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# Subclinical Hepatic Fibrosis is Associated with Coronary Microvascular Dysfunction by Myocardial Perfusion Reserve Index: A retrospective cohort study

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## Abstract

**Background.—**The heart-liver axis is of growing importance. Previous studies have identified independent association of liver dysfunction and fibrosis with adverse cardiac outcomes, but mechanistic pathways remain uncertain. We sought to understand the relations between the degree of hepatic fibrosis identified by the Fibrosis-4 (Fib-4) risk score and comprehensive cardiac MRI (CMR) measures of subclinical cardiac disease.

**Methods.—**We conducted a retrospective single-center cohort study of patients between 2011–2021. We identified consecutive patients who underwent a comprehensive CMR imaging protocol including contrast enhanced with stress/rest perfusion, and lacked pre-existing cardiovascular disease or perfusion abnormalities on CMR. We examined the association of hepatic fibrosis, using the Fibrosis-4 (Fib-4) score, with subclinical cardiac disease on CMR while adjusting for cardiometabolic traits. Given known associations of hepatic disease and coronary microvascular dysfunction, we prioritized analyses with the myocardial perfusion reserve index (MPRI), a marker of coronary microvascular function.

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**Competing Interests:** Dr Merz serves on the Board of Directors for iRhythm and has received fees paid through Cedars-Sinai Medical Center from Abbott Diagnostics and Sanofi. Dr Wei has served on an advisory board for Abbott Vascular. The other authors report no relevant conflicts.

**Ethics Approval:** Study was approved by Cedars Sinai IRB with informed consent waived due to retrospective study.

**Results.—**Of the 66 patients in our study cohort, 54 were female (81%) and the mean age was 53.7±15.3 years. We found that higher Fib-4 was associated with reduction in the MPRI (beta [SE]: −1.12 [0.46], P=0.02), after adjusting for cardiometabolic risk factors. Importantly, Fib-4 was not significantly associated with any other CMR phenotypes including measures of cardiac remodeling, inflammation, fibrosis, or dysfunction.

**Conclusions.—**We found evidence that hepatic fibrosis associated with coronary microvascular dysfunction, in the absence of overt associations with any other subclinical cardiac disease measures. These findings highlight a potentially important precursor pathway leading to development of subsequent heart-liver disease.

### Keywords

Cardiac MRI; hepatic fibrosis; coronary perfusion

## BACKGROUND

The importance of interconnected heart-liver pathophysiology is becoming increasingly evident. It has long been recognized that advanced fibrosis in liver disease is independently associated with higher risk for adverse cardiac outcomes even after accounting for different etiologies of cirrhosis.(1) Currently evolving demographic landscapes have increased attention on less severe but more prevalent hepatic conditions such as metabolic fatty liver disease, which is estimated to have a 25% worldwide prevalence based on imaging screening and surveillance data.(2, 3) Although fatty liver phenotypes can progress to advanced liver disease manifesting as cirrhosis or hepatocellular carcinoma, the most common cause of death among affected individuals is cardiovascular disease.(4, 5) Currently proposed pathways have included hepatically generated constituents that can incite inflammation, thrombogenicity, and fibrosis (Figure 1), all of which are mechanistically implicated in the development of endothelial dysfunction, accelerated atherosclerosis, and adverse cardiac remodeling.(6) While relatively understudied, putative pathways involving endothelial dysfunction are of particular interest given they could represent among the earliest phases of heart-liver pathogenesis and, in turn, targets for early intervention. An improved understanding of pre-clinical pathophysiology is needed given that advancing forms of hepatic disease are related cardiovascular outcomes even after adjusting for shared risk factors.(7, 8) Therefore, to further investigate mechanisms underlying hepatic and cardiac disease, we applied a comprehensive cardiac magnetic resonance imaging (CMR) phenotyping approach to assessing preclinical cardiac structural and functional alterations associated with hepatic dysfunction. Given the paucity of data relating preclinical hepatic disease with endothelial and microvascular phenotypes, we prioritized analyses of hepatic fibrosis and coronary microvascular dysfunction.

## METHODS

### Study Population

We conducted a single-center cohort study of patients with comprehensive CMR performed at a quaternary care center between 2011–2021. We identified patients who underwent

a complete CMR protocol that included contrast enhanced imaging with stress and rest perfusion as this is required for measurement of myocardial perfusion reserve index (MPRI), an established measure of coronary microvascular function.(9) To avoid potential confounding by pre-existing cardiac conditions, we excluded patients with evidence of pre-existing epicardial coronary disease including those with visible perfusion defects on stress CMR (N=21). We then identified those patients with laboratory markers of hepatic function (i.e. AST, ALT, and platelet count) assayed within 12 months of the CMR acquisition. Our final study sample of N=66 patients included those with both the comprehensive CMR measurement data available and laboratory markers of hepatic function available (Supplemental Table 1). All study protocols were approved by the Cedars-Sinai Medical Center institutional review board.

## Measures of Subclinical Cardiac Disease

We characterized subclinical cardiac disease using established CMR measures of cardiac structure and function involving assessments of cardiac remodeling, tissue composition, and coronary microvascular perfusion. The CMR measures were performed as part of standard clinical assessments and included the *a priori* prioritized myocardial perfusion reserve index (MPRI) in addition to left ventricular ejection fraction (LVEF), presence of left atrial enlargement, relative wall thickness (RWT), left ventricular mass index (LVMI), T1 time, T2 time, and extracellular volume (ECV). Standard volumetric and wall thickness measurements were performed to obtain ventricular mass, volumes, and ejection fractions. T1 and T2 images were obtained from standard sequences (MOLLI 5(3)3 and T2-prepped SSFP images), with standard ECV calculation using the ratio of change in relaxation in pre and post contrast T1 maps of the myocardium relative to the blood pool multiplied by the plasma proportion of blood (1-hematocrit).(10) Calculated structural markers included the relative wall thickness, left ventricular mass index, and left atrial enlargement defined by 4 chamber left atrial area normalized by body surface area being greater than 15 $cm^2/m^2$.(11) The MPRI was measured during standard clinical reading by calculating the stress to rest ratio of the myocardial signal upslope normalized to left ventricular signal upslope in mid-ventricular short axis views, using Vitrea software (v7.12, Vital Images) (Figure 2). Perfusion images were performed using a standard gradient-echo EPI hybrid sequence as previously performed.(9) MPRI has been previously validated as a marker of coronary microvascular dysfunction, correlating with invasive measures, with a normal MPRI >2.0, and severely abnormal ≤1.4.(9, 12)

## Hepatic Fibrosis Measure

We assessed presence of hepatic fibrosis using the validated Fibrosis-4 (Fib-4) score, which has a demonstrated high performance for predicting advanced fibrotic disease development and well documented indications for inclusion in screening pathways.(13–15) We calculated Fib-4 for each patient based on age, AST, ALT, and platelet count provided by laboratory data most recently collected prior to the CMR exam (median time difference: 58.5 (17.0–124.8) days). To assess for potential ascertainment bias, we also calculated alternate measurements of subclinical hepatic disease for each patient to evaluate in sensitivity analyses including the AST to platelet ratio (APRI) and the NAFLD fibrosis

score (NAFLD-FS). All hepatic disease measures were based on standard equations defined in the Supplemental Methods.

### Statistical Analyses

We used t-tests and chi-square tests to conduct descriptive statistics. In primary analyses, we used multivariable linear regression to assess the association between Fib-4 with MPRI while adjusting for age and sex then additionally for cardiometabolic risk factors. We then age- and sex-adjusted regression analyses adjusting additionally for alternate CMR measures of cardiac structure and function both with and without including MPRI. In secondary analyses, we examined the association of each individual component of the Fib-4 score one-by-one with the CMR measures to assess whether any identified associations are driven by any individual component of the score. In sensitivity analyses, we repeated all analyses using APRI and NAFLD-FS as surrogates of advanced fibrosis, rather than FIB-4. We conducted all statistical analyses using R (v3.6.1) and considered statistical significance as a two-tailed P value <0.05.

## RESULTS

Of our study cohort of 66 patients, 54 were female (81%) and the mean age was 53.7±15.3 years (Table 1). These individuals were identified from 200 patients who underwent comprehensive CMR protocols without evidence of perfusion defects on stress imaging, of whom N=66 had laboratory markers sufficient for calculating the Fib-4 score that were collected within one year of the CMR. The most frequent indications for CMR were chest pain (47%), followed by shortness of breath (12%), rule out coronary artery disease (10%), and workup of cardiomyopathy (8%). All other indications were < 5%. There were no significant demographic or risk differences between the included 66 patients and the excluded 134 patients (Supplemental Table 1).

In unadjusted analyses, MPRI was observed to be significantly lower across increasing tertiles of Fib-4 (P<0.001, Figure 3). In multivariable linear regression models, Fib-4 was significantly associated with MPRI in age-and sex-adjusted analyses (beta [SE], −1.10 [0.42], P=0.01; Table 2) as well as in analyses additionally adjusting for cardiometabolic risk factors including BMI, hypertension, hyperlipidemia, type 2 diabetes, and smoking (−1.12 [0.46], P=0.02). These associations also remained significant in models additionally adjusting for alternate CMR measures of cardiac structure and function (P=0.026). Notably, Fib-4 was not observed to be significantly associated with any alternate measure of cardiac structure and function in either age- and sex-adjusted for full multivariable-adjusted analyses (P>0.20 for all, Table 3).

In secondary analyses of the individual subcomponents and ratios from the Fib-4 equation, we found that none were significantly associated with MPRI except for the AST to platelet ratio (also known as the APRI) while age divided by platelets trended towards significance (Supplemental Table 2). In sensitivity analyses, we also examined alternative subclinical hepatic disease measures, including the APRI and NAFLD-FS. In unadjusted analyses, MPRI was observed to be significantly lower across increasing tertiles of APRI (P<0.001, Figure 2). In age- and sex-adjusted models, as well as models adjusting for

cardiometabolic risk factors, only APRI was also associated with MPRI (Supplemental Table 3). Notably, unlike the NAFLD-FS measure, APRI was observed to be similar to Fib-4 in its independence of traditional metabolic risk components (Supplemental Methods).

## DISCUSSION

We found that hepatic fibrosis assessed by the Fib-4 score was associated with cardiac MPRI – pointing to a putative primary role of coronary microvascular dysfunction in contributing to the adverse cardiovascular outcomes related to the hepatic-cardiac axis. Importantly, we found that Fib-4 was associated with MPRI even after adjusting for cardiometabolic risk traits often identified as features common to both hepatic and cardiac disease. Notably, Fib-4 was not overtly associated with alternate measures of subclinical cardiac disease. Furthermore, of the alternate hepatic disease measures studied, only those more specific to hepatic rather than systemic metabolic traits were also associated with MPRI – highlighting a potentially key relationship between hepatic and coronary microvascular dysfunction.

Our study results extend from prior literature relating earlier forms of hepatic fibrosis with cardiovascular outcomes and, in turn, reports of subclinical hepatic disease being associated with early forms of cardiovascular pathogenesis. Whereas some studies have linked advanced fibrosis with risk for CV events,(16) others have used liver histologic data to clarify that the patients with the milder F3 compared to F4 fibrosis degree are at equivalent or even higher risk of vascular events potentially due lower blood pressure and alterations of other cardiometabolic traits in overt cirrhosis.(17, 18) While mechanisms underlying associations between milder forms of hepatic fibrosis and vascular disease remain unclear, a number of studies have linked various types of subclinical hepatic disease with endothelial dysfunction as well as accelerated coronary atherosclerosis, and adverse cardiac remodeling.(19–21) The Fib-4 score itself is associated with increased all-cause mortality within patients with clinical heart failure, as well as associated with increases in incident heart failure with preserved ejection fraction (HFpEF).(22, 23) Microvascular dysfunction has similar associations with HFpEF, being potentially implicated as a pathway to incident HFpEF and a predictor of adverse outcomes within patients with pre-existing HFpEF.(24–26) In the current study, we found that preclinical hepatic fibrosis was associated specifically with coronary microvascular dysfunction in the absence of any relations to other CMR measures of cardiac disease. Prior investigations have similarly observed PET/CT imaging measures of coronary microvascular dysfunction(27) as well as quantitative CMR perfusion in relation to non-alcoholic fatty liver disease by hepatic CT attenuation.(28) Our results expand from this prior work by focusing on specifically on hepatic fibrosis and its relation to a specific measure of coronary microvascular perfusion(9) that appears independent from the influence of metabolic disease traits as well as distinct from relations with other subclinical cardiac structural and functional measures. In effect, our findings suggest a potential coronary microvascular-specific pathophysiologic link between pre-clinical hepatic fibrotic disease and cardiac disease that is not only separate from shared risk factors but also from more overt cardiac disease phenotypes.

There are several possible explanations underlying our findings that, in turn, offer a number of clinical implications. Hepatic fibrosis is commonly associated with metabolic liver

disease, which is known to predispose to a cascade of cardiovascular pathophysiologic processes including the release of inflammatory activators in addition to mediators of fibrosis, thrombosis, and atherogenic dyslipidemia.(6) Both accelerated atherosclerosis prior to obstructive stenosis and vascular inflammation causing endothelial dysfunction may result in adverse coronary microvascular dysfunction.(29) Coronary microvascular pathophysiology connecting hepatic changes to cardiac dysfunction may represent a mechanistic contributor to the high prevalence of coincident HFpEF and metabolic liver disease,(30) association of diastolic dysfunction with metabolic liver disease,(20) and association of coronary microvascular dysfunction with HFpEF.(26) Moreover, lack of overt cardiac fibrosis (i.e. T1 and ECV) associations in our study population suggest that these previously reported relations of pre-clinical as well as clinical HFpEF traits with hepatic disease could be primarily vascularly mediated. Additional prospective studies are needed to further investigate the potential implications of our findings.

Our study has several limitations including the retrospective study design that involved identifying patients with certain diagnostic data available; this approach may have introduced selection bias and residual confounding is possible. The use of Fib-4 as the primary measure of hepatic fibrosis did not involve any validation using imaging or biopsy confirmation in our study, although Fib-4 has been validated in prior studies.(31–33) Additionally, the MPRI as a measure of coronary microvascular dysfunction does not directly quantify perfusion due to signal saturation but acts as a surrogate marker for perfusion; this technical feature could have limited accuracy of the measurement that we anticipate would contribute non-differential misclassification. Given the relatively small size of our study sample, additional larger sized studies are needed to validate as well as further investigate our findings.

In conclusion, we found that elevated Fib-4 as a marker of hepatic fibrosis is associated with lower MPRI, a marker of microvascular perfusion. Importantly, across a comprehensive set of subclinical cardiac disease measures, Fib-4 was related to MPRI and not with any other measures of cardiac structure, function, or tissue composition. Furthermore, we found this relationship to be independent of traditional cardiometabolic risk factors. In effect, our results suggest that mechanisms underlying heart-liver axis pathology and disease development may specifically involve coronary microvascular disease.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Availability:

The datasets used during this study are available from the corresponding author on reasonable request.

## ABBREVIATIONS

| | |
|---|---|
| **APRI** | AST to platelet ratio |
| **CMR** | Cardiac magnetic resonance imaging |
| **ECV** | Extracellular volume |
| **Fib-4** | Fibrosis-4 score |
| **HFpEF** | Heart failure with preserved ejection fraction |
| **LVEF** | Left ventricular ejection fraction |
| **LVMI** | Left ventricular mass index |
| **MPRI** | Myocardial perfusion reserve index |
| **NAFLD-FS** | Non-alcoholic fatty liver disease fibrosis score |
| **RWT** | Relative wall thickness |

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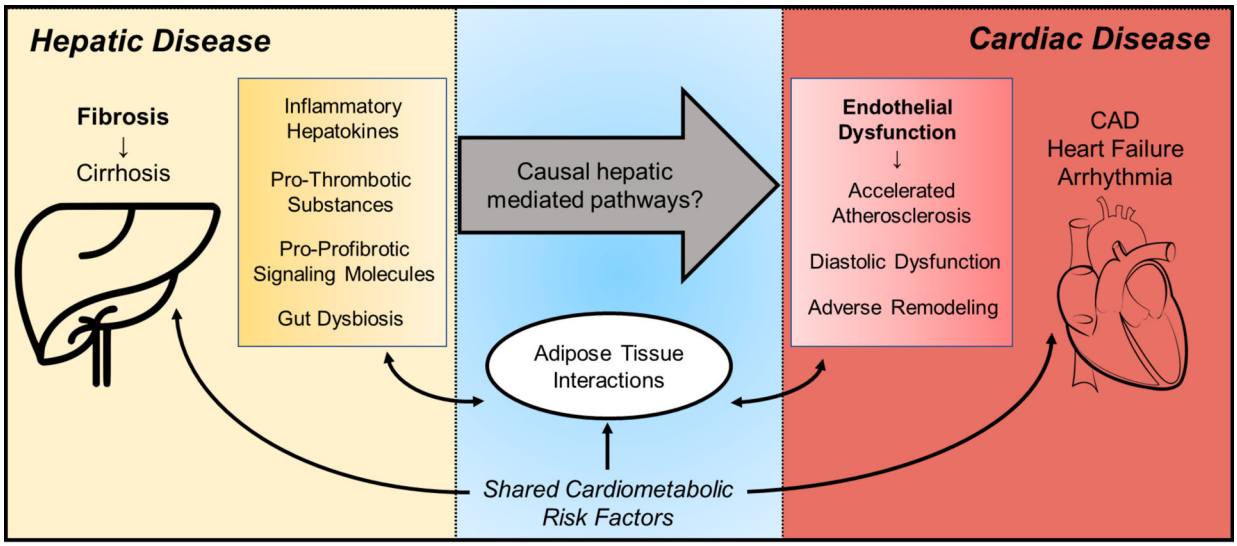


**Figure 1. Central Figure.**

Hepatic disease has been associated with cardiac disease; however, the relations are obscured by multiple shared risk factors. There are multiple putative potential pathways between the variety of metabolic effects from subclinical liver disease which may affect different aspects of subclinical cardiac disease. CAD: Coronary artery disease.

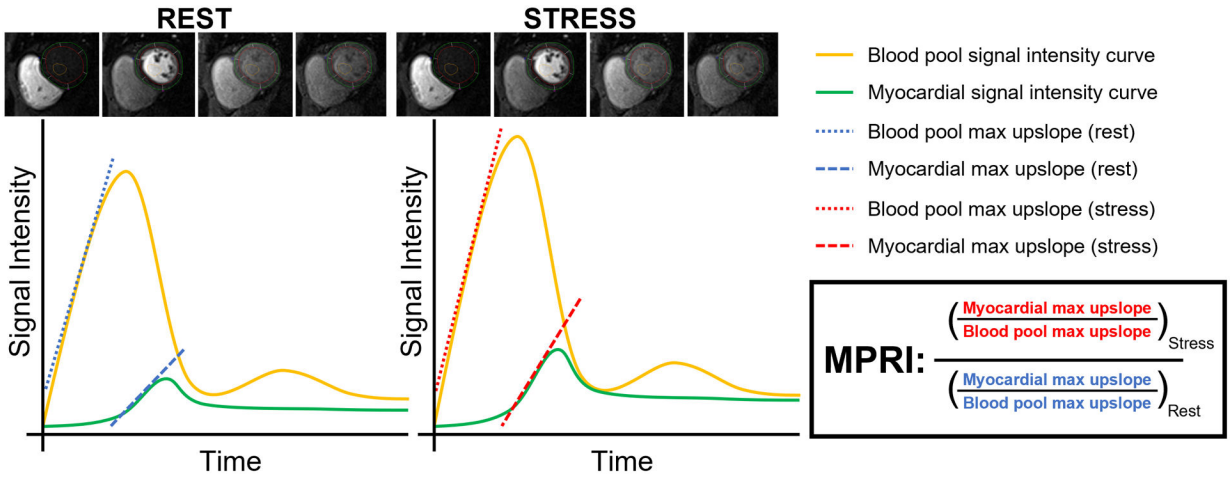


**Figure 2.**

The myocardial perfusion reserve index (MPRI) is the ratio of the maximum relative upslope at stress versus rest, where relative upslope is calculated by the change in myocardial signal intensity over time normalized to blood pool.

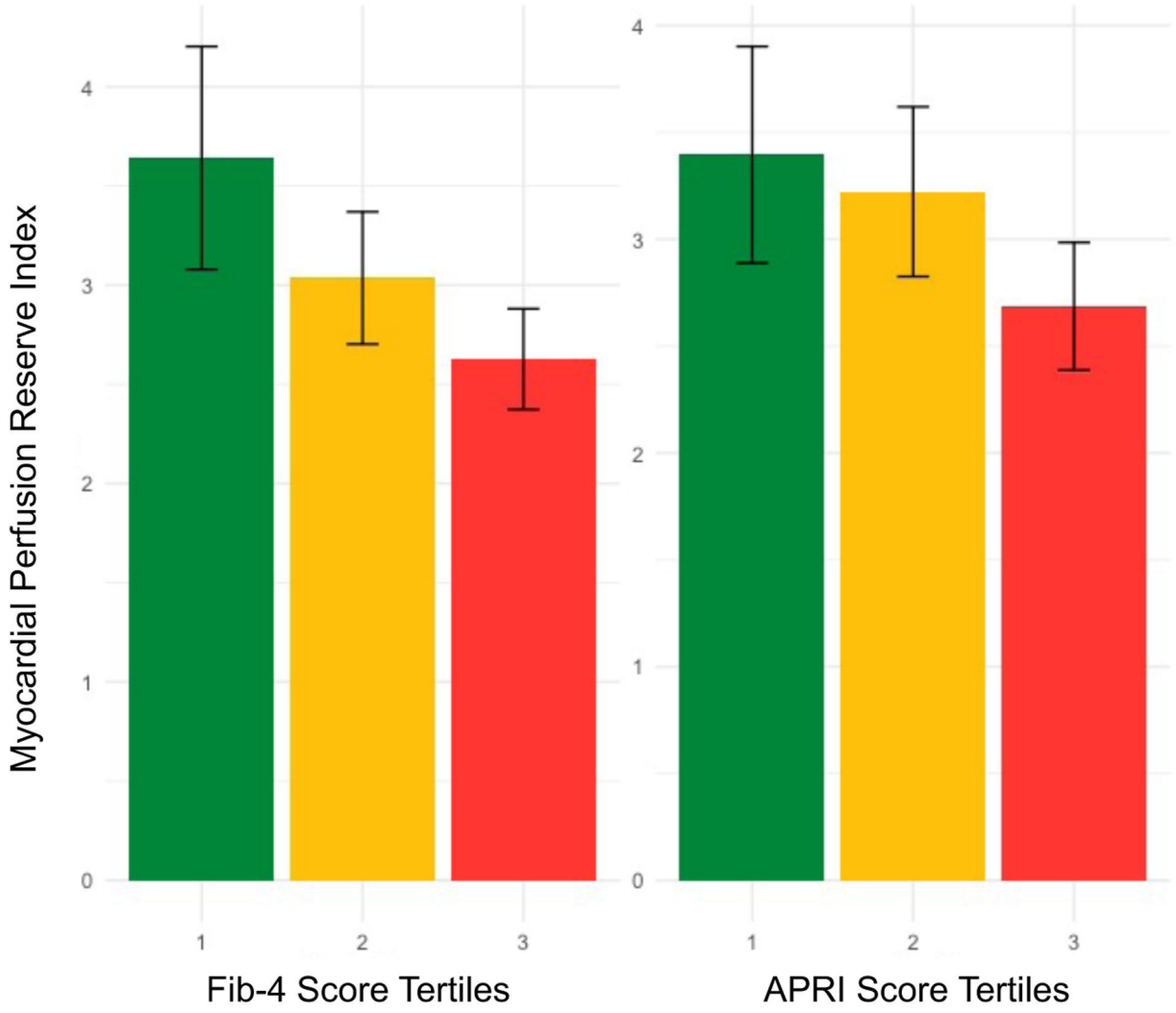


**Figure 3.**

Higher tertiles of Fib-4 and APRI scores are associated with reduced myocardial perfusion reserve index, a validated measure of coronary microvascular dysfunction.

**Table 1.**

Demographic and clinical characteristics of the study cohort.

| | Total | Women | Men |
|---|---|---|---|
| No. | 66 | 54 | 12 |
| Age | 53.7±15.3 | 54.5±14.6 | 49.8±18.1 |
| Height, inches | 65.2±3.4 | 64.3±2.9 | 69.3±2.7 |
| Weight, lbs | 153.7±37.4 | 147.7±36.9 | 180.6±27.2 |
| Body mass index | 25.5±6.2 | 25.3±6.5 | 26.6±4.6 |
| Systolic blood pressure | 124.1±16.6 | 124±15.9 | 124.7±20.6 |
| Hypertension | 32 (48.5%) | 26 (48.1%) | 6 (50.0%) |
| Hyperlipidemia | 33 (50.0%) | 25 (46.3%) | 8 (66.7%) |
| Diabetes | 7 (10.6%) | 5 (9.3%) | 2 (16.7%) |
| Smoking | 2 (3.0%) | 2 (3.7%) | 0 (0.0%) |
| | | | |
| MPRI | 3.10±1.92 | 3.03±1.76 | 3.43±2.58 |
| MPRI less than 1.4 | 8 (12.1%) | 7 (13.0%) | 1 (8.3%) |
| MPRI less than 2.0 | 18 (27.3%) | 15 (27.8%) | 3 (25.0%) |
| | | | |
| Left ventricular ejection fraction | 62.5±8.5 | 62.9±8.8 | 61.2±6.9 |
| Left atrial enlargement | 12 (22.6%) | 11 (25.0%) | 11 (25.0%) |
| Relative wall thickness | 0.64±0.86 | 0.56±0.54 | 0.97±1.6 |
| Left ventricular mass index | 42.4±11.6 | 40.7±10.8 | 50.0±12.4 |
| Scar Present by LGE | 3 (5.1%) | 1 (2.0%) | 2 (20.0%) |
| T1 time | 981.1±46.4 | 979.9±47.3 | 986.6±44.01 |
| T2 time | 46.8±3.6 | 46.7±2.9 | 47.6±6.1 |
| Extracellular Volume Fraction | 0.27±0.04 | 0.27±0.04 | 0.26±0.02 |
| | | | |
| Fib-4 Score | 1.16±0.62 | 1.11±0.56 | 1.40±0.81 |
| NAFLD-FS Score | −2.31±1.28 | −2.42±1.23 | −1.81±1.43 |
| BARD Score | 1.92±0.87 | 2.00±0.82 | 1.58±0.996 |
| APRI Score | 0.30±0.39 | 0.25±0.22 | 0.51±0.77 |

APRI: AST to platelet ratio index; LGE: Late gadolinium enhancement; MPRI: Myocardial perfusion reserve index; NAFLD-FS: non-alcoholic fatty liver disease fibrosis score.

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**Table 2.**

Relations of Fib-4 and cardiometabolic risk factors with myocardial perfusion reserve index (MPRI).

| *Predictor variables* | Adjusted for Age + Sex | | Adjusted for Age + sex + BMI + HTN + HLD + Smoking + Diabetes | |
|---|---|---|---|---|
| | **Beta (SE)** | **P** | **Beta (SE)** | **P** |
| Fib-4 | **−1.10 (0.42)** | **0.01** | **−1.12 (0.46)** | **0.02** |
| Body mass index | 0.02 (0.04) | 0.60 | - | - |
| Hypertension | −0.36 (−0.36) | 0.47 | - | - |
| Hyperlipidemia | −0.47 (0.53) | 0.38 | - | - |
| Diabetes | −0.49 (0.79) | 0.54 | - | - |
| Smoking | −0.63 (1.41) | 0.66 | - | - |

BMI: Body mass index; HTN: Hypertension; HLD: Hyperlipidemia.

*Beta coefficients (and standard error) values represent the multivariable adjusted change in the standardized value of the MPRI per increment increase in the predictor variables.

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**Table 3.**

Association of Fib-4 with conventional CMR measures of cardiac structure and function.

| ***Outcomes: Cardiac Measures*** | ***Predictor: Fib-4 Score*** | |
|---|---|---|
| | **Beta (SE)*** | **P value** |
| Left Ventricular Ejection Fraction | 0.16 (1.97) | 0.93 |
| Left Ventricular Mass Index | 2.75 (2.54) | 0.28 |
| Relative Wall Thickness | 0.1 (0.20) | 0.63 |
| T1 Time | −9.13 (12.33) | 0.46 |
| T2 Time | 0.31 (0.98) | 0.76 |
| Extracellular Volume Fraction | 0.00 (0.01) | 0.97 |
| Left atrial enlargement | 0.31 (0.61) | 0.61 |

*Beta coefficients (and standard error) values represent the age- and sex-adjusted change in the standardized value of the cardiac measure per increment increase in the Fib-4 score