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OBJECTIVES: **Nonalcoholic fatty liver disease fibrosis score (NFS), fibrosis-4 (FIB-4) score, aspartate aminotransferase (AST)-to-platelet ratio index (APRI) score, and AST–alanine aminotransferase (ALT) ratio are noninvasive fibrosis scoring systems for the staging of liver fibrosis in patients with chronic liver disease.**

METHODS: **In a large cohort of patients with nonalcoholic fatty liver disease, we compared AST–ALT ratio, NFS, FIB-4 score, and APRI score in predicting advanced fibrosis (defined as fibrosis stage ≥ 3) in histologically confirmed African American (AA) and white patients. We identified 907 patients: 677 (74.6%) white and 230 (25.3%) AA patients with nonalcoholic fatty liver disease.**

RESULTS: **Of the 907 patients, 115 (12.8%) patients had advanced fibrosis (stages 3 and 4) in the total cohort: 6 (2.6%) AAs, and 109 (16.2%) whites. In AAs, the area under the receiver operating characteristic (area under the curve) for predicting advanced fibrosis was 0.58 by NFS, 0.86 by APRI score, 0.77 by FIB-4 score, and 0.65 by AST–ALT ratio. In whites, the area under the receiver operating characteristic for predicting advanced fibrosis was 0.82 by NFS, 0.82 by APRI score, 0.88 by FIB-4 score, and 0.76 by AST–ALT ratio. In the AA population, NFS > 0.675, FIB-4 score > 2.67, and APRI score > 1.5 each has a negative predictive value of 98%, whereas the negative predictive values in whites are 91%, 88%, and 85%, respectively.**

DISCUSSION: **Noninvasive fibrosis scoring systems can reliably exclude advanced fibrosis in both AAs and whites and have acceptable discriminatory ability to predict advanced fibrosis in whites. The utility of noninvasive fibrosis scoring systems in predicting advanced fibrosis in AAs needs further validation in a larger multicenter cohort.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A263, http://links.lww.com/CTG/A264

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in developed countries with an estimated prevalence of 24.1% in the United States (1). NAFLD is characterized by histological changes ranging from simple fat accumulation in the liver to necroinflammation, fibrosis, cirrhosis, and hepatocellular carcinoma (2).

Fibrosis severity is strongly associated with the long-term prognosis in patients with NAFLD; thus, it is essential to identify patients with nonalcoholic steatohepatitis (NASH) and advanced fibrosis to screen for complications and management (3). Liver biopsy currently remains the "gold standard" for the diagnosis of inflammation and fibrosis but is limited because of its invasive nature, sampling error, expense, and complications (2). Many

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noninvasive fibrosis scoring systems, including aspartate aminotransferase (AST)–alanine aminotransferase (ALT) ratio (4), AST-to-platelet ratio index (APRI) score (5), fibrosis-4 (FIB-4) score (6), and NAFLD fibrosis score (NFS) (7), are used in routine clinical practice as attractive and affordable alternatives to identify patients with NAFLD and advanced fibrosis. These clinical noninvasive fibrosis scoring systems can aid in the early diagnosis and treatment and provide the long-term prognosis based on NASH/fibrosis progression. Originally, APRI and FIB-4 fibrosis scoring systems were used for chronic hepatitis C virus infection, and the NFS was used to predict advanced fibrosis in NAFLD predominantly in the white population (8). The utility of these noninvasive fibrosis scoring systems in the African American (AA) is not well established. In a study involving 2,287 subjects from multiple ethnicities (32.1% white, 48.3% black, and 17.5% Hispanic), using proton magnetic resonance spectroscopy, there were significant ethnic differences in the prevalence of hepatic steatosis (9). In addition, this finding was supported by a systematic review and meta-analysis by Rich et al. (10), which found significant racial and ethnic disparities in NAFLD, with the highest burden in Hispanics and the lowest burden in blacks. We hypothesize that the vast differences in the prevalence and severity of NAFLD will have a significant impact on the utility of currently used noninvasive fibrosis scoring systems in AAs and whites.

The current study aims to define the histologic spectrum of NAFLD between the 2 races and to determine the accuracy of noninvasive fibrosis scoring systems, such as AST–ALT ratio, NFS, FIB-4 score, and APRI score, in both predicting and ruling out advanced fibrosis in the AA and white cohorts.

METHODS

Patient population

We retrospectively reviewed the Electronic Medical Records and identified 5,696 consecutive adult patients (18 years or older) with at least one liver biopsy between January 2006 and December 2016 at the Methodist University Hospital in Memphis, Tennessee. As shown in Supplemental Figure 1 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A263), after exclusion of patients with significant alcohol abuse (n = 641), HIV/AIDS (n = 54), hepatitis B (n = 215), and hepatitis C (n = 1,026), 3,749 remaining patients were reviewed for the diagnosis of NAFLD by the International Classification of Diseases-9/-10 codes. Significant alcohol abuse was inferred from the medical record characterized as alcohol consumption (>30 g of alcohol per day for men and >20 g per day for women or a documented history suggestive of significant alcohol use) before the first biopsy or during the follow-up period. We identified 1,271 unique patients with NAFLD using this search criterion. Further manual review of the histological/surgical pathology reports was conducted (S.G.) to confirm NAFLD in these patients. A total of 328 patients with non-NAFLD were excluded. Patients with incomplete data and other ethnicities were excluded (n = 36) to form the final cohort consisting of 907 patients: 677 (74.6%) white and 230 (25.3%) AA patients with NAFLD.

Clinical and laboratory data were gathered retrospectively from the time of liver biopsy or within 1 year. The clinical details obtained include gender, age, weight, height, ethnicity, AST, ALT, platelets, total bilirubin, international normalized ratio, alkaline phosphatase and albumin. Body mass index (BMI) was calculated by the following formula: weight (kg)/height (m^2). Patients were identified as diabetic if they had HbA1c ≥ 6.5 or received diabetic medications. The laboratory values mentioned above were used to calculate the AST–ALT ratio, FIB-4 score, APRI score, and NFS using the original formulas (4–7). The study was approved by the University of Tennessee Health Science Center Institutional Review Board (IRB approval #16-04976-XP).

Histological assessment

All the liver biopsies were reviewed and reported by expert hepatopathologists. Most patients in this cohort underwent an intraoperative liver biopsy during bariatric surgery (n = 475 patients: 170 AAs and 305 whites), and others underwent a liver biopsy for evaluation of elevated transaminases or abnormal imaging. The pathology report of the liver biopsies was accessed, and the NASH Clinical Research Network Criteria (NASH CRN) was used to rescore each patient's liver biopsy (S.G., Y.K.R., and H.K.M.) (11). Nonalcoholic fatty liver was defined as having only steatosis and/or steatosis with mild lobular inflammation without hepatocyte ballooning. If the sum of the NAS score was ≥ 5, the patient was classified as having NASH (11). Any ambiguity in the pathology reports was resolved by further discussion with the pathologists. The stages of NASH-associated fibrosis were scored on a 5-point scale ranging from absent (stage 0) to cirrhosis (stage 4) (12). Stages F3 to F4 were defined as advanced fibrosis.

Statistical analysis

Continuous variables were represented as mean ± SD. Categorical variables were represented as median and range. The Student *t* test was used to compare the means of normally distributed continuous variables. The χ^2 test or Fisher exact test was used to determine the distribution of categorical variables. Continuous variables were compared using the Wilcoxon rank sum test. A P value < 0.05 was considered statistically significant. The receiver operating characteristic curves evaluated the diagnostic performance of the noninvasive fibrosis scoring systems for cirrhosis and advanced fibrosis. The area under the receiver operating characteristic (AUROC) was used to compare the accuracy of the tests. The AUROC ranges from 0 to 1. A value of 1 indicates perfect discrimination, whereas an AUC of 0.5 suggests no discrimination (i.e., ability to diagnose patients with and without the disease or condition based on the test), 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent, and more than 0.9 is considered outstanding (13). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) based on the cutoffs were calculated. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Clinical and biochemical characteristics of the cohort

Among the cohort of 907 patients, the mean age was 46.7 ± 12 years, and the majority were women (n = 620, 68.4%). The mean BMI was 39.9 ± 9 kg/m^2, and 34.1% of the patients had diabetes. Of all the patients, 32.9% had stage 0 fibrosis, whereas 36.4% had stage 1 fibrosis, 17.9% had stage 2 fibrosis, 6.9% had stage 3 fibrosis, and 5.9% had stage 4 fibrosis. Advanced fibrosis (stages 3 and 4) was noted in 12.8% of the total cohort: 6 (2.6%) of the AAs and 109 (16.2%) of the whites.

Clinical and biochemical characteristics based on ethnicity are presented in Table 1. In general, compared with whites, AAs were younger (43.5 ± 9.8 vs 47.8 ± 12.3, $P < 0.0001$), mostly women (81.3% vs 64%, $P < 0.0001$), and had higher BMI (42.6 ± 9.5 kg/m^2 vs 39 ± 8.6 kg/m^2, $P < 0.0001$). Interestingly, AAs had a lower ALT

Table 1. Characteristics of the study population (N = 907)

	All patients (N = 907)	AA (n = 230)	Whites (n = 677)	*P* value
Patient characteristics				
Age, yr ±SD	46.7 ± 12	43.5 ± 9.8	47.8 ± 12.3	<0.0001
Gender, % female	620 (68.4)	187 (81.3)	433 (64)	<0.0001
Clinical characteristics				
BMI, kg/m^2	39.9 ± 9	42.6 ± 9.5	39 ± 8.6	<0.0001
Diabetes, n (%)	295 (34.1)	86 (37.8)	209 (32.8)	0.17
Laboratory measures, mean				
Platelet, 10^9/L	266 ± 88	293 ± 87	257 ± 87	<0.0001
Albumin, g/dL	3.7 ± 0.6	3.64 ± 0.6	3.7 ± 0.6	0.055
Total bilirubin, mg/dL	0.74 ± 0.7	0.7 ± 0.9	0.76 ± 0.6	0.28
ALT, IU/L	52 ± 51	42 ± 44	55 ± 53	0.0004
AST, IU/L	40 ± 37	35.3 ± 43.2	41.3 ± 34	0.058
ALP, IU/L	86 ± 65	87 ± 59	86 ± 67	0.97
INR	1.06 ± 0.26	1.05 ± 0.13	1.1 ± 0.28	0.47
Cholesterol, mg/dL	181.8 ± 52.8	182.6 ± 39.2	181.4 ± 56.5	0.88
HDL cholesterol, mg/dL	42.3 ± 12	47.4 ± 88.9	40.4 ± 12.5	0.0002
LDL cholesterol, mg/dL	113.7 ± 43.2	113.6 ± 38.9	113.7 ± 44.9	0.99
Triglycerides, mg/dL	184.4 ± 202.3	118.7 ± 55.3	205.8 ± 227	0.0001
Serum creatinine, mg/dL	0.95 ± 0.54	0.96 ± 0.43	0.94 ± 0.58	0.60
A1c, %	6.4 ± 1.9	6.6 ± 1.3	6.4 ± 2.0	0.73
Noninvasive fibrosis scores				
APRI at biopsy	0.43 ± 0.58	0.36 ± 0.58	0.45 ± 0.57	0.039
<0.5, n (%)	687 (75.6)	197 (85.5)	492 (72.6)	
0.5, n (%)	186 (20.4)	24 (10.5)	160 (23.7)	
>1.5, n (%)	34 (4)	9 (4)	25 (3.7)	0.88
NFS at biopsy	−0.57 ± 1.87	−0.88 ± 1.55	−0.46 ± 1.96	0.0015
<−1.455, n (%)	382 (42.1)	92 (40)	290 (42.8)	
−1.455 to 0.675, n (%)	337 (37.2)	104 (45.2)	233 (34.4)	
>0.675, n (%)	188 (20.7)	34 (14.8)	154 (22.8)	0.01
FIB-4 score at biopsy	1.28 ± 1.75	0.95 ± 1.44	1.40 ± 1.84	0.0003
<1.3, n (%)	698 (77)	203 (88.3)	495 (73.1)	
1.3–2.67, n (%)	143 (15.7)	17 (7.4)	126 (18.6)	
>2.67, n (%)	66 (7.3)	10 (4.3)	56 (8.3)	0.047
AST–ALT ratio	0.87 ± 0.46	0.88 ± 0.43	0.86 ± 0.47	0.60
Histologic characteristics				
NAS score				<0.0001
Mean ± SD	2.42 ± 1.49	1.92 ± 1.3	2.58 ± 1.52	
Median (IQR)	2 (1–3)	2 (0–3)	2 (1–4)	
NAS score, 5–8, %	74 (8.2)	7 (3)	67 (9.8)	0.0007[a]
Fibrosis score				<0.0001
Mean ± SD	1.16 ± 1.13	0.8 ± 0.78	1.29 ± 1.21	
Median (IQR)	1 (0–2)	1 (0–1)	1 (0–2)	
Fibrosis, 3–4, %	115 (12.8)	6 (2.6)	109 (16.2)	<0.0001[a]
Fibrosis stage, %				<0.0001[a]

Table 1. (*continued*)

	All patients (N = 907)	AA (n = 230)	Whites (n = 677)	*P* value
None (stage 0)	297 (32.9)	92 (40.1)	205 (30.4)	
Mild (stage 1)	329 (36.4)	98 (42.8)	231 (34.2)	
Moderate (stage 2)	162 (17.9)	33 (14.4)	129 (19.1)	
Bridging (stage 3)	62 (6.9)	6 (2.62)	56 (8.31)	
Cirrhosis (stage 4)	53 (5.9)	0 (0)	53 (7.9)	

Total number of patients where lipid samples were available = 170; INR was available in 397 subjects; HbA1c was available only in 78 subjects. All other variables are complete.
AA, African American; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; NFS, nonalcoholic fatty liver disease fibrosis score; LDL, Low-density lipoprotein; NAS, NAFLD Activity Score; IQR, interquartile range.
[a]Fisher exact test.

level (42 ± 44 IU/L vs 55 ± 53 IU/L, $P < 0.0004$) and higher platelet counts (293 ± 87 vs 257 ± 87 10^9/L, $P < 0.0001$). In addition, AAs had a higher high-density lipoprotein (HDL) level (47.4 ± 88.9 vs 40.4 ± 12.5 mg/dL, $P < 0.0002$) and a lower triglyceride level (118.7 ± 55.3 vs 205.8 ± 227 mg/dL, $P < 0.0001$).

The mean APRI score ($P = 0.039$), NFS ($P = 0.0015$), and FIB-4 score ($P = 0.0003$) at the time of biopsy were significantly lower in AAs compared with whites, but AST–ALT ratio was not significantly different. The proportion of patients with advanced fibrosis (F3–F4) was significantly lower in the AAs (2.6% vs 16.2%, $P < 0.0001$) compared with the white population as measured using NFS (14.8% vs 22.8%, $P = 0.01$) and FIB-4 score (4.3% vs 8.3%, $P = 0.047$). There was no significant difference in the proportion of patients with advanced fibrosis (F3–F4) using APRI score.

The ability of the NFS, APRI score, and FIB-4 score to predict advanced fibrosis in whites vs AAs is illustrated in Figure 1. The bar graphs were divided into low, intermediate, and high probability to predict advanced fibrosis based on the score cutoffs (NFS: high cutoff = 0.675 and low cutoff = −1.455; APRI: high cutoff = 1.5 and low cutoff = 0.5; and FIB-4: high cutoff = 2.67 and low cutoff = 1.3).

Histologic characteristics

Using the NASH CRN, we systematically characterized the differences in the histological characteristics among the AAs and whites. As summarized in Table 1, both NAS score (1.92 ± 1.3 vs 2.58 ± 1.52, $P < 0.0001$) and fibrosis score (0.8 ± 0.78 vs 1.29 ± 1.21, $P < 0.0001$) were significantly lower in the AAs compared with the whites. The distribution of fibrosis stage in AA vs white was as follows: stage 0: 92 (40.1%) vs 205 (30.4%), stage 1: 98 (42.8%) vs 231 (34.2%), stage 2: 33 (14.4%) vs 129 (19.1%), stage 3: 6 (2.6%) vs 56 (8.3%), and stage 4: 0 (0%) vs 53 (7.9%). Advanced fibrosis (stages 3 and 4) was noted in 12.8% of the total cohort: 6 (2.6%) of the AAs and 109 (16.2%) of the whites.

Prediction of advanced fibrosis using noninvasive fibrosis scoring systems

The receiver operating characteristic curves were plotted, and the area under the curve (AUROC) was calculated for NFS, APRI, FIB-4, and AST–ALT ratio. Figure 2a shows a comparison of the diagnostic performances of these noninvasive fibrosis scoring systems in the cirrhosis population. The AUROC for predicting cirrhosis in the entire cohort using APRI, FIB-4, NFS, and AST–ALT ratio was 0.77, 0.76, 0.70, and 0.56, respectively. Figure 2b shows the diagnostic performances of these same systems in patients with advanced fibrosis. The AUROC for predicting advanced fibrosis (F3–F4) in the entire cohort using APRI, FIB-4, NFS, and AST–ALT ratio was 0.83, 0.88, 0.81, and 0.74, respectively.

The AUROC values analyzed the diagnostic performance of the noninvasive fibrosis scoring systems for advanced fibrosis in both AAs (Figure 2c) and whites (Figure 2d). For predicting advanced fibrosis in the whites, APRI (0.82), FIB-4 (0.88), NFS (0.82), and AST–ALT ratio (0.76) performed the best. For predicting advanced fibrosis in the AAs, APRI (0.86) and FIB-4 (0.77) performed the best compared with NFS (0.58) and AST–ALT ratio (0.65). Of note, none of the AA patients in this study had stage 4 fibrosis.

Based on the predetermined cutoff, the sensitivity, specificity, NPV, and PPV were calculated for FIB-4 score, NFS, and APRI score. These results are shown in Table 2. The NPV was interestingly higher for all the fibrosis scoring systems in the AAs compared with the whites. In the AAs, APRI score >1.5 was the most accurate diagnostic test with the highest NPV at 98.2% compared with 85% in the whites. The NPV of NFS (>0.675) was 98% in the AAs, whereas it was 91% in the whites. Similarly, the NPV of FIB-4 score (>2.67) was 98% in the AAs, whereas it was 88% in the whites.

As shown in Table 3, when comparing the patients in the bariatric group with those in the nonbariatric group, it is important to note that the NPVs of APRI (98%) and FIB-4 (97%) scoring systems were higher in the bariatric surgery group. The APRI score performed the best with an NPV of 98% in the bariatric surgery group compared with 78% in the nonbariatric surgery group. The NFS group had a similar NPV, 86%, across both the bariatric and nonbariatric surgery groups. Compared with whites, AAs had the higher NPV (>93%) across all noninvasive scoring systems in both the bariatric and nonbariatric surgery groups.

Characteristics of bariatric surgery population

Table 4 shows the characteristics of the patients who presented for bariatric surgery. It is interesting to note that the patients who underwent bariatric surgery were predominantly women (77.3% vs 58.6%, $P < 0.0001$) and as expected had a higher BMI (44.7 kg/m^2 vs 34.3 kg/m^2, $P < 0.0001$). Despite these patients having a significantly higher BMI, they did not present with a higher metabolic risk profile. The prevalence of diabetes was essentially similar in both the groups (34.1% vs 33.3%, $P = 0.81$) except for a higher HDL level (44.9 vs 37.4 mg/dL, $P < 0.0006$) in the bariatric

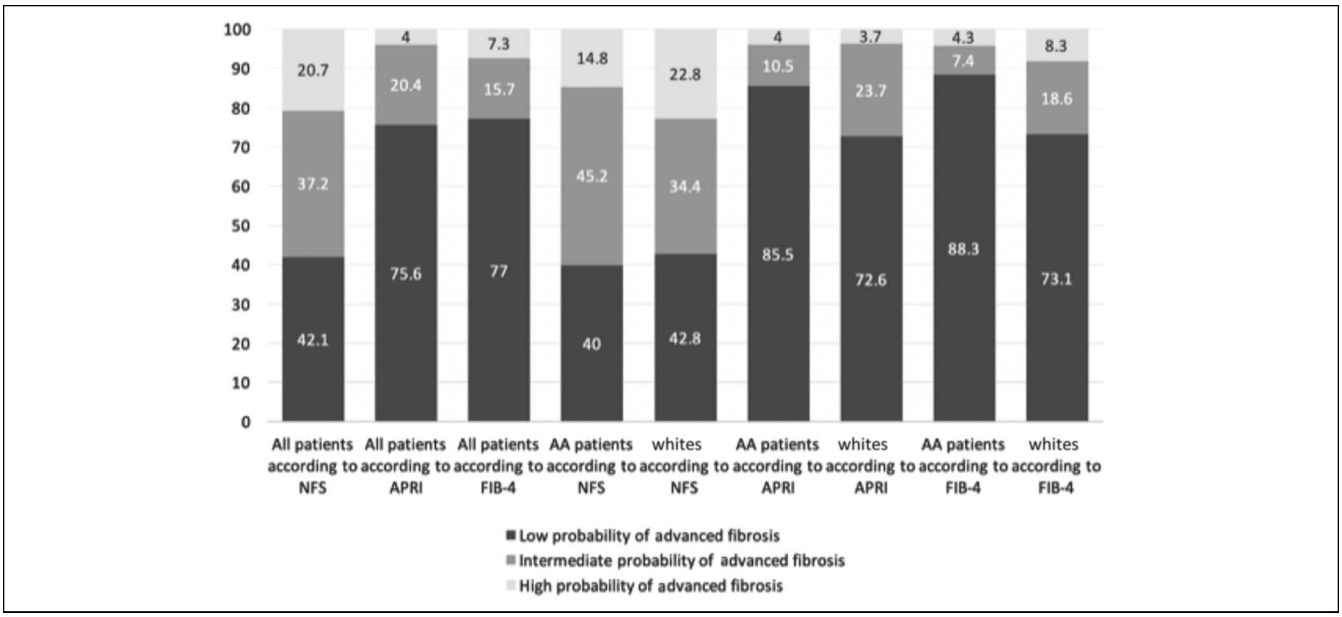

Figure 1. Probability of advanced fibrosis in African Americans vs whites based on noninvasive fibrosis models. APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4; NFS, nonalcoholic fatty liver disease fibrosis score.

surgery group. Interestingly, the bariatric surgery group had higher platelet counts ($P < 0.0001$), higher albumin ($P < 0.0001$), lower bilirubin ($P < 0.0001$), lower AST ($P < 0.0001$), lower ALT ($P < 0.0001$), and lower alkaline phosphatase ($P < 0.0001$) compared with the nonbariatric surgery group. The proportion of patients with advanced fibrosis (F3–F4) was significantly lower in the bariatric surgery group (2.8% vs 23.7%, $P < 0.0001$). The mean APRI score ($P < 0.0001$), NFS ($P < 0.0001$), and FIB-4 score ($P < 0.0001$) at the time of biopsy were significantly lower in bariatric surgery patients compared with nonbariatric surgery patients.

Characteristics of the study population based on bariatric surgery and race

Table 5 shows the characteristics of the patients who presented for bariatric surgery based on race. Both races presented for bariatric surgery at approximately the same age (AA, 42.04 years vs whites, 43.51 years, $P = -0.10$). In the bariatric population, AAs had a significantly higher platelet count (310.46 vs 288.93 10^9/L, $P = 0.005$); however, whites had higher liver tests (AST, ALT, albumin, and total bilirubin) compared with AAs. Despite the AAs having the higher BMI in the bariatric surgery group, they had a higher HDL level (49.09 vs 42.91 mg/dL, $P = 0.002$) and a lower triglyceride level compared with the whites (117.44 vs 197.15 mg/dL, $P < 0.0001$). It is important to note that only 1 AA patient with advanced fibrosis and 12 white patients with advanced fibrosis underwent bariatric surgery.

Prediction of advanced fibrosis using noninvasive fibrosis scoring systems in the bariatric and nonbariatric population

The receiver operating characteristic curves were plotted, and the area under the curve (AUROC) was calculated for NFS, APRI, FIB-4, and AST–ALT ratio in the bariatric and nonbariatric cohorts. Figure 3a shows a comparison of the diagnostic performances of these noninvasive fibrosis scoring systems in predicting advanced fibrosis (F3–F4) in the nonbariatric surgery cohort. The AUROC for predicting advanced fibrosis in the nonbariatric surgery cohort using APRI, FIB-4, NFS, and AST–ALT ratio was 0.71, 0.83, 0.79, and 0.78, respectively. Figure 3b shows the diagnostic performances of these same scoring systems in predicting advanced fibrosis in the bariatric surgery cohort. The AUROC for predicting advanced fibrosis (F3–F4) in the bariatric surgery cohort using APRI, FIB-4, NFS, and AST–ALT ratio was 0.79, 0.81, 0.73, and 0.53, respectively.

Within the nonbariatric surgery group, only 5 (8.5%) patients from the AA cohort had advanced fibrosis as compared with 97 (26.2%) in the white cohort. The AUROC for predicting advanced fibrosis in the AA nonbariatric surgery cohort using APRI, FIB-4, NFS, and AST–ALT ratio was 0.67, 0.63, 0.47, and 0.76, respectively (see Figure S2A, Supplementary Digital Content 2, http://links.lww.com/CTG/A264). The AUROC for predicting advanced fibrosis in the white nonbariatric surgery cohort using APRI, FIB-4, NFS, and AST–ALT ratio was 0.72, 0.84, 0.81, and 0.79, respectively (see Figure S2B, Supplementary Digital Content 2, http://links.lww.com/CTG/A264).

Within the bariatric surgery group, only a single patient (0.59%) from the AA cohort had advanced fibrosis as compared with 12 (3.97%) in the white cohort. As such, we were unable to assess the AUROC for predicting advanced fibrosis in the AA bariatric surgery cohort (see Figure S2C, Supplementary Digital Content 2, http://links.lww.com/CTG/A264). The AUROC for predicting advanced fibrosis in the white bariatric surgery cohort using APRI, FIB-4, NFS, and AST–ALT ratio was 0.75, 0.79, 0.72, and 0.56, respectively (see Figure S2D, Supplementary Digital Content 2, http://links.lww.com/CTG/A264).

DISCUSSION

There are currently no data demonstrating the utility of noninvasive fibrosis scoring systems in the AA population. In this large cohort of AAs and whites with biopsy-proven NAFLD, NFS, FIB-4 score, APRI score, and AST–ALT ratio were highly predictive of advanced fibrosis in the white population. However, only the APRI score and

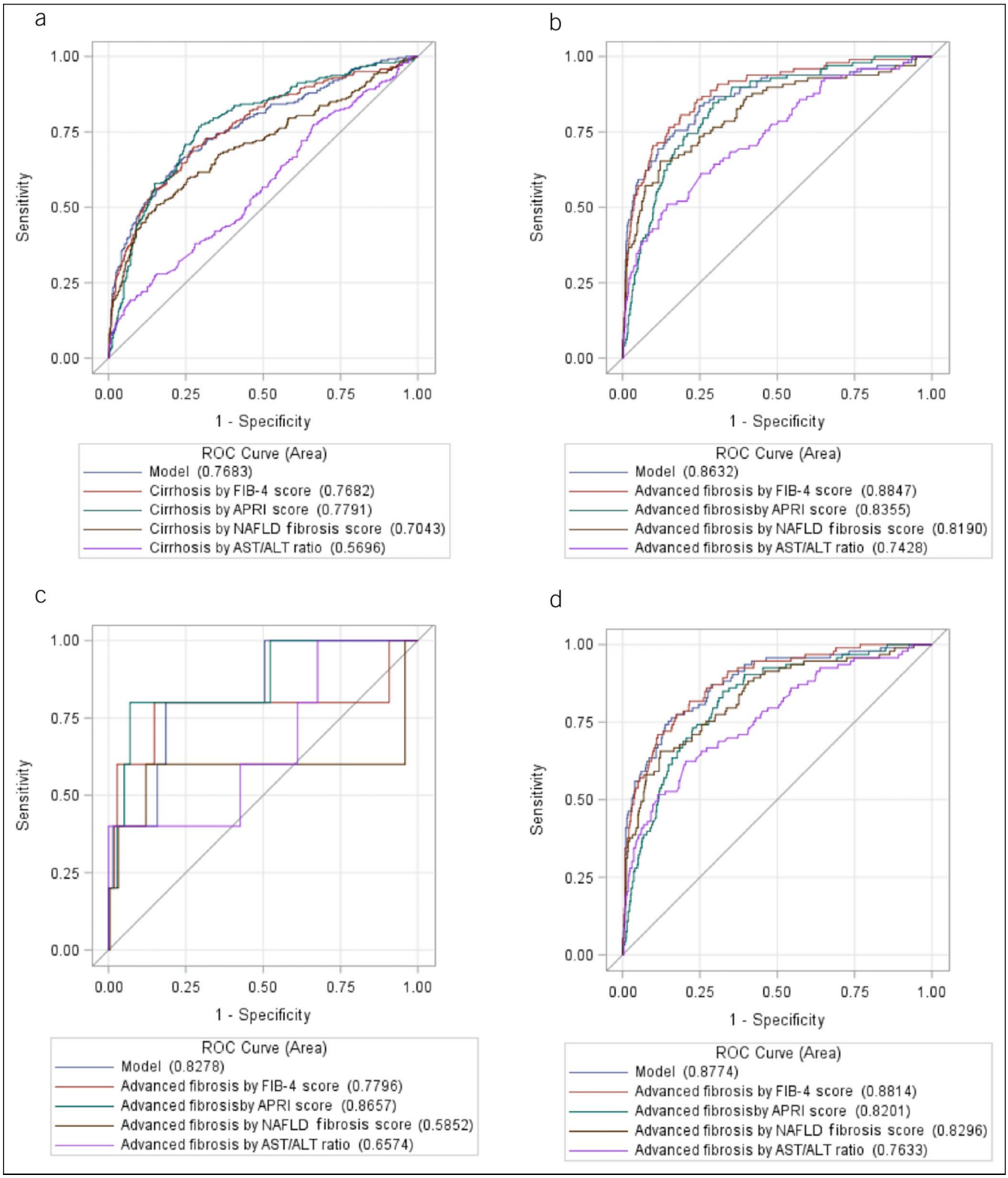

Figure 2. Overview of ROCs based on cirrhosis, advanced fibrosis, and race. (**a**) ROCs for all patients with cirrhosis. (**b**) ROCs for all patients with advanced fibrosis. (**c**) ROCs for the African American population with advanced fibrosis. (**d**) ROCs for the white population with advanced fibrosis. ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis-4; NAFLD, nonalcoholic fatty liver disease; ROC, receiver operating characteristic.

Table 2. Sensitivity, specificity, PPV, and NPV of noninvasive fibrosis scoring systems

	Sensitivity	Specificity	PPV	NPV
All patients				
APRI > 1.5	14 (8–20)	98 (97–99)	47 (30–64)	89 (86–91)
NFS > 0.675	57 (48–66)	84 (82–87)	35 (28–42)	93 (91–95)
FIB-4 score > 2.67	29 (20–37)	98 (97–99)	66 (53–79)	90 (88–92)
AAs				
APRI > 1.5	33 (0–71)	97 (95–99)	22.2 (0–49)	98.2 (96–99)
NFS > 0.675	50 (10–90)	86 (81–91)	9 (0–18)	98 (97–100)
FIB-4 score > 2.67	17 (0–47)	99 (97–100)	25 (0–67)	98 (96–100)
Whites				
APRI > 1.5	13 (7–19)	98 (97–99)	56 (37–75)	85 (83–88)
NFS > 0.675	58 (49–67)	84 (81–87)	41 (33–49)	91 (89–94)
FIB-4 score > 2.67	29 (21–38)	98 (96–99)	70 (56–83)	88 (85–90)

AA, African American; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4; NFS, nonalcoholic fatty liver disease fibrosis score; NPV, negative predictive value; PPV, positive predictive value.

Table 3. Sensitivity, specificity, PPV, and NPV of noninvasive fibrosis scoring systems based on bariatric surgery and race

	Sensitivity	Specificity	PPV	NPV
Nonbariatric surgery group				
APRI > 1.5	15 (8–22)	95 (92–97)	46 (28–62)	78 (74–82)
NFS > 0.675	60 (50–69)	79 (74–83)	47 (38–55)	86 (82–90)
FIB-4 score > 2.67	31 (22–40)	96 (94–98)	71 (58–84)	82 (78–86)
Nonbariatric surgery Group—AA				
APRI > 1.5	40 (0–82)	87 (78–96)	22 (0–49)	94 (87–100)
NFS > 0.675	40 (0–83)	78 (67–89)	14 (0–37)	93 (86–100)
FIB-4 score > 2.67	20 (0–55)	96 (91–100)	33 (0–87)	93 (86–100)
Nonbariatric surgery group—White				
APRI > 1.5	13 (7–20)	96 (94–98)	54 (34–74)	76 (71–80)
NFS > 0.675	51 (61–71)	79 (74–84)	50 (42–59)	85 (81–89)
FIB-4 score > 2.67	32 (23–41)	96 (94–98)	74 (61–87)	80 (76–84)
Bariatric surgery group				
APRI > 1.5	8 (0–22)	100 (100–100)	100 (100–100)	98 (96–99)
NFS > 0.675	60 (50–69)	79 (74–83)	47 (38–55)	86 (82–90)
FIB-4 score > 2.67	8 (0–22)	99 (98–100)	70 (56–83)	97 (96–99)
Bariatric surgery group—AA				
APRI > 1.5[a]	—	100 (100–100)	—	99 (98–100)
NFS > 0.675	100 (100–100)	89 (84–93)	5 (0–15)	100 (100–100)
FIB-4 score > 2.67[a]	—	99 (98–100)	—	99 (98–100)
Bariatric surgery group—White				
APRI > 1.5	8 (0–24)	100 (100–100)	100 (100–100)	96 (94–98)
NFS > 0.675	33 (6–60)	89 (85–92)	11 (1–20)	97 (95–99)
FIB-4 score > 2.67	8 (0–24)	99 (8–100)	25 (0–67)	96 (94–98)

AA, African American; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4; NFS, nonalcoholic fatty liver disease fibrosis score; NPV, negative predictive value; PPV, positive predictive value.
[a]Inadequate number of patients to calculate Sensitivity and PPV.

Table 4. Characteristics of the study population based on bariatric surgery (N = 907)

	Nonbariatric surgery n = 432	Bariatric surgery n = 475	*P* value
Age, yr ±SD	50.77 ± 12.48	48.98 ± 9.91	<0.0001
Gender, % female	253 (58.6)	367 (77.3)	<0.0001
Clinical characteristics			
BMI, kg/m^2	34.38 ± 7.62	44.79 ± 7.01	<0.0001
Diabetes, n (%)	140 (33.3)	162 (34.1)	0.81
Laboratory measures, mean			
Platelet, 10^9/L	231.10 ± 82.74	296.67 ± 81.13	<0.0001
Albumin, g/dL	3.54 ± 0.87	3.81 ± 0.36	<0.0001
Total bilirubin, mg/dL	0.89 ± 0.97	0.63 ± 0.27	<0.0001
ALT, IU/L	73.44 ± 67.23	35.69 ± 22.67	<0.0001
AST, IU/L	57.23 ± 47.77	26.66 ± 16.16	<0.0001
ALP, IU/L	102.83 ± 92.91	74.40 ± 27.4	<0.0001
INR	1.07 ± 0.27	1.03 ± 0.15	0.12
Cholesterol, mg/dL	178.04 ± 60.16	184.16 ± 47.49	0.48
HDL cholesterol, mg/dL	37.44 ± 14.09	44.99 ± 9.78	0.0006
LDL cholesterol, mg/dL	108.68 ± 50.14	116.59 ± 38.65	0.31
Triglycerides, mg/dL	205.96 ± 283.36	170.32 ± 123.55	0.34
Serum creatinine, mg/dL	1.02 ± 0.84	0.91 ± 0.21	0.023
A1c, %	6.4 ± 1.78	6.49 ± 2.14	0.85
APRI at biopsy, mean ± SD	0.63 ± 0.77	0.25 ± 0.20	<0.0001
<0.5, n (%)	251 (58.1)	436 (92.2)	<0.0001
0.5, n (%)	148 (34.3)	36 (7.6)	
>1.5, n (%)	33 (7.6)	1 (0.2)	
NFS at biopsy	0.02 ± 2.17	−1.01 ± 1.46	<0.0001
<−1.455, n (%)	183 (42.4)	199 (41.9)	<0.0001
−1.455 to 0.675, n (%)	118 (27.3)	219 (46.1)	
>0.675, n (%)	131 (30.2)	57 (12)	
FIB-4 score at biopsy	2.03 ± 2.43	0.73 ± 0.52	<0.0001
<1.3, n (%)	258 (59.7)	440 (92.6)	<0.0001
1.3–2.67, n (%)	111 (25.7)	32 (6.7)	
>2.67, n (%)	63 (14.6)	3 (0.6)	
AST–ALT ratio	0.93 ± 0.58	0.82 ± 0.35	0.002
Histologic characteristics[a]			
NAS score			<0.0001
Mean ± SD	3.03 ± 1.54	1.85 ± 1.2	
Median (IQR)	3 (2–4)	1 (1–3)	
NAS score, 5–8, %[b]	65 (15.1)	9 (1.9)	<0.0001
Fibrosis score			<0.0001
Mean ± SD	1.55 ± 1.32	0.81 ± 0.77	
Median (IQR)	1 (0–2)	1 (0–1)	
Fibrosis, 3–4, %	102 (23.7)	13 (2.8)	<0.0001
Fibrosis stage, %			<0.0001[a,b]

Table 4. (*continued*)

	Nonbariatric surgery n = 432	Bariatric surgery n = 475	*P* value
None (stage 0)	119 (27.6)	178 (37.7)	
Mild (stage 1)	108 (25.1)	221 (46.1)	
Moderate (stage 2)	102 (23.7)	60 (12.7)	
Bridging (stage 3)	51 (11.8)	11 (2.3)	
Cirrhosis (stage 4)	51 (11.8)	2 (0.4)	

Total number of patients where lipid samples were available = 170; INR was available in 397 subjects; HbA1c was available only in 78 subjects. All other variables are complete.
AA, African American; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; NFS, nonalcoholic fatty liver disease fibrosis score; LDL, Low-density lipoprotein; NAS, NAFLD Activity Score; IQR, interquartile range.
[a]Fibrosis state was not evaluated in 1 African American and 4 white patients and was not included in the analysis.
[b]Fisher exact test.

FIB-4 score could reliably predict advanced fibrosis (F3–F4) in AA patients. Because of a small number of advanced fibrosis in our cohort, the applicability of these fibrosis scoring systems could be underestimated in the AA cohort. However, all these noninvasive fibrosis scoring systems can be used at their higher cutoffs to exclude advanced fibrosis with high certainty (NPV > 85), thus preventing unnecessary invasive diagnostic tests in patients with mild disease irrespective of race. In addition, the current study highlights the significantly low prevalence of advanced fibrosis in the AA population as compared to the white population despite a similar prevalence of diabetes and higher mean BMI.

The significant finding in this study is the noninvasive fibrosis scoring systems: NFS (AUROC 0.82), FIB-4 (AUROC 0.88), APRI (AUROC 0.82), and AST–ALT ratio (AUROC 0.76); all have excellent diagnostic accuracy for detecting advanced fibrosis in the white cohort compared with only the APRI score (AUROC 0.86) and FIB-4 score (AUROC 0.77) in the AA cohort. In comparison to a meta-analysis involving 13,046 patients with NAFLD, the AUROC values were similar for NFS, FIB-4, and APRI scoring systems for diagnosing advanced fibrosis: 0.84, 0.84, and 0.77, respectively (14).

In addition, these noninvasive fibrosis scoring systems that demonstrated limited sensitivity, however, have high specificities (>84%) for predicting advanced fibrosis and have a high NPV (>85%) at their higher cutoffs to exclude advanced fibrosis in both whites and AAs, which can prevent invasive yet confirmatory tests. The findings of NFS and FIB-4 in this study were comparable to those of previous studies. In a meta-analysis, mentioned above, with NFS threshold of >0.675, the sensitivities and specificities were 43.1% and 88.4%, respectively, for advanced fibrosis (14). In comparison with our study, with NFS >0.675, the sensitivities and specificities were 50% and 86%, respectively, in AA patients and 58% and 84%, respectively, in white patients. In the meta-analysis, with a FIB-4 threshold of >2.67, the sensitivities and specificities were 26.6% and 96.5%, respectively, for advanced fibrosis (14). In our study, with FIB-4 score >2.67, the sensitivities and specificities were 17% and 99%, respectively, in AA patients and 29% and 88%, respectively, in white patients, whereas the sensitivities and specificities in the meta-analysis were 31.9% and 95.7%, respectively.

Previous studies have conflicting reports about the utility of APRI in predicting advanced fibrosis. In our study, APRI was a good predictor of advanced fibrosis in the whites (AUROC 0.82) and especially a good predictor among the AA population with an AUROC of 0.86. In the study by McPherson et al. (15), APRI was shown to be a poor predictor of fibrosis with an AUROC of 0.67. Imajo et al. (16) found similar results with an APRI AUROC of 0.61. In the meta-analysis mentioned above, the AUROC for APRI was 0.77. With an APRI threshold of >1.5, the sensitivities and specificities were 18.3% and 96.1%, respectively, for advanced fibrosis (14). In our study, with APRI score >1.5, the sensitivities and specificities were 33% and 97%, respectively, in AA patients and 13% and 98%, respectively, in white patients. Because of the conflicting results regarding the efficacy of APRI score, NAFLD practice guideline from the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association recommends the use of NFS or FIB-4 score to identify patients with NAFLD with fibrosis stage 3 or 4 (17).

We further performed a sensitivity analysis with the patients who had a biopsy for clinical indications (nonbariatric surgery group) and compared the results with those of the patients who had the biopsy during the bariatric surgery. We have shown that these noninvasive scoring systems have excellent specificity and NPV irrespective of whether the biopsies were performed for a clinical indication or per protocol for bariatric surgery. These results were quite similar to those of the entire cohort as previously described. However, the sensitivity and PPVs of these noninvasive models of fibrosis were suboptimal irrespective of the indication of the liver biopsies. The AUROC to predict advanced fibrosis was acceptable (>0.70) for NFS, FIB-4 score, and APRI score in both the bariatric and nonbariatric surgery cohorts, but excellent discrimination was noted only with FIB-4 score in both the groups. We were unable to assess the AUROCs for advanced fibrosis in the AA subgroups (bariatric vs nonbariatric groups) because of a small number of patients with advanced fibrosis in these cohorts. By contrast, the predictive abilities of these tests were quite robust in the white cohort.

Studies have indicated a degree of ethnic variation among patients with NAFLD, in which AAs are considered to be at a lower risk compared with whites (9,18). This study further supports the racial disparities in NAFLD. Genetic and environmental factors have been implicated for the disparities (19). The rise of NAFLD/NASH is associated with that of the incidence of diabetes, obesity, and metabolic syndromes (20). Interestingly, in the current cohort, despite the higher mean BMI and the equal incidence of diabetes in the AAs (although numerically higher)

Table 5. Characteristics of the study population based on bariatric surgery and race (N = 907)

	Nonbariatric surgery, n = 432			Bariatric surgery, n = 475		
	AAs (n = 60)	Whites (n = 372)	*P* value	AAs (n = 170)	Whites (n = 305)	*P* value
Patient characteristics						
Age, yr ±SD	47.75 ± 11.64	51.25 ± 12.56	0.0436	42.04 ± 8.67	43.51 ± 10.51	0.1013
Gender, % female	44 (73.3)	209 (56.2)	0.016	143 (84.1)	224 (73.4)	0.008
Clinical characteristics						
BMI, kg/m^2	33.81 ± 8.68	34.47 ± 7.44	0.5348	45.75 ± 7.69	44.25 ± 6.55	0.0318
Diabetes, n (%)	28 (47.5)	105 (31.3)	0.007	58 (34.1)	104 (34.1)	0.99
Laboratory measures, mean						
Platelet, 10^9/L	243.10 ± 75.85	229.11 ± 83.76	0.2295	310.46 ± 84.57	288.93 ± 78.22	0.0055
Albumin, g/dL	3.26 ± 1.01	3.59 ± 0.84	0.0211	3.74 ± 0.36	3.84 ± 0.35	0.0021
Total bilirubin, mg/dL	1.05 ± 1.73	0.86 ± 0.77	0.4350	0.58 ± 0.24	0.66 ± 0.28	0.0013
ALT, IU/L	77.96 ± 74.32	72.64 ± 66.01	0.5958	31.28 ± 18.23	38.15 ± 24.49	0.0006
AST, IU/L	70.43 ± 76.23	54.92 ± 40.54	0.1535	24.32 ± 12.39	27.96 ± 17.81	0.0093
ALP, IU/L	127.70 ± 107.85	98.61 ± 89.66	0.0405	74.38 ± 22.14	74.41 ± 29.98	0.9875
INR	1.06 ± 0.14	1.07 ± 0.29	0.6386	1.03 ± 0.08	1.03 ± 0.17	0.9988
Cholesterol, mg/dL	185.43 ± 52.74	177.18 ± 61.31	0.7342	182.29 ± 36.82	185.07 ± 52.18	0.7558
HDL cholesterol, mg/dL	40.13 ± 5.03	37 ± 15.07	0.2734	49.09 ± 8.74	42.91 ± 9.69	0.0023
LDL cholesterol, mg/dL	111.38 ± 47.06	108.22 ± 51.12	0.8711	114.18 ± 37.48	117.92 ± 39.51	0.6524
Triglycerides, mg/dL	124.71 ± 39.51	215.60 ± 298.22	0.0326	117.44 ± 58.48	197.15 ± 138.73	0.0001
Serum creatinine, mg/dL	1.09 ± 0.83	1.01 ± 0.84	0.5942	0.93 ± 0.25	0.89 ± 0.19	0.0515
A1c, %	6.8 ± 1.64	6.33 ± 1.81	0.4947	6.28 ± 0.45	6.56 ± 2.52	0.6752
Noninvasive fibrosis scores						
APRI at biopsy	0.77 ± 1.02	0.61 ± 0.72	0.2499	0.22 ± 0.16	0.27 ± 0.22	0.0048
<0.5, n (%)	40 (66.7)	218 (58.6)	0.3605	159 (94.08)	277 (91.12)	0.5932
0.5, n (%)	11 (18.3)	100 (26.9)		10 (5.92)	26 (8.55)	
>1.5, n (%)	9 (15)	54 (14.5)		0 (0.00)	1 (0.33)	
NFS at biopsy	−0.26 ± 1.78	0.06 ± 2.23	0.3140	−1.07 ± 1.42	−0.98 ± 1.48	0.4946
<−1.455, n (%)	21 (35)	162 (43.55)	0.0264	71 (41.76)	128 (41.97)	0.9896
−1.455 to 0.675, n (%)	25 (41.67)	93 (25)		79 (46.47)	140 (45.90)	
>0.675, n (%)	14 (23.33)	117 (31.45)		20 (11.76)	37 (12.13)	
FIB-4 score at biopsy	1.90 ± 2.68	2.05 ± 2.38	0.6856	0.65 ± 0.35	0.77 ± 0.60	0.0118
<1.3, n (%)	40 (66.67)	218 (58.60)	0.3823	163 (95.88)	277 (90.82)	0.0896
1.3–2.67, n (%)	11 (18.33)	100 (26.88)		6 (3.53)	26 (8.52)	
>2.67, n (%)	9 (15)	54 (14.52)		1 (0.59)	2 (0.66)	
AST–ALT ratio	0.97 ± 0.69	0.93 ± 0.56	0.7055	0.86 ± 0.31	0.80 ± 0.37	0.0864
Histologic characteristics						
NAS score			0.0110			0.0263
Mean ± SD	2.57 ± 1.44	3.11 ± 1.55		1.68 ± 1.16	1.95 ± 1.21	
Median (IQR)	2.5 (2–4)	3 (2–4)		1 (1–2)	2 (1–3)	
NAS score, 5–8, %[b]	4 (6.7)	61 (16.4)	0.05	3 (1.7)	6 (1.97)	0.88
Fibrosis score[a]			<0.0001			0.1719
Mean ± SD	0.93 ± 0.98	1.65 ± 1.34		0.75 ± 0.70	0.84 ± 0.81	
Median (IQR)	1 (0–2)	2 (0–3)		1 (0–1)	1 (0–1)	

Table 5. (*continued*)

	Nonbariatric surgery, n = 432			Bariatric surgery, n = 475		
	AAs (n = 60)	Whites (n = 372)	*P* value	AAs (n = 170)	Whites (n = 305)	*P* value
Fibrosis, 3–4, %[a,b]	5 (8.47)	97 (26.15)	0.003	1 (0.59)	12 (3.97)	0.038
Fibrosis stage, %[a,b]			0.0008			0.3452
None (stage 0)	25 (42.37)	94 (25.27)		67 (39.41)	111 (36.75)	
Mild (stage 1)	18 (30.51)	90 (24.19)		80 (47.06)	141 (46.69)	
Moderate (stage 2)	11 (18.64)	91 (24.46)		22 (12.94)	38 (12.58)	
Bridging (stage 3)	5 (8.47)	46 (12.37)		1 (0.59)	10 (3.31)	
Cirrhosis (stage 4)	0 (0)	51 (13.71)		0 (0)	2 (0.66)	

Total number of patients where lipid samples were available = 170; INR was available in 397 subjects; HbA1c was available only in 78 subjects. All other variables are complete.
AA, African American; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; NFS, nonalcoholic fatty liver disease fibrosis score; LDL, Low-density lipoprotein; NAS, NAFLD Activity Score; IQR, interquartile range.
[a]Fibrosis stage was not evaluable in 1 AA and 4 white patients and was not included in the analysis.
[b]Fisher exact test.

compared with the whites (37.8% in AAs and 32.8% in whites, $P = 0.17$), the AAs had a lower prevalence of NASH (NAS $\geq$ 5) and advanced fibrosis (F3–F4), raising the possible underlying genetic protective mechanism. These findings are supported by previous studies that show AAs have a higher rate of diabetes and insulin resistance compared with whites but a lower rate of prevalence of NAFLD because of their lower serum concentrations of triglycerides reflecting the ethnic differences in lipid homeostasis (21). In addition, previous studies have demonstrated that genetics plays a significant role in NAFLD. In particular, single-nucleotide polymorphisms in *PNPLA3* (22), TM6SF2 (23), and MBOAT (24) have unequal distributions across ethnicities, which may have contributed to the observed differences in the prevalence of NASH and advanced fibrosis in our cohort. Further studies are needed to study the genetic factors and environmental factors involved in NAFLD/NASH.

The limitations of this study are that it was performed at a single center and the generalizability of its results in other clinical settings remains unknown. The incidence of advanced fibrosis was low in AA patients compared with white patients who could have affected the PPV of advanced fibrosis. The lower incidence of advanced fibrosis in AAs could be partly related to the inclusion of a larger number of patients from the bariatric surgery cohort compared with the white population in the current study. However, all the biopsies were performed at the time of the bariatric surgery (intraoperative). In general, unless cirrhosis or portal hypertension is identified in patients evaluated for bariatric surgery, they are not denied the surgery, and hence, the inclusion of patients from the bariatric surgery cohort is unlikely to introduce a selection bias. However, the large number of AAs included in the current study is a strength because it reliably excludes advanced

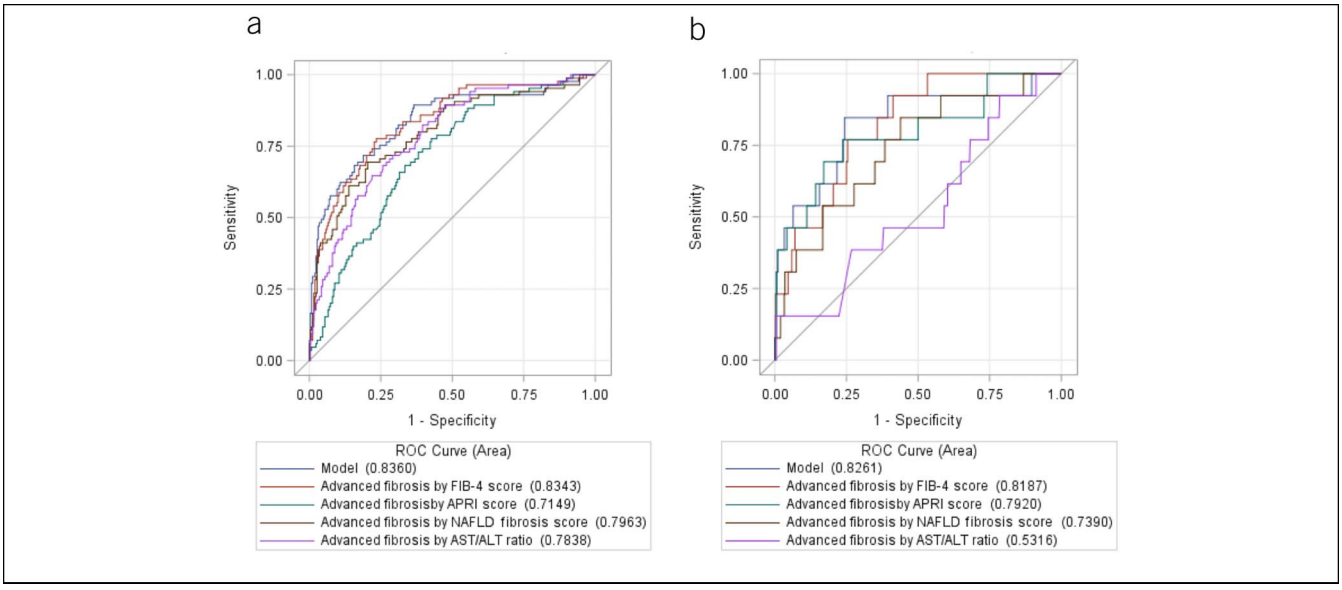

Figure 3. Comparison of ROCs between nonbariatric surgery patients and bariatric surgery patients. (**a**) ROC for all nonbariatric surgery patients with advanced fibrosis. (**b**) ROC for all bariatric surgery patients with advanced fibrosis. ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis-4; NAFLD, nonalcoholic fatty liver disease; ROC, receiver operating characteristic.

fibrosis. The retrospective review of liver biopsies has inherent limitations because of the possible interobserver and intraobserver variations considering several expert hepatopathologists were involved in the reporting. However, the pathology reports were manually reviewed and rescored using the NASH CRN to minimize the bias by the investigators, and any discrepancies were resolved by a review of the original slides with expert hepatopathologists. In addition, because histologic lesions of NASH are irregularly dispersed throughout the liver parenchyma, sampling error of liver biopsy can result in staging inaccuracies.

In conclusion, the ability of NFS, FIB-4 score, APRI score, and AST–ALT ratio to predict advanced fibrosis is acceptable in the white population. The low prevalence of advanced fibrosis in AAs likely affects the applicability of these noninvasive fibrosis scoring systems and thus will need further validation in a much larger multicenter cohort. However, these noninvasive fibrosis scoring systems are highly reliable in excluding advanced fibrosis in both AAs and whites, thus preventing unnecessary invasive diagnostic tests in patients with mild disease.

CONFLICTS OF INTEREST

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Specific author contributions: Hemnishil K. Marella, DO and Yala Kirthi Reddy, MD, contributed equally to this work. S.K.S. conceptualized and designed the study. H.K.M., Y.K.R., S.G., and P.S.B.P. collected the data. Y.J. and S.K.S. performed the statistical analysis. H.K.M. and Y.K.R. interpreted the data and wrote the initial draft of the paper. P.D.S., A.J.K., G.C., A.K.S., S.N., and B.M. interpreted the data and provided valuable intellectual input. All authors participated in the critical revision of the manuscript and approved the final version of the manuscript.
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Study Highlights

WHAT IS KNOWN

- ✓ Noninvasive fibrosis scoring systems have been primarily studied in the white population.
- ✓ There is a degree of ethnic variation among patients with NAFLD.

WHAT IS NEW HERE

- ✓ Noninvasive fibrosis scoring systems can reliably exclude advanced disease in both AAs and whites.
- ✓ The prevalence of advanced fibrosis in AAs with histologically confirmed NAFLD is low compared with that in whites.

TRANSLATIONAL IMPACT

- ✓ These findings will have potential diagnostic implications in NAFLD.

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