Validation of Transient Elastography Cut Points to Assess Advanced Liver Fibrosis in Children and Young Adults: The Boston Children's Hospital Experience

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Objective To derive an optimal liver stiffness measurement cut point to discriminate METAVIR fibrosis stage F4 and to validate both METAVIR fibrosis stage F3-F4 and F4 cut points in a separate cohort.

Study Design Patients at Boston Children's Hospital with liver stiffness measurement from 2006 to 2016 and liver biopsy ≤12 months before screening were eligible. Patients enrolled 2006-2011 were used to calibrate liver stiffness measurement cut points and those enrolled 2011-2016 for validation. Diagnostic performance was assessed by receiver operating curve analysis.

Results In total, 267 subjects were enrolled (97 calibration, 170 validation). The cohorts were similar with 54% male, aged 0-29 years (median 13 years), and liver diseases including 21% autoimmune, 19% viral, 11% nonalcoholic fatty liver, 9% cholestatic, and 9% primary sclerosing cholangitis. Cut points to discriminate F3-F4 and F4 were >8.6 kPa and >11.5 kPa with 81% and 84% accuracy, respectively. Applied to the validation cohort, accuracy was 67% and 75%, respectively. In 44 fasted subjects, the accuracy was 73% and 80%, respectively.

Conclusion This study validates previously determined liver stiffness measurement cut points of 8.6 kPa and 11.5 kPa to predict METAVIR F3-F4 and F4 fibrosis in children and young adults in separate cohorts. With increasing data on the utility and validity of liver stiffness measurement in children, transient elastography may help identify patients with greater risk of advanced fibrosis and those who need liver biopsy assessment and/or surveillance for the complications of cirrhosis in a variety of liver disorders. *(J Pediatr 2018;198:84-9).*

Liver fibrosis is associated with complications, morbidity, and mortality in chronic liver disease. Histopathologic assessment of fibrosis on liver biopsy remains the reference standard for determining the severity of fibrosis yet is associated with complications and sampling error.[1-4] Moreover, children are exposed to additional risks with liver biopsy as the result of the need for anesthesia or sedation and possibly postprocedure hospitalizations. Transient elastography is an ultrasound-based tool that has been shown to rapidly and reproducibly measure liver stiffness, which reflects hepatic fibrosis.[5,6] Multiple studies have shown that liver stiffness measurement by transient elastography can predict hepatic fibrosis in children with various chronic liver diseases.[7-10] Each study has reported slightly different liver stiffness measurement cut points to identify advanced fibrosis. These studies involved smaller sample sizes, use of limited patient populations, and mainly used the adult, medium-sized probe only. We reported an optimal liver stiffness measurement cut point >8.6 kPa to detect METAVIR fibrosis stage F3-F4 with a high area under the receiver operator characteristic curve (AUROC = 0.84).[7] Although cut points have been validated in adult populations, these cut points have not been validated in pediatric populations with liver disease.[11]

The aim of the present study was to validate our previously reported liver stiffness measurement cut point to detect advanced liver fibrosis (F3-F4) in children and young adults. In addition, we aimed to identify and validate an additional liver stiffness measurement cut point to detect cirrhosis (F4) in children and young adults. Although there are many published reports that have used transient elastography in children, most do not include the reference standard assessment for comparison.

Methods

This was a prospective 2-phase study of unselected children and young adults at Boston Children's Hospital who underwent liver stiffness measurements over a 10-year period from 2006 to 2016. All patients were required to have had a liver biopsy within 12 months of enrollment and been available to a study investigator for recruitment. Patients who had an uninterpretable or unavailable biopsy

AUROC	Area under the receiver operator characteristic curve
S	Small
TP	Thoracic perimeter

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Echosens provided the transient elastography machine and did not have a role in (1) study design; (2) collection, analysis, or interpretation of data; (3) writing of the manuscript; or (4) the decision to submit the paper for publication. The authors declare no conflicts of interest.

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specimen, who lacked critical clinical and/or biochemical data, or who were not candidates for transient elastography because of a technically invalid measurement, ascites, morbid obesity (body mass index >40 kg/m^2), pregnancy, or implantable cardiac device were excluded according to the manufacturer's guidelines. Patients who had undergone Fontan surgery also were excluded, given the known high degree of hepatic stiffness in these patients.[12,13] The calibration cohort included patients enrolled from August 2006 to April 2011 who were used to develop liver stiffness measurement cut points for discriminating F3-F4 and F4 fibrosis. Patients enrolled from April 2011 to March 2016 comprised the validation group and were used to test the diagnostic accuracy of these cut points. This study was approved by the Boston Children's Hospital 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 METAVIR system was used to stage fibrosis by 5 hepatopathologists blinded to liver stiffness measurement. Scoring to stage liver fibrosis was as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Scores of F3 or F4 were considered advanced fibrosis.

Liver Stiffness Measurements

Liver stiffness was measured by transient elastography (FibroScan, Echosens, Paris, France), an ultrasound-based technique that involves placing an ultrasonic transducer in a right intercostal space to transmit a vibration of mild amplitude and low frequency. The vibration on the skin surface creates a shear wave that propagates through the right lobe of the liver. The velocity of propagation is related directly to tissue stiffness; the harder the tissue (as in hepatic fibrosis), the faster the shear wave propagates. Eight to ten valid liver stiffness measurements were obtained and reported as a median value in kilopascals. Adequacy of measurement was assessed by the transient elastography device. Liver stiffness measurement was performed by 6 trained study investigators who were certified by the manufacturer and blinded to the liver biopsy results. Transient elastography probe size selection was based on thoracic perimeter (TP); the medium probe was used if TP was >75 cm and the small (S) if TP ≤75 cm. Before November 2009, when the S probe became available, no patients weighing <50 pounds were included.

Statistical Analyses

Patient characteristics and primary diagnostic indications for liver biopsy are presented as n (%) if categorical and either mean ± SD or median with IQR if continuous. Comparison for these characteristics between the calibration and validation cohorts was made by Pearson χ^2 test or Student *t* test, or by their nonparametric analogs, the Fisher exact test and Wilcoxon rank-sum test.

Box-whisker plots were used to illustrate the distribution of liver stiffness measurement across the 5 METAVIR stages, and comparisons between the calibration and validation cohorts were made by the Student *t* test. Differences in liver stiffness measurement within each METAVIR stage were investigated with 2-way ANOVA using an interaction term for cohort and METAVIR. Although liver stiffness measurement was right-skewed, results from nonparametric analysis and analysis of liver stiffness measurement after transforming to normal scores were consistent with the parametric results, and only the latter are reported.[14]

The calibration cohort was used to construct receiver operating characteristic curves to evaluate the ability of transient elastography to discriminate METAVIR stages F3-F4 from stages F0-F2 and F4 from stages F0-F3. The AUROC is reported with a 95% CI to compare the curve with the diagonal (AUROC = 0.5, indicating predictive ability no better than a coin flip). An optimal cut point was determined by minimizing the probability of a false-positive transient elastography result and maximizing the probability of a true-positive transient elastography result. These cut points were then used to construct 2 × 2 contingency tables comparing the disease status (presence/absence based on METAVIR dichotomy) to the transient elastography result (positive/negative based on cut point dichotomy). Diagnostic performance of transient elastography was assessed by sensitivity, specificity, accuracy, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio and shown with 95% CI.[15,16] Validation was assessed for the entire validation cohort as well as for a subgroup of subjects who fasted before transient elastography. Diagnostic performance characteristics were compared by the Fisher exact test.

All data analysis was performed and figures prepared with SAS, version 9.4 (SAS Institute, Cary, North Carolina). All tests of significance were 2-sided, with $P < .05$ indicating statistical significance.

Results

A total of 321 subjects were screened from 2006 to 2016, of whom 54 (17%) were excluded due to inability to obtain a valid liver biopsy or liver stiffness measurement, resulting in a sample of 267 subjects available for analysis (**Figure 1**; available at www.jpeds.com). The calibration cohort used to determine optimal cut points for discriminating F3-F4 and F4 fibrosis consisted of 97 subjects[7]; the cut points were validated by using a cohort of 170 subjects.

Demographic characteristics of the study population and primary diagnostic indications for liver biopsy are shown in **Table I**. In total, 230 subjects (86%) were <18 years of age. Subjects in the validation cohort were less likely to be of white race (59% vs 72%; $P = .03$) and to have had a liver transplant (1% vs 5%; $P = .03$) than those in the calibration cohort. The distribution of characteristics was otherwise statistically similar across the 2 cohorts. All METAVIR stages were well represented. Approximately one-third of subjects had advanced fibrosis (stage F3-F4), 35% in the calibration cohort and 28% in the validation cohort ($P = .25$).