Prevalence of Nonalcoholic Fatty Liver Disease in Children with Obesity

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Objectives To determine the prevalence of nonalcoholic fatty liver disease (NAFLD) in children with obesity because current estimates range from 1.7% to 85%. A second objective was to evaluate the diagnostic accuracy of alanine aminotransferase (ALT) for NAFLD in children with obesity.

Study design We evaluated children aged 9-17 years with obesity for the presence of NAFLD. Diseases other than NAFLD were excluded by history and laboratories. Hepatic steatosis was measured by liver magnetic resonance imaging proton density fat fraction. The diagnostic accuracy of ALT for detecting NAFLD was evaluated.

Results The study included 408 children with obesity that had a mean age of 13.2 years and mean body mass index percentile of 98.0. The study population had a mean ALT of 32 U/L and median hepatic magnetic resonance imaging proton density fat fraction of 3.7%. The estimated prevalence of NAFLD was 26.0% (95% CI 24.2%-27.7%), 29.4% in male patients (CI 26.1%-32.7%) and 22.6% in female patients (CI 16.0%-29.1%). Optimal ALT cut-point was 42 U/L (47.8% sensitivity, 93.2% specificity) for male and 30 U/L (52.1% sensitivity, 88.8% specificity) for female patients. The classification and regression tree model with sex, ALT, and insulin had 80% diagnostic accuracy for NAFLD.

Conclusions NAFLD is common in children with obesity, but NAFLD and obesity are not concomitant. In children with obesity, NAFLD is present in nearly one-third of boys and one-fourth of girls. *(J Pediatr 2019;207:64-70).*

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Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in children[1] and the most common indication for liver transplantation in young adults in the US.[2] Because obesity is the largest risk factor for NAFLD,[3] current recommendations for screening focus on children with obesity.[4] However, there is not a uniform agreement regarding the prevalence of NAFLD in children with obesity, as reported estimates range from 1.7% to 85%.[5-7] This wide range is due in part to variations in study design, including sample size, geography, race, ethnicity, and setting. In addition, prevalence estimates differ based on the reference method used to determine whether a child had NAFLD.

Obesity is recognized as a growing epidemic among youth in the US; however, the ability to assess the impact of NAFLD on children is incomplete because of the large range in the estimated prevalence of NAFLD in children with obesity. The Centers for Disease Control and Prevention estimate that the prevalence of pediatric obesity in the US is 17%, which represents 12.7 million children.[8] When combining this estimate with the range of estimates for the prevalence of NAFLD in children with obesity, there could be as few as 216 000 or as many as 10.8 million children with obesity in the US with NAFLD. This lack of understanding has ramifications for public health initiatives, which include developing optimal screening guidelines for NAFLD in children, determining the utility and cost effectiveness of such guidelines, and designing effective healthcare policy. Improvement estimates of the prevalence of NAFLD also may advance research by guiding the design of studies to further our understanding of the genetics, pathophysiology, and pathogenesis of the overlapping but discrete conditions of obesity and NAFLD.

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
HDL	High-density lipoprotein
MRI	Magnetic resonance imaging
NAFLD	Nonalcoholic fatty liver disease
PDFF	Proton density fat fraction

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Therefore, the primary aim of this study was to estimate the prevalence of NAFLD in children aged 9-17 years with obesity. Because serum alanine aminotransferase (ALT) is widely used to screen for NAFLD in children with obesity, a secondary aim was to evaluate the diagnostic accuracy of ALT for detecting NAFLD in such children.

Methods

Subject Selection

We evaluated children aged 9-17 years with obesity, defined as body mass index (BMI) ≥95th percentile for age and sex. Children were recruited in the County of San Diego from community health centers, community health fairs, and primary care practices. Exclusion criteria were as follows: (1) inability to complete a magnetic resonance imaging (MRI) evaluation (claustrophobia, metal implants, or body circumference greater than the imaging chamber); (2) established diagnosis of chronic liver disease; (3) the use of medications that can cause steatosis or raise liver chemistry; (4) diagnosis of other chronic diseases that may have secondary effects on the liver; (5) substance abuse; and (6) pregnancy. The protocol was approved by the institutional review board of the University of California, San Diego. The parents of all subjects provided written informed consent for their children. Written assent was obtained from all children.

Clinical Evaluation

Clinical data were obtained for each participant from a single fasting intake visit at the Altman Clinical and Translational Research Institute at the University of California, San Diego. Age, sex, and self-identified race and ethnicity were recorded. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with the subjects standing, wearing light clothing without shoes. BMI was calculated as weight (kilograms) divided by height squared (meters squared). Fasting laboratory assays included ALT, aspartate aminotransferase (AST), glucose, insulin, high-density lipoprotein (HDL) cholesterol, and triglyceride levels.

MRI Evaluation

Participants were scanned at 3 Tesla (3T) using an advanced magnitude-based liver fat-quantification MRI technique to measure proton density fat fraction (PDFF), a biomarker for hepatic steatosis.[9] T1 bias was avoided by using a gradient-recalled echo sequence with a low flip angle (10°) and a repetition time of ≥150 milliseconds.[10,11] Six gradient-recalled echoes were acquired at sequential out-of-phase and in-phase echo times to measure the fractional fat signal while correcting for T2* signal decay.[10,12,13] A multipeak fat spectral model was applied to correct for multifrequency interference effects of fat proton signals. A 1-cm radius circular region of interest was placed in each of the 9 Couinaud liver segments, and a composite PDFF value was calculated for each MRI examination by averaging the individual PDFF values from the 9 regions of interest.

Data Analysis

Descriptive statistics and exploratory graphing were used to assess the normality of the data in terms of the presence of skew and/or outliers. All data were within normal range, and none were transformed. All missing data were examined to assess randomness. Data were analyzed using ANOVAs for continuous variables and χ^2 for dichotomous variables. Fatty liver was defined as MRI-PDFF ≥5.0% for the primary analysis.[14,15] Overall prevalence estimates for NAFLD were directly standardized for the regional distribution of obesity by sex and ethnicity. Sex-specific estimates of prevalence with directly standardized for ethnicity. Optimal ALT cut-points were determined using receiver operating characteristics analysis. The classification and regression tree method was used to construct a decision tree for classifying children with obesity as having or not having NAFLD. The following variables were considered: age, sex, BMI z score, ALT, AST, triglycerides, HDL cholesterol, glucose, and insulin. The decision tree with the greatest predictive power was selected. A secondary analysis of the prevalence was performed using other PDFF cut-points that have been proposed in the literature (3.5%, 6.4%, and 9.0%).[16-18] All statistical tests were 2-tailed and conducted with SPSS, version 23 (IBM Corp, Armonk, New York). Differences were considered statistically significant at a P value < .05.

Results

Demographics

There were 408 children with obesity aged 9-17 years included in this study. The study population characteristics are presented in **Table I**. The mean age was 13.2 (±4.0) years and was not significantly different in those with and without NAFLD. The mean BMI percentile was 98.0 and was significantly greater in children with NAFLD than those without NAFLD (98.5 vs 97.8, $P < .001$). The mean ALT was 32 (±32) U/L and was also significantly greater in children with NAFLD than those without NAFLD (53 vs 24, $P < .0001$). As shown in **Table I**, the mean values of AST, triglycerides, HDL cholesterol, and insulin all differed significantly in children with and without NAFLD.

Prevalence of NAFLD

The overall estimated prevalence of NAFLD in children with obesity was 26.0% (95% CI 24.2-27.7). As shown in **Table II**, the prevalence was 29.4% in male patients (95% CI 26.1%-32.7%) and 22.6% in female patients (95% CI 16.0%-29.1%).

Diagnostic Accuracy of ALT Value for NAFLD

For male patients with obesity, the optimal ALT cut-point was 42 U/L (47.8% sensitivity, 93.2% specificity), which provided a diagnostic accuracy of 80%. A diagnostic accuracy of 80% also was achieved for female patients with obesity using an optimal ALT cut-point of 30 U/L (52.1% sensitivity, 88.8% specificity). See receiver operating characteristic curves in **Figure 1**.

Table I. Subject characteristics by fatty liver status

Characteristics	All participants, n = 408	Normal liver, n = 291	Fatty liver, n = 117	*P* value
Sex, n (%)				.137
Male	217 (53.2)	148 (50.9)	69 (59.0)	
Female	191 (46.8)	143 (41.1)	48 (41.0)	
Age, y, mean (SD)	13.2 (4)	13.9 (2.3)	13.7 (2.4)	.343
Weight, kg, mean (SD)	82.2 (19.3)	80.1 (18.2)	87.2 (20.8)	.001
Height, cm, mean (SD)	161.2 (11.8)	160.7 (12.1)	162.4 (11.1)	.172
BMI, kg/m^2, mean (SD)	31.3 (4.9)	30.7 (4.8)	32.6 (4.9)	.001
BMI percentile, mean (SD)	98.0 (1.3)	97.8 (0.1)	98.5 (1.2)	.000
BMI z score, mean (SD)	2.1 (0.3)	2.0 (0.3)	2.2 (0.3)	.000
Race, n (%)				.476
American Indian	7 (1.7)	5 (1.7)	2 (1.2)	
Asian	14 (3.4)	7 (2.4)	7 (6.0)	
Black	9 (2.2)	7 (2.4)	2 (1.2)	
White	241 (59)	175 (60.1)	66 (56.4)	
Other	137 (33.6)	97 (33.3)	40 (34.1)	
Ethnicity, n (%)				.038
Hispanic	314 (77.0)	216 (74.2)	98 (83.8)	
Non-Hispanic	94 (23.0)	75 (25.8)	19 (16.2)	
ALT, U/L, mean (SD),	32.0 (32.3)	23.6 (19.2)	53.1 (46.0)	.000
AST, U/L, mean (SD)	30.0 (18.9)	26.5 (12.1)	38.7 (28.0)	.000
Triglycerides, mg/dL, mean (SD)	117.4 (75.6)	111.1 (77.4)	132.9 (68.9)	.008
HDL, mg/dL, mean (SD)	43.2 (10.0)	44.5 (10.0)	40.2 (9.3)	.000
Glucose, mg/dL, mean (SD)	87.3 (10.1)	86.9 (9.7)	87.9 (11.0)	.389
Insulin, uU/mL, mean (SD)	25.5 (24.0)	21.3 (21.5)	35.6 (26.7)	.000

Decision Tree for Classification of NAFLD Status

The classification and regression tree model was based on sex, ALT, and insulin. As shown in **Figure 2**, for optimal classification, ALT was separated into 3 categories for female patients and 4 categories for male patients. Insulin was used to better sort female patients with ALT >11 through 29 U/L and to better sort male patients with ALT >21 through 61 U/L. The overall diagnostic accuracy of the model was 80%. Each node shows the probability of correct classification based on sex and a given ALT and insulin.

Impact of Using Alternate MRI-PDFF Cut-Points on Prevalence

As shown in **Table II**, using an MRI-PDFF cut-point of 3.5%, the prevalence of NAFLD in children with obesity was 49.3% (95% CI 47.9%-50.7%) with a similar estimate for male and female patients. Using a PDFF cut-point of 6.4%, the prevalence of NAFLD in children with obesity was 19.1%, with greater rates in male than female patients (23.5% in male patients; 14.7% in female patients). Finally, using a PDFF cut-point of 9.0%, the prevalence of NAFLD in children with obesity was 11.5% (95% CI 8.%- 14.4%) with a greater prevalence in male patients (15.2%; 95% CI 9.2%-21.3%) than in female patients (7.7%; 95% CI 0.2%-19.6%).

Table II. Prevalence of NAFLD by MRI PDFF threshold value in children with obesity

PDFF thresholds	Prevalence of fatty liver	95% CI
≥5.0%		
All	26.0%	24.2%-27.7%
Boys	29.4%	26.1%-32.7%
Girls	22.6%	16.0%-29.1%
≥3.5%		
All	49.3%	47.9%-50.7%
Boys	50.0%	49.0%-51.9%
Girls	48.5%	48.5%-52.8%
≥6.4%		
All	19.1%	16.7%-21.4%
Boys	23.5%	19.1%-27.9%
Girls	14.7%	5.5%-23.8%
≥9.0%		
All	11.5%	8.5%-14.4%
Boys	15.2%	9.2%-21.3%
Girls	7.7%	0.2%-19.6%

Discussion

We performed a large, community-based study to determine the prevalence of NAFLD in children aged 9-17 years with obesity. Using the most commonly reported threshold of liver MRI PDFF of 5.0%, the estimate for the prevalence of NAFLD in children with obesity was 26.0%. We identified sex-specific values for ALT for the classification of NAFLD in children with obesity. In addition, we developed a diagnostic tree that added insulin to sex and ALT to classify children with obesity as having or not having NAFLD. In addition, we evaluated the impact of alternate proposed MRI-PDFF thresholds and demonstrated that the choice of threshold has a substantial effect on the resulting prevalence estimate for NAFLD in children with obesity.

The estimate of the prevalence of NAFLD is influenced by the choice of study population, the sample size, and the accuracy of the diagnostic modality used. Previous studies have reported a wide range for the prevalence of NAFLD in children, from <2% to >80% depending on the study.[5-7] For example, in a study of 181 children with obesity drawn from a general pediatrics clinic that predominantly served children of black race, the prevalence of NAFLD was 8%.[19] Factors that

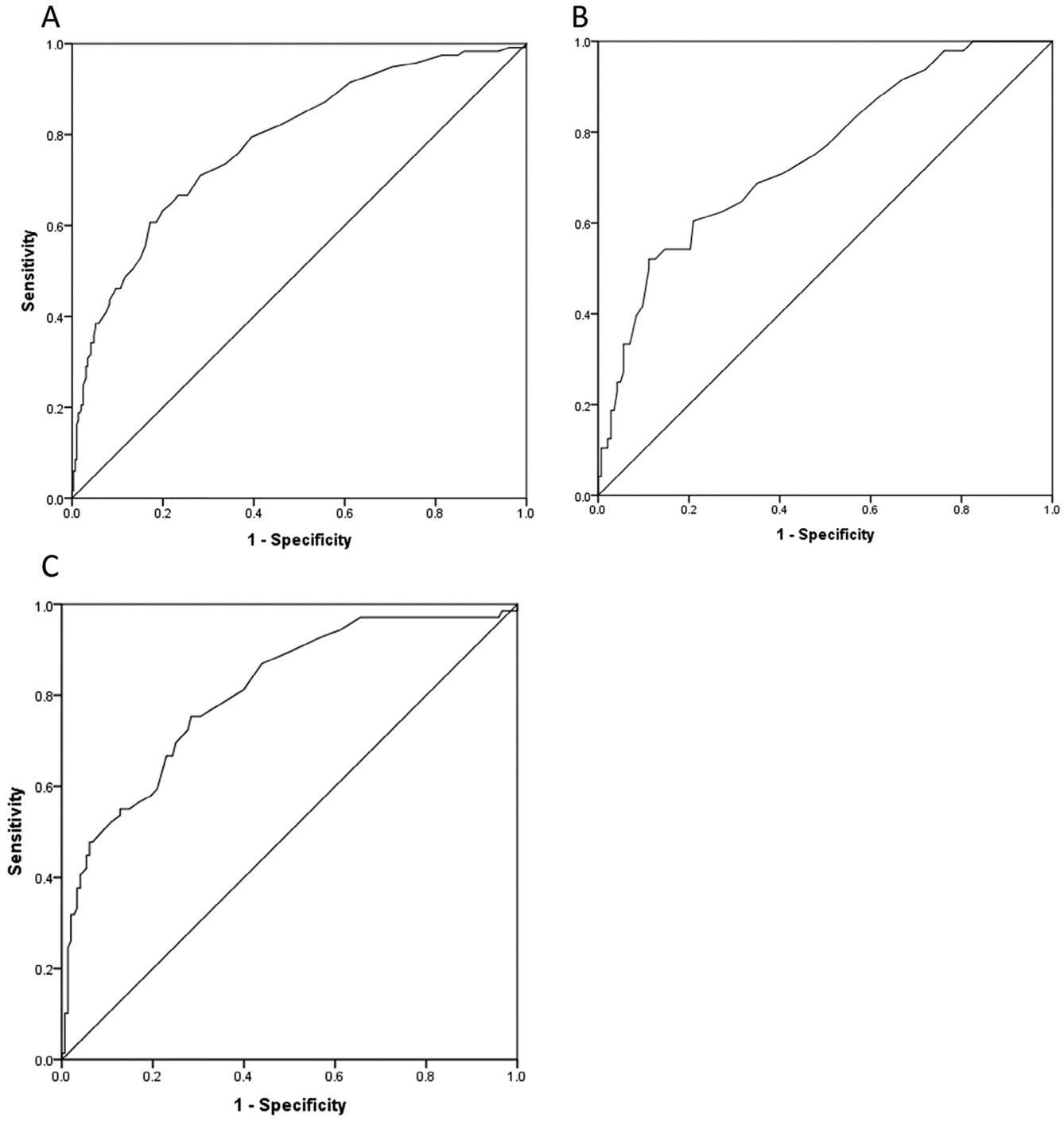

Figure 1. Shown are receiver operating characteristic (ROC) curves for ALT as a diagnostic tool for hepatic steatosis in children with obesity. **A,** ROC for all children with an area under the ROC curve of 0.78. **B,** ROC for girls with an area under the ROC curve of 0.75. **C,** ROC for boys with an area under the ROC curve of 0.81.

may have accounted for a relatively low prevalence estimate included a lower severity of obesity in general pediatrics, lower rates of NAFLD in children of black race, and the use of ALT as the diagnostic tool.[1] Studies that have used ALT to detect NAFLD, in general, have lower prevalence estimates. In contrast, a study of 84 children with obesity in a tertiary referral clinic in China reported a prevalence of NAFLD of 77%.[20] The high prevalence was likely influenced by the smaller sample size, the greater severity of obesity, greater rates of NAFLD in Asian children, and the use of ultrasonography as the diagnostic

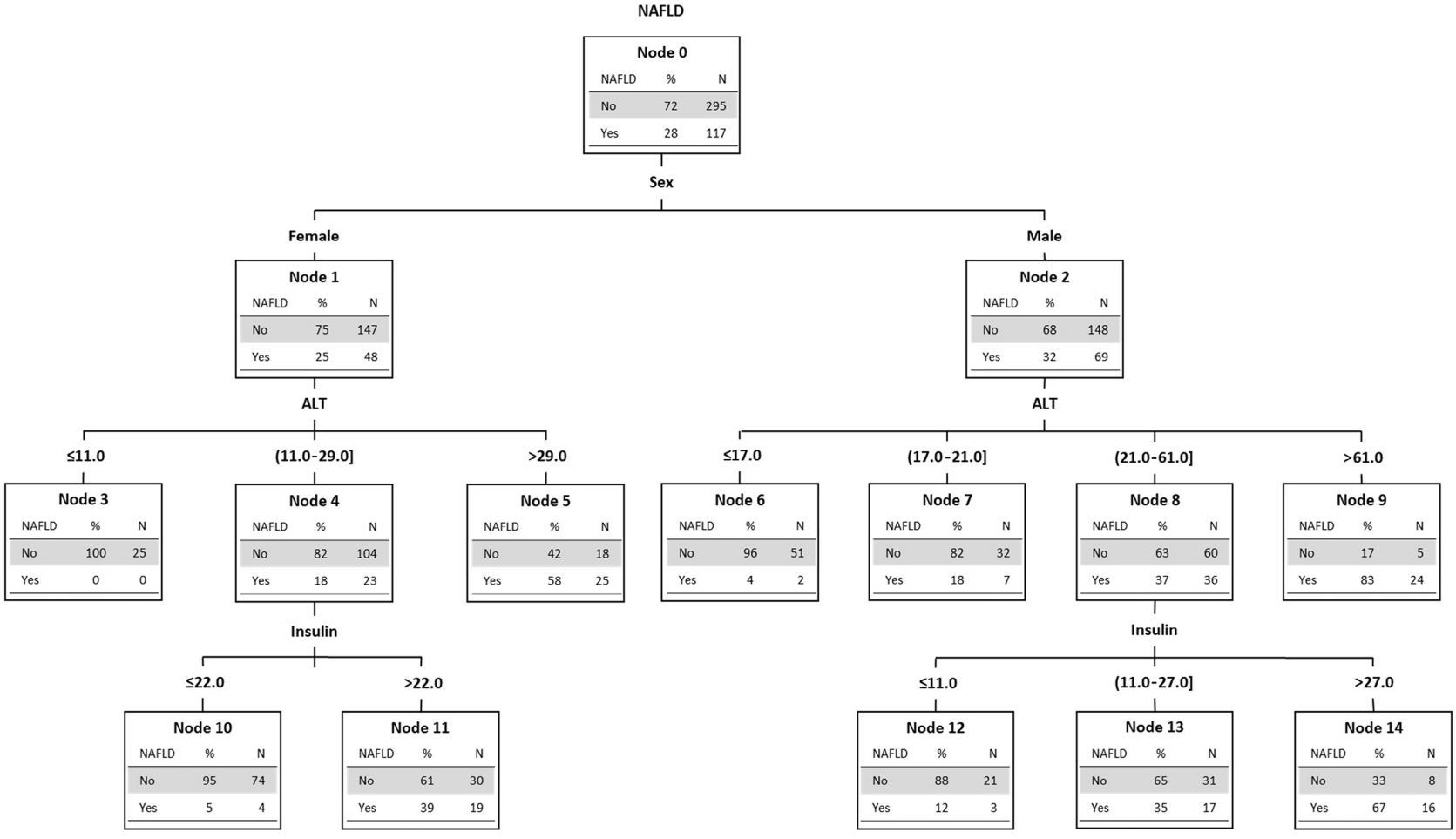

Figure 2. Decision tree algorithm for NAFLD in children with obesity developed by machine learning via classification and regression tree modeling. The tree separates by sex (nodes 1 and 2), then by ALT U/L (nodes 3-9), and then by fasting insulin uU/mL (nodes 10-14). Each node shows the separation of NAFLD and not NAFLD based on the specific parameters by total number and percentage.

tool. In general, studies using ultrasonography as the diagnostic modality have greater prevalence estimates.

In addition to the diagnostic modality used, sample size influences estimate of prevalence such that studies with small sample sizes tend to have extreme values (<20% and >50%), and those with sample sizes >300 have prevalence estimates that are in between (20%-40%).[21-23] Therefore, our observed prevalence of NAFLD of 28.7% in children with obesity was consistent with expected prevalence, given that our study included >400 children selected from the general community and used MRI-PDFF as the diagnostic modality.[9,24,25]

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines recommend ALT as the best screening test for NAFLD in children.[4] These guidelines propose an ALT ≥80 U/L on initial screening or ALT greater than or equal to twice the upper limit of normal (ALT ≥44 U/L for female and ALT ≥52 U/L for male children) on repeated screening as an indication for further evaluation.[4,26] The optimal cut-points from our study are lower than the current recommended evaluation points. In this study, we determined that ALT ≥30 U/L in female children with obesity and ≥42 U/L in male children with obesity provided a good diagnostic accuracy for determining the presence of NAFLD. Of note, these ALT levels are only slightly greater than the 95th percentile for all children. As demonstrated in the screening ALT for elevation in today's youth (SAFETY) study, for the general population including children with obesity, the 95th percentile for ALT was 26.0 U/L in female subjects and 37.2 U/L in male subjects.[24] On one hand, strong diagnostic accuracy reinforces that ALT is an effective screening tool. It is worth noting that there is not another commonly available marker with equivalent diagnostic accuracy. Moreover, of the other laboratory values commonly obtained clinically, only insulin improved the classification of an individual child with obesity as having or not having NAFLD. However, ALT alone is not a sufficient diagnostic tool. No matter what threshold is used, some children with obesity and ALT levels above a given threshold will have reasons for liver chemistry elevation other than NAFLD. In addition, ALT remains unable to differentiate disease severity.[27,28] Thus, for patient care purposes, ALT should be used as a screening tool and not as a diagnostic tool.

In this study, NAFLD was defined as an MRI-PDFF ≥5.0%, which is a threshold for hepatic steatosis that has been used in other studies.[28,29] Because a noninvasive diagnostic tool for NAFLD is of broad interest, having a set point for dichotomous determination of NAFLD is appealing for clinicians and patients alike. The data from the current study demonstrate that the choice of cut-point used can have a large impact on whether an individual child is considered to have NAFLD. As multiple cut-points have been used previously to delineate grade 0 from grade 1 steatosis, and no single MRI-PDFF has been proven to be diagnostic for pediatric NAFLD,[9] we also examined multiple MRI-PDFF cut-points to demonstrate the impact on estimated point prevalence. We observed large differences in estimated NAFLD prevalence in children with obesity resulted from changing the MRI-PDFF cut-point by small increments; a decrease of 1.5 percentage points in PDFF cutoff (eg, from 5.0% to 3.5% PDFF) resulted in an increase of estimated NAFLD prevalence from 28.7% to 53.2%. Moreover, response to treatment and natural history may be framed by the choice of MRI-PDFF cut-point. Thus, as the field continues to increasingly use MRI-PDFF as a noninvasive diagnostic tool for NAFLD, it is imperative that there be more uniform criteria established for diagnostic thresholds.

A major strength of this study was the large sample size and detailed phenotyping of the participants. Participants were obtained from a broad, community sample, which decreased the selection bias present in a sample from a tertiary referral center. In addition, the use of MRI-PDFF provided an accurate, reproducible measure of hepatic steatosis. One study limitation was the lack of liver histology; however, this is not feasible for population-based epidemiology. This study also had a large prevalence of Hispanic children and thus may not represent all communities. We adjusted our prevalence estimates for ethnicity, but similar data from other regions would be useful.

NAFLD is common in children with obesity, but NAFLD and obesity are not concomitant. We estimate that in children with obesity, NAFLD is present in nearly one-third of boys and one-fourth of girls. These data should be useful for future initiatives in the treatment and prevention of NAFLD. Moreover, the study data highlight the need to develop standardized diagnostic cutoffs for MRI-measured hepatic steatosis. Finally, we propose new, evidence-based ALT thresholds for the detection of NAFLD derived from a community sample without previous knowledge of presence of liver disease.

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Data Statement

Data sharing statement available at www.jpeds.com.

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