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Consensus Statement on Metabolic Dysfunction-Associated Steatotic Liver Disease in Children and Adolescents From the Joint TASL-TSPGHAN Expert Committee

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ABSTRACT

Background and Objective: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver condition in children and adolescents, driven by the global rise in pediatric obesity. In this consensus statement by the Taiwan Association for the Study of the Liver (TASL) and the Taiwan Society of Pediatric Gastroenterology, Hepatology, and Nutrition (TSPGHAN), we highlight the unique clinical challenges in diagnosing and managing this condition in Asian children.

Methods: This consensus was developed by expert members of TASL and TSPGHAN through a comprehensive review of current literature and clinical practice. Key topics included prevalence, screening policies, diagnostic criteria, disease characteristics, and management strategies relevant to pediatric MASLD.

Results: We emphasize the rising prevalence of pediatric MASLD, which correlates strongly with obesity but often remains underdiagnosed due to the lack of screening policy for at-risk individuals and variations in diagnostic criteria. This review also discusses the distinct natural history and histopathological features of pediatric MASLD, underscoring the critical need for a greater understanding of its long-term outcomes. Currently, liver enzymes and ultrasonography are commonly used for screening and diagnosis, though these methods have limitations. The diagnostic imaging and novel non-invasive biomarkers specifically tailored for pediatric MASLD are in urgent need. Clinical management continues to rely on lifestyle interventions, with no pharmacological treatments currently approved for pediatric MASLD.

Conclusion: Effective management of pediatric MASLD requires a comprehensive approach to risk assessment, early detection, and intervention, tailored to the disease's unique pathophysiology in children.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by excessive fat accumulation in the liver in the presence of cardiometabolic risk factors. The term MASLD encompasses a spectrum of liver conditions, ranging from simple hepatic steatosis to varying degrees of necroinflammation, with or without fibrosis (referred to as metabolic dysfunction-associated steatohepatitis, MASH), and can progress to end-stage liver cirrhosis [1]. The rise in pediatric obesity prevalence has led to an increase in metabolic diseases such as insulin resistance, type 2 diabetes mellitus, hypertension, and dyslipidemia in the pediatric population, all of which are closely linked to MASLD. Over the past decades, MASLD has become the most common chronic liver disease in children and adolescents [2].

The renaming of "nonalcoholic fatty liver disease (NAFLD)" to metabolic dysfunction-associated steatotic liver disease (MASLD) was proposed in 2020 to emphasize the metabolic dysfunction central to the disease's pathophysiology and to avoid the stigmatizing term "fatty" [3]. An international, multi-society Delphi process formalized the new nomenclature in June 2023, defining MASLD as the presence of hepatic steatosis alongside at least one cardiometabolic risk factor, such as obesity, type 2 diabetes, or other metabolic dysregulation [4]. However, despite this revised framework, other potential liver diseases must always be considered when evaluating pediatric hepatic steatosis. A recent report from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Association for the Study of the Liver (EASL) has highlighted the need for parallel assessment of MASLD and other potential liver diseases. Conditions such as Wilson's disease, autoimmune hepatitis, and lysosomal acid lipase deficiency can present with hepatic steatosis [5], and failure to identify these treatable conditions may lead to serious long-term consequences.

While controversies remain, the new term "MASLD" addresses many of the limitations of NAFLD and has been endorsed by multiple international pediatric academic societies [6]. In this consensus statement, we adopt the new nomenclature "MASLD" while acknowledging the diagnostic challenges unique to pediatric patients. This review aims to provide an updated overview of pediatric MASLD, with a particular emphasis on studies conducted in Asia.

This consensus statement was formed by a joint expert committee of the Taiwan Association for the Study of Liver Diseases (TASL) and Taiwan Society of Pediatric Gastroenterology, Hepatology, and Nutrition (TSPGHAN). The expert panel was established in October 2023 and held several rounds of consensus meetings to determine the scope and content of this article. The final content was approved by all committee members.

1.1 | Epidemiology

Over the past decades, the burden of overweight and obesity in children has increased significantly worldwide. As a consequence, the prevalence of MASLD in children is rising [7]. The prevalence of pediatric MASLD varies widely across different studies due to factors such as country of study, diagnostic tools, etc. The global prevalence of the disease is estimated to be 7.4% in the general pediatric population and up to 52.5% in obese children [8]. The prevalence is generally higher in males compared with females and increases with greater body mass index (BMI) [2]. Many children may remain undiagnosed, especially young children, due to no universal screening programs and a lack of awareness.

In Taiwan, the prevalence of pediatric MASLD in previous studies varies significantly due to differences in diagnostic criteria and target populations. In Taipei City, the capital of Taiwan, 19.5% of obese adolescents were diagnosed with MASLD using liver ultrasonography [9]. Among adolescents aged 12 or 13 years old in Hualien City, a suburban area on Taiwan's east coast, the prevalence of MASLD diagnosed by liver ultrasonography was 16.0% among those with normal weight, 50.5% among overweight individuals, and 63.5% among obese individuals [10]. The socioeconomic disparity may contribute to differences in MASLD prevalence between the two cities in Taiwan.

In Japan, Tominaga et al. reported a prevalence of MASLD of 2.6% in 810 Japanese children aged 4 to 12 years [11]. Another Japanese study involving 228 obese children aged 6–15 years found a prevalence of elevated serum alanine transferase (ALT) levels at 24.1% [12]. In Korea, the prevalence of elevated serum ALT levels was 8% among 1594 obese adolescents aged 10–19 years, as reported in the Korean National Health and Nutrition Examination Survey 1998 [13]. A recent meta-analysis revealed significant geographic variation in the prevalence of MASLD in the general pediatric population, with the highest rates observed in North America at 8.53%, followed by Asia at 7.01%, and the lowest in Europe at 1.65% [8]. Overall, MASLD represents a significant disease burden in the Asian pediatric population, particularly among children with obesity.

1.2 | Natural History

The natural history of adult MASLD is well-known, with progression to steatohepatitis (MASH), liver cirrhosis, hepatocellular carcinoma, and liver failure [14]. However, the long-term progression of pediatric MASLD is not as well established. For example, MASLD is a rare indication for liver transplantation in children [15] suggesting either a shorter time for disease progression or a different disease outcome compared to adults.

In a 20-year follow-up study of 66 children, two children died, and two underwent liver transplantation due to decompensated cirrhosis. The observed survival free of liver transplantation was significantly shorter in the MASLD cohort [16]. In a study comparing paired liver histologic changes from 122 children with MASLD who received standard-of-care lifestyle advice, half of the children improved in MASH or fibrosis severity. Ongoing progression occurred in more than one-third within 2 years. Fibrosis improved in 34% of the children but worsened in 23% [17]. A recent study conducted in Amsterdam followed

133 adolescents with obesity for MASLD screened by proton magnetic resonance spectroscopy (1H-MRS) and the Enhanced Liver Fibrosis (ELF) test for 10 years. One-third of adolescents with obesity developed steatosis, while in another third, steatosis resolved. Six percent of those with MASLD had developed advanced fibrosis at follow-up [18].

For the general pediatric population, a study conducted in Taiwan followed 440 children with obesity aged 9–10 and 12–13 years, recruited from schools, for 2 years. Among the subjects without MASLD at baseline, 7.6% developed MASLD. In contrast, among the subjects with MASLD at baseline, 52.9% experienced MASLD remission. Changes in BMI predicted whether children with obesity developed or resolved MASLD [9]. Other factors include insulin resistance, dietary habits, physical inactivity, genetic predisposition, and metabolic syndrome components like dyslipidemia and hypertension. Addressing these factors through lifestyle modifications is crucial for managing and potentially reversing MASLD progression.

1.3 | Histology

MASLD is categorized into metabolic dysfunction steatotic liver (MAFL), featured by isolated liver steatosis, and MASH, which includes additional features such as hepatocyte ballooning, lobular inflammation, apoptotic bodies, and Mallory-Denk bodies [19]. The distinct histologic morphologies make it discernible from other liver diseases. Common features include steatosis, affecting at least 5% of hepatocytes, predominantly appearing as macrovesicular. Initially concentrated in zone 3, steatosis may spread to zone 2 and 1 as the disease progresses. Hepatocellular injury in MASH involves ballooning degeneration and apoptosis. Portal inflammation is more commonly seen in pediatric patients. Mallory-Denk bodies indicate worse outcomes when combined with steatohepatitis and fibrosis. MASH-associated fibrosis includes zone 3 perisinusoidal/pericellular and portal fibrosis, which, if untreated, could potentially lead to cirrhosis. Biopsies at the late stage might lack active disease features.

Several grading systems have been proposed to determine the severity of MASH [20]. Brunt et al. introduced a grading system considering steatosis, ballooning degeneration, inflammation, and fibrosis patterns. The NASH Clinical Research Network (NASH CRN), sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), introduced a scoring system for MASLD histological changes. Bedossa et al. proposed a system similar to the NASH CRN but added an algorithm categorizing MASLD into MAFL and MASH based on specific histological scores.

Pediatric MASLD's histological features may differ from those of adult patients. Schwimmer et al. categorized pediatric MASLD into two types: type 1, resembling adult patterns and more prevalent in girls, and type 2, common in boys, featuring zone 1 or panacinar steatosis with minimal fibrosis [19, 21]. Subsequent studies highlighted overlapping traits. The NASH CRN identified a unique "zone 1 borderline pattern," similar to Schwimmer's type 2, often found in prepubertal boys and lacking typical adult MASH characteristics. The majority of children with advanced fibrosis exhibit the type 2 MASH pattern.

1.4 | Clinical Manifestations

Most patients with MASLD are asymptomatic. Some may experience right upper quadrant pain, fatigue, and hepatomegaly. Elevated liver enzymes, signs of insulin resistance like acanthosis nigricans, and abnormal lipid profiles may be incidentally discovered during routine testing. Patients typically seek medical care following school BMI screenings for obesity/overweight, incidental findings of elevated ALT levels, or referrals from other healthcare professionals due to physical problems related to metabolic disturbances. Therefore, screening individuals at risk for MASLD, such as children with obesity or a family history of MASLD, is crucial for early detection and proper management.

Clinically, the measurement of BMI, waist circumference (WC), and blood markers (ALT, AST, GGT, glucose, and lipid profiles) can facilitate the diagnosis of MASLD. WC has shown stronger associations with metabolic syndrome compared to BMI, and the risk of MASLD increases with increasing WC [22].

1.5 | Pathophysiology

The pathogenesis of MASLD is complex and multifactorial, with both environmental and genetic contributions, and the "multihit hypothesis" is currently accepted [23, 24]. The risk factors include intake of free sugars (e.g., sucrose or fructose), decreased physical activity, sleep shortages, socioeconomic deprivation, and psychological disorders [25]. Pathogenic drivers and the mechanisms leading to disease are likely to be heterogeneous among individual patients.

In contrast to adults, where environmental factors play a major role, maternal and perinatal risk factors may have a greater influence on the risk of MASLD development in children. Factors such as gestational diabetes and preterm birth are known to increase the risk of pediatric MASLD. Conversely, prolonged breastfeeding ($\geq$ 6 months) may provide a protective effect against its development [26]. Prenatal nutrition significantly impacts postnatal fatty liver development; for example, excessive maternal cholesterol intake during lactation and maternal obesity increase offspring susceptibility to fatty liver, a susceptibility that persists even with postnatal consumption of a low-fat diet [27]. Furthermore, prenatal steroids combined with a postnatal high-fat diet can lead to significant liver steatosis, associated with oxidative stress and inflammation [28].

Contaminants in the food chain, such as microplastics, pose significant health risks. Exposure to microplastics disrupts liver metabolites and increases intestinal permeability, leading to triglyceride accumulation [29]. These exposures are linked to adult MASLD and are particularly critical during key windows of growth and development in children [30].

1.6 | Gut Microbiota and Intestinal Barrier

The gut-liver axis, which describes the bidirectional interaction between gut microbiota and the liver, plays a crucial role in MASLD pathogenesis (Figure 1) [31, 32]. In pediatric MASLD, this relationship is particularly influenced by dietary patterns, gut microbiome maturation, and early-life exposures, including antibiotic use, making the gut-liver axis an especially relevant pathway in children [32]. Given the growing interest in microbiome-targeted therapies, such as probiotics and fecal microbiota transplantation (FMT), etc. [33, 34], understanding the gut-liver axis is essential for developing future MASLD treatment strategies. While mechanisms such as insulin resistance, lipotoxicity, and oxidative stress are well-recognized contributors to MASLD [35], this consensus statement highlights gut microbiota due to its emerging clinical relevance and potential as a modifiable therapeutic target.

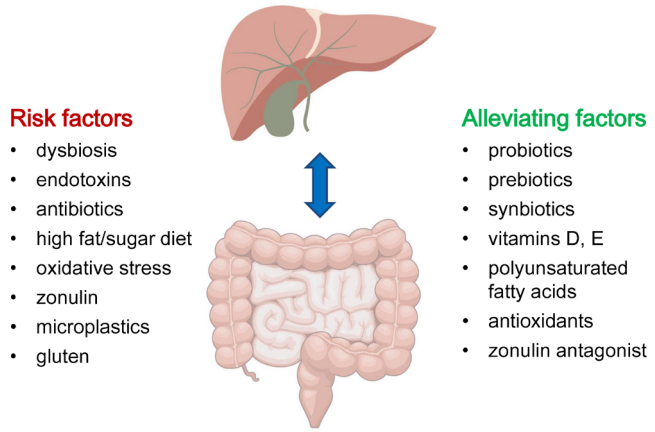

FIGURE 1 | Risk and alleviating factors associated with MASLD in the context of the gut-liver axis.

In mice, gut microbiota composition affected the response to a high-fat diet inducing hyperglycemia and hepatic steatosis [36]. A meta-analysis comparing gut microbiomes of MASLD patients and controls found that MASLD patients had higher levels of *Escherichia*, *Prevotella*, and *Streptococcus*, and lower levels of *Coprococcus*, *Faecalibacterium*, and *Ruminococcus*, indicating a strong link between gut microbiota and MASLD [37].

Clinical trials targeting gut microbiota modification have produced controversial results. Table 1 summarizes trials involving children. Vajro et al.'s study using *L. rhamnosus* GG (1.2×10^{10} CFU/day) reduced ALT levels but did not improve liver steatosis [38]. Alisi et al. employed VSL#3, showing improvements in moderate and severe MASLD [39]. Famouri et al.'s probiotic mixture reduced liver enzyme levels, cholesterol, triglycerides, and LDL in obese children with MASLD [40]. The efficacy of probiotics in pediatric MASLD remains debated due to the small sample sizes, variable inclusion criteria, and different intervention protocols in these studies. A trial in adults with MASLD found significant hepatic fat reduction following fecal microbiota transplantation (FMT), which correlated with shifts in gut microbiota composition toward that of healthy individuals [34]. However, there are still limited FMT trials for pediatric MASLD. Overall, while the current effectiveness of microbiome-focused therapies is limited, innovative advancements such as engineered bacteria, prebiotics, postbiotics, and phages may hold promise as therapeutic strategies for MASLD [33].

Impairment of intestinal wall integrity plays a significant role in the pathogenesis of MASLD [41]. Miele et al. were the first to demonstrate increased gut permeability and small intestinal

TABLE 1 | Effects of probiotics on pediatric MASLD.

Probiotics	Duration (week)	Patient no. (tested: controls)	Age (year)	Results
L. rhamnosus strain GG (1.2×10^{10} CFU/day) [38].	8	20 (18: 2)	10.7 (mean)	1. *L. rhamnosus* strain GG significantly decreased ALT irrespective of changes in BMI z-score and visceral fat. 2. TNF-α levels and ultrasonographic parameters remained unchanged
VSL#3: containing 8 strains, *S. thermophilus*, *Bifidobacteria* (*B. breve, B. infantis, B. longum*), *L. acidophilus, L. plantarum, L. paracasei*, and *L. delbrueckii subsp. Bulgaricus* [39].	16	44 (22: 22)	9–12	1. VSL#3: Moderate MASLD reduced 55%–9%, severe 45%–0%. Placebo: Moderate 64%–76%, severe 36%–17%. 2. BMI decreased and GLP-1 increased in the VSL#3 group.
L. acidophilus ATCC B3208, 3×10^{9} (CFU); *B. lactis* DSMZ 32269, 6×10^{9} CFU; *B. bifidum* ATCC SD6576 and *L. rhamnosus* DSMZ 21690, 2×10^{9} CFU [40].	12	64 (32: 32)	12.7 (mean)	1. The within-group comparison revealed a significant decrease in liver enzymes and waist circumferences in the intervention group. 2. Probiotic intervention normalized liver sonogram results and decreased liver enzymes, cholesterol, triglycerides, and LDL.

bacterial overgrowth in adults with MASLD [42]. Rosso et al. found that higher zonulin levels were associated with increased WC, a well-known risk factor for MASLD [43].

The dysbiosis of gut microbiota is linked with increased circulating zonulin concentration and reduced expression of intestinal tight junction (TJ) proteins. The zonulin signaling pathway contributes to TJ dysfunction and increased gut permeability. Autopsies of obese individuals have shown decreased intestinal TJ and adherens junction proteins [44]. Furthermore, obese children exhibit significantly higher zonulin levels compared to their healthy peers [45].

Investigations into the therapeutic potential of restoring intestinal integrity have been explored. Yeung et al. demonstrated the effects of a vitamin D-deficient diet on intestinal epithelial integrity and zonulin expression in a mouse model and suggested that vitamin D supplementation may reduce intestinal inflammation and restore intestinal barrier function [46]. Drugs targeting zonulin functions may hold therapeutic potential for MASLD and warrant further investigation (Figure 1).

1.7 | Genetics

Over the last two decades, genetic variations in loci such as *PNPLA3*, *TM6SF2*, *GCKR*, *MBOAT7*, *HSD17B13*, and more have been identified as contributors to MASLD susceptibility in children (Table 2) [47].

The *PNPLA3* I148M variant is associated with hepatic fat content and liver damage in adults and obese children [48]. It impairs triglyceride hydrolysis, leading to hepatic steatosis, and affects hepatic stellate cells, contributing to liver fibrosis. *TM6SF2* is a gene involved in lipid transfer and hepatic steatosis. The E167K variant is associated with high hepatic triglycerides, liver enzyme levels, and hepatic fibrosis [49]. Glucokinase regulatory protein (*GCKR*) is an inhibitor of glucokinase that regulates glucose storage and disposal and controls de novo lipogenesis by regulating the flux of glucose into hepatocytes. Variants in *GCKR* are associated with liver fat content, MASLD risk, and fibrosis progression [50]. The *MBOAT7* variant influences hepatic triglyceride synthesis, primarily by increasing the turnover of phosphatidylinositol. The rs641738 variant is associated with MASLD risk and liver fibrosis severity, but the effect may vary among ethnicities [51, 52]. HSD17B13 is crucial for hepatic lipid homeostasis and MASLD. A common loss-of-function variant of *HSD17B13* (rs72613567: TA) protects patients against MASLD [53]. A Korean study found *SAMM50*, alongside *PNPLA3* and *TM6SF2*, increased MASLD susceptibility in overweight children. SAMM50 regulates mitochondrial functions, affecting insulin resistance [54].

Genetic variations may help with risk stratification and treatment guidance. A recent meta-analysis found 17 loci linked to MASLD, revealing genetic predispositions involving genes like *TOR1B*, *COBLL1/GRB14*, *INSR*, and *SREBF1*, etc., along with previously validated MASLD-associated variants. These variants underscore mitochondrial, cholesterol, and lipid metabolism pathways. Notably, individuals with high genetic risk have a 2.5 to 6-fold increased risk of developing MASLD, cirrhosis, and hepatocellular carcinoma [55]. In adults with MASLD, the 2024 EASL-EASD-EASO Clinical Practice Guidelines recommend that genetic risk profiles (e.g., *PNPLA3* p.I148M variant and/or polygenic risk scores) can be assessed to personalize risk stratification in specialized centers [56]. However, due to insufficient clinical evidence, routine genetic testing for children with MASLD is not currently recommended, as stated in ESPGHAN and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines [1, 57].

1.8 | Screening

Currently, the recommendations for screening strategies from major academic societies are controversial. NASPGHAN guidelines recommend screening all obese children aged 9–11 years using ALT with sex-specific cutoffs (50 U/L for boys and 44 U/L for girls) [1]. In contrast, The AASLD guidelines do not recommend screening for MASLD in children, as its diagnosis may not significantly impact management beyond the existing

TABLE 2 | Genetic variations associated with pediatric MASLD.

Gene	Variant	Consequence	Effect	Phenotype
PNPLA3 [48]	rs738409 C>G	Missense variant	Lipid droplets remodeling	↑ MASLD
TM6SF2 [49]	rs58542926 C>T	Missense variant	Modulate hepatic VLDL secretion	↑ MASLD
GCKR[a] [50]	rs780094 C>T	Intronic variant	Modulate hepatic lipogenesis	↑ MASLD
	rs1260326 C>T	Missense variant		
MBOAT7 [51, 52]	rs641738 C>T	Missense variant	Remodeling of phosphatidylinositol	↑ MASLD
				No effect in a study conducted in Taiwan
HSD17B13 [53]	rs72613567: TA	Splice donor variant	Retinol dehydrogenase activity	↓ MASLD
SAMM50 [54]	rs2073080 C>T	Intronic variant	Regulate mitochondrial functions	↑ MASLD
	rs3761472 A>G	Missense variant		

[a]GCKR rs780094 and rs1260326 are in strong linkage disequilibrium.

treatment strategies for obesity [58]. Another concern is the variability in the upper normal limit of ALT across different countries/regions, which may impact the screening's effectiveness [59]. ESPGHAN guidelines recommend the use of liver ultrasonography because it is safe, widely available, and relatively inexpensive [57].

Given the substantial number of children with overweight and obesity, there is a pressing need for the early detection of MASLD in at-risk children. Pediatricians and other primary healthcare providers play a crucial role in screening these children and coordinating care with pediatric gastroenterology specialists. The 2023 AAP Clinical Practice Guideline recommends assessing serum ALT in children aged 10 years and older who are obese, and suggests that assessment may also be appropriate for children aged 10 years and older who are overweight with additional risk factors such as prediabetes and diabetes mellitus, obstructive sleep apnea, dyslipidemia, or a sibling with MASLD [60]. However, it is important to note that a normal ALT level does not definitively rule out MASLD [61]. Liver ultrasonography or transient elastography, such as vibration controlled transient elastography (VCTE), can be considered alternative screening options [62], depending on their availability, cost, and the experience of the operators at each institution. After disease identification, although there are currently no approved drugs for treating MASLD in children, adopting a healthy lifestyle, though challenging, can significantly improve health outcomes [63]. This approach helps manage not only liver-related outcomes but also addresses other cardiometabolic derangements, thereby promoting overall better health.

In East Asia, despite the increasing burden of pediatric MASLD, routine screening remains limited. This consensus statement recommends an age-based screening approach integrated into school-based health check-ups and pediatric obesity clinics. ALT should be used as the initial screening tool, with sex- and age-specific cutoff values tailored to local population data [59] Additionally, liver ultrasonography or transient elastography may be considered for obese children to improve the accuracy of identifying positive cases [64].

1.9 | Diagnostic Imaging Modalities

Ultrasonography-based modalities and magnetic resonance imaging (MRI)-derived techniques are two common clinical imaging tools used to assess MASLD.

Liver ultrasonography is safe, widely available, and relatively inexpensive for MASLD screening. However, its positive predictive value for diagnosing MASLD is relatively low, especially for mild hepatic steatosis with less than 30% fat accumulation. A study found that visceral fat thickness and abdominal subcutaneous fat thickness, as measured by ultrasonography, are positively correlated with the extent of hepatic steatosis in children [22]. As ultrasonography is widely used in Asia for assessing fatty liver in children, further research is needed to clarify its role in large-scale screening for pediatric MASLD.

Ultrasonography-based VCTE evaluates both hepatic steatosis, using the controlled attenuation parameter (CAP), and fibrosis, through liver stiffness measurement (LSM). Its clinical application in pediatric MASLD diagnosis is increasing, with recent studies demonstrating good inter- and intra-observer agreement [65]. The EASL Clinical Practice Guidelines recommend LSM as a reliable predictor of liver-related events, liver-related mortality, and overall mortality in adults, supporting its use for ruling in or ruling out advanced fibrosis. In adults, a VCTE-derived LSM < 8 kPa can effectively rule out advanced fibrosis, while LSM > 12 kPa is considered diagnostic for ruling in advanced fibrosis [56]. However, the applicability of these thresholds to pediatric patients remains uncertain. A meta-analysis evaluating VCTE-derived liver stiffness ranges in healthy children proposed an upper limit of normal liver stiffness at 5.56 kPa [66]. However, for diagnosing advanced fibrosis in children with MASLD, current studies lack sufficient evidence to establish definitive VCTE-derived LSM cut-offs. Therefore, this consensus statement does not propose a universal pediatric-specific LSM threshold.

Magnetic resonance-proton density fat fraction (MR-PDFF) and magnetic resonance elastography (MRE) provide an accurate assessment of fat distribution and fibrosis across the liver, with the highest diagnostic accuracy compared to other modalities [67, 68]. MRE measures liver stiffness using a modified phase-contrast method and is especially useful for patients with morbid obesity, ascites, or bowel interposition between the liver and anterior abdominal wall.

1.10 | Non-Invasive Biomarkers

Due to the invasive nature of liver biopsy and the impracticality of performing it on a large number of patients, there is an urgent need for non-invasive biomarkers for MASLD. Clinically, liver enzymes such as ALT, AST, and gamma-glutamyl transferase (GGT) are widely used as screening tools, but they lack specificity for diagnosing MASLD or differentiating between simple steatosis and MASH. Current efforts are underway to develop non-invasive biomarkers and combinations thereof for diagnosing MASLD, monitoring disease progression, and assessing responses to treatment.

Widely accepted methods to identify steatosis in adults include the fatty liver index (FLI), which consists of BMI, WC, triglycerides, and GGT; the hepatic steatosis index (HSI), which includes BMI and diabetes; and SteatoTest, which comprises 10 biochemical tests, age, gender, and BMI [69].

Among the biomarkers for assessing MASH, cytokeratin-18 (CK18) is extensively used to detect MASH and predict disease severity [70]. CK18 is also combined with other serum biomarkers to diagnose MASH, such as in combinations with ALT or with adiponectin and IL-6.

For assessing fibrosis severity, the Fibrosis (FIB)-4 index, which includes age, platelet count, AST, and ALT, and NAFLD fibrosis score (NFS), which includes age, BMI, hyperglycemia, AST/ALT ratio, platelets, and albumin, are most commonly used for MASLD in adults [71]. For children, the pediatric NAFLD fibrosis index (PNFI) developed by Nobili et al. uses age, WC, and triglycerides to determine the degree of fibrosis, showing good

predictive performance in predicting liver fibrosis [72]. However, a recent large-scale validation study assessing the predictive performance of several noninvasive fibrosis scores for pediatric MASLD found that for the detection of moderate fibrosis, the area under the receiver operating characteristic curve (AUROC) was 0.611 for FIB-4 and 0.712 for PNFI, indicating a lack of diagnostic accuracy to replace liver biopsy for staging fibrosis [73]. Recently, a new clinical prediction model, Fibro-PeN, based on 16 commonly available clinical parameters, has been proposed for discriminating moderate-to-severe fibrosis from none or mild fibrosis in children with MASLD, demonstrating an AUROC of 0.79 [74]. In addition to Fibro-PeN, two risk scores, pFIB-c and pFIB-6, were developed to exclude significant fibrosis (≥F2) in general obese pediatric populations [75]. Both pFIB-c and pFIB-6 exhibited high negative predictive values (>90%) and strong discriminatory capacity (AUROCs 0.839 and 0.826). However, Fibro-PeN, pFIB-c, and pFIB-6 were all developed based on Western pediatric cohorts, and their applicability to East Asian children remains uncertain. Further validation in this region is required before these models can be widely implemented in clinical practice.

2 | Treatment

The goal of treatment for MASLD is remission of the disease, with ALT commonly used as a surrogate marker for decreasing liver steatosis and inflammation. Liver histopathology remains the gold standard for evaluating treatment efficacy, but the frequency and timing of follow-up biopsies must be weighed against the risks of the procedure [1]. Treatment approaches include lifestyle intervention, pharmacological treatment, and metabolic bariatric surgery (Figure 2).

2.1 | Lifestyle Intervention

Since most pediatric MASLD patients are obese, lifestyle intervention is recommended as the first-line treatment, including dietary changes, physical exercise, and behavioral modifications. A weight reduction of 7%–10% through lifestyle intervention can reverse MASH in histology in adult patients [76]. In children with MASLD, a BMI z-score reduction of >0.25 is associated with significant changes in serum ALT levels [77]. However, individual responses and compliance to lifestyle intervention vary widely, making it difficult to define an optimal dietary or exercise program that can fit everyone. Therefore, a personalized approach and family-based lifestyle education are crucial. A multidisciplinary team, including a pediatrician, dietitian, physical therapist, psychologist, and nurse coordinator, is necessary to provide comprehensive medical advice [78]. In East Asia, dietary habits and lifestyle factors differ from Western populations, necessitating culturally adapted lifestyle interventions. Family-based programs should prioritize reducing sugar-sweetened beverage consumption, increasing dietary fiber intake, and promoting physical activity, ensuring long-term adherence and effectiveness [78].

2.2 | Pharmacological Treatment

In March 2024, the US Food and Drug Administration (FDA) approved resmetirom as the first medication for treating adult MASH patients with liver fibrosis. Adults with biopsy-confirmed MASH and a fibrosis stage of F1B, F2, or F3 showed both MASH resolution and fibrosis improvement after 52 weeks of resmetirom treatment [79]. However, there are still no FDA-approved pharmacotherapies for pediatric MASLD. Most of the pediatric

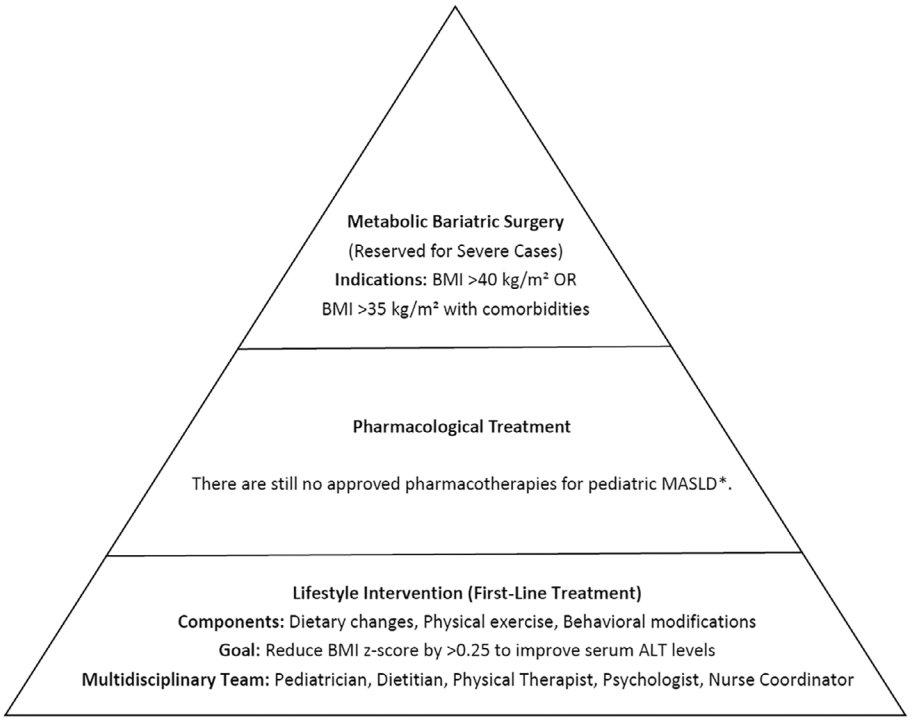

FIGURE 2 | Pediatric MASLD treatment pyramid.

TABLE 3 | Pharmacological treatments for pediatric MASLD.

Drug	Mechanism	Dose	Result	Evidence
Vitamin E [80]	Anti-oxidant to reduce oxidative stress	400 IU twice daily (RCT)	• Improvement in histology and resolution of MASH • No achievement of sustained ALT reduction	Long-term efficacy and safety unknown
Metformin [80, 81]	Increase insulin sensitivity	500 mg twice daily (RCT)	• No achievement of sustained ALT reduction • No improvement of histology	Not recommend
Vitamin D [82]	Anti-inflammation Anti-oxidant	2000 IU once daily for 6 months (RCT)	• Improvement steatosis by histology • ALT level reduction	For children with serum 25(OH) D levels below 20 ng/mL
Cysteamine bitartrate [83]	Anti-oxidant to reduce oxidative stress	Depend on body weight (RCT)	• No improvement in histology • ALT level reduction	Not recommend
Losartan [84]	Reducing PAI-1 production Increasing insulin sensitivity	100 mg/day (RCT)	No ALT reduction	Not recommend
Omega-3 fatty acids [85]	Anti-inflammation Anti-oxidant	Variable drug doses	Improve steatosis by ultrasonography	Controversial

Abbreviations: ALT, alanine aminotransferase; MASH, metabolic dysfunction-associated steatohepatitis; PAI-1, plasminogen activator inhibitor-1; RCT, double-blind randomized controlled trial.

studies are limited to small sample sizes and lack histology evidence for outcome measurement. The medications that have been studied in pediatric MASLD are summarized in Table 3.

Vitamin E is the only pharmacotherapy that has shown benefits in liver histology in pediatric MASLD and is recommended by the 2018 American Association for the Study of Liver Diseases (AASLD) practice guidelines for children with biopsy-proven MASH [58]. However, the long-term safety of high-dose vitamin E in children is unknown, and the risks and benefits should be discussed with each patient.

Ongoing clinical trials for pediatric MASLD treatment include the glucagon-like peptide-1 receptor (GLP-1) analogs (NCT05067621) and sodium-glucose co-transporter-2 (SGLT2) inhibitor (NCT03867487). Glucagon-like peptide-1 receptor (GLP-1) analogs show promise for treating pediatric MASLD, given their established efficacy and safety in managing pediatric type 2 diabetes mellitus and obesity [86]. In adults, GLP-1 analog treatments have been linked to decreased liver fibrosis in type 2 diabetic patients with MASLD [87]. Further large randomized controlled trials targeting liver outcomes in children with MASLD are needed.

2.3 | Metabolic Bariatric Surgery

Metabolic bariatric surgery is generally safe and effective for morbidly obese adolescents in reducing BMI. Studies in adolescents have shown histological reversion of MASH and fibrosis and improvement in obesity-related comorbidities like hypertension, diabetes, dyslipidemia, and sleep apnea after surgery [88]. However, long-term follow-up has revealed specific micronutrient deficiencies (e.g., hypoferritinemia) and the need for additional abdominal procedures in some participants [89]. Currently, metabolic bariatric surgery is not recommended solely for the treatment of pediatric MASLD, except in adolescents with a BMI over 40 kg/m^2 or those with a BMI over 35 kg/m^2 who also have serious obesity-related comorbidities [60].

3 | Future Direction and Conclusion

Research in the field of MASLD has rapidly increased over the past decade. Despite this progress, significant gaps in clinical practice remain. First, while the new MASLD definition has been proposed, its applicability to pediatric populations requires further consideration, as other potential hepatic conditions, including Wilson's disease, autoimmune hepatitis, and inborn errors of metabolism, should not be overlooked [5]. Second, it's crucial to develop age-based non-invasive biomarkers and imaging techniques to enable early disease detection in at-risk children and to monitor the disease without subjecting them to invasive procedures like liver biopsy. Third, large-scale, longitudinal studies are needed to optimize pediatric MASLD screening strategies and assess long-term disease progression, particularly in Asian populations, where unique genetic, environmental, and lifestyle factors may influence

disease trajectory. Fourth, drug development and clinical trials tailored specifically to children are imperative, as extrapolating results from adult trials is not justified [90]. Addressing the challenges posed by pediatric MASLD requires a multi-faceted approach. By focusing on these areas, we can better manage MASLD in children, ultimately improving their long-term health outcomes.

4 | Key Statements in Pediatric MASLD

4.1 | Screening

- Incidental findings of abnormal liver enzymes should prompt an evaluation for MASLD in individuals without other known causes.
- Providers may consider screening obese children older than 10 years or overweight children older than 10 years with additional risk factors such as insulin resistance, dyslipidemia, or a family history of MASLD. However, the cost-effectiveness of this approach should be evaluated in large prospective studies.
- Currently, liver enzymes and ultrasonography are commonly used for screening and diagnosis, though both methods have limitations.
- ALT is a relatively low-cost and widely available screening tool for the general obese pediatric population. However, optimal age- and sex-specific thresholds should be applied for accuracy.
- Liver ultrasonography may serve as an alternative screening option, depending on availability, cost, and the operator's experience at each institution.

4.2 | Diagnosis

- Liver biopsy remains the gold standard for assessing disease activity and staging MASLD, and it helps rule out alternative causes of liver disease.
- Unlike in adults, blood biomarker-derived scores such as FIB-4 have limited accuracy for assessing MASLD in children.
- The use of ultrasonography-based transient elastography (e.g., VCTE) to assess liver steatosis and fibrosis in children with MASLD is increasing, but optimal cutoffs specific to children still need to be defined.
- Clinicians should evaluate associated metabolic risk factors (e.g., obesity, diabetes, dyslipidemia, hypertension, sleep apnea) and coexisting liver diseases in children with MASLD.

4.3 | Treatment

- Lifestyle interventions, including dietary modifications, physical activity, and behavioral changes, are recommended as the first-line treatment.
- Despite the approval of resmetirom in March 2024 for treating MASH in adults, there are still no approved pharmacotherapies for pediatric MASLD.
- Glucagon-like peptide-1 receptor agonists (e.g., liraglutide, semaglutide) are approved for treating obesity in adolescents. Although the weight loss associated with GLP-1 receptor agonists may benefit liver health, there is currently insufficient evidence to recommend their specific use for the treatment of MASLD.

4.4 | Future Directions

- Further research is needed to better understand the natural history of MASLD in children.
- The development and validation of effective non-invasive tests (e.g., blood biomarker-based scores, transient elastography, etc.) for diagnosing and monitoring MASLD activity and progression in children is crucial.
- Efforts should focus on the development of effective pharmacologic treatments for children with MASH.

Conflicts of Interest

The authors declare no conflicts of interest.

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