

**ORIGINAL ARTICLE**

# The discriminatory ability of FibroScan liver stiffness measurement, controlled attenuation parameter, and FibroScan–aspartate aminotransferase to predict severity of liver disease in children

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**Abstract**

Vibration controlled transient elastography (FibroScan) is used to predict the severity of liver fibrosis and steatosis. In pediatrics, few studies have been performed directly comparing liver histologic features with FibroScan liver stiffness measurements (LSMs) and controlled attenuation parameters (CAPs). The FibroScan–aspartate aminotransferase (FAST) score, which predicts liver disease severity in adult nonalcoholic fatty liver disease (NAFLD), has not been analyzed in children. The aims of this study were to determine if LSM and CAP correlated with liver histologic fibrosis stage and steatosis grade, respectively, and to determine the predictive capacity of FAST in pediatric NAFLD. Research participants ( $n = 216$ ) included those with FibroScan within 90 days of a liver biopsy. The ability of LSM, CAP, and FAST to predict severity of liver disease was analyzed by Spearman correlation, linear regression, and receiver operating characteristic and C statistic. Significant correlations were identified between LSM and Ishak fibrosis stages, with the strongest correlation occurring in the non-NAFLD group (Spearman  $r = 0.47$ ,  $p < 0.0001$ ). LSM adequately predicted Ishak stages F0–2 versus F3–F6 (area under the receiver operating characteristic curve [AUROC], 0.73 for all; 0.77 for non-NAFLD). CAP strongly predicted histologic steatosis grade ( $r = 0.84$ ;  $p < 0.0001$ ; AUROC, 0.98). FAST had acceptable discriminatory ability for significant liver disease (AUROC, 0.75). A FAST cutoff  $\geq 0.67$  had a sensitivity of 89% but a specificity of only 62% at determining significant liver disease. This study encompasses one of the largest pediatric cohorts describing the accuracy of FibroScan LSM and CAP to predict liver histologic fibrosis stage and steatosis grade, respectively. In order to determine specific LSM, CAP, and FAST cut-off values for fibrosis stages, steatosis grades, and significant

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liver disease, respectively, a much larger cohort is necessary and will likely entail the need for multicentered studies.

## INTRODUCTION

Percutaneous liver biopsy followed by assessment of liver histology is the current gold standard for determining the stage of liver fibrosis.<sup>[1]</sup> Sampling errors related to liver biopsy include insufficient sample collection and the potential for overestimating or underestimating the degree of fibrosis.<sup>[2,3]</sup> Clinically significant complications related to liver biopsy include pain at the biopsy site, clinically relevant bleeding (0.3%), and mortality directly related to the procedure (0.04%–0.07%).<sup>[4]</sup> In pediatrics, both major complications (1.5%) and minor complications (25%) have been reported.<sup>[5]</sup> Therefore, noninvasive tools, such as vibration controlled transient elastography (VCTE), have been used to predict the severity of liver fibrosis. FibroScan is one such VCTE device that mechanically induces a shear wave that propagates through hepatic tissue and is recorded as a liver stiffness measurement (LSM) in kilopascals (kPa). The shear wave velocity is related to liver tissue stiffness—the firmer the tissue, the faster the shear wave propagates.<sup>[6]</sup> VCTE measures liver stiffness in a tissue volume that approximates 1 cm in diameter, 4 cm in length, and 15–75 mm in depth (a volume that is 100 times larger than a standard liver biopsy).<sup>[7,8]</sup>

There has been a great deal of research in adults with regard to the accuracy of VCTE-LSM in predicting the histologic liver fibrosis stage.<sup>[9,10]</sup> However, in pediatrics, very few studies have been performed comparing liver histology fibrosis stage with FibroScan LSM. Most studies have looked specifically at pediatric patients with nonalcoholic fatty liver disease (NAFLD),<sup>[11,12]</sup> with limited reporting of other pediatric liver diseases.<sup>[13]</sup> A recent systematic review evaluated various noninvasive methods for staging liver fibrosis in children with NAFLD and found that FibroScan LSM was the most accurate, with an area under the receiver operating characteristic curve (AUROC) between 0.92 and 1.00.<sup>[12]</sup> FibroScan can also approximate the degree of steatosis based on the controlled attenuation parameter (CAP). A new scoring system that uses aspartate aminotransferase (AST) and FibroScan CAP and LSM to predict liver disease severity in adults with NAFLD is the FibroScan-AST (FAST) score.<sup>[14]</sup> The FAST score provides an effective means to identify those adults at risk for significant NAFLD-related liver disease but has not yet been applied to the pediatric NAFLD population.

The aims of this study were 3-fold: (1) to determine if FibroScan LSM correlated with liver histology fibrosis stage or with another noninvasive serum biomarker of fibrosis, the AST-to-platelet ratio (APRI); (2) to determine if FibroScan CAP correlated with liver histology

steatosis grade; and (3) to determine if the FAST score could accurately predict significant liver disease in pediatric patients with NAFLD. With these assessments, we hope to identify LSM ranges that accurately predict liver fibrosis stages in children and that will have clinical applications for managing children with a variety of chronic liver diseases.

## MATERIALS AND METHODS

### Human subjects

This study was approved by the Colorado Multiple Institutional Review Board (#18–0868). Participants were enrolled in this study by either prospective or retrospective enrollment from April 2018 to May 2021. Prospective enrollment occurred in the procedure center of Children's Hospital Colorado (CHCO) at the time of a previously scheduled clinical liver biopsy (n = 68). Prospective participants were fasting for >4 hours before the FibroScan. Retrospective participants were identified from review of 1000 clinical FibroScans obtained as part of standard of care within the CHCO Pediatric Liver Clinic. Those patients who had received a liver biopsy within 90 days of the FibroScan were included in this study (n = 147). The fasting status of retrospective participants was not available. Inclusion criteria included ages 1–20 years, both sexes, all ethnicities, and, for the retrospective cohort, having had a FibroScan performed clinically within 90 days of liver biopsy. Exclusion criteria included patients with previous liver transplantation (n = 3), presence of ascites, or abdominal skin disease preventing ability to perform prospective FibroScan. FibroScan LSM measurements with an interquartile range (IQR)  $\geq 30\%$  were excluded from further analyses (n = 6). The final cohort for analysis included 206 participants (116 with NAFLD and 90 without NAFLD). Clinical data collected at the time of the FibroScan included age, ethnicity, sex, liver disease diagnosis, body mass index (BMI), serum albumin, total bilirubin, direct bilirubin, alanine aminotransferase, AST, gamma-glutamyltransferase, international normalized ratio, white blood cell count, platelet count, and APRI.

### FibroScan

LSM and CAP were obtained with the FibroScan 502 Touch (Echosens, Paris, France) and fitted with either the small probe (S1/S2), medium probe (M), or extra-large probe (XL), depending on participant's abdominal

circumference, according to the manufacturer's instructions. At least 10 valid measurements per participant were obtained, and mean LSM, CAP, and IQR were recorded. The FAST score uses LSM, CAP, and AST values and was calculated using the equation provided within the Echosens FAST application (Echosens.com) (Figure S1).

## Liver biopsy

Percutaneous liver biopsies were performed based on clinical standard of care. Specimens were formalin fixed, paraffin embedded, and stained with hematoxylin and eosin and trichrome. Histologic data collected included Ishak stage (0–6) and METAVIR score (0–4) for fibrosis, steatosis grade (0–3), and the NAFLD activity score (NAS). Incomplete histology interpretation on initial read was re-examined by a single pathologist (M.L.) blinded to other data collected within this study. All participants had Ishak scores, and a subset had previous METAVIR scores recorded by the pathologist. For those participants without a previous METAVIR score, the Ishak to METAVIR conversion was used in the Echosens FAST application (Echosens.com).

## Statistical analyses

A power analysis was performed based on published pediatric data on FibroScan<sup>[11,12]</sup> and the assumption that approximately 20% of patients would fall into the F3–F6 Ishak classification based on liver histology. A logistic regression F3–F6 Ishak stage versus score F0–F2 on a continuous, normally distributed, variable LSM with a sample size of 200 observations achieved 80% power at a 0.05 significance level to detect a difference between groups.

Descriptive statistics were reported using means and SDs for continuous variables and frequency and percentages for categorical variables, as appropriate. Medians and IQRs were reported for continuous variables that were not normally distributed. The Student *t* test or chi-square analysis was performed between groups.

To assess the relationship of Ishak stage with LSM, linear regression of Ishak stage on LSM and nonparametric Spearman correlation coefficient were performed. Spearman correlation coefficient cut-off values were interpreted as follows:  $r \leq 0.1$ , small correlation;  $r > 0.1 \leq 0.3$ , medium correlation;  $r > 0.3$ , large correlation. To examine the discriminating ability of LSM for Ishak stage, the Ishak variable was dichotomized in four ways and logistic regression analysis was applied to evaluate the ability of LSM to differentiate each of these four binary outcomes. Receiver operating characteristic (ROC) and C statistic (area under the ROC curve [AUROC]) were used to summarize discriminating ability. Interpretation of AUROC was as follows:

$< 0.5$ , no discrimination;  $0.5 < 0.7$ , poor discrimination;  $0.7 < 0.8$ , acceptable discrimination;  $0.8 - 0.9$ , excellent discrimination;  $> 0.9$ , outstanding discrimination. A similar methodology was used to assess the relationship of steatosis grade with the CAP score and the relationship of the FAST score with severity of liver disease. The Wilcoxon rank-sum test was used to determine if a FAST score  $\geq 0.67$  accurately predicted severe liver disease, defined as NAS  $\geq 4$  and METAVIR F  $\geq 2$ .

## RESULTS

### Characterization of participant cohort

A total of 206 research participants with a mean  $\pm$  SD age at the time of FibroScan of  $13.7 \pm 3.7$  years were analyzed in this study (Table 1). The average  $\pm$  SD time span between the FibroScan and liver biopsy was  $11 \pm 32$  days (range, 0–90). Based on previous data showing differences between NAFLD and other liver diseases with regard to FibroScan measurements, non-NAFLD and NAFLD groups were analyzed separately. The non-NAFLD group included 90 participants, and the NAFLD group had 116 participants. The non-NAFLD group encompassed a variety of liver diseases, listed as follows: autoimmune hepatitis ( $n = 33$ ), elevated liver blood tests/idiopathic chronic hepatitis ( $n = 14$ ), primary sclerosing cholangitis ( $n = 10$ ), cystic fibrosis ( $n = 5$ ), portal hypertension ( $n = 5$ ), Wilson disease ( $n = 3$ ), Alagille syndrome ( $n = 2$ ), hemochromatosis ( $n = 2$ ), and the following (each  $n = 1$ ): alpha-1 anti-trypsin deficiency, benign recurrent intrahepatic cholestasis, choledochal cyst, celiac disease, cholelithiasis, cryptogenic cirrhosis, Gardner syndrome, hemophagocytic lymphohistiocytosis, hepatitis B, hepatitis C, hepatocellular carcinoma, macrophage activation syndrome, pyridoxal phosphate responsive seizures, sickle cell disease, vascular malformation of the liver, and drug rash, eosinophilia, and systemic symptoms (the DRESS syndrome). The NAFLD group included participants with or without NASH. The NAFLD group was predominantly Hispanic individuals and had significantly higher mean BMI and CAP scores compared to the non-NAFLD group (Table 1). Interestingly, the non-NAFLD group had a significantly higher mean Ishak stage despite similar LSM means between groups. Both groups had low levels of LSM IQRs  $\geq 30\%$ , reflecting excellent quality control of the FibroScan measurements (Table 1).

### Accuracy of LSM in predicting Ishak stage

Spearman correlation and linear regression models were used to determine the accuracy of LSM in predicting the Ishak stage of fibrosis (Figure 1; Table 2; LSM and

**TABLE 1** Participant demographics

Descriptor	All participants (n = 206)	Non-NAFLD (n = 90)	NAFLD (n = 116)	p value (non-NAFLD vs. NAFLD)
Age (years)	13.7±3.7	12.9±4.1	14.2±3.2	NS
Sex	61% male	60% male	72%	NS
Race				
Caucasian	32%	54%	12%	NS
Hispanic	53%	26%	78%	*p < 0.00001
Other	15%	13%	10%	NS
BMI	28±8	21±6	33±6	*p < 0.0001
AST (IU/L)	132±152	142±196	117±93	NS
APRI	1.4±2.7	1.8±3.6	1.1±1.3	NS
Histology				
Ishak stage	1.3±1.4	1.6±1.5	1.1±1.2	*p = 0.007
NAS score	N/A	N/A	3.5±1.3	
FibroScan				
LSM (kPa)	7.6±5.6	7.9±5.5	7.3±2.9	NS
CAP	287±72	230±67	327±42	*p < 0.0001
IQR	14±6	14±6	14±7	NS
% IQR >30%	2.7%	2.9%	2.5%	NS

Note: Data show mean ± SD or percentage.

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; IQR, interquartile range; LSM, liver stiffness measurement; N/A, not applicable; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NS, not significant.

\*p ≤ 0.05.

METAVIR stage analyses are provided in Figure S2). Spearman correlation coefficient revealed that both non-NAFLD and NAFLD groups showed significant correlations between LSM and Ishak stage; however, the strongest correlation occurred in the non-NAFLD group (Figure 1A). The NAFLD group did not have any participants with Ishak stages 5 or 6. Similarly, linear regression analyses revealed that LSM in the non-NAFLD group had the highest level of correlation with Ishak stage (Figure 1B). For every 1-point increase in Ishak stage, the LSM increased by 18.5% in the non-NAFLD group and only 10.2% in the NAFLD group. Spearman correlation coefficient analyses revealed that both non-NAFLD and NAFLD groups showed significant correlations between LSM and APRI; however, the strongest correlation again occurred in the non-NAFLD group (Figure 1C).

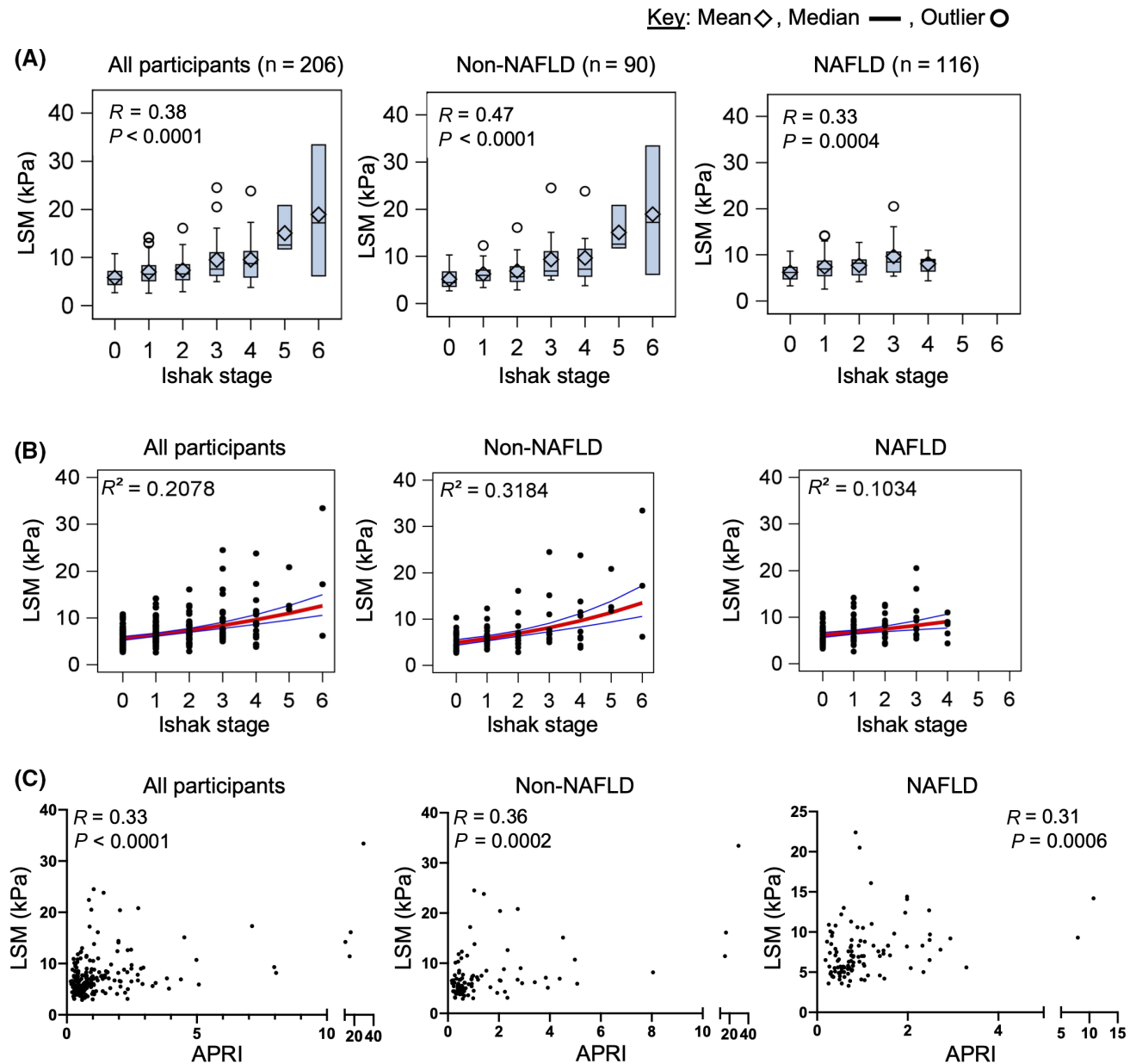
### Discriminating ability of LSM to predict Ishak stage

To examine the discriminating ability of LSM to predict Ishak stage(s), the Ishak variable was dichotomized in four ways: F0 versus F1–F6; F0–F1 versus F2–F6; F0–F2 versus F3–F6; and F0–F3 versus F4–F6 (Figure S3; Figure 2). Logistic regression analysis was conducted to evaluate the ability of LSM to differentiate each of these four binary outcomes. AUROC was

used to summarize discriminating ability. The ability of LSM to predict Ishak stage was strongest when comparing F0–F2 versus F3–F6, with an AUROC of 0.73 for all participants, reflecting adequate discrimination (Figure 2). LSM from the non-NAFLD group displayed the strongest discriminatory ability, with an AUROC of 0.77 (compared to the NAFLD group AUROC of 0.7).

### FibroScan CAP score is highly predictive of histologic steatosis grade

We next examined the accuracy of the CAP score to predict the severity of steatosis based on histologic grading of steatosis. There was a strong positive correlation between the CAP score and the histologic steatosis grade (Figure 3A; Table 3). As expected, the majority of the NAFLD group (blue symbols) had steatosis grades 1–3, while the majority of the non-NAFLD group (black symbols) had grade 0 steatosis. ROC analysis revealed that CAP had outstanding discriminatory ability to differentiate steatosis grades 1–3 from grade 0 (AUROC, 0.98) (Figure 3B). The Youden's J index was used to determine a CAP score cutoff for diagnosing steatosis grades 1–3. A CAP score ≥259 dB/m predicted steatosis grades 1–3, with a sensitivity of 94%, a specificity of 91%, a positive predictive value of 97% and a negative predictive



**FIGURE 1** Correlation of LSM with Ishak stage and APRI. (A) Spearman correlation of Ishak stage and LSM. Box and whisker plots (median  $\pm$  interquartile ranges). (B) Linear regression of Ishak stage and LSM. Regression line is shown in red; 95% confidence intervals are shown in blue. (C) Spearman correlation of APRI and LSM. APRI, aspartate aminotransferase-to-platelet ratio; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease

value of 91%. Finally, in addition to analyzing the ability of the CAP score to identify histologic steatosis, we also investigated if CAP correlated with the BMI. A strong positive correlation ( $p < 0.0001$ ) was identified between the BMI and CAP score (Figure 3C).

### FAST score is not specific for predicting significant liver disease in pediatric NAFLD

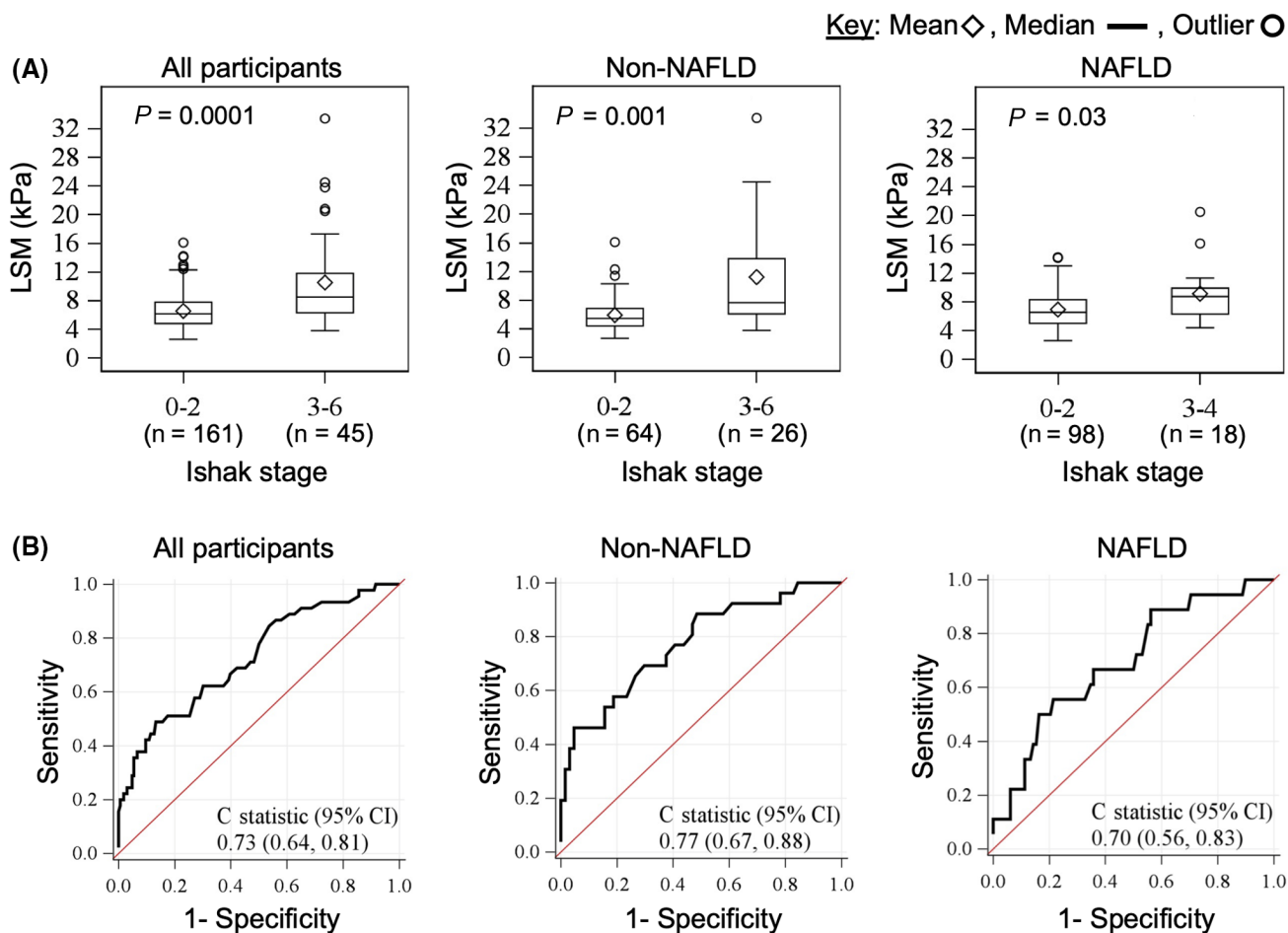
The FAST score incorporates LSM, CAP, and AST values to predict liver disease severity in adult NAFLD<sup>[14]</sup>

but has not yet been analyzed in pediatric NAFLD. In the adult study, significant liver disease was defined as having histologic NASH + NAS $\geq 4$  + METAVIR F $\geq 2$  (correlating with Ishak F $\geq 3$ ). FAST scores  $\geq 0.67$  predicted significant liver disease. FAST scores were calculated in our pediatric NAFLD cohort, and correlations of FAST score with biochemical, FibroScan, and histologic parameters were performed. As expected, based on the constituents within the FAST equation, the FAST score significantly correlated with LSM, CAP, and AST, with the strongest correlation between FAST and LSM (Figure 4A). The FAST score also correlated with the histologic NAS score but did not correlate with the

**TABLE 2** FibroScan LSM per Ishak stage

All participants-LSM (kPa) (n = 206)					Non-NAFLD-LSM (kPa) (n = 90)					NAFLD-LSM (kPa) (n = 116)				
Ishak	n	Mean	SD	Range	Ishak	n	Mean	SD	Range	Ishak	n	Mean	SD	Range
0	72	5.8	1.9	2.7–10.8	0	28	5.2	1.9	2.7–10.3	0	45	6.2	1.8	3.3–10.8
1	60	7.0	2.6	2.6–14.2	1	24	6.3	2.1	3.4–12.3	1	36	7.4	2.8	2.6–14.2
2	29	7.4	3.0	2.9–16.1	2	12	6.9	3.7	2.9–16.1	2	17	7.7	2.6	4.2–12.7
3	23	9.5	5.1	5.0–24.5	3	11	9.4	5.8	5.0–24.5	3	12	9.7	4.5	5.4–20.5
4	16	9.5	5.3	3.8–23.8	4	9	9.7	6.3	3.8–23.8	4	6	8.1	2.3	4.4–11.0
5	3	15.1	5.0	11.8–20.8	5	3	15.1	5.0	11.8–20.8	5	--	--	--	--
6	3	18.9	13.7	6.2–33.4	6	3	18.9	13.7	6.2–33.4	6	--	--	--	--

Abbreviations: LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease.

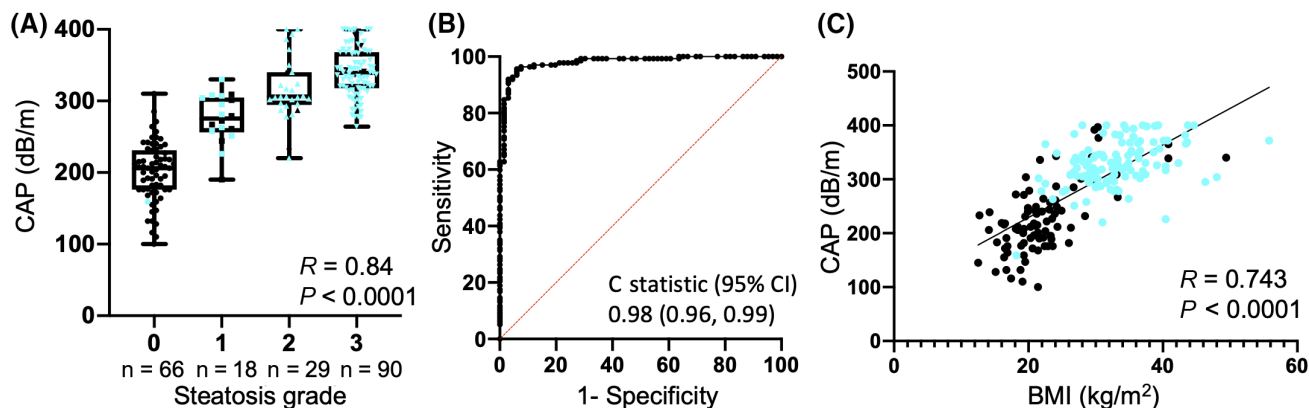


**FIGURE 2** LSM discriminates low from high Ishak stages. (A) Average LSM of low (F0–F2) versus high (F3–F6) Ishak stages (Student *t* test). Box and whisker plots (median  $\pm$  interquartile ranges). (B) Receiver operating characteristic of LSM ability to differentiate low versus high Ishak stages (C statistic with 95% confidence intervals). CI, confidence interval; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease

Ishak stage. The FAST score had moderate correlation with APRI, likely based on the previously determined correlation with AST alone (Figure 4A).

The NAFLD cohort was also characterized based on the adult FAST score cut-off value  $\geq 0.67$  reflecting significant liver disease. In our pediatric NAFLD group, 40% had a calculated FAST score  $\geq 0.67$ .

Comparison of biochemical, FibroScan, and histologic parameters was performed between those with FAST scores  $\geq 0.67$  compared to  $< 0.67$ . Those with FAST scores  $\geq 0.67$  had significantly higher values for LSM, AST, NAS score, and APRI; however, there were no differences between groups in the CAP score or Ishak stage (Figure 2B). Despite the



**FIGURE 3** CAP score is highly predictive of steatosis grade. Black symbols indicate non-NAFLD group; blue symbols indicate NAFLD group. (A) Spearman correlation of steatosis grade and CAP (dB/m). Box and whisker plots (median  $\pm$  interquartile ranges). (B) Receiver operating characteristic and C statistic of discriminatory ability of CAP to predict histologic steatosis grade. (C) Spearman correlation of BMI ( $\text{kg}/\text{m}^2$ ) and CAP (dB/m). CI, confidence interval; BMI, body mass index; CAP, controlled attenuation parameter; NAFLD, nonalcoholic fatty liver disease

**TABLE 3** FibroScan CAP (dB/m) per steatosis grade

CAP	n	Mean	SD	Range
0	66	201	42	100–310
1	18	275	34	190–330
2	29	316	43	220–400
3	90	341	34	264–400

Abbreviation: CAP, controlled attenuation parameter.

positive correlation of FAST and LSM identified in all participants as well as the significantly higher LSM in those with FAST scores  $\geq 0.67$ , FAST scores did not correlate with Ishak fibrosis stages.

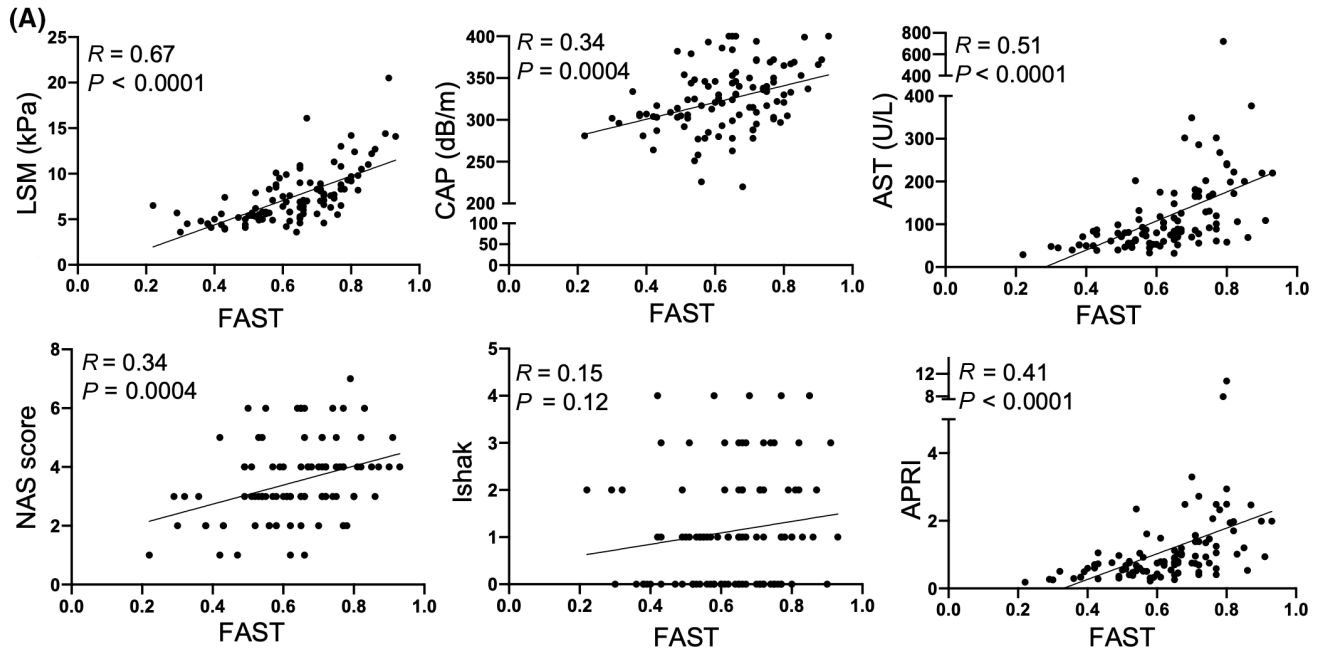
Although 40% of NAFLD participants had a FAST score  $\geq 0.67$ , only 9% met criteria for significant liver disease (NASH + NAS  $\geq 4$  + Ishak F  $\geq 3$  [METAVIR F  $\geq 2$ ]). Comparison of FAST scores between participants with significant liver disease ( $n = 9$ ; FAST mean  $\pm$  SD,  $0.7 \pm 0.1$ ; median, 0.8; range, 0.4–0.9) versus those without significant liver disease ( $n = 86$ ; FAST mean  $\pm$  SD,  $0.6 \pm 0.1$ ; median, 0.7; range, 0.2–0.9) revealed higher FAST scores in those with significant liver disease ( $p = 0.017$ ; Figure 4C). ROC analysis revealed that the FAST score had acceptable discriminatory ability for significant liver disease (AUROC, 0.75). A FAST score cutoff  $\geq 0.67$  had a sensitivity of 89% but a specificity of only 62% at determining significant liver disease (Figure 4C).

## DISCUSSION

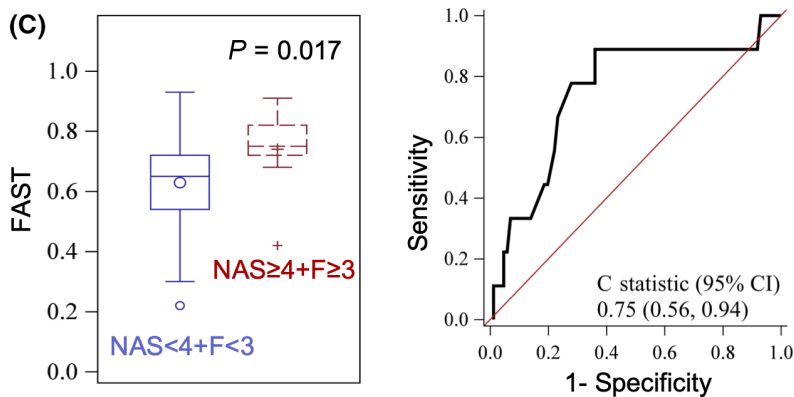
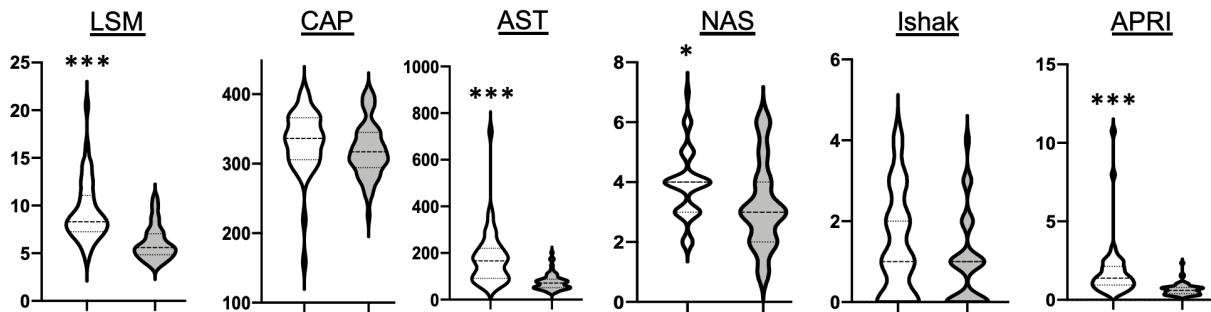
This study encompasses one of the largest pediatric cohorts analyzing FibroScan LSM correlations with liver fibrosis stage. We found that FibroScan LSM significantly correlated with Ishak stages and that LSM adequately discriminated between low and high Ishak stages. These

findings are comparable to a recent study that assessed FibroScan LSM and histologic fibrosis stages in a cohort of 80 pediatric patients.<sup>[16]</sup> Importantly in our study, the strongest correlations and predictive ability were found in the non-NAFLD group. This finding may be due in part to the limitations of the NAFLD cohort as no participants with NAFLD in our study had severe histologic fibrosis (Ishak 5–6; METAVIR F4), which may have impacted our ability to discriminate between low- and high-fibrosis stages. Furthermore, there is a theoretical possibility that the LSM accuracy was altered in the setting of obesity with central adiposity or in the steatotic infiltrative nature of the liver parenchyma. Another limitation is that our cohort included a comparison of liver histologic fibrosis and LSM over a 0–90-day time frame. It is possible that a longer time frame between liver biopsy and FibroScan results in a less accurate correlation of LSM and Ishak stage. In order to determine LSM cut-off values for each stage of fibrosis, a much larger cohort may be necessary and will likely entail the need for multicentered studies.<sup>[17,18]</sup>

FibroScan CAP scores strongly correlated with steatosis grade, and CAP had an outstanding ability to discriminate no steatosis from steatosis grades 1–3. The accuracy of CAP to predict severity of steatosis has been previously described in a large adult cohort within the NASH Clinical Research Network (NASH-CRN).<sup>[19]</sup> Interestingly, in the NASH-CRN study, the average CAP scores were approximately 20–70 dB/m higher for individual steatosis grades 0–2 compared to our cohort, with similar CAP scores for steatosis grade 3. Indeed, the median CAP score in adults with steatosis grade 0 (S0) was 274 dB/m compared to our study median of 206 dB/m. In addition, a published pediatric study reported a similar average CAP score to our study, with a median CAP of 198 dB/m for S0.<sup>[20]</sup> Despite the discrepancies between the adult and pediatric studies, the NASH-CRN study CAP cut-off value of 263 dB/m that differentiated no steatosis



(B) Key:  $\diamond$  FAST  $\geq 0.67$   $\blacklozenge$  FAST  $< 0.67$



**FIGURE 4** FAST scores in pediatric NAFLD. (A) Spearman correlation of FAST scores with biochemical, FibroScan, and histologic parameters for all participants with NAFLD. (B) Volcano plots. Dashed lines indicate mean; dotted lines indicate interquartile range. Comparison of biochemical, FibroScan, and histologic parameters between participants with NAFLD with FAST scores  $\geq 0.67$  versus those with scores  $< 0.67$  (unpaired Student *t* test, \* $p < 0.05$ , \*\*\* $p < 0.0001$ ). (C) Comparison of FAST scores in participants with NAFLD with significant liver disease (NAS  $\geq 4$  and Ishak  $\geq 3$  in red) versus those without significant liver disease (NAS  $< 4$  and Ishak  $< 3$  in blue). Wilcoxon rank-sum test, box and whisker plots (median  $\pm$  interquartile ranges); ability of the receiver operating characteristic of the FAST score to determine significant liver disease (C statistic with 95% CIs). APRI, aspartate aminotransferase-to-platelet ratio; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; CI, confidence interval; FAST, FibroScan–aspartate aminotransferase; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score



from any steatosis was similar to our calculated CAP cutoff of 259 dB/m in children. Furthermore, our finding in children of a strong correlation of CAP scores with BMI was also identified in the NASH CRN adult study ( $\beta$ -coefficient, 2.8 dB/m/kg/m<sup>2</sup>).

Finally, the FAST score had only moderate predictive value in children with NAFLD, and the adult FAST cut-off value  $\geq 0.67$  was sensitive but not specific for significant liver disease in children. Furthermore, the FAST cut-off value  $\geq 0.67$  was not associated with higher Ishak stages compared to those with FAST  $< 0.67$ . In contrast, the FAST score positively correlated with the NAS score, and participants with FAST scores  $\geq 0.67$  had significantly higher NAS scores. This suggests that the FAST score in children is likely a reflection of the higher degree of inflammation<sup>[21]</sup> and not the stage of fibrosis compared to adults. As mentioned earlier, the limitation of few patients with NAFLD with severe fibrosis in our study would also likely impact the findings related to the FAST score. To decisively determine the utility of the FAST score in children, a larger cohort of participants would be necessary in order to create a new cutoff that accurately reflects significant liver disease.

### CONFLICT OF INTEREST

The authors have no conflicts of interest with the information provided in this manuscript and specifically no conflicts of interests pertaining to Echosens, the company manufacturing FibroScan.

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### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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