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Liver stiffness by magnetic resonance elastography is associated with increased risk of cardiovascular disease in patients with non-alcoholic fatty liver disease

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Summary

Background: Magnetic resonance elastography (MRE) is a reliable non-invasive, alternative to liver biopsy for assessing liver fibrosis. There are limited data regarding an association between liver fibrosis by MRE and risk of cardiovascular disease.

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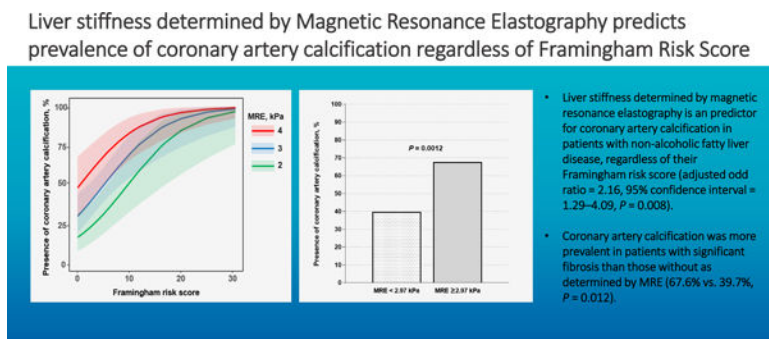
Aim: To investigate the association of high risk cardiovascular disease phenotype determined by coronary artery calcification (CAC) with liver fibrosis by MRE in patients with non-alcoholic fatty liver disease (NAFLD).

Method: This was a cross-sectional analysis of well-characterized, prospective cohorts including 105 patients with NAFLD (MR imaging-derived proton density fat fraction 5%) with contemporaneous cardiac computed tomography (CT) and MRE. Patients were assessed using MRE for liver stiffness, and cardiac CT for presence of CAC (defined as coronary artery calcium score > 0). Odds of presence of CAC were analyzed using logistic regression analysis.

Results: The average age and body mass index were 54.9 years and 32.9kg/m^2, respectively. 49.5% of patients had CAC and 35.2% had significant liver fibrosis (defined as MRE 2.97kPa). Compared to patients without CAC, those with CAC were older (50.0[39.0–59.0] vs 63.0[55.5–67.5], $P < 0.001$), and had higher Framingham risk score (FRS, 1.0 [0.5–3.5] vs. 6.0 [2.0–12.0], $P < 0.001$). In multivariable-adjusted analysis, liver stiffness as a continuous trait on MRE was independently associated with the presence of CAC in a sex and age-adjusted model (adjusted odd ratios [aOR] = 2.23, 95% confidence interval [CI] = 1.31–4.34, $P = 0.007$) as well as in a FRS-adjusted model (aOR = 2.16, 95% CI = 1.29–4.09, $P = 0.008$). When analyzed as a dichotomous trait, significant fibrosis (MRE-stiffness 2.97 kPa) remained independently associated with the presence of CAC in both FRS-adjusted model and sex and age-adjusted model (aOR = 3.21–3.53, $P = 0.013–0.017$). In addition, CAC was more prevalent in patients with significant fibrosis than those without as determined by MRE (67.6% vs. 39.7%, $P = 0.012$).

Conclusion: Liver stiffness determined by MRE is an independent predictor for presence of CAC in patients with NAFLD. Patients with NAFLD and significant fibrosis by MRE should be considered for further cardiovascular risk assessment, regardless of their FRS.

Graphical Abstract

Liver stiffness determined by Magnetic Resonance Elastography predicts prevalence of coronary artery calcification regardless of Framingham Risk Score

Keywords

NAFLD; liver stiffness; fibrosis; MRE; cardiovascular disease; coronary artery calcification

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent chronic liver diseases worldwide, affecting approximately one-fourth of the Western population[1]. NAFLD is a liver manifestation of metabolic syndrome characterized by hepatic fat accumulation

5%.[2,3] Although NAFLD can progress to fibrosis, cirrhosis and hepatocellular carcinoma, the most common cause of death in adults with NAFLD is cardiovascular disease (CVD).[4,5]

Many epidemiological studies have reported the association of NAFLD with increased risk of CVD.[6] While the evidence from these studies is robust, most non-invasive assessments of CVD risk, such as Framingham Risk Score (FRS) and Atherosclerotic Cardiovascular Disease risk algorithm, do not include the presence of NAFLD in calculating CVD risk.[7,8]

Due to NAFLD's high prevalence and heterogeneity of clinical course, it is important to identify predictors for incident CVD among patients with NAFLD.[4] Prior studies have reported that advanced fibrosis (stage ≥ 3) is associated with all-cause mortality in patients with NAFLD.[9,10] A recent study demonstrated the association of advanced fibrosis with incident CVD in a biopsy-proven NAFLD cohort.[11] However, liver biopsy is limited in clinical practice due to its invasiveness and sampling variability.[12] Non-invasive assessments for fibrosis based on indirect serum biomarkers such as NAFLD fibrosis score (NFS) and fibrosis-4 (FIB-4) index are also limited due to a significant proportion of patients being classified as having intermediate risk.[13]

Magnetic resonance elastography (MRE) is one of the most accurate non-invasive modalities for assessing liver stiffness[14] and has low technical failure rates compared with ultrasound based elastography.[14] Recently, we demonstrated that liver stiffness by MRE is associated with increased CVD risk in patients with type 2 diabetes.[15] However, there is no data regarding association of liver stiffness by MRE with CVD risk in patients with NAFLD.

This study aimed to investigate the association of liver stiffness by MRE with high risk CVD phenotype based on the presence of coronary artery calcification (CAC) in patients with NAFLD. Then, we further analyzed the data with FRS of the patients to investigate association of significant fibrosis with risk of CVD.

METHODS

Study Design and Data Collection

This was a cross-sectional analysis of a single-center study from two previous studies of adults with Type 2 diabetes (Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE) or non-alcoholic steatohepatitis (NASH, Magnetic Resonance Imaging and Elastography in Ezetimibe Versus Placebo for the Assessment of Response to Treatment in NASH trial, Supplementary Figure 1). [16,17] All participants were prospectively recruited at the University of California at San Diego (UCSD) NAFLD Research Center from January 2013 to August 2014. A research study visit included demographics, anthropometric measurements, physical exam, biochemical testing, coronary calcium scan, MRE and magnetic resonance image derived proton density fat fraction (MRI-PDFF). The eligibility criteria for the two studies are described in previous publications.[16,17] Main exclusion criteria were as followed: non-NAFLD chronic liver diseases, steatogenic medications, significant systemic illness, renal insufficiency, excessive alcohol use, human immunodeficiency virus, pregnancy, documented history of cardiovascular disease (CVD), such as acute coronary syndrome (ST elevation myocardial

infarction, non-ST elevation myocardial infarction, unstable angina), stable angina, history of angioplasty or stent placement, cerebrovascular disease (ischemic or hemorrhagic stroke), and peripheral vascular disease for type 2 diabetes study[17], and significant coronary artery disease for NASH study.[16] The studies received UCSD institutional review board approval (approval numbers: UCSD IRB #121508 and #121314) and all patients provided written informed consent prior to enrollment.

Non-invasive fibrosis scores such as the NFS and FIB-4 index were calculated and categorized accordingly.[18,19] The FRS was calculated using the algorithm from a previous publication.[8] Homoeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR = [glucose (mg/dL) * insulin (mIU/mL)]/405. Adipose tissue IR (Adipo-IR) was calculated using the following formula: Adipo-IR = free fatty acids (mmol/L) * insulin (mIU/mL). Both insulin resistance tests underwent in a fasting state.

Primary and secondary outcome

Primary outcome of the study was defined as the presence of CAC in patients with NAFLD defined by MRI-PDFF ≥ 5%. The secondary outcome of the study was defined as the prevalence of CAC in patients with NAFLD and significant fibrosis defined by MRE-stiffness ≥ 2.97 kPa.

MRE and MRI-PDFF

All MR examinations were performed by the UCSD Liver Imaging Group at the MR3T Research laboratory using a 3T research scanner (GE Signa EXCITE HDxt; GE Healthcare, Waukesha, WI, USA). Trained and experienced MR technologists performed all the MR examinations. Patients were instructed to fast for a minimum of four hours before the MR scan to reduce potential physiological confounding factors. A torso phased-array coil was placed over the abdomen as the patient lay supine during imaging. Two MR techniques were utilized in the study: for NAFLD diagnosis, hepatic PDFF was estimated by chemical-shift-encoded MRI; for liver fibrosis assessment and diagnosis of significant fibrosis, hepatic stiffness was estimated by MRE. Significant fibrosis was defined as MRE-stiffness ≥ 2.97 kPa according to previous published study.[14] Trained image analysts under the supervision of a faculty radiologist performed the PDFF and stiffness measurements blinded to clinical and biochemical data.

Cardiac computed tomography for CAC

A non-contrast cardiac prospective electrocardiogram-triggered volumetric computed tomography (CT) was performed using a 320-slice CT scanner (Aquilion One, Toshiba Medical Systems, Otawara, Japan). No administered medications for heart rate control or vasodilation were administered before the scan. At the end of inspiration, the patient held their breath as the scan ranged from the base of the heart to the carina; the field of view was 220 mm while the scan collimation was 320×0.5 mm. As determined by the SUREExposure 3D scanner software, a tube current ranging from 40 mA to 580 mA (± 10) at 120 kVp was administered. Rotation time was 0.35 s. Using five filter revolutions, 3 mm thick reconstruction slices were made. The Agatston scoring method, previously

described by a fellowship-trained cardiac radiologist using independent post-processing software (Vital Images, Inc., Minnetonka, MN, USA)[20], was used to quantify CAC. The presence of CAC was defined as coronary artery calcium score > 0.

Statistical analysis

Continuous data were shown with a mean and standard deviation (mean ± SD) or median with interquartile range. Continuous data were compared using Student's t-test or the Mann-Whitney U test after Shapiro-Wilk normality testing. Categorical data were compared by a χ-squared test or Fisher's exact test when more than 20% of cells expected frequencies below 5. The predictive factors for the presence of CAC were analyzed by a logistic regression model with stepwise backward elimination for odds ratio (OR). All statistical analyses were performed using R software (version 3.0, http://cran.r-project.org/, install. packages("devtools")). Logistic regression model-based plotting for probability of the presence of CAC were generated using ggplot2. A two tailed P value of 0.05 was used to determine statistical significance.

RESULTS

Baseline characteristics

105 patients with NAFLD who underwent MRE and cardiac CT for coronary calcium were included in this study. Median interval of cardiac CT and MRE with MRI-PDFF was 4.0 days and not more than 6 months. The average age and body mass index was 54.9 years and 32.9 kg/m^2, respectively. 37 (35.2%) patients had significant liver fibrosis defined as MRE-stiffness 2.97kPa. 52 (49.5%) patients had CAC, with a median coronary artery calcium score of 121.0 [47.0–516.0]. The baseline characteristics of participants with and without CAC are shown in Table 1. Compared to those without CAC, patients with CAC were more likely to be older (50.0[39.0–59.0] vs 63.0[55.5–67.5], $P < 0.001$), more likely to have hypertension (48.1% vs 76.5%, $P = 0.006$), had higher FRS (1.0 [0.5–3.5] vs. 6.0 [2.0–12.0], $P < 0.001$), had lower platelet counts (271.0 [221.0–317.0] vs. 236.5 [192.5–274.0], $P = 0.002$), had higher HOMA-IR (5.3 [3.4–7.9] vs 7.0 [4.6–13.0], $P = 0.016$), had higher FIB-4 (0.8 [0.5–1.0] vs. 1.3 [0.9–1.7], $P < 0.001$) and NFS (-1.6 ± 1.3 vs -0.4 ± 1.2, $P < 0.001$), and were more likely to have higher median MRE-stiffness (2.7 [2.4–3.0] vs. 2.9 [2.4–3.6], $P=0.037$) and significant fibrosis (defined as MRE-stiffness 2.97kPa) (22.6% vs 48.1%, $P = 0.012$).

Association between liver stiffness and CAC in patients with NAFLD

The association between the presence of CAC and liver stiffness is shown in Table 2. In the unadjusted analysis, sex, age, FRS, and liver stiffness were significant factors associated with the presence of CAC. In sex and age-adjusted analysis, liver stiffness (aOR = 2.23, 95% confidence interval [CI] = 1.31–4.34, $P = 0.007$) was independently associated with the presence of CAC (Figure 1a). In FRS-adjusted analysis, liver stiffness (aOR = 2.16, 95% CI = 1.29–4.09, $P = 0.008$) was also independently associated with the presence of CAC (Figure 1b).

Association between significant fibrosis and CAC in patients with NAFLD

Significant fibrosis (defined as MRE-stiffness $\geq$ 2.97 kPa) was independently associated with the presence of CAC in sex and age-adjusted analysis (aOR = 3.53, 95% CI = 1.29–10.48, P = 0.017, Figure 2) as well as in FRS-adjusted analysis (aOR = 3.21, 95% CI = 1.30–8.28, P = 0.013). In addition, the presence of CAC was more prevalent in patients with significant fibrosis than those without (67.6% vs. 39.7%, P = 0.012, Figure 3).

DISCUSSION

Main findings

We demonstrated that liver stiffness by MRE was an independent predictor for the presence of CAC in a well-characterized NAFLD cohort using both sex and age-adjusted and FRS-adjusted analysis. For patients with NAFLD, significant fibrosis (defined by MRE-stiffness $\geq$ 2.97 kPa) was an also independent predictor for the presence of CAC. In addition, CAC was more prevalent in patients with significant fibrosis.

These findings demonstrate that patients with NAFLD and significant fibrosis would be at higher risk for CVD regardless of their traditionally classified risk of CVD. Since NAFLD is prevalent in one fourth of the global population, traditional CVD risk scoring, such as FRS, may not be enough to assess the risk of CVD without accounting for NAFLD. Thus, MRE may benefit patients with NAFLD by helping to predict their risk of CVD.

In context with published literature

Association of NAFLD with CAC has been reported in several cohort studies.[21–24] Most of these studies have demonstrated that NAFLD is an independent risk factor among the traditional risk factors.[21–23] A recent study demonstrated the association of both NAFLD and alcoholic fatty liver disease with CAC in young and middle-aged population.[23] While they also demonstrated association of NAFLD with their severity based on FIB-4 with CAC, their results had limited power as very few subjects had advanced fibrosis.[23]

Association of hepatic fibrosis with the risk of CVD in patients with NAFLD has been reported in several studies.[9,11,25–28] NASH related fibrosis is associated with increased small dense low-density lipoprotein and oxidized phospholipids leading to oxidative stress and mitochondrial damage which may also increase the risk of atherosclerosis.[29,30] Neutralization of these oxidized phospholipids leads to resolution of NASH as well as reduction of atherosclerosis.[30] Most of clinical studies have demonstrated this association using non-invasive assessment for fibrosis based on indirect serum biomarkers, such as NFS and FIB-4 index.[25,26] Only a few studies have demonstrated an association of hepatic fibrosis with the risk of CVD in patients with biopsy-proven NAFLD.[9,11,27] To the best of our knowledge, this is the first study to evaluate the association of CAC with MRE-determined liver stiffness in patients with NAFLD. Unlike other studies[9,11,25,26] which have demonstrated the association of advanced (stage $\geq$ 3) fibrosis with the risk of CVD, we found that significant (stage $\geq$ 2) fibrosis was associated with CAC. As the presence of CAC, a highly specific feature of subclinical coronary atherosclerosis, is associated with subclinical CVD[31], we believe that the presence of CAC is associated with significant fibrosis rather

than advanced fibrosis. Traditional CVD risk scoring models included established risk factors of CVD, such as age, sex, body mass index, race, smoking status, hypertension, diabetes, and dyslipidemia, which predicted 10-year risk of CVD.[7,8] When traditional risk scoring model leads to unclear results, cardiac CT for CAC has been considered to assist treatment decisions.[7] The presence of CAC is known to be associated with increased risk for CVD in many cohort studies.[31] In this study, the prevalence of CAC was approximately 25% higher in patients with significant fibrosis compared to those without. Thus, we believe that MRE in patients with NAFLD may help reduce the burden for radiation exposure in cardiac CT for CAC.

Strengths and limitations

The strengths of this study are as followed: first, this is a cross-sectional study derived from two well-characterized prospective cohorts. Second, unlike previous studies, NAFLD and liver stiffness was defined by MRI-PDFF and MRE, which is one of most reliable modality for assessing liver fibrosis non-invasively. Previous studies using liver biopsy have shown limitations for diagnosing significant fibrosis due to inter- and intra-observer variability. Thus, this study provides new evidence of clinical significance regarding the risk of CVD in patients with NAFLD and significant fibrosis.

However, there are several limitations in this study. First, this study is a single-center study with a relatively small number of patients; therefore, a large scaled, longitudinal study is needed to validate the findings. Second, there was no study investigating association of liver stiffness by MRE or significant fibrosis with CAC, thus we were not able to perform a power analysis. Third, since the patients enrolled in this study were referred to participate in the clinical trial to be evaluated for NAFLD, they had relatively severe NASH compared to a random, general population. In addition, different eligibilities from two studies could cause selection bias. Therefore, further validations from the general population are needed.

Future implications

Even though some patients with NAFLD are classified as low risk of CVD by the traditional risk scoring model, significant fibrosis was an independent predictor for subclinical CVD. These results suggest that FRS is not enough to assess the risk of CVD in patients with NAFLD. Thus, in order to evaluate the risk of CVD in patients with NAFLD, liver stiffness should be considered. In addition, models for assessing the risk of CVD in patients with NAFLD, including traditional risk factors for CVD, need to be investigated in the near future.

In conclusion, liver stiffness by MRE is an independent factor for the risk of the presence of CAC in patients with NAFLD. Patients with MRE   2.97 kPa should be considered for cardiovascular risk assessment, regardless of their FRS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations:

Adipo-IR	Adipose tissue insulin resistance
CAC	coronary artery calcification
CT	computed tomography
CVD	cardiovascular disease
FIB-4	fibrosis-4
FRS	Framingham risk score
HOMA-IR	homoeostatic model assessment of IR
MRE	magnetic resonance elastography
MRI-PDFF	magnetic resonance imaging proton density fat fraction
NAFLD	nonalcoholic fatty liver disease
NFS	NAFLD fibrosis score
UCSD	University of California San Diego

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Figure 1.

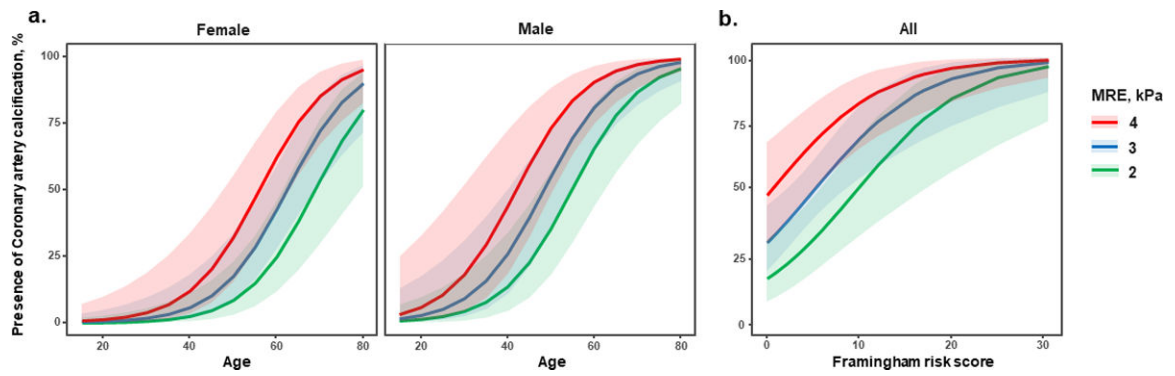Predicted probability of presence of coronary artery calcification (defined as coronary artery calcium score > 0) according to liver stiffness by magnetic resonance elastography in patient with non-alcoholic fatty liver disease (a) Sex and age-adjusted model, (b) Framingham risk score-adjustedmodel

*The area covered by the prediction intervals is 95% confidence interval.

MRE, magnetic resonance elastography
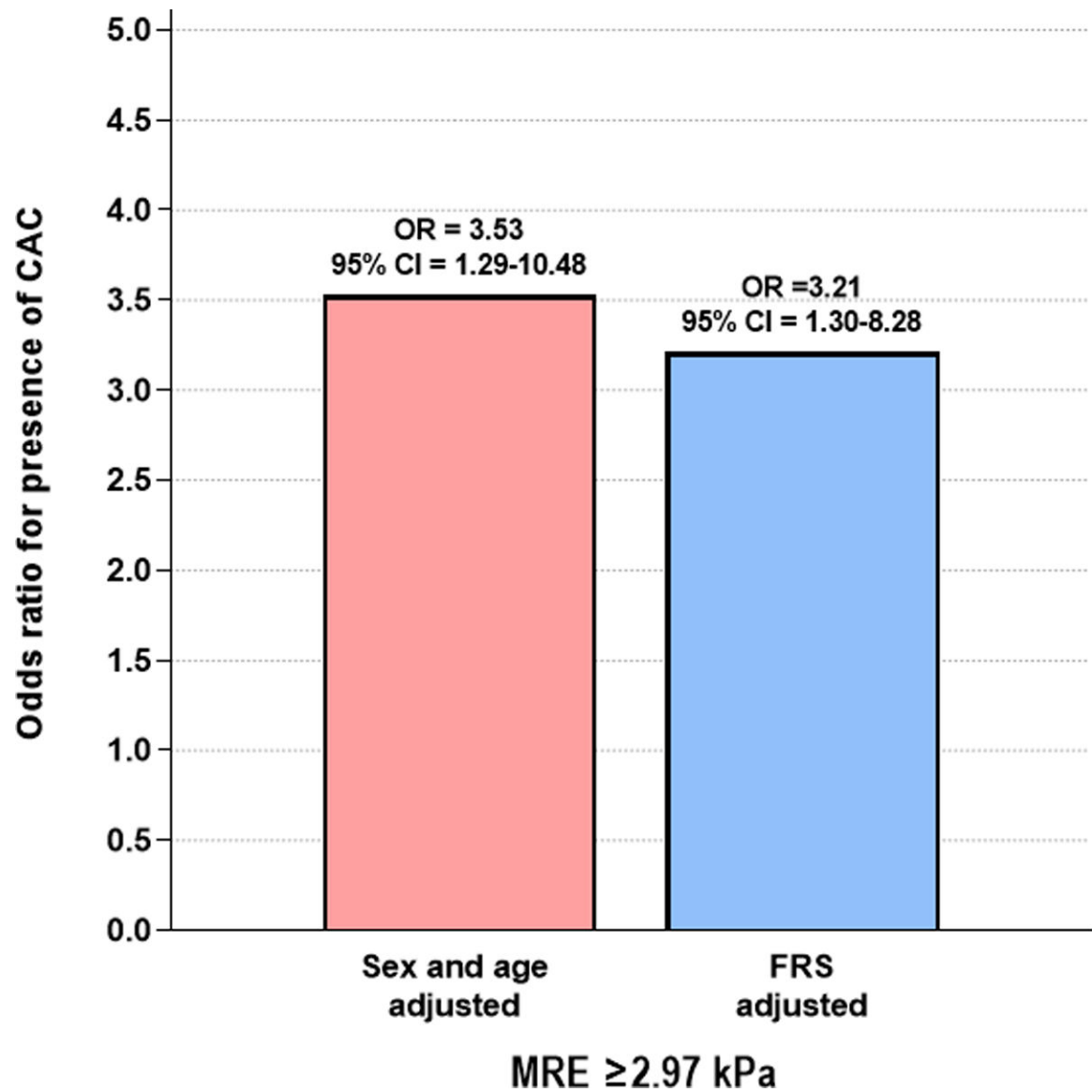
Figure 2.
Odds ratio for the presence of coronary artery calcification (defined as coronary artery
calcium score > 0) in sex and age-adjusted and FRS-adjusted logistic analysis in patients
with non-alcoholic fatty liver disease and significant fibrosis (defined as MRE ≥ 2.97kPa)
MRE, magnetic resonance elastography; FRS, Framingham Risk Score; CAC, coronary
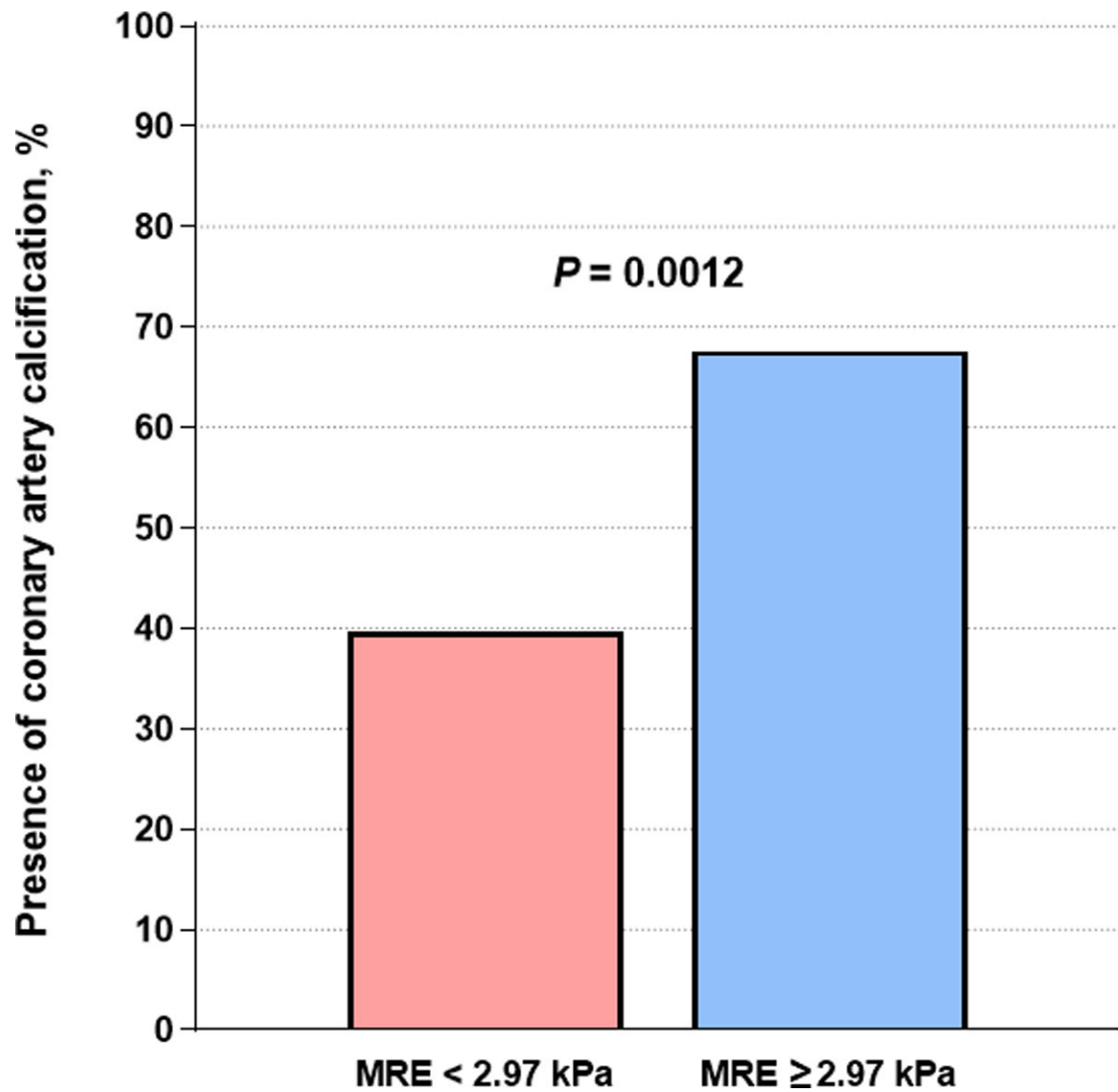artery calcification

Figure 3.
Prevalence of the presence of coronary artery calcification (defined as coronary artery calcium score > 0) in patients with non-alcoholic fatty liver disease according to significant fibrosis (defined as MRE 2.97kPa)
MRE, magnetic resonance elastography

Table 1.

Baseline characteristics

	Absence of CAC group (N=53)	Presence of CAC group (N=52)	*P* value
Male	20 (37.7)	30 (57.7)	0.064
Age, years	50.0 [39.0–59.0]	63.0 [55.5–67.5]	< 0.001 [*]
BMI, kg/m^2	33.3 ± 5.7	32.6 ± 5.0	0.529
Waist circumference, cm	101.0 [96.0–112.5]	105.5[98.8–115.8]	0.139
Race/ethnicity, n (%)			
White	31 (58.5)	34 (65.4)	0.599
Hispanic	17 (32.1)	10 (19.2)	0.200
Hypertension, n (%)	25 (48.1)	39 (76.5)	0.006 [*]
Diabetes mellitus, n (%)	34 (64.2)	45 (86.5)	0.015 [*]
History of smoking, n (%)			
Current smoker	4 (7.7)	3 (5.8)	1.000
Ex-smoker	14 (26.9)	21 (40.4)	0.213
Biochemical data			
Platelet counts, x10^9/L	271.0 [221.0–317.0]	236.5 [192.5–274.0]	0.002 [*]
AST, U/L	30.0 [23.0–45.5]	31.0 [20.5–41.0]	0.430
ALT, U/L	31.0 [20.0–55.0]	24.0 [18.5–34.0]	0.030 [*]
Total bilirubin, mg/dL	0.4 [0.3–0.6]	0.5 [0.3–0.7]	0.245
Albumin, g/dL	4.5 ± 0.2	4.5 ± 0.3	0.356
Alkaline phosphatase, U/L	72.0 [57.0–87.0]	73.0 [64.5–89.0]	0.463
GGT, U/L	30.0 [21.5–49.5]	32.0 [24.5–50.5]	0.595
Lipid profile			
Total cholesterol, mg/dL	186.6 ± 39.4	173.8 ± 33.2	0.075
HDL, mg/dL	49.0 [40.5–60.0]	49.0 [38.5–59.0]	0.753
LDL, mg/dL	99.0 [80.0–119.0]	88.0 [70.5–112.5]	0.141
TG, mg/dL	153.0 [113.0–189.0]	147.5 [107.5–189.5]	0.703
Metabolic data			
Fasting glucose, mg/dL	111.0 [99.0–135.0]	132.0 [98.5–160.5]	0.158
HOMA-IR	5.3 [3.4–7.9]	7.0 [4.6–13.0]	0.016 [*]
Adipo-IR	8.7 [6.5–12.6]	11.8 [6.9–22.6]	0.053
Use of statin, n (%)	15 (28.3)	30 (57.7)	0.004 [*]
Framingham risk score	1.0 [0.5–3.5]	6.0 [2.0–12.0]	< 0.001 [*]
20%, n (%)	1 (1.9)	8 (15.4)	0.031 [*]
10%, n (%)	45 (86.5)	30 (57.7)	0.002 [*]
MRI PDFF, %	12.6 [9.6–20.5]	12.3 [6.9–17.8]	0.213
15.7%, n (%)	19 (35.8)	19 (36.5)	1.000

	Absence of CAC group (N=53)	Presence of CAC group (N=52)	P value
MRE, kPa	2.7 [2.4–3.0]	2.9 [2.4–3.6]	0.037*
4.69, n (%)	0 (0.0)	7 (13.5)	0.006*
3.62, n (%)	6 (11.3)	12 (23.1)	0.181
2.97, n (%)	12 (22.6)	25 (48.1)	0.012*
FIB-4	0.8 [0.5–1.0]	1.3 [0.9–1.7]	< 0.001*
> 2.67, n (%)	0 (0.0)	6 (11.5)	0.013*
NFS	−1.6 ± 1.3	−0.4 ± 1.2	< 0.001*
0.676, n (%)	2 (3.8)	9 (17.3)	0.052
Coronary artery calcium score		121.0 [47.0–516.0]	

*P value < 0.05

Data are expressed as median or mean, and interquartile range (IQR) or numbers (%).

Calculated by Student's t test (or the Mann-Whitney U test, if appropriate) and chi-squared test (or Fisher's exact test, if appropriate)

Presence of coronary artery calcification is defined as coronary artery calcium score > 0

CAC, coronary artery calcification; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma glutamyl transferase; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; HOMA-IR, homoeostatic model assessment of insulin resistance; Adipo-IR, Adipose tissue insulin resistance; MRI PDFF, magnetic resonance imaging proton density fat fraction; MRE, magnetic resonance elastography; FIB-4, fibrosis-4; NFS, non-alcoholic fatty liver disease fibrosis score

Table 2.

Association between presence of coronary artery calcification and liver stiffness by MRE

		Male	**Age, years**	**MRE, kPa**	**FRS**	
Unadjusted analysis	OR (95% CI)	2.25 (1.04–4.98)	1.11 (1.07–1.17)	1.99 (1.24–3.56)	1.17 (1.08–1.28)	
	P value	0.042[*]	< 0.001[*]	0.010[*]	< 0.001[*]	

		Sex and age-adjusted model			FRS-adjusted model[§]	
		Male	Age, years	MRE, kPa	FRS	MRE, kPa
Multivariable-adjusted analysis	OR (95% CI)	5.76 (2.04–18.31)	1.13 (1.08–1.21)	2.23 (1.31–4.34)	1.18 (1.09–1.30)	2.16 (1.29–4.09)
	P value	0.002[*]	< 0.001[*]	0.007[*]	< 0.001[*]	0.008[*]

[*]*P* value < 0.05

[§]FRS includes age, sex, history of smoking, total cholesterol, high density lipoprotein cholesterol, systolic blood pressure, medication for hypertension, diabetes, and history of vascular disease.

FRS, Framingham risk score; MRE, magnetic resonance elastography