Hepatic Inflammation May Influence Liver Stiffness Measurements by Transient Elastography in Children and Young Adults

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ABSTRACT

Objectives: Transient elastography (TE) measures liver stiffness to assess fibrosis. Studies in adults have shown that inflammation increases stiffness, leading to an overestimation of fibrosis. We investigated the contribution of inflammation to liver stiffness measurements (LSMs) in children/young adults.

Methods: This was a cohort analysis of children/young adults who underwent TE within 1 year of liver biopsy. Alanine aminotransferase (ALT) was obtained within 30 days of the biopsy and LSM. Fibrosis was assessed by METAVIR stage and inflammation by ALT and Ishak score. Data were stratified into METAVIR F0–F2 versus F3–F4. Change between ALT and LSM over time was also assessed.

Results: A total of 154 patients (50% male patients) ages 3 weeks to 24 years (18% <3 years) were studied. Diagnoses included autoimmune (N = 38, 25%), viral (N = 25, 16%), cholestasis (N = 17, 11%), fatty liver (N = 9, 6%), biliary atresia (N = 8, 5%), metabolic (N = 5, 3%), allograft rejection (N = 4, 3%), and other (N = 48, 31%). Thirty-four percent of patients had F3–F4. In patients with F0–F2, the proportion of those with LSM >8.6 kPa increased with increasing ALT ($P = 0.002$). In patients with F3–F4, there was no association between ALT and LSM ($P = 0.17$). A correlation between change in ALT and LSM was observed in patients with no/minimal fibrosis and inflammatory liver diseases ($r = 0.33$).

Conclusions: In children with no/minimal hepatic fibrosis and inflammatory liver disease, high ALT values are associated with LSM in the range typical of advanced fibrosis. However, with more advanced fibrosis, inflammation does not appear to contribute to LSM. Caution must be taken when interpreting LSM for assessing fibrosis severity in the setting of inflammation.

Key Words: hepatitis, liver disease, liver fibrosis, pediatrics

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What Is Known

- Transient elastography measures liver stiffness to assess fibrosis.
- Studies in adults have shown that inflammation can increase liver stiffness measurements.

What Is New

- In children/young adults with no/minimal hepatic fibrosis and inflammatory liver disease, high alanine aminotransferase values are associated with liver stiffness measurement in the range of advanced fibrosis, as has been noted in adult studies. In subjects with more advanced fibrosis, however, inflammation does not contribute to the liver stiffness measurement.
- Caution must be taken when interpreting liver stiffness measurement for assessing fibrosis severity in the setting of inflammation.

Transient elastography (TE) (Fibroscan; Echosens, Paris, France) is a noninvasive, ultrasound-based tool, used to rapidly measure liver stiffness. Liver stiffness measurements (LSMs) have been shown to reflect hepatic fibrosis (1,2). Studies in children have shown that TE is a reliable and effective tool for evaluating and predicting hepatic fibrosis in patients with various chronic liver diseases (3–6). Although fibrosis is certainly a major contributing factor to LSMs, other characteristics of liver disease, including inflammation, necrosis, and fatty infiltration or edema, may potentially affect LSM. In fact, studies in adult patients have shown that hepatic inflammation results in inflated LSMs that are higher than those expected from fibrosis alone (7–11). In a study of 240 healthy children between 0 and 18 years of age, median liver stiffness was 4.7 kPa with an upper limit of 6.47 kPa (12). The optimal cutoff to predict significant to severe fibrosis (METAVIR F3–F4) in a pediatric population was found to be 8.6 kPa

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Echosens provided the transient elastography machine used in this study. It did not have any role in study design, collection/analysis/interpretation of data, writing of the manuscript, or the decision to submit the paper for publication.

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($P < 0.001$) based upon correlation with histological staging of fibrosis (3), similar to those of other studies (4,6).

The aims of this study were to investigate the contribution of inflammation to liver stiffness, as measured by TE, in a pediatric cohort, and to determine whether there is an association between the change in alanine aminotransferase (ALT) and the change in LSM with serial measurements over time. This study is the first to investigate the relation between TE measurements, fibrosis, and inflammation in a pediatric population. Unlike the studies in adults primarily with viral and autoimmune hepatitis (AIH), this study includes patients with a wide range of liver diseases.

METHODS

This was a retrospective cohort analysis of children and young adults who had undergone liver biopsy and LSM between January 2006 and May 2014 at Boston Children's Hospital. All subjects must have had a first LSM within 1 year of the liver biopsy and ALT measured within 30 days of LSM. Serial LSM was obtained in a subset of patients to correlate with biochemical data over time. The second LSM was performed at a minimum of 6 months after the initial study, at the time of scheduled medical appointments. A second ALT was obtained in these patients within 30 days of their second LSM. Patients with ascites, morbid obesity (body mass index >40 kg/m^2), implantable cardiac devices, and those who were pregnant were excluded, per the manufacturer's guidelines. Patients who had undergone Fontan surgery were also excluded given the known high degree of hepatic stiffness in these patients (13,14). Patients with invalid LSM were not included in the final data analysis. This study was approved by the Boston Children's Hospital's institutional review board. Written informed consent was obtained from parents, legal guardians, or patients ≥18 years of age. Patient assent was obtained when appropriate.

Liver Histology

All patients underwent liver biopsy for clinical indications. The majority of liver biopsy specimens were evaluated by 2 pathologists who were blinded to clinical data and LSM. Liver biopsies were assessed for the degree of fibrosis with METAVIR staging (15). Histological grading of inflammation was assessed by the Ishak score (modified histological activity index [HAI] grading: necroinflammatory score) (16). The modified HAI grading score was used wherein each biopsy was given a score from 0 to 18. This score was based on periportal or periseptal interface hepatitis, confluent necrosis, focal lytic necrosis, apoptosis and focal inflammation, and portal inflammation (16). If the study pathologists no longer had access to the biopsy material, histologic data were obtained from patients' medical records, and the clinical pathology reports previously generated by a hepatopathologist were used for METAVIR staging. The METAVIR scores for these subjects were reviewed and confirmed by a study investigator. If the clinical METAVIR score was not available, clinical pathology reports were used by study investigators to determine METAVIR scoring using the following definitions: F0, absent fibrosis; F1, portal fibrosis without septae/bridging; F2, portal fibrosis with few septae/bridging; F3, portal fibrosis with many septae/bridges; F4, cirrhosis. Ishak scoring for these subjects was not possible.

Liver Stiffness Measurements

Liver stiffness was measured by TE (Fibroscan). A total of 8 to 10 valid LSM were obtained and reported as a median value in kiloPascals (kPa). The adequacy of measurement was assessed by the TE device. LSM was performed by trained study investigators who were certified by the manufacturer and blinded to the liver biopsy results. The TE probe size selection was based upon thoracic perimeter (TP); the M (medium) probe was used if TP >75 cm, and the S (small) if TP ≤75 cm. Before November 2009, when the S probe became available, those patients weighing <50 pounds did not undergo TE and were excluded from this analysis.

Biochemical Marker

Inflammation was assessed with ALT obtained within 30 days of each LSM.

Statistical Analysis

Patient characteristics and METAVIR stages are presented as N (%). Ishak inflammation scores were categorized as low (0–4), moderate (5–9), and high (10–18), whereas ALT was categorized as normal (<30 U/L), >1 × 3 upper limit of normal (ULN), >3 – 10 × ULN, and >10 × ULN. These too were reported as N (%). For some comparisons, METAVIR staging was dichotomized as no/minimal fibrosis (F0–F2) and advanced fibrosis (F3–F4). LSM was right-skewed, and therefore presented as median (interquartile range [IQR]) and compared across METAVIR stages by the Kruskal–Wallis test.

The proportion of patients with LSM >8.6 kPa was compared across Ishak and ALT categories, stratified by METAVIR staging (no/minimal fibrosis vs advanced fibrosis). Analysis was therefore in the form of stratified 2×3 tables for the Ishak comparisons and 2×4 tables for the ALT comparisons ($k = 2$ strata). The Mantel–Haenszel statistic was used to test for linear association between the rows and columns in ≥1 stratum (17). The proportion of patients with LSM >8.6 kPa from each table is shown in bar graphs in Figure 1, with P values from the Cochran–Armitage test for trend when the Mantel–Haenszel statistic was significant and Fisher exact test for general association otherwise (18).

Analysis for aim 2, change in LSM with change in ALT over time, was restricted to 45 patients with paired LSM and ALT data. Because both LSM and ALT were right skewed, data were first normalized to a standard normal distribution using the method of Blom (19). The change in LSM was plotted against change in ALT and assessed by Spearman rank correlation. Data were assessed for all 45 patients combined and then stratified into 2 groups: 22 patients with no/minimal fibrosis and an inflammatory liver disease diagnosis, and the remaining 23 patients not included in group 1. This analysis was repeated after dropping 1 outlier to determine the influence of this subject's data on the results.

All comparisons involving Ishak scores were limited to n = 119 patients because of missing data. Pairwise comparisons were conservatively made using Bonferroni P values to adjust for multiplicity. All data analysis and figures were performed with SAS (SAS Institute, Cary, NC).

RESULTS

A total of 224 patients were enrolled. Twenty-four patients with invalid LSM were excluded (Supplemental Digital Content 1, Fig., *http://links.lww.com/MPG/A767*). Invalid measurements were because of patients' inability to cooperate (n = 7), body habitus with fatty abdominal wall (n = 3), and undocumented reasons (n = 14). No adverse events occurred during LSM. An additional 46 patients were excluded because of the first LSM being obtained >12 months from the time of liver biopsy, or the first ALT being obtained >30 days from either the liver biopsy or first LSM, resulting in 154 of 224 (69%) patients available for aim 1. A second LSM was obtained in 49 of these patients, from which 4 with a second ALT

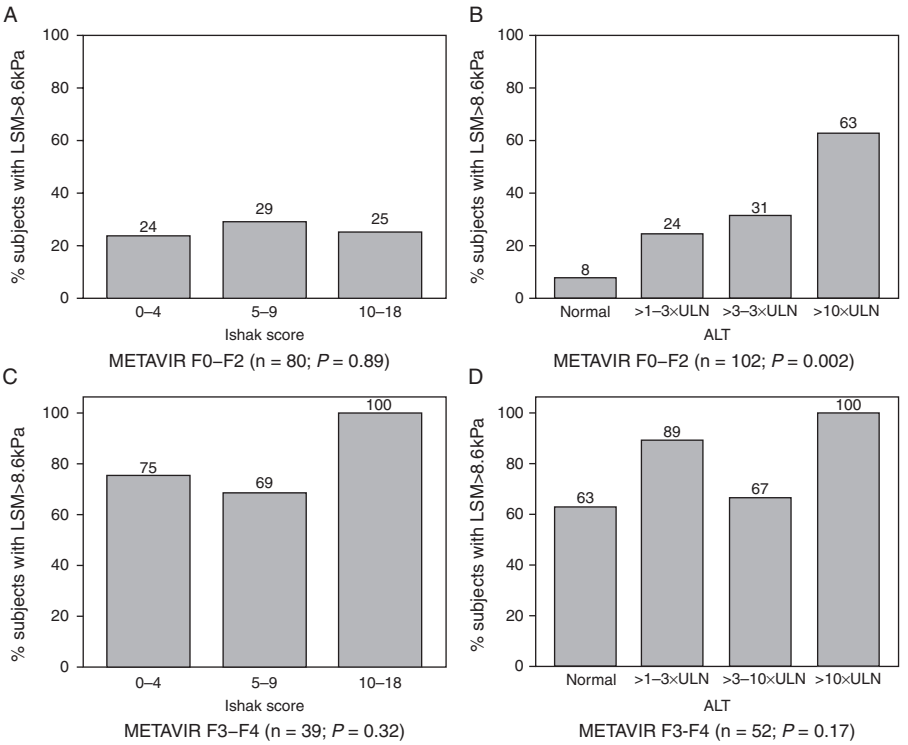

FIGURE 1. Proportion of subjects with advanced fibrosis, as determined by LSM >8.6 kPa, compared across Ishak and ALT categories. Comparisons are stratified by METAVIR stage (no/minimal fibrosis vs advanced fibrosis). There were no differences among Ishak categories; however, there was a monotonically increasing trend across ALT categories among patients with no/minimal fibrosis ($P = 0.002$) and no association across ALT categories in patients with advanced fibrosis. ALT = alanine aminotransferase; LSM = liver stiffness measurement.

obtained >30 days from the second LSM were omitted, resulting in 45 of 154 (29%) patients available for aim 2.

Demographic characteristics of the study population and primary diagnostic indications for liver biopsy are listed in Table 1. Patients were 50% boys, ages 3 weeks to 24 years (18% <3 years and 8% ≥18 years). Although the protocol specified that LSM was to be obtained within 1 year of the liver biopsy, 82% of LSM were obtained within 6 months of biopsy. The median interval between the time of biopsy and LSM was 1.4 months (IQR 0.6–3.7).

Study pathologists did not have access to the biopsy material for 24 subjects to reassess METAVIR scoring. In 18 of those subjects, the clinical pathology reports were reviewed and METAVIR scoring, previously reported by a hepatopathologist, was confirmed by a study investigator. In 6 subjects, the previously reported clinical METAVIR score was not available. In these subjects, the clinical pathology report was used by study investigators to calculate the METAVIR score. In these 24 subjects, Ishak scoring could not be determined.

The distribution of first LSM by METAVIR stage is shown in Table 2 and Supplemental Digital Content 2, Figure, *http://links.lww.com/MPG/A768*. The age distribution of subjects and METAVIR stage by diagnosis is shown in Supplemental Digital Content 3, Table, *http://links.lww.com/MPG/A769*. Of the 154 patients, 34% had advanced fibrosis (METAVIR F3–F4). A majority (75%) of patients with no or minimal fibrosis (METAVIR F0–F2) had LSM below the previously established cut-point of 8.6 kPa, whereas a majority (77%) of those with advanced fibrosis had LSM >8.6 kPa. LSM was statistically higher among those with advanced fibrosis compared with those with no/minimal fibrosis (median [IQR] 14.4 [8.8, 21.9] versus 6.4 [5.1, 8.7] kPa, respectively; $P < 0.0001$). Table 2 also shows the distribution of first LSM by Ishak score and ALT. A monotonically increasing trend was observed in median LSM for both. Although group differences among Ishak scores were suggested by the omnibus Kruskal–Wallis test ($P = 0.03$), the incremental increases in LSM from Ishak 0–4 to Ishak 5–9 and from Ishak 5–9 to Ishak 10–18 were not statistically different. The comparison of Ishak 0–4 versus Ishak 10–18 was not significant ($P = 0.08$) after adjustment for multiple comparisons. Patients with normal ALT (<30) had lower LSM than those with ALT $>1-3 \times$ ULN ($P = 0.004$), whereas the incremental changes from ALT $>1-3 \times$ ULN to ALT $>3-10 \times$ ULN and from ALT $>3-10 \times$ ULN to ALT $>10 \times$ ULN were not statistically significant. There was the expected association between higher LSM and increasing fibrosis. In addition, in patients with ALT >10 times ULN, LSM was in the range associated with advanced fibrosis. Ishak scores could be calculated in 119 (77%) subjects. Supplemental Digital Content 2, Figure, *http://links.lww.com/MPG/A768*, illustrates the distribution of LSM by METAVIR stage F0–F4. There is a difference in the proportion of patients with LSM >8.6 kPa across the levels of each METAVIR stage ($P < 0.0001$).

To investigate the association between LSM and inflammation, the patients were dichotomized into 2 groups: 102 with no/minimal fibrosis (METAVIR F0–F2) versus 52 with advanced fibrosis (METAVIR F3–F4 fibrosis). The association of LSM and Ishak scores was not statistically different between subjects with no/minimal fibrosis and those with advanced fibrosis ($P = 0.36$; Mantel–Haenszel test). Furthermore, there were no statistical differences across Ishak scores either among subjects

TABLE 1. Patient characteristics (n = 154)

Characteristic	N (%)
Age group, y	
0–2	28 (18.2)
3–6	15 (9.7)
7–11	32 (20.8)
12–17	67 (43.5)
18–24	12 (7.8)
Male sex	77 (50.0)
Race/ethnicity (8 unknown)	
White	96 (65.8)
Asian	18 (12.3)
Black	13 (8.9)
Hispanic	11 (7.5)
Other	8 (5.5)
Liver disease diagnosis	
Autoimmune hepatitis	38 (24.7)
Viral hepatitis	25 (16.2)
Cholestasis	17 (11.0)
Fatty liver (3 NAFLD, 6 NASH)	9 (5.8)
Biliary atresia	8 (5.2)
Metabolic disease	5 (3.3)
Cellular rejection	4 (2.6)
Other	48 (31.2)

Other diagnoses include portal vein thrombosis, cryptogenic cirrhosis, abnormal liver enzymes not otherwise specified. NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis.

with no/minimal fibrosis or among subjects with advanced fibrosis (Fig. 1A and C). There were, however, differences in the association of LSM with ALT between patients with no/minimal fibrosis and those with advanced fibrosis ($P = 0.005$, Mantel–Haenszel test). Among patients with no/minimal fibrosis, the proportion of patients with LSM >8.6 kPa monotonically increased with greater degree of inflammation ($P = 0.002$, Cochran–Armitage test for trend, Fig. 1B); however, no statistical differences were found among patients with advanced fibrosis ($P = 0.17$, Fisher exact test, Fig. 1D).

TABLE 2. Distribution of LSM by METAVIR, Ishak, and ALT (n = 154)

Score	N (%)	LSM median (IQR)
METAVIR		
F0	28 (18.2)	6.1 (5.0, 7.3)
F1	40 (26.0)	6.5 (5.2, 9.0)
F2	34 (22.1)	6.7 (5.6, 8.9)
F3	31 (20.1)	10.4 (7.9, 15.8)
F4	21 (13.6)	22.0 (14.6, 42.3)
Ishak inflammation score (35 unknown)		
0–4	75 (63.0)	6.6 (4.9, 11.2)
5–9	33 (27.7)	8.4 (6.0, 15.7)
10–18	11 (9.2)	9.9 (8.1, 21.0)
ALT		
Normal (<30)	34 (22.1)	5.7 (4.4, 8.0)
>1–3 × ULN	52 (33.8)	7.8 (5.7, 16.3)
>3–10 × ULN	56 (36.4)	8.0 (6.1, 20.6)
>10 × ULN	12 (7.8)	11.3 (8.4, 15.8)

ALT = alanine aminotransferase; IQR = interquartile range; LSM = liver stiffness measurement; ULN = upper limit of normal.

To study the association between change in ALT and change in LSM over time, data from 45 patients with paired ALT and LSM were analyzed. Demographic characteristics of this subset are shown in Supplemental Digital Content 4, Table, *http://links.lww.com/MPG/A770*. Because of the high degree of skew in the data, ALT and LSM were first transformed to a standard normal distribution. Looking at all 45 patients, there was no clear correlation between the change in ALT and change in LSM over time (Fig. 2A, $r = 0.17$). The 45 patients were then stratified into 2 groups: those with no/minimal fibrosis (F0–F2) and an inflammatory liver disease diagnosis (autoimmune hepatitis, viral hepatitis, primary sclerosing cholangitis, drug-induced hepatitis, chronic hepatitis of unknown etiology, or nonalcoholic steatohepatitis), and those with no/minimal fibrosis and a noninflammatory liver disease diagnosis plus those with advanced fibrosis (METAVIR F3–F4). In group 1, there appeared to be a stronger correlation between ALT and LSM than for the 45 patients combined (Fig. 2B, $r = 0.33$). There was 1 outlier located in the upper left quadrant. This patient had autoimmune hepatitis with an initial ALT of 600 U/L, which decreased to 54 U/L at follow-up while LSM remained high. This patient did not have a follow-up biopsy to confirm the extent of fibrosis. As part of a sensitivity analysis, the outlier was removed and the correlation improved to $r = 0.53$. The correlation among the remaining 23 patients (group 2) was near 0 (Fig. 2C, $r = 0.06$).

DISCUSSION

TE, a tool utilized to measure liver stiffness, has been shown to rapidly and reliably assess fibrosis in adults and children. Recent studies in adults have shown that LSM can be confounded by other components of liver disease. These studies highlight the association between hepatic inflammation and the overestimation of LSM by TE (7–10). This is the first study to investigate the contribution of hepatic inflammation to the relation between LSM and fibrosis in children and young adults, and shows a significant elevation of LSM in patients with advanced fibrosis (METAVIR F3–F4; Supplemental Digital Content 2, Fig., *http://links.lww.com/MPG/A768*), supporting previous findings of the efficacy of TE to accurately and reliably measure fibrosis (1–6). In addition, we found a monotonically increasing trend in the proportion of patients with LSM >8.6 kPa across increasing ALT levels among patients with no/minimal fibrosis (Fig. 1B). Previous studies have shown that there is minimal progression of fibrosis over the course of 1 year, suggesting a greater role of changes in inflammation on changes in LSM in this timeframe (20–23). In patients with advanced fibrosis (METAVIR F3–F4), there was no significant contribution of inflammation to LSM, presumably because the baseline fibrosis had already established a high level of liver stiffness; so the additional effect of inflammation was not detectable. These findings are consistent with studies in adults, which have shown that in the setting of inflammation, as defined biochemically with ALT, LSM were increased (7–9,11). In a group of 18 adult patients with acute viral hepatitis and no known history of liver disease, there was a positive correlation between ALT and LSM, but liver biopsies were not obtained, and patients were presumed to have minimal to no fibrosis (7). This direct correlation between ALT and LSM was also observed in patients with METAVIR F1–F2 and acute liver injury who had LSM in the cirrhotic range (8). In a series of adult patients with chronic hepatitis B, those with elevated ALT levels had higher LSM values regardless of the degree of fibrosis, but in those with more severe fibrosis and cirrhosis, elevated ALT had a lesser effect on LSM compared with those with no fibrosis (24). In another report, adult patients with no/minimal fibrosis (METAVIR F0–F2) and high ALT values had TE measurements in the cirrhotic range as defined by previous studies (>11.9 kPa (25), >12.5 kPa (26), and >14.5 kPa[2]).

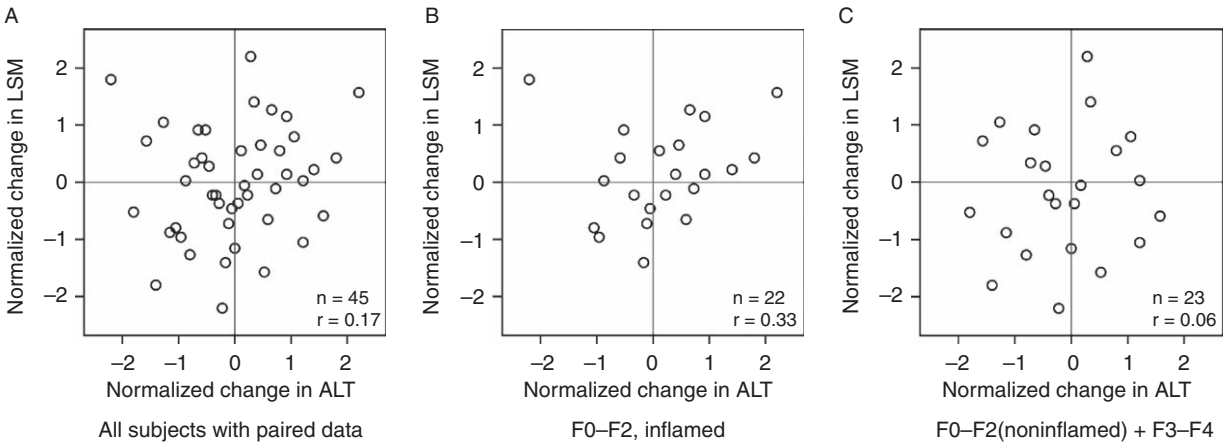

FIGURE 2. Change in ALT as a predictor of change in LSM (n = 45 with paired data). ALT and LSM were transformed to a standard normal distribution, with mean 0 and standard deviation 1. The association of ALT with LSM is shown (A) for all 45 subjects with paired data, (B) for a subset of 22 subjects with METAVIR F0–F2 and an inflammatory diagnosis (autoimmune hepatitis, viral hepatitis, primary sclerosing cholangitis, drug-induced hepatitis, chronic hepatitis of unknown etiology, or nonalcoholic steatohepatitis), and (C) for the remaining 5 subjects with METAVIR F0–F2 and a noninflammatory diagnosis +18 subjects with METAVIR F3–F4. The Spearman rank correlation coefficient (*r*) is reported. ALT = alanine aminotransferase; LSM = liver stiffness measurement.

In this pediatric study, a significant correlation between Ishak score and proportion of patients with LSM >8.6 kPa, after adjusting for histological assessment of inflammation, was not seen. Ishak is a validated system used to grade inflammation. The Ishak scoring system includes some factors of bridging fibrosis and focal necrosis. The inclusion of fibrosis assessments in the Ishak score could have made correlation to simple inflammation more problematic. Limiting Ishak scoring to inflammation-related criteria only may have demonstrated an effect that was not seen utilizing the full scoring system. Furthermore, histological assessment of liver biopsies is limited because of sampling error. Perhaps ALT may be a better correlate of overall inflammation than changes in a single biopsy sample.

We obtained repeat LSM and ALT after ≥6 months in 45 patients. In the 22 patients with METAVIR F0–F2 fibrosis and an inflammatory liver disease diagnosis (Fig. 2C), there was a weak correlation ($r = 0.33$) between ALT and LSM that increased to a moderate correlation ($r = 0.53$) after omission of a single outlier. The explanation of this outlier is puzzling. Because this 1 outlier had such a significant impact on our data, we reasoned that if statistical significance were achieved by 1 data point, this too would be subject to removal. With removal of the outlier, there is a clear linear correlation between the change in ALT and change in LSM in patients with METAVIR F0–F4 (Fig. 2D).

This study had several limitations. First, most of the liver biopsies were reviewed by 2 blinded pathologists. Because of the inability to retrieve all biopsy slides, METAVIR scores for a small portion (16%), however, were obtained from patient's medical record: either from the patient's clinically determined METAVIR score, or, if a METAVIR score was not reported, it was assigned by study investigators based on the clinical pathology report. By having METAVIR designation based on the nonblinded clinical liver biopsy assessment or study investigator–assigned METAVIR scores, variability and observer bias is introduced. This variability is further compounded by the known sampling variability inherent with liver biopsies. In addition, Ishak scores were not available for some patients, leading to smaller cohort size for this analysis and limiting statistical power.

Furthermore, the timing of data collection was not uniform across patients. Ideally, biopsy and TE with associated ALT results would be obtained simultaneously and consistently at set time points for each patient. This would allow for more accurate biochemical assessment of inflammation at the time of biopsy and TE, and may explain a weaker-than-expected correlation between change in LSM and change in ALT. Data collection, however, occurred when clinically indicated; therefore biochemical data could not always be obtained at the time of biopsy and TE. Last, paired LSM and ALT data were available in only 29% of the cohort, limiting statistical power and possibly introducing selection bias.

Although other studies in adults were done with specific liver disease etiologies, our cohort included a wide range of liver diseases. For these reasons, the results may not be applicable to each individual diagnosis in the cohort. Nonetheless, the findings are consistent with published data showing that in the setting of minimal fibrosis, there is a positive correlation between the presence of inflammation as determined by elevated ALT and TE measurements. Based on these findings, future studies could develop cutoff values to define severe fibrosis in the context of elevated ALT in children as have been developed in adults (24,27). This, in turn, would improve the accuracy of predicting the degree of fibrosis by TE in children.

In conclusion, this is the first study to investigate the potential influence of hepatic inflammation on the relation between LSM and fibrosis in children and young adults. With this new information, caution should be taken when interpreting TE values for assessing hepatic fibrosis in children and young adults in the setting of high ALT/inflammation.

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