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Identification of pediatric MASLD using insulin resistance indices

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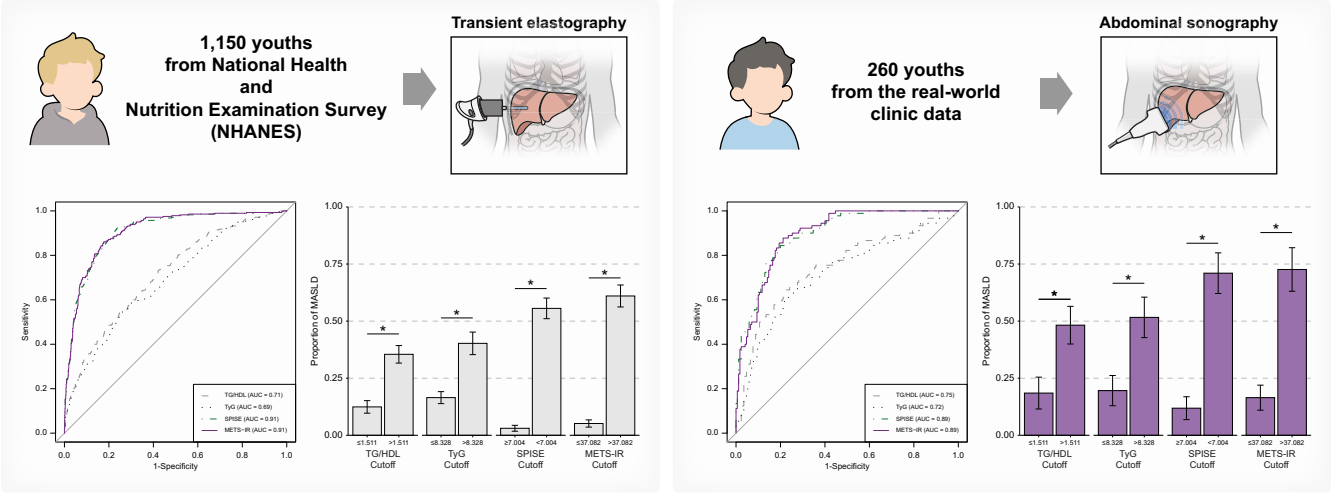
Graphical abstract



Conclusion **SPISE and METS-IR are powerful predictive markers for pediatric MASLD. The optimal cutoff values of SPISE and METS-IR for predicting pediatric MASLD are <7.004 and >37.082, respectively.**

Highlights:

- SPISE and METS-IR are powerful predictive markers of pediatric MASLD.
- SPISE and METS-IR have superior MASLD predictive ability than TG/HDL and TyG.
- The optimal cut-off values for SPISE and METS-IR are <7.004 and >37.082, respectively.

Impact and implications:

The increasing prevalence of pediatric metabolic dysfunction-associated steatotic liver disease (MASLD) and its strong association with cardiometabolic risk factors underscore the need for effective early detection tools. Our study demonstrates that single-point insulin sensitivity estimator (SPISE) and metabolic score for insulin resistance (METS-IR) are superior, non-invasive markers for predicting MASLD in children and adolescents, with validated cut-off values applicable to both population-based and real-world clinical settings. These findings are particularly relevant for clinicians and healthcare policymakers, as they provide practical, easily accessible screening tools derived from routine laboratory tests, aiding in the early identification and risk stratification of pediatric MASLD. However, given the study's retrospective design and variations in diagnostic methods across datasets, further validation in larger, diverse cohorts is warranted to refine age-specific cut-off values and optimize screening approaches.

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Identification of pediatric MASLD using insulin resistance indices

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Background & Aims: We investigated the triglyceride-to-high density lipoprotein (HDL) ratio (TG/HDL), triglyceride–glucose index (TyG), single-point insulin sensitivity estimator (SPISE), and metabolic score for insulin resistance (METS-IR) as potential predictors of pediatric metabolic dysfunction-associated steatotic liver disease (MASLD) by addressing the limited research on insulin-resistance markers in this population.

Methods: This cross-sectional study included data from 1,150 and 260 youths from the National Health and Nutrition Examination Survey (NHANES) and a real-world clinic, respectively. Hepatic steatosis was assessed using transient elastography and abdominal sonography. Logistic regression analysis was performed using MASLD as the dependent variable. Receiver operating characteristic (ROC) curves were used to evaluate predictability.

Results: The MASLD group had higher TG/HDL, TyG, METS-IR, and obesity proportions but lower SPISE than the normal group in both NHANES and real-world data. All markers were significantly related to MASLD in logistic regression analyses, even after adjusting for age and sex, in both the NHANES and real-world clinic data (all p <0.001). The areas under the ROC curves (AUCs) for SPISE and METS-IR were 0.91 and 0.91 in the total group, 0.92 and 0.92 in the male group, and 0.90 and 0.89 in the female group, respectively—all higher than those for TG/HDL and TyG in the NHANES dataset (all p <0.001). In the real-world clinical data, the AUCs of SPISE and METS-IR were significantly higher than those of TG/HDL and TyG in the total and male groups (all p <0.001). In the female group, the AUC for SPISE was significantly higher than that for TG/HDL or TyG.

Conclusions: METS-IR and SPISE are effective, non-invasive markers for predicting pediatric MASLD, which offer valuable tools for early detection and improved clinical management.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a newly recognized condition defined to reflect the close relationship between hepatic steatosis and metabolic risk factors.[1] Initially proposed as an update to the previous concept of non-alcoholic fatty liver disease (NAFLD), MASLD encompasses the broader metabolic dysfunction commonly observed in patients with steatotic liver disease (SLD) who do not consume significant amounts of alcohol.[1,2] MASLD and NAFLD are highly prevalent among adults and are also increasingly recognized in younger individuals.[3–5] As MASLD can progress to end-stage liver disease, including liver cirrhosis, and has been closely associated with cardiovascular disease (CVD), the leading cause of death worldwide, early detection of MASLD is crucial.[5–7] Pediatric MASLD is associated with renal impairment and metabolic syndrome, which has a systemic impact.[8,9] Simon *et al.*[10] reported that pediatric NAFLD, the previous term for MASLD, was linked to future cardiometabolic diseases, including CVD, type 2 diabetes, and long-term mortality. However, effective screening tools for pediatric MASLD remain limited.

Insulin resistance (IR) plays a central role in the pathogenesis of MASLD by promoting the accumulation of triglycerides (TG) in the liver.[6,11] Based on this evidence, screening for hepatic steatosis by assessing IR has been suggested.[6,12] However, measuring IR accurately in children is challenging. Although the glucose clamp technique is considered the gold standard, it is generally deemed impractical for routine use because of its highly invasive nature.[13] The homeostasis model assessment (HOMA)-IR index, a marker derived from an individual's insulin and glucose levels, has been proposed as an alternative method for assessing IR and suggested as a parameter to predict hepatic steatosis. However, insulin measurement is not routinely performed in children and lacks a standardized protocol.[12,13]

Given these limitations, non-insulin-based parameters, including the TG-to-high density lipoprotein (HDL) ratio (TG/HDL) and TG–glucose index (TyG), have been proposed as

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alternative markers for IR and hepatic steatosis.[12,14,15] More recently, newer indices such as the single-point insulin sensitivity estimator (SPISE) and metabolic score for IR (METS-IR) have also been developed to provide alternative, non-invasive methods for predicting IR and MASLD.[15–18] The SPISE index, which was developed using oral glucose tolerance tests and euglycemic–hyperinsulinemic clamp tests in a large cohort, is calculated using the HDL, TG, and body mass index (BMI).[15] METS-IR, which integrates glucose, TG, BMI, and HDL, was developed through linear regression analysis using anthropometric and biochemical measurements as independent variables, and its accuracy was validated against the euglycemic–hyperinsulinemic clamp method.[16] Although these markers have shown potential as predictors of IR and MASLD in adults in prior studies, their application in youth and for MASLD prediction remains limited.[16–19]

In this context, the present study aimed to evaluate the effectiveness of the parameters, including the TG/HDL, TyG index, SPISE, and METS-IR, for predicting pediatric MASLD. Herein, we analyzed data from the National Health and Nutrition Examination Survey (NHANES) and real-world clinic data. The specific objectives were as follows: (1) to compare the predictability of SPISE and METS-IR and other parameters for MASLD in youths and (2) to determine optimal cut-off values for SPISE and METS-IR and other markers for predicting pediatric MASLD.

Patients and methods

Study design and participants

This retrospective cross-sectional study included two distinct populations. The first population was derived from the NHANES 2017–2020 dataset (aged 12–18 years), which includes a nationally representative sample of the US population. The second population comprised pediatric patients (aged 6–18 years) who visited either Gangnam Severance Hospital (GSH) Health Promotion Center between January 2007 and December 2023 or Yongin Severance Hospital (YSH) between September 2022 and February 2024 for health check-ups. Fig. 1 presents the inclusion and exclusion criteria. Following application of these criteria, 1,150 youths (aged 12–18 years) from the NHANES and 260 youths (aged 6–18 years) from the real-world clinic data, GSH and YSH, were included.

Ethics statement

Written informed consent was obtained from all participants in the NHANES and GSH, but its requirement was waived for participants in YSH because of the retrospective nature of the study. This retrospective study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of the Yongin Severance Hospital (IRB No: 9-2024-0135).

Study variables

The height, weight, and BMI standard deviation scores (SDS) from participants in the NHANES dataset were calculated based on the CDC growth reference data.[20] The waist circumference (WC) SDS was determined using the NHANES-based reference specific to the study population.[21] For the GSH and YSH dataset, the corresponding values were calculated using the Korean reference values.[22] BMI was classified as normal (<85th percentile), overweight (85–95th percentile), or

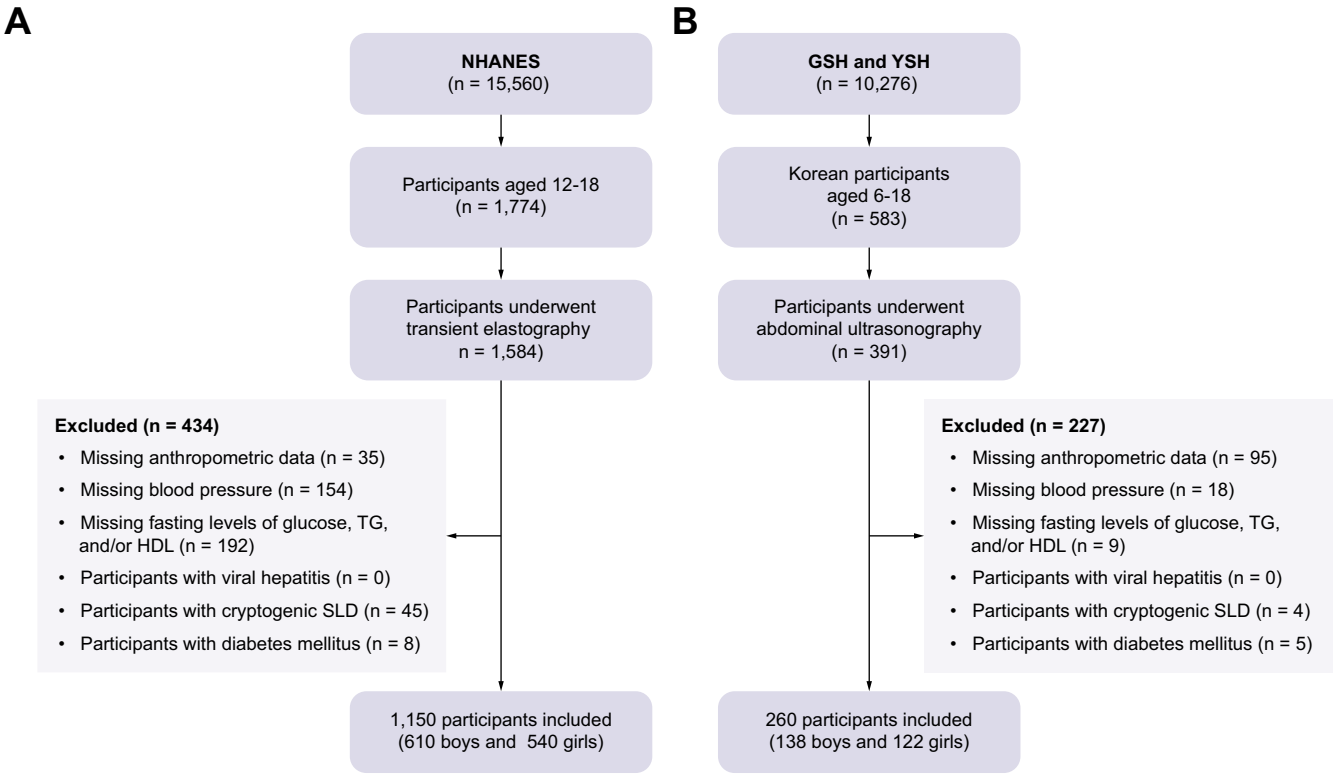

Fig. 1. Flowchart of participant inclusion. (A) Participants in the NHANES. (B) Participants in the real-world clinic data. GSH, Gangnam Severance Hospital; NHANES, National Health and Nutrition Examination Survey; SLD, steatotic liver disease; TG, triglycerides; YSH, Yongin Severance Hospital.

obese (>95th percentile). The waist-to-height ratio (WHtR) is calculated by dividing WC (in cm) by height (in cm). Abdominal obesity was defined as a WC above the 95th percentile according to age and sex.[21,23] In addition, the proportion of participants with WHtR >0.5 was investigated.[4,24]

Diagnosis of MASLD

MASLD was defined as the presence of hepatic steatosis, assessed by either controlled attenuation parameter (CAP) values in the NHANES dataset or ultrasound imaging in the GSH and YSH dataset, combined with at least one cardiometabolic risk factor.[1,25] In the NHANES, vibration-controlled transient elastography was performed using the FibroScan model 502 V2 Touch (Echosens, Paris, France), equipped with medium and extra-large probes. CAP values reflect the amount of liver fat, with higher values indicating more fat accumulation; thus, hepatic steatosis was diagnosed in individuals with a median CAP value >248 dB/m.[11,26,27] In both the GSH and YSH, hepatic steatosis was identified using abdominal sonography to assess liver echogenicity. In the GSH, a 3.5 MHz transducer (HDI 5000, Philips, Bothell, WA, USA) was used, whereas in the YSH, a C1-8 MHz transducer (Aplio i800, Canon Medical Systems, Otawara, Japan) and a C1-6 MHz transducer (LOGIQ E10, GE Healthcare, Wauwatosa, WI, USA) were alternately used. Abdominal ultrasonography was performed by skilled radiologists who were blinded to the clinical and laboratory data of the participants at the time of examination. At GSH, seven experienced radiologists conducted the examinations, whereas at YSH, one experienced radiologist performed them. All radiologists followed a standardized protocol for diagnosing SLD. SLD was defined as the presence of at least two of the following ultrasonographic features:[28,29] (1) a diffuse increase in fine echoes of the liver parenchyma relative to the kidney or spleen, (2) attenuation of the ultrasound beam, and (3) poor visualization of intrahepatic structures. Each feature was assigned a score, with 2 indicating a definite positive, 1 a probable positive, and 0 a negative. The total score ranged from 0 to 6, with scores of 1–2 indicating mild fat infiltration, 3–4 indicating moderate infiltration, and 5–6 indicating severe infiltration. A score of 0 indicated the absence of hepatic steatosis.[29,30]

Cardiometabolic risk factors included overweight or obesity or abdominal obesity, impaired fasting glucose (fasting glucose ≥100 mg/dl) or HbA_{1c} ≥5.7%, high blood pressure ([BP] ≥130/85 mmHg in participants aged 13 years and older, or BP ≥130/80 mmHg or ≥95th percentile in those younger than 13 years, or antihypertensive treatment), high TG (TG ≥150 mg/dl in participants aged 10 years and older, or TG ≥100 mg/dl in those younger than 13 years, or the use of lipid-lowering medication), and low ([HDL] <40 mg/dL or the use of lipid-lowering medication).[1,19,25,31]

Definition of markers

The following formulae were used to calculate parameters:[14–16] TyG index = Ln [(TG (mg/dl) × glucose (mg/dl))/2]; SPISE = (600 × HDL (mg/dl)$^{0.185}$)/(TG (mg/dl)$^{0.2}$ × BMI (kg/m^2)$^{1.338}$); METS-IR = Ln [(2 × glucose (mg/dl) + TG (mg/dl))] × BMI (kg/m^2)/Ln HDL (mg/dl).

Statistical analysis

Categorical and continuous variables are presented as numbers (percentages) and mean ± SD, respectively. To compare the mean values of continuous variables, independent *t* tests were applied, whereas the Chi-square test was used for categorical variables. Subgroup analyses were performed after dividing the participants according to sex and the presence of MASLD. Logistic regression analyses were performed using MASLD as the dependent variable. The optimal cut-off values for markers were identified to maximize the sum of sensitivity and specificity using Youden's index in the NHANES dataset. Receiver operating characteristic (ROC) curves were generated to assess and compare the diagnostic performance of the different markers in predicting MASLD. In addition to determining a single optimal cut-off value applicable to all pediatric participants, age-specific optimal cut-off values were also identified through subgroup analyses in the NHANES, stratifying participants into two age groups: 12–15 and 16–18 years. Pairwise comparisons of the areas under the ROC curves (AUCs) were conducted using Delong's method. The proportion of participants with MASLD, based on the specific cut-off values for each marker, was analyzed using the Chi-square test. Statistical significance was set at p <0.05. All statistical analyses were conducted using SAS version 9.4 (SAS Inc., Cary, NC, USA) and R version 4.4.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Table 1 presents the baseline characteristics of the participants in the NHANES. The mean age was 15.02 ±1.95 years. Sex-based comparisons revealed that height SDS, systolic BP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, TG, and TG/HDL were higher in males than in females, whereas total cholesterol and HDL were lower. In participants with MASLD, weight SDS, BMI SDS, WC, diastolic BP, AST, ALT, glucose, total cholesterol, TG, TG/HDL, TyG, METS-IR, CAP, and proportion of obesity and abdominal obesity were higher than the values in the normal group, whereas HDL and SPISE were lower. Among the participants with MASLD, 5.71% had high BP, 11.79% had impaired fasting glucose, 24.64% had high TG, and 26.79% had low HDL.

Among the participants in the real-world clinic data, the mean age was 13.98 ± 4.04 years, 53.08% were males, and the mean BMI SDS was 1.19 ± 1.81 (Table S1). The prevalence of MASLD was 34.62%. Males exhibited higher WC, systolic BP, AST, ALT, glucose, and METS-IR, whereas females exhibited lower SPISE. Among the participants with MASLD, height SDS, weight SDS, BMI SDS, WC, AST, ALT, HDL, TG/HDL, TyG, METS-IR, and the proportion of obesity and abdominal obesity were higher than the values in the normal group, while age, systolic BP, TG, and SPISE were lower. Among the participants with MASLD, 33.33% had high BP, 8.89% had impaired fasting glucose, 34.44% had high TG, and 14.44% had low HDL.

Logistic regression analyses

Univariable logistic regression analyses revealed that TG/HDL, TyG, and METS-IR were positively correlated with MASLD,

Table 1. Baseline characteristics of the participants in NHANES.

	Total (n = 1,150)	Male (n = 610)	Female (n = 540)	*p*	MASLD (n = 280)	Normal (n = 870)	*p*
Age (years)	15.02 ± 1.95	15.00 ± 1.97	15.04 ± 1.93	0.691	15.19 ± 1.87	14.96 ± 1.98	0.092
(min–max)	(12.00–18.00)	(12.00–18.00)	(12.00–18.00)	0.700	(12.00–18.00)	(12.00–18.00)	0.094
Sex (male), n (%)	610 (53.04)				158 (56.43)	452 (51.95)	0.192
Height SDS	0.02 ± 1.05	0.14 ± 1.06	-0.13 ± 1.01	<0.001	0.10 ± 1.03	-0.01 ± 1.05	0.140
(min–max)	(-3.74 to 3.11)	(-2.90 to 3.11)	(-3.74 to 2.93)	<0.001	(-2.74 to 2.78)	(-3.74 to 3.11)	0.183
Weight SDS	0.75 ± 1.20	0.76 ± 1.27	0.75 ± 1.13	0.876	1.92 ± 0.83	0.38 ± 1.06	<0.001
(min–max)	(-5.25 to 4.02)	(-5.25 to 4.02)	(-2.91 to 2.89)	0.795	(-1.15 to 4.02)	(-5.25 to 3.30)	<0.001
BMI SDS	0.76 ± 1.16	0.69 ± 1.23	0.83 ± 1.08	0.047	1.92 ± 0.62	0.38 ± 1.04	<0.001
(min–max)	(-5.65 to 3.43)	(-5.65 to 3.43)	(-2.65 to 2.75)	0.051	(-0.99 to 3.43)	(-5.65 to 2.81)	<0.001
BMI category, n (%)				0.051			<0.001
Normal	751 (53.41)	359 (58.85)	284 (52.59)		13 (4.64)	630 (72.41)	
Overweight	209 (18.17)	98 (16.07)	111 (20.56)		59 (21.07)	150 (17.24)	
Obesity	298 (25.91)	153 (25.08)	145 (26.85)		208 (74.29)	90 (10.34)	
WC (cm)	83.13 ± 15.90	83.12 ± 16.53	83.14 ± 15.16	0.987	101.57 ± 15.26	77.19 ± 10.70	<0.001
(min–max)	(53.60–157.90)	(53.60–157.90)	(57.00–148.80)	0.489	(60.30–157.90)	(53.60–130.10)	<0.001
Abdominal obesity, n (%)	210 (18.26)	115 (18.85)	95 (17.59)	0.581	52 (5.98)	158 (56.43)	<0.001
WHtR	0.50 ± 0.09	0.49 ± 0.09	0.52 ± 0.09	<0.001	0.61 ± 0.09	0.47 ± 0.07	<0.001
(min–max)	(0.36–0.90)	(0.36–0.90)	(0.37–0.90)	<0.001	(0.40–0.90)	(0.36–0.79)	<0.001
WHtR >0.5	483 (42.00)	220 (36.07)	263 (48.70)	<0.001	258 (92.14)	225 (25.86)	<0.001
SBP (mmHg)	108.61 ± 9.77	111.97 ± 9.87	104.83 ± 8.15	<0.001	109.55 ± 9.88	108.31 ± 9.72	0.065
(min–max)	(80.50–152.50)	(80.50–152.50)	(84.00–139.00)	<0.001	(80.50–140.50)	(84.00–152.50)	0.111
DBP (mmHg)	64.20 ± 8.06	64.02 ± 8.48	64.40 ± 7.56	0.422	67.87 ± 8.57	63.02 ± 7.52	<0.001
(min–max)	(37.50–99.50)	(37.50–92.00)	(47.00–99.50)	0.528	(48.50–93.50)	(37.50–99.50)	<0.001
High BP, n (%)	39 (3.39)	30 (4.92)	9 (1.67)	0.002	16 (5.71)	23 (2.64)	0.014
AST (IU/L)	19.74 ± 8.46	21.77 ± 10.51	17.44 ± 4.23	<0.001	21.19 ± 8.88	19.27 ± 8.27	<0.001
(min–max)	(10.00–192.00)	(10.00–192.00)	(10.00–38.00)	<0.001	(10.00–86.00)	(10.00–192.00)	<0.001
ALT (IU/L)	16.19 ± 11.10	18.86 ± 13.53	13.16 ± 6.20	<0.001	23.11 ± 16.87	13.96 ± 7.15	<0.001
(min–max)	(2.00–152.00)	(4.00–152.00)	(2.00–66.00)	<0.001	(6.00–152.00)	(2.00–64.00)	<0.001
Glucose (mg/dl)	88.29 ± 7.53	89.39 ± 7.42	87.05 ± 7.46	<0.001	90.05 ± 7.73	87.72 ± 7.38	<0.001
(min–max)	(50.00–119.00)	(59.00–117.00)	(50.00–119.00)	<0.001	(70.00–117.00)	(50.00–119.00)	<0.001
Impaired fasting glucose, n (%)	73 (6.35)	40 (6.56)	33 (6.11)	0.757	33 (11.79)	40 (4.60)	<0.001
TC (mg/dl)	153.26 ± 29.61	149.52 ± 28.53	157.49 ± 30.25	<0.001	159.69 ± 30.23	151.19 ± 29.12	<0.001
(min–max)	(73.00–322.00)	(73.00–251.00)	(91.00–322.00)	<0.001	(88.00–252.00)	(73.00–322.00)	<0.001
TG (mg/dl)	92.29 ± 53.99	94.62 ± 60.12	89.66 ± 46.03	0.114	120.26 ± 74.15	83.29 ± 41.91	<0.001
(min–max)	(25.00–607.00)	(25.00–607.00)	(32.00–418.00)	0.967	(36.00–607.00)	(25.00–378.00)	<0.001
High TG, n (%)	131 (11.39)	83 (13.61)	48 (8.89)	0.012	69 (24.64)	62 (7.13)	<0.001
HDL (mg/dl)	51.46 ± 11.71	49.24 ± 11.72	53.97 ± 11.18	<0.001	45.62 ± 10.05	53.34 ± 11.58	<0.001
(min–max)	(19.00–104.00)	(19.00–104.00)	(27.00–98.00)	<0.001	(19.00–85.00)	(21.00–104.00)	<0.001
Low HDL, n (%)	161 (14.00)	122 (20.00)	39 (7.22)	<0.001	75 (26.79)	86 (9.89)	<0.001
TG/HDL	1.99 ± 1.66	2.17 ± 1.97	1.79 ± 1.18	<0.001	2.94 ± 2.54	1.69 ± 1.09	<0.001
(min–max)	(0.37–21.68)	(0.37–21.68)	(0.38–12.29)	0.009	(0.59–21.68)	(0.37–11.12)	<0.001
TyG	8.19 ± 0.49	8.21 ± 0.51	8.16 ± 0.46	0.113	8.45 ± 0.53	8.10 ± 0.44	<0.001
(min–max)	(7.00–10.17)	(7.00–10.17)	(7.07–10.02)	0.371	(7.33–10.17)	(7.00–9.78)	<0.001
SPISE	7.84 ± 2.75	7.98 ± 2.81	7.68 ± 2.67	0.069	5.03 ± 1.68	8.74 ± 2.39	<0.001
(min–max)	(2.03–17.13)	(2.03–17.13)	(2.39–16.96)	0.073	(2.03–14.77)	(2.62–17.13)	<0.001
METS-IR	35.62 ± 11.06	35.48 ± 11.26	35.78 ± 10.85	0.643	48.10 ± 11.52	31.61 ± 7.28	<0.001
(min–max)	(18.17–91.11)	(18.17–91.11)	(18.60–81.31)	0.397	(20.99–91.11)	(18.17–73.27)	<0.001
CAP	220.03 ± 53.13	222.63 ± 53.87	217.08 ± 52.18	0.077	293.07 ± 35.38	196.52 ± 32.53	<0.001
(min–max)	(100.00–400.00)	(100.00–400.00)	(100.00–400.00)	0.118	(249.00–400.00)	(100.00–248.00)	<0.001
MASLD, n (%)	280 (24.35)	158 (25.90)	122 (22.59)	0.192	—	—	—

Continuous variables are presented as mean ± SD and (min–max), and categorical data as n (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; DBP, diastolic blood pressure; MASLD, metabolic dysfunction-associated steatotic liver disease. METS-IR, the metabolic score for insulin resistance; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure; SDS, standard deviation score; SPISE, single-point insulin sensitivity estimator; TC, total cholesterol; TG, triglycerides; TyG, triglyceride–glucose index; WC, waist circumference; WHtR, waist-to-height ratio.

whereas SPISE was negatively correlated with MASLD among the total, male, and female groups across both the NHANES and real-world clinic data (all p <0.001) (Table 2). These relationships remained consistent, even after adjusting for age and sex in the total group, and for age in the male and female groups, in both datasets (all p <0.001).

ROC curve analyses

In the ROC curve analysis, the AUCs (95% confidence intervals [CIs]) of TG/HDL, TyG, SPISE, and METS-IR were 0.71 (0.68–0.75), 0.69 (0.65–0.72), 0.91 (0.89–0.93), and 0.91 (0.89–0.93) in the total group; 0.72 (0.68–0.77), 0.70 (0.65–0.75), 0.92 (0.89–0.94), and 0.92 (0.89–0.95) in the male group; and 0.71 (0.65–0.76), 0.67 (0.62–0.72), 0.90 (0.87–0.92), and 0.89 (0.87–0.92) in the female group, respectively, in the NHANES dataset (Table 3, Fig. 2A, and Fig. S1A and B). The optimal cut-off values for TG/HDL, TyG, SPISE, and METS-IR were >1.511, >8.328, <7.004, and >37.082, respectively, among the total participants. These optimal cut-off values were applied to the real-world clinic data, where the AUCs (95% CIs) of TG/HDL, TyG, SPISE, and METS-IR were 0.75 (0.69–0.82), 0.72 (0.65

Table 2. Logistic regression analyses of the markers for MASLD.

	OR (95% CI)	*p* value	Adjusted OR (95% CI)*	*p* value
NHANES				
Total				
TG/HDL	1.67 (1.50–1.86)	<0.001	1.67 (1.50–1.86)	<0.001
TyG	4.45 (3.30–6.00)	<0.001	4.43 (3.28–5.98)	<0.001
SPISE	0.40 (0.35–0.45)	<0.001	0.39 (0.34–0.44)	<0.001
METS-IR	1.20 (1.18–1.23)	<0.001	1.21 (1.18–1.24)	<0.001
Male				
TG/HDL	1.57 (1.38–1.78)	<0.001	1.57 (1.38–1.78)	<0.001
TyG	4.57 (3.10–6.73)	<0.001	4.56 (3.09–6.72)	<0.001
SPISE	0.38 (0.32–0.45)	<0.001	0.37 (0.31–0.43)	<0.001
METS-IR	1.25 (1.20–1.30)	<0.001	1.26 (1.21–1.31)	<0.001
Female				
TG/HDL	1.90 (1.57–2.29)	<0.001	1.91 (1.58–2.32)	<0.001
TyG	4.21 (2.63–6.75)	<0.001	4.29 (2.67–6.89)	<0.001
SPISE	0.41 (0.35–0.49)	<0.001	0.41 (0.35–0.48)	<0.001
METS-IR	1.17 (1.14–1.21)	<0.001	1.17 (1.14–1.21)	<0.001
Real-world clinic data				
Total				
TG/HDL	2.33 (1.75–3.11)	<0.001	2.26 (1.66–3.08)	<0.001
TyG	6.60 (3.30–13.21)	<0.001	6.86 (3.22–14.61)	<0.001
SPISE	0.32 (0.24–0.43)	<0.001	0.31 (0.22–0.43)	<0.001
METS-IR	1.35 (1.25–1.45)	<0.001	1.34 (1.23–1.45)	<0.001
Male				
TG/HDL	1.66 (1.22–2.25)	<0.001	1.76 (1.25–2.49)	<0.001
TyG	3.83 (1.74–8.41)	<0.001	4.61 (1.91–11.14)	<0.001
SPISE	0.37 (0.26–0.52)	<0.001	0.35 (0.24–0.52)	<0.001
METS-IR	1.31 (1.19–1.44)	<0.001	1.31 (1.18–1.44)	<0.001
Female				
TG/HDL	5.06 (2.75–9.29)	<0.001	3.99 (2.16–7.38)	<0.001
TyG	22.76 (5.59–92.56)	<0.001	15.57 (3.69–65.63)	<0.001
SPISE	0.26 (0.15–0.44)	<0.001	0.25 (0.13–0.45)	<0.001
METS-IR	1.39 (1.23–1.56)	<0.001	1.40 (1.21–1.61)	<0.001

*Adjusting for age and sex in the total group and age in the male and female groups. CI, confidence interval; MASLD, metabolic dysfunction-associated steatotic liver disease; METS-IR, metabolic score for insulin resistance; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; SPISE, single-point insulin sensitivity estimator; TG, triglycerides; TyG, triglyceride–glucose index.

–0.79), 0.89 (0.86–0.93), and 0.89 (0.86–0.93) in the total group; 0.69 (0.60–0.78), 0.68 (0.59–0.77), 0.87 (0.82–0.93), and 0.88 (0.82–0.93) in the male group; and 0.83 (0.74–0.92), 0.78 (0.68–0.88), 0.91 (0.86–0.96), and 0.91 (0.86–0.96) in the female group, respectively (Table 3, Fig. 2B, and Fig. S1C and D).

In the pairwise comparison, the AUCs of SPISE and METS-IR were significantly higher than those of TG/HDL and TyG among the total, male, and female groups in the NHANES dataset (p <0.001) (Table S2). The AUCs of TG/HDL were significantly higher than those of TyG in both the total and female groups. In the real-world clinical data, the AUCs of SPISE and METS-IR were significantly higher than those of TG/HDL and TyG in the total and male groups (all p <0.001). In the female group, the AUC of SPISE was significantly higher than that of TG/HDL and TyG (p for SPISE *vs*. TG/HDL = 0.031; p for SPISE *vs*. TyG = 0.003), whereas that of METS-IR was significantly higher than that of TyG. In addition, the AUC of TG/HDL was significantly higher than that of TyG in both the total and female groups.

When applying the single optimal cut-offs (TG/HDL >1.511, TyG >8.328, SPISE <7.004, and METS-IR >37.082) to each age subgroup, the AUCs (95% CIs) of TG/HDL, TyG, SPISE, and METS-IR were 0.74 (0.69–0.78), 0.72 (0.68–0.78), 0.91 (0.88–0.93), and 0.90 (0.88–0.93) in the 12- to 15-year age group and 0.69 (0.63–0.74), 0.65 (0.59–0.70), 0.91 (0.88–0.94), and 0.92 (0.89–0.94) in the 15- to 18-year age group, respectively (all p <0.001) (Table S3). In the ROC curve analysis for age-specific optimal cut-off values in the NHANES, SPISE cut-off values were slightly higher, whereas METS-IR cut-offs were lower in younger children (Table S4 and Fig. S2).

Proportion of the participants with MASLD in relation to each marker's cut-off values

Fig. 3A and B presents the proportions of MASLD based on each marker's cut-off values in both the NHANES and real-world clinic data, respectively. The proportion of MASLD was significantly higher in participants over the cut-off values for TG/HDL, TyG, and METS-IR and in those below the cut-off values for SPISE in both the NHANES (Fig. 3A) and real-world clinical data (Fig. 3B). The same outcomes were observed in sex-based subgroup analyses in both datasets (Fig. S3A–D).

Discussion

Overall, the present study demonstrated a strong ability of TG/HDL, TyG index, METS-IR, and SPISE to predict MASLD in youth, using optimal cut-off values established in population-based data. TG/HDL, TyG, and METS-IR were all positively associated with MASLD, whereas SPISE was negatively related. These associations remained significant even after adjusting for age and sex. In the ROC curve analyses, SPISE and METS-IR were superior to TG/HDL and TyG in predicting MASLD across the total, male, and female groups in both the NHANES and real-world clinical data. When applying NHANES-derived cut-off values to real-world clinical data, SPISE and METS-IR showed high diagnostic accuracy. The proportion of MASLD was higher in participants exceeding the cut-off values for TG/HDL, TyG, and METS-IR but lower in those below the SPISE cut-off. In the subgroup analyses according to age, SPISE cut-off values were higher, whereas METS-IR cut-offs were lower in younger children and adolescents than in older adolescents.

In the present study, all markers related to IR, each of which includes TG in its formula, were able to meaningfully predict MASLD in youth. However, TG/HDL showed superior predictive ability compared with TyG. IR is a key factor influencing the physiology of MASLD, as it promotes TG accumulation in the liver, leading to hepatic steatosis and inflammation.[6,32] In addition, IR contributes to the dysregulation of glucose metabolism, impairing glucose uptake and increasing insulin levels, while reducing HDL levels, further exacerbating lipid imbalances and the progression of MASLD.[32,33] Based on this evidence, IR-related markers have been indicated as predictors of NAFLD and MASLD. Indeed, one prior meta-analysis reported that the pooled OR of TyG was 6.0 for NAFLD prediction.[34] In a sex-specific study, the AUCs of TyG for MASLD were 0.69 and 0.80 in men and women, respectively.[35] In one prior pediatric study, the cut-off value and AUC of TyG were 8.47 and 0.76 for predicting NAFLD,[12] whereas in another, the associated values for TG/HDL were 2.27 and 0.64, respectively, for NAFLD prediction.[36]

In our study, SPISE and METS-IR were superior to TG/HDL and TyG in predicting MASLD in both of the examined datasets. This superiority of SPISE and METS-IR may be attributed to the more elaborate statistical methods used in their development

Table 3. Cut-off values and AUCs of the markers for predicting MASLD.

	Cut-off	AUC (95% CI)	*p*	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy	PPV	NPV
NHANES								
Total								
TG/HDL	>1.511	0.71 (0.68–0.75)	<0.001	0.75 (0.70–0.80)	0.56 (0.53–0.59)	0.61 (0.58–0.63)	0.35 (0.32–0.39)	0.88 (0.85–0.90)
TyG	>8.328	0.69 (0.65–0.72)	<0.001	0.55 (0.49–0.60)	0.74 (0.71–0.77)	0.69 (0.67–0.72)	0.40 (0.35–0.45)	0.84 (0.81–0.86)
SPISE	<7.004	0.91 (0.89–0.93)	<0.001	0.93 (0.89–0.96)	0.76 (0.73–0.79)	0.80 (0.78–0.82)	0.56 (0.51–0.60)	0.97 (0.96–0.98)
METS-IR	>37.082	0.91 (0.89–0.93)	<0.001	0.86 (0.82–0.90)	0.82 (0.80–0.85)	0.83 (0.81–0.85)	0.61 (0.56–0.66)	0.95 (0.93–0.96)
Male								
TG/HDL	>1.76	0.72 (0.68–0.77)	<0.001	0.67 (0.60–0.74)	0.66 (0.62–0.70)	0.66 (0.62–0.70)	0.41 (0.35–0.47)	0.85 (0.81–0.89)
TyG	>8.332	0.70 (0.65–0.75)	<0.001	0.58 (0.50–0.65)	0.74 (0.70–0.78)	0.70 (0.66–0.73)	0.44 (0.37–0.50)	0.83 (0.80–0.87)
SPISE	<7.005	0.92 (0.89–0.94)	<0.001	0.92 (0.88–0.97)	0.79 (0.76–0.83)	0.83 (0.80–0.86)	0.61 (0.55–0.67)	0.97 (0.95–0.99)
METS-IR	>37.089	0.92 (0.89–0.95)	<0.001	0.87 (0.81–0.92)	0.85 (0.81–0.88)	0.85 (0.82–0.88)	0.66 (0.60–0.73)	0.95 (0.93–0.97)
Female								
TG/HDL	>1.545	0.71 (0.65–0.76)	<0.001	0.70 (0.62–0.79)	0.60 (0.55–0.65)	0.62 (0.58–0.66)	0.34 (0.28–0.40)	0.87 (0.84–0.91)
TyG	>8.291	0.67 (0.62–0.72)	<0.001	0.57 (0.48–0.65)	0.71 (0.67–0.76)	0.68 (0.64–0.72)	0.37 (0.30–0.43)	0.85 (0.81–0.89)
SPISE	<6.918	0.90 (0.87–0.92)	<0.001	0.93 (0.88–0.97)	0.73 (0.69–0.78)	0.78 (0.74–0.81)	0.50 (0.44–0.57)	0.97 (0.95–0.99)
METS-IR	>36.488	0.89 (0.87–0.92)	<0.001	0.88 (0.82–0.94)	0.78 (0.74–0.82)	0.80 (0.77–0.83)	0.54 (0.47–0.60)	0.96 (0.93–0.98)
Real-world clinic data								
Total								
TG/HDL	>1.511	0.75 (0.69–0.82)	<0.001	0.76 (0.67–0.84)	0.57 (0.50–0.64)	0.63 (0.58–0.69)	0.48 (0.40–0.56)	0.82 (0.75–0.88)
TyG	>8.328	0.72 (0.65–0.79)	<0.001	0.70 (0.61–0.79)	0.65 (0.58–0.72)	0.67 (0.61–0.73)	0.52 (0.43–0.61)	0.80 (0.74–0.87)
SPISE	<7.004	0.89 (0.86–0.93)	<0.001	0.79 (0.70–0.87)	0.83 (0.77–0.89)	0.82 (0.77–0.86)	0.71 (0.62–0.80)	0.88 (0.83–0.93)
METS-IR	>37.082	0.89 (0.86–0.93)	<0.001	0.68 (0.58–0.77)	0.86 (0.81–0.92)	0.80 (0.75–0.85)	0.73 (0.63–0.82)	0.84 (0.78–0.89)
Male								
TG/HDL	>1.76	0.69 (0.60–0.78)	<0.001	0.67 (0.55–0.80)	0.64 (0.54–0.74)	0.65 (0.57–0.73)	0.55 (0.43–0.67)	0.75 (0.65–0.85)
TyG	>8.332	0.68 (0.59–0.77)	<0.001	0.67 (0.55–0.80)	0.66 (0.56–0.76)	0.67 (0.59–0.75)	0.57 (0.45–0.69)	0.75 (0.65–0.85)
SPISE	<7.005	0.87 (0.82–0.93)	<0.001	0.80 (0.69–0.91)	0.80 (0.71–0.88)	0.80 (0.73–0.86)	0.72 (0.61–0.83)	0.86 (0.78–0.94)
METS-IR	>37.089	0.88 (0.82–0.93)	<0.001	0.69 (0.57–0.81)	0.82 (0.74–0.90)	0.77 (0.70–0.84)	0.72 (0.60–0.84)	0.80 (0.71–0.89)
Female								
TG/HDL	>1.545	0.83 (0.74–0.92)	<0.001	0.80 (0.67–0.93)	0.63 (0.53–0.73)	0.68 (0.60–0.76)	0.47 (0.34–0.59)	0.89 (0.81–0.97)
TyG	>8.291	0.78 (0.68–0.88)	<0.001	0.80 (0.67–0.93)	0.61 (0.51–0.71)	0.66 (0.58–0.75)	0.45 (0.33–0.58)	0.88 (0.80–0.96)
SPISE	<6.918	0.91 (0.86–0.96)	<0.001	0.77 (0.63–0.91)	0.87 (0.80–0.94)	0.84 (0.78–0.91)	0.71 (0.57–0.85)	0.90 (0.84–0.97)
METS-IR	>36.488	0.91 (0.86–0.96)	<0.001	0.69 (0.53–0.84)	0.91 (0.85–0.97)	0.84 (0.78–0.91)	0.75 (0.60–0.90)	0.88 (0.81–0.95)

AUC, area under the receiver operating characteristic curve; MASLD, metabolic dysfunction-associated steatotic liver disease; METS-IR, metabolic score for insulin resistance; NHANES, National Health and Nutrition Examination Survey; NPV, negative predictive value; PPV, positive predictive value; SPISE, single-point insulin sensitivity estimator; TG, triglycerides; TyG, triglyceride–glucose index.

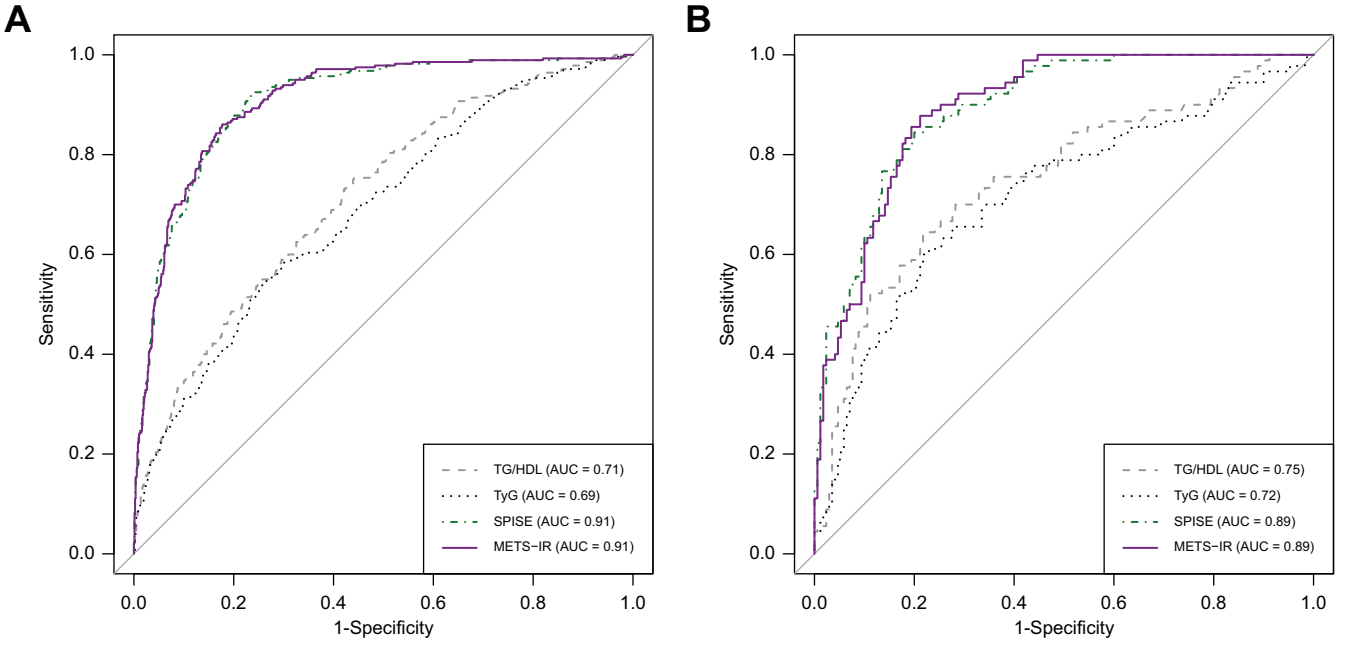

Fig. 2. ROC curve of each parameter for predicting MASLD among the total participants. (A) ROC curve of each parameter for predicting MASLD among the total participants in the NHANES. (B) ROC curve of each parameter for predicting MASLD among the total participants in the real-world clinic data. MASLD, metabolic dysfunction-associated steatotic liver disease; METS-IR, metabolic score for insulin resistance; NHANES, National Health and Nutrition Examination Survey; ROC, receiver operating characteristic; SPISE, single-point insulin sensitivity estimator; TG, triglycerides; TyG, triglyceride–glucose index.

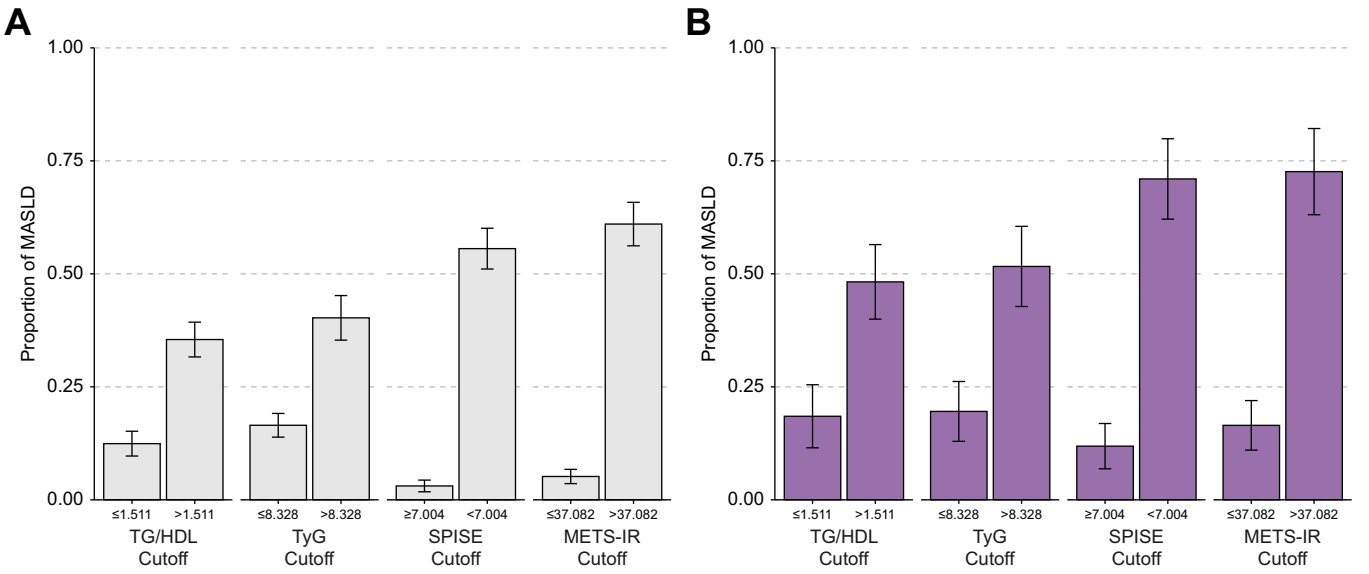

Fig. 3. Proportion of participants with MASLD relative to the cut-off points of each parameter among the total participants. (A) NHANES. (B) Real-world clinic data. The numbers on the bars indicate the proportion (%) of participants with MASLD. MASLD, metabolic dysfunction-associated steatotic liver disease; METS-IR, metabolic score for insulin resistance; NHANES, National Health and Nutrition Examination Survey; SPISE, single-point insulin sensitivity estimator; TG, triglycerides; TyG, triglyceride–glucose index.

compared with those for simpler markers such as TyG and TG/HDL.[15,16] In addition, both the SPISE and METS-IR formulas include BMI, a key factor in the definition of obesity, further enhancing their predictive ability.[15,16,37] Obesity plays a critical role in the physiology of MASLD, as it contributes to excessive fat accumulation in the liver and exacerbates metabolic dysfunction.[1,6,38] Obesity is strongly associated with IR, inflammation, and the progression of MASLD.[6,32,39] In one prior meta-analysis, the relative risk of BMI for NAFLD was 1.20.[37] In a NHANES-based study, the proportion of severe hepatic steatosis was eight-fold higher in adolescents with obesity than in those with a normal BMI.[26] In another cross-sectional study, the combination of BMI added incremental value to TyG in predicting NAFLD in youth.[12] In another cross-sectional study, the AUC of uric acid for predicting ALT elevation was 0.66, whereas that of uric acid combined with BMI was 0.80 in youth.[33] In an adult study, the AUC of METS-IR for metabolic dysfunction-associated fatty liver disease was 0.85 in a US cohort and 0.90 in a Chinese cohort.[40] An Iranian study reported AUCs of METS-IR and SPISE for MASLD as 0.72 and 0.73 in men and 0.70 and 0.73 in women, respectively.[17] A Korean study found the AUC of METS-IR for NAFLD prediction to be 0.82 in adults.[18] A pediatric study among Korean children reported the AUCs of SPISE and METS-IR for ALT elevation as 0.82 and 0.81, respectively.[41] An Austrian study reported the AUC of SPISE for NAFLD as 0.71 in boys and 0.74 in girls.[42]

In our study, participants with values above the cut-off for TG/HDL, TyG, and METS-IR exhibited a markedly higher prevalence of MASLD, as did those with values below the cut-off for SPISE. This trend was consistently observed across both the NHANES and real-world clinical data, as well as in sex-based subgroup analyses. Overall, these findings demonstrate the robustness of these markers in stratifying MASLD risk and emphasize the potential of precise cut-off values to improve early detection and address the limitations of current pediatric screening methods in real-world clinics.

In this study, we found that SPISE cut-off values were slightly higher, whereas METS-IR cut-offs were lower in younger children and adolescents, consistent with expected age-related metabolic changes. Because BMI in children naturally increases with age, these indices may be influenced by age-related variations in BMI. The impact of age on metabolic indices has been demonstrated in a previous study,[43] which emphasized the need for age-specific reference values for fasting glucose–insulin metabolism to improve risk stratification and predict glycemic deterioration in children with obesity. Consistent with these findings, our results suggested that age-related differences in BMI could potentially impact the diagnostic accuracy of SPISE and METS-IR for MASLD (Table S4). However, despite this theoretical consideration, our analyses demonstrated that the single optimal cut-offs derived from the total pediatric group maintained consistently acceptable diagnostic accuracy across all pediatric age groups (Table S3). Thus, our findings support the practical applicability and generalizability of the single optimal cut-offs proposed in this study for pediatric clinical practice.

This study has several limitations that should be acknowledged. First, the retrospective and cross-sectional design limits our ability to infer causality between IR-related markers and MASLD. As such, future prospective studies are required to understand better the temporal relationships and progression of MASLD in relation to these markers. Second, MASLD diagnosis was performed using different techniques across the two datasets, specifically, CAP values in the NHANES data and abdominal sonography in the real-world clinical data. These differing diagnostic approaches may have introduced inconsistencies in the assessment of hepatic steatosis. Third, although experienced radiologists performed the ultrasonography following a standardized protocol, we acknowledge that the interrater agreement was not assessed in the real-world clinic data. Fourth, children and adolescents visiting the real-world clinics were likely seeking medical evaluation for health concerns, which may have led to a higher prevalence of obesity

and metabolic risk factors than the general pediatric population. Therefore, selection bias may be present, and further validation of these findings in a larger, nationally representative Korean sample is warranted. Finally, the real-world clinical dataset had a smaller sample size than the NHANES dataset, which may have reduced the statistical power of subgroup analyses and limited the ability to detect certain associations, potentially affecting the generalizability of the findings. Despite these limitations, this study has several notable strengths. First, it analyzed data from both a large, nationally representative cohort (NHANES) and real-world clinical dataset from Korea, which enhances the external validity of the findings. Second, this is one of the first studies to comprehensively evaluate the performance of SPISE, METS-IR, TG/HDL, and TyG in predicting MASLD in youth using data from different countries.

Conclusions

Overall, the present study demonstrated that both METS-IR and SPISE are effective markers for predicting MASLD in pediatric populations. Furthermore, we identified specific cut-off values for each marker, which proved valuable for assessing MASLD risk in youth. These findings align with recent guidelines highlighting the need for early identification and management of MASLD in populations with cardiometabolic risk factors, such as children and adolescents.[1,25] The diagnostic accuracy of these cut-offs was validated in a real-world clinical dataset to support their clinical applicability. By using non-invasive, reliable tools, including SPISE and METS-IR, which incorporate key metabolic parameters for MASLD diagnosis, our study provides a foundation for improved screening strategies in pediatric populations. These markers, derived from routine laboratory tests, offer practical solutions for early detection, particularly in resource-limited settings. Furthermore, the stepwise approach emphasized in the guidelines highlights integrating these tools into clinical workflows to facilitate timely interventions and mitigate MASLD progression; this ultimately improves long-term outcomes in children and adolescents.

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Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the receiver operating characteristic curve; BP, blood pressure; CAP, controlled attenuation parameter; CI, confidence interval; CVD, cardiovascular disease; GSH, Gangnam Severance Hospital; IR, insulin resistance; MASLD, metabolic dysfunction-associated steatotic liver disease; METS-IR, metabolic score for insulin resistance; NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; ROC, receiver operating characteristic; SDS, standard deviation scores; SLD, steatotic liver disease; SPISE, single-point insulin sensitivity estimator; TG, triglycerides; TG/HDL, triglyceride-to-HDL ratio; TyG, triglyceride–glucose index; WC, waist circumference; WHtR, waist-to-height ratio; YSH, Yongin Severance Hospital.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: KS, Y-JK. Data curation: KS, YHY, SJB, HJS. Formal analysis: KS, EL, HSL. Funding acquisition: Y-JK. Investigation: KS, Y-JK. Methodology: KS, Y-JK. Project administration: KS, Y-JK. Resources: EGS, YHY, SJB. Software: KS, EL. Supervision: HWC. Validation: HSL. Visualization: KS. Writing—original draft: KS. Writing—review & editing: Y-JK. Have read and agreed to the published version of the manuscript: all authors.

Data availability statement

The data used in this study are available on the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/).

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Supplementary data

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Author names in bold designate shared co-first authorship

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