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Prediction Model for Insulin Resistance and Implications for MASLD in Youth: A Novel Marker, the Pediatric Insulin Resistance Assessment Score

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Purpose: Insulin resistance (IR) is a condition closely associated with cardiovascular risk factors and metabolic dysfunction-associated steatotic liver disease (MASLD) is emerging as a significant IR-related complication. We aimed to develop a predictive model for IR in youths and implicate this model for MASLD.

Materials and Methods: A total of 1588 youths from the population-based data were included in the training set. For the test sets, 121 participants were included for IR and 50 for MASLD from real-world clinic data. Logistic regression analysis, random forest, extreme gradient boosting (XGBoost), light gradient boosting machine (GBM), and deep neural network (DNN) were used to develop the models. A nomogram scoring system was constructed based on a model used to predict the probability of IR and MASLD.

Results: After stepwise selection, age, body mass index (BMI) standard deviation score (SDS), waist circumference (WC), systolic blood pressure, HbA1c, high-density lipoprotein cholesterol, triglyceride, and alanine aminotransferase levels were included in the model. A nomogram scoring system was constructed based on a multivariable logistic regression model. The areas under the curves (AUCs) of the models for IR prediction in external validation were 0.75 (logistic regression), 0.78 (random forest), 0.72 (XGBoost), 0.71 (light GBM), and 0.71 (DNN). For MASLD prediction, the AUCs were 0.93 (logistic regression), 0.95 (random forest), 0.90 (XGBoost), 0.91 (light GBM), and 0.85 (DNN). BMI SDS and WC SDS were the most important contributors to IR prediction in all models.

Conclusion: The Pediatric Insulin Resistance Assessment Score is a novel scoring system for predicting IR and MASLD in youths.

Key Words: Insulin resistance, metabolic dysfunction-associated steatotic liver disease, machine learning, child, adolescent

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INTRODUCTION

Insulin resistance (IR), a condition closely related to metabolic syndrome and type 2 diabetes, is a risk factor for future cardiovascular disease (CVD), a leading cause of death worldwide.[1-3] The prevalence of IR-related complications is worsening with the adverse trend of obesity in children and adolescents, such as in prediabetes, increasing from 0.93% to 10.66% worldwide, while the prevalence of metabolic syndrome is 3% in children and 5% in adolescents globally.[4-7] Early detection and management of IR are crucial to prevent these complications and reduce the risk of future CVD.[8-10]

The euglycemic clamp test is the gold standard to detect IR, but it is highly invasive and a burden for children.[8,11] Although the homeostasis model assessment of IR (HOMA-IR), a marker derived from the serum level of insulin and glucose, is suggested as a practical parameter, insulin measurement is not a routine laboratory test and is limited due to the standardization problem.[12] To overcome these limitations, prediction models and markers for IR have been proposed for adults; however, these markers were developed based on studies conducted in adults and do not account for the age-related growth and developmental changes specific to children and adolescents, thereby limiting their applicability in younger populations.[10,13]

Meanwhile, metabolic dysfunction-associated steatotic liver disease (MASLD), a steatotic liver disease (SLD) combined with metabolic risk factors, is emerging as an important IR-related complication.[14-16] This new concept, suggested in 2023, replaces the older term, non-alcoholic fatty liver disease (NAFLD), and reflects a more comprehensive understanding of the metabolic aspects of the condition.[14] While NAFLD primarily considered the absence of significant alcohol consumption, MASLD accounts for both alcohol intake and the presence of metabolic risk factors. Additionally, MASLD adopts the term "steatotic liver disease" to move away from the potentially stigmatizing language associated with "fatty liver disease."[14,17] While the global rise in NAFLD prevalence is well-documented,[18,19] a recent U.S. study reported that the prevalence of MASLD was high: 33.6% in adults and 5.8% in adolescents and young adults.[15] MASLD is closely related to type 2 diabetes and CVD and can progress to severe liver conditions, including cirrhosis, making early detection essential.[20,21] Although alanine aminotransferase (ALT) has been suggested as a screening tool for pediatric NAFLD, its usefulness is limited due to its low sensitivity and specificity.[9,22] Moreover, there is a notable lack of research on effective screening strategies or guidelines for pediatric MASLD.

We, therefore, aimed to develop a prediction model with a scoring system for IR in children and adolescents using data from the Korea National Health and Nutrition Examination Survey (KNHANES) and to validate the model with a test set derived from real-world clinical data. In addition, we investigated the clinical implications of this model by evaluating the predictability of MASLD.

MATERIALS AND METHODS

Study design and participants

For the training set, we analyzed data from children and adolescents aged 10–18 years who participated in the KNHANES,

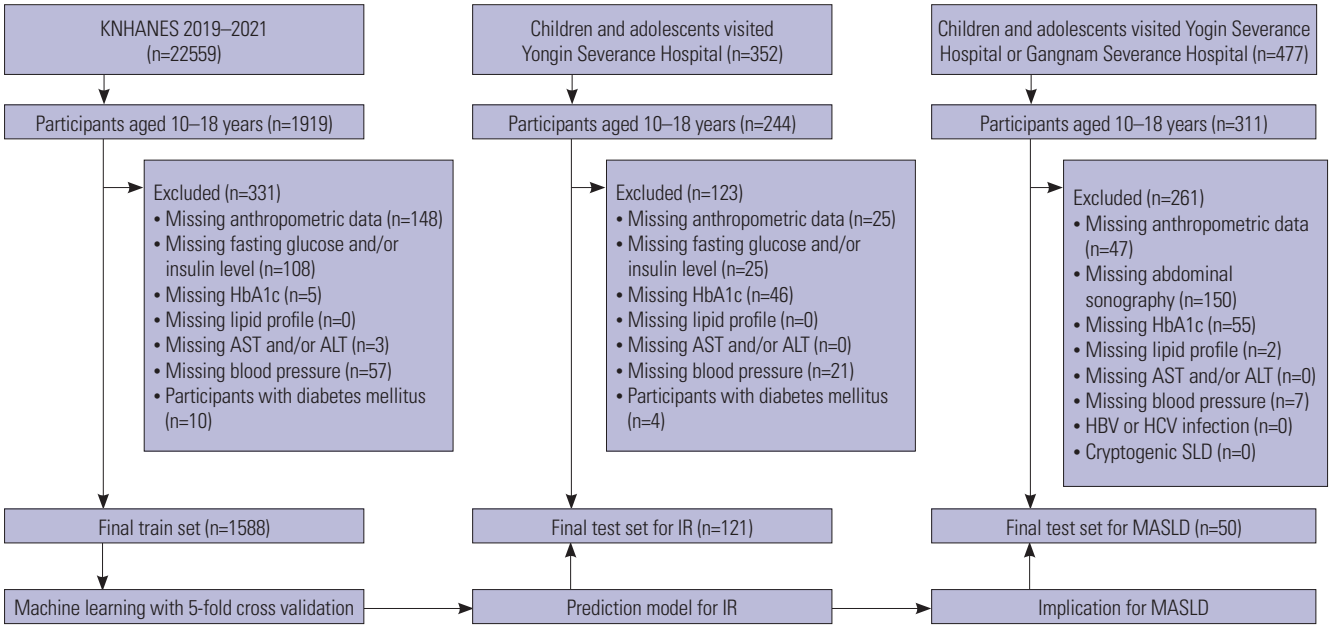

Fig. 1. Study flowchart. KNHANES, Korea National Health and Nutrition Examination Survey; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IR, insulin resistance; HBV, hepatitis B virus; HCV, hepatitis C virus; SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease.

a nationwide survey conducted in Korea for health screening and nutrition between 2019 and 2021. For the test set used to evaluate IR, we retrospectively reviewed the medical records of Korean children and adolescents who visited the outpatient clinic of the Department of Pediatrics at Yongin Severance Hospital with complaints of overweight or obesity, specifically for the evaluation of obesity-related comorbidities. For the test set evaluating the clinical implications related to MASLD, we included Korean children and adolescents who visited the outpatient clinic of the Department of Pediatrics at Yongin Severance Hospital with complaints of overweight or obesity, as well as those who underwent check-ups at Gangnam Severance Hospital. Finally, 1588, 121, and 50 participants were included in the training set, test set for IR, and test set for MASLD, respectively. Fig. 1 depicts the flowchart of the study.

This 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: 9-2024-0098). Written informed consent was obtained from all participants in the KNHANES and Gangnam Severance Hospital, while it was waived for participants at Yongin Severance Hospital.

Study variables

Heights were measured with a stadiometer (range: 850–2060 mm; Seriter, Holtain Ltd., Crymych, UK) with an accuracy of 0.1 cm in both KNHANES and Yongin Severance Hospital. Weights were measured using a Giant 150N scale (HANA, Seoul, South Korea) in KNHANES and DB150 (CAS, Yangju, South Korea) in Yongin Severance Hospital with a precision of 0.1 kg. In Gangnam Severance Hospital, height and weight were measured using ACCUNIQ BC720 (SELVAS Healthcare, Daejeon, South Korea). Body mass index (BMI) was calculated by dividing the weight in kilograms by the height in square meters. The height, weight, and BMI standard deviation score (SDS) were calculated according to the 2017 Korean National Growth Charts.[23] Children were classified into three groups based on their BMI: normal weight (BMI <85th percentile), overweight (BMI between the 85th and 95th percentiles), and obese (BMI ≥95th percentile). Waist circumference (WC) was measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest in the horizontal plane. Blood pressure (BP) was measured on the right arm, which was supported at the heart level, after the participants had been seated and at rest for 5 minutes. High systolic BP (SBP) was defined as SBP ≥95th percentile, and high diastolic BP (DBP) was defined as DBP ≥95th percentile for age and sex according to Korean reference data.[24]

Blood samples were drawn from the antecubital vein after a minimum 8-hour overnight fast. The collected samples were processed immediately and refrigerated. In KNHANES, fasting levels of glucose, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), aspartate transferase (AST), ALT, and uric acid were measured using the Labospect 008AS (Hitachi, Tokyo, Japan), while serum HbA1c levels were measured using the Tosoh G8 (Tosoh, Tokyo, Japan), and insulin levels were determined using the Modular E801 (Roche, Basel, Switzerland). In Yongin Severance Hospital, fasting levels of glucose, total cholesterol, HDL-C, TG, AST, ALT, and uric acid were measured using the Roche Cobas 8000 c702 (Roche). Serum HbA1c levels were measured using the D-100 (Bio-Rad, Hercules, CA, USA), and insulin levels were determined using the Roche Cobas e801 (Roche). In Gangnam Severance Hospital, fasting levels of glucose, total cholesterol, HDL-C, TG, AST, ALT, and uric acid were measured using the AU580 (Beckman Coulter, Brea, CA, USA). Serum HbA1c levels were measured using the HLC-723 G11 (Tosho), and insulin levels were determined using the cobas e 801 (Roche).

The Friedewald formula was used to compute low-density lipoprotein-cholesterol (LDL-C) levels as LDL-C=total cholesterol-HDL-C-TG/5 with TG levels of ≤400 mg/dL, whereas it was set as missing for samples with TG values >400 mg/dL.[12] HOMA-IR was calculated by multiplying fasting insulin (mg/dL) by fasting glucose (mg/dL) and then dividing the result by 22.5. IR was defined as a HOMA-IR value above the 95th percentile for each age and sex group, according to Korean reference data.[25]

Body composition was assessed using InBody720 (Inbody, Seoul, South Korea) through bioelectrical impedance analysis (BIA), including measurements of skeletal muscle mass (SMM) and percentage of body fat (PBF). BIA was conducted exclusively at Yongin Severance Hospital.

Diagnosis of MASLD

The diagnosis of SLD was made based on the results of an abdominal ultrasound using Aplio i800 (Canon Medical Systems, Otawara, Japan) and LOGIQ E10 (GE Healthcare, Wauwatosa, WI, USA) at Yongin Severance Hospital, and HDI 5000 (Philips, Bothell, WA, USA) at Gangnam Severance Hospital, by experienced radiologists. The participants were categorized into four grades according to the presence and severity of hepatic fat accumulation. This categorization was based on the assessment of liver tissue echogenicity, the contrast between the liver and the right kidney, and the visibility of vascular structures.[9] Grades 1 to 3 of hepatic fat accumulation were considered indicative of SLD, while grade 0 indicated a normal condition. MASLD was defined as SLD with the presence of at least one of five cardiometabolic risk factors according to the international consensus.[14] Cardiometabolic risk factors included: 1) overweight, obesity, or abdominal obesity (WC at or above the 95th percentile) based on Korean reference;[23,26] 2) BP thresholds of ≥130/85 mm Hg for individuals aged 13 years and older, or ≥130/80 mm Hg or the 95th percentile for those under 13 years; 3) fasting glucose levels of at least 100 mg/dL or HbA1c of 5.7% or higher; 4) TG levels of 150 mg/dL or higher; and 5) HDL-C levels below 40 mg/dL.[14]

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Statistical analysis and machine learning

All continuous variables are depicted as the mean±standard deviation, while categorical variables are presented as numbers (percentages). Continuous variables were compared using the independent t-test, whereas categorical variables were compared using the chi-squared test or Fisher's exact test. Subgroup analyses were conducted based on the presence or absence of IR within the respective set, and BIA parameters were specifically examined in participants with obesity, categorized by the presence or absence of IR, at Yongin Severance Hospital. Univariate logistic regression analysis was performed with IR as the dependent variable and multivariable logistic regression analyses were performed using stepwise selection.

To develop the IR prediction model, logistic regression analyses, random forest, extreme gradient boosting (XGBoost), light gradient boosting machine (GBM), and deep neural network (DNN) were used in the training set, and hyperparameter tuning of the model was performed using a grid search with five-fold cross-validation. Internal validation was performed on the training set and external validation was performed on the test set for IR. Additionally, the model was validated for MASLD prediction by external validation of the test set for MASLD. Receiver operating characteristic (ROC) curve analyses were performed to assess the model performance, and the Delong test was performed for pairwise comparisons. A nomogram scoring system was constructed based on a logistic regression model used to predict the probability of IR. Nomogram points for each predictor were determined by the ratio of the absolute coefficient to the largest absolute coefficient, scaled to 100 points. The probability of IR was calculated from the total points summed by the patient's predictor points. The Shapley's additive explanation (SHAP) values were computed to quantify the impact of each parameter. Data were analyzed using SAS (version 9.4; SAS Inc., Cary, NC, USA) and R, version 4.3.2 (The R Foundation for Statistical Computing, Vienna, Austria; http://www. R-project. org/). Statistical significance was set at $p<0.05$.

RESULTS

Baseline characteristics

Table 1 shows the baseline characteristics of the training set based on the presence or absence of IR. The IR group consisted of 376 participants, while the non-IR group included 1212 participants. Age, HDL-C level, and the proportion of female sex were lower in participants with IR than in those without IR. Height SDS, weight SDS, BMI SDS, WC SDS, SBP, DBP, glucose, insulin, HbA1c, total cholesterol, TG, LDL-C, non-HDL-C, AST, ALT, uric acid, HOMA-IR, and the proportion of obesity, high SBP, and high DBP were higher in participants with IR than in those without IR.

Supplementary Table 1 (only online) shows the baseline characteristics of participants in the training and test sets for IR and the test sets for MASLD. Age, DBP, glucose, HbA1c, and HDL-C levels were higher in the training set than in the test set for the IR group. Height SDS, weight SDS, BMI SDS, WC SDS, SBP, insulin level, TG, AST, ALT, uric acid, HOMA-IR, and the proportions of obesity, high SBP, high DBP, and IR were higher in the test set for IR than in the training set. Age, DBP, and HDL-C levels were higher in the training set than in the MASLD test set. The height SDS, weight SDS, BMI SDS, SBP, glucose, HbA1c, TG, AST, ALT, and uric acid levels, and the proportion of obesity, high SBP, and high DBP were higher in the test set for MASLD than in the training set.

Supplementary Table 2 (only online) presents a comparison of body composition among participants with obesity, categorized by the presence of IR, at Yongin Severance Hospital. No significant differences were observed in SMM, PBF, or WC SDS between participants with IR and those without IR.

Table 1. Baseline Characteristics of the Train Set according to IR

	IR (n=376)	Non-IR (n=1212)	*p* value
Age, yr	13.40±2.54	13.96±2.56	<0.001
Sex, female	137 (36.44)	577 (47.61)	<0.001
Height SDS	0.58±1.08	0.30±1.04	<0.001
Weight SDS	1.50±1.26	0.01±1.08	<0.001
BMI SDS	1.54±1.33	-0.16±1.13	<0.001
WC SDS	1.48±0.99	0.10±0.95	<0.001
BMI percentile			<0.001
Normal	130 (34.57)	1033 (85.23)	<0.001
Overweight	73 (19.41)	95 (7.84)	<0.001
Obesity	173 (46.01)	84 (6.93)	<0.001
SBP, mm Hg	112.73±10.33	106.91±9.77	<0.001
DBP, mm Hg	67.60±9.43	66.48±8.65	0.041
High SBP	41 (10.90)	36 (2.97)	<0.001
High DBP	28 (7.45)	51 (4.21)	0.012
Glucose, mg/dL	96.23±7.42	91.29±6.37	<0.001
Insulin, IU/L	31.47±21.36	10.94±4.21	<0.001
HbA1c, %	5.49±0.25	5.38±0.25	<0.001
Total cholesterol, mg/dL	169.99±29.03	162.33±26.93	<0.001
HDL-C, mg/dL	47.16±8.87	53.54±10.01	<0.001
TG, mg/dL	120.04±64.45	78.24±39.73	<0.001
LDL-C, mg/dL	101.05±26.46	93.43±23.44	<0.001
Non-HDL-C, mg/dL	122.83±28.37	108.79±25.18	<0.001
AST, IU/L	25.01±13.74	21.01±10.90	<0.001
ALT, IU/L	29.20±29.17	15.03±11.67	<0.001
Uric acid, mg/dL	6.05±1.45	5.29±1.29	<0.001
HOMA-IR	7.53±5.70	2.48±1.01	<0.001

IR, insulin resistance; SDS, standard deviation score; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment of IR.
Values are presented as mean±SD for continuous variables and number (percentage) for categorical variables.

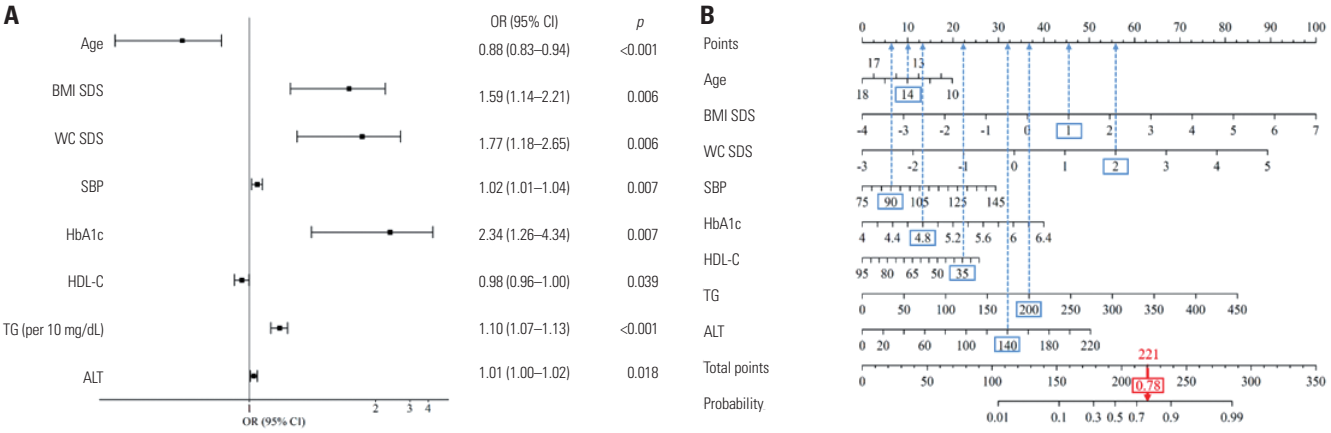

Fig. 2. Multivariable logistic regression model (A) and nomogram of the model for prediction of IR (B). (A) Forest plot of odds ratio (OR) [95% confidence interval (CI)] of the stepwise logistic regression model. (B) A scoring system with a nomogram for predicting IR using the results of multivariable logistic regression analysis. The participants were 14 years old (9.92 points). The BMI SDS, WC SDS, and SBP were 1 (45.45), 2 (55.85), and 90 mm Hg (6.30), respectively. HbA1c, HDL-C, TG, and ALT levels were 4.8% (13.33 points), 35 mg/dL (22.06 points), 200 mg/dL (36.75 points), and 140 IU/L (32.01 points), respectively. According to the nomogram, the probability of IR was 0.795 (79.5%) for 221.67. IR, insulin resistance; BMI, body mass index; SDS, standard deviation score; WC, waist circumference; SBP, systolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; ALT, alanine aminotransferase.

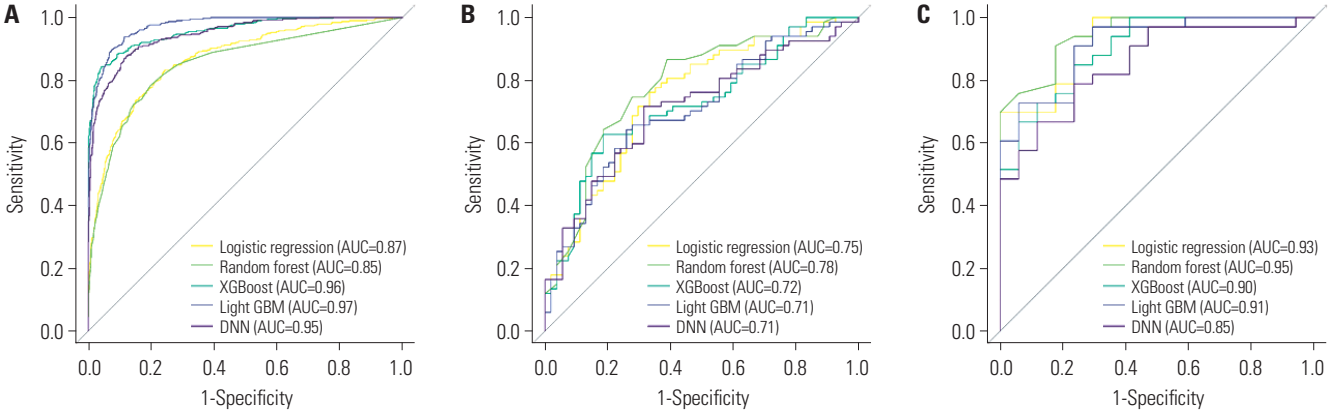

Fig. 3. ROC curves from internal and external validation for IR and external validation for MASLD. (A) ROC curves from internal validation in train set for IR. (B) ROC curves from external validation in test set for IR. (C) ROC curves from external validation in the test set for MASLD. IR, insulin resistance; MASLD, metabolic dysfunction-associated steatotic liver disease; ROC, receiver operating characteristic; AUC, area under the receiver operating characteristic curve; XGBoost, extreme gradient boosting; GBM, gradient boosting machine; DNN, deep neural network.

Logistic regression analyses and scoring system

Fig. 2A shows a forest plot of the multivariable logistic regression analyses after stepwise selection. Age and HDL-C levels were negatively associated with IR, whereas BMI SDS, WC SDS, SBP, HbA1c, TG, and ALT levels were positively associated with IR.

We constructed a nomogram scoring system, the Pediatric Insulin Resistance Assessment Score (PIRAS), for IR prediction based on a multivariable logistic regression model as follows:

Probability (IR)=1/[1+exp(-y)]

where y=-7.320-0.126×Age+0.463×BMI SDS+0.569×WC SDS +0.021×SBP+0.849×HbA1c-0.019×HDL-C+0.009 ×TG+0.012×ALT

Fig. 2B shows a representation of the scoring system using a nomogram for IR. The participants were 14 years old (9.92 points). The BMI SDS, WC SDS, and SBP were 1 (45.45), 2 (55.85), and 90 mm Hg (6.30), respectively. HbA1c, HDL-C, TG, and ALT levels were 4.8% (13.33 points), 35 mg/dL (22.06 points), 200 mg/dL (36.75 points), and 140 IU/L (32.01 points), respectively. According to the nomogram, the probability of IR was 0.795 (79.5%) for 221.67.

ROC curve analyses of the models

In ROC curve analyses, the area under the ROC curves (AUCs) of the models for IR prediction were 0.87 (logistic regression), 0.85 (random forest), 0.96 (XGBoost), 0.97 (light GBM), and 0.95 (DNN) in internal validation for the training set (Fig. 3). For external validation of the test set, the corresponding values were 0.75 (logistic regression), 0.78 (random forest), 0.72 (XGBoost), 0.71 (light GBM), and 0.71 (DNN) for IR prediction, respectively. For MASLD prediction, AUCs of the models were 0.93 (logistic regression), 0.95 (random forest), 0.90 (XGBoost), 0.91 (light GBM), and 0.85 (DNN). Supplementary Table 3 (only online) summarizes the hyperparameters for each IR

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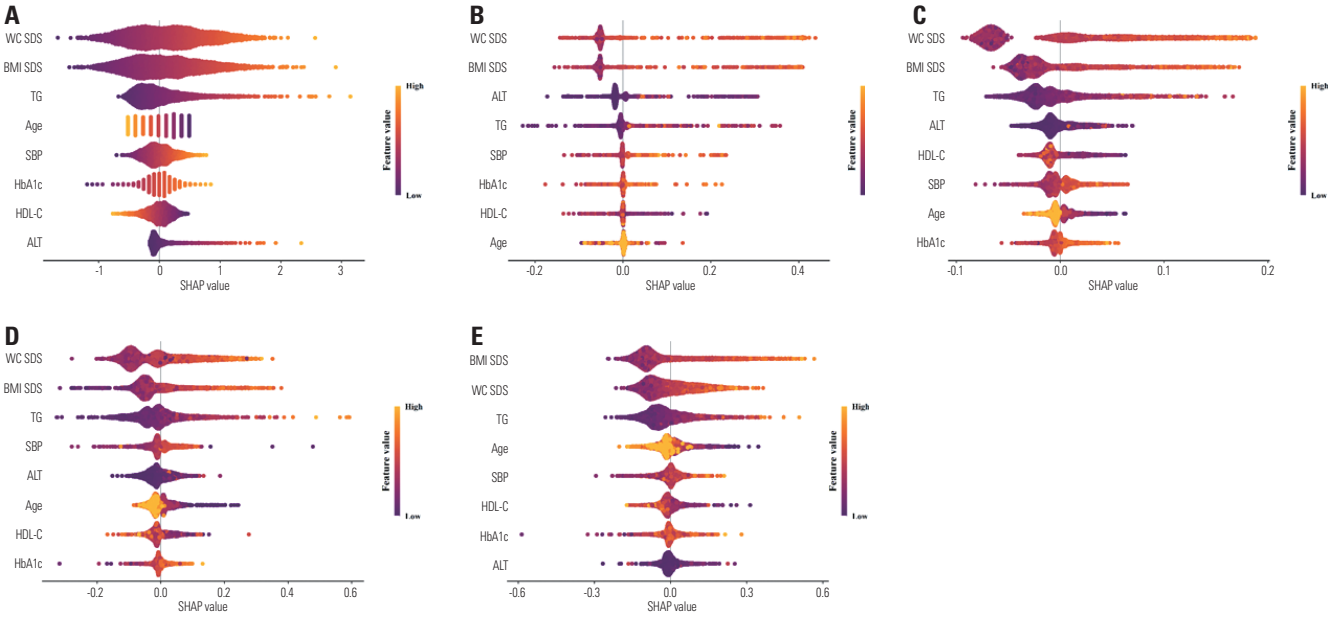

Fig. 4. SHAP summary plots for contribution of the variables for prediction of IR. (A) SHAP summary plot of the prediction model using logistic regression analysis. (B) SHAP summary plot of the prediction model using random forest. (C) SHAP summary plot of the prediction model using XGBoost. (D) SHAP summary plot of the prediction model using light GBM. (E) SHAP summary plot of the prediction model using DNN. The color in the plot indicates whether a parameter has a high or low value within the participant dataset. The horizontal position on the plot indicates whether the parameter has a higher or lower impact on the prediction. IR, insulin resistance; SHAP, Shapley's additive explanation; XGBoost, extreme gradient boosting; GBM, gradient boosting machine; DNN, deep neural network; WC, waist circumference; SDS, standard deviation score; BMI, body mass index; TG, triglycerides; SBP, systolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; ALT, alanine aminotransferase.

prediction model, including random forest, XGBoost, light GBM, and DNN, along with the final values selected through hyperparameter tuning to optimize model performance.

In pairwise comparisons, the light GBM model was superior to the other models, followed by XGBoost, DNN, logistic regression, and random forest for IR prediction in the training set (Supplementary Table 4, only online). The AUCs were not significantly different among the models in the test sets for IR. In the test sets for MASLD, the AUC was higher in the random forest model compared to the DNN model.

SHAP

The SHAP values of the variables were computed to demonstrate their importance in the prediction model for IR in the external validation of the test set (Fig. 4). Among these parameters, WC SDS and BMI SDS were the most important contributors to IR prediction in all models. TG was the third most important contributor in the logistic regression, XGBoost, light GBM, and DNN models. In the random forest model, ALT was the third most important contributor, followed by TG.

DISCUSSION

Our prediction models developed prediction models for IR and implicated the models for MASLD using population-based data demonstrating outstanding performance across various machine learning methods among children and adolescents. Key contributors included age, BMI SDS, WC SDS, SBP, TG, HDL-C, ALT, and HbA1c levels. In addition, we developed a scoring system, the PIRAS, using these variables, making it a practical tool for real-world clinical settings.

We developed IR prediction models and a scoring system using various machine learning techniques, which demonstrated AUCs from 0.85 to 0.97 in internal validation and 0.77 to 0.84 in external validation. The performance differences among the machine learning models were influenced by hyperparameter tuning and data characteristics, but all models consistently showed excellent predictive power for IR overall. Although prediction models for IR have been extensively studied in adults owing to their clinical significance, to our knowledge, similar investigations in children have not been conducted. An IR prediction model developed in Taiwan using logistic regression and various machine learning showed AUCs ranging from 0.83 to 0.87 among adults.[10] A Korean study developed a prediction model for IR in adults aged over 40 years, which demonstrated an AUC of 0.82 using logistic regression.[13]

Biomarkers such as TG-glucose index (TyG) and TG-to-HDL-C ratio (TG/HDL-C) have been suggested for predicting IR in adults and validated in children.[8,11] In a cross-sectional study, the AUC of TyG for IR was 0.723 in children and adolescents.[8] In another cross-sectional study, the AUC of TG/HDL-C for IR was 0.729 in children and adolescents.[27]Although these existing markers, such as TyG and TG/HDL-C, were originally proposed as simple markers in studies involving adults, they inherently have limitations when applied to children.[28] Specifi-

cally, these markers fail to account for the dynamic changes in BMI and metabolic factors associated with age and growth during childhood and adolescence.[29] In contrast, the proposed new marker, PIRAS, is designed to overcome these limitations. PIRAS incorporates variables that reflect age-related growth and metabolic changes in children, such as age, BMI SDS, and WC SDS. Furthermore, PIRAS was developed using diverse machine learning with external validation, providing a distinct advantage over traditional markers in capturing the unique metabolic dynamics of children and adolescents.

In the model developed in our study, BMI SDS and WC SDS were the most important contributors to IR prediction, followed by TG, age, SBP, HbA1c, HDL-C, and ALT, in the logistic regression analysis. In addition, the BMI SDS, WC SDS, and TG were major contributors to all machine learning-based models. These findings suggest the validity of our model, aligning with the pathophysiology of IR and corroborating previous research on factors related to IR.[9,30-32] Excess body fat, particularly visceral fat associated with BMI and WC, releases inflammatory cytokines that impair insulin signaling.[8,33] This disruption leads to decreased glucose uptake in the muscles and increased glucose production in the liver, exacerbating IR.[9] Moreover, IR exacerbates obesity and abdominal obesity by inducing an increase in free fatty acids, which promote fat accumulation, especially in the abdominal region.[30,34] In addition, increases in TG levels lead to an increased influx of free fatty acids into the liver, which impairs insulin signaling and promotes hepatic glucose production.[8,9,35] This process exacerbates IR by further increasing blood glucose levels and insulin demand, creating a vicious cycle that perpetuates metabolic disturbances.[34,35] In a meta-analysis, the pooled relative risks of BMI and WC for incident diabetes were both 1.87.[33] A cross-sectional study reported that increased WC and TG levels were positively associated with IR among adolescents.[34] An adult study developing an IR prediction model identified BMI, glucose, TG, and HDL-C as major risk factors.[10] Furthermore, a cohort study reported that improvements in BP in non-obese patients with hypertension might reduce the severity of NAFLD.[32]

In our study, the models demonstrated powerful predictability for MASLD, with AUCs ranging from 0.85 to 0.95. IR is a key factor in the pathogenesis of MASLD; IR is also worse in individuals with MASLD[9,31] and contributes to MASLD by promoting hepatic fat accumulation through increased de novo lipogenesis and impaired lipid oxidation.[31,35] This hepatic fat accumulation, in turn, exacerbates IR by disrupting insulin signaling and promoting inflammatory pathways.[9] A cohort study reported that adipose tissue IR is higher in youth with MASLD compared to those without.[36] Based on this evidence, we predicted MASLD using the IR prediction model, and the predictability was powerful in external validation. Although investigations on the prediction of MASLD have been performed in adults,[21,37] to our knowledge, our study is the first to extend the utility of an IR prediction model to include MASLD in children. An adult study developed an IR model and applied it in the assessment of CVD risk.[10] Furthermore, a German study developed a machine learning-based model for metabolic dysfunction-associated steatohepatitis in adults, which demonstrated an AUC of 0.899.[21]

This study had several limitations. First, this was a retrospective study, which inherently limits the ability to establish causal relationships and may have been subject to selection bias. Additionally, the study population was limited to Korean children and adolescents, which may restrict the generalizability of the findings to other ethnic groups or populations with different demographic and genetic backgrounds. Second, several potential confounding factors, including dietary intake, physical activity level, and socioeconomic status, were not considered in this study. These factors are known to influence both IR and MASLD, and their omission can affect the accuracy and applicability of the prediction models. Third, IR was defined using HOMA-IR, a widely used but indirect measure, rather than the euglycemic clamp test, which is considered the gold standard for assessing insulin sensitivity. Fourth, differences in physical measurement devices and diagnostic equipment between the two institutions and the KNHANES, despite using standardized definitions for IR and MASLD, may have introduced variability that could have influenced the results. Fifth, SLD was diagnosed using ultrasonography, which is a non-invasive and widely accessible imaging technique, but is less sensitive and specific than liver biopsy, the gold standard for diagnosing and staging liver disease.

Despite these limitations, this study had some strengths, including the development of an IR prediction model and a scoring system specifically for children and adolescents using population-based data. The model was externally validated using real-world clinical data to enhance its robustness. Furthermore, the model demonstrated reliable predictability of pediatric MASLD, a key IR-related complication, and was validated using multicenter data, suggesting its potential applicability in diverse clinical settings.

In conclusion, we developed machine learning-based models and a scoring system, the PIRAS, for IR, which demonstrated good predictability in external validation using real-world clinical data. Moreover, the models demonstrated powerful predictability for pediatric MASLD. The variables contributing to the model were easily accessible even in local clinics, demonstrating its usefulness in real-world clinical settings. These findings suggest that the prediction model has the potential to provide practical assistance in screening strategies for IR and related complications including MASLD in children and adolescents. Additionally, PIRAS addresses a significant gap in existing IR markers by incorporating age- and growth-specific variables such as BMI SDS and WC SDS, which are critical for pediatric populations. As a novel tool, PIRAS has the potential to enhance early identification and management of IR and MASLD, and future research should explore its utility in longi-

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tudinal studies involving children of diverse racial and ethnic backgrounds.

DATA AVAILABILITY

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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