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RESEARCH

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Evaluating the non-invasive tools for assessment of liver fibrosis in children with intrahepatic cholestasis prior to partial biliary diversion: tertiary-center experience

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Abstract

Background The liver biopsy is an essential element of evaluating progression of liver disease in children with Progressive Familial Intrahepatic Cholestasis (PFIC) and Allagille Syndrome (AGS). Several noninvasive techniques, including radiological imaging and blood biomarkers assay, can be used to evaluate liver stiffness.

Objectives To identify whether liver Transient elastography (FibroScan) and AST/PLT Ratio Index (APRI) could be reliable tools to assess the degree of fibrosis prior to partial biliary diversion (PBD).

Methods A prospective cohort in which all patients with PFIC and AGS who underwent PBD from July 2019 to July 2021 were included. Preoperative liver functions, pelvic-abdominal ultrasonography and FibroScan assessments were performed while intraoperative liver biopsy was obtained.

Results Eight patients with chronic cholestatic liver disease who were candidates for PBD due to intractable pruritus were enrolled, including PFIC ($n=6$; 75%), and AGS ($n=2$; 25%). The liver FibroScan results were similar to the liver biopsy histopathological assessment in 87.5% of cases. APRI ranged from 0.1 to 3.2 (median = 1.2). In four cases (50%), APRI was consistent with histological evaluation of liver samples. The FibroScan results were in concordance with APRI results in three patients (37.5%).

Conclusion The current cohort demonstrated that fibroScan was consistent with histopathology in 87.5% of patients, highlighting its value in determining the degree of liver fibrosis prior to surgery, whereas the APRI was only consistent with histopathology in half of cases.

Keywords Progressive familial intrahepatic cholestasis, Allagille syndrome, Liver fibrosis, APRI, FibroScan, Liver biopsy

Background

Progressive familial intrahepatic cholestasis (PFIC) and Alagille syndrome (AGS) constitute rare childhood cholestatic liver disorders that can result in liver cirrhosis. In non-cirrhotic patients, the partial biliary diversion (PBD) procedure is still a therapeutic option. Hence, determining the degree of fibrosis is deemed necessary prior to biliary diversion procedure [1].

The Liver biopsy has always been the standard method for staging the fibrosis. However, its complications

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pointed our focus to different several non-invasive methods including both radiologic tests and serum biomarker tests [2, 3]. The Biomarkers associated with fibrosis are detected at higher levels in serum. The Aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) tool has been found to be useful as a non-invasive index that correlates with fibrosis and cirrhosis findings on liver biopsy [4]. Transient elastography (FibroScan) is a peculiar, noninvasive, quick bedside approach for assessing liver fibrosis in adult patients by evaluating liver stiffness. Although experience is expanding, FibroScan is not thoroughly explored in pediatrics [5].

We aim to evaluate whether FibroScan and APRI could be reliable tools to assess the degree of fibrosis prior to partial biliary diversion (PBD), as patients with PFIC and AGS may benefit from correlation between non-invasive tools to assess the degree of liver fibrosis and liver biopsy.

Methods

This study was carried out at Pediatric Surgery Department, Cairo University Specialized Pediatric Hospital (CUSPH), between July 2019 and July 2021. It is a prospective, tertiary center, intraoperative liver biopsy-validated study that looked at the efficacy of APRI and FibroScan as fibrosis surrogates in children with PFIC or AGS. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) principles were followed to develop the study [6]. Subjects had to have clinical evidence of AGS or PFIC with refractory pruritus and to be candidates for partial biliary diversion to be eligible for the study. The study was registered in the local ethics committee of Cairo University Teaching Hospitals. Informed consents obtained from patients' guardians.

Non-invasive preoperative fibrosis assessment tools

Bloods tests included Complete blood count (CBC), Aspartate aminotransferase (AST), Alanine amino transferase (ALT), Alkaline Phosphatase (ALP), Gamma-glutamyl transferase (GGT), albumin, and total and direct bilirubin were all obtained preoperatively. APRI was calculated according to the formula: APRI = AST level/upper normal limit for AST Platelet count (103/L) × 100. APRI was interpreted as following; no to moderate fibrosis (< 0.5), indeterminate (0.5–1.5), advanced fibrosis (bridging fibrosis to cirrhosis) (≥ 1.5), cirrhosis (> 2) [7].

The radiological evaluation included abdominal ultrasonography to exclude the presence of ascites then FibroScan to assess liver stiffness. FibroScan is a device that monitors the velocity of the sound wave as it goes through the liver and then translates that data into a measurement of liver stiffness (in kilopascals). This is accomplished by placing a little transducer at the end of the FibroScan probe into an intercostal space near the right lobe of the liver and sending a 50-MHz pulse into the liver [3]. For $F > 2$, $F > 3$, and $F > 4$, the fibroscan Cut-off values are 7.1 kPa, 9.5 kPa, and 12.5 kPa, respectively [8]. The FibroScan results were classified based on the Metavir fibrosis score (F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, and F4 = cirrhosis) [2].

Intra-operative biopsy

During the biliary diversion procedure, a liver biopsy was obtained to figure out the extent of fibrosis. Each biopsy was staged for fibrosis using the Metavir fibrosis score [2].

Statistical analysis

SPSS version 22.0 for Windows was used for statistical analysis. Patient and clinical characteristics are summarized as medians with minimum and maximum ranges, and categorical data as percentages.

Results

Eight patients with chronic cholestatic liver disease who were candidates for PBD due to intractable pruritus were enrolled, including PFIC ($n = 6$; 75%), and AGS ($n = 2$; 25%). Seven cases (87.5%) were females. The median age was 4 years (range 2–12 years).

The median values for total bilirubin, direct bilirubin, and liver function tests are shown in the Table 1. The median APRI was 1.2, with a range of 0.1 to 3.2. The APRI matched the histological evaluation of liver specimens in 4 patients (50%), as APRI 3.2, 0.79, 1.6, and 1.6 correlate to the fibrosis grades F4, F1, F3, and F3, respectively.

Pelvic-abdominal ultrasonography revealed a homogeneous liver with regular borders in 7 patients (87.5%) and irregular edges in just one patient (12.5%), with no ascites in any of the patients. According to FibroScan results, three patients (43%) had mild liver fibrosis (F1), two patients (14%) had mild to moderate fibrosis (F2), one patient (14%) had moderate fibrosis (F3), and two patients (14%) had substantial fibrosis/cirrhosis (F4). Histopathological examination of the intraoperative liver samples indicated that two patients had mild fibrosis (F1), two (28.5%) had mild to moderate fibrosis (F2), two (14%) had moderate fibrosis, and two (28.5%) had significant fibrosis (F4) Table 2. The FibroScan results were identical to the liver biopsy histological evaluation in seven patients (87.5%). The FibroScan results were in concordance with APRI results among three patients (37.5%) Table 2.

Table 1 The biochemical assessment of PFIC and AGS patients

	Total bilirubin	Direct bilirubin	AST	ALT	GGT	ALP	Albumin	pc	Hb	PLT
Case 1	19.9	16.2	336	196	189	593	2.1	87	11.5	170
Case 2	2.9	1.5	81	145	357	737	3.8	100	11.5	205
Case 3	5.2	2.8	31	34	28	348	3.4	100	10	462
Case 4	20.9	19.2	205	114	32	314	3	99	10.4	486
Case 5	18.6	10	316	181	69	651	3	89	10.5	384
Case 6	7.1	3.2	276	219	574	529	3.6	70.6	12.2	349
Case 7	11.9	10.2	106	93	22	1113	3.7	81.9	12.2	564
Case 8	2.8	2.07	64	56	25	835	4.1	100	10.5	269
Median range	9.5 2.8–20.9	6.6 1.5–19.2	155.5 31–336	129.5 56–219	50.5 22–574	622 314–1113	3.5 2.1–4.1	94 70.6–100	11 10–12.2	366.5 170–564

AST Aspartate aminotransferase, *ALT* Alanine amino transferase, *ALP* Alkaline phosphatase, *GGT* Gamma-glutamyl transferase, *HB* Hemoglobin, *PLT* Platelets, *PC* Prothrombin concentration

Table 2 The non-invasive liver fibrosis assessment tools

	Ultrasonography	APRI	FibroScan	Histopathology
Case 1	Irregular liver with no ascites	3.2 cirrhosis	F4 18.7	F4
Case2	Echogenic liver with no absence of ascites	0.79 Intermediate fibrosis	F1 6.5 kPa	F1
Case 3	Homogenous hepatomegaly with no ascites	0.1 No fibrosis	F2 7.9 kPa	F2
Case 4	Homogenous hepatomegaly with regular outline and no ascites	0.8 Intermediate fibrosis	F4-S1 18.6 kPa	F4
Case 5	Homogenous liver with no ascites	1.6 Advanced fibrosis	F3 11 kPa	F3
Case 6	Homogenous liver with a regular outline and no ascites	1.6 Advanced fibrosis	F1 6.1 kPa	F3
Case 7	Homogenous liver with regular outline and no ascites	1.6 Advanced fibrosis	F1 6.1 kPa	F1
Case 8	Homogenous hepatomegaly with a regular outline and no ascites	0.5 No to moderate fibrosis	F2 8.5 kPa	F2

APRI AST to Plt ratio index < 0.5 no to moderate fibrosis, 0.5–1.5 indeterminate, ≥ 1.5 advanced fibrosis (bridging fibrosis to cirrhosis), > 2 cirrhosis [6]

Metavir fibrosis score (F0 = no fibrosis, *F1* = portal fibrosis without septa, *F2* = portal fibrosis with few septa, *F3* = numerous septa without cirrhosis, and F4 = cirrhosis [2]

Discussion

The treatment strategy in PFIC and AGS patients must be planned before hepatic cirrhosis develop. Therefore, staging liver fibrosis is required to evaluate disease progression during therapy and particularly prior to partial biliary diversion procedure [1]. A liver biopsy is considered the gold standard for staging liver fibrosis. However, it is an invasive procedure with potential complications such as pain, bleeding, sample inaccuracy, inter-observer variability, in addition to risks of anesthesia in children. Furthermore, frequent consecutive biopsies are not clinically practical for monitoring the ongoing liver fibrosis. Thus, developing precise non-invasive ways to detect disease progression is crucial [9].

Numerous non-invasive indicators have been suggested, including laboratory and radiographic studies. APRI, fibrosis-4 index (FIB-4), (AST)/ (ALT) ratio (AAR), and other less typically used indicators are included in laboratory panel markers [4]. Biomarker tests take advantage of the fact that changes in liver stiffness result in measurable changes in biomarkers produced by the liver [10]. Thus, we investigated the use of APRI as a biomarker of liver fibrosis in children with AGS and PFIC who underwent PBD. Our findings suggested that APRI was ineffective for staging liver fibrosis in those patients. De Le'dinghen et al. [5] reported that the APRI was substantially linked with Metavir fibrosis scores in children with chronic liver diseases. on the other hand,

Biochemical tests incorporate markers such as bilirubin, AST, or glutamyl transpeptidase, which are raised due to cholestasis or liver disease, their value in the diagnosis of cirrhosis is restricted [5]. Shah et al. reported that APRI is pointless for evaluating fibrosis or cirrhosis in children with intrahepatic cholestasis [9]. Additionally, The Metavir Index, albeit widely used, is known to have inconsistencies in staging between different studies, consequently co-relationship with APRI could be inadequate [11]. On the other hand, Shiau et al. justified the use of APRI as a noninvasive biomarker for the degree of liver fibrosis in both AGS and PFIC [12].

Meta-analysis has been conducted to evaluate the effectiveness of FibroScan in liver fibrosis assessment demonstrating that it functions well for staging patients with little or mild fibrosis, as well as those with severe fibrosis or cirrhosis [13]. The architecture of fibrosis deposits varies between children with autoimmune hepatitis or viral illness and those with intrahepatic cholestasis. Children with viral or autoimmune hepatitis have homogeneous fibrosis throughout the liver, but children with cholestasis have heterogeneous fibrosis [5]. Hence, more studies of FibroScan performance in children based on each etiology of illness are required. We found that 87.5% of FibroScan results of our intrahepatic cholestasis patients were similar to the liver biopsy histological examination. The precision of quantifying liver stiffness for the identification of cirrhosis was reported in literature to be greater than 90% (5). FibroScan paired with the specific pediatric probe has the potential to be a beneficial tool in grading the fibrosis of chronic liver disorders in pediatric patients [5].

The APRI score and FibroScan have inconsistent efficiency and do not function equivalent to liver biopsy, when used to assess patients with midlevel illness like in patients with Metavir stage F2 [3]. In our study, FibroScan results didn't match APRI of 62.5% of patients.

The frequent use of FibroScan and APRI score may reduce the amount of liver biopsies conducted and provide a reliable means of non-invasive monitoring of the ongoing liver disease in children [14]. Although FibroScan methods have evolved in children, they remain pricey and are not yet generally available in all pediatric hospitals [12].

It was recently observed that when the Metavir scoring method was used, only 75% of biopsy samples were accurately identified in terms of fibrosis stage [9]. Regardless the histological scoring method utilized, FibroScan correlates well with histological findings in children with hepatopathy [15].

The limitation of our study is the low number of patients due to the rarity of the diseases; therefore, further multi-center studies are needed to fully assess the value of the non-invasive tools in assessment of liver fibrosis.

Conclusion

In pediatrics, non-invasive tools to assess liver fibrosis is an expanding subject. In our cohort, APRI was insufficient for evaluating the degree of fibrosis in children with intrahepatic cholestatic disease. However, FibroScan could be considered as a viable method for assessing the degree of liver fibrosis in PFIC or AGS patients.

Abbreviations

AGS	Alagille syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APRI	AST to PLT ratio index
AST	Aspartate aminotransferase
CBC	Complete blood count
GGT	Gamma-glutamyl transferase
Hb	Hemoglobin
PC	Prothrombin concentration
PFIC	Progressive familial intrahepatic cholestasis
PLT	Platelets
TLC	Total leucocyte count

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Authors' contributions

HN collected the data, analyzed the results of different assessment tools, and wrote the final manuscript. NA participated in patients' clinical assessment, data collection, and wrote the initial draft. NK designed the frame of work. AO edited the manuscript with a substantial revision. SK contributed to the conception of the work and revised the work substantially. GT contributed to the conception of the work. WM participated in patients' clinical assessment in addition to patients' data analysis and interpretation. All authors read and approved the final manuscript.

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Availability of data and materials

All the data supported the results can be found within the article.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the declaration of Helsinki and was approved by the local ethics committee of Cairo University Teaching hospitals (Ref MD110-2019). Guardians of eligible children signed written informed consent before study enrollment.

Consent for publication

A written informed consent for publication was obtained from the guardians of eligible children.

Competing interests

The authors declare that they have no competing interests.

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