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Predicting hepatic steatosis in a racially and ethnically diverse cohort of adolescent girls

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Abstract

Objectives—To develop a risk assessment model for early detection of hepatic steatosis using common anthropometric and metabolic markers.

Study design—Cross-sectional study of 134 girls, age 11–22 years (mean 13.3±2), Ethnicity: 27% Hispanic, 73% Non-Hispanic; Race: 64% Caucasian, 31% African-American, 5% Asian, from a middle school and clinics (Madison, WI). Fasting glucose, fasting insulin, alanine aminotransferase (ALT), body mass index (BMI), waist circumference (WC) and other metabolic markers were assessed. Hepatic fat was quantified using magnetic resonance proton density fat fraction (MR-PDFF). Hepatic steatosis was defined as MR-PDFF >5.5%. Outcome measures were sensitivity, specificity, and positive predictive value (PPV) of BMI, WC, ALT, fasting insulin and ethnicity as predictors of hepatic steatosis, individually and combined, in a risk assessment model. Classification and regression tree methodology constructed a decision tree for predicting hepatic steatosis.

Results—MR-PDFF revealed hepatic steatosis in 16% of subjects (27% overweight, 3% non-overweight). Hispanic ethnicity conferred an odds ratio of 4.26 (CI 1.65–11.04, p=0.003) for hepatic steatosis. BMI and ALT did not independently predict hepatic steatosis. A BMI > 85% combined with ALT > 65 U/L had 9% sensitivity, 100% specificity and 100% PPV. Lowering

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ALT to 24 U/L increased sensitivity to 68%, but reduced PPV to 47%. A risk assessment model incorporating fasting insulin, total cholesterol, WC, and ethnicity increased sensitivity to 64%, specificity to 99% and PPV to 93%.

Conclusions—A risk assessment model can increase specificity, sensitivity, and PPV for identifying risk of hepatic steatosis and guide efficient use of biopsy or imaging for early detection and intervention.

Key Terms

Hepatic Steatosis; Nonalcoholic hepatic steatosis; Metabolic Syndrome; Child and Adolescent

Nonalcoholic fatty liver disease (NAFLD) comprises a continuum from isolated hepatic steatosis, to steatohepatitis (NASH), to bridging fibrosis, to cirrhosis^{1–3}. The prevalence of NAFLD approaches 25% in overweight adolescent girls and ranges from 25–38% of all overweight children^{1, 4, 5}. Studies have shown higher prevalence of NAFLD in Hispanics and lower prevalence in non-Hispanic blacks compared with non-Hispanic whites^{6–9}. Even in non-overweight children, Hispanic ethnicity influences the risk of NAFLD¹⁰. In both children and adults, NAFLD is strongly associated with metabolic syndrome and insulin resistance, which can lead to the development of NASH^{11–14}. Hyperinsulinemia is not only more common in children with NAFLD, but also contributes to disease progression by facilitating intracellular accumulation of triglycerides and fatty acids in hepatocytes^{15, 16}. Accumulation of fatty acids in hepatocytes causes oxidative stress, activation of stellate cells, and hepatocellular injury and fibrosis¹⁷. Importantly, up to 68% of children and adolescents with NAFLD already have NASH at diagnosis^{5, 18}.

Early diagnosis is important, as prognosis is significantly better when NAFLD is diagnosed before progression to NASH^{1, 6}. Although isolated hepatic steatosis is reversible with weight loss, scarring and inflammation associated with NASH can lead to irreversible changes including cirrhosis and end stage liver disease^{19, 20}. Unfortunately, it is difficult to identify children with isolated steatosis and predict which of these children will progress to NASH. Although elevated liver transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] signify hepatocellular injury, liver enzymes are often normal in obese children despite evidence of hepatic steatosis on biopsy^{21, 22}. In multiple pediatric NAFLD studies, ALT has been shown to either correlate poorly or not at all with early steatosis^{1, 4, 15, 21, 23} and degree of elevation does not predict severity or presence of NASH²⁴. In addition, the National Health and Nutrition Examination Survey 1999–2004 survey found that ALT values vary by sex, race and ethnicity, further limiting the utility of ALT as a screening tool for NAFLD in adolescents²³. Lack of correlation of ALT with the presence of NAFLD has led to significant confusion among health care providers about screening for NAFLD in overweight and obese children²⁵. Both the American Academy of Pediatrics and the Endocrine Society recommend using ALT to screen for NAFLD in this group^{26, 27}. However, there is not sufficient evidence to recommend the use of ALT for screening in overweight children or adults²⁸.

Given the relative insensitivity of ALT as a marker of NAFLD and lack of consensus on appropriate screening of overweight and obese children, pediatric NAFLD is likely under-

diagnosed, particularly in the early stages²². Comprehensive NAFLD prediction scores have been proposed to improve early detection, but two pediatric NAFLD scores that were developed use only obese, white children and do not address the effect of race and ethnicity on NAFLD risk^{29, 30}.

The objectives of this study were to identify early hepatic steatosis using quantitative magnetic resonance imaging-derived proton density fat fraction (MR-PDFF), correlate hepatic fat with metabolic disease in an ethnically and racially diverse group of adolescent girls, and to develop a prediction model to identify high risk of hepatic steatosis and guide efficient use of a model for risk assessment to increase early identification.

Methods

Study subjects were females who responded to a general invitation distributed to University of Wisconsin (UW) pediatric clinics and a local middle school to participate in the study. After obtaining informed written consents and assents, MRI safety screen and a brief survey of personal and family medical history, medication use, and self-identified race and ethnicity (per National Institute of Health race and ethnicity criterion for subjects in clinical research) were collected. Study entrance criteria were female sex and age 11–22 years old. Exclusion criteria included a history of chronic disease that affected hepatic or renal function including: Type 1 or Type 2 diabetes mellitus, known liver disease or other chronic illness, treatment with medications including oral contraceptives, lipid-lowering or glucose metabolism altering agents, or Vitamin E supplements greater than 100 IU daily, pregnancy, or excess alcohol consumption defined as greater than an average of 1.5 drinks per day and standard contraindications to MRI (metallic implants, claustrophobia, etc.). A total of 136 subjects were enrolled in the study.

Height was measured using a stadiometer and recorded to the nearest 0.5 cm. Waist circumference (WC) was measured twice just above the iliac crests with Graham-Field[®] cloth woven measuring tape, and the average was recorded to the nearest 1mm. Weight was measured without shoes in light clothes on a beam balance platform scale to the nearest 0.1 kg. Body mass index (BMI) was then calculated. Self-assessment of Tanner staging for breast and pubic hair was performed³¹.

Fasting blood samples were analyzed for lipids [total cholesterol, high-density lipoprotein (HDL), low density lipoprotein (LDL)-calculated, and triglycerides], AST, ALT, hemoglobin A1c (HgbA1c), glucose and insulin. HgbA1c determined by ion exchange chromatography/spectrometry. AST and ALT determined by NADH with Pyridoxal-5 phosphate assay. Sex hormone binding globulin (SHBG) was measured using a quantitative electrochemiluminescent immunoassay. Free testosterone was measured using a quantitative high performance liquid chromatography-tandem mass spectrometry/electrochemiluminescent immunoassay. Adiponectin was analyzed by radioimmunoassay and leptin by enzyme-linked immunosorbent assay. Homeostasis model of assessment-insulin resistance (HOMA-IR) was calculated as [fasting glucose (mg/dL) × fasting insulin (μU/ml)/405]. The presence of metabolic syndrome was identified using two different sets of criteria. The first, Met-IFG, requires the presence of at least 3 of the 5 criteria: fasting blood

glucose 100 mg/dL, blood pressure > 90% for age/sex³², waist circumference >90% for age/sex³³, HDL < 40 mg/dl, triglycerides > 150mg/dL³⁴. The second, Met-IR, substitutes HOMA-IR > 4.0, for impaired fasting glucose³⁵.

Quantitative magnetic resonance imaging was performed at the Wisconsin Institute for Medical Research (WIMR). The Human Subjects Committee of the University of Wisconsin approved all procedures.

Single breath-hold magnetic resonance imaging was performed over the entire liver using a clinical 3T scanner (MR750, GE Healthcare, Waukesha, WI) with a 32-channel phased array body coil (Neocoil, Pewaukee WI). MR-PDFF was determined using an investigational version of a chemical shift encoded water-fat separation method (3D-IDEAL-SPGR)^{36, 37}. Separated water-only and fat-only images, as well as hepatic MR-PDFF maps³⁸ were provided using an on-line reconstruction algorithm method that includes spectral modeling of fat³⁹, corrects for eddy currents⁴⁰, T1 bias⁴¹, T2* decay⁴², and noise related bias⁴¹. Because all known confounders have been addressed, the resulting MR-PDFF map provides an accurate and fundamental measure of the fat concentration in tissue³⁷.

Hepatic PDFF was determined by averaging MR-PDFF values measured from 9 regions of interest placed in each of the 9 Couinaud segments of the liver³⁶. Hepatic steatosis was defined as a hepatic MRPDFF >5.5%⁸.

Statistical Analyses

Subject characteristics were summarized using standard descriptive statistics. Variables measured on a continuous scale were summarized in terms of means $\pm$ standard deviations (SD). The comparisons between subjects with and without hepatic steatosis were performed using a two-sample t-test or nonparametric Wilcoxon Rank Sum test. Categorical variables were summarized in tabular format using frequencies and percentages and comparisons between subjects with and without hepatic steatosis were performed using a Chi-square test. Post-hoc analysis between racial groups made using a Bonferroni correction. Univariate and multivariate logistic regression analysis was conducted to evaluate the associations between markers (eg, ALT, fasting glucose, total cholesterol) and the presence of hepatic steatosis. First, univariate logistic regression analysis was conducted for each marker. Markers that were identified as significant predictors in the univariate analysis were then included as predictors in the initial non-parsimonious multivariate model. The backward selection procedure with a *P* value cut-off of <0.10 was used to identify a parsimonious multivariate model with independent predictors for hepatic steatosis. Receiver Operating Characteristics (ROC) analyses were conducted to evaluate the predictive power of NAFLD predictors. The Youden Index was used to determine optimal cutoffs.

The classification and regression tree (CART) method was utilized to construct a decision tree for predicting hepatic steatosis because the CART approach toward classifying cases is based on recursive partitioning of the data and is particularly well suited for identifying complex interactions among variables that are predictive of disease status. The CART algorithm calculates optimal threshold values for continuous variables to categorize subjects into a low- or high-risk group⁴³. The CART algorithm selects the best predictor variables

using recursive splitting. It starts with the best possible predictor from the data set and successively splits the data into categories predicted to observe the event or not. CART attempts to maximize the purity of each split, striving to accurately categorize cases into the appropriate outcome grouping. Subsequent partitioning of the data follows this same method, using other predictor variables to guide the classification accuracy or purity of the final tree. As a splitting method, the exponential scaling method was used. The splitting process stopped when a minimum of 5 patients per group was reached or when there was no further decrease in prediction error. Cross-validation studies were performed to compare the predictive power levels of various decision trees. The results of the decision tree with the highest predictive power were presented. Sensitivity, specificity, negative (NPV) and positive predictive values (PPV) for the results of the proposed classification tree were calculated along with the corresponding 95% confidence intervals (CI).

The prediction characteristics of the decision tree were compared with the prediction characteristics obtained from recently proposed NAFLD disease prediction models^{29, 30}. The NAFLD prediction scores of these models were constructed using logistic regression analysis involving waist to height ratio, ALT, HOMA-IR, adiponectin and leptin. The NAFLD prediction scores for these models were calculated for the study population and ROC analyses were conducted to determine optimal cutoffs based on the Youden criterion. Statistical analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC). All *P* values were 2-sided, and *P* < 0.05 was used to indicate statistical significance.

Results

Characteristics of 136 subjects with and without hepatic steatosis are presented in Table I. Hepatic steatosis, defined as hepatic MR-PDFF greater than 5.5%, was found in 16% (22/136) of subjects, including 2 with a BMI < 85th percentile. Median MR-PDFF in subjects with hepatic steatosis was 9.2%. Even though Hispanic subjects made up only 27% (37/136) of our overall sample, more than half (13/22) of subjects with hepatic steatosis were Hispanic. Hispanic ethnicity was associated with an odds ratio of 4.26 (CI 1.65–11.04, *p*=0.003) for the presence of hepatic steatosis. In contrast, a lower proportion of African American girls, 5% (2/40), had hepatic steatosis. Twenty-seven percent of overweight girls had hepatic steatosis. Comparing overweight subjects with and without hepatic steatosis, no significant difference in mean age or mean BMI was seen (Table I). All subjects in both groups were pubertal and the average self-assessed breast Tanner Stage³¹ was not statistically different for overweight subjects with hepatic steatosis (4, SD 1) and overweight subjects without hepatic steatosis (3.7, SD 1.6), *p*-value 0.55. ALT was significantly higher in overweight subjects with hepatic steatosis, but the mean ALT for subjects with hepatic steatosis was 38 U/L (SD 25 U/L), and was within the normal range (less than 65 U/L) in 18 of 22 subjects with hepatic steatosis.

Anthropometric and metabolic measures in overweight subjects with and without hepatic steatosis are compared in Table II. Significant differences were noted in total cholesterol, triglycerides, fasting insulin, fasting glucose, HOMA-IR and SHBG. Notably, WC, HDL, LDL, HgbA1c, and androgens (total testosterone, free testosterone) were not significantly different between groups, although differences in WC approached significance (*p* 0.07). The

strength of association of hepatic steatosis with metabolic syndrome varied depending upon metabolic syndrome diagnostic criteria. Met-IFG was observed in 30% (6/20) of overweight subjects with hepatic steatosis compared with 13% (7/55) of overweight subjects without hepatic steatosis, but the difference was not statistically significant (OR 2.94; CI 0.85–10.2, $p=0.85$). Met-IR, however, was observed in 60% (12/20) of overweight subjects with hepatic steatosis compared with 27% (12/55) of overweight subjects without hepatic steatosis (27%; 15/55) and increased the odds of hepatic steatosis by 4.95 (CI 1.66–14.78, $p=0.003$).

Comparison of common predictors for hepatic steatosis

Both logistic regression analysis and ROC analysis were performed on commonly used predictors of hepatic steatosis. Although in the univariate logistic analysis multiple markers increased likelihood of hepatic steatosis, in multivariate logistic regression analysis only HOMA-IR (OR 1.46, CI 1.22–1.76, $p<0.001$) and triglycerides (OR 1.02, CI 1.002–1.026, $p=0.02$) remained as independent predictors for hepatic steatosis. Notably, ALT and BMI were not independent predictors of hepatic steatosis. ROC analysis using optimal thresholds for BMI percentile, triglycerides, fasting insulin, and HOMA-IR improved sensitivity and specificity, but positive predictive value remained poor for each measure. A HOMA-IR threshold of 6.7 resulted in the highest PPV at 53, and BMI percentile greater than 84%, the lowest PPV of 28 (Table III; available at www.jpeds.com). Application of current pediatric and endocrine NAFLD screening guidelines based on elevated BMI and an ALT above the upper limit of normal (UW lab reference range: 12 – 65 U/L) resulted in 100% (CI 97%–100%) specificity, but only 9% (CI 1.4%–29%) sensitivity, missing 20/22 adolescents with hepatic steatosis^{26, 27}. Lowering ALT threshold to 24 U/L (the optimal upper limit for ALT obtained by ROC analysis; Table III) improved sensitivity to 68% (CI 45%–85%), but reduced specificity to 85% (CI 77%–91%) and positive predictive value to 47% (CI 30%–65%).

Comparison of multivariable prediction scores to improve identification of subjects at risk for hepatic steatosis

Decision tree analysis was constructed using a classification and regression tree (CART) methodology³⁷. Initially, all clinically available demographic, anthropometric and metabolic markers obtained for these subjects were included, and the CART algorithm (Figure 1) was allowed to select best predictor variables using recursive splitting. The result incorporated fasting insulin, total cholesterol, ethnicity and waist circumference, yielding a sensitivity of 64% (CI 43%–80%), specificity to 99% (CI 95%–100%), positive predictive value to 93% (CI 70%–99%) and a negative predictive value of 93% (CI 87%–97%). In addition, the Pediatric NAFLD SCORE (with and without adiponectin) developed by Maffeis et al was applied to the complete cohort and the prediction score developed by Koot et al was applied to a subset of 68 subjects who had leptin levels measured^{29, 30}. A comparison of prediction characteristics for the CART algorithm, and previous NAFLD prediction scores showed good sensitivity and specificity for all prediction methods. PPV and overall accuracy for predicting hepatic steatosis (weight average of PPV and NPV) was significantly better using the CART risk assessment strategy as compared with other prediction scores (Table IV).

Discussion

Hepatic steatosis is common in a racially and ethnically diverse population of asymptomatic adolescent girls, and steatosis occurs in both obese and non-obese children. The median hepatic fat fraction for these adolescents with hepatic steatosis (9.2%) is below the level of detection for most ultrasound techniques⁴⁴. However, even at this low hepatic fat fraction, subjects with hepatic steatosis showed adverse metabolic effects of hepatic fat deposition, including significantly higher triglycerides, HOMA-IR, fasting glucose and rates of metabolic syndrome compared with similar weight children without hepatic steatosis. Importantly, in overweight adolescents, age, BMI and waist circumference were not significantly different between those with and without hepatic steatosis, and were not independent predictors of disease. Although ALT was significantly higher in those with hepatic steatosis, 91% (20/22) of children with hepatic steatosis still had an ALT within the normal reference range.

Current pediatric and endocrine screening guidelines for NAFLD recommend using a combination of BMI and ALT for assessing NAFLD risk^{26, 27}. In this study, the finding of an ALT level above laboratory reference range of 65 U/L had 100% specificity, but low sensitivity (9%) for detecting hepatic steatosis. Lowering the ALT threshold to 24 U/L (suggested by ROC analysis and similar to the suggested threshold of 22.1 U/L from the SAFETY study) increased sensitivity to 68%, but decreased specificity to 85% and positive predictive value to 47%; i.e. less than half of overweight children referred for evaluation of hepatic steatosis based on this combination of BMI and ALT level truly have disease²⁴. This observation strengthens previous findings that the combination of ALT and BMI is a suboptimal screen for a disease that currently requires liver biopsy for definitive diagnosis^{1, 21, 23, 45}.

Development of a risk assessment model for hepatic steatosis with high positive predictive value could facilitate targeted use of imaging modalities such as ultrasound, computerized tomography (CT) or MRI to establish diagnosis. The hepatic steatosis predictive model which was developed with CART analysis for this study (Figure 1) using commonly available clinical measurements and biomarkers - fasting insulin, total cholesterol, ethnicity, and waist circumference - significantly increases sensitivity, specificity, and positive predictive value compared with current guidelines. Even though the specific laboratory thresholds suggested by the CART model may vary in other laboratories, a focus on the components of this model could improve identification of those at risk for hepatic steatosis. Specifically, using data from this cohort and the authors' institutional laboratory, an insulin ~ 2 SDs above the normal upper limit (value of 36 uIU/mL) and a total cholesterol of 141 mg/dL, waist circumference > 102 cm correctly predicted hepatic steatosis with an accuracy of 93%. Notably, the CART analysis did not show ALT to be a factor that positively influenced the risk assessment model for hepatic steatosis. This model could facilitate efficient and appropriate referral of patients for imaging or liver biopsy to identify early steatosis before progression to steatohepatitis. When compared with previously reported NAFLD prediction scores, the model proposed here has higher overall accuracy for predicting hepatic steatosis in this racially and ethnically diverse cohort.

In Hispanic subjects, elevation in fasting insulin and total cholesterol alone identify increased risk with equally high accuracy. Hispanics, particularly those of Mexican descent, have a higher frequency of the PNPLA3 gene variant (rs78409 SNP) than Non-Hispanics⁴⁶. Children who were homozygous carriers of this variant had 2.4 times higher liver fat content than heterozygous carriers and nearly 5 times higher than in those who did not carry the gene variant⁴⁷. However, the overall prevalence of the higher risk allele in the Hispanic population is only 48% and the risk of NAFLD is likely only increased in individuals of Hispanic heritage who also display other signs of metabolic disease, such as insulin resistance and dyslipidemia⁴⁶.

There are several limitations to this study. This model was developed using only female subjects. Several studies, including the SAFETY study, suggest that sex-specific guidelines are necessary to increase sensitivity of NAFLD screening²⁴. Given that puberty has a significant influence on the development of IR and NAFLD, we analyzed only girls, who have less variability in stages of puberty compared with boys at this age. Based on a self-assessment survey, the majority of girls were pubertal with Tanner stage 2–5. Future studies of male and female adolescents could include determination of Tanner stage by clinician exam. Furthermore, although the model shows excellent overall accuracy for predicting hepatic steatosis, the sensitivity of 64% could be improved by use of more detailed assessment of insulin resistance (e.g. insulin sensitivity index), given the day-to-day variability in fasting insulin levels. However, this change would make the model more cumbersome for use in clinical practice.

In summary, hepatic steatosis is common in overweight girls, particularly those of Hispanic ethnicity, and BMI and ALT screening alone misses the majority of subjects with hepatic steatosis. Early detection is important because even a modest amount of hepatic fat is associated with metabolic disease, which may contribute to progression of NASH – a more severe form of NAFLD. Incorporation of a clinically feasible risk assessment model with a high predictive value for NAFLD, such as the one proposed in this study, could guide efficient use of biopsy or imaging for detection of early hepatic steatosis in children and adolescents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

AA	African American
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CART	classification and regression tree
CI	confidence interval
H	Hispanic
HOMA-IR	homeostatic model assessment of insulin resistance
IR	insulin resistance
Met-IFG	metabolic syndrome with impaired fasting glucose
Met-IR	metabolic syndrome with insulin resistance
MR-PDFF	magnetic resonance proton density fat fraction
NAFLD	nonalcoholic hepatic steatosis
NASH	nonalcoholic steatohepatitis
NPV	negative predictive value
NH	non-Hispanic
OR	odds ratio
PPV	positive predictive value
ROC	receiver operating characteristics
SHBG	sex hormone binding globulin
WC	waist circumference

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Risk Assessment Strategy for Hepatic Steatosis

Figure 1.

Risk assessment strategy incorporating readily available clinical measures improves prediction of hepatic steatosis risk. Sensitivity = 64%, Specificity = 99%, Positive predictive value = 93%, Negative predictive value = 95%

*This is equivalent to a fasting insulin value 2 standard deviations above the mean.

Table 1Subject characteristics in those with and without hepatic steatosis^a

	All subjects n=136	All subjects without HS n = 114	All subjects with HS n = 22	P value	Overweight subjects without HS n=55	Overweight subjects with HS n=20	P value
Age (years)	13.2 (2.0)	13.2 (1.9)	13.6 (2.4)	0.668	13.6 (2.3)	13.7 (2.5)	0.904
AA	40 (29.4)	38 (33.3)	2 (9.1)		26 (47.3)	2 (10.0)	
AS	8 (5.9)	5 (4.4)	3 (13.6)	0.002*	1 (1.8)	2 (10.0)	0.003 [#]
W	88 (64.7)	71 (62.3)	17 (77.3)		28 (50.9)	16 (80.0)	
H	37	25 (21.9)	12 (54.5)		14 (25.5)	11 (55.0)	
NH	99	89 (78.1)	10 (45.5)	0.003	41 (74.5)	9 (45.5)	0.014
BMI (kg/m ²)	25.1 (7.2)	24.0 (6.8)	31.0 (6.6)	<0.001	29.4 (5.7)	31.0 (6.5)	0.124
WC (cm)	82.7 (19.1)	79.9 (18.5)	97.0 (16.4)	<0.001	94.8 (12.5)	99.0 (15.4)	0.070

Abbreviation: HS, hepatic steatosis. AA, African American. AS, Asian. W, white. H, Hispanic. NH, Non-Hispanic.

^aThe data are mean (SD) or number (percent)

* Post-hoc testing using Bonferroni correction: Between group comparisons were not significant

[#] Post-hoc testing using Bonferroni correction: W vs AA, p=.005; other group comparisons were not significant

Table 2Comparison of metabolic markers of HS in overweight subjects^a

	No HS n=55	HS n=20	<i>P</i> value
ALT	27.4 (31.6)	38 (24.7)	0.001
Fasting Glucose	84.5 (6.8)	90.8 (9.1)	0.004
Fasting Insulin	24.2 (11.3)	45.2 (18.4)	<.0001
HOMA IR	5.1 (2.5)	10.2 (4.5)	<.0001
HgA1c	5.4 (0.4)	5.5 (0.3)	0.200
Total Cholesterol	147.8 (25.2)	159.8 (26)	0.041
Triglycerides	91.9 (39.2)	151.7 (73.1)	<.0001
HDL	44.5 (10)	41.2 (9.5)	0.3651
LDL	84.9 (24.3)	88.4 (21.3)	0.458
Adiponectin	10 (5.2)	7.1 (3.5)	0.016
Free Testosterone	5 (3.1)	6.7 (3.7)	0.119
Total Testosterone	37.7 (21.4)	39.0 (27.4)	0.880
SHBG	34.2 (17.9)	21.3 (11.3)	0.002

Abbreviation: HS, hepatic steatosis. AA, African American. AS, Asian. W, white. H, Hispanic. NH, Non-Hispanic.

^aThe data are mean (SD) or number (percent)

Table 3Receiver Operating Characteristics Analysis of common NAFLD predictors^a

	AUC	Optimal Cutoff ²	Sensitivity	Specificity	PPV	NPV
ALT	79 (69–89)	24 U/L	73 (55–91)	73 (64–81)	34	93
BMI %	80 (71–88)	84 % tile	95 (77–99)	51 (42–61)	28	98
TG	78 (66–89)	94 mg/dL	77 (59–95)	68 (60–76)	32	94
Fasting Insulin	87 (78–96)	28 mg/dL	82 (64–95)	84 (77–90)	50	96
HOMA IR	87 (79–96)	6.7	77 (55–93)	87 (81–93)	53	95

¹ Area under the Curve (AUC) of ROC curve: An AUC close to 1 indicates better prediction² Optimal Cutoff was determined using the Youden method which maximizes both sensitivity and specificity^a The data are percent (95% CI)

Table 4

Comparison of prediction characteristics of risk assessment decision tree and NAFLD prediction score

	Risk Assessment	NAFLD Prediction	NAFLD Prediction	NAFLD Prediction
	Decision Tree ¹	Score 1 ²	Score 2 ³	Score 3 ⁴
Sensitivity	0.64	0.73	0.75	1
Specificity	0.99	0.9	0.85	0.83
PPV	0.93	0.59	0.48	0.35
NPV	0.93	0.94	0.95	1
Positive LR	64	7.3	5.02	5.64
Negative LR	0.36	0.3	0.29	0
Accuracy in predicting Hepatic Steatosis*	0.93	0.87	0.83	0.84
Kappa	0.72	0.58	0.49	0.45

Abbreviations: PPV, positive predictive value, NPV, negative predictive value, LR, likelihood ratio

¹ Risk assessment decision tree shown in Figure 1² $\log(p/(1 - p)) = -13.83 + 0.16 \times \text{Waist-to-Height} + 0.07 \times \text{ALT} + 0.78 \times \text{HOMA}$ (see Ref. 29)³ $\log(p/(1 - p)) = -10.79 + 0.22 \times \text{Waist-to-Height} + 0.08 \times \text{ALT} + 0.82 \times \text{HOMA} - 77 \times \text{Adiponectin}$ (see Ref. 29)⁴ $\log(p/(1 - p)) = -6.043 + 0.058 \times \text{ALT} + 0.564 \times \text{HOMA} - 0.45 \times \text{gender} \times \text{HOMA} + 2.456 \times \text{gender} + 0.044 \times \text{leptin}$ (see Ref. 30)

* weighted average of PPV and NPV