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LETTER TO THE EDITOR

Exploring non-invasive diagnostics and non-imaging approaches for pediatric metabolic dysfunction-associated steatotic liver disease

Toshifumi Yodoshi

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Abstract

In this article, we comment on the article by Qu and Li, focusing specifically on the non-invasive diagnostic approaches for metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD is the most common chronic liver disease in children. Nearly half of pediatric MASLD cases progress to metabolic dysfunction-associated steatohepatitis at diagnosis, often with comorbidities like renal disease, hypertension, type 2 diabetes, and mental health disorders. Early diagnosis and continuous intervention are crucial for managing this "silent organ" disease. Screening is recommended for children aged nine and older with obesity. Liver biopsy remains the diagnostic gold standard; however, due to its invasiveness, non-invasive methods - biomarkers, anthropometric algorithms, serum tests, and imaging - are increasingly vital. This editorial provides an overview of the current non-invasive diagnostic approaches for pediatric MASLD or liver fibrosis.

Key Words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Metabolic dysfunction-associated steatotic liver disease; Metabolic dysfunction-associated steatohepatitis; Insulin resistance; Oxidative stress

Core Tip: This article reviews non-invasive diagnostic approaches and liver fibrosis assessment methods for pediatric metabolic dysfunction-associated steatotic liver disease (MASLD), highlighting the recent nomenclature change and the significance of early diagnosis. MASLD is the most common chronic liver disease in children, with approximately half of the pediatric cases progressing to metabolic dysfunction-associated steatohepatitis at diagnosis and already having comorbidities such as renal disease, sarcopenia, hypertension, and type 2 diabetes mellitus. While liver biopsy is the gold standard for diagnosing MASLD, it is invasive. To avoid liver biopsy in children, developing non-invasive methods such as biomarkers, serum tests, and imaging is essential.

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TO THE EDITOR

In 2023, the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, and 36 other global societies reached a Delphi consensus, agreeing that the condition formerly known as non-alcohol fatty liver disease should henceforth be referred to as metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated steatotic hepatitis (MASH)[1]. Pediatric MASLD is the most prevalent chronic liver disease in children. A meta-analysis reported a prevalence of 7.6% in the general pediatric population and 34.2% in obese children[2]. Risk factors for pediatric MASLD include obesity in the child or their parents, male sex, and ethnicities such as White, Asian, and Hispanic, as well as low serum vitamin D levels, patatin-like phospholipase domain-containing protein 3 gene polymorphisms, glucose intolerance/diabetes, sleep apnea, and mental health disorders[3-6]. Additionally, socioeconomic status is associated with pediatric MASLD, highlighting the importance of considering the socioeconomic conditions of the patient's family when managing pediatric MASLD[7].

Pediatric MASLD, similar to its adult counterpart, presents with the highest prevalence among chronic liver diseases in children[2]. It is frequently associated with comorbidities such as type 2 diabetes mellitus (T2DM)[8,9], sarcopenia[10,11], renal impairment[12], and mental health disorders[4], all of which can complicate the diagnosis and prognosis of the disease. Although the precise impact of these comorbidities on MASLD progression is still under investigation, their presence highlights the complexity of pediatric MASLD management. For example, sarcopenia has been associated with more severe liver outcomes in both children and adults, although the causal relationship between muscle mass and liver disease is not well established. In addition, while renal impairment is associated with worse liver outcomes in adults, more studies are needed to understand its role in pediatric MASLD. Approximately 50% of the pediatric MASLD cases diagnosed through liver biopsy in the United States already show signs of progression to MASH at the time of diagnosis [13]. Currently, MASH-induced cirrhosis is the leading indication for liver transplantation among young individuals in the United States[14], underscoring the importance of proactive prevention and intervention before the liver manifests symptoms of cirrhosis.

In a recent issue of the *World Journal of Gastroenterology*, Qu and Li[15] published an intriguing paper on exploring non-invasive diagnostics for MASLD or assessment for liver fibrosis. This paper provides a valuable summary of non-invasive diagnostic methods for the widely prevalent condition of MASLD. Non-invasive diagnostics are particularly crucial for pediatric MASLD because of the desire to avoid invasive procedures in children. In this article, we focus on the non-invasive diagnostic methods for MASLD and the assessment for liver fibrosis in children with the condition, which were not addressed in their paper. We emphasize the importance of accurately diagnosing MASLD in children, highlighting that the current definitive diagnosis for MASLD relies on liver biopsy, whereas patients diagnosed through ultrasound or magnetic resonance imaging (MRI) are considered to have presumed MASLD[13].

Non-invasive imaging approaches for assessing liver fat accumulation

Imaging techniques such as ultrasound, computed tomography, and MRI are commonly used for MASLD screening. However, when using ultrasound alone to diagnose MASLD, caution should be applied because of its limited sensitivity in the detection of early or mild steatosis. Abdominal ultrasound findings, such as positive liver-kidney contrast and a bright liver, have low diagnostic accuracy for pediatric MASLD, particularly in cases where hepatic fat accumulation affects less than 33% of hepatocytes. This can result in significant MASLD underdiagnosis in the early stages, where symptoms may not yet be apparent and steatosis is less pronounced[3,16]. Due to this limitation, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines do not recommend ultrasound alone for screening[3]. Computed tomography scans, though more accurate than ultrasound with a diagnostic sensitivity of 46%-72% and specificity of 88%-95%, are also unsuitable for routine screening because their use entails radiation exposure and they are less sensitive for detecting mild steatosis[17]. Conversely, MRI, particularly MRI-proton density fat fraction (PDFF), allows for liver fat quantification by integrating specific software such as iterative decomposition of water and fat with asymmetry and least squares estimation quantitative fat imaging into existing MRI systems[18]. MRI-PDFF offers several advantages: It accurately measures liver fat independent of the patient's age, sex, and weight. Also, it can be

performed in less than five minutes, does not require contrast-enhancement, and can detect early stages of fat accumulation (more than 5% of hepatocytes)[18]. Despite its high cost, the accuracy and ability to quantify fat make MRI-PDFF a valuable imaging tool, although its high cost and limited availability are significant drawbacks.

Although simple ultrasound should be avoided for diagnosis, the latest ultrasound techniques using transient elastography (TE) can be utilized for diagnosing MASLD. Meta-analyses on the TE-controlled attenuation parameter (CAP) and MRI-PDFF for diagnosing MASLD in children and adolescents have revealed that MRI-PDFF accurately diagnoses advanced steatosis, with a summary sensitivity of 0.95 [95% confidence interval (CI): 0.92-0.97], specificity of 0.92 (95%CI: 0.77-0.98), and hierarchical summary receiver operating characteristic curves of 0.96 (95%CI: 0.94-0.98) in Table 1[19]. Similarly, TE-CAP accurately diagnoses advanced steatosis, with a summary sensitivity of 0.86 (95%CI: 0.70-0.94), specificity of 0.88 (95%CI: 0.71-0.96), and hierarchical summary receiver operating characteristic curves of 0.94 (95%CI: 0.91-0.95)[19]. Both MRI-PDFF and TE-CAP are highly accurate non-invasive techniques for grading hepatic steatosis in children and adolescents with MASLD. However, a recent study conducted in the United States in 2023 compared the accuracy of MASLD diagnosis using liver histology, CAP, and MRI-PDFF. The findings concluded that CAP did not correlate well with MRI-PDFF modalities and biopsy measures of liver fat[20]. Therefore, while TE-CAP is very convenient and easy to perform, caution is required when using it for diagnosing pediatric MASLD. Other imaging diagnostics include body composition based on bioelectrical impedance analysis, which correlates muscle mass with liver fat[11]. However, predictive equations for the diagnosis of pediatric MASLD based on bioelectrical impedance analysis have not yet been established.

Non-imaging, non-invasive approaches for assessing liver fat accumulation

Similar to adults, studies have used anthropometrics and routine blood tests to predict liver fat content and diagnose MASLD in children. However, no highly accurate equations have been developed so far. Yodoshi *et al*[21] developed a predictive equation for fat accumulation using age, sex, race/ethnicity, anthropometrics, presence of T2DM, blood pressure, and blood tests such as alanine aminotransferase (ALT), aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, insulin, and lipid panels, in pediatric patients diagnosed with MASLD *via* liver biopsy. However, the best cutoff point achieved a sensitivity of 0.74, specificity of 0.75, and area under curve of 0.78, which was not sufficiently useful for MASLD diagnosis. Conversely, a study conducted on presumed MASLD patients diagnosed *via* MRI-PDFF developed a predictive equation using ALT, homeostasis model assessment of insulin resistance, triglycerides, waist circumference, and Tanner stage. This equation demonstrated high sensitivity and specificity in both internal and external validation[22].

Non-invasive imaging approaches for assessing liver stiffness or fibrosis

Liver biopsy remains the gold standard for assessing fibrosis, and several histological scoring systems are used to grade liver injury. Hepatic histology is commonly scored using the classification developed by the non-alcoholic steatohepatitis (NASH) clinical research network. This system evaluates liver steatosis (score 0-3), lobular inflammation (score 0-3), hepatocyte ballooning (score 0-2), and fibrosis stage (score 0-4). The non-alcoholic fatty liver disease activity score, which ranges from 0 to 8, is calculated as the sum of the steatosis, lobular inflammation, and ballooning scores. Non-alcoholic fatty liver disease activity score is widely used as a key tool for NASH activity assessment and fibrosis staging[23]. Definite NASH is diagnosed on the basis of a pattern of liver injury that includes all three components (hepatic steatosis, lobular inflammation, and ballooning degeneration). This scoring system constitutes the foundation for clinical decision-making and provides an essential framework for risk stratification in both pediatric and adult patients. However, due to its invasive nature, novel fibrosis markers such as Mac-2 binding protein glycosylation isomer and autotaxin have been introduced for adults, and they show promising utility[24]. Fibrosis scores such as the fibrosis-4 (FIB-4) index are also used in adults[25]. The FIB-4 score is primarily used in adults, and its application in pediatric MASLD is limited and not widely validated. Currently, there is a paucity of reliable blood tests and scoring systems for the evaluation of fibrosis in pediatric MASLD[21,26]. Xanthakos *et al*[27] reported that setting the liver stiffness cutoff at 2.71 kPa for magnetic resonance elastography (MRE) could enable the detection of advanced fibrosis in pediatric MASH patients diagnosed *via* liver biopsy with 88% sensitivity and 85% specificity. MRE requires an expensive external passive driver device to induce vibrations in the liver during scanning, making it costly. Vibration-controlled TE (VCTE) might be a good alternative for the assessment of liver fibrosis in children. Chaidez *et al*[28] found that VCTE liver stiffness measurements predicted Ishak stages F0-F2 *vs* F3-F6 with an area under the receiver operating characteristic curve of 0.73 for all patients and 0.77 for non-MASLD patients. However, a 2023 study conducted in the United States comparing liver biopsy, MRE, and VCTE found that VCTE did not correlate well with established imaging modalities and biopsy measures of liver stiffness[20]. Therefore, while VCTE is convenient and easy to use, it should be employed cautiously for fibrosis assessment in pediatric MASLD.

Non-imaging, non-invasive approaches for assessing liver stiffness

According to the multicenter observational study in the United States, we previously developed a predictive equation for liver stiffness using age, sex, race and ethnicity, anthropometrics, presence of T2DM, blood pressure, and blood tests in pediatric patients with biopsy-confirmed MASLD. However, the correlation coefficient was low (0.30), making it not useful[21]. A recent Belgian study developed predictive scores for excluding significant fibrosis (≥ F2) in pediatric MASLD patients diagnosed *via* TE, incorporating patient sex, ethnicity, weight *Z*-score, homeostatic model assessment for insulin resistance index, ALT, and presence of hypertension into the scores[29]. Logistic regression analyses established continuous (pFIB-c) and simplified (pFIB-6) diagnostic scores[29]. The pFIB-c and pFIB-6 demonstrated good discriminatory capacity (c-statistic of 0.839 and 0.826), surpassing the existing indices. Both scores achieved negative predictive

Table 1 Comparison of magnetic resonance imaging-proton density fat fraction and transient elastography-controlled attenuation parameter for diagnosing hepatic steatosis in pediatric metabolic dysfunction-associated steatotic liver disease

Method	Sensitivity (advanced steatosis)	Specificity (advanced steatosis)	Advantages	Disadvantages
MRI-PDFF	0.95	0.92	High accuracy for quantifying liver fat, detects early stages of MASLD, non-invasive	High cost, limited availability
TE-CAP	0.86	0.88	More accessible, cost-effective, non-invasive	Less reliable for early-stage MASLD, underdiagnoses when < 33% liver fat

MRI-PDFF: Magnetic resonance imaging-proton density fat fraction; TE-CAP: Transient elastography-controlled attenuation parameter; MASLD: Metabolic dysfunction-associated steatotic liver disease.

values in excess of 90% in the derivation and elastography validation cohorts. However, their performance in the histological cohorts varied (area under receiver operating characteristic curve for the pFIB-c ranged from 0.710 to 0.770), as the scores were less accurate in tertiary referral center populations with a high prevalence of significant fibrosis and elevated ALT levels. Thus, although FIB-6 and pFIB-6 are capable of ruling out significant fibrosis, they cannot effectively detect advanced fibrosis. Although these results are promising, further external validation is necessary to confirm their reliability.

CONCLUSION

MRI-PDFF and MRE are currently the most valuable alternatives to liver biopsy in the diagnosis and assessment of fibrosis in MASLD. In settings where MRI is unavailable, TE-ultrasound and VCTE constitute useful alternatives. These methods, while highly promising, require careful interpretation when used in children to ensure the accurate diagnosis and staging of fibrosis. Although their accessibility and cost-effectiveness should be explored further, these limitations do not overshadow the potential of these non-invasive techniques. Future research focusing on their cost-effectiveness and broader validation in pediatric populations will enhance the utility of these techniques and pave the way for more routine clinical use in pediatric MASLD.

FOOTNOTES

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