Differential Outcomes and Clinical Challenges of NAFLD With Extreme Obesity

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Nonalcoholic fatty liver disease (NAFLD) is closely associated with obesity. The prevalence of extreme obesity, defined as body mass index (BMI) of 50 kg/m^2 or higher, is rising more rapidly than overall obesity. We aimed to compare the clinical outcomes and performance of noninvasive fibrosis assessment tools in NAFLD with or without extreme obesity. A retrospective analysis was performed in 304 patients with NAFLD with extreme obesity and compared them to patients with NAFLD with BMI of 40 kg/m^2 or less, matched for age, gender, race, and liver fibrosis stage. The mean age of the NAFLD with extreme obesity cohort was 55.9 years, BMI 55 kg/m^2, and 49.7% had cirrhosis at initial evaluation. Baseline cirrhosis and coronary artery disease were associated with increased risk of death, and dyslipidemia with decreased risk of mortality. Age, insulin use, hypertension, albumin and platelet count were associated with cirrhosis. Fifteen percent of patients had weight-loss surgery, but this was not associated with survival or risk of cirrhosis. Of the 850 abdominal ultrasound scans performed in 255 patients, 24.1% were deemed suboptimal for hepatocellular carcinoma screening. The mean NAFLD fibrosis score (NFS) in the extreme obesity cohort, versus a propensity-matched cohort with BMI of 40 kg/m^2 or less, was significantly different for both low fibrosis (F0-F2) (0.222 vs. −1.682, $P < 0.0001$) and high fibrosis (F3-F4) (2.216 vs. 0.557, $P < 0.001$). *Conclusion:* NAFLD with extreme obesity is associated with increased risk of liver-related and overall mortality. Accurate noninvasive assessment of liver fibrosis, low rates of weight loss surgery, and high failure rate of ultrasound were identified as clinical challenges in this population. (*Hepatology Communications* 2020;4:1419-1429).

Nonalcoholic fatty liver disease (NAFLD) is closely associated with obesity.[1-4] The prevalence of NAFLD increases with increasing severity of obesity.[5] In patients undergoing bariatric surgery, prevalence of hepatic steatosis is 66% and prevalence of nonalcoholic steatohepatitis (NASH) is 14%.[4] Screening for NAFLD has been proposed in patients undergoing bariatric surgery, but there is no consensus on best strategies for screening and risk stratification for fibrosis staging.[6,7]

Although overall obesity rates are increasing in the United States, the prevalence of extreme obesity, termed super obesity for body mass index (BMI) over 50 kg/m^2, or super super obesity for BMI over 60 kg/m^2, is rising more rapidly.[8,9] Overall health risks increase with severity of obesity.[10,11] Compared to individuals with normal BMI, every 5-kg/m^2 incremental increase in BMI over 40 kg/m^2 was associated with an estimated 6.5, 8.9, 9.8, and 13.7 years, respectively, of life lost.[10] Bariatric surgery may be less effective in individuals with extreme obesity, and there is no consensus on weight management for this high-risk population.[12,13]

Thus, clinicians managing patients with NAFLD with extreme obesity encounter several clinical

Abbreviations: ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; BARD, BMI, AST/ALT ratio, T2DM score; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; FIB-4, Fibrosis-4 index; HCC, hepatocellular carcinoma; INR, international normalized ratio; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; T2DM, type 2 diabetes mellitus; US, ultrasonography.

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challenges. First, the accuracy of noninvasive assessment of liver fibrosis using simple clinical calculators is unknown in this population. Second, whether patients with NAFLD with extreme obesity have higher risk of liver-related and extrahepatic complications compared to patients with lower BMI is uncertain. Third, in patients with cirrhosis and extreme obesity, the diagnostic utility of abdominal ultrasound scans for hepatocellular carcinoma (HCC) screening has not be validated. Fourth, optimum treatment strategies for NAFLD with extreme obesity remain undefined. The aim of our study was to address differences in clinical outcomes, accuracy of diagnosing fibrosis noninvasively, and utility of abdominal ultrasound in HCC screening in a well-phenotype cohort of patients, with and without extreme obesity, referred for evaluation of NAFLD.

Patients and Methods

STUDY DESIGN AND PATIENT COHORT

This single-center, retrospective study was approved by the Human Research Protection Office at the University of Pittsburgh as a minimal-risk, consent-waived study. We identified 304 patients over 18 years of age with a diagnosis of NAFLD and BMI of 50 kg/m^2 or higher, evaluated at the Center for Liver Diseases at the University of Pittsburgh Medical Center between May 2007 and September 2017, who were included in the analysis. Data were extracted from electronic medical records. Exclusion criteria, based on serologic and/or biopsy evidence of other etiologies of liver disease, were current or previous history of alcohol use disorder, hepatitis C or B infection, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, alpha-1 antitrypsin deficiency, Wilson disease, and idiopathic portal vein thrombosis based on abdominal ultrasound.

STUDY VARIABLES AND DEFINITION OF OUTCOMES

Baseline characteristics were recorded at the first visit to the hepatology clinic. BMI was calculated using the following formula: BMI = mass (kg)/height (m^2). Follow-up period was defined as the interval between the first visit and last visit recorded in the electronic medical record. Presence of comorbid conditions were recorded, including type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, coronary artery disease (CAD), and liver-related comorbidities (liver cirrhosis, HCC, and thrombocytopenia), and previous type and date of weight-loss surgery were recorded. Laboratory data, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, international normalized ratio (INR), and albumin, were obtained. For noninvasive assessment of liver fibrosis, we used laboratory data closest to the biopsy date either 3 months before or after the biopsy date. Fibrosis stage, percent steatosis, and type (macrovascular, microvascular, or mixed) were extracted from liver biopsy pathology reports. Ishak fibrosis score was converted to equivalent metavir score.[14] Our study did not use a central

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pathologist, and fibrosis staging (F0-F4) was determined by reviewing the original pathology reports from clinically indicated liver biopsies.

Definitions of conditions identified in the cohort were as follows: extreme obesity: BMI ≥50 kg/m^2 recorded any time during the follow-up period; T2DM: glycosylated hemoglobin ≥6.5 [14] or on treatment for T2DM; hypertension: previous recorded diagnosis or on antihypertensive medication; dyslipidemia: abnormal lipid panel or on therapy for dyslipidemia; and CAD: history of CAD found on left cardiac catheterization, coronary artery bypass graft surgery, history of stroke, positive stress test, and hospital admission for myocardial infarction. We used a combination of liver biopsy reports, clinical documentation, and radiographic evidence by ultrasonography (US), computed tomography (CT), or magnetic resonance imaging for the diagnosis of NAFLD, HCC, and cirrhosis. Thrombocytopenia was defined as platelet count <150 × 10^9/L. Significant fibrosis was defined as metavir stage ≥F2, and advanced fibrosis as F3 or F4. An abdominal ultrasound scan was defined as suboptimal if the radiology report mentioned "limited study" or "difficult visualization due to body habitus."

Noninvasive fibrosis assessment tools were used as follows: AST-to-platelet ratio index (APRI) = AST (IU/L)/AST upper limit of normal [IU/L])/platelets (10^9/L)[15]; NAFLD fibrosis score (NFS) = −1.675 + (0.037*age [years]) + (0.094*BMI [kg/m^2]) + (1.13*IFG/diabetes [yes = 1, no = 0]) + (0.99*AST/ALT ratio) − (0.013*platelet count [×10^9/L]) − (0.66*albumin [g/dL])[16]; BARD score = BMI ≥ 28 = 1 point, AST/ALT ratio ≥ 0.8 = 2 points, T2DM = 1 point[17]; and Fibrosis-4 index (FIB-4) = (Age*AST)/(Platelets*√[ALT]).[18]

STATISTICAL ANALYSIS

Categorical variables were compared using Fisher exact tests, and continuous variables were compared with Welch's *T* tests. Cox proportional hazards models were used to analyze overall survival. Logistic regression models were used to determine factors associated with cirrhosis. For both analyses, variables with *P* values less than 0.1 in univariate models were included in the multivariate model development. To generate a parsimonious model, a backward stepwise elimination algorithm was performed to determine regressors for the final models. A case-control analysis was performed in patients with BMI ≥ 50 kg/m^2 who underwent liver biopsy compared to a cohort of patients with biopsy-proven NAFLD with BMI ≤ 40 kg/m^2. The control population was identified using propensity-score matching for age, gender, race, and fibrosis severity.[19] To minimize bias, data for the comparison group was collected by another investigator (D.J.). Performance characteristics of noninvasive fibrosis scores were assessed with receiver-operator curve analysis, and optimal cutoffs were identified using the Youden index.[20] A *P* value <0.05 was considered statistically significant.

Results

BASELINE CLINICAL CHARACTERISTICS OF THE STUDY COHORT

Between May 2007 and September 2017, 406 patients with extreme obesity were seen in the liver clinic, of which 304 patients were diagnosed with NAFLD (Table 1). The mean (±95% confidence interval [CI]) follow-up period was 4.54 (4.18-4.91) years, and the mean age at presentation was 55.9 (54.5-57.3) years. Most of the patients were female (69.7%) and white (90.8%), 150 patients (49.3%) had T2DM, and 67 patients (44.7%) were on insulin therapy. At baseline, dyslipidemia, hypertension, and CAD were present in 45.1%, 60.9%, and 7.2%, respectively, and 151 patients (49.7%) had a clinical diagnosis of cirrhosis. Patients with cirrhosis were older (60.6 [59.0-57.3] versus 51.3 [49.2-53.4] years; $P < 0.0001$) and had higher rates of T2DM (94 [62.3%] vs. 56 [36.6%]; $P < 0.001$), insulin use (47 [50.0%] vs. 20 [35.6%]; $P = 0.001$), and hypertension (103 [68.2%] vs. 82 [53.6%]; $P = 0.006$). The prevalence of dyslipidemia, liver cancer, and weight-loss surgery was similar between the groups with or without cirrhosis. The two groups had significant differences in several laboratory tests, including platelet count, albumin, and ALT.

PREDICTORS OF OVERALL MORTALITY IN NAFLD WITH EXTREME OBESITY

Insulin use, CAD, and cirrhosis were associated with increased mortality in univariate analysis,

TABLE 1. BASELINE CHARACTERISTICS OF THE NAFLD COHORT WITH EXTREME OBESITY, STRATIFIED BY THE PRESENCE OR ABSENCE OF CIRRHOSIS

Characteristics	All (n = 304)	Cirrhosis (n = 151)	No Cirrhosis (n = 153)	*P*
Age	55.9 (54.5-57.3)	60.6 (59.0-57.3)	51.3 (49.2-53.4)	<0.0001
Female	212 (69.7%)	96 (63.4%)	116 (75.8%)	0.014
Race	276 (90.8%)	139 (92.1%)	137 (89.5%)	0.289
Diabetes	150 (49.3%)	94 (62.3%)	56 (36.6%)	<0.001
Insulin use among diabetics	67 (44.7%)	47 (50.0%)	20 (35.6%)	0.001
Dyslipidemia	137 (45.1%)	64 (42.4%)	73 (47.7%)	0.207
Hypertension	185 (60.9%)	103 (68.2%)	82 (53.6%)	0.006
CAD	22 (7.2%)	13 (8.6%)	9 (5.9%)	0.244
Liver cancer	4 (1.3%)	4 (2.6%)	0 (0%)	0.060
AST	45 (41-49)	45 (41-49)	44 (37-51)	0.5637
ALT	46 (42-50)	38 (33-43)	55 (47-62)	0.0001
ALP	103 (94-111)	108 (98-117)	98 (83-113)	0.2933
INR	1.2 (1.1-1.2)	1.3 (1.2-1.4)	1.1 (1.0-1.1)	<0.0001
Albumin	3.7 (3.6-3.8)	3.4 (3.3-3.5)	4.0 (3.9-4.0)	<0.0001
Bilirubin	1.0 (0.8-1.2)	1.3 (1.1-1.6)	1.1 (0.9-1.3)	0.342
Platelets	194 (183-204)	141 (130-153)	246 (234-257)	<0.0001
Weight-loss surgery	47 (15.5%)	18 (11.9%)	29 (19.0%)	0.062
BMI	55.0 (54.3-55.8)	54.3 (53.5-55.1)	55.7 (54.5-56.9)	0.035

Abbreviation: ALP, alkaline phosphatase.

TABLE 2. PREDICTORS OF SURVIVAL IN THE EXTREME OBESITY COHORT

	Univariate		Multivariate Model	
Characteristics	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Age	1.021 (0.999-1.043)	0.063	1.001 (0.978-1.026)	0.883
Female	0.598 (0.367-0.975)	0.039	0.901 (0.547-1.484)	0.682
White race	2.378 (0.747-7.569)	0.143		
Diabetes	1.416 (0.8718-2.300)	0.160		
Insulin use	1.983 (1.197-3.285)	0.008	1.627 (0.961-2.758)	0.070
Dyslipidemia	0.473 (0.282-0.793)	0.005	0.428 (0.248-0.737)	0.002
Hypertension	1.045 (0.639-1.708)	0.862		
CAD	3.327 (1.737-6.373)	<0.001	3.157 (1.622-6.145)	0.001
Weight-loss surgery	0.570 (0.270-1.250)	0.161		
BMI	0.992 (0.957-1.027)	0.638		
Cirrhosis	9.161 (4.372-19.195)	<0.001	7.395 (3.395-16.107)	<0.001

Note: The mean (±95% CI) follow-up period was 4.54 years (4.18-4.91 years).

whereas only CAD and cirrhosis were associated with increased mortality in multivariable analysis (Table 2). Cirrhosis was associated with the highest risk of mortality in both models. Female gender was protective in univariate models, and dyslipidemia was protective in both univariate and multivariate analyses. Age, hypertension, T2DM, and weight-loss surgery were not predictive of mortality.

We then created a multivariable model with interaction terms after omitting age, gender and ethnicity, and found that dyslipidemia (decreased risk) and cirrhosis (increased risk) continued to be significantly associated with overall mortality. However, the interaction between CAD and cirrhosis reduced the contribution of each to the relative risk of mortality (0.175 [0.033-0.926]; $P = 0.040$) (Supporting Table S1).

RISK FACTORS ASSOCIATED WITH CIRRHOSIS IN NAFLD WITH EXTREME OBESITY

Because cirrhosis was associated with the highest risk of mortality in patients with NAFLD and extreme obesity, we performed univariate and multivariate logistic regression analysis to determine the risk factors associated with cirrhosis at initial presentation in this population (Table 3). Age, T2DM, insulin use, and hypertension were associated with cirrhosis in univariate models. However, only age, insulin use, and hypertension were associated with cirrhosis in the multivariate model. Among laboratory tests, INR was associated with cirrhosis in the univariate analysis ($P < 0.001$), whereas albumin and platelet count were associated with cirrhosis in the multivariate model (Table 3).

Liver biopsy was performed in 136 patients during the follow-up period in the cohort of patients with NAFLD with extreme obesity. We also explored risk factors for advanced fibrosis (F3-F4) determined by liver biopsy in this cohort. In univariate models, age, T2DM, insulin use, hypertension, AST, INR, albumin, and platelets were associated with advanced fibrosis. However, only age, T2DM, AST, and albumin were significantly associated with advanced fibrosis in the multivariate model (Supporting Table S2).

In the propensity-matched cohort with BMI ≤40 kg/m^2, we found that age, T2DM, serum albumin, and platelet count were associated with advanced fibrosis. In contrast, dyslipidemia was associated with lower risk of advanced fibrosis in both models (Supporting Table S3).

In the cohort of patients with NAFLD with extreme obesity cohort, 47 (15.5%) patients had weight-loss surgery (Roux-en-Y gastric bypass in 29, laparoscopic sleeve gastrectomy in 9, and gastric banding in 9), with 28 surgeries performed before the initial visit and 18 in the follow-up period. In this cohort, weight-loss surgery was not associated with survival (0.570 [0.270-1.250]; $P = 0.161$) or the risk of cirrhosis (0.579 [0.306-1.094]; $P = 0.092$) (Tables 2 and 3). There were no patients with previous gastric bypass surgery in the propensity-matched cohort with BMI ≤40 kg/m^2, to enable comparison. We also did not have outcome data on patients with extreme obesity who underwent weight-loss surgery and subsequently achieved BMI <50 kg/m^2.

DIFFERENCE IN SURVIVAL BETWEEN NAFLD WITH OR WITHOUT EXTREME OBESITY

We used propensity scores to match for age, gender, ethnicity, and fibrosis stage those patients with

TABLE 3. FACTORS ASSOCIATED WITH CIRRHOSIS IN PATIENTS WITH NAFLD WITH EXTREME OBESITY

	Univariate		Stepwise Multivariate Model	
Characteristics	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Age	1.074 (1.050-1.099)	<0.001	1.072 (1.034-1.111)	<0.001
Female	0.557 (0.339-0.915)	0.021		
White race	1.353 (0.617-2.965)	0.450		
Diabetes	2.856 (1.794-4.549)	<0.001		
Insulin use	3.005 (1.678-5.382)	<0.001	2.313 (1.034-5.173)	0.006
Dyslipidemia	0.806 (0.513-1.268)	0.351		
Hypertension	1.858 (1.164-2.964)	0.009	3.016 (1.370-6.636)	<0.001
CAD	1.507 (0.624-3.639)	0.362		
AST	1.001 (0.994-1.007)	0.872		
ALT	0.986 (0.978-0.994)	0.001		
ALP	1.002 (0.998-1.005)	0.311		
INR	7.774 (2.923-20.673)	<0.001		
Albumin	0.120 (0.066-0.217)	<0.001	0.105 (0.045-0.240)	<0.001
Bilirubin	1.003 (0.901-1.228)	0.372		
Platelets	0.981 (0.977-0.985)	<0.001	0.981 (0.976-0.986)	<0.001
Weight-loss surgery	0.579 (0.306-1.094)	0.092		
BMI	0.965 (0.930-1.002)	0.066	0.931 (0.878-0.988)	0.018

Abbreviation: ALP, alkaline phosphatase.

TABLE 4. UNIVARIATE AND MULTIVARIATE COX PROPORTIONAL HAZARD MODEL PREDICTIVE OF MORTALITY IN MATCHED BIOPSY COHORT

	Univariate		Multivariate Model	
Characteristics	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Age	1.050 (1.021-1.079)	0.001	1.048 (1.017-1.081)	0.002
Female	1.333 (0.692-2.570)	0.390		
White race	1.000 (0.472-2.121)	1.000		
Diabetes	1.189 (0.670-2.111)	0.554		
Insulin use	1.622 (0.854-3.079)	0.139		
Dyslipidemia	0.528 (0.288-0.965)	0.038	0.421 (0.227-0.782)	0.006
Hypertension	0.754 (0.424-1.341)	0.338		
CAD	2.628 (1.303-5.300)	0.007	2.776 (1.373-6.615)	0.004
Weight-loss surgery	0.692 (0.239-2.003)	0.497		
BMI	1.346 (0.755-2.401)	0.314		
Advanced fibrosis	6.369 (2.517-16.116)	<0.001	5.229 (2.054-13.307)	0.001

Note: The mean (±95% CI) follow-up period was 4.54 years (4.18-4.91 years).

NAFLD and extreme obesity who had a liver biopsy with a cohort of patients with NAFLD with BMI ≤40 kg/m^2 (n = 136 in each group). The two groups differed in BMI, albumin, and NFS, a noninvasive diagnostic score for fibrosis in NAFLD that incorporates BMI in the calculation (Supporting Table S4). The steatosis type was different between the groups, with mixed steatosis higher and macrovesicular steatosis lower in the extreme obesity group.

We then performed Cox proportional hazards analysis to identify risk factors associated with mortality in biopsy-proven NAFLD with extreme obesity. In both univariate and multivariate models, age, CAD and increased fibrosis stage with associated increased mortality, while dyslipidemia was associated with reduced mortality. T2DM, insulin use, hypertension, and BMI were not associated with mortality risk (Table 4).

DIAGNOSTIC UTILITY OF ABDOMINAL ULTRASOUND FOR HCC SURVEILLANCE

Current guidelines recommend abdominal ultrasound every 6 months for HCC surveillance in patients with cirrhosis. We hypothesized that the diagnostic accuracy and clinical utility of US scan may be affected by BMI, due to poor acoustic penetration related to body habitus. Of the 304 patients in the extreme obesity cohort, 255 (83.9%) patients underwent 850 US scans. Among these patients, 122 (47.8%) patients had at least one suboptimal US scan, while 205 (24.1%) scans were deemed to be inadequate for HCC surveillance. We also found that in 57 (46%) of these 122 patients, there was no subsequent cross-sectional imaging performed for HCC surveillance, while 65 patients underwent subsequent cross-sectional imaging, with only 16 undergoing two or more subsequent CT scans.

Highlighting the challenges associated with HCC surveillance in this population, 4 patients in the extreme obesity cohort developed HCC. Before the diagnosis of HCC, there was one compromised US in 3 patients, and two in the fourth patient. The maximum dimensions of the tumors were 2.1, 2.2, 2.5, and 5 cm, respectively, in the 4 patients. All four tumors were moderately differentiated HCC on targeted biopsy.

We also compared the differences in diagnostic utility of US for HCC surveillance between the propensity-matched BMI ≥50 and ≤40 kg/m^2 cohorts. The number of patients with at least one available US, as well as the total number of scans performed, were similar between the groups. In the BMI ≥50 kg/m^2 cohort, there was a significantly higher percentage of failed US scans and patients with at least one failed scan (both $P < 0.0001$; Table 5).

DIAGNOSTIC PERFORMANCE OF NONINVASIVE TOOLS FOR FIBROSIS ASSESSMENT

Noninvasive tools for fibrosis assessment, based on commonly measured clinical and laboratory

TABLE 5. DIAGNOSTIC UTILITY OF ABDOMINAL US SCAN FOR HCC SURVEILLANCE IN PROPENSITY-MATCHED COHORTS WITH BMI ≥50 KG/M^2 VERSUS ≤40 KG/M^2

Feature	All (n = 272)	BMI ≥ 50 kg/m^2 (n = 136)	BMI ≤ 40 kg/m^2 (n = 136)	*P*
Patients with at least one US performed, n (%)	239 (87.9%)	120 (88.2%)	119 (87.5%)	0.500
Patients with at least one failed US, n (%)	120 (86.3%)	53 (44.1%)	12 (10.1%)	<0.0001
Total number of US scans, n	875	468	407	0.0571
Failed US scans, n (%)	108 (12.3%)	93 (19.8%)	15 (3.9%)	<0.0001

TABLE 6. AUROC OF THE DIAGNOSTIC PERFORMANCE OF NONINVASIVE FIBROSIS SCORES BETWEEN THE HIGH BMI (≥50 KG/M^2) AND THE LOW BMI (≤40 KG/M^2) COHORTS

Characteristics	AUROC (95% CI) BMI ≥ 50 kg/m^2 (n = 136)	AUROC (95% CI) BMI ≤ 40 kg/m^2 (n = 136)	*P*
APRI	0.774 (0.688-0.860)	0.712 (0.622-0.802)	0.3327
NFS	0.796 (0.720-0.872)	0.868 (0.807-0.928)	0.1491
BARD	0.710 (0.623-0.797)	0.803 (0.731-0.874)	0.1081
FIB-4	0.8091 (0.731-0.887)	0.846 (0.778-0.913)	0.4899

parameters, have not been validated in patients with NAFLD with extreme obesity. We compared the diagnostic performance of four noninvasive fibrosis assessment tools, APRI, NFS, BARD and FIB-4, in the extreme obesity (BMI ≥ 50 kg/m^2) cohort with available liver biopsy to the propensity-matched cohort with lower BMI (≤ 40 kg/m^2). The diagnostic performance of FIB-4 was the best in the high BMI group, whereas NFS was superior in the low BMI group, but the differences in model performance were not statistically significant (Table 6).

We then used the area under the receiver operating characteristic curve (AUROC) data to obtain the optimal cutoffs of the four tools to optimize sensitivity and specificity. We found different optimal cutoffs between the high and low BMI cohorts, with APRI score cutoffs (0.382 vs. 0.688) (normal cutoff = 0.7), NFS (0.885 vs. –1.095; normal cutoff between –1.455 and 0.675), BARD (1.5 vs. 2.5; normal cutoff between 1 and 2), and FIB-4 (1.202 vs. 1.861; normal cutoff for age 35 to 64 = 1.3-2.67 and 2.0-2.67 for age ≥ 65) (Supporting Table S5).

NFS and FIB-4 have upper (high fibrosis stage, F3-F4) and lower cutoffs (low fibrosis stage, F0-F2), whereas APRI and BARD have only one cutoff, which discriminate between high (above the cutoff value) or low fibrosis stages (below the cutoff value).

After applying these reported cutoff values to our study population, we found that the upper cutoff value for NFS (NFS > 0.676) demonstrated high sensitivity and low specificity (80.49% and 62.26%, respectively) for the diagnosis of advanced fibrosis (F3-F4). Conversely, FIB-4 demonstrated moderate sensitivity and specificity (74.51% and 78.82%, respectively) when the lower cutoff value (FIB-4 <1.30) for the diagnosis of nonadvanced fibrosis (F0-F2) was applied to our study population (Table 7).

BMI is a component of NFS and BARD scores, but not FIB-4 and APRI, and the four tools incorporate different combinations of AST, ALT, INR, albumin, or platelets in their calculations. We compared these parameters in patients with low fibrosis (F0-F2) on liver biopsy stratified by BMI (>50 kg/m^2 vs. propensity matched ≤40 kg/m^2). ALT, AST, and albumin were higher in the low BMI cohort (Supporting Table S6). We also found significant differences in mean NFS score (0.222 [–0.217-0.662] vs. –1.682 [–1.999-1.365]; $P < 0.0001$] and percent patients with BARD 0-2 score between the high and low BMI cohorts (Fig. 1 and Supporting Table S6). In the high fibrosis cohort (F3-F4), we found no difference in biochemical parameters but the NFS scores were significantly different between them (2.216 [1.820-2.612] vs. 0.557 [0.198-0.913]; $P = 0.001$), and this was likely explained by differences in BMI (Fig. 1 and Supporting Table S7).

Discussion

We report several clinically relevant insights in a large cohort of patients with NAFLD and extreme obesity, a high-risk population with particular clinical challenges and limited data on optimum management

TABLE 7. SENSITIVITY AND SPECIFICITY FOR NONINVASIVE FIBROSIS SCORES APPLIED TO STUDY POPULATION

	BMI ≥ 50 kg/m^2	BMI ≤ 40 kg/m^2		BMI ≥ 50 kg/m^2	BMI ≤ 40 kg/m^2
NFS > 0.676			NFS < –1.455		
Sensitivity	80.49%	43.21%	Sensitivity	15.69%	61.82%
Specificity	62.26%	96.36%	Specificity	97.65%	88.89%
PPV	76.74%	94.59%	PPV	80.0%	79.07%
NPV	67.35%	53.54%	NPV	65.87%	77.42%
FIB-4 > 2.67			FIB-4 <1.30		
Sensitivity	41.18%	50.62%	Sensitivity	74.51%	58.18%
Specificity	90.20%	90.91%	Specificity	78.82%	88.89%
PPV	87.50%	89.13%	PPV	67.86%	78.05%
NPV	47.92%	55.56%	NPV	83.75%	75.79%
APRI > 1			BARD > 2		
Sensitivity	28.24%	40.74%	Sensitivity	89.41%	87.64%
Specificity	90.20%	83.64%	Specificity	43.14%	58.18%
PPV	82.76%	78.57%	PPV	72.38%	77.23%
NPV	42.99%	48.94%	NPV	70.97%	74.42%

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

strategies. First, cirrhosis and CAD are predictors of mortality, whereas dyslipidemia is associated with lower risk of death. Second, 50% of the patients with extreme obesity had cirrhosis and age, hypertension, and insulin use were the primary clinical factors associated with higher risk of cirrhosis in this cohort, while low albumin and platelet count were the main laboratory parameters associated with cirrhosis. Interestingly, higher BMI was associated with lower risk of cirrhosis. Third, noninvasive diagnostic tools for liver fibrosis assessment had different optimal cutoffs compared with a lower BMI cohort. Fourth, nearly a quarter of abdominal US scans performed for HCC surveillance were deemed suboptimal due to body habitus. Finally, in our cohort, weight-loss surgery did not have an effect on survival.

In patients with NAFLD, liver fibrosis is the strongest predictor of liver-related outcomes.[21] However, most patients with NAFLD do not have advanced fibrosis, and CAD is the most common cause of death.[22] In NAFLD with extreme obesity, presence of cirrhosis and CAD were predictive of increased mortality with hazard ratios of 7.3 and 3.1, respectively. Interestingly, dyslipidemia was associated with lower mortality risk in both the extreme obesity and lower BMI cohorts. Although dyslipidemia is a CAD risk factors, dyslipidemia may be a marker of preserved hepatic synthetic function and intact hepatic cholesterol synthesis. Furthermore, dyslipidemia may also be a surrogate marker for statin therapy, which may confer a survival advantage in both cirrhosis and coronary disease.[23]

Although we found that previous weight-loss surgery was not associated with either survival or cirrhosis in our cohort, our observations need to be interpreted with caution due to the possibility of selection bias. We could not compare the effect of weight-loss surgery in the propensity-matched cohorts because of few patients with previous weight-loss surgery. Due to our selection criteria, patients with prior extreme obesity who achieved BMI <50 kg/m^2 after weight-loss surgery were excluded from the study, which may have affected our results. It is possible that our follow-up period may not have been long enough to capture weight-loss surgery–related outcomes over a longer time course. There are also plausible biological explanations for our findings. Some studies have reported improvement in fatty liver and fibrosis after weight-loss surgery, while others have reported increased mortality with bariatric surgery in NASH.[24-26] Furthermore, bariatric surgery may not confer equal weight-reduction benefit in all patients and may increase mortality in some subgroups.[27,28] Finally, it is possible that in individuals with extreme obesity, weight-loss surgery may be less beneficial than in lower BMI individuals.[13] Given the limitations of our study design, further research is warranted to study the risks and benefits of weight-loss surgery in this high-risk population.

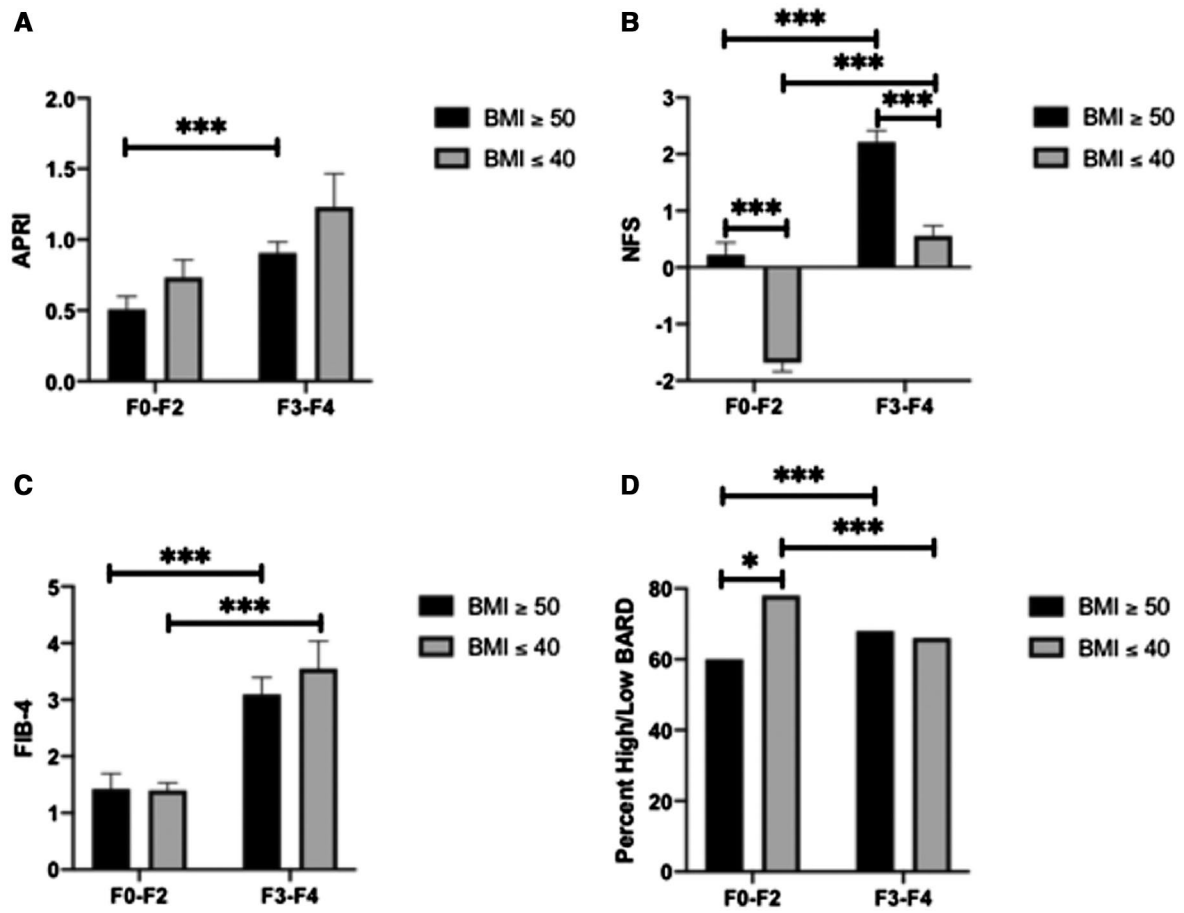

FIG. 1. Mean values of noninvasive fibrosis scores in patients with early (F0-F2) or advanced (F3-F4) fibrosis, stratified by BMI ≥50 or ≤40 kg/m^2. For APRI (A), NFS (B), and FIB-4 score (C), the means and SEM are depicted. For BARD score (D), proportions of patients with low (BARD 0-2) or high (BARD 3-4) scores are shown. *P < 0.05; **P < 0.01; ***P < 0.001.

An important observation in our study was the high prevalence of cirrhosis in the extreme obesity cohort, suggesting that clinicians should have a high index of suspicion for underlying liver disease during evaluation. Noninvasive assessment of liver fibrosis in patients with NAFLD and extreme obesity is a challenging problem in clinical practice, as previous studies have shown that high BMI is also associated with lowered diagnostic accuracy of imaging-based fibrosis assessment techniques.[29] When we applied laboratory-based fibrosis models to this population, we found that optimal NFS cutoffs in extreme obesity are different than in patients with less severe obesity. Previous studies have demonstrated diagnostic accuracy of NFS in ruling out advanced fibrosis in patients with severe obesity undergoing bariatric surgery, although the mean BMI of the cohorts were lower at 41 kg/m^2 and 48.2 kg/m^2, respectively.[2,30] NFS has high negative predictive value in ruling out advanced fibrosis with a lower cutoff of −1.455 and high positive predictive value in diagnosing advanced fibrosis with a high positive predictive value of 0.675.[16] However, we found that these optimum cutoffs for individuals with extreme obesity were 0.222 for the lower and 2.216 for the higher cutoff. In contrast, the optimum cutoff for FIB-4 of 1.4 for BMI >50 or <40 kg/m^2 were quite similar to the published cutoff of 1.45.[18] Additionally, we found that a FIB-4 cutoff of 3 would have high positive predictive value for advanced fibrosis, regardless of BMI.

Abdominal US is recommended for HCC screening in cirrhosis.[31] The high prevalence of cirrhosis in NAFLD with extreme obesity raises the question of diagnostic utility of abdominal US for HCC screening

in this population. A high percentage of US scans were deemed suboptimal by the interpreting radiologist for the evaluation of hepatic lesions, as nearly 25% of scans were compromised due to body habitus, and almost half of the patients had at least one suboptimal study. The American College of Radiology recently proposed standardized guidelines on interpretation, reporting, and management recommendations for US-based HCC screening.[32] All US scans in our study population predated the publication of these guidelines, and limitation of US and optimum strategies for HCC surveillance in this population will require further research.

Weight-loss surgery is currently the most effective treatment for severe obesity, associated with the highest degrees of weight loss and durability of effect.[33] In our cohort with a mean BMI of 55 kg/m^2, we found low rates of weight-loss surgery, with 15% of patients with previous surgery for Roux-en-Y, sleeve gastrectomy, or laparoscopic gastric band. We identified a particular management challenge in this population, the finding of cirrhosis or portal hypertension during weight-loss surgery. Fourteen (23.3%) patients of the 60 scheduled for bariatric surgery had their surgery aborted due to intraoperative findings of cirrhosis and/or portal hypertension. Thus, the risk of undiagnosed underlying cirrhosis combined with the challenges of noninvasive assessment of liver fibrosis in NAFLD with extreme obesity make it imperative to define optimum screening strategies for advanced fibrosis/cirrhosis. Noninvasive imaging-based modalities have yet to be validated in populations with such high BMI ranges, but our study provides clinicians with additional insights to effective-use biochemistry-based calculators for fibrosis staging.

This study has many strengths. Our cohort included a large number of well-phenotyped patients with a high percentage of liver biopsies (44.7%) in an era of noninvasive testing for liver fibrosis. This allowed for better assessment of the performance of fibrosis scores. We also used a propensity-matched cohort with available liver biopsies and confirmed NAFLD diagnosis. This study also has some limitations. It is a single-center and retrospective study, with the inherent limitations of retrospective analyses. Selection bias at the time of biopsy is a possibility. NAFLD is a slowly progressive disease and patients were followed for 4.5 years, which may have missed more complications that may manifest later in the course of the disease. Our definition of CAD was consistent with established, advanced heart disease and may not have accounted for mild to moderate CAD or unstable angina on outcomes. Finally, our study design precluded studying the true long-term effect of the degree of metabolic control (i.e., poorly vs. well-controlled metabolic risk factors), and as discussed previously, the potential benefits of weight-loss surgery in this population.

In conclusion, we highlight several important clinical challenges in the management of NAFLD with extreme obesity and define optimal parameters for noninvasive assessment of liver fibrosis, which has immediate clinical relevance for the management of this population.

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