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Clinical utility of liver fat quantification for determining cardiovascular disease risk among patients with type 2 diabetes

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Summary

Background: Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) are independent risk factors for cardiovascular disease (CVD).

Aims: To examine the clinical utility of liver fat quantification for determining CVD risk among a well-phenotyped cohort of patients with T2DM.

Methods: This was a cross-sectional analysis of a prospective cohort of adults aged ≥50 with T2DM. Liver fat was quantified with magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF), an advanced imaging-based biomarker. Patients were stratified into a higher liver fat group (MRI-PDFF ≥ 14.6%), and a lower liver fat group (MRI-PDFF < 14.6%). The co-primary outcomes were CVD risk determined by Framingham and Atherosclerotic Cardiovascular Disease (ASCVD) risk scores. High CVD risk was defined by risk scores ≥20%.

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AUTHOR CONTRIBUTIONS

Selena Zhao Kuo: Data curation (equal); formal analysis (equal); writing – original draft (equal); writing – review and editing (equal). **Sandra Cepin:** Data curation (equal); formal analysis (equal); writing – original draft (equal); writing – review and editing (equal). **Jaclyn Bergstrom:** Data curation (equal); formal analysis (equal); writing – review and editing (equal). **Harris Siddiqi:** Writing – review and editing (equal). **Jinho Jung:** Writing – review and editing (equal). **Scarlett Lopez:** Writing – review and editing (equal). **Daniel Huang:** Writing – review and editing (equal). **Pam Taub:** Writing – review and editing (equal). **Maral Amangurbanova:** Writing – review and editing (equal). **Rohit Loomba:** Conceptualization (equal); data curation (equal); funding acquisition (equal); methodology (equal); project administration (equal); writing – review and editing (equal).

AUTHORSHIP

Guarantor of the article: Dr. Rohit Loomba.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

Results: Of the 391 adults (66% female) in this study, the mean (±SD) age was 64 (±8) years and BMI 30.8 (±5.2) kg/m^2, respectively. In multivariable analysis, adjusted for age, gender, race, and BMI, patients in the higher liver fat group had higher CVD risk [OR = 4.04 (95% CI: 2.07–7.88, $p < 0.0001$)] and ASCVD risk score [OR = 2.85 (95% CI: 1.19–6.83, $p = 0.018$)], respectively.

Conclusion: Higher liver fat content increases CVD risk independently of age, gender, ethnicity and BMI. These findings raise the question whether liver fat quantification should be incorporated into risk calculators to further stratify those with higher CVD risk.

1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease worldwide, particularly in Western countries.[1,2] In the United States, NAFLD is estimated to affect approximately one-third of the adult population and is strongly associated with metabolic syndrome, obesity, and type 2 diabetes mellitus (T2DM).[3,4] There is a particularly high prevalence of NAFLD in individuals with T2DM, with some studies suggesting around one-third to two-thirds of patients with T2DM have NAFLD.[5–7]

Patients with T2DM and NAFLD are independently at increased risk of CVD,[8–10] with CVD being the most common cause of mortality among both patients with T2DM and patients with NAFLD.[4,8] In a cross-sectional analysis of a case–control study in patients with biopsy-proven NAFLD and individuals without NAFLD, increased liver fat content in NAFLD patients was associated with increased rates of metabolic syndrome, and subsequently increased CVD risk.[11] Liver fat quantity was determined using magnetic resonance imaging proton density fat fraction (MRI-PDFF), the most accurate, quantitative biomarker of liver fat.[12–16]

While previous studies have shown an association between a diagnosis of NAFLD and CVD risk, there is a current gap in knowledge about whether higher liver fat content is associated with even higher CVD risk among patients with T2DM, who are already at increased risk. It is currently unknown whether liver fat quantification using MRI-PDFF would further risk stratify CVD risk among patients with T2DM. We hypothesized that higher quantity of liver fat would be associated with higher risk of CVD in patients with T2DM. The aim of this study was to examine the clinical utility of liver fat quantification in determining CVD risk among a well-phenotyped cohort of patients with T2DM.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a cross-sectional analysis of a prospective cohort study of adults with T2DM conducted at the NAFLD Research Center at the University of California, San Diego (UCSD). Participants were recruited from primary care and endocrinology clinics in the greater San Diego area as well as through the distribution of educational brochures, ads in local newspapers, local fairs, and social media. This analysis included 391 patients who underwent a standardised research visit including history, physical exam, biochemical testing, and imaging assessment including MRI-PDFF, magnetic resonance elastography (MRE), and vibration-controlled transient elastography (VCTE) between 2016 and 2022 at

the UCSD NAFLD Research Center.[17–20] All patients provided written informed consent before enrollment and the study was approved by the UCSD Institutional Review Board.

2.2 | Inclusion and exclusion criteria

Participants included were ages 50–80 years old. The diagnosis of T2DM was made based on the presence of one or more of the following criteria: diabetes symptoms and plasma glucose ≥200 mg/dL or fasting plasma glucose ≥126 mg/dL or plasma glucose ≥200 mg/dL during a 75-g oral glucose tolerance test on two separate tests or HbA1c ≥ 6.5%, as per American Diabetes Association recommendations. All patients had HbA1c and glucose assessed as part of the study protocol. Alcohol consumption was assessed in the research clinic using the Alcohol Use Disorders Identifications Test (AUDIT) and the Skinner questionnaire. Other causes of liver disease were systematically ruled out based on history and laboratory tests. Participants were excluded from the study if they had significant alcohol intake (defined as ≥14 drinks/week for men or ≥7 drinks/week for women) within the previous 2-year period, biochemical evidence of liver disease other than NAFLD, or if they had a previous history of CVD. Patients with MRE ≥ 3.62 kPA and MRI-PDFF < 5% ($N = 18$) were excluded, as this group may represent advanced fibrosis with burnt-out NASH.

2.3 | Clinical assessment and laboratory tests

All patients underwent a standardised clinical evaluation including a detailed history and a physical examination, which included vital signs, height, weight, and anthropometric measurements, performed by a trained clinical investigator. Body mass index (BMI) was defined as the body weight (kg) divided by height (m) squared. Alcohol consumption was documented outside clinical visits and confirmed in the research clinic using the Alcohol Use Disorders Identifications Test (AUDIT) and the Skinner questionnaire. Patients underwent the following biochemical tests: glucose, albumin, haemoglobin A1c, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, fasting lipid panel, platelets, insulin, international normalised ratio. Participants were instructed to fast for a minimum of 8 h before the collection of laboratory tests.

2.4 | Magnetic resonance imaging

Participants underwent a non-contrast MR (magnetic resonance) exam with liver fat quantification and liver stiffness assessment using MRI-PDFF and MRE.[12–15,17,18,20–22] Imaging was performed at the UCSD MR3T Research Laboratory using a 3T research scanner (GE Signa EXCITE HDxt; GE Healthcare). Liver stiffness data were obtained using 2D MRE at 60 Hz. Acquired MR images were interpreted by a radiologist who was blinded to clinical and laboratory data.

2.5 | Vibration controlled transient elastography

CAP for the detection of liver fat and VCTE for the quantification of liver stiffness were obtained using FibroScan® (Echosens).[12] All exams were performed by an experienced technician after a minimum fast of 4 h as recommended.[21] During patient breath holding, a minimum of 10 repeated valid measurements, assessed automatically by the FibroScan®

system, was performed. All participants were first scanned using the M probe (3.5 MHz). If indicated upon initial assessment, participants were re-scanned using the XL probe (2.5 MHz).

2.6 | Outcome measures

The co-primary outcomes were the association of high liver fat (defined a priori as the top quartile of MRI-PDFF) with CVD risk determined by Framingham and Atherosclerotic Cardiovascular Disease (ASCVD) risk scores. High CVD risk, as determined by Framingham risk score (FRS), was defined as 10-year cardiovascular risk ≥20%. CVD is defined as a composite of coronary heart disease (coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular events (including ischemic stroke, hemorrhagic stroke, and transient ischemic attack), peripheral artery disease (intermittent claudication), and heart failure.[23] High CVD risk, as determined by the ASCVD risk score, was defined as a 10-year cardiovascular risk ≥20%. The 10-year risk was defined as the risk of developing a first ASCVD event, defined as nonfatal myocardial infarction or coronary heart disease (CHD) death or fatal or nonfatal stroke, over 10 years among people free from ASCVD at the beginning of the period.[24]

2.7 | Statistical analysis

For patient characteristics, a *t* test was performed on continuous variables presented as mean (SD) and Kruskal–Wallis performed on those presented as median (IQR). Chi-square or Fisher's exact test was performed as appropriate on all categorical variables. Unadjusted logistic regression was used to assess for the association between liver fat content, determined by MRI-PDFF, and elevated CVD risk, defined as FRS or ASCVD 10-year risk score ≥20%, among patients with T2DM. Multivariable logistic regression was performed, adjusting for age, gender, ethnicity, and BMI. The current sample size is powered at 0.8 with two-tailed $\alpha = 0.05$. All statistical analyses were performed using SAS 9.4 (SAS Institute) and supervised by an experienced statistician. A $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Study population characteristics

A total of 391 patients with T2DM were included in this study. Participants had a mean age of 64 (±8) years and were predominately female (66%). The mean liver fat content by MRI-PDFF was 10.3 (±7.8), 69% of the population had NAFLD (MRI-PDFF ≥ 5%) and 5.6% had advanced fibrosis (MRE ≥ 3.63 kPa or VCTE ≥ 8.8 kPa). The patients were stratified into two groups based on their liver fat content as determined by MRI-PDFF. The group with higher liver fat consisted of those with MRI-PDFF measurements within the highest quartile (MRI-PDFF ≥ 14.6%; $N = 97$) and was compared against the group with lower liver fat (MRI-PDFF < 14.6%; $N = 294$). Those in the group with higher liver fat were younger (62 vs. 67; $p < 0.01$) and consisted of fewer males (22% vs. 38%; $p < 0.01$) compared to those in the lower liver fat group. Table 1 provides the full quantitative data on other baseline characteristics and laboratory results stratified by liver fat.

3.2 | Prevalence of cardiovascular disease risk factors

Compared to those in the lower liver fat group, patients in the higher liver fat group had a higher median BMI (32.1 vs. 30.2 kg/m^2; $p = 0.015$), higher Hgb A1c (7.2 vs 6.7%; $p = 0.019$), lower HDL levels (44 vs. 47 mg/dL; $p = 0.04$), higher LDL levels (99 vs. 85 mg/dL; $p < 0.01$), and higher triglyceride levels (170 vs. 137.5 mg/dL; $p < 0.01$). The higher liver fat group was associated with more severe insulin resistance as assessed by the HOMA-IR (5.8 vs. 4.6; $p = 0.01$) and Adipo-IR scores (13.5 vs 8.4; $p < 0.001$), respectively. Both groups had similar waist circumference, fasting glucose levels, and a similar quantity of patients on anti-hypertensive medications. Both groups had similar rates of insulin and metformin use, which were the most common diabetic medications reported. Only 58% of patients in the higher liver fat group were using a statin compared to 71% of patients in the lower liver fat group (Table 2).

3.3 | Association between liver fat quantity and cardiovascular disease risk

In multivariable analysis, after adjusting for age, gender, BMI, and race, higher liver fat was significantly associated with a high risk of cardiovascular disease by both Framingham Risk (adjusted OR = 4.04; 95% CI: 2.07–7.88) and ASCVD Risk (adjusted OR = 2.85; 95% CI: 1.19–6.83). The multivariable analysis is depicted in Figure 1 and the full model is provided in Figure 2. Each 5% increase in MRI-PDFF in the multivariable analysis was associated with both Framingham Risk ≥20% (adjusted OR = 1.56 95% CI: 1.28–1.90) and ASCVD ≥ 20% (adjusted OR = 1.27 95% CI: 1.01–1.59) (Table 3). In multivariable analysis, after adjusting for age, gender, BMI, and race, higher liver fat as characterised by the highest quartile CAP score (CAP ≥ 351) was significantly associated with high CVD risk by Framingham Risk (adjusted OR = 2.52; 95% CI: 1.28–4.94) but not ASCVD Risk (adjusted OR = 2.02; CI: 0.79–5.16) (Table S1). MRI-PDFF and CAP are significantly correlated ($r = 0.63$ $p < 0.0001$) but there is a discordance between those in the highest quartile of each (Figure S1).

The association between higher liver fat and Framingham risk ≥20% (adjusted OR = 3.74 95% CI: 1.87–7.49) and ASCVD risk ≥20% (adjusted OR = 2.74 95% CI: 1.10–6.80) remained consistent after adjustment for statin use (Table S1). The direction of results remained consistent even after adjustment for cholesterol, smoking, blood pressure, and the use of anti-hypertensives (Table S1).

4 | DISCUSSION

By using a well-phenotyped, prospective cohort of older adults with T2DM, we demonstrated in this study that an increased quantity of liver fat, as measured by MRI-PDFF, is associated with a higher risk of cardiovascular disease independent of age, gender, race/ethnicity and BMI. Despite a higher prevalence of cardiovascular disease risk factors in the higher liver fat group, there were lower rates of statin use in this group (58%) compared to those with lower liver fat content. Overall, these findings support the potential clinical utility of quantifying liver fat to further risk stratify those with higher CVD risk among patients with T2DM.

4.1 | In context with published literature

Multiple prospective studies have shown that a diagnosis of NAFLD is associated with an increased incidence of major CVD events, independent of other cardiovascular risk factors.[9,11,25,26] In a prospective cohort of patients with T2DM, NAFLD as diagnosed by ultrasound, was found to be an independent predictor of incident cardiovascular events.[27] These studies used liver ultrasonography to diagnose NAFLD and therefore were unable to quantify liver fat. Our study is the first to utilise advanced MRI-based imaging to accurately quantify liver fat with CVD risk in patients with T2DM.[13] NAFLD is associated with cardiovascular disease, and so is T2DM. Furthermore, T2DM is considered CVD risk equivalent. However, there are limited data on whether the quantity of liver fat may modify the CVD risk among patients with T2DM who are already considered at high risk for CVD. This study fills that gap in knowledge by providing new data that the quantity of liver fat further risk stratifies CVD risk even among those with T2DM who are already considered CVD risk equivalent. Similar to previous studies, we demonstrate that there is a high prevalence of NAFLD (69%) in patients with diabetes. Furthermore, our study adds novel information that higher liver fat (MRI-PDFF ≥ 14.6%) was associated with higher CVD risk, and each 5% increase in MRI-PDFF correlated with higher CVD risk. This is in contrast to the conventional thinking that there is a threshold effect after diagnosing NAFLD and that increases in the quantity of liver fat are not clinically significant.[28,29]

4.2 | Strengths and limitations

Strengths of this study include its prospective design, well-phenotyped cohort, and the use of the advanced imaging modality of MRI which provides the most accurate quantification of liver fat content as measured by PDFF. A limitation of the study is that it was performed at a single-center research unit and will require external validation to examine generalizability. In addition, the threshold for high liver fat requires further validation in distinct cohorts. This study population has a significant proportion of Hispanic patients, whereas the ASCVD and Framingham risk calculators are best validated in non-Hispanic populations, and potentially overestimate the CVD risk in this cohort.[30–32] However, there are no available ethnicity-specific risk algorithms, and per guidelines, these risk calculators can still be applied to help guide clinical decision-making.[32] Furthermore, ethnicity was adjusted for in our multivariable model. There was a lower proportion of Hispanic people in the group with lower liver fat, but it is hard to make firm conclusions as the number of participants stratified by race/ethnicity was limited. The current study is cross-sectional, which limits the ability to determine causality and this study reports outcomes as determined by cardiovascular risk calculators rather than cardiovascular outcomes. Further long-term prospective studies will need to validate if high risk for CVD as defined by the risk calculators, translates into clinical CVD events and increased cardiovascular mortality.

4.3 | Implications for clinical practice and future research

In patients with type 2 diabetes, where the prevalence of NAFLD is high, our study supports the notion that quantifying liver fat can be an additional prognostic factor to risk stratify those at the highest risk of CVD in a patient population where CVD is the leading cause of mortality. If liver fat quantity can be used to identify patients at the highest CVD risk, we

can target those that need earlier and more aggressive CVD risk modification. This includes interventions such as optimising lipid-lowering therapy, which is underutilised in previous studies[33] and our study population. Further research is needed to determine if there are optimal targets for liver fat quantity and whether a reduction in liver fat leads to decreased CVD risk in patients with T2DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of personal interests: All authors approved the final version of this manuscript.

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CONFLICT OF INTEREST STATEMENT

RL serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics. In addition, his institutions received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes and Terns Pharmaceuticals. Co-founder of LipoNexus Inc. PT serves as a consultant to Amarin, Amgen, Bayer, Boehringer Ingelheim, Edwards, Esperion, Medtronic, Novartis, Novo-Nordisk, and Sanofi and is a shareholder of Epirium Bio.

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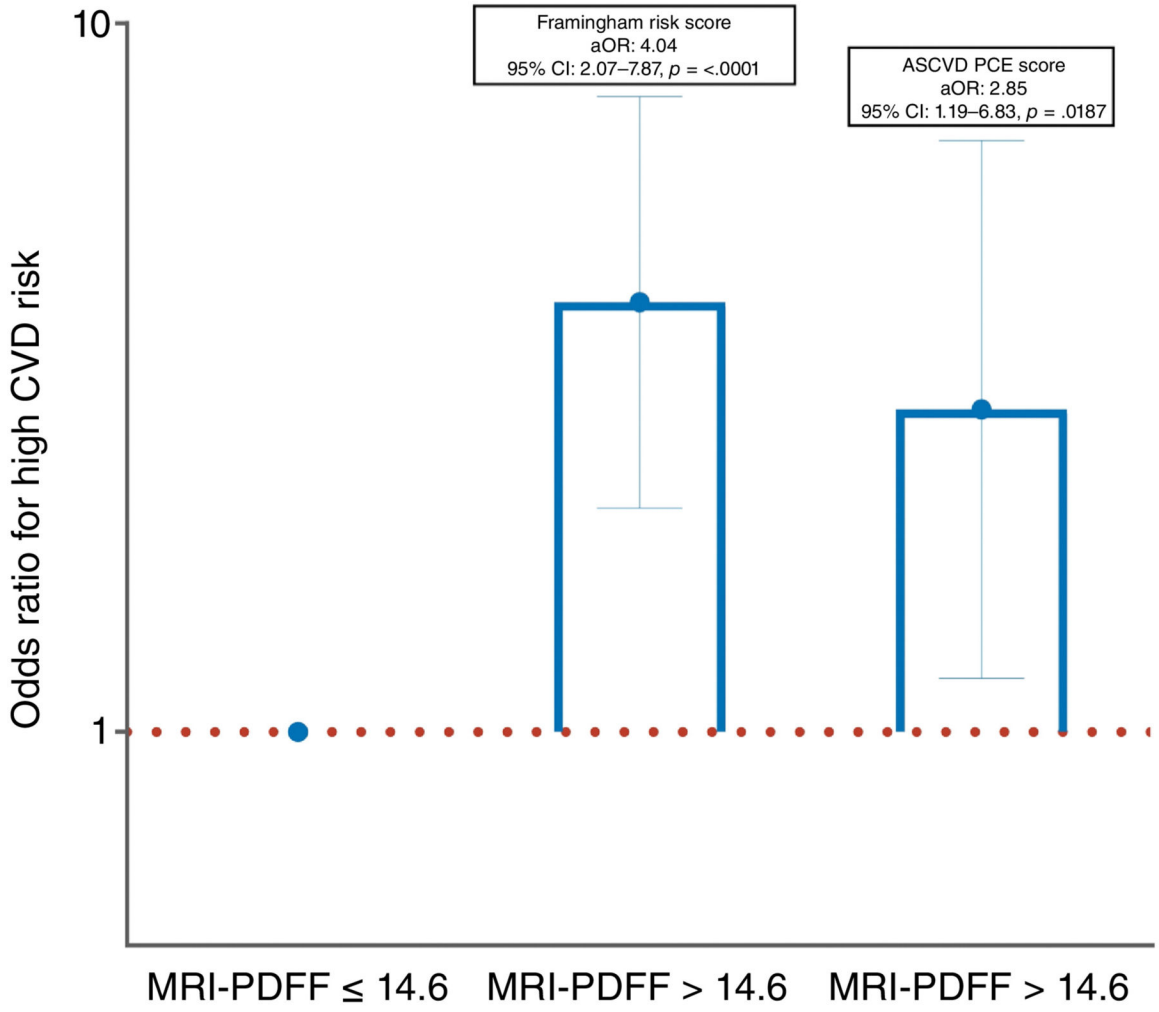

FIGURE 1.

Multivariable analysis for CVD risk score stratified by higher (MRI-PDFF > 14.6) and lower liver fat groups (MRI-PDFF < 14.6). Adjusted for age, gender, race, and BMI. MRI-PDFF high quartile is associated with CVD risk > 20%.

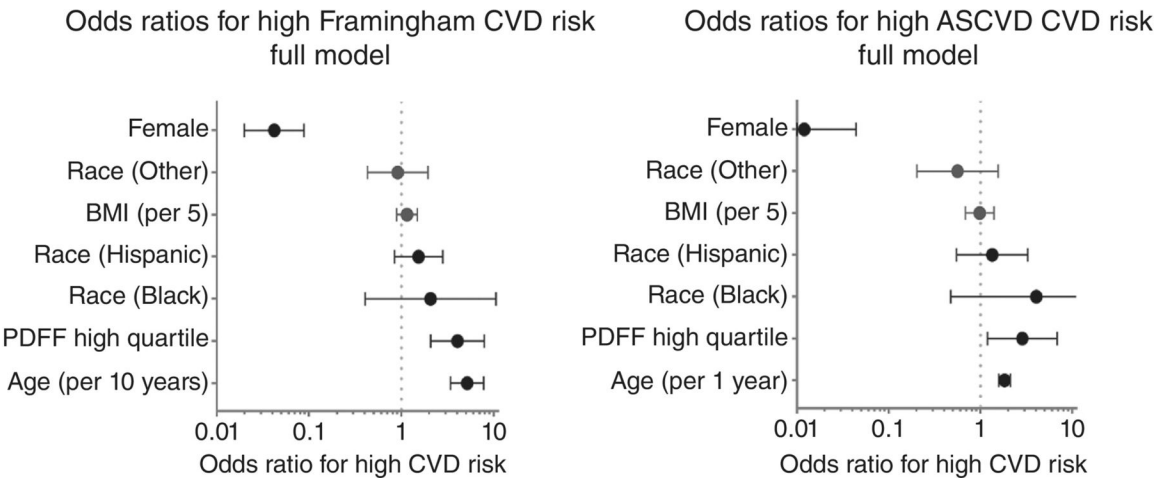

FIGURE 2.

The adjusted odds ratio for high cardiovascular risk. Full multivariable model forest plots.

TABLE 1.

Baseline characteristics by liver fat [*N* (%), median (IQR)].

	PDFF < 14.6 (*N* = 294)	**PDFF ≥ 14.6 (*N* = 97)**	***p* value**
Male, *n* (%)	113 (38%)	21 (22%)	0.0025
Age, years	67.0 (14.0)	62.0 (11.0)	0.0002
BMI, kg/m^2	30.2 (6.4)	32.1 (6.4)	0.0154
Waist circumference, cm	102.0 (19.0)	103.0 (16.0)	0.2136
Race/ethnicity, *n* (%)			
White	97 (34%)	40 (42%)	0.0019
Hispanic	137 (48%)	25 (26%)	
Black	8 (3%)	3 (3%)	
Other	46 (16%)	27 (28%)	
Biochemical data			
Platelet counts, ×10^9/L	244.0 (88.0)	254.0 (77.0)	0.0430
AST, U/L	22.0 (11.0)	35.0 (23.0)	<0.0001
ALT, U/L	22.0 (17.0)	41.0 (37.0)	<0.0001
Total bilirubin, mg/dL	0.44 (0.24)	0.45 (0.22)	0.8572
Albumin, g/dL	4.4 (0.3)	4.5 (0.4)	0.0233
Alkaline phosphatase, U/L	80.0 (32.0)	80.0 (34.0)	0.9594
GGT, U/L	26.0 (22.0)	41.0 (30.5)	<0.0001
Ferritin	90.0 (135.0)	153.0 (195.5)	0.0003
Imaging findings			
MRI-PDFF, %	6.2 (6.8)	20.0 (6.4)	<0.0001
CAP, dB/m	302.0 (68.5)	356.0 (39.0)	<0.0001
NAFLD[a], *n* (%)	172 (59%)	97 (100%)	<0.0001

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; GGT, gamma glutamyl transferase; HDL, high density lipoprotein; LDL, low density lipoprotein; MRE, magnetic resonance elastography; MRI PDFF, magnetic resonance imaging proton density fat fraction; TG, triglyceride; VCTE, vibration-controlled transient elastography.

[a]NAFLD is defined as MRI-PDFF ≥ 5%.

TABLE 2.

Cardiovascular risk factors stratified by liver fat [*N* (%), median (IQR)][a].

	PDFF < 14.6 (*N* = 294)	PDFF ≥ 14.6 (*N* = 97)	*p* value
Hypertension, *n* (%)	187 (64%)	57 (59%)	0.3932
Antihypertensive med, *n* (%)	214 (73%)	75 (77%)	0.3782
SBP	130.0 (22.0)	136.0 (21.0)	0.0015
DBP	72.0 (15.5)	76.0 (14.0)	0.0142
History of smoking, *n* (%)			
Current smoker	17 (6%)	4 (4%)	0.2387
Ex-smoker	89 (30%)	22 (23%)	
Never	187 (73%)	71 (73%)	
HgbA1c	6.7 (1.6)	7.2 (1.6)	0.0197
Lipid profile			
Total cholesterol, mg/dL	164.5 (52.0)	181.0 (68.0)	0.0037
HDL, mg/dL	47.0 (16.0)	44.0 (12.0)	0.0445
LDL, mg/dL	85.0 (43.0)	99.0 (56.5)	0.0082
Non-HDL, mg/dL	112.5 (51.0)	135.0 (56.0)	0.0004
TG, mg/dL	137.5 (85.0)	170.0 (94.0)	0.0004
Metabolic data			
Fasting glucose, mg/dL	122.0 (42.0)	121.0 (52.0)	0.7266
HOMA-IR	4.6 (5.3)	5.8 (6.8)	0.0105
Adipo-IR	8.4 (8.5)	13.5 (11.1)	<0.0001
Use of a statin, *n* (%)	203 (71%)	54 (58%)	0.0181
Use of a fibrate, *n* (%)	12 (4.1%)	5 (5.2%)	0.6532
Use of insulin, *n* (%)	55 (19%)	17 (18%)	0.7840
Use of metformin, *n* (%)	219 (75%)	69 (71%)	0.4832
Cardiovascular risk scores			
Framingham risk score	21.5 (16.3)	24.8 (16.3)	0.4839
High-risk ≥20%, *n* (%)	167 (57%)	58 (60%)	0.6053
ASCVD risk score	20.2 (26.4)	15.2 (16.3)	0.0027
High-risk ≥20%, *n* (%)	149 (51%)	35 (36%)	0.0125

Abbreviations: Adipo-IR, adipose tissue insulin resistance; HOMA-IR, homoeostatic model assessment of insulin resistance.

[a]Data are expressed as either number (%) or mean (SD), median (interquartile range), as indicated.

TABLE 3.

Unadjusted and adjusted[a] odds of high CVD risk based on liver fat content.

	MRI-PDFF per 5% increase OR (95% CI)	NAFLD MRI-PDFF ≥5% OR (95% CI)	High quartile MRI-PDFF ≥14.6 OR (95% CI)
Framingham risk score ≥20%			
Unadjusted	1.02 (0.9–1.2)	1.01 (0.66–1.56)	1.13 (0.71–1.80)
Adjusted	1.56 (1.28–1.90)	2.93 (1.59–5.38)	4.04 (2.07–7.88)
ASCVD risk score ≥20%			
Unadjusted	0.78 (0.68–0.89)	0.41 (0.26–0.63)	0.55 (0.34–0.88)
Adjusted	1.27 (1.01–1.59)	1.29 (0.57–2.90)	2.85 (1.19–6.83)

[a]Adjusted for age, gender, race, BMI.