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Original Article

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Serologic Biomarkers for Hepatic Fibrosis in Obese Children with Nonalcoholic Steatohepatitis

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ABSTRACT

Purpose: The prevalence of nonalcoholic steatohepatitis (NASH) is increasing with the increasing prevalence of childhood obesity. Although NASH has a high risk of progression to liver fibrosis and cirrhosis, few studies have reported noninvasive markers for predicting hepatic fibrosis in children. This study aimed to evaluate and compare the diagnostic accuracies of serologic biomarkers and scoring systems for hepatic fibrosis in obese children with NASH.
Methods: A total of 96 children were diagnosed with NASH based on liver biopsy findings and divided into two groups according to the degree of liver fibrosis: mild (stage 0–1) or advanced (stage 2–4). Clinical and laboratory parameters and serum levels of hyaluronic acid and type IV collagen were measured. The aspartate aminotransferase/platelet ratio index (APRI) and fibrosis-4 (FIB-4) score were calculated.
Results: Among the noninvasive markers, only serum type IV collagen level and FIB-4 were significantly different between the two groups. The area under the receiver operating curve of each biomarker and scoring system was 0.80 (95% confidence interval [CI]: 0.70–0.90) for type IV collagen at an optimal cutoff of 148 ng/mL (sensitivity 69.8%, specificity 84.6%), followed by 0.69 (95% CI: 0.57–0.83) for APRI, 0.68 (95% CI: 0.56–0.80) for FIB-4, and 0.65 (95% CI: 0.53-0.77) for hyaluronic acid.
Conclusion: Type IV collagen as a single noninvasive serologic biomarker for hepatic fibrosis and FIB-4 as a hepatic fibrosis score are beneficial in predicting advanced hepatic fibrosis and determining proper diagnosis and treatment strategies before fibrosis progresses in obese children with NASH.

Keywords: Nonalcoholic fatty liver disease; Fibrosis; Serum marker; Diagnosis; Obesity; Child

INTRODUCTION

The prevalence of obesity among children and adolescents worldwide, including in South Korea, has increased in recent years [1]. Accordingly, the prevalence of obesity-related complications, such as nonalcoholic fatty liver disease (NAFLD) and metabolic syndromes, is rapidly increasing [2,3].

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NAFLD is a spectrum of diseases, including simple steatosis, nonalcoholic steatohepatitis (NASH), liver fibrosis, and cirrhosis. NASH has a high risk of progression to advanced liver diseases such as liver fibrosis and cirrhosis, even in children [4-6].

Liver fibrosis is a dynamic process involving two conflicting processes: fibrogenesis and fibrolysis. These processes result in the deposition of collagen and extracellular matrix proteins in tissues [7]. Therefore, the degree of liver fibrosis is an important prognostic factor for determining the prognosis and timing of chronic liver disease.

Liver biopsy is the gold standard for diagnosing hepatic fibrosis [8,9]. However, it has limitations, such as complications due to invasive techniques, sample errors, and cost. Therefore, research interest in noninvasive diagnostic methods is increasing. However, studies on noninvasive serologic markers for liver fibrosis screening in NASH have mainly been conducted in adult patients [10]. Few studies have been conducted on children or adolescents. Furthermore, no single biochemical marker for liver fibrosis has been reported, and studies on noninvasive fibrosis scoring systems remain insufficient.

Therefore, this study aimed to evaluate and compare the diagnostic accuracy of serologic markers related to the pathophysiology of liver fibrosis and scoring systems for hepatic fibrosis according to the severity of liver fibrosis in obese children with NASH.

MATERIALS AND METHODS

Study population and data collection

This study was a retrospective review of the medical records of 96 obese children and adolescents aged <18 years with biopsy-proven NASH who visited the Department of Pediatric Gastroenterology and Hepatology at Seoul National University Bundang Hospital between July 2003 and May 2019.

The medical data of each participant, including age, sex, weight, height, body mass index (BMI), abdominal circumference (AC), laboratory test values, and radiologic and histopathologic findings, were reviewed and retrospectively analyzed.

Obesity was defined as BMI >95th percentile for age and sex. BMI was calculated as weight (kg) divided by height squared (m^2). BMI was determined according to age and sex based on the 2017 Korean National Growth Chart [11].

All participants were diagnosed with NAFLD after excluding those with other causes of chronic hepatitis, such as hepatitis (A, B, C, and E) virus, cytomegalovirus, Epstein-Barr virus, Wilson's disease, metabolic disease, autoimmune hepatitis, and drug toxicity.

The study participants were divided into two groups according to the histopathologic grading and staging of NAFLD. Hepatic fibrosis at stage 0–1 was defined as mild fibrosis, and fibrosis at stage 2–4 was defined as advanced fibrosis.

This retrospective study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (approval no. B-1909-562-104).

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Laboratory tests and serologic markers of hepatic fibrosis

All study participants underwent laboratory tests for fasting glucose, insulin, hemoglobin A1c, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and apoprotein A1 and B levels. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, γ-glutamyl transpeptidase, total bilirubin, albumin, and prothrombin time were also measured.

Among the potential biomarkers based on the pathogenesis of hepatic fibrosis, type IV collagen and hyaluronic acid (HA) were measured at the time of diagnosis in all study participants. Type IV collagen was measured using a radioimmunological assay, and HA was measured using a latex agglutination immunoassay.

Hepatic fibrosis scoring systems

The AST/ALT ratio was calculated as the ratio of AST to ALT [12]. The AST/platelet ratio index (APRI) was calculated as follows: (AST level/AST upper level of normal/platelet count)×100 [13]. Fibrosis-4 (FIB-4) was calculated as (age×AST level/platelet count×√ALT) [14]. The prothrombin, gamma-glutamyl tanspeptidase, apoprotein A1 (PGA) index combines the measurements of the prothrombin index, GGT level, and apolipoprotein A1 level [15].

Radiologic investigations of the liver

Fatty liver was evaluated in each patient using abdominal sonography and/or non-contrast abdominal magnetic resonance imaging. Abdominal sonography was used to classify the degree of fatty liver as mild, moderate, or severe.

Histopathologic findings of the liver and staging of fibrosis

All study participants underwent percutaneous needle liver biopsy under local anesthesia. Specimens were evaluated to diagnose NAFLD and assess the stage of liver fibrosis according to the Knodell scoring system [16,17]. Fibrosis stages were categorized into four groups: none (stage 0), perisinusoidal or periportal fibrosis (stage 1), perisinusoidal and portal/periportal fibrosis (stage 2), bridging fibrosis (stage 3), and cirrhosis (stage 4) [17].

Statistical analysis

The results are expressed as mean±standard deviation. Data were analyzed using IBM SPSS Statistics software (version 22.0; IBM Co.). The Kruskal-Wallis test was used to compare three or more quantitative nonparametric variables. Chi-square tests were used to compare categorical variables. For all statistical analyses, a two-sided p-value of <0.05 was considered statistically significant.

Receiver operating characteristic (ROC) curves were used to evaluate the optimal cutoff levels, and the area under the ROC curve (AUROC) was calculated.

RESULTS

Patient characteristics

A total of 96 children diagnosed with NASH were included in this study. Of the 96 patients, 78 (81.3%) were boys and 18 (18.7%) were girls, with a mean age of 12.4±3.1 years. The mean AC was 91.5±11.7 cm. The mean BMI was 27.0±4.6 kg/m^2. The clinical characteristics of obese children with NAFLD are shown in **Table 1**.

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Table 1. Comparison of clinical features and laboratory parameters between mild fibrosis (stage 0–1) and advanced fibrosis (stage 2–4) in obese children with nonalcoholic steatohepatitis

Parameter	Total (n=96)	Mild fibrosis (stage 0–1) (n=51)	Advanced fibrosis (stage 2–4) (n=45)	*p*-value
Clinical features				
Sex (M:F)	78:18	42:9	36:9	0.768
Age (yr)	12.4±3.1	12.2±3.3	12.7±2.9	0.409
AC (cm)	91.5±11.7	89.0±10.7	94.5±12.3	0.025
Height (cm)	156.5±15.0	153.8±15.4	159.8±13.9	0.056
BMI (kg/m^2)	27.0±4.6	26.1±4.3	27.9±4.8	0.058
Laboratory findings				
AST (IU/L)	81.5±73.2	71.2±78.3	93.2±65.9	0.143
ALT (IU/L)	154.5±117.7	140.7±134.2	170.2±94.7	0.223
ALP (IU/L)	260.4±112.5	260.9±118.5	259.8±106.6	0.961
rGT (IU/L)	57.0±60.0	54.3±57.0	60.0±40.8	0.584
Total bilirubin (mg/dL)	0.6±0.3	0.5±0.3	0.7±0.3	0.057
Albumin (g/dL)	4.6±0.3	4.61±0.4	4.5±0.3	0.384
PT INR	2.0±9.3	2.82±12.7	1.0±0.1	0.351
Triglyceride (mg/dL)	137.8±75.7	139.2±91.3	136.1±53.8	0.839
LDL (mg/dL)	108.2±28.8	108.9±30.1	107.3±27.5	0.786
HDL (mg/dL)	47.5±13.4	48.8±16.0	46.1±9.8	0.333
Apoprotein A (mg/dL)	125.8±23.8	128.7±25.3	122.5±21.8	0.255
Apoprotein B (mg/dL)	98.6±22.9	98.0±25.4	99.2±20.0	0.819
Fasting glucose	106.1±24.9	105.2±20.1	107.1±29.6	0.706
Insulin (μIU/mL)	27.4±16.7	25.0±16.1	30.0±17.1	0.149
HOMA-IR	7.3±5.0	6.6±4.7	8.1±5.3	0.146
HbA1c (pg/mL)	5.7±0.9	5.5±0.6	5.9±1.2	0.105
Platelets (×10^9 L)	0.3±0.3	0.2±0.3	0.3±0.2	0.057
Hyaluronic acid	22.2±18.9	18.4±13.7	25.3±22.9	0.088
Type IV collagen	158.34±72.50	131.33±44.00	183.56±84.40	0.001

Values are presented as mean±standard deviation, unless otherwise specified.
M: male, F: female, AC: abdominal circumference, BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, rGT: γ-glutamyl transpeptidase, PT INR: prothrombin time international normalized ratio, LDL: low-density lipoprotein, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment-estimated insulin resistance, HbA1c: hemoglobin A1c.

Comparison of clinical and laboratory parameters between mild and advanced fibrosis

Of the 96 patients diagnosed with NASH, 51 were in the mild fibrosis group, and 45 were in the advanced fibrosis group. Significant differences were observed in AC measured at diagnosis between the mild and advanced fibrosis groups (p=0.025) (**Table 1**). However, the other clinical and laboratory parameters did not differ significantly between the two groups (**Table 1**).

Comparison of noninvasive hepatic fibrosis markers between mild and advanced fibrosis

When comparing the serum levels of biomarkers of hepatic fibrosis between the mild and advanced fibrosis groups, a statistically significant difference was found in type IV collagen (131.3±44.0 ng/mL vs. 183.6±84.4 ng/mL, p=0.001) (**Table 2**). The HA levels did not differ significantly between the two groups (p=0.088).

In the comparison of hepatic fibrosis scores between the mild and advanced fibrosis groups, the FIB-4 score revealed statistically significant differences between the two groups (0.23±0.15 vs. 0.32±0.22, p=0.016) (**Table 2**). No significant differences were observed between the AST/ALT ratio and the APRI.

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Table 2. Comparison of noninvasive hepatic fibrosis markers between mild fibrosis and advanced fibrosis in obese children with nonalcoholic steatohepatitis

Parameters and hepatic fibrosis scores	Total (n=96)	Mild fibrosis (stage 0–1) (n=51)	Advanced fibrosis (stage 2–4) (n=45)	*p*-value
Hyaluronic acid	22.18±44.04	18.94±13.66	25.73±22.90	0.088
Type IV collagen	158.34±0.31	131.33±44.04	183.56±84.41	0.001
AST/ALT ratio	0.58±0.26	0.57±0.31	0.59±0.30	0.807
AST/platelet ratio index	0.28±0.15	0.23±0.26	0.33±0.24	0.057
FIB-4 score	0.27±0.00	0.23±0.15	0.32±0.22	0.016

Values are presented as mean±standard deviation.
AST: aspartate aminotransferase, ALT: alanine aminotransferase, FIB-4: fibrosis-4.

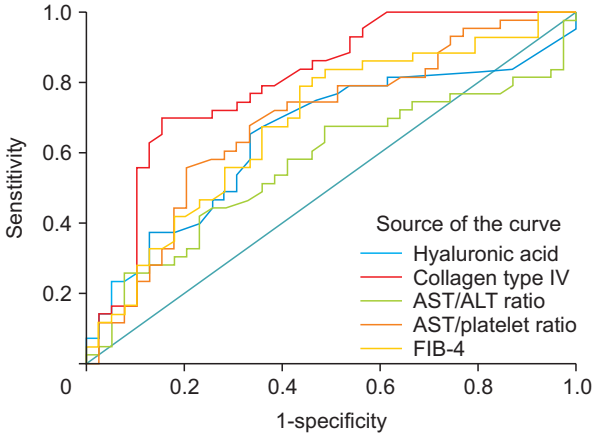

Fig. 1. Receiver operating characteristic curves for noninvasive hepatic fibrosis scoring systems (hyaluronic acid, type 4 collagen, AST/ALT ratio, AST/platelet ratio, and FIB-4) used to diagnose clinically advanced fibrosis (stage 2–4) in obese children with nonalcoholic steatohepatitis.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, FIB-4: fibrosis-4.

Comparison of diagnostic accuracy of noninvasive hepatic fibrosis markers

The ROC curves of noninvasive serologic markers and hepatic fibrosis scoring systems in obese children with NASH are shown in **Fig. 1**.

The AUROC of each biomarker and scoring system was 0.80 (95% confidence interval [CI]: 0.70–0.90) for type IV collagen at an optimal cutoff of 148 ng/mL (sensitivity 69.8%, specificity 84.6%), followed by 0.69 (95% CI: 0.57–0.83) for APRI, 0.68 (95% CI: 0.56–0.80) for FIB-4, 0.65 (95% CI: 0.53–0.77) for HA, and 0.57 (95% CI: 0.44-0.69) for the AST/ALT ratio (**Fig. 1**).

DISCUSSION

In the present study, we evaluated the diagnostic accuracy of potential serologic biomarkers related to liver fibrosis pathophysiology. Furthermore, we compared the diagnostic accuracy of these significant serologic biomarkers with that of noninvasive hepatic fibrosis scoring systems according to the severity of hepatic fibrosis on liver histopathology in obese children with NASH. Our results reveal, for the first time, that type IV collagen is a useful single biomarker that can noninvasively distinguish advanced fibrosis at an optimal cutoff in pediatric patients with NASH.

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Hepatic fibrosis, a dynamic process in which the contrasting processes of fibrogenesis and fibrolysis occur together, results in the deposition of collagen and extracellular matrix proteins in the hepatic tissue [7]. Continued deposition of these substances results in structural changes in the liver tissue and functional disorders of the parenchyma, ultimately leading to chronic complications, such as liver cirrhosis. Thus, the severity of liver fibrosis is crucial in determining the prognosis and timing of chronic liver disease [18].

In general, liver biopsy is used to diagnose the presence and severity of hepatic fibrosis because it is the gold standard diagnostic method for adults and children [19]. However, it has some limitations in clinical practice because of its invasiveness, sampling errors, cost, and complications, especially in pediatric patients [20]. For these reasons, it is difficult to perform repeat liver biopsies for the short-term follow-up of hepatic fibrosis [7]. Therefore, there is an increasing need to identify noninvasive markers of hepatic fibrosis.

To date, several studies have investigated noninvasive tools for evaluating liver fibrosis in adult patients [7,10,21-27]. With respect to noninvasive methods of detecting hepatic fibrosis, there are two major classes: class I comprises serologic biomarkers of fibrosis, and class II consists of hepatic fibrosis scores, both of which have mainly been developed for adult patients with chronic liver diseases [21]. However, validation studies on noninvasive markers that can predict the severity of liver fibrosis in children and adolescents are lacking.

For class II noninvasive hepatic fibrosis scoring systems, there have been many studies on multiparametric algorithms that have been statistically validated with respect to the detection of the presence and activity of ongoing fibrosis [21]. To date, various noninvasive hepatic fibrosis scores, including the AST/ALT ratio [12], APRI [13], PGA index [28], Forns index [29], FIB-4 [14], and NAFLD fibrosis score [30], have been developed and applied to chronic liver diseases such as hepatitis B, hepatitis C, alcoholic fatty liver disease, and NAFLD [31,32]. These hepatic fibrosis scores applied to adults with NAFLD have been validated in several previous studies [30]. However, hepatic fibrosis scores are less accurate in pediatric patients. Moreover, not all these scores are liver-specific [26]. One disadvantage is that these scores can be affected by comorbid conditions [26]. Recently, a few validation studies, including our previous study, have been conducted in obese children with NAFLD for the noninvasive diagnosis of hepatic fibrosis using the AST/ALT ratio, APRI, PGA index, Forns index, NAFLD fibrosis score, FIB-4, and pediatric NAFLD fibrosis index [12,25]. The results of these studies revealed that only the APRI and FIB-4 scores significantly distinguished advanced fibrosis (stage 2–3) from no/mild fibrosis (stage 0–1). However, the diagnostic accuracies of single biomarkers in children have not yet been evaluated or compared [25,33]. Even in the present study, among the noninvasive hepatic fibrosis scoring systems, FIB-4 was significantly different between the no/mild fibrosis and advanced fibrosis groups (p=0.016). The APRI also differed between the groups, although this difference was not statistically significant (p=0.057). Furthermore, the diagnostic accuracy of these hepatic fibrosis scores was compared with that of potential single serologic markers in this study.

Potential serologic biomarkers for noninvasive screening of hepatic fibrosis can be divided into direct and indirect markers. Direct markers indicate the levels of synthesis and degradation products of the extracellular matrix, such as type IV collagen and HA. In contrast, indirect markers such as platelet count, serum cholesterol, and transaminases do not directly reflect the metabolism of the extracellular matrix but rather represent hepatic function [34]. In studies on adults, collagen IV has been reported to have a statistically

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significant association with the degree of liver fibrosis [22,35]. Yoneda et al. [35] reported that collagen IV had an AUROC of 0.828, 70% sensitivity, 81% specificity, and 86% positive predictive value. In addition, HA has been reported as a sensitive test according to several studies, which are recent investigations of cirrhosis due to NAFLD and other etiologies [36-38]. Lydatakis et al. [36] reported that HA in patients with NAFLD had an AUROC of 0.97, a sensitivity of 86–100%, and a specificity of approximately 88%. Oberti et al. [37] reported that HA (86%) was superior to laminin and procollagen when examining the diagnostic accuracy of direct markers of liver fibrosis. However, the accuracy of fibrosis biomarkers in children has not yet been determined, although studies on scoring systems such as panels with the same AST-to-platelet ratio have been conducted [39].

There are several studies on noninvasive serologic markers in obese children and adolescents with NASH, but most have focused on indirect markers. Moreover, no direct serologic biomarker has been identified or used in pediatric clinical practice. Nobili et al. [18] evaluated the association between HA and liver fibrosis in 100 children with NAFLD, for which a biopsy was proven. In their study, HA values >1,200 ng/mL were likely to indicate the absence of fibrosis (F0) (7%, 95% CI: 1–14%), and HA values >2,100 ng/mL indicated F2 to F4 fibrosis (89%, 95% CI: 75–100%).

Therefore, in this study, we evaluated all possible serologic markers of hepatic fibrosis in 99 obese children diagnosed with NAFLD using liver biopsy. We evaluated all clinical and biochemical markers and compared them according to the histopathologic stages of hepatic fibrosis; however, no clinical or laboratory parameters (including age, sex, BMI, platelet count, liver enzymes, cholesterol or triglycerides, and homeostasis model assessment-estimated insulin resistance index) as indirect markers, except abdominal adiposity, were significantly different between the no/mild fibrosis and advanced fibrosis groups. However, when we compared the direct serologic markers of fibrosis based on the mechanism of hepatic fibrinogenesis, the serum levels of type IV collagen were significantly different between the two fibrosis groups and distinguished pediatric patients with NASH with advanced fibrosis from those with no/mild fibrosis.

In the present study, to determine the most accurate noninvasive diagnostic tools for detecting hepatic fibrosis in obese children and adolescents with NASH, we additionally compared the diagnostic accuracy and AUROCs of potential noninvasive markers, including the serum levels of HA and type IV collagen as class I serologic markers of hepatic fibrosis and FIB-4 and APRI as class II hepatic fibrosis scores, between the mild and advanced fibrosis groups of obese children diagnosed with NAFLD. According to our findings, the AUROC of each serologic biomarker and hepatic fibrosis scoring system was 0.80 (95% CI: 0.70–0.90) for type IV collagen, which had the highest diagnostic accuracy, followed by 0.69 (95% CI: 0.57–0.83) for APRI, 0.68 (95% CI: 0.56–0.80) for FIB-4, and 0.65 (95% CI: 0.53–0.77) for HA.

Furthermore, in our study, the optimal cutoff of type IV collagen (≥148 ng/mL) was highly likely to distinguish advanced fibrosis from no or mild fibrosis with a sensitivity of 69.8% and a specificity of 84.6%. In recent studies on liver cirrhosis related to NAFLD or other chronic liver diseases, HA was reported to be a biomarker of hepatic fibrosis with an AUROC of 0.97, a sensitivity of 83% to 100%, and a specificity of 66% to 88% [7,36]. In a recent study, the negative prediction (98–100%) was significantly higher than the positive prediction (61%) at a cutoff value of 60 μg/L for HA; thus, HA as a serologic marker was considered capable of excluding advanced fibrosis and cirrhosis in adult patients [36]. A study performed in

children with NAFLD reported that a serum HA level of ≥21 μg/L indicates a high probability of developing advanced fibrosis (89%, 95% CI: 75–100%). In contrast, our study showed that the serum levels of HA did not significantly differ between the no/mild and advanced fibrosis groups, whereas the highest AUROC value was noted for the serum levels of type IV collagen, with significant differences between the two groups.

Our study has some limitations. As suggested in previous studies, the histopathologic findings of pediatric NASH are somewhat different from those of adult NASH [4,5]. Thus, previous fibrosis scores developed for adults may not be applicable to pediatric patients. In adult studies, one study compared serum markers that could replace liver biopsy with non-serum markers, such as FibroScan. Further validation studies may be needed in the future to apply noninvasive markers, not only single serologic markers but also hepatic fibrosis scores and non-serum markers, in pediatric clinical practice.

Nevertheless, our study has clinical significance because it revealed that type IV collagen is a useful noninvasive serologic biomarker for predicting liver fibrosis in obese children with NASH. We suggest an optimal cutoff value for the serum level of type IV collagen that can distinguish advanced hepatic fibrosis from no/mild fibrosis. Furthermore, the diagnostic accuracy of other potential noninvasive clinical and serologic markers and hepatic fibrosis scores was evaluated in the present study. If the degree of fibrosis in NAFLD can be predicted using these noninvasive markers in clinical practice, it will help determine proper diagnostic and therapeutic strategies as soon as possible before hepatic fibrosis progresses. Therefore, future studies on noninvasive markers of liver fibrosis should be conducted, especially in children.

REFERENCES

1. Oh K, Jang MJ, Lee NY, Moon JS, Lee CG, Yoo MH, et al. Prevalence and trends in obesity among Korean children and adolescents in 1997 and 2005. Korean J Pediatr 2008;51:950-5. CROSSREF
2. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. Dig Dis 2010;28:155-61. PUBMED | CROSSREF
3. Barshop NJ, Sirlin CB, Schwimmer JB, Lavine JE. Review article: epidemiology, pathogenesis and potential treatments of paediatric non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2008;28:13-24. PUBMED | CROSSREF
4. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the expert committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr 2017;64:319-34. PUBMED | CROSSREF
5. Powell EE, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. Hepatology 1990;11:74-80. PUBMED | CROSSREF
6. Molleston JP, White F, Teckman J, Fitzgerald JF. Obese children with steatohepatitis can develop cirrhosis in childhood. Am J Gastroenterol 2002;97:2460-2. PUBMED | CROSSREF
7. Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. Hepatology 2006;43 (2 Suppl 1):S113-20. PUBMED | CROSSREF
8. Straub BK, Schirmacher P. Pathology and biopsy assessment of non-alcoholic fatty liver disease. Dig Dis 2010;28:197-202. PUBMED | CROSSREF
9. Schwimmer JB, Behling C, Newbury R, Deutsch R, Nievergelt C, Schork NJ, et al. Histopathology of pediatric nonalcoholic fatty liver disease. Hepatology 2005;42:641-9. PUBMED | CROSSREF
10. Guha IN, Parkes J, Roderick PR, Harris S, Rosenberg WM. Non-invasive markers associated with liver fibrosis in non-alcoholic fatty liver disease. Gut 2006;55:1650-60. PUBMED | CROSSREF

11. Kim JH, Yun S, Hwang SS, Shim JO, Chae HW, Lee YJ, et al. The 2017 Korean National Growth Charts for children and adolescents: development, improvement, and prospects. Korean J Pediatr 2018;61:135-49. PUBMED | CROSSREF
12. Iacobellis A, Marcellini M, Andriulli A, Perri F, Leandro G, Devito R, et al. Non invasive evaluation of liver fibrosis in paediatric patients with nonalcoholic steatohepatitis. World J Gastroenterol 2006;12:7821-5. PUBMED | CROSSREF
13. Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, Sánchez-Avila F, Vargas-Vorácková F. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. Ann Hepatol 2008;7:350-7. PUBMED | CROSSREF
14. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and FibroTest. Hepatology 2007;46:32-6. PUBMED | CROSSREF
15. Poynard T, Aubert A, Bedossa P, Abella A, Naveau S, Paraf F, et al. A simple biological index for detection of alcoholic liver disease in drinkers. Gastroenterology 1991;100 (5 Pt 1):1397-402. PUBMED | CROSSREF
16. Kim JM. Pathologic diagnosis of hepatic fibrosis. Korean J Hepatol 2006;12 (4s):69-74.
17. Strauss S, Gavish E, Gottlieb P, Katsnelson L. Interobserver and intraobserver variability in the sonographic assessment of fatty liver. AJR Am J Roentgenol 2007;189:W320-3. PUBMED | CROSSREF
18. Nobili V, Pinzani M. Paediatric non-alcoholic fatty liver disease. Gut 2010;59:561-4. PUBMED | CROSSREF
19. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313-21. PUBMED | CROSSREF
20. Nobili V, Comparcola D, Sartorelli MR, Natali G, Monti L, Falappa P, et al. Blind and ultrasound-guided percutaneous liver biopsy in children. Pediatr Radiol 2003;33:772-5. PUBMED | CROSSREF
21. Gressner AM, Gao CF, Gressner OA. Non-invasive biomarkers for monitoring the fibrogenic process in liver: a short survey. World J Gastroenterol 2009;15:2433-40. PUBMED | CROSSREF
22. Lesmana CR, Hasan I, Budihusodo U, Gani RA, Krisnuhoni E, Akbar N, et al. Diagnostic value of a group of biochemical markers of liver fibrosis in patients with non-alcoholic steatohepatitis. J Dig Dis 2009;10:201-6. PUBMED | CROSSREF
23. Alkhouri N, Carter-Kent C, Lopez R, Rosenberg WM, Pinzani M, Bedogni G, et al. A combination of the pediatric NAFLD fibrosis index and enhanced liver fibrosis test identifies children with fibrosis. Clin Gastroenterol Hepatol 2011;9:150-5. PUBMED | CROSSREF
24. Alkhouri N, De Vito R, Alisi A, Yerian L, Lopez R, Feldstein AE, et al. Development and validation of a new histological score for pediatric non-alcoholic fatty liver disease. J Hepatol 2012;57:1312-8. PUBMED | CROSSREF
25. Yang HR, Kim HR, Kim MJ, Ko JS, Seo JK. Noninvasive parameters and hepatic fibrosis scores in children with nonalcoholic fatty liver disease. World J Gastroenterol 2012;18:1525-30. PUBMED | CROSSREF
26. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology 2019;156:1264-81.e4. PUBMED | CROSSREF
27. Enomoto H, Bando Y, Nakamura H, Nishiguchi S, Koga M. Liver fibrosis markers of nonalcoholic steatohepatitis. World J Gastroenterol 2015;21:7427-35. PUBMED | CROSSREF
28. Teare JP, Sherman D, Greenfield SM, Simpson J, Bray G, Catterall AP, et al. Comparison of serum procollagen III peptide concentrations and PGA index for assessment of hepatic fibrosis. Lancet 1993;342:895-8. PUBMED | CROSSREF
29. Forns X, Ampurdanès S, Llovet JM, Aponte J, Quintó L, Martínez-Bauer E, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology 2002;36 (4 Pt 1):986-92. PUBMED | CROSSREF
30. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846-54. PUBMED | CROSSREF
31. Poynard T, Morra R, Ingiliz P, Imbert-Bismut F, Thabut D, Messous D, et al. Biomarkers of liver fibrosis. Adv Clin Chem 2008;46:131-60. PUBMED | CROSSREF
32. Adams LA. Biomarkers of liver fibrosis. J Gastroenterol Hepatol 2011;26:802-9. PUBMED | CROSSREF
33. Ko JS, Yoon JM, Yang HR, Myung JK, Kim H, Kang GH, et al. Clinical and histological features of nonalcoholic fatty liver disease in children. Dig Dis Sci 2009;54:2225-30. PUBMED | CROSSREF
34. Carey E, Carey WD. Noninvasive tests for liver disease, fibrosis, and cirrhosis: is liver biopsy obsolete? Cleve Clin J Med 2010;77:519-27. PUBMED | CROSSREF

35. Yoneda M, Mawatari H, Fujita K, Yonemitsu K, Kato S, Takahashi H, et al. Type IV collagen 7s domain is an independent clinical marker of the severity of fibrosis in patients with nonalcoholic steatohepatitis before the cirrhotic stage. J Gastroenterol 2007;42:375-81. PUBMED | CROSSREF

36. Lydatakis H, Hager IP, Kostadelou E, Mpousmpoulas S, Pappas S, Diamantis I. Non-invasive markers to predict the liver fibrosis in non-alcoholic fatty liver disease. Liver Int 2006;26:864-71. PUBMED | CROSSREF

37. Oberti F, Valsesia E, Pilette C, Rousselet MC, Bedossa P, Aubé C, et al. Noninvasive diagnosis of hepatic fibrosis or cirrhosis. Gastroenterology 1997;113:1609-16. PUBMED | CROSSREF

38. Suzuki A, Angulo P, Lymp J, Li D, Satomura S, Lindor K. Hyaluronic acid, an accurate serum marker for severe hepatic fibrosis in patients with non-alcoholic fatty liver disease. Liver Int 2005;25:779-86. PUBMED | CROSSREF

39. Kim E, Kang Y, Hahn S, Lee MJ, Park YN, Koh H. The efficacy of aspartate aminotransferase-to-platelet ratio index for assessing hepatic fibrosis in childhood nonalcoholic steatohepatitis for medical practice. Korean J Pediatr 2013;56:19-25. PUBMED | CROSSREF