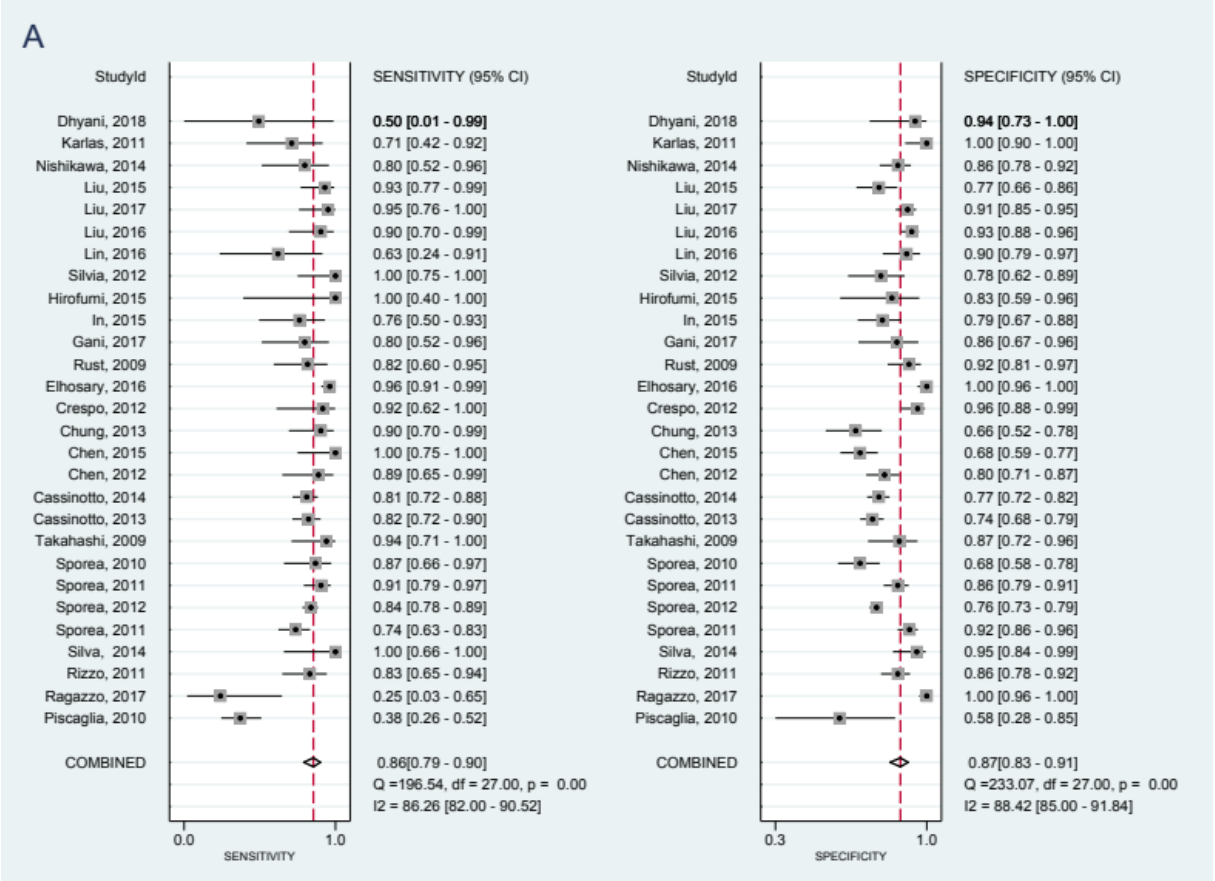

Figure 3. Forest plot of estimates of sensitivity and specificity of US elastography for diagnosis of hepatic fibrosis. The 95% confidence intervals (CI) are shown around point estimates and the pooled result. Plots show (a) sensitivity and (b) specificity of US elastography.

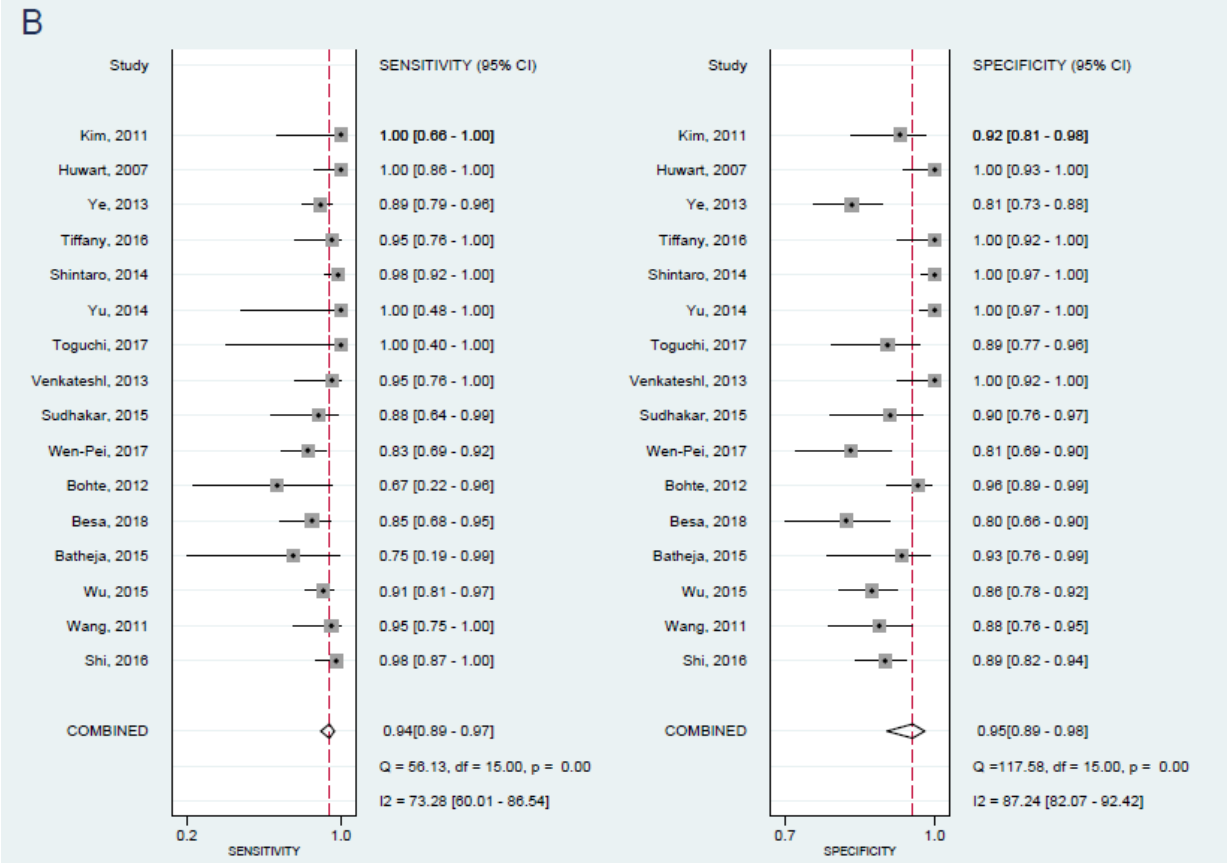

Figure 4. Forest plot of estimates of sensitivity and specificity of MR elastography for diagnosis of hepatic fibrosis. The 95% confidence intervals (CI) are shown around point estimates and the pooled result. Plots show (a) sensitivity and (b) specificity of MR elastography.

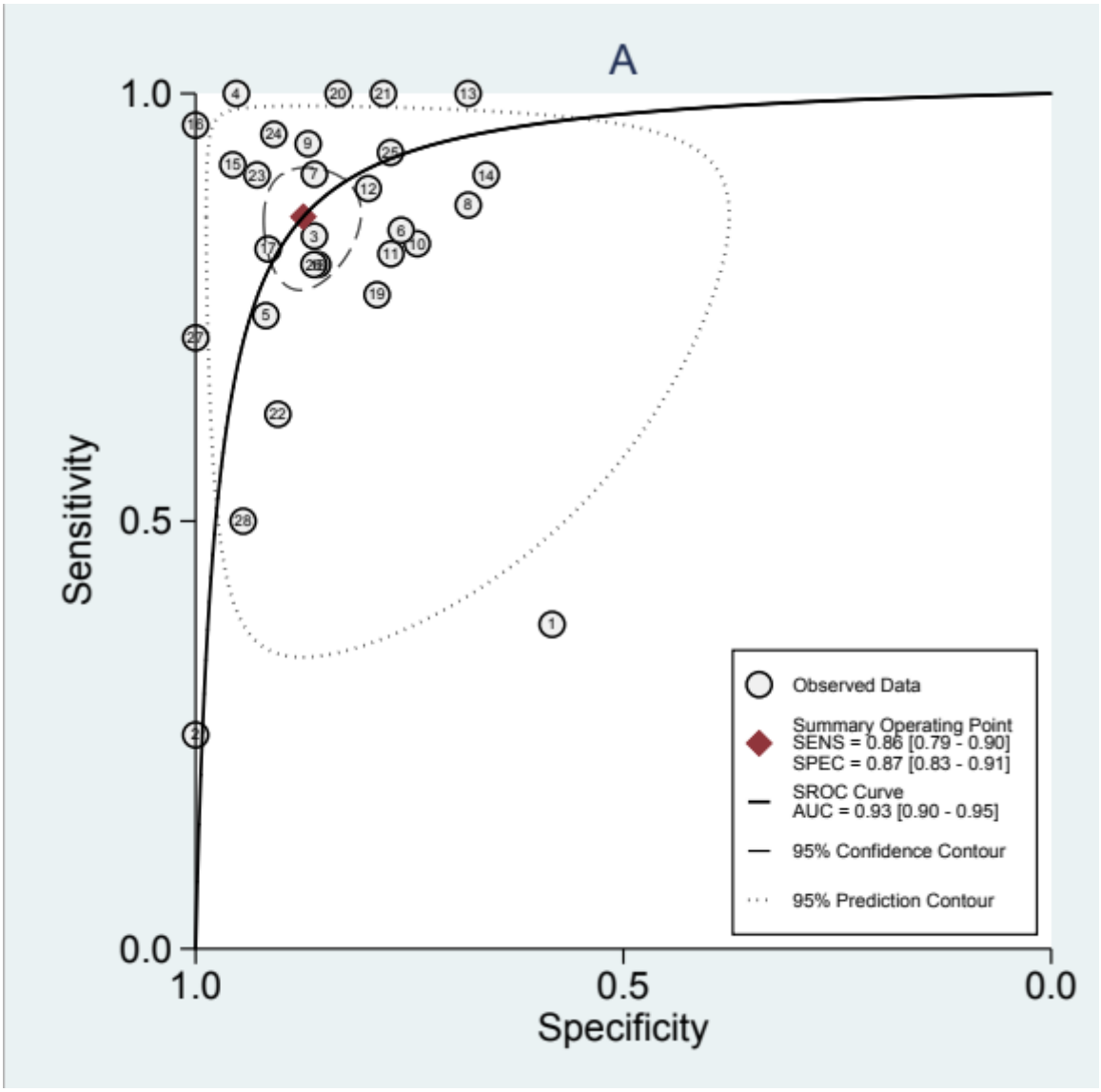

Figure 5. Summarized receiver operating characteristic (SROC) curves for US elastography in diagnostic of hepatic fibrosis.

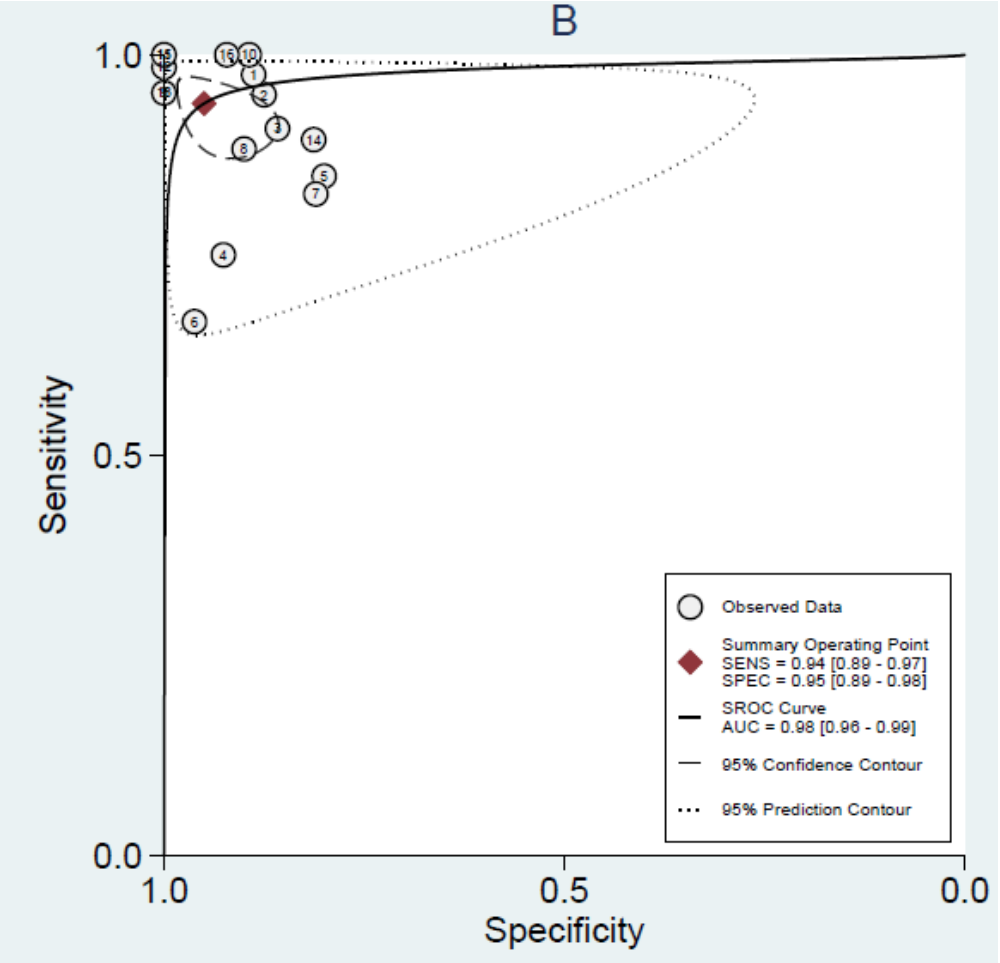

Figure 6. Summarized receiver operating characteristic (SROC) curves for MR elastography in diagnostic of hepatic fibrosis.

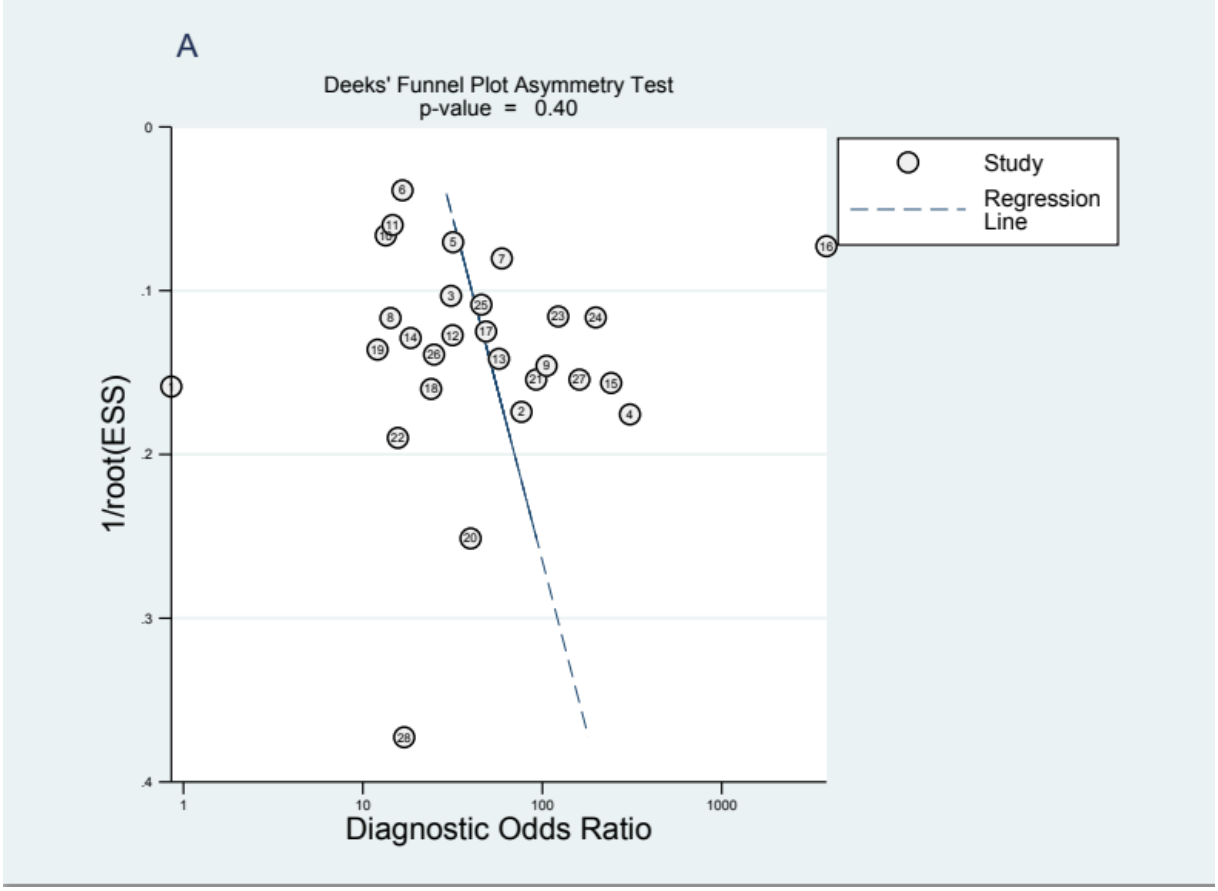

Figure 7. Funnel graph for assessment of potential publication bias of US elastography for evaluation hepatic fibrosis. Thirty-one circles represent the studies in meta-analysis. Line in center indicates summary diagnostic odds ratio.

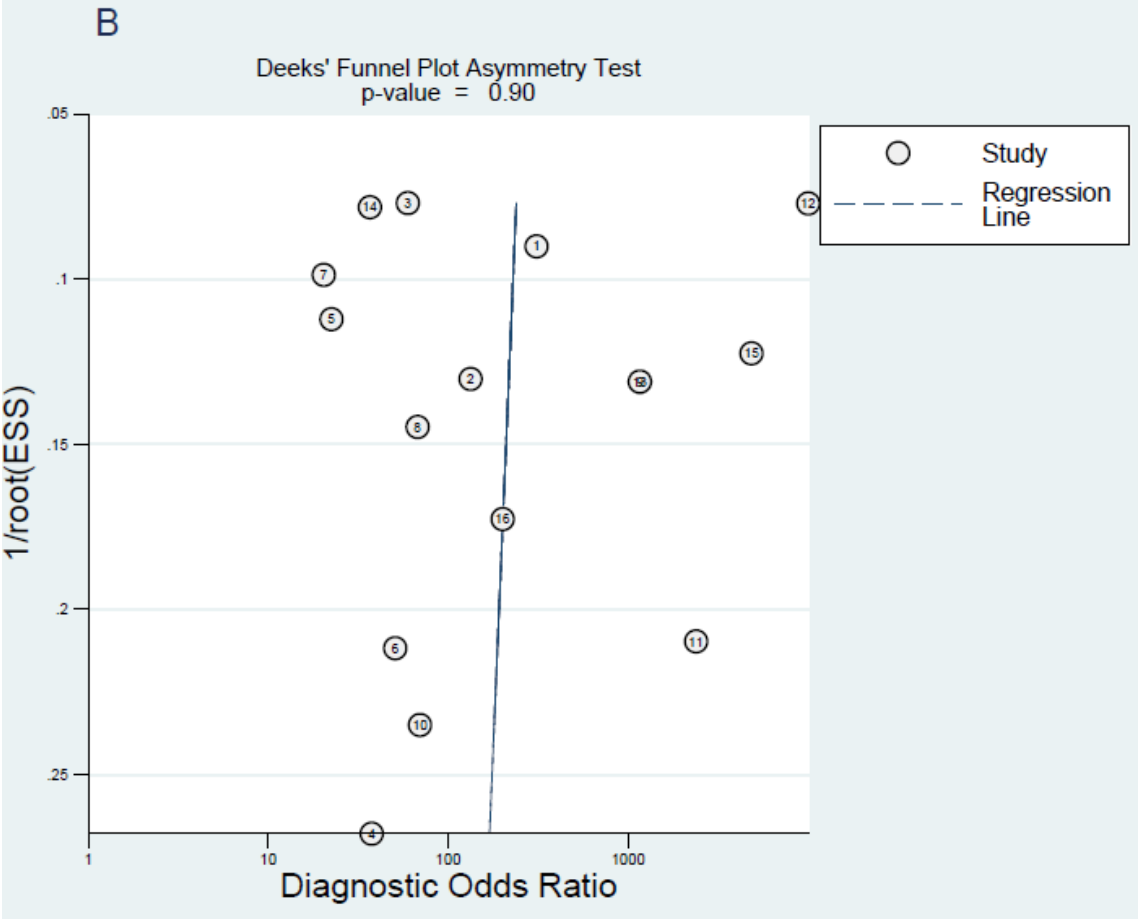

Figure 8. Funnel graph for assessment of potential publication bias of MR elastography for evaluation hepatic fibrosis. Thirty-one circles represent the studies in meta-analysis. Line in center indicates summary diagnostic odds ratio.

Supplement 1. Search strategy

(((Magnetic Resonance Elastography) OR Elastographies, Magnetic Resonance) OR Elastography, Magnetic Resonance) OR Magnetic Resonance Elastographies) OR Resonance Elastographies, Magnetic) OR Resonance Elastography, Magnetic))) OR (((((((Sonoelastography) OR Sonoelastographies) OR Acoustic Radiation Force Impulse Imaging) OR ARFI Imaging) OR ARFI Imagings) OR Imaging, ARFI) OR Imagings, ARFI)) AND ((((Fibrosis, Liver) OR Fibroses, Liver) OR Liver Fibroses) OR Liver Fibrosis)

3. Justificativa

A doença hepática é um dos principais problemas de saúde pública no mundo (TSOCHATZIS; BOSCH; BURROUGHS, 2014). No entanto, a fibrose hepática é reversível com tratamentos específicos, e sua detecção precoce faz com que se inicie o tratamento antes de um grau irreversível (ASRANI *et al.*, 2019; TSOCHATZIS; BOSCH; BURROUGHS, 2014).

A biópsia hepática é considerada o padrão ouro para a detecção de fibrose hepática. Entretanto, é um método invasivo, sujeito a possíveis complicações (CAREY; CAREY, 2010; SUMIDA; NAKAJIMA; ITOH, 2014). Desse modo, inúmeras técnicas não invasivas têm sido testadas a fim de implementar métodos não invasivos para diagnóstico (ASRANI; TALWALKAR, 2018; BANERJEE *et al.*, 2014; MARTÍNEZ *et al.*, 2011; PETITCLERC *et al.*, 2017; TALWALKAR *et al.*, 2008; VENKATESH; YIN; EHMAN, 2013). Faz-se necessário, portanto, avaliar, previamente, a relação da rigidez hepática, avaliada ressonância magnética por elastografia, nos pacientes que apresentam alteração morfológica prévia, diagnosticada por ressonância magnética convencional. Além disso, há uma escassez de estudos que avaliam os fatores associados à rigidez hepática e às alterações morfológicas do parênquima hepático.

4. Hipótese

A hipótese do presente estudo é que a rigidez hepática, avaliada mediante a ressonância magnética por elastografia, é significativamente maior nos pacientes que apresentam alterações morfológicas do parênquima hepático. Além disso, fatores demográficos, ambientais, clínicos e nutricionais podem estar associados tanto com as alterações relacionadas à rigidez hepática quanto com as alterações relacionadas à morfologia do parênquima hepático.

5. Objetivos

Objetivo principal

Avaliar a relação entre dados demográficos e clínicos, rigidez hepática e alteração morfológica do parênquima hepático.

Objetivo específico

- Avaliar os fatores preditivos associados à alteração morfológica do parênquima hepático.
- Descrever o perfil sociodemográfico, clínico e nutricional dos pacientes incluídos no estudo
- Descrever os achados relacionados à fibrose hepática, através da rigidez avaliada mediante ressonância magnética com elastografia, e as alterações morfológicas no parênquima hepático, observadas através da ressonância magnética.
- Avaliar a concordância interobservador para a presença de rigidez hepática

6. Metodologia

Delineamento

O presente estudo caracteriza-se por ser um estudo transversal, retrospectivo, duplo-cego.

Participantes

Foram incluídos indivíduos adultos, de ambos os sexos, submetidos à ressonância magnética do abdome no Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), no ano de 2018.

Critérios de inclusão

Foram incluídos no estudo todos os pacientes que realizaram ressonância magnética do abdômen, independente da indicação clínica, e que tenham sido obtido valores validos de elastografia. Esse estudo faz parte de um estudo prévio multiparamétrico do fígado, o qual também quantificou os níveis de ferro hepático e o percentual de gordura hepática.

Critérios de exclusão

Foram excluídos do estudo os pacientes cujas imagens apresentavam artefatos que impediam a interpretação correta dos exames, e os indivíduos cuja concentração de ferro hepática estava muito elevada no momento do exame, impedindo a avaliação da rigidez hepática.

Variáveis do estudo

Foram avaliados dados sociodemográficos (idade e sexo), dados clínicos (indicação clínica para o exame, peso, estatura, índice de massa corporal, presença de diabetes melito e/ou hipertensão, concentração de ferro hepático, fração de gordura hepática).

A rigidez hepática média foi avaliada mediante o exame de ressonância magnética por elastografia, enquanto o a morfologia do parênquima hepático e suas estruturas adjacentes foram avaliadas pelo exame de ressonância magnética convencional (sem elastografia).

A ressonância magnética é um método de aquisição de imagens que não utiliza radiação e sim um campo magnético. As alterações da morfologia do parênquima hepático foram categorizadas em presente e ausente.

Desfechos

Desfecho primário: avaliar a diferença entre a rigidez hepática por elastografia e as alterações morfológicas no fígado.

Desfechos secundários: avaliar a associação entre os dados sociodemográficos, clínicos e de estado nutricional com a rigidez hepática, medida através da ressonância magnética por elastografia, e com as alterações do parênquima hepática, avaliadas através da ressonância magnética.

Coleta dos dados

Todos os dados foram coletados de prontuário eletrônico dos pacientes e dos protocolos realizados de rotina previamente ao exame de ressonância magnética. As imagens foram interpretadas por dois radiologistas, com mínimo de cinco anos de experiência na área de radiologia abdominal, cegados para os desfechos.

Tamanho amostral

A amostra consistiu de todos os pacientes que realizaram exames de ressonância magnética de abdome no serviço de radiologia e diagnóstico por imagem do Hospital São Lucas da PUCRS, e que se enquadraram nos critérios de inclusão do estudo.

Análise estatística

Os dados foram analisados com auxílio do programa *estatístico Statistical Package for the Social Sciences*, versão 18.0 para Windows (SPSS Inc., Chicago, IL, EUA).

As variáveis contínuas foram descritas através de média e desvio padrão (distribuição simétrica) ou mediana e amplitude interquartílica (distribuição assimétrica). As variáveis categóricas foram descritas através de frequências absolutas e relativas.

A avaliação da diferença entre a rigidez hepática (média ± DP) e as alterações morfológicas do fígado (presente/ausente) foi realizada através do teste t de *Student* para variáveis independentes.

Foi realizada análise univariada usando a Regressão Logística Binária por Modelos Lineares Generalizados para identificar as variáveis independentes associadas à rigidez hepática e às alterações morfológicas do parênquima hepático. A concordância entre os dois radiologistas foi avaliada através do coeficiente de Kappa.

Todos os testes estatísticos utilizados foram bicaudais, e foi estabelecido um nível de significância de 5%.

Considerações Éticas

O projeto de pesquisa foi submetido e aprovado pelo Sistema de Pesquisa da Pontifícia Universidade Católica do Rio Grande do Sul (SIPESQ), pela Comissão Científica da Escola de Medicina e pelo Comitê de Ética em Pesquisa (CEP) da Pontifícia Universidade Católica do Rio Grande do Sul, sob o número CAAE: 94804318.5.0000.5336.

Todos os pesquisadores envolvidos assinaram o Termo de Compromisso para Utilização de Dados, mantendo a confidencialidade das informações e utilizando-as apenas para fins de pesquisa.

7. Resultados

Artigo em apêndice 1.

8. Considerações finais

Tendo em vista que a classificação correta de fibrose hepática ser extremamente importante, uma vez que o estadiamento de fibrose hepática influencia a terapia e prediz os resultados das doenças, esse trabalho pode proporcionar além de uma revisão sistemática e metanálise sobre os diferentes métodos de elastografia (por ressonância magnética e ultrassonografia) usados para *screening* da fibrose hepática, um trabalho original que avaliou a diferença entre a rigidez hepática nos indivíduos que apresentavam alteração morfológica do parênquima hepático.

Em conclusão, encontrou-se uma diferença estatística entre a rigidez média do fígado e as alterações morfológicas no parênquima hepático. Também observamos associação entre alcoolismo e alterações hepáticas da hepatite C tanto por ressonância magnética por elastografia quanto por ressonância magnética convencional.

Futuros estudos de base populacional, com maior tamanho amostral, avaliando a relação da fibrose hepática por ressonância magnética convencional e por elastografia, e por biopsia.

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Apêndices

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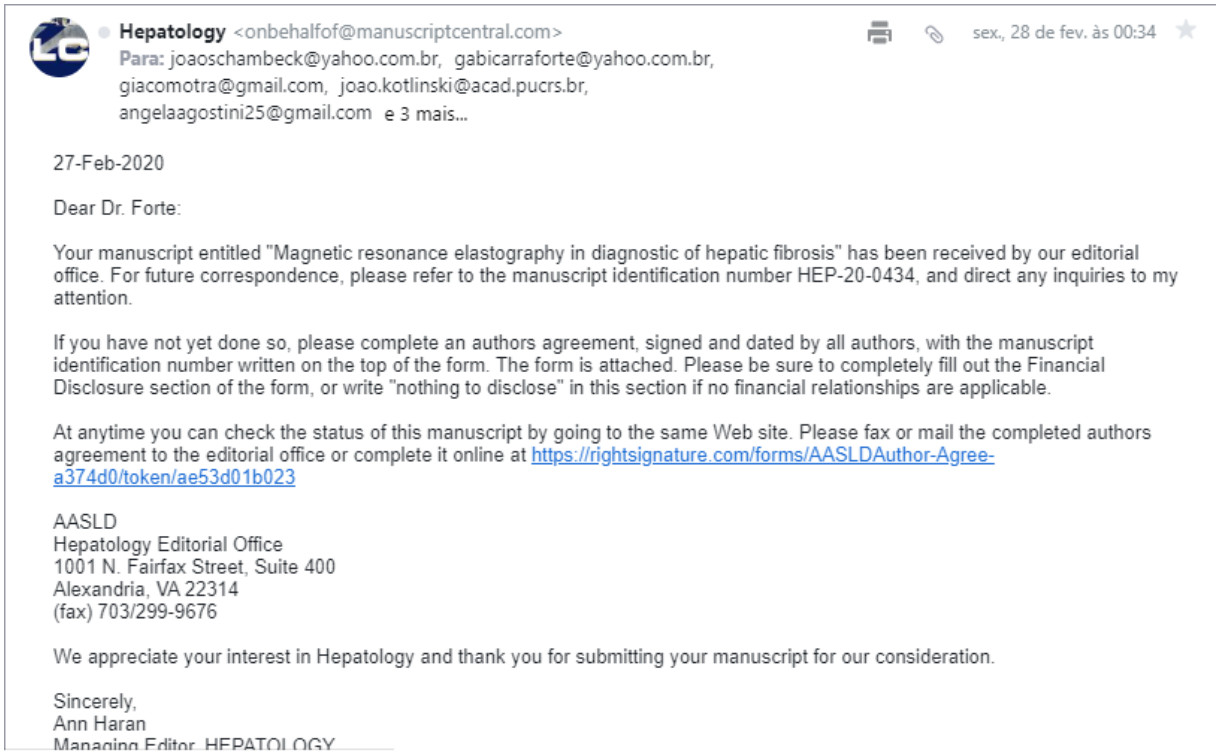

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Title Magnetic resonance elastography in diagnostic of hepatic fibrosis

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List of Abbreviations

MRI - magnetic resonance imaging

MRE - magnetic resonance elastography

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

ROI - region of interest

SD - standard deviation

CI – confidence interval

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ABSTRACT

Background & Aims: Magnetic resonance elastography (MRE) has been shown to be 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. Secondly, to evaluate the predictive factors associated with the morphological alteration of the hepatic parenchyma.

Approach & Results: This is a cross-sectional and double blind study. Data from the electronic medical records of these patients were evaluated. MRE was performed at 1.5 T by using a gradient-recalled-echo pulse sequence, and analyzed by two independent readers, blinded to clinical information and morphological scoring. 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). 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 “abnormal” showed a mean liver stiffness significantly higher (4.10 ± 1.45 kPa) compared to those without morphological alteration of the hepatic parenchyma (2.48 ± 0.53 kPa, $p < 0.001$). In addition, we identified alcoholism ($p = 0.044$), hepatitis C ($p = 0.008$) and cirrhosis ($p = 0.016$) as independent factors associated with morphological alterations of the hepatic parenchyma.

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

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(5–7).

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(8,9). In addition, it can present some interobserver variability in the interpretation of results(10). Therefore, numerous non-invasive techniques have been tested to diagnose liver fibrosis, including magnetic resonance imaging(11,12) and, more recently, elastography(7,13–15).

Currently, the magnetic resonance imaging (MRI) is one of the most used imaging tests to assess liver changes. 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(11,12). However, these changes are considered to be advanced and, in many cases, irreversible.

On the other hand, magnetic resonance elastography (MRE) has shown to be effective non-invasive method for detecting and graduating 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.

MATERIALS AND METHODS

The present study followed the guidelines for writing observational articles STROBE Statement(20).

Study design

This is a cross-sectional study.

Setting and Participants

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, in 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 a high concentration of hepatic iron, which prevented with the assessment of liver stiffness.

Data measurements

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 the 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 Analysis

MRI were performed by using different 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 thicknesses ranged from 3 mm to 5 mm.

Degree of hepatic iron was evaluated by MRI, 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 (≥ 15 mg/g), according Roxanne et al.(21).

Hepatic steatosis also was evaluated by MRI, 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 ≥ 30 %), according Lidia et al.(22).

Liver stiffness measurement

We used the two-dimensional real-time MRE to estimate liver stiffness. MRE was performed 1.5 T by using a gradient-recalled-echo pulse sequence. A region of interest (ROI) 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 ROI 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). The fibrosis stages were defined as ≥F2 (significant fibrosis) and ≥F3 (advanced fibrosis), with thresholds of 3.5 and 4 kPa respectively.

Statistical analysis

Statistical analysis of the data was performed with the IBM SPSS Statistics software package, version 18.0 (IBM Corporation, Armonk, NY, USA).

A Shapiro-Wilk test verified the normal distribution for all parameters. The results

were presented as cases (proportion), mean ± standard deviation (SD), or by median and interquartile range (P25-P75) for asymmetric distributions. The Cohen kappa coefficient between the two specialties was calculated, and classified according to the following classification: between 0.81 and 1.0 as almost perfect concordance, values 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(25).

For analysis purposes, the patients were categorized according to the architecture of the hepatic parenchyma: normal (without 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 $p < 0.05$.

The study protocol was approved by the Research Ethics Committee of the *Hospital São Lucas* (CAAE no. 94804318.5.0000.5336) and all the researchers signed the data confidentiality term.

RESULTS

From January to December 2018, 123 subjects were evaluated. General characteristic of the study population are presented in Table 1. Mean age was 52.8±12.7 years, and there was a predominance of males, 73 (59.3%) subjects. The mean body mass index was 29.1 ± 5.6kg/m², which of 25 (22.3%) subjects were normal weight, and 87 (77.7%), were overweight and obesity. The medians of serum iron levels was 1.4 (1.2 – 1.8) mg/dl. Fifty-eight (47.5) patients had hepatic steatosis, which of 34 (27.9%) were classified as mild, 18 (14.8%) as moderate, and six (4.9%) as severe degree.

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.

Table 2 showed the imaging characteristics. The mean liver stiffness value was 2.9 kPa (95% CI 2.7 – 3.1). The prevalence of F2 and F3 in the overall cohort was 3.4% and 16.8% respectively.

Table 3 shows a significant association between architecture of the hepatic parenchyma and alcoholism (normal 2.3% *vs* abnormal 20.6%, $p = 0.002$), cirrhosis (normal 1.1% *vs* abnormal 20.6%, $p = 0.001$), and hepatitis C (normal 14.8% *vs* abnormal 44.1%, $p = 0.001$). However, no significant association was found for age, sex, body mass index and diabetes mellitus.

In addition, subjects “abnormal” showed a mean liver stiffness significantly higher (4.10 ± 1.45 kPa) compared to those without morphological alteration of the hepatic

parenchyma (2.48 ± 0.53 kPa, $p < 0.001$) (figure 1).

Generalized Linear Model, adjusted by age, identified alcoholism ($p = 0.044$), hepatitis C ($p = 0.008$) and cirrhosis ($p = 0.016$) as independent factors associated with morphological alterations of the hepatic parenchyma (table 4).

DISCUSSION

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

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 (26). 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 structure 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 occurs gradually and asymptomatically, corroborating with diagnosis in the final stages, in which the progression to cirrhosis becomes inevitable(28–30). Thus, since

MRE may allow measurements of liver stiffness while the morphological changes yet are minor, the use of MRE becomes attractive(31–33). 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(8,13). Other advantage of this technique is that it not affected by the presence of ascites, as shear waves generated in vivo have good hepatic penetration(7,14,34)

Regarding the potential predictive factors of hepatic alterations, as the expected, it was observed a positive association between alcoholism, hepatitis C, and cirrhosis with hepatic morphological alteration. These factors may explain the significant increase of the liver stiffness in patients with morphological alterations, given that directly affect the hepatocytes(35–37). 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.

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 conclusions, we found a significant relationship between architecture alteration of the hepatic parenchyma and alcoholism, hepatic comorbidities and liver stiffness. In addition, we observed the 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 of liver stiffness and hepatic biopsy should be

performed.

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Table 1. General characteristics of patients

Variables	N= 123
Age (years), mean ± SD	52.8 ± 12.7
Sex, n (%)	
Male	73 (59.3)
Alcoholism, n (%)	9 (7.4)
Body mass index (kg/m²), mean ± SD	29.1 ± 5.6
Nutritional Status, n (%)	
Normal weight	25 (22.3)
Overweight	43 (38.4)
Obesity	44 (39.3)
Degree of hepatic iron by MRI, n (%)	
Normal liver	104 (84.6)
Mild iron overload	19 (15.4)
Moderate iron overload	0
Severe iron overload	0
Hepatic steatosis by MRI, n (%)	
Normal	64 (52.5)
Mild steatosis	34 (27.9)
Moderate steatosis	18 (14.8)
Severe steatosis	6 (4.9)
Comorbidities, n (%)	
Cirrhosis	8 (6.6)
Hepatitis C	28 (23)
Hepatitis B	4 (3.3)
Focal Liver Injury	10 (8.2)
Human Immunodeficiency Virus	5 (4.1)
Pancreatitis	2 (1.6)
Acute Hepatitis	2 (1.6)
Systemic arterial hypertension	11 (8.9)
Diabetes Mellitus	10 (8.1)
Others	7 (5.7)

N= sample size; SD = standard deviation; MRI = magnetic resonance imaging.

Table 2. Resonance Magnetic Elastography and Resonance Magnetic Imaging characteristics

Imaging characteristics	**N= 123**
MR elastography, n (%)	
Normal	54 (45.4)
Normal or chronic inflammation	30 (25.2)
Stage 1 – 2	11 (9.2)
Stage 2 – 3	4 (3.4)
Stage 3 – 4	10 (8.4)
Stage 4-	10 (8.4)
MR imaging, n (%)	
Normal	88 (71.5)
Abnormal	35 (28.5)

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

Variables	Normal (n = 88)	Abnormal (n=35)	p-value
Age (years), mean ± SD	51.84 ± 13.71	55.34 ± 9.73	0.115
Sex, n (%)			
Male	49 (55.7)	24 (68.6)	0.133
Female	39 (44.3)	11 (31.4)	
Alcoholism, n (%)			
Yes	2 (2.3)	7 (20.6)	0.002
No	86 (97.7)	27 (79.4)	
Body mass index (kg/m²), mean ± SD	28.94 ± 5.79	29.70 ± 5.40	0.528
Comorbidities, n (%)			
Cirrhosis			
Yes	1 (1.1)	7 (20.6)	0.001
No	87 (98.9)	27 (79.4)	
Hepatitis C			
Yes	13 (14.8)	15 (44.1)	0.001
No	75 (85.2)	19 (55.9)	
Diabetes Mellitus			
Yes	5 (5.7)	5 (14.3)	0.116
No	83 (94.3)	30 (85.7)	

N= sample size, SD = standard deviation. Patients with morphological alteration of the hepatic parenchyma was considered “abnormal”. Chi-square test for categorical variable. Student t-test of Mann-Whitney U-test for continuous variables.

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	0.215
Alcoholism	7.39	1.05 - 51.85	0.044
Hepatitis C	4.39	1.46 – 13.21	0.008
Cirrhosis	26.40	1.83 – 379.14	0.016

OR = Odds ratio; CI = confidence interval; *Generalized linear model,* adjusted by age.

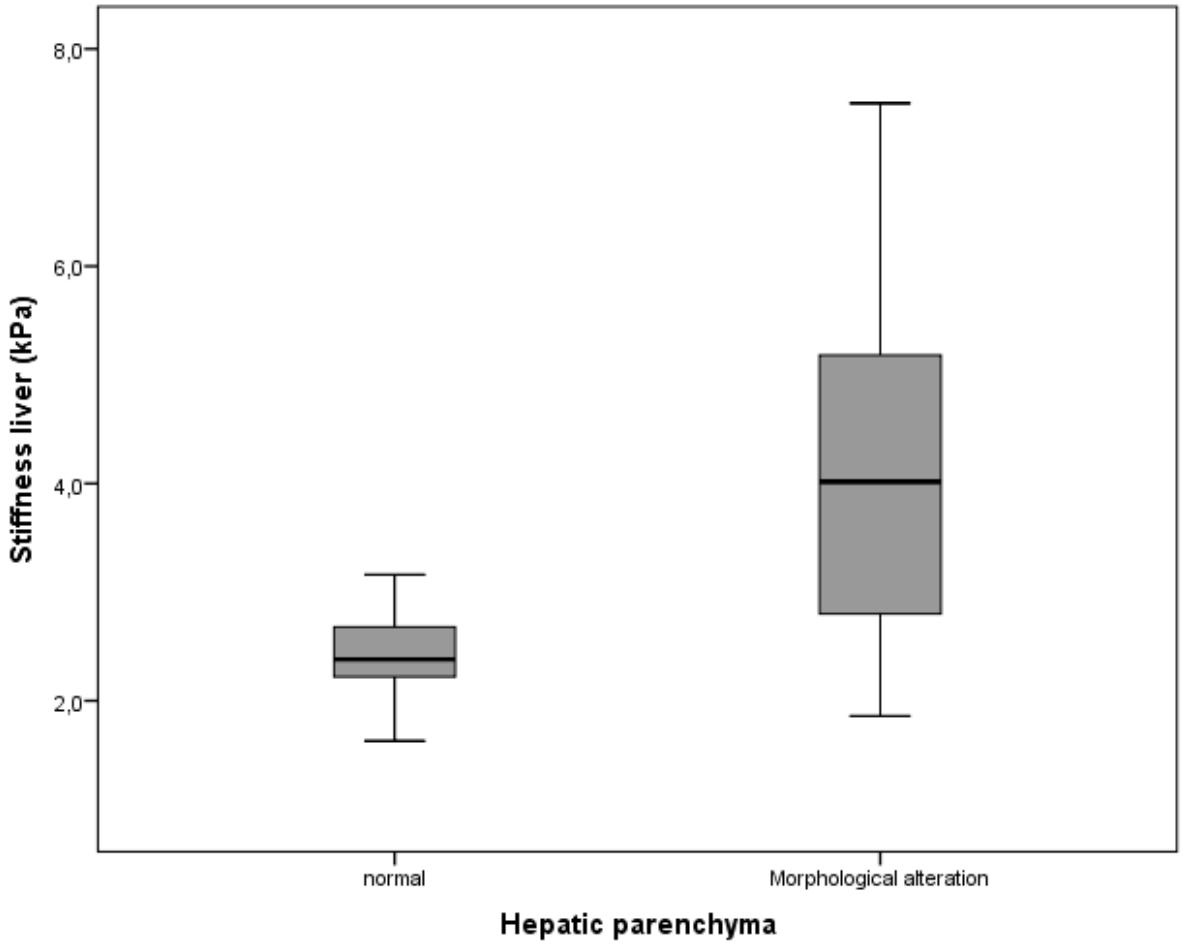

Figure 1. Mean liver stiffness and morphological alteration of the hepatic parenchyma.

Aprovação do SIPESQ

SIPESQ

Sistema de Pesquisas da PUCRS

Código SIPESQ: 8796

Porto Alegre, 11 de julho de 2018.

Prezado(a) Pesquisador(a),

A Comissão Científica da ESCOLA DE MEDICINA da PUCRS apreciou e aprovou o Projeto de Pesquisa "Desempenho diagnóstico de ressonância magnética com estudo de elastografia para avaliação de lesões hepáticas". Este projeto necessita da apreciação do Comitê de Ética em Pesquisa (CEP). Toda a documentação anexa deve ser idêntica à documentação enviada ao CEP, juntamente com o Documento Unificado gerado pelo SIPESQ.

Atenciosamente,

Comissão Científica da ESCOLA DE MEDICINA

Aprovação do CEP

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: DESEMPENHO DIAGNÓSTICO DE RESSONÂNCIA MAGNÉTICA COM ESTUDO DE ELASTOGRAFIA PARA AVALIAÇÃO DE LESÕES HEPÁTICAS

Pesquisador: Bruno Hochhegger

Área Temática:

Versão: 1

CAAE: 94804318.5.0000.5336

Instituição Proponente: UNIÃO BRASILEIRA DE EDUCAÇÃO E ASSISTENCIA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.828.116

Apresentação do Projeto:

É um estudo piloto do tipo transversal, retrospectivo e acadêmico envolvendo seres humanos. Será duplo cego (médicos radiologistas com experiência), através da reanálise dos exames de ressonância magnética com e sem elastografia por Ressonância Magnética armazenados no banco de dados do Hospital São Lucas da PUCRS no ano de 2018.

Objetivo da Pesquisa:

Objetivo Primário:

O objetivo desse trabalho é avaliar os resultados da elastoRM no estudo das lesões hepáticas.

Objetivo Secundário:

Descrever o incremento do diagnóstico de doença fibrosante hepática com elastoRM em comparação ao exame normal de RM.Avaliar o padrão de dureza das lesões focais hepáticas a elastoRM.

Avaliação dos Riscos e Benefícios:

Riscos:

Não haverá riscos aos participantes da pesquisa já que serão avaliados dados já existentes em

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estudos prévios realizados no Serviço de Diagnóstico por Imagem do HSL, sem coleta de material biológico ou ônus financeiro para os participantes.

Benefícios:

O estudo trará como benefício um maior conhecimento da prevalência das alterações hepáticas, assim como poderá padronizar os resultados de rigidez para as diferentes lesões hepáticas, agregando informações às técnicas existentes.

Comentários e Considerações sobre a Pesquisa:

A importância do estudo resume-se nas evidências de que a alteração da rigidez nos tecidos produza padrões que estabelecem diferenças entre lesões benignas e malignas e que esse parâmetro possa ser considerado nos diagnósticos diferenciais entre as inúmeras
alterações benignas do fígado.

Considerações sobre os Termos de apresentação obrigatória:

1. No Cronograma (Plataforma Brasil) consta que a coleta de dados inicia-se no dia 01/08/2018. A data deve ser atualizada para após a aprovação pelo CEP-PUCRS.

2. No TCLE cita que "Não haverá riscos...". Mesmo os estudos retrospectivos devem ser considerados os riscos mínimos, como a exposição dos dados pessoais.

Conclusões ou Pendências e Lista de Inadequações:

Há pendências, conforme acima.

Considerações Finais a critério do CEP:

Diante do exposto, o CEP-PUCRS, de acordo com as suas atribuições definidas na Resolução CNS nº 466 de 2012 aguarda a realização das adequações indicadas nos itens: "Considerações sobre os Termos de apresentação obrigatória" e "Conclusões ou Pendências e Lista de Inadequações" em um prazo de TRINTA DIAS conforme previsto na Norma Operacional nº 001 de 2013 do CNS onde se lê: Aspectos Operacionais dos CEPs, E) Se o parecer for de pendência, o pesquisador terá o prazo de trinta (30) dias, contados a partir de sua emissão na Plataforma Brasil, para atendê-la."

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1179525.pdf	17/07/2018 10:15:04		Aceito
Outros	LinkCurriculoLattes.pdf	17/07/2018	Bruno Hochhegger	Aceito

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

Continuação do Parecer: 2.828.116

Outros	LinkCurriculoLattes.pdf	10:14:36	Bruno Hochhegger	Aceito
Outros	ApresentacaoCEPJoaoPaulo.pdf	17/07/2018 10:14:20	Bruno Hochhegger	Aceito
Outros	AutorizacaoDiretorHSLJoaoPaulo.pdf	17/07/2018 10:14:05	Bruno Hochhegger	Aceito
Parecer Anterior	DocumentoUnificadoJP.pdf	17/07/2018 10:13:48	Bruno Hochhegger	Aceito
Parecer Anterior	CartaAprovacaoCCientifica.pdf	17/07/2018 10:13:35	Bruno Hochhegger	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCUDJoaoPaulo.pdf	17/07/2018 10:13:24	Bruno Hochhegger	Aceito
Orçamento	OrcamentoJoaoPaulo.pdf	17/07/2018 10:13:15	Bruno Hochhegger	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoFinal0506.pdf	17/07/2018 10:13:04	Bruno Hochhegger	Aceito
Folha de Rosto	FolhaderostoJP1707.pdf	17/07/2018 10:10:16	Bruno Hochhegger	Aceito

Situação do Parecer:
Pendente

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 17 de Agosto de 2018

Assinado por:
Paulo Vinicius Sporleder de Souza
(Coordenador)

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