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Role of Transient Elastography (Fibroscan) in Diagnosis and Staging of Liver Fibrosis in Chronic Liver Diseases among Paediatrics

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Abstract

Background: Transient elastography (TE) is a reliable tool for the non-invasive assessment of liver fibrosis in routine clinical practice. The widespread adoption of this technology is certain to increase the use of TE worldwide. Although TE has been well validated in chronic viral hepatitis, its clinical role in other liver diseases remains less clear.

Aim of Study: To assess the role of transient elastography (fibroscan) in diagnosis and staging of liver fibrosis in chronic liver diseases among paediatrics in comparison to liver biopsy,

Subjects and Methods: This is cross sectional study, was carried out on Children with chronic liver disease undergoing biopsy in Ain Shams University Hospitals during a period of 6 months.

Result: Fibroscan and biopsy showed high substantial agreement regarding fibrosis stage (fibrosis or no fibrosis) with kappa (x) 0.667.

Conclusion: Noninvasive methods, such as transient elastography and fibrosis marker scores, seem to be useful tools to assess liver fibrosis in these patients and may be helpful to recognize a progression of the liver disease during routine follow-up. TE is a portable, highly accessible, reliable, and reproducible noninvasive modality that can be used to screen for liver disease and assess severity of fibrosis in children with CF.

Key Words: *Transient elastography – Non- invasive – Fibrosis – Chronic.*

Introduction

LIVER fibrosis is the common end-point of a variety of chronic liver diseases. The progression of liver fibrosis leads to cirrhosis, decompensation, liver failure, hepatocellular carcinoma (HCC) and death [1].

Accurate diagnosis of liver fibrosis and cirrhosis is essential for prognostication of liver disease and for timely intervention to prevent negative outcome [2].

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Histopathologic assessment of fibrosis on liver biopsy remains the reference standard for determining the severity of fibrosis, yet is associated with complications [3]. Children are exposed to additional risk with liver biopsy due to need for anesthesia or sedation and possibly post-procedure hospitalizations [4].

Limitations for liver biopsy include invasive nature, complications, low level of individual's satisfaction and sampling variation. Pain and hypotension are major complications of liver biopsy and can lead to increased length of hospital stay and cost. Therefore performing continuous liver biopsy for follow-up is practically impossible [5].

The ideal non-invasive technique should be valid, painless, reproducible, easy-to-learn, easy-to-perform and cheap [6]. Non-invasive markers of fibrosis include serum markers which assess the biochemical properties of fibrosis and elastography devices which assess the physical stiffness of the fibrotic liver [7].

Transient elastography (TE), also known as Fibroscan, is a well-validated method with advantages of a short procedure time (<5min), immediate results, and the ability to perform the test at the bedside or in an outpatient clinic [8].

Transient elastography (TE) measured by Fibroscan was the first of such elastography devices, followed by magnetic resonance elastography (MRE), acoustic radiation force impulse (ARFI) and shear wave elastography (SWE). In current clinical practice, TE is the most widely used elastography device for non-invasive assessment of liver fibrosis [9].

The study aimed to assess the role of transient elastography (fibroscan) in diagnosis and staging of liver fibrosis in chronic liver diseases among paediatrics in comparison to liver biopsy.

Material and Methods

Patients: A total of 30 Egyptian patients with mean ± SD age of 12.57±3.47 (range: 6-18) years, with the diagnosis of chronic liver disease undergoing biopsy from April 2021 till October 2021.

Exclusion criteria: Children who are too small for TE using the M probe (chest circumference <70cm), children with ascites and children with known extrahepatic fibrogenic disease.

Approval and consent:

This study was performed in the Ain Shams University Hospitals, Cairo, Egypt between April 2021 and October 2021. The study was approved by Ethical Committee of Ain Shams Faculty of Medicine. An informed verbal consent from parents of all participants was taken and confidentiality of information was assured.

Methods:

Clinical assessment: History: Complete history taking from parents: In history taking, age, sex, residency, presenting complaint, jaundice, itching, abdominal pain, presence of comorbidities, History of previous gastrointestinal bleeding, upper GI endoscopy and therapeutic procedures done and clinical examination:

Body mass index measuring: BMI and categorization According to the NHLBI, 1998 BMI is calculated as weight in kilograms divided by the square of the height in meters (kg/m^2) and is categorized into four groups according to the Asian-Pacific cutoff points: 25 underweight ($18.5kg/m^2$), normal weight ($18.5\text{-}22.9kg/m^2$), overweight ($23\text{-}24.9kg/m^2$), and obese ($\$25kg/m^2$). For comparison, BMI was also categorized into four groups according to the conventional WHO classification: 10 underweight ($18.5kg/m^2$), normal weight ($18.5\text{-}24.9kg/m^2$), overweight ($25\text{-}29.9kg/m^2$), and obese ($\$30kg/m^2$).

Laboratory assessment: (Routine and general evaluation tests): Complete blood count (CBC): Hemoglobin (HB)% (g/dl), white blood cells (WBCS) (c/mm), platelet count (cmm). Kidney functions: Blood urea (mg/dl), Serum creatinine (mg/dl), liver profile including: Alanine amino transferase (ALT) (Iu/l), aspartate amino transferase (AST) (Iu/l), serum albumin (g/dl), total and direct serum bilirubin(mg/dl) and prothrombin time (P.T) and I.N.R.

Imaging: Ultrasonographic Examination: Abdominal sonography was performed by a radiologist of at least 3 years' experience after patient underwent overnight fast. The ultrasonographic (US) fatty score included parenchymal echogenicity, far gain attenuation, gallbladder wall blurring, portal vein wall blurring, and hepatic vein blurring. Moreover, the US fibrosis score included liver surface, parenchyma, vascular structure, and splenic size.

Transient elastography (fibroscan): A single operator of at least 3 years' experience unaware of fibrosis stage and blood biomarker results performed TE. TE was measured with the standard M probe using the right lobe of the liver. 11 valid readings were taken in each case aiming for an interquartile range (IQR) of <30% with at least 60% success rate. with the results expressed in kilopascals (kPa).

Controlled attenuation parameter measurement: Controlled Attenuation Parameter (CAP) is a new ultrasound-based technique for measuring fat content in the liver independently from the presence of fibrosis. It measures the attenuation of ultrasound waves and compares it with the attenuation in normal liver. CAP was measured using Fibroscan probes, grading steatosis according to the level of CAP into 3 grades as absent (S0), mild (S 1), moderate (S2) and severe (S3).

Liver biopsy: Liver biopsy was undertaken by an interventional radiologist via the percutaneous route. The biopsies were scored for fibrosis by a single hepato-histopathologist blinded to the results of the biomakers. This was done using either the METAVIR or the Kleiner scoring systems according to the diagnosis of the child. Inflammation is scored as none, mild, moderate, and severe. Degrees of steatosis will be also recorded.

Main outcome measures: Calculation of sensitivity, specificity, PVP, PVN and accuracy.

Statistical analysis: Analysis of data was done using Statistical Program for Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation. Qualitative variables were described as number and percent. In order to compare parametric quantitative variables between two groups, Student *t*-test was performed. Qualitative variables were compared using chi-square (X^2) test or Fisher's exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, A p-value <0.05 is considered significant.

Results

A total of 30 patients were included in this study. Their mean ± SD age were 12.57±3.47 with range (6-18) and according to sex there were 15 (50.0%) female and 15 (50.0%) male. Characteristics of patients are listed in Table (1).

Table (1)

Demographic data	Cases (n=30)	
Age (Years):	6.0-18.0	
Min. - Max.	12.57±3.47	
Mean ± SD.		
Sex:	No.	%
Female	15	50.0
Male	15	50.0

According to final diagnosis among the studied cases there were 14 (46.7%) with metabolic diseases, 4 (13.3%) with AILD, 5 (16.7%) with viral hepatitis, 1 (3.3%) with Wilson disease, and 6 (20%) with other diseases. Table (2), Fig. (1).

Table (2): Final diagnosis of the study population.

Final diagnosis	Cases	
	No.	%
Metabolic disease	14	46.7
AILD	4	13.3
Viral hepatitis	5	16.7
Wilson disease	1	3.3
Others	6	20.0

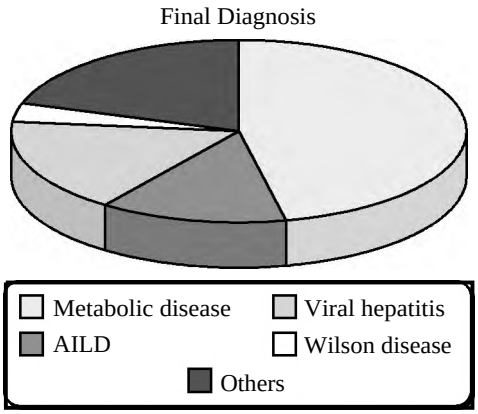

Fig. (1): Final diagnosis of studied cases.

Table (3): Roc curve analysis for the use of Fibroscan to predict fibrosis same as biopsy.

	AUC	Sens %	Spec %	PPV %	NPV %	Accuracy %
Fibroscan	0.842	80.0	86.7	85.7	81.3	83.3

Using fibroscan it was shown that at F2, it can predict fibrosis same as biopsy with AUC of 0.843, level of sensitivity 80%, specificity 86.7%, PPV 85.7%, NPV 81.3% and accuracy 83.3%. Table (3), Fig. (2).

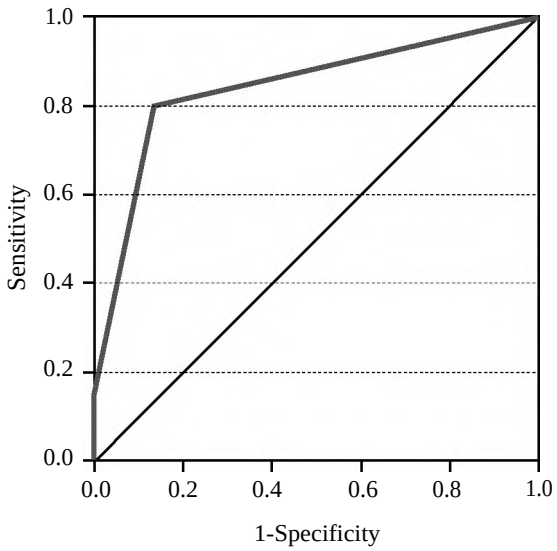

Fig. (2): Roc curve analysis for the use of Fibroscan to predict fibrosis same as biopsy.

Fibroscan and biopsy showed high substantial agreement regarding fibrosis stage (fibrosis or no fibrosis) with kappa (κ) 0.667. Table (4).

Table (4): Agreement between fibroscan and biopsy regarding fibrosis stage as fibrosis or no fibrosis.

Fibroscan	Biopsy				Kappa (κ)
	Fibrosis		No fibrosis		
	No.	%	No.	%	
Fibrosis	12	40.0	2	6.7	0.667
No fibrosis	3	10.0	13	43.3	

The individual values of 10 measurements are shown as well the median of the 10 measurements and two quality parameters, the interquartile range and the interquartile range divided by the median.

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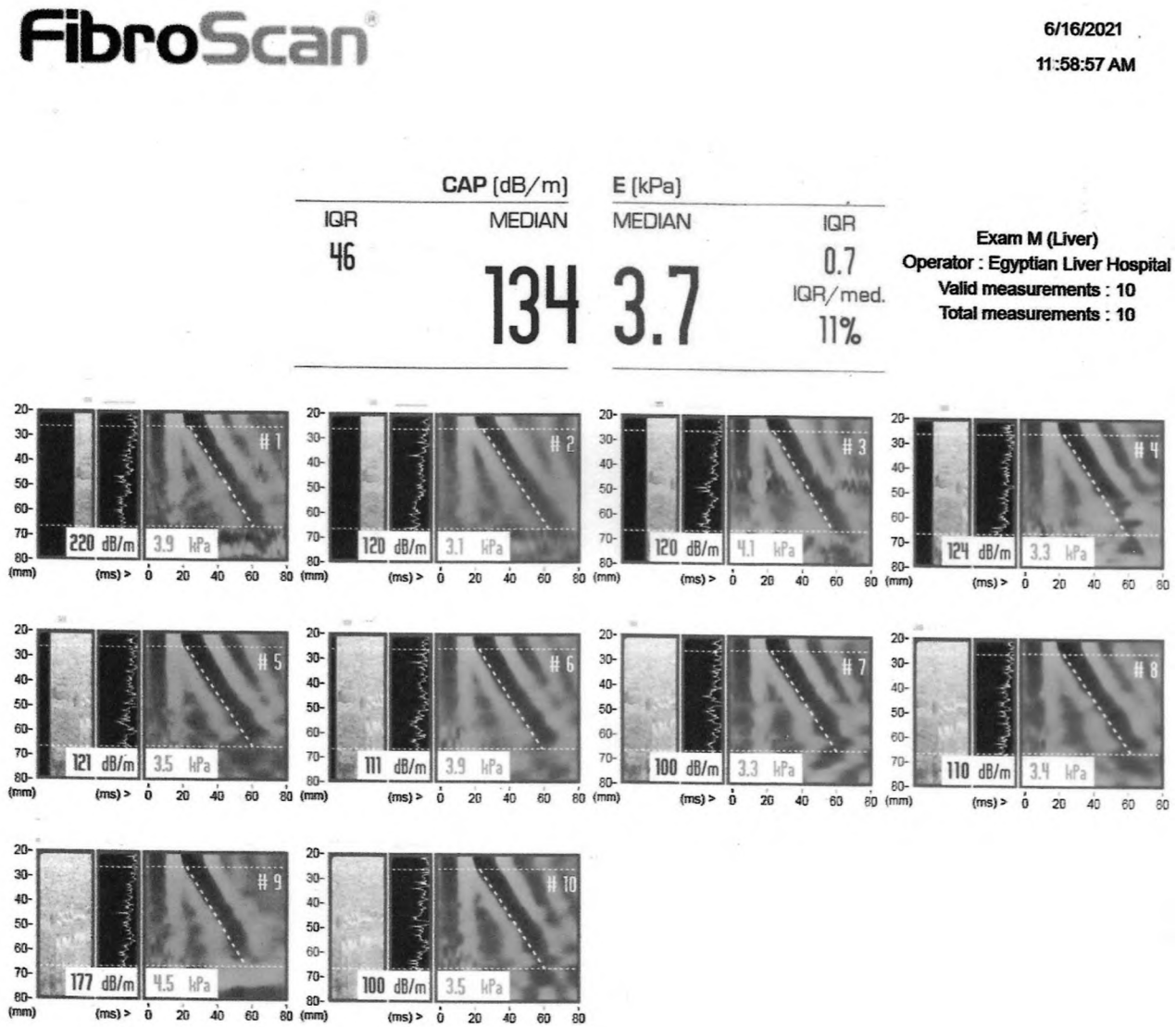

Fig. (3): Transient elastography (TE) (M probe) in a child with chronic liver disease. The individual values of 10 measurements are shown as well the median of the 10 measurements and two quality parameters, the interquartile range and the interquartile range divided by the median.

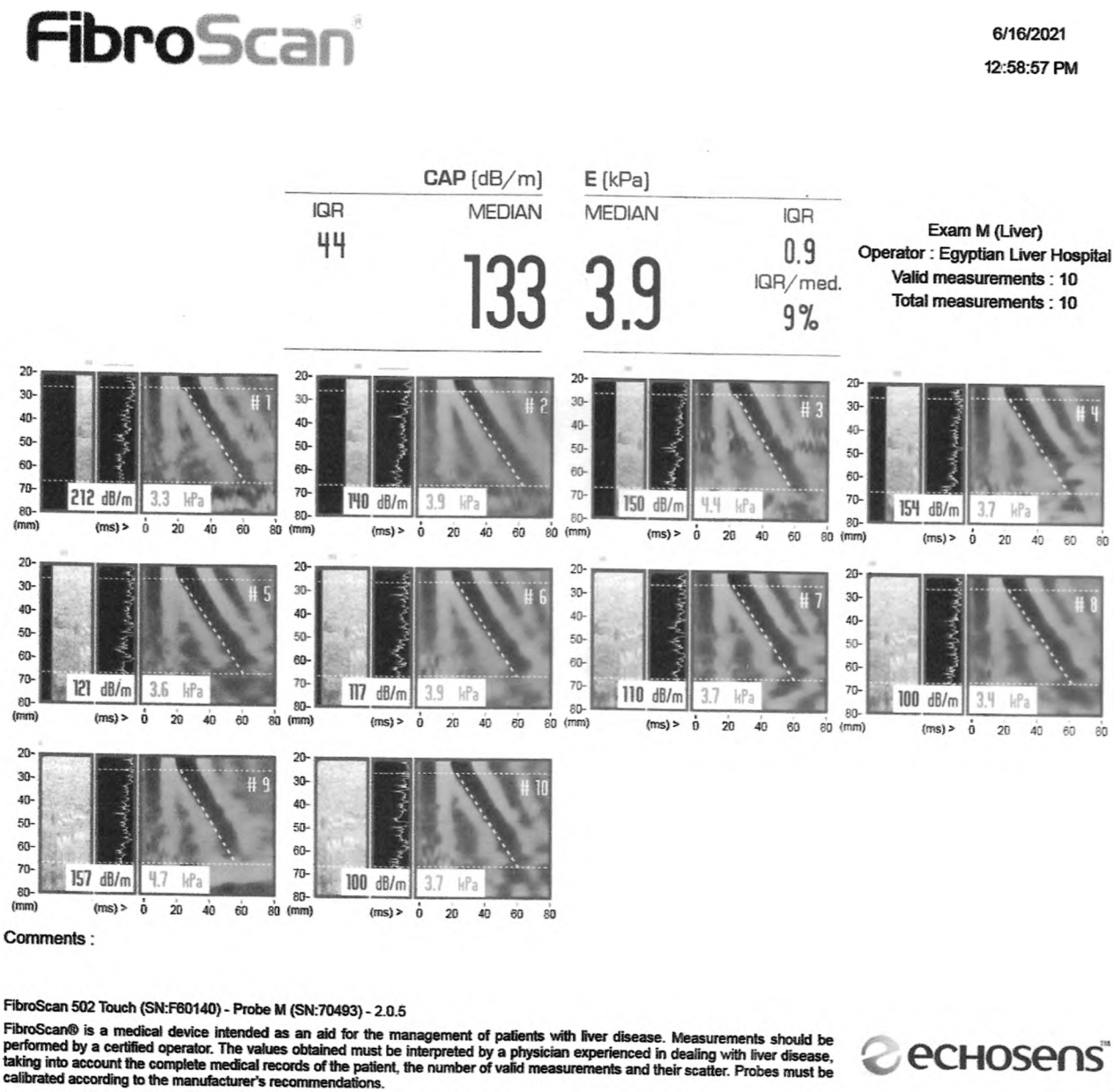

Fig. (4): Transient elastography (TE) (M probe) in a child with chronic liver disease. The individual values of 10 measurements are shown as well the median of the 10 measurements and two quality parameters, the interquartile range and the interquartile range divided by the median.

Discussion

The main aim of this study was to assess the role of transient elastography (fibroscan) in diagnosis and staging of liver fibrosis in chronic liver diseases among pediatrics in comparison to liver biopsy.

Our study was carried out on 30 Children with chronic liver disease undergoing biopsy. In Ghaffar et al., **[10]** study liver biopsy was done for 42 children and as regard Lee et al., **[4]**, they enrolled a total of 267 subjects and Lewindon et al., **[11]** was performed on 160 children.

Patients included in the current study comprised 15 (50.0%) female and 15 (50.0%) male.

In accordance with the studies of Ghaffar et al., **[10]**, Lewindon et al., **[11]** and Lee et al., **[4]** where females approximately same as males. In Lee et al., **[4]**, The METAVIR system was used to stage fibrosis.

The study by Ghaffar et al., **[10]** reported that 38.1% of the cases had Wilson disease, 23.8% had autoimmune hepatitis, 7.1% had Glycogen storage disease, 7.1% had congenital hepatic fibrosis and 7.1% had cryptogenic cirrhosis. Stage of fibrosis

was assessed according to METAVIR system, the found that 35% of children had no or mild fibrosis (=F2 METAVIR) (G 2).

In our study, using the area under the Roc curve analysis for the use of Fibroscan to predict fibrosis at F2 was the same as the use of biopsy with AUC of 0.843, level of sensitivity 80%, specificity 86.7%, PPV 85.7%, NPV 81.3% and accuracy 83.3%.

Lee et al., [4] reported that in phase 1, the cut point to predict F2 fibrosis or greater was 8.4 kPa with AUROC 0.89, 82% sensitivity, 79% specificity, and to predict F4 fibrosis was 12.8kPa with AUROC 0.92, 84% sensitivity, 86% specificity. When these cut points were tested in the validation cohort, the F2 fibrosis or greater cut point had 58% sensitivity, 75% specificity and for the F4 fibrosis cut point 76% sensitivity and 85% specificity.

Lewindon et al., [11] found that using Youden's index to maximize specificity for the differential diagnosis of CFLD, a cutoff LSM of 5.55kPa demonstrated 70% sensitivity, 82% specificity, and odds ratio 1/4 10.4. An LSM increase of 1kPa was associated with a 2.4-fold (95% CI, 1.6-3.5) increased odds of having CFLD. APRI alone discriminated CFLD with an AUC 1/4 0.66 (sensitivity 1/4 70%, specificity 1/4 53%; p 1/4 .02).

The exact causes of such discrepancies between our findings and the above mentioned studies are unclear. However, it can be attributed to many methodological differences. Moreover, patient's characteristics were apparently different in which some studies.

In our results, Fibroscan and biopsy showed high substantial agreement regarding fibrosis stage (fibrosis or no fibrosis) with kappa (ic) 0.667.

Ghaffar et al., [10] reported that transient elastography was a good discriminator of fibrosis in the present study, a cut off value of 8.1Kpas could differentiate between significant fibrosis (›_ F2) and absent or insignificant fibrosis (<F2) irrespective of the etiology of chronic liver disease, with AUROC, sensitivity, specificity, PPV and NPV of 0.883, 78%, 73%, 77.8% and 73.3% respectively. This is in agreement with an adult study by Fraquelli et al., [12] on 200 patients with chronic liver diseases who found that a cut-off (7.9kpas) is the cut-off for diagnosis of significant liver fibrosis (›_ F2) with AUROC, sensitivity, specificity, PPV and NPV were 0.86, 72%, 84%, 82% and 70% respectively.

Our results were supported by Lee et al., [4] as they reported that the calibration cohort was used to construct ROC 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). In phase 1, the cut point to predict F2 fibrosis or greater was 8.4kPa with AUROC 0.89, 82% sensitivity, 79% specificity, and to predict F4 fibrosis was 12.8kPa with AUROC 0.92, 84% sensitivity, 86% specificity. When these cut points were tested in the validation cohort, the F2 fibrosis or greater cut point had 58% sensitivity, 75% specificity and for the F4 fibrosis cut point 76% sensitivity and 85% specificity.

Furthermore Lewindon et al., [11] reported that ROC curve analysis demonstrated good clinical utility for liver stiffness measurement (LSM) in detection of cystic fibrosis-associated liver disease (CFLD) with an area under the receiver operating characteristic curve (AUROC) of 0.82 (p<.0001). Using Youden's index to maximize specificity for the differential diagnosis of CFLD, a cutoff LSM of 5.55kPa demonstrated 70% sensitivity, 82% specificity, and odds ratio=10.4. An LSM increase of 1kPa was associated with a 2.4-fold (95% CI, 1.6-3.5) increased odds of having CFLD.

Afdhal et al., [13], performed a prospective 2-phase, multicenter study of transient elastography in adult patients with chronic hepatitis C or B included 188 subjects in the developmental phase and 560 subjects in the validation phase. In phase 1, the cut point to predict F2 fibrosis or greater was 8.4kPa with AUROC 0.89, 82% sensitivity, 79% specificity, and to predict F4 fibrosis was 12.8kPa with AUROC 0.92, 84% sensitivity, 86% specificity. When these cut points were tested in the validation cohort, the F2 fibrosis or greater cut point had 58% sensitivity, 75% specificity and for the F4 fibrosis cut point 76% sensitivity and 85% specificity.

Conclusion:

Noninvasive methods, such as transient elastography and fibrosis marker scores, seem to be useful tools to assess liver fibrosis in these patients and may be helpful to recognize a progression of the liver disease during routine follow-up. TE is a portable, highly accessible, reliable, and reproducible noninvasive modality that can be used to screen for liver disease and assess severity of fibrosis in children with CF.

Declaration:

- No Funds.
- All participants in the research agree to publish.

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دور التصوير الطبى باستخدام المرونة تصوير التليف فى تشخيص وتصنيف تليف الكبد فى أمراض الكبد المزمنة بين الأطفال

أمراض الكبد المزمنة عند الأطفال لها مسببات مختلفة، بما فى ذلك الخلقية، والتمثيل الغذائى، والسامة، والمعدية. معظم أمراض الكبد التى تم تشخيصها فى مرحلة الطفو لة تتطور إلى تليف وفى النهاية تليف الكبد مما يستدعى زراعة الكبد. يحتاج الأطفال المصابون بأمراض الكبد المزمنة إلى مراقبة منتظمة لتطور مرض الكبد لديهم.

تعتبر خزعة الكبد الطريقة التقليدية لتقييم تلف الأنسجة مثل التليف الكبدى فى المرضى الذين يعانون من أمراض الكبد المزمنة. ومع ذلك، فهو مرتبط بانزعاج واضح للمريض وخطر حدوث مضاعفات تتراوح من الألم إلى الأحداث الأكثر خطورة مع معدل الاستشفاء من ١.٤–٣.٢٪ والوفيات تتراوح من ٠.٠٠٨٨ إلى ٠.٣٪. إلى جانب ذلك، تظهر جزءاً صغيراً جداً من العضو، وبالتالى هناك خطر ألا يكون الجزء الصغير ممثلاً للتليف الحى فى الكبد بالكامل.

لذلك، يجب البحث على طرق غير جراحية لتقييم تليف الكبد. تشمل الأساليب المختلفة اختبارات الدم والكيمياء الحيوية الروتينية وعلامات التليف البديلة فى الدم والتصوير الطبى باستخدام المرونة مؤخراً.

هناك حاجة سريرية كبيرة لتحديد العلامات البديلة لتليف الكبد. يمكن استخدام مثل هذه الاختبارات لتقدير مدى التليف بدلاً من الخزعة أو استخدامها جنباً إلى جنب مع خزعة كبد لمتابعة تطور أو تراجع التليف. من الناحية المثالية، تعتمد هذه العلامات على اختبارات دقيقة ويمكن تنفيذها بشكل متكرر مع القليل من الإزعاج للمرضى.

يعد التصوير الطبى باستخدام المرونة طريقة بسيطة وآمنة وفعالة لتقدير تندب الكبد. يعتبر جهاز تصوير التليف هو الجهاز الغير جراحى الأكثر استخداماً لتقييم (صلابة) (أو تصلب) الكبد عبر التصوير الطبى باستخدام المرونة. ويوفر طريقة موثوقة لاكتشاف تليف الكبد واستبعاد التليف الكبدى عند إجرائها فى بيئة سريرية مناسبة، خاصة عندما تكون النتائج مدعومة بالبيانات السريرية. بالمقارنة مع اختبارات الدم، يمتلك التصوير الطبى باستخدام المرونة أداءً مشابهاً للتنبؤ بالتليف الكبدى ودقة أعلى لتحديد تليف الكبد.

تهدف الدراسة إلى تقييم دور التصوير الطبى باستخدام المرونة (جهاز تصوير التليف) فى تشخيص وتحديد مراحل تليف الكبد فى أمراض الكبد المزمنة بين الأطفال بالمقارنة مع خزعة الكبد.