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# Good correlation between liver stiffness measurement and APRI, FIB-4, platelet count, in pediatric autoimmune hepatitis

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## HIGHLIGHTS

- Due to the invasive nature of the liver biopsy, there is a growing interest in the use of non-invasive markers of liver fibrosis.
- There is a significant and positive correlation between APRI, FIB-4 and platelet count and liver stiffness measurement evaluated by transient elastography in pediatric autoimmune hepatitis.

**ABSTRACT – Background –** There is limited evidence focusing on the use of non-invasive markers to assess liver fibrosis in pediatric chronic liver diseases. **Objective –** The aim of the study was to evaluate the correlation between liver stiffness measurement (LSM) using transient liver elastography (TLE) and serum non-invasive markers in pediatric autoimmune hepatitis (AIH). **Methods –** Cross-sectional study between May 2016 and February 2020. Twenty-eight children with AIH (age range between 3 and 20 years old) who had undergone TLE and had routine serum tests were enrolled. Patients were divided into 2 groups: (1) Liver fibrosis degree ≥F2 (TLE ≥6.45 kPa) and (2) <F2 (TLE <6.45 kPa). The groups were compared using Fisher's exact test for categorical variables and the Mann-Whitney test for quantitative variables. The correlation between TLE, APRI, FIB-4 and platelet count was assessed using the Spearman coefficient (Rs). **Results –** Twenty-eight AIH pediatric patients were enrolled, 21 were female and 22 had AIH type 1. Following the cut-off of 6.45 kPa in TLE, 20 patients (71%) were included in group 1, and 8 in group 2. A statistically significant difference was found between the two groups on APRI and FIB-4 results ($P$=0.0306 and $P$=0.0055, respectively). There was a significant correlation between TLE with APRI and FIB-4 (Rs=0.67 and 0.78, respectively; $P$<0.01) as well as with platelet count (Rs=-0.68; $P$<0.01). **Conclusion –** APRI, FIB-4 and Platelet Count showed a good and positive correlation with transient liver elastography in pediatric patients with AIH.

**Keywords** – Autoimmune hepatitis; liver elastography; non-invasive markers; chronic liver disease; liver fibrosis.

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## INTRODUCTION

Autoimmune hepatitis (AIH) is an immune-mediated chronic liver disease characterized by elevated transaminases, hypergammaglobulinemia, positivity of specific autoantibodies, and, on histologic examination, interface hepatitis and portal plasma cell infiltration[1,2]. The clinical presentation in children and adolescents ranges from acute liver failure, insidious and asymptomatic forms, or as a manifestation of cirrhosis and complications of portal hypertension. The diagnosis is based on clinical, biochemical, immunological, and histological features through different scores (classic and simplified scores)[2-5].

Liver biopsy, although remains the gold standard in the assessment of liver fibrosis – however, it is considered an invasive procedure and involves risks. It is essential to establish the diagnosis of AIH but is not routinely recommended solely for the evaluation of fibrosis in pediatric AIH. Therefore, non-invasive surrogates based on imaging, such as liver stiffness measurement (LSM) evaluated with transient liver elastography (TLE), or biochemical tests and indexes, such as APRI (AST to platelet ratio index), FIB-4 (fibrosis 4 index) and platelet count have been studied over the last years[2,6-8]. There is strong positive correlation between LS and histological fibrosis stage in AIH[9]. However, in our reality, TLE is not widely available, and there is a scarcity of professionals trained to perform TLE (especially in pediatric patients).

In this context, this study aimed to evaluate the correlation of TLE with the other non-invasive biochemical markers of liver fibrosis (APRI, FIB-4, and platelet count) in children with AIH.

## METHODS

This cross-sectional study was conducted with children diagnosed with AIH at a tertiary university. Patients were enrolled between May 2016 and February 2020. Inclusion criteria were: 1) definitive diagnosis of AIH[2,4]; and 2) ongoing immunosuppressive treatment with Prednisone and/or Azathioprine for at least 6 months[9] in biochemical remission[2]. Patients were excluded from the study if: 1) they had not undergone TE; 2) they had undergone liver transplantation during follow-up; 3) there was any other congenital or acquired liver disease; or 4) biochemical remission was not reached. The study was approved by the local Research Ethics Board (REB) (project #78492017.0.0000.5404, approval #4.094.893).

TLE was performed with FibroScan® as part of routine clinical care for these patients, according to institutional protocols. All children were fasting for 6 hours, and 10 valid measurements were taken with an interquartile range (IQR) <30% and a success rate greater than 60%. The exam was performed by the first author and verified in real-time by the principal investigator. Patients were stratified according to the TLE results: group 1 – TLE ≥6.45 kPa; and group 2 – TLE <6.45 kPa[10]. The FIB-4 and APRI scores were calculated according to the following formulas[11]: FIB-4 = age [years] x AST (U/L) / platelet count [$10^9$/L] x √ ALT (U/L); APRI = (AST / upper limit of normality) x 100 / platelet count [$10^9$/L]). The platelet count was obtained as part of routine clinical care (complete blood count). Biochemical tests required to calculate APRI, FIB-4, and Platelet Count were collected within three months before or after the TLE.

The comparison between groups 1 (TLE ≥6.45 kPa) and 2 (TLE <6.45 kPa) was performed using the Mann-Whitney test for quantitative variables and Fisher's exact test for categorical variables. The correlation between TLE, APRI, FIB-4, and platelet count was assessed using the Spearman coefficient (Rs) and the level of significance was set at 5%.

### Ethics approval and consent to participate

The study was approved by the Human Research Ethics Committee of UNICAMP on 12/14/2017, under the number 4.094.893 and CAAE: 78492017.0.0000.5404.

All methods were performed in accordance with the relevant guidelines and regulations. All families involved (parent and/or legal guardian) signed the Informed Consent Form.

## RESULTS

Twenty-eight patients with AIH were included, 21 were female (75%) and 22 had AIH type 1 (78.5%). According to the cut-off of 6.45 kPa in TE, 20 patients

(71%) were included in group 1, and 8 in group 2. There was a statistically significant difference between the two groups in relation to the APRI and FIB-4 scores ($P$=0.0306 and $P$=0.0055, respectively), but not significant differences were seen regarding age, gender, type of AIH, and platelet count.

When TLE was compared with the non-invasive surrogates, there was a significant and positive correlation with APRI and FIB-4 (Rs=0.67 and 0.78, respectively; $P$<0.01) as well as with platelet count (Rs=-0.68; $P$<0.01). The clinical characteristics of the patients in the two groups with the values of platelet count, APRI and FIB-4 scores, as well as the correlation are presented in TABLE 1.

## DISCUSSION

In this cross-sectional study with twenty-eight children and adolescents with AIH (age range between 3 and 20 years old), TLE cutoff value of 6.45 kPa to classify the patients in relation to liver fibrosis without using histology – as previously described by Xu et al. in a cohort of patients with biopsy-proven AIH[10]. We also found that the APRI, FIB-4, and platelet count showed a good and positive correlation with TLE in pediatric patients with AIH.

Data on non-invasive markers to assess liver fibrosis in pediatric patients with AIH are relatively scarce and mainly focuses on the scenario of portal hypertension[8,12,13] Behairy et al. evaluated 90 children with chronic liver disease (20 with AIH) assessing the accuracy of TLE (FibroScan®) to predict liver fibrosis and found that TLE was reliable to predict the degree of liver fibrosis, however, the results varied according to the etiology, so the authors concluded that the cut-off points must be individualized according to the etiology of the liver disease[12].

Although convenience sampling was used for the present study, the prevalence of females (75%) reported is heavily corroborated by medical literature on autoimmune liver diseases[2,3], including national (Brazilian) data on pediatric AIH[14]. The decision to include patients who had undergone immunosuppressive treatment for at least 6 months was based on the fact that liver inflammation has a major impact on liver stiffness in the first months of AIH treatment as demonstrated by Hartl et al.[9] – despite that, TLE has a high diagnostic accuracy for diagnosing cirrhosis and severe fibrosis after 6 months of immunosuppressive treatment. It is hypothesized that the histological response in AIH takes place at a much slower pace than the biochemical response.

In contrast to our findings, in adults with chronic liver diseases, the correlation between LSM assessed with TLE and other non-invasive methods was not supported[6,7,9,15]. To the best of our knowledge, this is a pioneer study assessing the correlation between LSM and serum non-invasive markers in pediatric AIH. Our finding of a significant correlation has important clinical implications in monitoring children with AIH, and, therefore, should be further assessed and confirmed in future studies. Some of our study limitations included the lack of a healthy control group, a cross-sectional study design, and a relatively small sample.

**TABLE 1.** Clinical characteristics of AIH patients and the values of APRI (AST to platelet ratio index), FIB-4 (fibrosis 4 index) and platelet count; and correlation of TE with the other non-invasive biochemical markers of liver fibrosis.

| | Group 1 (n=20) | Group 2 (n=8) | *P*-value* |
|---|---|---|---|
| Gender | Female: 14<br>Male: 6 | Female: 7<br>Male: 1 | 0.6334 |
| Age | 14.5±4.2 | 11.5±5.1 | 0.1250 |
| AIH type 1 | 19/20 | 3/5 | 0.0913 |
| APRI | 2.6±5.7 | 0.3±0.1 | 0.0306 |
| FIB-4 | 1.5±2.7 | 0.3±0.2 | 0.0055 |
| Platelet count | 160.000±89.000 mm$^3$ | 236.000±103.000 mm$^3$ | 0.0793 |
| Correlation between transient elastography and APRI, FIB-4 and platelet count | | | |
| | APRI | FIB-4 | Platelet count |
| Transient | Rs=0.67 | Rs=0.78 | Rs=-0.68 |
| Elastography | $P$<0.01 | $P$<0.01 | $P$<0.01 |

AIH: autoimmune hepatitis; TE: transient elastography. *Mann-Whitney test for quantitative variables and Fisher's exact test for categorical variables.

Nevertheless, our findings suggest that in pediatric patients with AIH, LSM assessed by TLE has a significant correlation with APRI, FIB-4, and platelet count.

## Authors' contribution

Alvarenga LR conceptualized the article, obtained REB approval and collected the data, drafted the initial manuscript, reviewed and revised the manuscript, and approved the final draft as submitted. Sandy NS drafted the initial manuscript, reviewed and revised the manuscript, and approved the final draft as submitted. Pereira TS and Hessel G reviewed and revised the manuscript, and approved the final draft as submitted. Bellomo-Brandão MA supervised throughout all the different phases of this study, analyzed the data, reviewed and revised the manuscript, and approved the final draft as submitted.

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**RESUMO – Contexto** – Há evidências limitadas com foco no uso de marcadores não invasivos para avaliar a fibrose hepática em doenças hepáticas crônicas pediátricas. **Objetivo –** O objetivo do estudo foi avaliar a correlação entre avaliação da rigidez hepática com elastografia hepática transitória (EHT) e marcadores séricos não invasivos na hepatite autoimune (HAI) pediátrica. **Métodos –** Estudo transversal entre maio de 2016 e fevereiro de 2020. Foram incluídas 28 crianças com HAI (faixa etária entre 3 e 20 anos) que haviam sido submetidas a EHT e realizaram exames séricos de rotina. Os pacientes foram divididos em dois grupos de acordo com o resultado da EHT: (1) grau de fibrose hepática ≥F2 (rigidez hepática ≥6,45 kPa) e (2) <F2 (rigidez hepática <6,45 kPa). Os grupos foram comparados utilizando o teste exato de Fisher para variáveis categóricas e o teste de Mann-Whitney para variáveis quantitativas. A correlação entre EHT, APRI, FIB-4 e contagem de plaquetas foi avaliada pelo coeficiente de Spearman (Rs). **Resultados –** Foram incluídos 28 pacientes pediátricos com HAI, 21 eram do sexo feminino e 22 tinham HAI tipo 1. Seguindo o ponto de corte de 6,45 kPa na EHT, 20 pacientes (71%) foram incluídos no grupo 1 e 8 no grupo 2. avaliação da rigidez hepática com significativa entre os dois grupos nos resultados APRI e FIB-4 ($P$=0,0306 e $P$=0,0055, respectivamente). Houve correlação significativa entre EHT com APRI e FIB-4 (Rs=0,67 e 0,78, respectivamente; $P$<0,01), bem como com a contagem de plaquetas (Rs=-0,68; $P$<0,01). **Conclusão –** APRI, FIB-4 e contagem de plaquetas apresentaram correlação positiva com a medição da rigidez hepática avaliada com elastografia hepática transitória em pacientes pediátricos com HAI.

**Palavras-chave –** Hepatite autoimune; elastografia hepática; marcadores não invasivos; doença hepática crônica; fibrose hepática.

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