CHILDHOOD OBESITY
December 2021 | Volume 17, Number 8

DOI: 10.1089/chi.2021.0054

Prediction of Nonalcoholic Fatty Liver Disease by Anthropometric Indices and Bioelectrical Impedance Analysis in Children

Li-Wen Lee, MD, PhD,[1,2,i] Ju-Bei Yen, MD,[3,4] Hsueh-Kuan Lu, PhD,[5] and Yu-San Liao, MD, PhD[1,6]

Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is highly prevalent in children and is associated with obesity.

Objectives: To test whether addition of bioelectrical impedance analysis (BIA) parameters to BMI and anthropometric indices improves the prediction performance of NAFLD than BMI *z* score (BAZ) alone.

Methods: This cross-sectional study recruited 933 children 6–12 years of age for anthropometric measure, BIA, and liver ultrasound. Prediction models of the BAZ, anthropometric, and BIA sets were built in children with obesity using machine learning algorithms.

Results: Prevalences of NAFLD were 44.4% (59/133) and 20% (12/60) in boys and girls with obesity, respectively. In both sexes, BAZ set performed worst; adding anthropometric indices into the model improved the model performance, whereas BIA parameters were the best approach for predicting NAFLD. The best result in boys achieved had an accuracy of 75.9% and area under receiver operating characteristic curve of 0.854. In girls, the best result achieved had an *F*-measure score of 0.615, Matthews correlation coefficient of 0.512, and area under precision-recalled curve of 0.697.

Conclusion: BIA is a simple and highly precise tool that yields better NAFLD prediction model than anthropometric indices, and much better performance than BAZ. This study suggests BIA as a potential predictor for pediatric NAFLD.

Keywords: bioelectrical impedance analysis; body composition; nonalcoholic fatty liver disease; pediatric obesity

Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined by the presence of hepatic steatosis in individuals without significant alcohol consumption and other causes of liver disease. It is associated with body weight status and weight gain.[1,2] With the rising trend of childhood obesity, NAFLD has become the most common liver disease in children. The overall prevalence of NAFLD is estimated to be 6.8% in boys and 5.5% in girls in general pediatric population and up to 41.9% and 27.9% in boys and girls with obesity, respectively, based on ultrasound findings.[3] In Taiwan, the rate of NAFLD assessed by ultrasound is 13.8%–21% in general pediatric population and 17.8%–76% in children with obesity.[4–6] Screening for children at risk of NAFLD is appropriate because it is asymptomatic and can be potentially reversed by lifestyle intervention before the development of advanced liver fibrosis.

The diagnosis of NAFLD can be performed by liver histology, imaging, and alanine aminotransferase (ALT) test. Liver biopsy is regarded as the best available standard for diagnosing and staging NAFLD but it is invasive with sampling variability.[7] Imaging-based tools for NAFLD include ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Ultrasound is widely accepted as the first-line imaging modality, providing satisfactory accuracy for detecting moderate to severe degrees of fatty liver with low cost. However, ultrasound is less

[1]Department of Diagnostic Radiology, [3]Department of Pediatrics, Chang Gung Memorial Hospital, Chiayi, Taiwan.
[2]Department of Nursing, Chang Gung University of Science and Technology, Chiayi, Taiwan.
[4]Graduate Institute of Clinical Medical Sciences, Chang Gung University, Taoyuan, Taiwan.
[5]General Education Center, National Taiwan University of Sport, Taichung, Taiwan.
[6]Department of Diagnostic Radiology, Chang Gung Memorial Hospital, Yunlin, Taiwan.
[i]ORCID ID (https://orcid.org/0000-0001-8019-1772).

accurate for detecting fatty liver with <33% hepatic steatosis.[8,9] CT and MRI can detect and quantify hepatic fat content more accurately but are more expensive and less available.[10] Of note, CT involves the use of ionizing radiation and is not suitable for monitoring disease progression.

ALT and ultrasound are the most commonly used tools for diagnosing NAFLD but provide only moderate accuracy in children with obesity.[11] The Normal American Society for Pediatric Gastroenterology, Hepatology and Nutrition practice guideline recommends ALT as the screening tool for NAFLD for children who are overweight and obese and with additional risk factors, but recommends against using routine ultrasound because of low sensitivity.[12] Evidence showed that normal ALT level could not exclude liver fibrosis and was seen in 14%–21% children with biopsy-confirmed NAFLD.[13–15] Thus, ALT may not be sufficiently sensitive to serve as a screening test for NAFLD. Given that many children with ultrasound-diagnosed NAFLD may have normal ALT levels,[3,16] ultrasound may be a potential screening tool, but its utility is unproven. Owing to insufficient evidence, the American Association for Study of Liver Disease guideline recommends against screening for pediatric NAFLD, even in high-risk populations.[17]

Obesity is the known risk factor for NAFLD. At present, BMI adjusted for age and sex is the most common approach to stratify obesity in children. However, BMI is a measure of excess weight rather than excess body fat mass (BFM) and may not necessarily reflect body composition. Bioelectrical impedance analysis (BIA) is an established body composition method in children that estimates BFM and fat free mass (FFM) separately.[18,19] Therefore, BIA parameters may provide better surrogate for body adiposity and thus better predictor for NAFLD, compared with BMI and BMI *z* score (BAZ). We hypothesized that BIA parameters rather than BAZ and other anthropometric indices could more accurately predict the risk of childhood NAFLD. This study aimed to test whether addition of BIA parameters to BMI and anthropometric indices improves NAFLD discrimination over BAZ alone.

Materials and Methods

Study Design and Ethical Considerations

This prospective school-based cross-sectional study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (IRB No: 201802057B0), and written informed consent was provided by all subjects and their parents or legal guardians. Studies were conducted between September 2019 and June 2020.

Participants

Eligible participants were healthy Taiwanese children attending primary schools who had agreed to participate in the study in southwestern Taiwan. Exclusion criteria were participants with known liver disease, significant alcohol use, limb defect, pacemaker implant, and chronic illness.

Data Collection

All measurements were performed at the school health center on the morning section. Before study, participants were fasted for 2 hours and instructed to empty their bladders. Anthropometric and BIA measures were performed by trained research assistants. One measurement per subject was performed using each instrument. Liver ultrasound studies were performed by a skilled radiologist with over 20-year experience of ultrasound.

Anthropometric Measures

Body height and weight were measured using a digital scale with subjects wearing no shoes and light cloth. Weight was recorded to the nearest 0.1 kg and height to the nearest 0.1 cm. The World Health Organization (WHO) AnthroPlus software (WHO, Basel, Switzerland) was used to calculate BMI, height *z* score (HAZ), and BAZ according to the WHO Reference 2007 for children 5–19 years of age.[20] Children with BAZ above +1 standard deviation (SD) were classified as overweight, above +2SD as obese, below −2SD as underweight, and −2SD to +1SD as normal weight.

Bioelectrical Impedance Analysis

A dual-frequency BIA device (Inbody 230; Biospace Corp., Seoul, Korea) was used to measure BFM, FFM, and percentage body fat (PBF) in total body and body segments at 20 and 100 kHz, as described previously.[18] Interclass correlation (ICC) for PBF was excellent (ICC coefficient = 0.99, $n = 10$).

Ultrasound Examination

Ultrasound was performed using an OPUS 5000 scanner equipped with a 3.5 MHz curved array probe (Chang Gung Medical Technology Co., Ltd., Taipei, Taiwan). Scan parameters including overall gain, time gain compensation, focal zone, and dynamic range were optimized for each participant. All scans were performed and interpreted by a single experienced radiologist, blinded to the body composition data. Normal liver was defined as homogeneous echotexture, isoechoic compared with the renal cortex and adequate visualization of the intrahepatic vessels and the diaphragm. Fatty liver was defined as bright liver and graded as described previously.[10]

Machine Learning Models

Three subsets of features were selected to investigate the role of BAZ, anthropometric indices, and BIA parameters for predicting NAFLD. The BAZ set included only one attribute, the BAZ. The anthropometric set included six anthropometric attributes: age, height, weight, BMI, BAZ, and HAZ. The BIA set included features as follows: age, height, BMI, BAZ, HAZ, total BFM, trunk BFM, fat mass index (FMI), total PBF, trunk PBF, FFM, skeletal muscle mass (SMM), and skeletal muscle index (SMI). FMI was defined as BFM in kilograms divided by height in meter squared. SMM was calculated as total FFM in the four extremities. SMI was defined as SMM in kilograms divided by height in meter squared.

Classification algorithms, including Zero-R, Naive Bayes, *k*-Nearest Neighbors (*k*NN), J48 Decision Tree, and Logistic Regression, were applied using fivefold cross-validation. Feature selection was applied using Correlation-based Feature Subset Evaluation (CfsSubsetEval) with Best-First search to reduce the dimensions of the modeling.[21] *k*NN algorithm was tested repeatedly with different *k* values ranging from 1 to 10.

Statistical Analysis

Descriptive statistics was performed using SPSS version 25 (IBM Corp., Armonk, NY). Student's *t*-test was used to compare group means. The statistical significance level was set at $\alpha = 0.05$. Waikato Environment for Knowledge Analysis (WEKA) software version 3.8.3 was used to run machine learning experiments.[22] Evaluation metrics including accuracy, area under receiver operating characteristic curve (ROC area), true-positive rate, false-positive rate, precision, recall, *F*-measure, area under precision-recalled curve (PRC area), and Matthews correlation coefficient (MCC) were obtained. Accuracy is the fraction of instances classified correctly. An ROC curve is built by plotting true-positive rate against false-positive rate at different probability thresholds and ROC area is a summary measure of performance.[23] Precision is the percentage of true positive in relation to the classified positives. Recall, also known as sensitivity, refers to the fraction of actual positives that are classified correctly as positives. *F*-measure is the harmonic mean of the precision and recall. A precision-recall curve is built by plotting precision and recall pairs calculated from different thresholds.[24] PRC area is a single performance measure for the precision-recall curve. MCC is a correlation coefficient calculated from all four values of the confusion matrix and incorporates the dataset imbalance.[25]

Results

Participant Demographics

Table 1 shows the descriptive values for the included children. Of the 933 children, 50.6% were boys. Participants had a wide range of BAZ (–3.5 to 6.9) and total PBF (9.6%–51.6%). Regardless of the BMI category, the prevalence of NAFLD was higher in boys than girls (Supplementary Table S1). In boys, prevalences of NAFLD were 14% ($n = 66$) in the total group and 0% ($n = 0$), 1.1% ($n = 3$), 6.2% ($n = 4$), and 44.4% ($n = 59$) in children with underweight, normal weight, overweight, and obesity. In girls, prevalences of NAFLD were 3.3% ($n = 15$) in the total group and 0% ($n = 0$), 0.3% ($n = 1$), 2.0% ($n = 2$), and 20.0% ($n = 12$) in children with underweight, normal weight, overweight, and obesity.

Factors Associated with Ultrasonically Diagnosed NAFLD

Table 2 shows the participant characteristics in children with obesity with and without ultrasound-diagnosed

Table 1. Subject Characteristics

	Boys ($n = 472$)				Girls ($n = 461$)				
Characteristic	Mean	SD	Min	Max	Mean	SD	Min	Max	*p*
Age (years)	9.3	1.8	6.2	12.2	9.6	1.8	6.2	12.7	0.004
Height (cm)	134.9	11.9	106.7	173.8	136.3	12.7	107.0	164.1	0.069
Weight (kg)	35.7	13.3	16.4	98.3	34.9	11.9	15.9	98.4	0.347
BMI (kg/m^2)	19.0	4.6	12.3	37.0	18.3	3.8	12.3	40.4	0.006
BMI z-score	0.9	1.6	–3.5	6.9	0.5	1.3	–3.2	6.1	<0.001
Height z-score	0.1	1.0	–3.1	3.5	0.0	1.0	–3.1	2.7	0.026
Total BFM (kg)	10.5	7.7	2.1	50.0	9.9	6.2	1.9	50.4	0.245
Trunk BFM (kg)	4.3	4.2	0.1	24.4	4.1	3.4	0.1	22.7	0.307
FMI (kg/m^2)	5.5	3.4	1.3	18.8	5.1	2.7	1.4	20.7	0.111
Fat free mass (kg)	25.2	6.7	13.6	53.8	25.0	6.7	13.1	48.0	0.576
Skeletal muscle mass (kg)	12.9	4.0	5.9	30.0	12.7	3.9	5.7	26.4	0.425
Skeletal muscle index (kg/m^2)	6.9	1.0	4.6	10.4	6.6	1.0	4.8	10.8	<0.001
Total PBF (%)	26.5	10.0	9.6	51.6	26.5	8.4	11.0	51.2	0.940
Trunk PBF (%)	22.9	13.3	3.0	50.6	23.5	11.6	3.0	50.6	0.517

BFM, body fat mass; FMI, fat mass index; PBF, percentage body fat; SD, standard deviation.

Table 2. Subject Characteristics of Children with Obesity with/without Nonalcoholic Fatty Liver Disease

	Boys with obesity					Girls with obesity				
	Fatty liver (−)		Fatty liver (+)			Fatty liver (−)		Fatty liver (+)		
	Mean	SD	Mean	SD	*p*	Mean	SD	Mean	SD	*p*
Anthropometric indices										
Age (years)	9.1	1.7	10.4	1.3	<0.001	9.1	1.8	10.0	1.4	0.104
Height (cm)	137.3	11.5	145.4	9.0	<0.001	136.8	12.3	142.0	8.0	0.171
Weight (kg)	44.4	11.5	57.3	11.5	<0.001	45.4	13.1	58.3	15.7	0.005
BMI (kg/m^2)	23.1	3.1	26.8	3.2	<0.001	23.7	3.1	28.5	4.7	<0.001
BMI z-score	2.8	0.9	3.1	0.8	0.040	2.7	0.8	3.1	0.7	0.119
Height z-score	0.8	1.0	0.8	0.9	0.706	0.7	0.7	0.5	1.0	0.555
BIA estimates										
Total BFM (kg)	16.4	5.5	24.1	6.5	<0.001	17.8	6.1	27.0	9.2	<0.001
Trunk BFM (kg)	7.6	3.0	11.7	3.2	<0.001	8.4	3.3	12.9	4.0	<0.001
FMI (kg/m^2)	8.6	2.4	11.3	2.4	<0.001	9.2	2.1	13.1	3.2	<0.001
Total PBF (%)	36.5	6.0	41.9	4.2	<0.001	38.5	5.3	45.7	3.7	<0.001
Trunk PBF (%)	36.3	6.7	42.3	3.7	<0.001	38.6	7.3	45.9	2.8	0.001
Fat free mass (kg)	28.0	7.2	33.1	6.1	<0.001	27.6	7.4	31.3	6.9	0.121
Skeletal muscle mass (kg)	14.6	4.3	17.6	3.6	<0.001	14.3	4.4	16.5	4.1	0.119
Skeletal muscle index (kg/m^2)	7.5	1.0	8.2	0.8	<0.001	7.4	1.0	8.1	1.1	0.057

BIA, bioelectrical impedance analysis; NAFLD, nonalcoholic fatty liver disease.

NAFLD. In boys, children with NAFLD were significantly older, taller, heavier, and had significantly greater values in BMI, BAZ, and all BIA estimates than those without NAFLD, except for the HAZ ($p=0.706$). In girls, children with NAFLD were significantly heavier and had significantly higher values in BMI and fat-related estimates by BIA but not for FFM-related estimates. There was no association between NAFLD and BAZ in girls with obesity.

The NAFLD Prediction Models

The final dataset had 933 instances and 14 numeric attributes with a binary class. With the low prevalence of NAFLD in children with underweight, normal weight, and overweight, the prediction models were developed only for children with obesity. The Zero-R classifier was used to predict the majority class (non-NAFLD) ignoring all predictors. In boys with obesity, there were 59 positive compared with 74 negative instances, yielding an accuracy of 55.6% by Zero-R. In girls with obesity, there were 12 positive compared with 48 negative instances, and the Zero-R classifier yielded an accuracy of 80%. The dataset was further divided into three subsets: the BAZ set, the anthropometric set, and the BIA set.

Performance of the Prediction Model in Boys with Obesity

Table 3 provides the optimal features and model evaluation metrics for predicting NAFLD in boys with obesity ($n=133$). Accuracy and ROC area are commonly used metrics providing overall performance for a binary classifier system. According to both metrics, BAZ set performed worst, adding age, weight, and BMI into the model improved the model performance, whereas BIA predictors had a marginal increase in model performance. These suggested that BIA parameters were the best approach for predicting NAFLD. The results were similar with the other model evaluation metrics. The best results achieved had an accuracy of 75.9%, *F*-measure of 0.714, MCC of 0.510, ROC area of 0.854, and PRC area of 0.802 (Supplementary Fig. S1).

Performance of the Prediction Model in Girls with Obesity

Table 4 provides the optimal features and model evaluation metrics for predicting NAFLD in girls with obesity. There were 12 positive compared with 48 negative instances, making it an unbalanced dataset with the ratio of 1:4. For unbalanced dataset, accuracy and ROC area may

Table 3. Model Performance for Predicting Nonalcoholic Fatty Liver Disease in Male Children with Obesity

	Accuracy	TP rate	FP rate	Precision	Recall	*F*-measure	MCC	ROC area	PRC area
Zero R	55.6%	0	0	—	0	—	—	0.488	0.437
BAZ set Attribute selection: BAZ									
Naive Bayes	59.4%	0.305	0.176	0.581	0.305	0.400	0.152	0.639	0.558
*k*NN (*k* = 1)	52.6%	0.339	0.324	0.455	0.339	0.388	0.015	0.445	0.428
Multilayer Perceptron (layers = 1)	62.4%	0.475	0.257	0.596	0.475	0.528	0.226	0.640	0.554
J48 Decision Tree	57.9%	0.627	0.459	0.521	0.627	0.569	0.167	0.607	0.525
Logistic Regression	59.4%	0.237	0.122	0.609	0.237	0.341	0.152	0.664	0.567
Anthropometric set attribute selection: age, weight, BMI									
Naive Bayes	73.7%	0.763	0.284	0.682	0.763	0.720	0.476	0.806	0.760
*k*NN (*k* = 3)	74.4%	0.763	0.270	0.692	0.763	0.726	0.489	0.763	0.670
Multilayer Perceptron (layers = 2)	72.2%	0.627	0.203	0.712	0.627	0.667	0.432	0.801	0.736
J48 Decision Tree	68.4%	0.644	0.284	0.644	0.644	0.644	0.360	0.717	0.614
Logistic Regression	71.4%	0.678	0.257	0.678	0.678	0.678	0.421	0.807	0.761
BIA set attribute selection: age, BFM, FMI, trunk PBF									
Naive Bayes	69.9%	0.729	0.324	0.642	0.729	0.683	0.402	0.836	0.794
*k*NN (*k* = 6)	75.9%	0.678	0.176	0.755	0.678	0.714	0.510	0.854	0.802
Multilayer Perceptron (layers = 3)	73.7%	0.695	0.230	0.707	0.695	0.701	0.466	0.831	0.772
J48 Decision Tree	72.9%	0.678	0.230	0.702	0.678	0.690	0.450	0.789	0.685
Logistic Regression	70.7%	0.678	0.270	0.667	0.678	0.672	0.407	0.820	0.786

BAZ, BMI z-score; FP, false positive; *k*NN, *k*-Nearest Neighbors; MCC, Matthews correlation coefficient; PRC area, area under precision-recalled curve; ROC area, area under receiver operating characteristic curve; TP, true positive.

have pitfalls for model evaluation and metrics proposed to handle unbalanced data such as *F*-measure, MCC, and PRC area should also be explored.

In BAZ set, only the *k*NN classifier predicted NAFLD with acceptable discrimination ability (*F*-measure = 0.435, MCC = 0.302, and PRC area = 0.373). The other classifier did not predict the NAFLD class (*F*-measure = 0 and MCC <0). Prediction performance was slightly improved when BMI was included in the model using most of the classifiers. With BIA parameters, performance of the model showed further improvement. The best results achieved had a *F*-measure score of 0.615, MCC of 0.512, and PRC area of 0.697 (Supplementary Fig. S1).

Discussion

The prevalence of NAFLD from the full dataset was 14% for boys and 3.3% for girls, which was lower than previous estimates from the Taiwanese pediatric population.[4,5] This may owing to differences between study designs. In this study, the performances of BAZ, anthropometric indices, and BIA parameters for predicting NAFLD in apparently healthy Taiwanese children 6–12 years of age with obesity was explored using machine learning algorithms. BAZ alone was found to be a poor predictor of pediatric NAFLD, although it is the most common index for classifying a child's obesity-related risk. Our experiment suggests BIA parameters are better predictors for ultrasound-diagnosed NAFLD in primary school children in both sexes.

This study aimed to explore the prediction performance of BAZ, anthropometric indices, and BIA parameters for NAFLD. Therefore, it was important that all children with NAFLD had positive test results (high sensitivity), whereas the number of children with false-positive results (low sensitivity) was considered less important. This is because the accurate prediction of positive class was considered more important than that of negative class because under-detection may indicate further missed diagnosis and delayed treatment of disease, whereas overdiagnosis just means unnecessary venous sampling or ultrasound examination. For the imbalance dataset including girls with obesity, metrics that weigh both classes equally, such as overall accuracy and ROC area, were biased toward the majority class because of its higher prior probability. To reduce the impact of unbalanced

Table 4. Model Performance for Predicting Nonalcoholic Fatty Liver Disease in Female Children with Obesity

	Accuracy	TP rate	FP rate	Precision	Recall	*F*-measure	MCC	ROC area	PRC area
Zero R	80.0%	0	0	—	0	—	—	0.417	0.178
BAZ set attribute selection: BAZ									
Naive Bayes	76.7%	0	0.042	0	0	0	–0.093	0.479	0.205
*k*NN (*k* = 1)	78.3%	0.417	0.125	0.455	0.417	0.435	0.302	0.749	0.373
Multilayer Perceptron (layers = 1)	78.3%	0	0.021	0	0	0	–0.065	0.688	0.304
J48 Decision Tree	78.3%	0	0.021	0	0	0	–0.065	0.550	0.233
Logistic Regression	76.7%	0	0.042	0	0	0	–0.093	0.646	0.310
Anthropometric set attribute selection: BMI									
Naive Bayes	80.0%	0.250	0.063	0.500	0.250	0.333	0.250	0.777	0.565
*k*NN (*k* = 3)	85.0%	0.417	0.042	0.714	0.417	0.526	0.467	0.781	0.486
Multilayer Perceptron (layers = 1)	80.0%	0.250	0.063	0.500	0.250	0.333	0.250	0.750	0.440
J48 Decision Tree	76.7%	0	0.042	0	0	0	–0.093	0.447	0.183
Logistic Regression	80.0%	0.250	0.063	0.500	0.250	0.333	0.250	0.795	0.598
BIA set Attribute selection: FMI, PBF, trunk PBF									
Naive Bayes	83.3%	0.667	0.125	0.571	0.667	0.615	0.512	0.898	0.697
*k*NN (*k* = 2)	85.0%	0.250	0	1.000	0.250	0.400	0.459	0.846	0.590
Multilayer Perceptron (layers = 1)	83.3%	0.417	0.063	0.625	0.417	0.500	0.417	0.856	0.531
J48 Decision Tree	83.3%	0.667	0.125	0.571	0.667	0.615	0.512	0.898	0.542
Logistic Regression	83.3%	0.417	0.063	0.625	0.417	0.500	0.417	0.849	0.622

classes, other performance measures or resampling techniques can be used to handle the imbalanced classification problems.[26] In this study, metrics effective for evaluating unbalanced class distribution such as *F*-measure, MCC, and PRC area were also explored.[27,28] Taking into consideration all model evaluation metrics, BAZ alone was considered a poor method for predicting NAFLD, whereas including anthropometric indices in the model improved the performance greatly. Further improvement of model performance is possible with BIA parameters entered into the predictors.

BAZ is the most widely used index by which to stratify children at risk of obesity-related complications in research and clinical settings,[3] but its prediction performance for NAFLD is less known. Similar to results of this study, Jimenez-Rivera et al.[29] studied 97 obese children 8–17 years of age and showed that BAZ alone cannot be used to discriminate between children with or without NAFLD. In that study, the authors investigated associations between NAFLD and a wide range of blood tests, including liver enzymes, lipid profiles, Homeostatic Model Assessment Insulin Resistance, and adiponectin. Results showed that only triglycerides acted as a screening tool for NAFLD with a sensitivity of 90% and a specificity of 40% (ROC area = 0.69). Other body composition methods such as skinfold thickness[30,31] and waist-to-height ratio[5] have been shown to be useful predictors for NAFLD in general pediatric population. However, their role in predicting NAFLD in children with obesity is not clear.

Zhang et al.[32] reported that BMI percentile predicted NAFLD with 86.2% sensitivity, 87.6% specificity, and an ROC area of 0.93 at a cutoff of 80th BMI percentile in 7229 Chinese children 7–18 years of age. In that study, the reported prevalence was only 5%. In a screening test with such a low prevalence, the positive and negative predictive values are also of interest, as specificity is likely to be inflated.[33,34] However, the Zhang study[32] did not report the relevant measures and sex differences were not taken into account and therefore it is difficult to evaluate the differences between these previous studies and ours.[33,34]

Pediatric NAFLD is a rapidly increasing disease with growing epidemics of childhood obesity while lifestyle intervention and effective methods are available to treat the disease.[35] Although most NAFLD is asymptomatic and reversible, long-term NAFLD may result in severe irreversible complications such as cirrhosis and hepatocellular carcinoma. Therefore, NAFLD screening in children is a worthwhile endeavor and can detect the disease at early stages when treatment may be more successful and, at the same time, reduce subsequent morbidity or mortality.

At present, BAZ is the most commonly used method for weight category in children. However, our study showed that BAZ was insufficient to identify children who are most likely to have ultrasound-diagnosed NAFLD and that additional screening and assessment such as anthropometric indices and BIA parameters may be more useful to estimate obesity risks.

As far as we know, no similar study design is found in the published literature regarding the use of BIA parameters in predicting NAFLD in children with obesity. BIA is more sensitive than BAZ in assessing body composition. Our study further established that screening NAFLD with BIA is superior to BAZ in school children. In boys with obesity, the best results achieved had an accuracy of 75.9% for predicting NAFLD using BIA parameters in this study. This is comparable with the result of a meta-analysis which showed that ALT level had an accuracy of 75% for diagnosing patients with NAFLD.[36] BIA is a simple and highly precise tool for body composition analysis, and it may also be a practical and highly cost-effective tool for screening NAFLD in large-scale surveys. This study also has the advantage of recruiting the general pediatric population in community settings to avoid referral bias.

There are limitations in this study. First, ultrasound was chosen as the reference method and it is relatively insensitive to detect mild fatty liver. This study used ultrasound as the reference method because ultrasound is noninvasive and more readily available. Second, the sample size was small and subgroup analysis could not be performed for children with overweight. Third, ultrasound examination results require interpretation and it is possible that interobserver variation may affect the diagnosis of NAFLD. To reduce the bias, all ultrasound tests in this study were performed by a single experienced investigator using the same ultrasound scanner. Fourth, our study design did not allow adjustment for potential confounders such as liver enzyme, dietary sugar, physical activity, and genetic risk factors. Finally, only one measure per subject was taken for each instrument in this study. This may lead to measurement errors.

Conclusion

This study addressed the issue of screening children with potential NAFLD using body composition methods, showing BIA is a simple and highly precise tool that yields better performance for predicting NAFLD than anthropometric indices, and much better performance than BAZ. Future study is needed to explore the role of BIA in predicting other obesity-related complications.

Authors' Contributions

L.W.L. obtained funding for the study. L.W.L., J.B.Y. and Y.S.L. conceptualized, designed, and interpreted the analyses. L.W.L. carried out the literature research, conducted the analyses, generated tables and figures, and drafted the initial version of the article. All authors contributed to the interpretation of analyses and reviewed and revised the article. All authors were involved in writing the article and had final approval of the final version of the article for submission.

Acknowledgment

The authors thank the Chang Gung Medical Technology Company for allowing free use of their ultrasound scanner.

Funding Information

This work was funded by the Ministry of Science and Technology of Taiwan under grant MOST 108-2314-B-182A-080- and by the Chang Gung Medical Foundation under grant CMRPG6K0082.

Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Table S1
Supplementary Figure S1

References

1. Zimmermann E, Gamborg M, Holst C, et al. Body mass index in school-aged children and the risk of routinely diagnosed non-alcoholic fatty liver disease in adulthood: A prospective study based on the Copenhagen School Health Records Register. *BMJ Open* 2015;5:e006998.
2. Du S, Wang C, Jiang W, et al. The impact of body weight gain on nonalcoholic fatty liver disease and metabolic syndrome during earlier and later adulthood. *Diabetes Res Clin Pract* 2016;116:183–191.
3. Anderson EL, Howe LD, Jones HE, et al. The prevalence of non-alcoholic fatty liver disease in children and adolescents: A systematic review and meta-analysis. *PLoS One* 2015;10:e0140908.
4. Huang SC, Yang YJ. Serum retinol-binding protein 4 is independently associated with pediatric NAFLD and fasting triglyceride level. *J Pediatr Gastroenterol Nutr* 2013;56:145–150.
5. Lin MS, Lin TH, Guo SE, et al. Waist-to-height ratio is a useful index for nonalcoholic fatty liver disease in children and adolescents: A secondary data analysis. *BMC Public Health* 2017;17:851.
6. Lin YC, Chang PF, Yeh SJ, et al. Risk factors for liver steatosis in obese children and adolescents. *Pediatr Neonatol* 2010;51:149–154.
7. Ratziu V, Charlotte F, Heurtier A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005;128:1898–1906.
8. Khov N, Sharma A, Riley TR. Bedside ultrasound in the diagnosis of nonalcoholic fatty liver disease. *World J Gastroenterol* 2014;20:6821–6825.

9. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology* 2002;123:745–750.
10. Ma X, Holalkere NS, Kambadakone RA, et al. Imaging-based quantification of hepatic fat: Methods and clinical applications. *Radiographics* 2009;29:1253–1277.
11. Draijer LG, Feddouli S, Bohte AE, et al. Comparison of diagnostic accuracy of screening tests ALT and ultrasound for pediatric nonalcoholic fatty liver disease. *Eur J Pediatr* 2019;178:863–870.
12. Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). *J Pediatr Gastroenterol Nutr* 2017;64:319–334.
13. Molleston JP, Schwimmer JB, Yates KP, et al. Histological abnormalities in children with nonalcoholic fatty liver disease and normal or mildly elevated alanine aminotransferase levels. *J Pediatr* 2014;164:707–713.e703.
14. HH AK, Henderson J, Vanhoesen K, et al. Nonalcoholic fatty liver disease in children: A single center experience. *Clin Gastroenterol Hepatol* 2008;6:799–802.
15. Manco M, Alisi A, Nobili V. Risk of severe liver disease in NAFLD with normal ALT levels: A pediatric report. *Hepatology (Baltimore, Md)* 2008;48:2087–2088.
16. Devadason CA, Scheimann AO. Overview of screening methods for fatty liver disease in children. *World J Hepatol* 2012;4:1–4.
17. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018;67:328–357.
18. Lee L-W, Liao Y-S, Lu H-K, et al. Validation of two portable bioelectrical impedance analyses for the assessment of body composition in school age children. *PLoS One* 2017;12:e0171568.
19. Kyle UG, Earthman CP, Pichard C, Coss-Bu JA. Body composition during growth in children: Limitations and perspectives of bioelectrical impedance analysis. *Eur J Clin Nutr* 2015;69:1298–1305.
20. de Onis M, Onyango AW, Borghi E, et al Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 2007;85:660–667.
21. Green SB. How many subjects does it take to do a regression analysis. *Multivariate Behav Res* 1991;26:499–510.
22. Frank E, Hall MA, Witten IA. *The WEKA Workbench. Online Appendix for ''Data Mining: Practical Machine Learning Tools and Techniques'',* 4th ed. San Francisco, CA: Morgan Kaufmann, 2016.
23. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143:29–36.
24. de Luca C, Olefsky JM. Stressed out about obesity and insulin resistance. *Nat Med* 2006;12:41–42; discussion 42.
25. Matthews BW. Comparison of the predicted and observed secondary structure of T4 phage lysozyme. *Biochim Biophys Acta* 1975;405:442–451.
26. Kotsiantis S, Kanellopoulos D, Pintelas P. Handling imbalanced datasets: A review. *GESTS Int Trans Comput Sci Eng* 2006;30: 25–36.
27. Saito T, Rehmsmeier M. The precision-recall plot is more informative than the ROC plot when evaluating binary classifiers on imbalanced datasets. *PLoS One* 2015;10:e0118432.
28. Chicco D, Jurman G. The advantages of the Matthews correlation coefficient (MCC) over F1 score and accuracy in binary classification evaluation. *BMC Genomics* 2020;21:6.
29. Jimenez-Rivera C, Hadjiyannakis S, Davila J, et al. Prevalence and risk factors for non-alcoholic fatty liver in children and youth with obesity. *BMC Pediatr* 2017;17:113.
30. Freedman DS, Katzmarzyk PT, Dietz WH, et al. Relation of body mass index and skinfold thicknesses to cardiovascular disease risk factors in children: The Bogalusa Heart Study. *Am J Clin Nutr* 2009;90:210–216.
31. Yan Y, Hou D, Zhao X, et al. Childhood adiposity and nonalcoholic fatty liver disease in adulthood. *Pediatrics* 2017;139: e20162738.
32. Zhang X, Wan Y, Zhang S, et al. Nonalcoholic fatty liver disease prevalence in urban school-aged children and adolescents from the Yangtze River delta region: A cross-sectional study. *Asia Pac J Clin Nutr* 2015;24:281–288.
33. Hernaez R, Thrift AP. High negative predictive value, low prevalence, and spectrum effect: Caution in the interpretation. *Clin Gastroenterol Hepatol* 2017;15:1355–1358.
34. van Stralen KJ, Stel VS, Reitsma JB, et al. Diagnostic methods I: Sensitivity, specificity, and other measures of accuracy. *Kidney Int* 2009;75:1257–1263.
35. Utz-Melere M, Targa-Ferreira C, Lessa-Horta B, et al. Non-alcoholic fatty liver disease in children and adolescents: Lifestyle Change—A systematic review and meta-analysis. *Ann Hepatol* 2018;17:345–354.
36. Ma X, Liu S, Zhang J, et al. Proportion of NAFLD patients with normal ALT value in overall NAFLD patients: A systematic review and meta-analysis. *BMC Gastroenterol* 2020;20:10.

Address correspondence to:
Yu-San Liao, MD
Department of Diagnostic Radiology
Chang Gung Memorial Hospital
1500 Gongye Road
Mailiao Township
Yunlin County 63862
Taiwan

E-mail: mm601200@gmail.com