Mortality Risk Detected by Atherosclerotic Cardiovascular Disease Score in Patients With Nonalcoholic Fatty Liver Disease

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Cardiovascular diseases (CVDs) are the leading cause of mortality in patients with nonalcoholic fatty liver disease (NAFLD). Our aim was to assess the association of atherosclerotic cardiovascular disease (ASCVD) risk scores with overall and cardiac-specific mortality among patients with NAFLD. We used the National Health and Nutrition Examination Survey III with the National Death Index-linked mortality files. NAFLD was defined by ultrasound as presence of steatosis in the absence of secondary causes of liver disease. High risk for CVD was defined as a 10-year ASCVD score ≥7.5%. Hazard ratios (HRs) and population-attributable fractions (PAFs) of high risk for CVD were calculated. Among 1,262 subjects with NAFLD (47.9% men; 41.2% white; mean age, 56.3 years), the prevalence of high risk for CVD was 55.9% and 4.8% had advanced fibrosis. After a median follow-up of 17.7 years, 482 subjects (38.2%) died of overall causes, of whom 382 (79.3%) had a high risk for CVD. The unadjusted overall and cardiac-specific mortality were higher for patients with NAFLD who had a high risk for CVD compared to subjects with NAFLD with a low risk for CVD (57.3% vs. 16.8% for overall mortality; 16.4% vs. 3.5% for cardiovascular mortality). After controlling for risk factors associated with mortality, high risk for CVD was associated with a 42% higher overall mortality rate (adjusted HR [aHR], 1.42; 95% confidence interval [CI], 1.05-1.91) and twice the risk of cardiovascular mortality (aHR, 2.02; 95% CI, 1.12-3.65). Adjusted PAFs were 11.4% for overall mortality and 44.9% for cardiovascular mortality. *Conclusion:* Among patients with NAFLD, ASCVD score ≥7.5% was associated with a higher risk of overall and cardiac-specific mortality. (*Hepatology Communications* 2019;3:1050-1060).

The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing worldwide, and NAFLD is now considered to be the most common cause of chronic liver disease in many developed countries.[1,2] Diagnosis of NAFLD is made by the presence of hepatic steatosis on histology or imaging in the absence of other causes of fatty liver or chronic liver disease.[3]

The rising prevalence of NAFLD is linked to the alarming rise in obesity, insulin resistance, and diabetes mellitus.[4,5] These factors are common risk factors for both NAFLD and cardiovascular disease (CVD). Therefore, not surprisingly, there is a higher prevalence of CVD among individuals with NAFLD compared to those without NAFLD, and CVD is a leading cause of mortality in individuals with

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; aHR, adjusted hazard ratio; ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; FRS, Framingham Risk Score; HDL, high-density lipoprotein; HL, hyperlipidemia; HR, hazard ratio; HTN, hypertension; IDI, integrated discrimination improvement; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NFS, nonalcoholic fatty liver disease fibrosis score; NHANES, National Health and Nutrition Examination Survey; NRI, net reclassification improvement; PAF, population-attributable fraction; T2DM, type 2 diabetes mellitus.

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NAFLD.[6,7] In this context, an emerging body of literature suggests there is a strong association between NAFLD and a broad spectrum of CVDs, including premature atherosclerotic heart disease,[8,9] left ventricular cardiac dysfunction,[10] and atrial fibrillation.[11] In fact, evidence suggests that NAFLD may be actively involved in the pathogenesis of CVD, independent of features of metabolic syndrome (MS).[12,13]

Although there is growing recognition that NAFLD is becoming the most commonly encountered liver disease in clinical practice, there is a paucity of data to guide clinicians in how to risk stratify these patients regarding their future risk for CVD.[14-16] One widely used predictive risk score for CVD is the Framingham Risk Score (FRS), which estimates the sex-specific 10-year risk of coronary heart disease in adults without known CVD, based on age, smoking status, diabetes, total cholesterol, high-density lipoprotein (HDL), and blood pressure.[8,17,18] Although the FRS has been widely adopted in both research and clinical practice, it is also known to have limitations, such as being derived from data exclusively obtained from a white middle-class population, overestimating the absolute coronary risk for other races.[18] In this context, the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force has released a new guideline with a revised assessment tool to estimate the 10-year lifetime risk for developing atherosclerotic cardiovascular disease (ASCVD).[19] The 2013 ACC/AHA guidelines identified a 10-year risk of ASCVD ≥7.5% as a threshold for initiating statin therapy. In the 2018 guide,[20] a 10-year risk for CVD is categorized as low-risk (<5%), borderline risk (5% to <7.5%), intermediate risk (7.5% to <20%), and high risk (≥20%). In a recent study from South Korea, there was a correlation between the severity of hepatic steatosis and risk of CVD as calculated by the ASCVD score.[21] In our study, the aim is to determine if high ASCVD scores are associated with increased overall and CVD mortality among individuals with NAFLD.

Participants and Methods

DATA SOURCE AND POPULATION

The study cohorts were identified from the National Health and Nutrition Examination Survey III (NHANES III) (1988-1994) database, which examined the health and nutritional status of a nationally representative sample of approximately 34,000 participants in the United States.[22] From 1988 through 1994, the data were compiled through household interviews, physical examinations, and laboratory assays on collected blood and urine specimens to assess the prevalence of disease, disease risk factors, and nutritional status of the civilian noninstitutionalized U.S. population by use of a multistage stratified sampling design. The inclusion criteria for the current analyses were chosen to match the study cohort used in the development of the ASCVD risk score (ACC/AHA). We restricted the analysis to adults with NAFLD aged 40 to 74 years without a history of CVD. The initial cohort included 19,172 adults in NHANES III, and 17,367 (90.6%) attended an examination at a mobile examination center. We excluded 6,880 participants due to blood draws without an 8-hour fasting period; 259 who had positive results for hepatitis B surface antigen or hepatitis C antibody; 406 who had a transferrin saturation >50%; 1,742 who were ineligible for an ultrasound examination due to age older than 75 years or younger than 20 years; 443 who had an ultrasound that was ungradable or missing; and

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650 with significant alcohol consumption (≥20 g per day for men and ≥10 g per day for women). We also excluded 3,356 participants who were not applicable for the ASCVD risk score due to age younger than 40 years; 107 participants with missing data on one or more components of the ASCVD risk score; and 2,092 participants without NAFLD. After those with previous self-reported CVD were excluded, 1,262 participants with NAFLD were available for analysis.

BASELINE CHARACTERISTICS AND DEFINITIONS

The following parameters were obtained at baseline: age (years); race/ethnicity (Native Americans, non-Hispanic white, non-Hispanic black, Hispanic, or other race, which included Asian); sex; history of smoking and alcohol consumption; self-reported history of CVD and cancer; self-reported medication use for diabetes, hypertension (HTN), and hyperlipidemia (HL); body mass index (BMI); albumin (g/dL); alanine aminotransferase (ALT, U/L); aspartate aminotransferase (AST, U/L); transferrin saturation (%); platelet count (1,000 cell/μL); gamma-glutamyl transpeptidase (U/L); creatinine (mg/dL); fasting glucose (g/dL); fasting insulin (μlU/mL); triglycerides (mg/dL); total cholesterol (mg/dL); HDL (mg/dL); low-density lipoprotein (LDL, mg/dL); hemoglobin A1c (HbA1c); and viral hepatitis serology.

DIAGNOSIS OF NAFLD

NAFLD was identified by the presence of mild, moderate, or severe hepatic steatosis on ultrasound (hepatic ultrasound video images using the Toshiba Sonolayer SSA-90A and Toshiba video recorders; detailed information on methodology and quality control are described elsewhere[23]) in the absence of other causes of chronic liver disease (alcohol consumption <20 g/day for male participants and <10 g/day for female participants, hepatitis B surface antigen negative, anti-hepatitis C virus antibody negative, transferrin saturation <50%).

HIGH RISK FOR CVD BY ASCVD RISK SCORE

The 10-year risk for developing ASCVD was calculated from the ASCVD risk score (ACC/AHA) with each participant's age, race, sex, smoking status, presence of diabetes, systolic blood pressure, antihypertensive medication, serum cholesterol, and HDL levels. In this study, individuals with a 10-year ASCVD risk score of ≥7.5% were referred to as high risk for CVD.[19]

ADVANCED FIBROSIS BY NAFLD FIBROSIS SCORE

Because liver biopsies are not available for NHANES data sets, we used a previously validated noninvasive test, the NAFLD fibrosis score (NFS),[24] to establish the presence of advanced fibrosis. NFS was calculated with age, BMI, diabetes status, AST to ALT ratio, serum albumin, and platelet count. Subjects with NAFLD meeting NFS >0.676 were considered to have NAFLD with advanced fibrosis.

OTHER DEFINITIONS

Chronic kidney disease (CKD) was defined as a glomerular filtration rate, estimated by the CKD Epidemiology Collaboration equation, of ≤60 mL/minute/1.73 m^2 or urinary albumin-to-creatinine ratio ≥30 mg/g.[25] Obesity was defined as individuals with BMI ≥30 kg/m^2. Type 2 diabetes mellitus (T2DM) was defined by a fasting glucose level ≥126 mg/dL, self-reported medical history of diabetes, oral hypoglycemic agents, insulin use, or HbA1c ≥6.5%. HTN was defined by a systolic blood pressure measure ≥130 mm Hg or diastolic blood pressure measurement ≥80 mm Hg from an average of three measurements or history of high blood pressure measurements.[26] HL was defined by either a serum cholesterol level ≥200 mg/dL, LDL level ≥130 mg/dL, HDL level ≥40 mg/dL for men and ≥50 for women, or history of HL. MS was defined as having at least three of the following: waist circumference ≥102 cm among men or ≥88 cm among women, fasting plasma glucose ≥100 mg/dL, blood pressure >130/85 mm Hg, triglycerides >150 mg/dL, and HDL ≤40 mg/dL among men or ≤50 mg/dL among women.[27]

MORTALITY FOLLOW-UP

Mortality status for NHANES III participants was available as of December 31, 2015, by considering a probabilistic match between NHANES III and the

National Death Index death certificate records.[28] The 2015 public-use-linked mortality files were available at the Centers for Disease Control and Prevention website (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm). Follow-up years, overall death, and cardiac-specific deaths were collected.[29] For cardiac-specific mortality analysis, follow-up continued until death attributable to CVD, with censoring at the time of death due to causes other than CVD. Participants who did not have any death records were presumed alive through the follow-up period. Because NHANES III was completed over 6 years, time to death was counted from baseline to date of death or 21 years of follow-up, whichever came first.

DATA ANALYSIS

Subjects with NAFLD were categorized into two groups according to their ASCVD risk score of <7.5% and ≥7.5%. NAFLD characteristics, including components of ASCVD risk score and NFS, overall, and cardio-specific mortality, were calculated within each ASCVD risk group. Differences between groups were tested using the chi-square or Kruskal-Wallis test. Age-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality to examine baseline risk factors significantly associated with the end point. Risk factors significantly associated with mortality by using bidirectional stepwise selection (significance level for entry, 0.2; for stay, 0.05) were added to final Cox models calculating HRs and population-attributable fraction (PAF), an estimate of the percentage of mortality that would be reduced or avoided if the specific risk factors were removed under the assumption of a causal relationship.[30] Cardiac-specific cause mortality risks were estimated using a competing risk analysis. Mortality resulting from other causes was treated as a competing risk. The proportional hazards assumption of the Cox models was examined by testing time-dependent covariates, [31] which showed no significant departure from proportionality over time. To assess the reliability and predictive accuracy of our Cox models, calibration and discrimination were considered. Calibration noted the model's ability to correctly rank the subjects by risk. Discrimination referred to the power of the model to correctly classify subjects for their actual outcomes. To measure discrimination, an extended Hosmer-Lemeshow statistical test for survival models was conducted. A χ^2 value of ≥20 or $P < 0.05$ indicates poor calibration. As a discrimination measure, the Harrell C statistic of survival models by bootstrapping with 1,000 replications [32] was calculated. A C statistic value >0.7 indicated a good model and >0.8 indicated a strong model.[33]

As a sensitivity analysis, we tested a round of ASCVD risk score rule-in thresholds to determine the value returning the best possible association with mortality. We also evaluated clinical reclassification of the Cox model with an ASCVD risk score of 10.0% over the model with the current threshold of 7.5%, as described for survival models.[34] The continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were also reported. NRI measures the net number of subjects reclassified correctly using the new model over the current model. IDI measures an improvement of the new model in average sensitivity without sacrificing average specificity.

All analyses were performed without applying sampling weights and stratified design as recommended for NHANES data. [22] As a result, the findings of the current study should not be generalizable to the U.S. population. We used SAS software, version 9.4 (SAS Institute, Cary, NC), and $P < 0.05$ was considered significant.

Results

CHARACTERISTICS OF NAFLD COHORTS ACCORDING TO ASCVD STATUS

Of 19,172 adults in NHANES III, the final cohort included 1,262 participants with NAFLD. Differences in patient demographics and comorbidities of patients with NAFLD overall and ASCVD risk group are summarized in Table 1. Of 1,262 patients with NAFLD, 47.9% were men, 41.2% were white, and mean age was 56.3 years. Prevalence of high risk for CVD was 55.9% among patients with NAFLD, and 4.8% had advanced fibrosis. Patients with NAFLD with a high risk for CVD were substantially older (62.9 vs. 48.8 years), more likely to be male individuals (61.2% vs. 32.9%), non-Hispanic black (23.7% vs. 17.1%), current smokers (27.6% vs. 12.8%), and taking an antihypertensive medication (37.2% vs. 10.6%)

TABLE 1. CHARACTERISTICS OF ADULTS AGED 40-74 WITH NAFLD IN NHANES III, UNITED STATES, 1988-1994

Variables	NAFLD	Atherosclerotic Cardiovascular Disease Risk Score		*P* Value
		NAFLD With Low Risk for CVD	NAFLD With High Risk‡ for CVD	
Participants, n (%)	1,262	595 (47.15%)	667 (52.85%)	
Age, mean ± SD*†	56.25 ± 10.33	48.84 ± 6.93	62.86 ± 8.14	<0.0001
Male, n (%)*	604 (47.86%)	196 (32.94%)	408 (61.17%)	<0.0001
Race, n (%)				
non-Hispanic white	520 (41.20%)	234 (39.33%)	286 (42.88%)	0.2008
non-Hispanic black*	260 (20.60%)	102 (17.14%)	158 (23.69%)	0.0041
Hispanic	468 (37.08%)	248 (41.68%)	220 (32.98%)	0.0014
BMI, mean ± SD†	30.06 ± 5.96	30.24 ± 6.50	29.90 ± 5.42	0.6508
Current smoker, n (%)*	260 (20.60%)	76 (12.77%)	184 (27.59%)	<0.0001
Metabolic components, %				
HT	843 (66.80%)	295 (49.58%)	548 (82.16%)	<0.0001
HL	1,078 (85.42%)	488 (82.02%)	590 (88.46%)	0.0012
Diabetes*†	293 (23.22%)	73 (12.27%)	220 (32.98%)	<0.0001
MS	746 (59.11%)	268 (45.04%)	478 (71.66%)	<0.0001
Antihypertensive medication, n (%)*	311 (24.64%)	63 (10.59%)	248 (37.18%)	<0.0001
History of cancer, n (%)	94 (7.45%)	29 (4.87%)	65 (9.75%)	0.0010
Advanced fibrosis, n (%)§	73 (5.90%)	12 (2.05%)	61 (9.36%)	<0.0001
CKD, n (%)‖	201 (16.20%)	49 (8.35%)	152 (23.24%)	<0.0001
Laboratory parameters, mean ± SD				
Albumin (g/dL)†	4.08 ± 0.34	4.08 ± 0.34	4.08 ± 0.34	0.8292
AST (U/L)†	22.44 ± 10.89	22.81 ± 12.42	22.12 ± 9.31	0.5066
ALT (U/L)†	19.74 ± 13.72	21.12 ± 15.93	18.50 ± 11.25	0.0060
Total cholesterol(mg/dL)*	218.53 ± 42.81	211.53 ± 39.57	224.78 ± 44.62	<0.0001
HDL cholesterol (mg/dL)*	47.04 ± 14.39	49.26 ± 14.64	45.06 ± 13.87	<0.0001
Systolic blood pressure average*	132.02 ± 18.47	122.96 ± 14.09	140.10 ± 18.17	<0.0001
Platelet count (1,000 cells/μL)†	276.58 ± 70.76	288.34 ± 71.39	266.07 ± 68.55	<0.0001
Mortality data				
Overall deaths, n (%)	482 (38.22%)	100 (16.84%)	382 (57.27%)	<0.0001
Cardiac-specific deaths, n (%)	130 (10.33%)	21 (3.54%)	109 (16.39%)	<0.0001
Cancer deaths, n (%)	132 (10.46%)	43 (7.35%)	89 (13.97%)	0.0002

*Components of ASCVD risk score equation.
†Components of NFS equation.
‡High risk for CVD is defined as a 10-year ASCVD risk score ≥7.5%.
§Advanced fibrosis is defined as an NFS score ≥0.676.
‖CKD is defined as an estimated glomerular filtration rate ≤60 mL/minute/1.73 m^2 or a urinary albumin-to-creatinine ratio ≥30 mg/g.

compared to patients with NAFLD with a lower risk for CVD. As expected, patients with NAFLD with a high risk for CVD had significantly higher rates of MS and its components (obesity, T2DM, HTN, and HL) in comparison to patients with NAFLD but without a high risk for CVD. Additionally, patients with NAFLD with a high risk for CVD had a substantially higher prevalence of advanced hepatic fibrosis, CKD, and history of cancer. Characteristics of NAFLD within the four ASCVD risk groups (low, borderline, intermediate, and high risk) are also reported in Supporting Table S1.

RISK FACTORS OF OVERALL AND CARDIAC-SPECIFIC MORTALITY AMONG NAFLD COHORTS

After a median follow-up of 17.7 years in the NAFLD cohort, 482 (38.2%) died of overall causes, of whom 382 (79.3%) had a high risk of CVD. Of

decedents, 130 (27.0%) deaths were from cardiac-specific causes. The unadjusted overall and cardiac-specific mortality were higher for those with high risk for CVD compared to those with a low risk for CVD (57.3% vs. 16.8% for overall; 16.4% vs. 3.5% for cardiac-specific mortality). Although cardiac causes were the leading etiology for mortality in patients with a high risk for CVD, cancer-related death was the leading cause of mortality in patients with a low risk for CVD. Estimated HRs and PAFs of each risk factor for overall and cardiac-specific mortality are shown in Tables 2 and 3. The analyses using a new threshold ASCVD risk score of 10.0% for both overall and cardiac mortality are also reported in Tables 4 and 5.

OVERALL MORTALITY

After controlling for risk factors that are closely associated with mortality, the increased risk of overall mortality was independently associated with having a high risk for CVD (adjusted HR [aHR], 1.42; 95% CI, 1.05-1.91), advanced fibrosis (aHR, 1.49; 95% CI, 1.09-2.02), CKD (aHR, 1.88; 95% CI, 1.52-2.31), current smoking (aHR, 1.64; 95% CI, 1.32-2.05), and T2DM (aHR, 1.32; 95% CI, 1.07-1.63). The highest adjusted PAFs on overall mortality were 16.1% for CKD, followed by 11.4% for high risk for CVD, 11.1% for current smoking, 8.5% for T2DM, and 5.0% for advanced fibrosis.

CARDIAC-SPECIFIC MORTALITY

After controlling for risk factors closely associated with cardiac-specific mortality, the multivariable Cox model indicated that the increased risk for cardiac-specific mortality was independently associated with a high risk for CVD (aHR, 2.02; 95% CI, 1.12-3.65) and CKD (aHR, 2.82; 95% CI, 1.95-4.08). The highest adjusted PAFs on cardiac-specific mortality were 44.9% for having a high risk for CVD and 28.7% for CKD. Notably, among patients with NAFLD with a high risk for CVD, cardiac-specific mortality in patients with advanced fibrosis was not significantly different from patients without advanced fibrosis (23.0% vs. 16.1%; P = 0.175) (Supporting Table S2). Along with this, advanced fibrosis was not associated with a high risk of cardiac-specific death.

TABLE 2. ADJUSTED HRs AND PAFs OF INDEPENDENT RISK FACTORS ON OVERALL MORTALITY AMONG ADULTS AGED 40-74 WITH NAFLD

		Hazard Ratio* (95% CI)		
Risk Factors	Cases/Subjects	Age Adjusted	Fully Adjusted†	Adjusted PAF† (%)
High risk for CVD‡				
No	100/594	1.00 (Reference)	1.00 (Reference)	11.4%
Yes	382/667	1.925 (1.463-2.534)	1.417 (1.05-1.912)	
Advanced fibrosis§				
No	414/1,163	1.00 (Reference)	1.00 (Reference)	5.0%
Yes	55/73	1.933 (1.448-2.58)	1.486 (1.094-2.019)	
CKD‖				
No	335/1,039	1.00 (Reference)	1.00 (Reference)	16.1%
Yes	134/201	2.058 (1.68-2.523)	1.876 (1.523-2.312)	
Current smoking				
No	360/1,001	1.00 (Reference)	1.00 (Reference)	11.1%
Yes	122/260	1.842 (1.497-2.266)	1.642 (1.315-2.051)	
Diabetes				
No	331/969	1.00 (Reference)	1.00 (Reference)	8.5%
Yes	151/292	1.562 (1.288-1.894)	1.316 (1.065-1.626)	

*Cox models were used.
†Adjusted for age, current smoking status, diabetes, kidney disease, advanced fibrosis, and high risk for CVD.
‡High risk for CVD is defined as a 10-year ASCVD risk score ≥7.5%.
§Advanced fibrosis is defined as an NFS score ≥0.676.
‖CKD is defined as an estimated glomerular filtration rate ≤60 mL/minute/1.73 m^2 or a urinary albumin-to-creatinine ratio ≥30 mg/g.

TABLE 3. ADJUSTED HRs AND PAFs OF INDEPENDENT RISK FACTORS ON CARDIAC-SPECIFIC MORTALITY AMONG ADULTS AGED 40-74 WITH NAFLD

Risk Factors	Cases/Subjects	Hazard Ratio* (95% CI)		Adjusted PAF† (%)
		Age Adjusted	Fully Adjusted†	
High risk for CVD‡				
No	21/593	1.00 (Reference)	1.00 (Reference)	44.9%
Yes	109/665	2.239 (1.269-3.952)	2.018 (1.117-3.646)	
CKD§				
No	78/1,036	1.00 (Reference)	1.00 (Reference)	28.7%
Yes	47/201	2.987 (2.067-4.318)	2.820 (1.949-4.080)	

*Cox models were used.
†Adjusted for age, kidney disease, and high risk for CVD.
‡High risk for CVD is defined as a 10-year ASCVD risk score ≥7.5%.
§CKD is defined as an estimated glomerular filtration rate ≤60 mL/minute/1.73 m^2 or a urinary albumin-to-creatinine ratio ≥30 mg/g.

TABLE 4. ADJUSTED HRs AND PAFs OF INDEPENDENT RISK FACTORS ON OVERALL MORTALITY AMONG ADULTS AGED 40-74 WITH NAFLD (BEST THRESHOLD HIGH RISK FOR CVD OF 10.0%)

Risk Factors	Cases/Subjects	Hazard Ratio* (95% CI)		Adjusted PAF† (%)
		Age Adjusted	Fully Adjusted†	
High risk for CVD (best threshold of 10.0%)‡				
No	136/715	1.00 (Reference)	1.00 (Reference)	31.9%
Yes	346/546	2.165 (1.683-2.785)	1.656 (1.254-2.185)	
Advanced fibrosis§				
No	414/1,163	1.00 (Reference)	1.00 (Reference)	5.5%
Yes	55/73	1.933 (1.448-2.58)	1.517 (1.116-2.062)	
CKD‖				
No	335/1,039	1.00 (Reference)	1.00 (Reference)	16.1%
Yes	134/201	2.058 (1.68-2.523)	1.826 (1.482-2.25)	
Current smoking				
No	360/1,001	1.00 (Reference)	1.00 (Reference)	10.5%
Yes	122/260	1.842 (1.497-2.266)	1.589 (1.274-1.982)	
Diabetes				
No	331/969	1.00 (Reference)	1.00 (Reference)	7.4%
Yes	151/292	1.562 (1.288-1.894)	1.253 (1.012-1.551)	

*Cox models were used.
†Adjusted for age, current smoking status, diabetes, kidney disease, advanced fibrosis, and high risk for CVD.
‡High risk for CVD is defined as a 10-year ASCVD risk score ≥10.0%.
§Advanced fibrosis is defined as an NFS score ≥0.676.
‖CKD is defined as an estimated glomerular filtration rate ≤60 mL/minute/1.73 m^2 or a urinary albumin-to-creatinine ratio ≥30 mg/g.

VALIDATION OF THE NEW THRESHOLD ASCVD RISK SCORE ON MORTALITY

Sensitivity analysis showed the best association of high risk for CVD (ASCVD score ≥10.0%) with mortality was higher (aHR, 1.66; 95% CI, 1.25-2.19; PAF, 31.9% for overall mortality and aHR, 3.27; 95% CI, 1.88-5.70; PAF, 60.6% for cardiac-specific mortality). The comparison of the Hosmer-Lemeshow χ^2 and C statistic between Cox models with the current threshold of 7.5% and the new threshold of 10.0% is summarized in Table 6. For overall deaths, χ^2 indicated good calibration with both models (χ^2 = 9.41 and P = 0.49 for the new threshold; χ^2 = 8.63 and P = 0.57 for the current threshold). Additionally, no difference

TABLE 5. ADJUSTED HRs AND PAFs OF INDEPENDENT RISK FACTORS ON CARDIAC-SPECIFIC MORTALITY AMONG ADULTS AGED 40-74 WITH NAFLD (BEST THRESHOLD HIGH RISK FOR CVD OF 10.0%)

Risk Factors	Cases/Subjects	Hazard Ratio* (95% CI)		Adjusted PAF† (%)
		Age Adjusted	Fully Adjusted†	
High risk for CVD (Best threshold of 10.0%)‡				
No	25/714	1.00 (Reference)	1.00 (Reference)	60.6%
Yes	105/544	3.503 (2.057-5.968)	3.269 (1.876-5.697)	
CKD§				
No	78/1,036	1.00 (Reference)	1.00 (Reference)	27.3%
Yes	47/201	2.987 (2.067-4.318)	2.607 (1.801-3.773)	

*Cox models were used.
†Adjusted for age, kidney disease, and high risk for CVD.
‡High risk for CVD is defined as a 10-year ASCVD risk score ≥10.0%.
§CKD is defined as an estimated glomerular filtration rate ≤60 mL/minute/1.73 m^2 or a urinary albumin-to-creatinine ratio ≥30 mg/g.

TABLE 6. SUMMARY OF PERFORMANCE OF COX MODELS WITH DIFFERENT THRESHOLDS OF ASCVD RISK SCORE

	Hosmer-Lemeshow χ^2 (*P* Value)	C Statistic (95% CI)	NRI, Total (Events/Nonevents), %	IDI %, Absolute (Relative)
Overall deaths				
Model* (threshold of 7.5%)	8.63 (0.567)	0.755 (0.730-0.778)	Reference	Reference
Model* (threshold of 10.0%)	9.41 (0.493)	0.757 (0.732-0.782)	12 (52/–40)	1 (4)
Cardiac-specific deaths				
Model† (threshold of 7.5%)	3.19 (0.922)	0.790 (0.749-0.831)	Reference	Reference
Model† (threshold of 10.0%)	2.41 (0.966)	0.799 (0.760-0.838)	52 (56/–4)	2 (9)

*Adjusted for age, current smoking status, diabetes, kidney disease, advanced fibrosis, and high risk for CVD.
†Adjusted for age, kidney disease, and high risk for CVD.

was found in the C statistics of different thresholds, with values of 0.757 (95% CI, 0.732-0.782) for the new threshold and 0.755 (95% CI, 0.730-0.778) for the current threshold. We found improvements in the model using the new threshold over the current one. The NRI was 12% (event NRI, 52%; nonevent NRI, –40%) for overall deaths and 52% (event NRI, 56%; nonevent NRI, –4%) for cardiac-specific deaths. The absolute and relative IDI indexes were 1% and 4%, respectively, for overall death and 2% and 9%, respectively, for cardiac-specific deaths.

Discussion

In this study, we used a population-based database to explore the overall and cardiac-specific mortality in a large cohort of adult subjects with NAFLD. Our data showed that both overall and cardiac-specific mortality were significantly higher among patients with NAFLD with an ASCVD score of ≥7.5%, which indicates a high risk for CVD over the next 10 years. In this context, we compared patients with NAFLD with a high risk for CVD to patients with NAFLD without a high risk for CVD (NAFLD with ASCVD ≥7.5% vs. NAFLD without ASCVD ≥7.5%) and demonstrated that the presence of ASCVD ≥7.5% was associated with an almost 3 times higher risk for cardiac-specific mortality. Furthermore, elimination of this high risk for CVD in subjects with NAFLD would result in a 61% lower cardiac-specific mortality risk. This is important and highly relevant because cardiovascular mortality is the main cause of death among NAFLD; these changes in ASCVD risk scores could therefore have substantial cardiac benefits to these patients. [35]

Risk assessment for CVD has been undertaken using a number of scores, such as ASCVD score and FRS.[8,36,37] In previous studies, FRS has been associated with severity of steatosis and noninvasive markers of fibrosis (NFS) but not with mortality in NAFLD.[38] Given the limitation of FRS, ACC/AHA has developed the ASCVD risk score as a comprehensive tool to assess 10-year and lifetime risk for cardiovascular events.[39] In this context, our study confirms the value of the ASCVD score in patients with NAFLD. In fact, among patients with NAFLD, those with ASCVD ≥7.5% are not only at a higher risk for cardiac-specific mortality but also for a higher risk for overall mortality. These data provide a simple noninvasive method to determine which patients with NAFLD are at the greatest risk for cardiovascular mortality and overall mortality. In this context, these individuals can be approached clinically to optimize the management of their cardiovascular risks and potentially lower their future risk for cardiovascular mortality.

In addition, we used NFS to establish any association between a high risk for CVD (ASCVD score ≥7.5%) and advanced fibrosis. As expected, patients with NAFLD with ASCVD ≥7.5% also showed significantly higher rates of advanced hepatic fibrosis. More importantly, among patients with an ASCVD ≥7.5%, presence of advanced fibrosis also had a significant impact on overall mortality. In fact, patients with NAFLD with both ASCVD ≥7.5% and advanced fibrosis had the highest risk for overall mortality. In contrast, this observation was not true for cardiac-specific mortality. One possible explanation for this finding is that patients with ASCVD ≥7.5% already have an increased risk for cardiac-specific mortality and so the presence of advanced fibrosis does not seem to add additional risks. Our finding is supported by a recent study by Hagstrom et al.[40], which evaluated liver histology and traditional cardiovascular risk factors as a predictor of CVD outcomes in patients with biopsy-proven NAFLD. This study concluded that when CVD risk factors were taken into account, the presence of nonalcoholic steatohepatitis or advanced fibrosis was not associated with incident CVD risk in patients with NAFLD. However, further studies assessing the association of severity of hepatic fibrosis with CVD risk are needed.

It is important to emphasize several important findings of this study. First, to our knowledge, there have been no other studies that determined the association of ASCVD risk score with mortality in patients with NAFLD. Additionally, this study provides a unique opportunity to assess the interaction of ASCVD scores with noninvasive fibrosis scores in NAFLD and their combined effect on mortality.

On the other hand, our study does have several limitations. First, we were only able to establish the diagnosis of NAFLD by ultrasound and not nonalcoholic steatohepatitis, which requires histologic confirmation. Also, ASCVD risk score was developed in 2013 and its accuracy and applicability in different populations are still being established.[41] Although the ASCVD risk score aims to improve generalizability among multiethnic populations, its applicability outside of the United States also needs to be established.[42] Finally, one caveat of NHANES III is the oversampling of Mexican Americans, which is limiting the generalizability of our findings to other race/ethnicity groups because the progression rates in chronic liver diseases vary among different ethnicities.[43,44] The association of ASCVD risk score with liver-related mortality was not evaluated because of the unavailability of specific cause of death in the public-use mortality files.

In summary, NAFLD is highly prevalent, with a proportion of these patients developing liver disease.[1-4,42,45-50] On the other hand, cardiovascular mortality is the main cause of death in NAFLD, and predictive models, such as ASCVD risk score, can provide an easy tool to identify patients with NAFLD who are at the greatest risk for CVD. This can lead to the ability to potentially modify these risks and possibly change their long-term cardiovascular outcomes.

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