ORIGINAL ARTICLE

Risk factors for cardiovascular disease among individuals with hepatic steatosis

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Abstract

Cardiovascular disease (CVD) is the leading cause of mortality in adults with hepatic steatosis (HS). However, risk factors for CVD in HS are unknown. We aimed to identify factors associated with coronary artery disease (CAD) and incident major adverse cardiovascular events (MACE) in individuals with HS. We performed a nested cohort study of adults with HS detected on coronary computed tomography in the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) trial. Obstructive CAD was defined as ≥50% coronary stenosis. MACE included hospitalization for unstable angina, nonfatal myocardial infarction, or all-cause death. Multivariate modeling, adjusted for age, sex, atherosclerotic CVD (ASCVD) risk score and body mass index, identified factors associated with obstructive CAD. Cox regression, adjusted for ASCVD risk score, determined the predictors of MACE. A total of 959 of 3,756 (mean age 59.4 years, 55.0% men) had HS. Obstructive CAD was present in 15.2% (145 of 959). Male sex (adjusted odds ratio [aOR] = 1.83, 95% confidence interval [CI] 1.18–1.2.84; p =0.007), ASCVD risk score

(aOR = 1.05, 95% CI 1.03–1.07; $p < 0.001$), and n-terminal pro-b-type natriuretic peptide (NT-proBNP; aOR = 1.90, 95% CI 1.38–2.62; $p < 0.001$) were independently associated with obstructive CAD. In the 25-months median follow-up, MACE occurred in 4.4% (42 of 959). Sedentary lifestyle (adjusted hazard ratio [aHR] = 2.53, 95% CI 1.27–5.03; $p = 0.008$) and NT-proBNP (aOR = 1.50, 95% CI 1.01–2.25; $p = 0.046$) independently predicted MACE. Furthermore, the risk of MACE increased by 3% for every 1% increase in ASCVD risk score (aHR = 1.03, 95% CI 1.01–1.05; $p = 0.02$). *Conclusion*: In individuals with HS, male sex, NT-pro-BNP, and ASCVD risk score are associated with obstructive CAD. Furthermore, ASCVD, NT-proBNP, and sedentary lifestyle are independent predictors of MACE. These factors, with further validation, may help risk-stratify adults with HS for incident CAD and MACE.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of liver-related morbidity and mortality worldwide, and in the United States it affects approximately 30%–37% of adults.[1–3] NAFLD is a spectrum of hepatic pathology characterized by the accumulation of fat in the liver including hepatic steatosis (HS), nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis.[4]

While HS can progress to cirrhosis and hepatocellular carcinoma in a subset of patients, the leading cause of mortality in HS is cardiovascular (CV) disease (CVD).[5] A recent meta-analysis including 34,043 person-years found that HS was associated with increased fatal and/or nonfatal CV events (odds ratio [OR] = 1.64, 95% confidence interval [CI] 1.26–2.13).[6] Furthermore, data from the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) study found that HS, independent of traditional CV risk factors and baseline CVD burden assessed by coronary computed tomography (CT) imaging, was associated with major adverse cardiovascular events (MACE) when compared to those without radiographic HS.[7] Thus, the preponderance of evidence suggests that HS is an independent risk factor for CVD, including adverse CV outcomes.

While the relationship between HS and CVD has been studied, the risk factors for MACE among those with HS has yet to be evaluated in a large population with a comprehensive evaluation of baseline CV risk factors and atherosclerotic burden and prospective determination of outcomes. Henson et al. evaluated a cohort of 285 adults with histologically defined NAFLD who were followed for a median of 5.2 years. They found that risk factors for prevalent disease and incident CV events included tobacco use and advanced fibrosis, while alanine aminotransferase (ALT) and albumin were inversely related to CV events.[8] In addition, there are limited data on the value of CV risk scores such as the Framingham risk score (FRS) and atherosclerotic cardiovascular disease (ASCVD) risk

score in HS. A small study demonstrated value for the FRS; however, Henson et al. did not find that either the FRS or ASCVD were predictive of CVD events.[8] While this study provides important data on risk factors for CVD in NAFLD, it is limited by small size and lack of detailed assessment of baseline CVD burden. This lack of comprehensive identification of CVD risk factors in NAFLD limits the clinician's ability to risk-stratify and modify CVD risk in adults with NAFLD.

The present study is a nested cohort study from the PROMISE trial and addresses the limitations of prior studies to evaluate the risk factors for both prevalent coronary artery disease (CAD) as well as incident MACE in subjects with HS. In this study we seek to assess the determinants of CV risk in patients with HS with comprehensive phenotyping of prevalent CV risk factors and atherosclerotic burden as well as a prospective collection of adjudicated CV events.

METHODS

Study design and patient population

The study design of the PROMISE trial has been described in detail previously (NCT01174550).[9,10] Briefly, the PROMISE trial is a multicenter, pragmatic comparative effectiveness trial that compared the impact of noninvasive functional versus anatomical CV testing on incident MACE. It recruited 10,003 symptomatic outpatients presenting with suspected CAD whose referring physician requested nonurgent, noninvasive CV testing to assess for obstructive CAD. Patients were randomized either to initial functional or anatomical testing with cardiac computed tomography (CT) angiography. Patients with acute or unstable presentation, history of CAD, contraindications for contrast-enhanced coronary CT, and known ejection fraction of ≤40% were excluded from the trial. All included patients provided written, informed consent. The local or central institutional review

board approved the study protocol at each coordinating center and enrolling sites.

This current substudy of the PROMISE trial included those who were randomized to anatomical testing, underwent coronary CT evaluation, and after liver and spleen attenuation measurement were diagnosed with HS by core-laboratory evaluation of noncontrast images from the CT. To demonstrate the differences between patients with HS and those without HS, we included a comparison of their baseline characteristics, as published previously.[7] Participants for whom coronary CT data sets were unavailable or nondiagnostic or did not fit the diagnostic criteria for hepatic steatosis based on noncontrast CT were excluded (Figure 1).

Demographic data

Demographic data, symptoms, CV risk factors, and CAD risk estimates were collected at enrollment. ASCVD risk scores were calculated based on demographic information (age, sex, ethnicity) and clinical variables (systolic and diastolic blood pressure, blood cholesterol, history of diabetes, smoking, hypertension, and the use of preventive CV medications), as described previously.[11]

Blood samples and analysis of blood samples

Nonfasting blood samples were collected in tubes containing ethylenediaminetetraacetic acid and immediately processed and frozen at −80°C.

Total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL),

apolipoprotein-B (ApoB), and apolipoprotein-A1 (ApoA1) levels were measured in plasma samples at LabCorp (Morrisville, NC). Nuclear magnetic resonance (NMR) spectra were acquired on a Vantera Clinical Analyzer for the NMR LipoProfile test. The NMR MetaboProfile analysis, which reports lipoprotein particles concentrations and sizes, was performed using the recently developed LP4 lipoprotein profile deconvolution algorithm.[12] Branched-chain amino acids (BCAAs; valine, leucine, and isoleucine) were measured using NMR as previously described.[13] High-sensitivity C-reactive protein (HS-CRP) was measured on a Beckman Coulter AU analyzer (Beckman Coulter). High-sensitivity troponin I (HsTnI), N-terminal pro-brain natriuretic peptide (NT-proBNP), creatinine, ALT, and galectin-3 concentrations were measured in serum samples on the ARCHITECT iSystem with STAT protocol (Abbott Diagnostics). Concentrations of adiponectin were quantified by using a single-molecule counting method (Singulex, Inc.) on an Erenna platform (MilliporeSigma).

Cardiac CT image acquisition and evaluation

Electrocardiogram-gated coronary CT scans were performed on CT scanners with at least 64 detector rows (64-row, 128-row, 256-row, 320-row, and dual source), developed by five different vendors (General Electric, Hitachi, Phillips, Siemens, and Toshiba).

Hepatic steatosis evaluation

The CT definition of HS has been reported previously in detail.[7] Briefly, five core laboratory readers analyzed
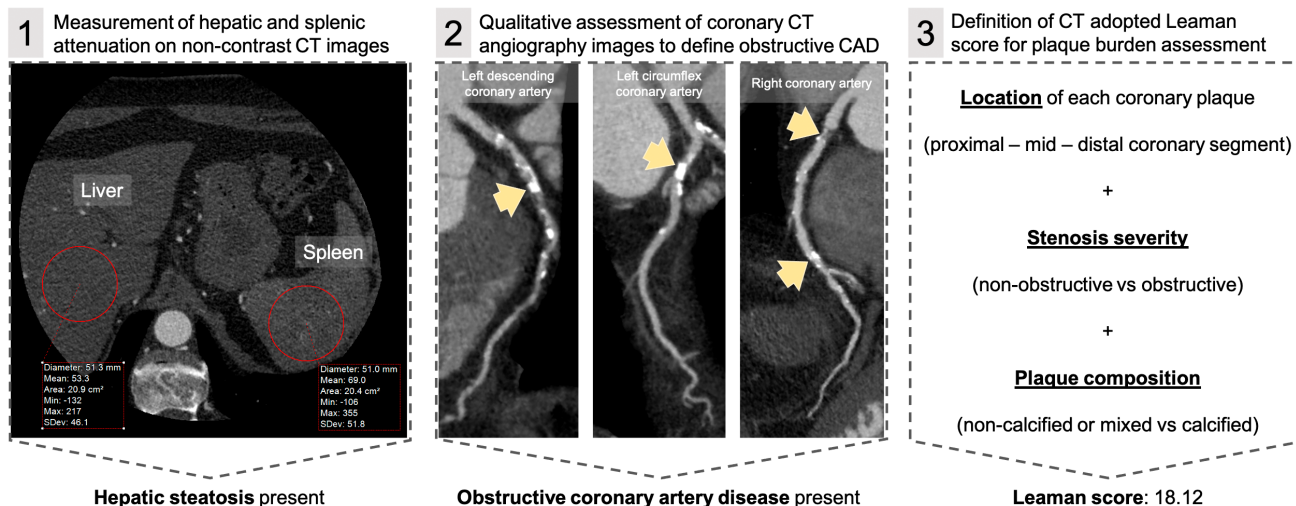

FIGURE 1 Computed tomography (CT)–based measurement of hepatic steatosis (HS), diagnosis of obstructive coronary artery disease (CAD), and calculation of Leaman score.

noncontrast CT images in a randomly assigned, blinded fashion. Hepatic and splenic CT attenuations were measured on three cross-sections obtained at different levels by drawing circular regions of interest with an area of at least $2\,cm^2$, avoiding areas of hepatic vascular and biliary structures.[7,14,15] Hepatic and splenic attenuation were calculated as the mean of the three measurements. Hepatic steatosis was defined as the presence of at least one of the following criteria: (1) hepatic CT attenuation minus splenic CT attenuation of <1 HU; (2) the mean CT number ratio of liver-to-spleen parenchyma of ≤1.1; or (3) absolute hepatic CT attenuation <40 HU.[14,16,17]

CAD evaluation

The presence and severity of CAD identified on CT scans were based on core laboratory reads. Coronary CT angiography data sets were randomly assigned to one of six, level III–trained core laboratory readers with 3 to 10 years of experience interpreting coronary CT angiography images.[18]

Coronary CTA findings were reported using dedicated three-dimensional coronary analysis software (AQi, version 4.4.8; TeraRecon) and were assessed for the presence and extent of CAD. Stenosis severity was qualitatively reported according to the current Society of Cardiovascular Computed Tomography Guidelines.[19] In this current analysis we defined obstructive CAD as a lesion with ≥50% stenosis. We also evaluated the obstructive CAD defined as a lesion with ≥70% stenosis in any coronary artery or ≥50% stenosis in the left main artery. CT measurements are demonstrated in Figure 1.

We further determined the extent and severity of CAD (overall burden of CAD) by calculating the CT-adopted Leaman score. To calculate the Leaman score, three sets of weighting factors were used: (1) coronary plaque location, accounting for coronary artery dominance; (2) plaque type, with multiplication factor 1 for calcified plaque and 1.5 for noncalcified and partially calcified plaque; and (3) degree of stenosis with multiplication factor 0.615 for nonobstructive (<50% stenosis) and multiplication factor 1 for obstructive (≥50% stenosis) lesions (Table S1).[20]

Clinical CV events

MACE was defined as the composite of all-cause death, nonfatal myocardial infarction, or hospitalization for unstable angina during follow-up. We further performed a sensitivity analysis in which MACE was defined as cardiovascular death, nonfatal myocardial infarction, or hospitalization for unstable angina. A blinded and independent clinical events committee adjudicated all endpoint events using prospectively determined definitions, as previously described.[9,10]

Endpoint definition

The primary endpoint of the study was the prevalence of obstructive CAD, defined as ≥50% stenosis in one or more coronary arteries. Secondary endpoints included the baseline burden of CAD determined by the Leaman score and incident MACE, measured as a composite of all-cause death, nonfatal myocardial infarction, or hospitalization for unstable angina during follow-up.

We assessed the predictors of these endpoints in patients with HS. Furthermore, to identify unique markers of obstructive CAD, Leaman score and MACE for those with HS, we compared these to predictors of the non-HS population.

Statistical analysis

Continuous variables are reported as means and SDs or medians and interquartile ranges (25th to 75th percentile), whereas categorical variables are indicated as absolute and relative frequencies. Differences in baseline characteristics among patients with and without obstructive CAD were tested using independent sample Student t-test or Wilcoxon rank-sum test and the Fisher exact test as appropriate. Due to skewness, the Leaman score was log-transformed and biomarker variables were log-transformed and standardized, except in models with continuous dependent variables (i.e., the log-transformed Leaman score, in which biomarkers were log-transformed but not standardized). Logistic regression was used to identify independent predictors of obstructive CAD, and linear regression was used to identify independent predictors of the Leaman score. In a sensitivity analysis we used negative binomial regression models instead of linear regression models to account for excessive zeros in the Leaman Score. Results were similar to the log–log linear regression models and therefore are not shown. Multivariate models were adjusted for age, sex, ASCVD risk score, and body mass index (BMI). We used univariate and multivariate Cox proportional hazards models, the latter adjusted for ASCVD risk score, to determine hazard ratios (HRs) for the composite MACE endpoint. The proportional hazards assumption was assessed before performing the Cox models. Cumulative event rates below and above the median ASCVD risk of 12.3% were computed using the Kaplan–Meier method and tested using the log-rank test. A two-sided p value ≤0.05 was considered statistically significant. All statistical analyses were performed using Stata 14.2 (StataCorp LP).

RESULTS

Study population

Of the 10,003 individuals included in the PROMISE trial, 3,756 were randomized to the anatomical testing arm and evaluated for HS. Of these, 25.5% (959 of 3,756) had HS on CT scan as previously described (Figure 2).[7] Among those with HS, the mean age was 59.4±7.7 years, and subjects were more often men (55%). Baseline characteristics of the included patients are described in Table 1 stratified by the presence of obstructive CAD. Patients who were found to have obstructive CAD on CT, compared to those without obstructive CAD, were older (61.5±7.8 vs. 59.0±7.7; p <0.001) and more frequently male (69.2% [101 of 146] vs. 52.4% [426 of 813]; p <0.001). Those with obstructive CAD more frequently had an elevated 10-year risk of events by ASCVD risk being greater than or equal to the median of 12.3% (75.5% [108 of 143] vs. 45.4% [364 of 801]; p <0.001) at baseline compared to those without obstructive CAD. In addition, patients with obstructive CAD were more likely to be on beta-blockers (35.9% [51 of 142] vs. 26.3% [206 of 782]; p = 0.025) and aspirin (57.0% [81 of 142] vs. 45.1% [353 of 782]; p = 0.010) at baseline compared to those without obstructive CAD, whereas the use of statin (52.1% [74 of 142] vs. 44.8% and [350 of 782];

p = 0.12) angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (52.1% [74 of 142] vs. 49.2% [385 of 782]; p = 0.58) and insulin (5.6% [8 of 142] vs. 7.4% [58 of 782]; p = 0.06) were similar between the groups (Table 1).

Comparing individuals with HS to patients in PROMISE free from HS (n = 2,797), we found that patients with HS were younger (59.4±7.7 vs. 61.0±8.3 years; p <0.001), were more likely to be male (55.0% [527 of 959] vs. 46.2% [1,292 of 2,797]; p <0.001), more frequently Hispanic ethnicity (9.2% [87 of 959] vs. 6.7% [186 of 2,797]; p = 0.014), and had greater CV risk burden (median ASCVD risk score: 10.7 [5.8–19.0] vs. 12.3 [7.4–20.0]; p <0.001) (Table S2).[7]

Factors associated with prevalent obstructive CAD in individuals with HS

On coronary CTA, obstructive CAD was found in 15.1% (146 of 959) of individuals with HS. In multivariate analysis, male sex (adjusted OR [aOR] = 1.83, 95% CI 1.18–2.84; p = 0.01) and ASCVD risk score (aOR = 1.05, 95% CI 1.03–1.07; p <0.001) were independently associated with obstructive CAD (Table 2). For every 1-point increase in ASCVD risk score, the odds of obstructive CAD increased by 5%. Lipid levels were also strongly and independently associated with prevalent
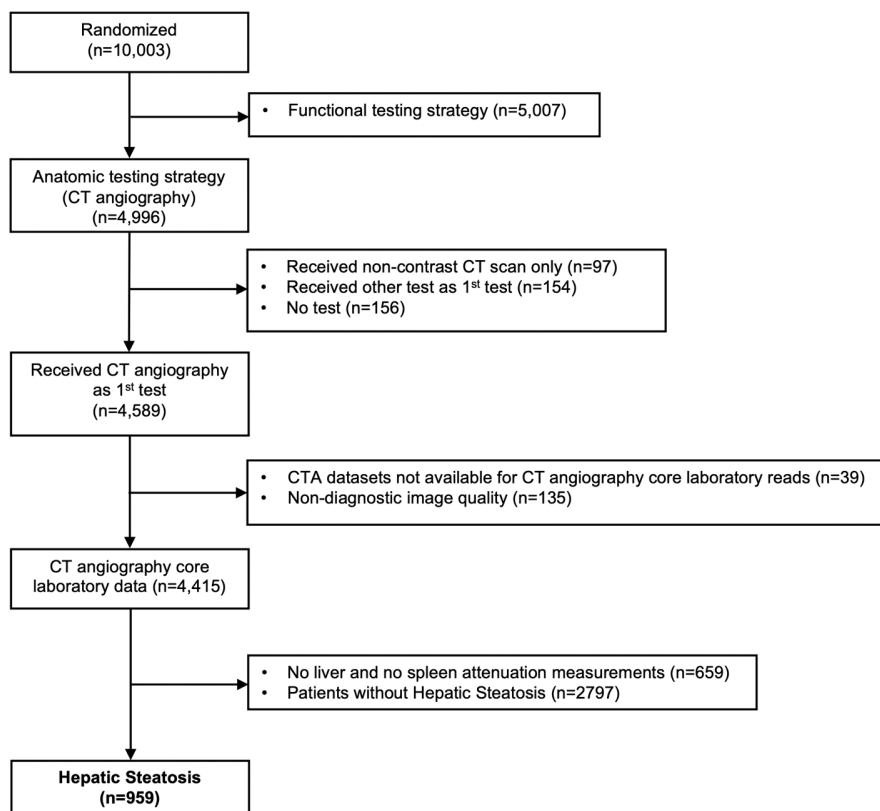

FIGURE 2 Consort flow diagram—patient inclusion and exclusion criteria. Abbreviation: CTA, computed tomography angiography.

TABLE 1 Clinical characteristics of patients with HS stratified by the presence of obstructive CAD with luminal narrowing of ≥50%

	Patients with HS (n = 959)	No obstructive CAD (n = 813)	Obstructive[a] CAD (n = 146)	p
Age, mean ± SD (years)	59.4 ±7.7	59.0 ±7.7	61.5 ±7.8	**<0.001**
Male, n (%)	527 (55.0)	426 (52.4)	101 (69.2)	**<0.001**
Race, n (%) (ethnic minority)[b]				
Non-Hispanic White	731 of 945 (77.4)	613 of 801 (76.5)	118 of 144 (81.9)	0.16
Asian	36 of 945 (3.8)	29 of 801 (3.6)	7 of 144 (4.9)	0.48
Non-Hispanic Black	78 of 945 (8.3)	71 of 801 (8.9)	7 of 144 (4.9)	0.14
Hispanic	87 of 945 (9.2)	76 of 801 (9.5)	11 of 144 (7.6)	0.54
CV risk factors				
BMI, mean ± SD (kg/m^2)	32.1 ±5.8	32.3 ±5.9	30.7 ±5.0	**<0.001**
Obesity (BMI≥30 kg/m^2), n (%)	594 of 954 (62.3)	516 of 809 (63.8)	78 of 145 (53.8)	**0.03**
Hypertension, n (%)	680 (70.9)	572 (70.4)	108 (74.0)	0.43
Diabetes, n (%)	298 (31.1)	237 (29.2)	61 (41.8)	**0.003**
Dyslipidemia, n (%)	674 (70.3)	561 (69.0)	113 (77.4)	**0.04**
Family history of premature CAD, n (%)	331 of 956 (34.6)	278 of 810 (34.3)	53 of 146 (36.3)	0.64
Metabolic syndrome, n (%)	513 (53.5)	431 (53.0)	82 (56.2)	0.53
Current or past tobacco use, n (%)	510 (53.2)	407 (50.1)	103 (70.6)	**<0.001**
Sedentary lifestyle, n (%)	495 (51.6)	418 (51.4)	77 (52.7)	0.79
History of depression, n (%)	209 (21.8)	178 (21.9)	31 (21.2)	0.91
Risk burden	2.60 ±1.09	2.5 ±1.1	3.0 ±1.1	**<0.001**
ASCVD risk				
Median (IQR)	12.3 (7.4-20.0)	11.3 (6.8-18.6)	18.8 (12.7-29.4)	**<0.001**
ASCVD≥7.5	698 of 944 (73.9)	570 of 801 (71.2)	128 of 143 (89.5)	**<0.001**
ASCVD≥median of 12.3	472 of 944 (50.0)	364 of /801 (45.4)	108 of 143 (75.5)	**<0.001**
Baseline medications, n (%)				
Beta-blocker	257 of 924 (27.8)	206 of 782 (26.3)	51 of 142 (35.9)	**0.03**
ACE inhibitor or ARB	459 of /924 (49.7)	385 of 782 (49.2)	74 of 142 (52.1)	0.58
Statin	424 of 924 (45.9)	350 of 782 (44.8)	74 of 142 (52.1)	0.12
Aspirin	434 of 924 (47.0)	353 of 782 (45.1)	81 of 142 (57.0)	0.01
Insulin	66 (6.9)	58 (7.1)	8 (5.5)	0.59

Note: Obstructive CAD defined as the presence of at least one coronary lesion with a luminal narrowing of ≥50%.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BMI, body mass index; CV, cardiovascular; IQR, interquartile range.

[a]Obstructive CAD defined as the presence of at least one coronary lesion with liminal narrowing of ≥50%. [b] Defined as Asian, non-Hispanic Black, and Hispanic races.

obstructive CAD, including TC (aOR = 1.48, 95% CI 1.10–1.99; p = 0.01), LDL (aOR = 1.44, 95% CI 1.07–1.94; p = 0.02), TG (aOR = 1.33, 95% CI 1.02–1.75; p = 0.04), TG/HDL ratio (aOR = 1.36, 95% CI 1.03–1.79; p = 0.03), non-HDL cholesterol (aOR = 1.52, 95% CI 1.12–2.07; p = 0.01), and ApoB levels (aOR = 1.47, 95% CI 1.08–1.98; p = 0.01). HDL, Lipoprotein(a), and ApoA-1 levels were not independently associated with prevalent obstructive CAD. In addition, BCAA and NT-proBNP were both directly associated with prevalent obstructive CAD (aOR = 1.48, 95% CI 1.07–2.05; p = 0.02 and aOR = 1.90, 95% CI 1.38–2.62; p <0.001; respectively), whereas galectin-3 levels were inversely associated with obstructive CAD (aOR = 0.64, 95% CI 0.46–0.90; p = 0.01). ALT, a marker for CAD recognized by previous literature, was not significantly associated

with obstructive CAD (aOR = 1.32; 95% CI 0.97–1.79; p = 0.08).

When compared to patients without HS, in the PROMISE population unique markers of obstructive CAD among people with HS are TC, TG, BCAAs, NT-proBNP, and galectin-3 (Table S3).

As a sensitivity analysis, we restricted our analysis to the 7.3% (70 of 959) subjects with severe obstructive CAD defined as ≥70% stenosis in any epicardial artery or≥50% in the left main branch. Variables associated with obstructive CAD using the 70% threshold were similar to those using a of 50% threshold: Male sex (OR = 3.05, 95% CI 1.57–5.92; p = 0.001) and ASCVD risk (OR = 1.05, 95% CI 1.03–1.08; p <0.001) were independently associated with severe obstructive CAD. Among biomarkers, non-HDL cholesterol (aOR = 1.52,

TABLE 2 Association of obstructive CAD with luminal narrowing of ≥50% with clinical parameters and biomarkers in patients with HS

DEPENDENT VARIABLE: Obstructive CAD (≥50% stenosis)	Unadjusted			Adjusted[a]		
	OR	95% CI	p	OR	95% CI	p
Demographics						
Age (years)	1.04	1.02-1.07	**<0.001**	0.99	0.96–1.03	0.76
Sex, % (males)	2.04	1.40-2.97	**<0.001**	1.83	1.18–2.84	**0.007**
Race, % (ethnic minority)[b]	0.72	0.46-1.13	0.150	0.65	0.40–1.06	0.09
CV risk factors						
Hypertension, %	1.20	0.80–1.78	0.376	1.03	0.66–1.60	0.90
Diabetes, %	1.74	1.21–2.50	**0.003**	1.35	0.83–2.22	0.23
Hyperlipidemia, %	1.54	1.02–2.33	**0.042**	1.38	0.89–2.14	0.15
Smoker, % (current, past)	2.39	1.63–3.50	**<0.001**	1.50	0.98–2.31	0.07
Obese, % (BMI≥30 kg/m^2)	0.66	0.46–0.94	**0.023**	1.12	0.62–2.04	0.70
Sedentary lifestyle[c]	1.05	0.74–1.50	0.768	1.13	0.77–1.66	0.52
ASCVD risk score	1.05	1.04–1.07	**<0.001**	1.05	1.03–1.07	**<0.001**
CAD equivalent						
Positive family history, %	1.09	0.76–1.57	0.643	1.27	0.85–1.88	0.24
PAD, %	1.46	0.69–3.11	0.325	1.19	0.52–2.70	0.69
Stroke, %	—	—	—	—	—	—
Any CAD equivalent, %	1.79	1.25–2.56	**0.001**	1.40	0.87–2.23	0.16
Serum biomarkers[d]						
TC, mg/dl	1.21	0.94–1.57	0.141	1.48	1.10–1.99	**0.01**
TG, mg/dl	1.30	1.00–1.68	**0.047**	1.33	1.02–1.75	**0.04**
LDL, mg/dl	1.19	0.91–1.55	0.194	1.44	1.07–1.94	**0.02**
HDL, mg/dl	0.88	0.65–1.18	0.389	0.91	0.65–1.27	0.57
TG/HDL ratio	1.34	1.03–1.73	**0.027**	1.36	1.03–1.79	**0.03**
Non-HDL-C	1.25	0.95–1.64	0.109	1.52	1.12–2.07	**0.01**
Lp(a), mg/dl	0.97	0.73–1.28	0.832	0.92	0.68–1.24	0.58
ApoA-1, mg/dl	0.86	0.65–1.15	0.323	0.88	0.64–1.21	0.43
ApoB, mg/dl	1.24	0.94–1.62	0.122	1.47	1.08–1.98	**0.01**
BCAA, μmol/L	1.44	1.06–1.94	**0.018**	1.48	1.07–2.05	**0.02**
Homocysteine (tHCY), umol/L	1.13	0.89–1.44	0.305	1.06	0.80–1.42	0.68
HS-CRP, mg/l	1.07	0.82–1.41	0.610	1.24	0.92–1.67	0.17
HsTnI, pg/ml	1.36	1.06–1.74	**0.014**	1.14	0.87–1.50	0.35
NT-proBNP, pg/ml	1.68	1.28–2.20	**<0.001**	1.90	1.38–2.62	**<0.001**
Creatinine, mg/dl	1.06	0.81–1.39	0.650	0.84	0.60–1.19	0.33
ALT, U/L	1.17	0.89–1.55	0.261	1.32	0.97–1.79	0.08
Galectin-3, ng/ml	0.74	0.56–0.98	**0.035**	0.64	0.46–0.90	**0.01**
Adiponectin, ug/ml	0.98	0.71–1.35	0.894	1.06	0.74–1.52	0.77

Abbreviations: ALT, alanine aminotransferase; ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; BCAA, branched chain amino acids; CI, confidence interval; HDL, high-density lipoprotein; HS-CRP, highly sensitive C-reactive protein; HsTnI, highly sensitive troponin I; LDL, low-density lipoprotein; Lp(a), Lipoprotein(a); NT-proBNP, N-terminal proB-type natriuretic peptide; OR, odds ratio; PAD, peripheral artery disease; TC, total cholesterol; TG, triglyceride.

[a]Adjusted for age, sex, BMI, and ASCVD risk score (except for ASCVD risk score, which was only adjusted for age, sex, and BMI).

[b]Defined as Asian, non-Hispanic Black, and Hispanic races.

[c]Defined by the patient as not participating in regular physical activities at least one time per week over the previous month.

[d]All biomarkers are log-transformed and standardized.

95% CI 1.01–2.30; $p = 0.05$), HS-CRP (OR = 1.55, 95% CI 1.08–2.23; $p = 0.02$), and NT-proBNP (OR = 2.01, 95% CI 1.35–3.02; $p = 0.001$) were independently associated with CAD≥70% (Table S4). Biomarkers of TC, TG, LDL, TG/HDL, ApoB, BCAA and galectin, which were significantly associated with obstructive CAD≥50%, were not significantly associated with severe obstructive CAD.

Factors associated with coronary plaque burden and severity

The median Leaman score was 4.6 (interquartile range [IQR]: 0–9.1). On multivariate analysis, a number of traditional CV risk factors were independently associated with plaque burden and severity, expressed by the log-transformed Leaman score, including male sex (adjusted Coef = 0.58, 95% CI 0.44–0.72; $p < 0.001$) and ASCVD risk score (aβ-coefficient = 0.02, 95% CI 0.01–0.02; $p < 0.001$) (Table 3). Among the lipid markers, TG (adjusted Coef = 0.17, 95% CI 0.02–0.32;

TABLE 3 The association of log-transformed Leaman score with clinical parameters and biomarkers in patients with HS

DEPENDENT VARIABLE: Log-transformed Leaman score	Unadjusted			Adjusted[a]		
	Coef.	95% CI	p	Coef.	95% CI	p
Demographics						
Age (years)	0.05	0.04–0.05	**<0.001**	0.03	0.02–0.04	**<0.001**
Sex, % (males)	0.68	0.55–0.81	**<0.001**	0.58	0.44–0.72	**<0.001**
Race, % (ethnic minority)[b]	−0.18	−0.32 to −0.04	**0.014**	−0.24	−0.39 to −0.09	**0.001**
CV risk factors						
Hypertension, %	0.21	0.06–0.35	**0.006**	0.18	0.04–0.32	**0.01**
Diabetes, %	0.27	0.13–0.41	**<0.001**	0.25	0.09–0.41	**0.002**
Hyperlipidemia, %	0.21	0.07–0.36	**0.004**	0.15	0.02–0.29	**0.02**
Smoker, % (current, past)	0.32	0.19–0.45	**<0.001**	0.18	0.04–0.31	**0.01**
Obese, % (BMI > 30 kg/m^2)	−0.19	−0.33 to −0.06	**0.005**	−0.06	−0.25–0.13	0.53
Sedentary lifestyle[c]	−0.07	−0.20–0.06	0.306	−0.05	−0.17–0.08	0.46
ASCVD risk score	0.03	0.03–0.04	**<0.001**	0.02	0.01–0.02	**<0.001**
CAD equivalent						
Positive family history, %	0.10	−0.03–0.24	0.141	0.18	0.05–0.31	**0.01**
PAD, %	0.33	0.01–0.64	**0.041**	0.20	−0.08–0.49	0.16
Stroke, %	—	—	—	—	—	—
Any CAD equivalent, %	0.30	0.16–0.43	**<0.001**	0.26	0.11–0.41	**0.001**
Serum biomarkers[d]						
TC, mg/dl	−0.21	−0.69–0.27	0.398	0.16	−0.30–0.62	0.50
TG, mg/dl	0.20	0.03–0.37	**0.018**	0.17	0.02–0.32	**0.03**
LDL, mg/dl	−0.13	−0.46–0.20	0.434	0.10	−0.21–0.41	0.52
HDL, mg/dl	−0.79	−1.24 to −0.34	**0.001**	−0.67	−1.12 to −0.22	**0.004**
TG/HDL ratio	1.38	1.14–1.68	**0.001**	1.31	1.09–1.57	**0.003**
Non-HDL-C	1.02	0.71–1.48	0.902	1.30	0.91–1.84	0.14
Lp(a), mg/dl	−0.03	−0.12–0.06	0.470	−0.02	−0.11–0.06	0.57
ApoA-1, mg/dl	−1.01	−1.56 to −0.46	**<0.001**	−0.93	−1.48 to −0.39	**0.001**
ApoB, mg/dl	0.04	−0.34–0.41	0.851	0.25	−0.10–0.60	0.16
BCAA, μmol/L	0.71	0.24–1.19	**0.003**	0.58	0.12–1.03	**0.01**
Homocysteine (tHCY), umol/L	0.16	−0.18–0.51	0.347	−0.04	−0.36–0.29	0.82
HS-CRP, mg/L	−0.05	−0.18–0.08	0.440	0.03	−0.10–0.16	0.644
HsTnI, pg/ml	0.21	0.05–0.36	**0.010**	0.02	−0.13–0.17	0.81
NT-proBNP, pg/ml	0.08	−0.02–0.18	0.096	0.08	−0.02–0.18	0.13
Creatinine, mg/dl	0.09	−0.82–1.00	0.847	−1.54	−2.47 to −0.61	**0.001**
ALT, U/L	0.03	−0.18–0.24	0.766	0.10	−0.10–0.29	0.32
Galectin-3, ng/ml	−0.18	−0.50–0.13	0.256	−0.25	−0.56–0.06	0.12
Adiponectin, ug/ml	−0.26	−0.46 to −0.06	**0.011**	−0.27	−0.46 to −0.07	**0.008**

[a]Adjusted for age, sex, BMI, and ASCVD risk score.
[b]Defined as Asian, non-Hispanic Black, and Hispanic races.
[c]Defined by the patient as not participating in regular physical activities at least one time per week over the previous month.
[d]All biomarkers are log-transformed.

p = 0.029) and TG/HDL ratio (adjusted Coef = 1.31, 95% CI 1.09–1.57; p = 0.003) were positively associated with higher Leaman score, whereas HDL (adjusted Coef = −0.67, 95% CI −1.12 to −0.22; p = 0.004) and Apo-A1 levels (adjusted Coef = −0.93, 95% CI −1.48 to −0.39; p = 0.001) were inversely associated with Leaman score. BCAA (adjusted Coef = 0.58, 95% CI 0.12–1.03; p = 0.013) were positively associated with a higher Leaman score, while both creatinine (adjusted Coef = −1.54, 95% CI −2.47 to −0.61; p = 0.001) and adiponectin (adjusted Coef = −0.27, 95% CI −0.46 to −0.07; p = 0.008) levels were significantly inversely associated with Leaman score. ALT was not associated with Leaman score (adjusted Coef = 0.10, 95% CI: −0.10–0.29; p = 0.318).

When compared with patients included in the PROMISE study who were not diagnosed with HS, variables associated with increased Leaman score specifically in patients with HS were hypertension, diabetes, the presence of any CAD-equivalent disease, TG, TG/HDL ratio, BCAA, creatinine, and adiponectin (Table S5).

Predictors of MACE

In total, 4.3% (42 of 959) patients experienced MACE over a median (IQR) follow-up time of 25 (18–34) months. Of these events, 33.3% (14 of 42) were hospitalization for unstable angina, 21.4% (9 of 42) were nonfatal myocardial infarction, and 45.2% (19 of 42) were all-cause death. Sedentary lifestyle, independent of ASCVD risk score, was a significant, independent predictor of incident MACE (adjusted hazard ratio [aHR] = 2.53, 95% CI 1.27–5.03; p = 0.008). Furthermore, the risk of incident MACE increased by 3% for each 1%-increase in ASCVD risk (HR = 1.03; 95% CI 1.01–1.05; p = 0.022). Individuals with an ASCVD risk of ≥12.3% 10-year risk of CVD events had a significantly higher rate of MACE over the study duration compared to those with ASCVD risk < 12.3% (p = 0.002; Figure 3). Among biomarkers, only NT-proBNP independently predicted incident MACE: We observed per 1-SD increase in NT-proBNP (SD = 142.9 pg/ml), the risk of MACE increased by 5% (aHR = 1.50; 95% CI 1.01–2.25; p = 0.046) (Table 4).

When compared to patients with no HS, unique predictors of MACE among those with HS were sedentary lifestyle and NT-proBNP (Table S6).

As a sensitivity analysis, we assessed the predictors of MACE defined as cardiovascular death, myocardial infarction, and hospitalization for unstable angina. Independent predictors of events were sedentary lifestyle (aHR = 2.53, 95% CI 1.27–5.03; p = 0.01), ASCVD risk score (HR = 1.03; 95% CI 1.01–1.05; p = 0.002), and HS-CRP (aHR = 1.52; 95% CI 1.06–2.19; p = 0.025) when using the modified MACE definition (Table S7).
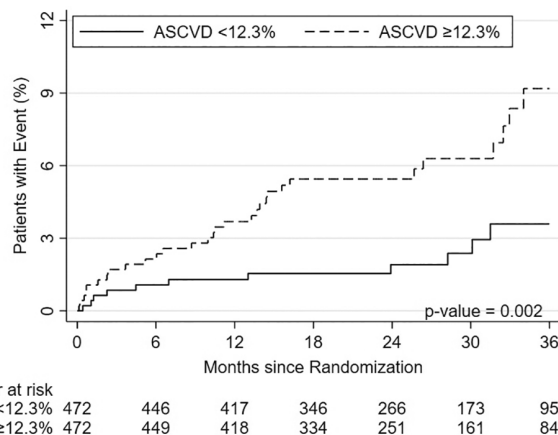

FIGURE 3 Kaplan–Meier curve demonstrating cumulative event rates for major adverse cardiovascular events (MACE) in individuals with HS in the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) trial, based on 10-year atherosclerotic cardiovascular disease (ASCVD) risk less and greater or equal than the median ASCVD of 12.3%.

DISCUSSION

In the present study, using a large cohort with comprehensively defined CVD risk factors and adjudicated outcomes from the PROMISE trial, we determined the risk factors for prevalent obstructive CAD, plaque burden and severity, and incident MACE in a contemporary population of adults with HS. We found that male sex, ASCVD risk score, and NT-proBNP were associated with prevalent obstructive CAD and remained associated even when confining obstructive CAD to a more stringent endpoint of ≥70% obstruction. Male sex and ASCVD risk were also associated, among other factors, with atherosclerotic plaque burden and severity. Finally, ASCVD risk score, NT-proBNP, and sedentary lifestyle were the only independent risk factors for incident MACE in this cohort of individuals with HS.

ASCVD risk and CAD in HS

Pooled cohort equations that estimate the 10-year risk of ASCVD are essential tools in cardiovascular practice to identify the need for and intensity of preventive therapy. The ASCVD risk score is computed with the use of an online calculator using basic demographic information (age, sex, ethnicity) and clinical variables (systolic and diastolic blood pressure, serum cholesterol, history of diabetes, smoking, hypertension, and the use of preventive CV medication).[21] Thus, it is a tool that is used by primary care physicians and cardiologists throughout the United States to estimate CVD risk and guide use of CVD risk-modifying therapy.

The present study assesses the use of ASCVD score to predict incident MACE in adults with CT-defined HS.

TABLE 4 Predictors of major adverse CV events in patients with HS

DEPENDENT VARIABLE: MACE (Death, nonfatal MI, or hospitalization for UAP)	Unadjusted			Adjusted[a]		
	HR	95% CI	p	aHR	95% CI	p
Demographics						
Age (years)	1.02	0.99–1.06	0.224	0.99	0.94–1.03	0.58
Sex, % (males)	1.45	0.77–2.72	0.249	1.34	0.71–2.52	0.37
Race, % (ethnic minority)[b]	1.12	0.55–2.27	0.759	1.10	0.54–2.23	0.80
CV risk factors						
Hypertension, %	1.05	0.54–2.05	0.887	0.83	0.41–1.66	0.59
Diabetes, %	1.40	0.75–2.60	0.295	0.93	0.45–1.92	0.84
Hyperlipidemia, %	0.77	0.41–1.44	0.408	0.71	0.38–1.35	0.30
Smoker, % (current, past)	1.43	0.77–2.66	0.261	1.10	0.57–2.14	0.77
Obese, % (BMI > 30kg/m^2)	0.64	0.35–1.17	0.150	0.64	0.35–1.18	0.15
Sedentary lifestyle[c]	2.57	1.29–5.11	**0.007**	2.53	1.27–5.03	**0.01**
ASCVD risk score	1.03	1.01–1.05	**0.002**	1.03	1.01–1.05	**0.002**
CAD equivalent						
Positive family history, %	0.54	0.26–1.14	0.106	0.59	0.28–1.23	0.16
PAD, %	0.91	0.22–3.79	0.902	0.74	0.18–3.08	0.68
Stroke, %	—	—	—	—	—	—
Any CAD equivalent, %	1.32	0.71–2.45	0.371	0.88	0.43–1.80	0.72
Serum biomarkers[d]						
TC, mg/dl	0.94	0.64–1.37	0.731	1.05	0.71–1.54	0.82
TG, mg/dl	0.79	0.52–1.21	0.284	0.80	0.53–1.22	0.30
LDL, mg/dl	1.06	0.72–1.55	0.764	1.18	0.80–1.73	0.42
HDL, mg/dl	0.86	0.54–1.37	0.528	0.89	0.56–1.43	0.64
TG/HDL ratio	0.86	0.56–1.31	0.479	0.85	0.55–1.31	0.46
Non-HDL-C	0.96	0.65–1.42	0.845	1.08	0.72–1.60	0.72
Lp(a), mg/dl	0.89	0.59–1.36	0.597	0.86	0.56–1.31	0.48
ApoA-1, mg/dl	0.72	0.47–1.12	0.143	0.73	0.47–1.14	0.17
ApoB, mg/dl	0.98	0.66–1.44	0.912	1.08	0.73–1.61	0.69
BCAA, µmol/L	1.15	0.74–1.80	0.530	1.13	0.72–1.76	0.60
Homocysteine (tHCY), umol/L	1.07	0.75–1.52	0.728	1.03	0.70–1.49	0.90
HS-CRP, mg/L	1.39	0.98–2.00	0.068	1.33	0.93–1.91	0.11
HsTnI, pg/ml	1.26	0.91–1.75	0.169	1.16	0.82–1.64	0.40
NT-proBNP, pg/ml	1.62	1.09–2.40	**0.016**	1.50	1.01–2.25	**0.046**
Creatinine, mg/dl	0.81	0.53–1.24	0.340	0.78	0.51–1.18	0.24
ALT, U/L	1.14	0.76–1.72	0.522	1.22	0.80–1.88	0.36
Galectin-3, ng/ml	1.17	0.81–1.69	0.413	1.07	0.73–1.59	0.73
Adiponectin, ug/ml	1.40	0.89–2.21	0.150	1.51	0.94–2.42	0.09

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; UAP, unstable angina pectoris.

[a]Adjusted for ASCVD risk score.

[b]Defined as Asian, non-Hispanic Black, and Hispanic races.

[c]Defined by the patient as not participating in regular physical activities at least one time per week over the previous month.

[d]All biomarkers are log-transformed and standardized.

Although a previous study showed an association between HS by ultrasound and ASCVD risk, it did not assess the relationship between baseline ASCVD and future cardiac events in patients with HS.[22] In another study of 1,262 individuals with HS defined by ultrasound (mean age = 56 years, 48% male), individuals with ASCVD ≥ 7.5% were shown to have a 2-fold increase in the likelihood of dying due to CVD compared to those at low risk after a median of 17.7 years.[23] The significant outcomes in that study, however, were confined to

CVD-related death and did not demonstrate an association between ASCVD risk score and MACE in HS. Our study demonstrated that ASCVD is a strong independent predictor of MACE. However, to further interrogate the discriminatory power of ASCVD risk, studies with longer follow-up are warranted so that the calibration and discrimination of ASCVD can be established.

We demonstrate in a cohort of patients with radiographic HS that ASCVD is not only an independent predictor of future MACE (even when using the modified definition of MACE), but is associated with prevalent obstructive CAD (with both definitions of the presence of obstructive CAD with ≥ 50% and ≥ 70% luminal narrowing) and CAD burden (as measured with the Leaman score). Not surprisingly, this is not different from those without HS, but importantly, our finding thus confirms that ASCVD risk score is a valid method to identify prevalent CAD in patients with HS who present with stable outpatient chest pain. Thus ASCVD risk score could be used for predicting incident CVD risk, thereby identifying adults with HS who would benefit from CVD risk modification including initiation of statin therapy.

In the 2019 American College of Cardiology and American Heart Association Guidelines on the Primary Prevention of Cardiovascular Disease, statin treatment is recommended for individuals with increased ASCVD risk.[24] We demonstrated in a cohort of individuals with HS that the incidence of MACE was significantly greater in those with a 10-year risk for ASCVD with ≥ 12.3% compared to those with <12.3%. Importantly, based on current guidelines, these individuals may have benefited from ASCVD risk estimation and subsequent statin therapy. Among adults with HS, the ASCVD risk score can identify prevalent CAD and predict incident MACE, showing its value in adults with HS to risk-stratify patients and consider disease-modifying therapy.

Sedentary lifestyle: modifiable risk factor of MACE in HS

Sedentary lifestyle was a significant and independent predictor of incident MACE after controlling for ASCVD risk score, which includes relevant covariates including age, sex, race, blood pressure, cholesterol levels, smoking, diabetes status, and use of risk-modifying medications. Among general population, sedentary lifestyle is the leading modifiable risk factor of CVD.[25] Physical activity, including both aerobic exercise and resistance training, is beneficial in the management of HS[26,27] and has been shown to reduce HS. The current study suggests that, unlike among patients without HS, sedentary lifestyle is associated with an increased risk of MACE in those with HS, even when using a modified definition for MACE

and including cardiovascular death instead of all-cause death in its definition. Thus, increased physical activity in individuals with HS may improve not only liver histology but also decrease the risk of MACE, although randomized controlled trials are needed to confirm this finding.

Blood biomarkers and CVD in HS

Lipid biomarkers

Decades of research including both observational studies and randomized trials determined that serum lipids are independent risk factors for CVD in the general population. Moreover, dyslipidemia, characterized by increased serum TG and small dense LDL and low HDL cholesterol, is known as a key characteristic of NAFLD.[28] In fact, TG/HDL ratio was shown to be associated with HS among about 18,000 apparently healthy individuals and was suggested as a biomarker surrogate for HS.[29] In our study, both levels of TG and TG/HDL are independently associated with the presence of underlying obstructive CAD and plaque burden and severity, as defined by the Leaman score. Thus, TG/HDL may be a useful marker not only in identifying underlying HS as suggested by others, but also for the detection of underlying extensive coronary atherosclerosis. Furthermore, elevated LDL was independently associated with underlying obstructive CAD, but not with high plaque burden and severity, whereas lower levels of HDL were independently associated with higher Leaman score, but not with obstructive CAD. One probable explanation for these inconsistent associations is that in HS the absolute values of LDL and HDL are not able to capture incremental risk for underlying CVD, because HS itself influences blood lipid parameters. However, when two biomarkers are analyzed relative to each other (TG/HDL), a pathologic lipid profile associated with CVD can be detected.

Elevated serum lipid levels alone constitute an indication for preventive medications. In addition, our results emphasize that among individuals with HS, severe CAD phenotype is strongly associated with unfavorable lipid parameters. These results suggest that individuals with HS might benefit from detailed serum lipid analysis for CV risk assessment during their routine clinical work up; and for those with elevated serum lipids disease, modifying therapy (e.g., statins) could be considered. Furthermore, some of the lipid variables were different for the subcohort of patients with HS when compared to those without HS in PROMISE, although these results need to be confirmed with further investigations.

BCAAs, amino acids with nonlinear aliphatic side-chains, composed of leucine, isoleucine and valine[30],

in the general population are associated with higher plaque burden, independent of traditional CV factors.[31,32] Higher circulating BCAAs are also associated with cardiometabolic disease including obesity, metabolic syndrome, and type 2 diabetes[33] and HS progression.[34] In our study, among adults with HS, BCAAs were independently associated with prevalent obstructive CAD and overall atherosclerotic burden, but not with MACE. Thus, similar to the general population, BCAAs may be important predictors for underlying obstructive CAD and high Leaman score in the population with HS, especially as assessed in PROMISE; but without HS, BCAAs were not associated with CAD endpoints. Because BCAAs are associated with both HS and obstructive CAD, further study into their role as a possible mechanistic link between these conditions is warranted.

N-terminal pro-b-type natriuretic peptide

NT-proBNP is key marker of cardiac distress and is used primarily to diagnose and monitor the severity of heart failure.[35] We demonstrated among patients with HS that elevated NT-proBNP levels are associated with prevalent underlying obstructive CAD. Moreover, every SD increase in NT-proBNP concentration independently increased the risk of MACE by 50%. Important to note, in PROMISE, individuals with an ejection fraction ≤40% were excluded, but 3.6% (35 of 959) of the patients had a history of heart failure. In a sensitivity analysis, after further adjusting for the history of heart failure, NT-proBNP remained independently associated with MACE (aOR = 1.89, 95% CI 1.37–2.61; $p < 0.001$).

Among patients with stable chest pain, elevated levels of NT-proBNP are associated with myocardial ischemia independent of left ventricular function,[36,37] and the extent of underlying CAD is proportionally associated with the extent of NT-proBNP elevation even in the absence of LV dysfunction.[38] Moreover, NT-proBNP is prognostic for future MACE events among those with stable CAD.[39] Importantly, among those with NAFLD, emerging evidence suggests that plasma levels of NT-proBNP are lower after controlling for BMI or metabolic syndrome.[40–42] The present study demonstrates that in those with HS, higher NT-proBNP levels are associated with obstructive CAD and MACE, which was not the case among patients without HS. Therefore, even NT-proBNP levels are lower among patients with HS; based on these results, NT-proBNP levels are relatively higher in those with HS and underlying CAD or who are at risk for future MACE. When using the modified MACE definition, however, NT-proBNP was not a significant predictor of MACE. This discrepancy may be the result of the limited study sample, as those with biomarker samples available were limited, as well as the lower event rate when using the definition of MACE by

including cardiovascular death versus when including all cause death. Therefore, we believe that NT-proBNP could be a potential parameter to use clinically to identify individuals with HS at an increased risk for CVD, but further study is required.

Other biomarkers

Adiponectin, a peptide hormone responsible for the regulation of blood glucose level and free fatty acid metabolism, is inversely related to CAD in the general population.[43] In our unique population, confined to those with HS presenting with stable outpatient chest pain, adiponectin was also inversely associated with greater plaque burden and severity as determined by the Leaman score. Galectin-3, a protein responsible for numerous molecular processes, including cell growth, apoptosis, differentiation, transformation, angiogenesis, inflammation and fibrosis, was described as a potential new marker for CVD.[44] In CVD, galectin-3 levels were shown to increase; however, in our study we found an inverse association between galectin-3 and severity of CAD among individuals with HS. An explanation for this finding may be that prior investigations suggest that the severity of HS is associated with decreased levels of galectin-3.[45–47] However, due to the contrasting data on the role of galectin-3 in the development of HS,[48] this result warrants further investigation.

Male sex and CVD in HS

In the general population, male sex is strongly associated with obstructive CAD.[49] We have confirmed that among adults with HS, male sex is also an important risk factor for prevalent CVD. Although male sex is associated with incident MACE in the general population, in this specific cohort of individuals with HS we were not able to show this association, perhaps due to the low number of MACE events (4.3%).

Strengths and limitations

Several strengths of this study are noteworthy. This current study demonstrates its key findings based on the assessment of a well-phenotyped cohort of patients, with comprehensive demographics and CV risk factors and centrally adjudicated events. Addressing some of the limitations of prior studies to evaluate the risk factors for CVD among patients with HS, we describe factors associated with the presence of obstructive CAD and increased CAD burden and severity as determined by the Leaman score as well as predictors of incident MACE. Finally, given that the PROMISE trial consisted of individuals without HS, we were able to compare and thus

identify those factors that may be uniquely associated with obstructive CAD and increased Leaman score, and predicted MACE in patients with HS. This could carry an important role in designing future research to target these specific markers, to confirm our results.

Nevertheless, there are limitations of this study that should be noted. First, diagnosis of HS was based on radiographic findings; thus, the relationship among steatosis, NASH, fibrosis, and CVD outcomes could not be assessed. Second, blood testing was not required to be performed in a nonfasting state, which somewhat limited our results of associations with lipid parameters. Third, the current cohort has a limited history of alcohol consumption. Based on prior data on the relatively low prevalence of alcoholic fatty liver disease compared with NAFLD in the general population (alcoholic fatty liver disease prevalence 4%[50] vs. NAFLD 30%–37%[1–3]), we presume that most of our patients had NAFLD but emphasize that our analysis is for HS of any cause. Fourth, the patient population assessed in the PROMISE study presented to medical care due to symptoms suggestive of underlying obstructive CAD, and therefore may be at higher overall CV risk as compared with the general population. Arguing against this is the relatively low event rate in the overall PROMISE population and consequently in the subcohort of patients with HS, suggesting that this study population may represent a more general HS population.

CONCLUSIONS

In adults with radiographic HS, independent risk factors for obstructive CAD included ASCVD risk score, NT-proBNP, BCAAs, and serum lipid levels. In addition, ASCVD score, NT-proBNP, and sedentary lifestyle were prognostic of incident MACE. Therefore, ASCVD risk estimation and the measurement of NT-proBNP may be useful for CV risk stratification in patients with HS, while sedentary lifestyle is a modifiable risk factor for MACE that could be targeted to decrease the risk for CV events.

CONFLICT OF INTEREST
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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.