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Development and validation of a risk score for detecting non-alcoholic fatty liver disease

Zhili Jiang, MD[a], Xiang Li, MD[a], Duo Yang, MD[a], Chao Qu, MD[a], Jiayi Yi, MD[a], Hai Gao, MD[a,*]

Abstract

The development of an easy-to-use noninvasive model to screen nonalcoholic fatty liver disease (NAFLD) is warranted. This study aimed to develop and validate a simple noninvasive NAFLD risk score (NARS). We used the National Health and Nutrition Examination Survey 2017 to March 2020 cycle data. The sample size of derivation and validation cohort were 4056 and 2502, separately. The NAFLD was determined by FibroScan® measured controlled attenuation parameter scores of >285 dB/m in the absence of excessive alcohol use, steatogenic medications use, and viral hepatitis. The NARS was derived from a multivariable logistic regression model and variables were selected based on Boruta analysis. The performance of NARS was internally validated and compared with previous models using receiver-operating characteristics curve and C-statistics. The NARS was established using waist circumference, triglycerides, alanine aminotransferase, and fasting glucose, and the total score ranges from 0 to 8, with an increasing risk of NAFLD. NARS demonstrated ideal discrimination in the validation cohort, with C-statistics of 0.832 (95% confidence interval, 0.801–0.824), and was not inferior to any existing models. The optimal cutoff point for predicting NAFLD was obtained at 4 scores with a sensitivity of 82% and specificity of 69%. We reported the derivation and internal validation of a novel and easy-to-use risk score for detecting the presence of NAFLD. NARS demonstrated ideal discrimination performance and was practical in clinical practice for selecting individuals at higher risk of NAFLD for further examination or intervention.

Abbreviations: AIC = Akaike information criterion, ALT = alanine aminotransferase, AST = aspartate aminotransferase, AUROC = areas under the receiver-operating characteristic curve, CAP = controlled attenuation parameter, CI = confidence interval, FLI = fatty liver index, GGT = γ-glutamyl transferase, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HSI = hepatic steatosis index, ION = Index of nonalcoholic steatohepatitis, K-NAFLD = Korean National Health and Nutrition Examination Survey nonalcoholic fatty liver disease, LAP = Lipid accumulation product, NAFLD = nonalcoholic fatty liver disease, NAFLD-LFS = nonalcoholic fatty liver disease liver fat score, NARS = nonalcoholic fatty liver disease risk score, NCHS = National Center for Health Statistics, NHANES = National Health and Nutrition Examination Survey, ROC = receiver-operating characteristic, TG = triglycerides.

Keywords: NHANES, nonalcoholic fatty liver disease, noninvasive assessment, risk score

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disorders characterized by excess fat accumulation in hepatocytes.[1] Globally, NAFLD affects approximately one-third of the population, with its prevalence steadily rising from 2005 to 2016 and beyond.[2,3] Patients with NAFLD are at risk of developing liver disease-related morbidity, including cirrhosis, end-stage liver disease, even hepatocellular carcinoma, and mortality.[4,5] Given that NAFLD patients are generally asymptomatic or experience nonspecific symptoms, leading to delayed diagnosis,[6,7] which result in insufficient intervention and a worse prognosis. It is essential to identify individuals with an increased risk of NAFLD at an early stage.

Biopsy was regarded as the "gold standard" for diagnosing and grading liver steatosis. The invasive procedure is costly, prone to complications, and has a potential sampling error, which limits the application of the biopsy in clinical practice.[8] Conventional radiological imaging technology, such as ultrasonography, computed tomography, and magnetic resonance imaging, have been shown to be reasonably accurate in detecting hepatic steatosis. However, most imaging examinations

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Informed consent was taken from all individuals who were willing to participate in the study.

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The datasets generated during and/or analyzed during the current study are publicly available.

The National Center for Health Statistics (NCHS) ethics review board has approved the NHANES protocols, and this study was reviewed by the Anzhen Hospital Institutional Review Board and considered exempt. The NHANES study was conducted in accordance with the Declaration of Helsinki.

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[a] *Center for Coronary Heart Disease, Beijing Anzhen Hospital, Capital Medical University, Beijing, China.*

** Correspondence: Hai Gao, Center for Coronary Heart Disease, Beijing Anzhen Hospital, Capital Medical University, Beijing, 100029, China (e-mail: gaohai1221@mail.ccmu.edu.cn).*

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were too expensive for mass screening in the general population.[9–12] Consequently, there is growing interest in noninvasive approaches to NAFLD assessment, leveraging serum biomarkers, and anthropometric parameters.

Various predictive models have been developed to diagnose steatosis, including the fatty liver index (FLI), hepatic steatosis index (HSI), index of nonalcoholic steatohepatitis (ION), lipid accumulation product (LAP), and NAFLD liver fat score (NAFLD-LFS).[13–17] The diagnosis of NAFLD in previous models was mainly determined by liver ultrasound, a semiquantitative, operator-dependent, prone to bias NAFLD assessment,[8] which may undermine the reliability of the diagnosis. In addition, most of these predictive models were developed from small samples, and it was complicated to calculate these model results making them inconvenient to use in clinical practice.

The controlled attenuation parameter (CAP), a newly developed parameter measured by vibration-controlled transient elastography, was a more reliable indicator of fatty liver and can overcome limitations of liver ultrasonography.[18–23] Several biopsy-controlled studies confirmed that increased CAP was highly correlated with histologically defined steatosis.[22,23] Taking the CAP-determined NAFLD as the diagnostic standard, the present study aims to propose a novel, simple-to-use noninvasive assessment tool to predict NAFLD.

2. Methods

2.1. Study design and population

The National Health and Nutrition Examination Surveys (NHANES) is a nationally representative health survey program for the United States civilian noninstitutionalized resident population. The National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention administered the survey. It has been conducted on 2-year cycles since 1999 to monitor the health and nutritional status of the US population. The NCHS ethics review board has approved the NHANES protocols, and this study was reviewed by the Anzhen Hospital Institutional Review Board and considered exempt. Written informed consent was obtained from all participants before completing the survey. Before being published, all data were de-identified by the NCHS. This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis reporting guidelines for prognostic studies.[24]

In the 2017 to March 2020 cycle, 15,560 participants were enrolled. Six thousand five hundred ninety five individuals aged <18 years were excluded. We further excluded 1198 participants in whom elastography examination status was ineligible (n = 348), not performed (n = 233), partial (n = 616), or data missing (n = 1). Individuals were additionally excluded if they had one of the following conditions: (1) taking steatogenic medications for at least 3 months or more before the survey (n = 91), (2) consuming more than 2 or 3 standard alcoholic drinks per day on average for both women and men, respectively (n = 230), (3) having hepatitis B or C history or positively in viral test (n = 142), (4) having missing values for anthropometric or laboratory data (n = 746), leaving a total of 6558 participants for the present analysis. For subsequent prediction performance evaluation, the study population was divided into the derivation cohort (2017–2018 cycle) and the validation cohort (2019–March 2020 cycle) according to NHANES cycles (Figure S1, Supplemental Digital Content, http://links.lww.com/MD/N927).

2.2. Definition of demographic, anthropometric, and laboratory variables

Demographic variables were collected by standardized questionnaires during in-person interviews, including sex, age (years), and race/ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian, and Other race). Body measurements, including standing height, weight, waist circumference, and blood pressure, were measured during the physical examination, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Serum was tested for high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, γ-glutamyl transferase (GGT), hemoglobin A1c (HbA1c), fasting glucose, and fasting insulin. Diabetes was self-reported by participants who had been diagnosed by a health professional or determined by a prescription history for medications used to treat the condition. Self-report questionnaires collected medication history and alcohol consumption information. Steatogenic medications were defined as prednisone, tamoxifen, and methotrexate. Alcohol consumption frequencies were converted into an estimated number per day using the median value (e.g., 3–4 times per week = 0.5 times per day). Viral hepatitis was identified either with hepatitis C virus RNA, hepatitis B surface antigen (NHANES 2017–2018) or with self-report previous hepatitis B/C diagnosis, or prescription medication treatment (NHANES 2019–March 2020).

2.3. Measurements and definition of NAFLD

For the 2017 to March 2020 cycle, NHANES conducted transient elastography examinations for all participants aged 12 years and older. A detailed protocol of transient elastography examinations has been published previously.[25] Participants were examined to assess the CAP score and liver stiffness measurements using the FibroScan® model 502 V2 Touch (Echosens, Waltham, MA). According to NHANES protocol, a complete examination was defined as 10 or more valid stiffness measurements, fasting time of at least 3 hours, and liver stiffness interquartile range/median ≤ 30%. According to the literature, the median CAP was dichotomized using 285 dB/m as a threshold for liver steatosis diagnosis with optimum diagnostic performance (sensitivity of 80% and specificity of 77%).[22]

2.4. Statistical analysis

Continuous variables were presented as mean ± standard deviation, and categorical data were presented as counts and percentages. Logistic regression was applied to derive the NAFLD risk score (NARS). Variable selection and modeling were conducted in the derivation cohort in the following steps: (1) variables that were statistically significant by Boruta analysis were added to a full model to obtain the best predictive performance; (2) in variable selection, we began with the full model and tested multiple candidate models using a purposeful selection approach based on the trade-off of variable importance and accessibility and model simplicity. Different candidate models were assessed using the Akaike information criterion (AIC) and areas under the receiver-operating characteristic curve (AUROC) and 95% confidence intervals (CIs); (3) the predictive performance of the final model was evaluated in terms of calibration plot. Ideal calibration would be indicated by points lying along a 45-degree diagonal line; (4) based on the regression coefficients of the final model, the NARS was developed according to the methods of literature.[26]

The predictive performance of the NARS was evaluated and compared in the validation cohort in the following steps: (1) sensitivities, specificities, positive predictive value, and negative predictive value under different cutoff points of the total score were accessed. A receiver-operating characteristic (ROC) curve of the NARS was plotted, and the optimum cutoff point was

Table 1

Clinical characteristics of study population.

		Derivation		Validation	
	Overall	Normal	NAFLD	Normal	NAFLD
Characteristics*	(N = 6558)	(N = 2549)	(N = 1507)	(N = 1626)	(N = 876)
Age (y)	48.6 (18.2)	46.9 (18.9)	52.8 (16.5)	45.9 (18.7)	51.2 (15.8)
Male (%)	3199 (48.8)	1139 (44.7)	830 (55.1)	753 (46.3)	477 (54.5)
Race/ethnicity (%)					
Mexican American	825 (12.6)	283 (11.1)	124 (7.6)	297 (19.7)	121 (13.8)
Other Hispanic	696 (10.6)	248 (9.7)	199 (12.2)	137 (9.1)	112 (12.8)
NH White	2293 (35.0)	857 (33.6)	553 (34.0)	546 (36.2)	337 (38.5)
NH Black	1606 (24.5)	622 (24.4)	520 (32.0)	259 (17.2)	205 (23.4)
NH Asian	812 (12.4)	395 (15.5)	163 (10.0)	195 (12.9)	59 (6.7)
Other Race	326 (5.0)	144 (5.6)	67 (4.1)	73 (4.8)	42 (4.8)
BMI (kg/m^2)	29.6 (7.0)	27.1 (5.8)	33.4 (6.8)	27.6 (5.9)	34.4 (7.3)
Waist circumference (cm)	99.9 (16.8)	93.2 (14.3)	110.4 (14.9)	93.9 (14.3)	112.0 (15.1)
HDL-C (mg/dL)	53.1 (15.4)	56.1 (15.3)	47.5 (12.9)	56.7 (16.4)	47.2 (13.4)
TC (mg/dL)	185.1 (40.4)	185.7 (40.2)	190.7 (42.0)	180.2 (39.2)	183.0 (39.4)
TG (mg/dL)	136.2 (98.4)	118.5 (77.4)	181.0 (129.6)	107.9 (64.5)	163.1 (108.9)
ALT (U/L)	21.8 (16.1)	19.1 (14.6)	27.3 (19.3)	18.4 (11.2)	26.7 (18.3)
AST (U/L)	21.3 (11.6)	20.5 (10.4)	23.2 (14.0)	20.2 (9.4)	22.1 (13.7)
ALP (U/L)	77.5 (25.5)	76.3 (26.6)	82.6 (25.1)	73.9 (23.4)	79.0 (25.3)
Albumin (g/dL)	4.1 (0.3)	4.1 (0.3)	4.1 (0.3)	4.1 (0.3)	4.0 (0.3)
Total bilirubin (mg/dL)	0.5 (0.3)	0.5 (0.3)	0.4 (0.3)	0.5 (0.3)	0.4 (0.2)
GGT (U/L)	29.8 (40.9)	25.3 (37.4)	38.4 (47.7)	25.8 (35.9)	35.5 (43.5)
HbA1c (%)	5.8 (1.1)	5.6 (0.8)	6.2 (1.3)	5.6 (0.8)	6.2 (1.4)
Fasting glucose (mg/dL)	101.1 (34.8)	95.7 (26.0)	111.5 (43.0)	94.4 (25.6)	111.5 (47.6)
Diabetes (%)	893 (13.6)	226 (8.9)	356 (23.6)	120 (7.4)	191 (21.8)

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, GGT = γ-glutamyl transferase, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, NAFLD = nonalcoholic fatty liver disease, TC = total cholesterol, TG = triglycerides.

* Continuous variables are shown as mean (SD). Categorical variables are shown as numbers (percentage).

identified using Youden index. (2) The C-statistics and 95% CIs were used to evaluate the discrimination of NARS and existing models, and the difference among these models was tested by the DeLong test. Model discrimination was compared globally using 5 % as an alpha threshold, and the Bonferroni adjustment was used in pairwise comparisons (1% alpha threshold for significance).

All analyses were conducted using R, version 4.0.5 (R Core Team, Vienna, Austria). Data analysis was performed in May 2022.

3. Results

3.1. Clinical characteristics of derivation and validation cohorts

Among 6558 participants aged 18 years or older included in this study, the overall mean age was 48.6 (standard deviation 18.2) years and 3199 (48.8%) were male. A total of 36.3% (2383 of 6558) had NAFLD. 4056 of them from the 2017 to 2018 cycle were divided into the derivation cohort, and 2502 from the 2019 to March 2020 cycle were partitioned into the validation cohor. In the derivation cohort, the prevalence of NAFLD was 37.2% (1507 of 4056). Compared to the individuals without NAFLD, participants with NAFLD were more likely to be older (52.8 vs 46.9 years), male (55.1% vs 44.7%), and had higher BMI (33.4 vs 27.1 kg/m^2) and waist circumference (110.4 vs 56.1 cm). Regarding laboratory parameters, total cholesterol (190.7 vs 185.7 mg/dL), TG (181.0 vs 118.5 mg/dL), ALT (27.3 vs 19.1 U/L), AST (23.2 vs 20.5 U/L), GGT (38.4 vs 25.3 U/L), HbA1c (6.2% vs 5.6%), and fasting glucose (111.5 vs 95.7 mg/dL) levels were consistently higher in those with NAFLD while HDL-C (47.5 vs 56.1 mg/dL) levels were lower. Diabetes was more prevalent in NAFLD participants (23.6% vs 8.9%) (Table 1). Similar characteristics pattern was also found in the validation cohort (Table 1).

3.2. Variable selection

The Boruta analysis results were presented as a boxplot of variables' importance (Z-score) distribution (Figure S2, Supplemental Digital Content, http://links.lww.com/MD/N927). Among 17 potential variables, 16 were identified as significant important variables (green boxes). These 16 variables were added into a multivariable logistic regression (model 1) to achieve the optimal predictive performance as a reference. The AIC of model 1 was 3805, and the AUROC of model 1 in the derivation cohort was 0.849 (95% CI, 0.838–0.861). In model 2, the top 7 important variables (waist circumference, TG, ALT, fasting glucose, HbA1c, GGT, BMI) remained, and the fitness and performance of model 2 dropped slightly compared with model 1 (AIC = 3906, AUROC = 0.839 [95% CI, 0.827–0.851]). In model 2, waist circumference, ALT, TG, and HbA1c were significant ($P < .001$). We intended to use these 4 significant variables to build the final model (model 3). Considering HbA1c was not as routinely measured as fasting glucose, we replaced HbA1c with fasting glucose in model 3. Model 3, based on the remaining 4 predictors (waist circumference, ALT, TG, and fasting glucose), had an AIC of 3925 and AUROC of 0.837 (95% CI, 0.825–0.849) (Table S1, Supplemental Digital Content, http://links.lww.com/MD/N927). The results of the multivariate logistic regression analysis were summarized in Table 2.

3.3. Development of the NAFLD risk score (NARS)

In model 3, waist circumference (per 10 cm increase odds ratio (OR), 2.06; 95% CI, 1.95–2.19), TG (per 10 mg/dL increase OR, 1.05; 95% CI, 1.04–1.06), glucose (per 10 mg/dL increase OR, 1.09; 95% CI, 1.06–1.12), and ALT (per 10 U/L increase OR, 1.09; 95% CI, 1.06–1.12) were independent risk factors of NAFLD (Table 2). The calibration of model 3 was excellent across the spectrum of risk in derivation sets (Fig. 1A). The NARS was constructed based on

model 3. The detailed developing process was described in Appendix 1, Supplemental Digital Content, Results, http://links.lww.com/MD/N927. In brief, scores were weighted according to the regression coefficients. The NARS assigns 1 score for fasting glucose ≥ 100 mg/dL or ALT ≥ 25 U/L, separately. Two scores were given to waist circumference in the range of 90 to 109 cm or TG ≥ 120 mg/dL. Four scores were assigned for waist circumference ≥ 110 cm (Table 3). The total score of NARS ranges from 0 to 8, and the estimated risks of NAFLD constantly increase with the increase in total score (Table 4).

3.4. Performance of the NARS in the validation cohort

The performance of the NARS at different cutoff total scores to diagnose NAFLD in the validation cohort was summarized in Table 5. The optimum diagnosis performance of the NARS for identifying NAFLD was achieved at 4 scores with the maximum Youden index (sensitivity: 82%, specificity: 69%) (Fig. 1B). We calculated the NARS and 5 previously proposed NAFLD predictive models (FLI, HSI, ION, LAP, and NAFLD-LFS) results of participants in the validation cohort. The variables needed for these models and the formulas were summarized in Tables S2 and S3, Supplemental Digital Content,

Table 2

Multivariable logistic regression models for NAFLD in the derivative set.

	Model 1		Model 2		Model 3	
Variable	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Waist circumference*	1.87 (1.62–2.16)	<.001	2.01 (1.79–2.25)	<.001	2.06 (1.95–2.19)	<.001
TG*	1.03 (1.02–1.04)	<.001	1.05 (1.04–1.06)	<.001	1.05 (1.04–1.06)	<.001
ALT*	1.28 (1.12–1.40)	<.001	1.26 (1.12–1.34)	<.001	1.26 (1.20–1.34)	<.001
Fasting glucose*	1.00 (0.96–1.04)	.88	1.00 (0.97–1.05)	.83	1.09 (1.06–1.12)	<.001
HbA1c	1.32 (1.14–1.52)	<.001	1.37 (1.21–1.55)	<.001	—	–
GGT*	1.03 (1.01–1.05)	.02	1.01 (0.99–1.03)	.46	–	–
BMI*	1.45 (1.05–2.01)	.03	1.04 (0.80–1.35)	.76	–	–
Age*	1.16 (1.01–1.23)	<.001	–	–	–	–
HDL-C*	0.86 (0.80–0.93)	<.001	–	–	–	–
TC*	1.01 (0.99–1.03)	.40	–	–	–	–
AST*	0.93 (0.83–1.05)	.25	–	–	–	–
ALP*	0.98 (0.95–1.01)	.23	–	–	–	–
Albumin	1.62 (1.22–2.15)	<.001	–	–	–	–
Female	1.13 (0.93–1.37)	.23	–	–	–	–
Race/ethnicity			–	–	–	–
Mexican American	Reference		–	–	–	–
Other Hispanic	0.51 (0.37–0.70)	<.001	–	–	–	–
NH White	0.54 (0.42–0.69)	<.001	–	–	–	–
NH Black	0.35 (0.26–0.46)	<.001	–	–	–	–
NH Asian	0.89 (0.67–1.19)	.44	–	–	–	–
Other race	0.41 (0.27–0.61)	<.001	–	–	–	–
Diabetes	1.02 (0.77–1.34)	.91	–	–	–	–

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, GGT = γ-glutamyl transferase, HbA1c = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, NAFLD = nonalcoholic fatty liver disease, OR = odds ratio, TC = total cholesterol, TG = triglycerides.

* The ORs and 95% CIs of these variables were calculated per 10 units increase.

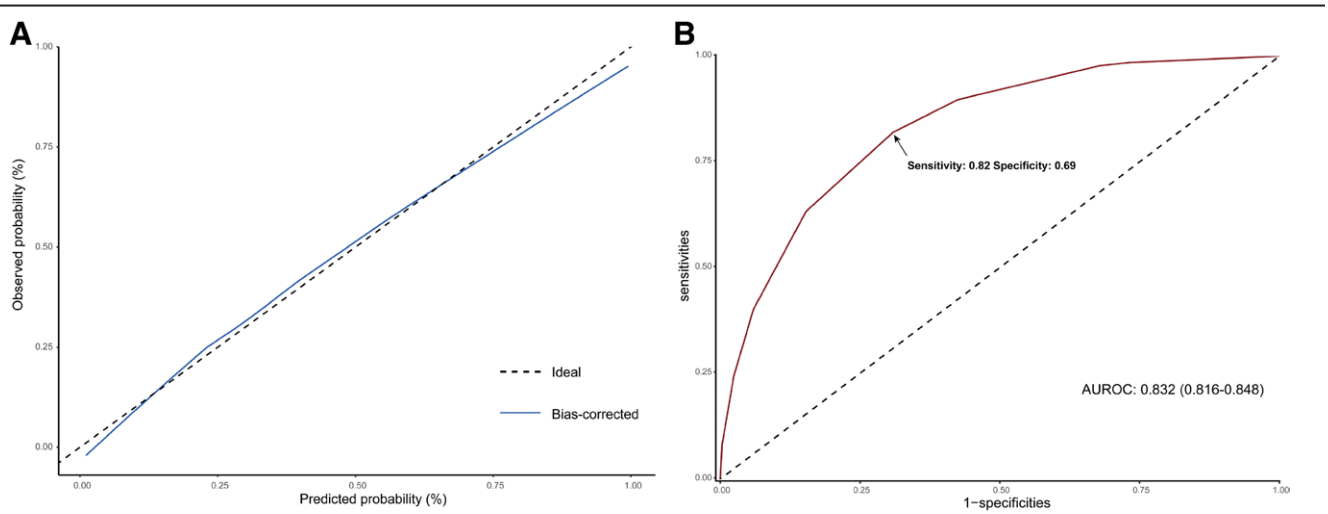

Figure 1. Diagnostic performance of the final model (model 3) in the derivation cohort and NARS in the validation cohort. (A) Calibration plot. The dashed line represents the ideal calibration. The solid blue line represents the bias-corrected calibration estimated in model 3. (B) ROC curve. Numbers in brackets are 95% CI. AUROC = the area under the receiver-operating characteristic curve; NARS = nonalcoholic fatty liver disease risk score.

http://links.lww.com/MD/N927 and http://links.lww.com/MD/N927. The C-statistics of NARS was higher than LAP (0.832 vs 0.815, pairwise comparisons $P < .01$), and the difference in C-statistics between NARS and the other 4 models was not significant (NARS 0.832; FLI 0.836; HSI 0.814; ION 0.816; NAFLD-LFS 0.823, all pairwise comparisons $P > .01$) (Table S4, Supplemental Digital Content, http://links.lww.com/MD/N927).

4. Discussion

In this study, we developed and validated the NARS, a novel and easy-to-use noninvasive assessment tool for detecting the presence of NAFLD in the general population using data from a large national population-based database. The risk of NAFLD could be evaluated with minimum computation cost based on waist circumference and the results of a few routinely performed laboratory tests, including fasting glucose, ALT, and TG. Moreover, the performance of NARS for detecting NAFLD was confirmed in the validation cohort.

The FLI, developed by Bedogni et al, uses BMI, waist circumference, TG, and GGT to predict fatty liver.[13] While FLI is a widely recognized tool, it heavily relies on BMI, which may not fully capture visceral adiposity's role in NAFLD. In contrast, NARS emphasizes waist circumference, a more direct measure of visceral fat, which is a critical factor in hepatic steatosis. The HSI, introduced by Lee et al, incorporates ALT, AST, BMI, and diabetes status.[14] HSI relies on AST and BMI may limit its application in capturing the nuances of metabolic dysfunctions associated with NAFLD. NARS, by utilizing fasting glucose and ALT, concentrates on markers that more directly reflect insulin resistance and liver inflammation, offering a possibly more refined assessment of NAFLD risk. The Korean National Health and Nutrition Examination Survey nonalcoholic fatty liver disease (K-NAFLD) score, as presented by Jeong et al, integrates clinical and laboratory parameters.[27] While comprehensive, its complexity might pose challenges in routine clinical settings. NARS, however, is designed to be user-friendly, utilizing widely available clinical measurements, thus facilitating its application in primary care and enabling quick risk assessment without extensive calculations. Our findings suggest that NARS strikes a balance between simplicity and accuracy, making it a practical tool for widespread clinical use. While FLI, HSI, and K-NAFLD scores each have their strengths, NARS's focus on waist circumference and metabolic parameters aligns closely with the pathophysiological underpinnings of NAFLD.

NARS was more reflected in visceral abdominal adiposity, which is a key link to NAFLD.[28,29] Compared to the previous model, NARS included waist circumference, rather than BMI. Waist circumference was a recognized surrogate measure of visceral fat, the most abundant form of ectopic fat deposition.[16] Visceral adiposities is associated with a hyperlipolytic state that contributes to insulin resistance and a set of metabolic dysfunctions specifically associated with increased liver fat.[30] Although BMI was also commonly used in previous models, and it was proved that the combination of BMI and waist circumference identify the highest-risk phenotype of obesity better than either measure alone,[31–33] the regression coefficient of BMI was not significant in the multivariable model and the predictive capacity did not go worse after the exclusion of BMI from the model. This might be explained by the worldwide trends that the relative increases in waist circumference were larger than the relative increases in BMI.[34] The phenotype of obesity might be changing over time to one that reflects an increase in abdominal adiposity.[30] This emerging evidence might explain the failure of BMI to provide extra information to detect the presence of NAFLD.

Variables included in NARS were more available. Previous models included insulin to reflect glucose metabolic, in our model, fasting glucose was included, fasting glucose performed similar ability to predict NAFLD as insulin, and is

Table 3

The nonalcoholic fatty liver disease risk score (NARS).

Variables	Categories	Scores
Waist circumference (cm)		
	<90	0
	90–109	2
	≥110	4
TG (mg/dL)		
	<120	0
	≥120	2
Fasting glucose (mg/dL)		
	<100	0
	≥100	1
ALT (U/L)		
	<25	0
	≥25	1

ALT = alanine aminotransferase, TG = triglycerides.

Table 4

The estimated NAFLD risk under different total scores of NARS.

Total score	Estimate of risk (%)
0	0.06
1	0.12
2	0.24
3	0.41
4	0.61
5	0.77
6	0.88
7	0.94
8	0.97

NAFLD = nonalcoholic fatty liver disease, NARS = nonalcoholic fatty liver disease risk score.

Table 5

Predictive performance of NARS in the validation cohort.

Cutoff point	Accuracy	Sensitivity	Specificity	Pos pred value	Neg pred value
1	0.52	0.99	0.27	0.42	0.97
2	0.55	0.98	0.32	0.44	0.96
3	0.69	0.90	0.58	0.53	0.91
4	0.74	0.82	0.69	0.59	0.88
5	0.77	0.63	0.85	0.69	0.81
6	0.75	0.40	0.94	0.79	0.74
7	0.72	0.24	0.98	0.84	0.70
8	0.68	0.08	1.00	0.93	0.67

NARS = nonalcoholic fatty liver disease risk score.

more available in clinical practice. Insulin is the dominant hepatic glucose and lipid metabolism regulator, and insulin resistance was also identified as a metabolic mechanism responsible for developing NAFLD.[35] Previous studies have demonstrated a good correlation between fasting serum insulin and NAFLD.[36] However, compared with NARS, the model using fasting glucose as the surrogate indicator of diabetes, models applied fasting insulin (NAFLD-LFS) or homeostasis model assessment of insulin resistance (ION) did not demonstrate superior predictive performance in the validation cohort. This finding suggests that combined with TG; fasting glucose could be used as an effective predictor of NAFLD, flagging the glucose and lipid dysmetabolism given their correlation with insulin resistance and impaired glucose tolerance.[37]

NARS based on widely available physical examinations and laboratory test variables is easy to use and very practical. Most existing NAFLD noninvasive predictive models were derived from complex statistical models, and efforts to get these models' results were also troublesome. Some models require relatively expensive laboratory tests and are not widely available in primary care. The calculation of these models' results often requires multiple steps of multiplication, division, or even exponential operations. In addition, the sensitivity–specificity trade-off was ambiguous under various continuous cutoff points. Due to the above inconvenience, the clinical utility of these models has yet to be established. NARS is one way to simplify the assessment of the multi-factorial nature of NAFLD risk. With the given results of routinely measured risk factors in clinical practice, clinicians can quickly obtain NARS results of patients and evaluate the risk of NAFLD without complicated calculations. The results could help professionals select patients for further assessments or intervention under given reference sensitivity and specificity of different cutoff scores. This tool is also readily available to patients who can easily estimate their own NAFLD risk and monitor this risk over time.

4.1. Strengths and limitations

The current study has several strengths. First, we used the latest available national representative population-based dataset of the US for model derivation and validation. As described above, obesity phenotypes are changing over time. Models developed from earlier data might not be accurate as time passes by. Second, the diagnosis of NAFLD in this study was determined by FibroScan® measured CAP. FibroScan® is a quantitative assessment of fatty infiltration in the liver, which has higher sensitivity than B-mode ultrasound and lower cost than histology and proton magnetic resonance spectroscopy. It is an optimum noninvasive diagnostic method for large-scale general population-based modeling studies. Third, we developed a simple predictive model for NAFLD based on widely available physical examinations and laboratory tests commonly evaluated in individuals with metabolic risk factors. This model is very practical as a clinical instrument.

A potential weakness of our study is that although the NARS was internally validated, it has not been evaluated to predict liver steatosis in different populations. Therefore, the predictive performance in populations other than the U.S. remains to be tested.

5. Conclusion

We proposed and validated a risk score system to predict NAFLD based on waist circumference, fasting glucose, ALT, and TG. This simple and accurate noninvasive assessment tool could be used to select subjects at higher risk of NAFLD for further examination or lifestyle counseling.

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Author contributions

Conceptualization: Zhili Jiang, Xiang Li, Duo Yang, Chao Qu.
Data curation: Jiayi Yi.
Formal analysis: Jiayi Yi.
Funding acquisition: Hai Gao.
Methodology: Zhili Jiang, Xiang Li, Duo Yang.
Supervision: Hai Gao.
Writing – original draft: Zhili Jiang, Xiang Li.
Writing – review & editing: Zhili Jiang, Xiang Li, Duo Yang, Chao Qu, Jiayi Yi, Hai Gao.

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