

Article

The Association of Cardiovascular Disease (CVD) with Progression of Advanced Fibrosis Risk in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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Abstract

Objective: Advanced fibrosis is the best predictor of future severe liver outcomes in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Our study aims to determine the association between cardiovascular disease (CVD) with time to a high-risk Fibrosis-4 Index (FIB-4) in patients with low-risk MASLD. **Methods:** This retrospective cohort study was conducted at a primary care clinic between 2012 and 2021. The cohort included patients with MASLD and a FIB-4 score at low risk for advanced fibrosis (<1.3). Patients were followed for the outcome of having a high-risk FIB-4 (≥ 2.67) or until the end of the study period. The primary predictor variable was CVD, a composite of ICD-9/10 codes for coronary artery, cerebrovascular, and peripheral arterial disease. Covariates included demographic and comorbidity variables. Unadjusted and adjusted Cox regression models were developed for the outcome of time to a high-risk FIB-4 score. **Results:** The cohort included 859 patients with a mean age of 49.6 years (± 13.7) and mean body mass index of 34.1 (± 8.3) kg/m². The included patients were 70% female and 41% non-white. Of the cohort, 32%, 36%, and 74% had CVD, type 2 diabetes mellitus, and hypertension, respectively. During a mean follow-up of 3.8 (± 2.7) years, 9.3% (80) of the sample had a subsequent high-risk FIB-4 score. The multivariable Cox regression model demonstrated a significant association between CVD (HR 2.13; 95%CI 1.33–3.40) and chronic kidney disease (HR 2.05; 95%CI 1.23–3.42) with the time to transition to a high-risk FIB-4 score. **Conclusion:** Our study showed that CVD is associated with an increased risk of progression of FIB-4 scores at low to high risk for advanced fibrosis in MASLD patients. Future research investigating how control of cardiometabolic comorbidities impact fibrosis progression in MASLD is warranted.

Keywords: liver fibrosis; MASLD; FIB-4; cardiometabolic

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1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly non-alcoholic fatty liver disease [NAFLD]) is the most prevalent chronic liver disease globally, affecting an estimated 25% of the world's population [1,2]. MASLD comprises a spectrum of liver injury that ranges from steatosis to steatohepatitis to fibrosis and eventually to cirrhosis, with advanced fibrosis being the best predictor of future cirrhosis, complications of cirrhosis (e.g., portal hypertension), hepatocellular carcinoma, and need for liver transplantation [3–6]. Recently issued MASLD care guidelines highlight the importance of detecting

advanced fibrosis in primary care using noninvasive tests, beginning with the Fibrosis-4 Index (FIB-4), a non-proprietary, serum-based test with commonly available inputs (age, platelets [Plt], alanine [ALT], and aspartate [AST] aminotransferase) and a relatively simple calculation ($\text{FIB-4} = [\text{Age} \times \text{AST}] / [\text{Plt} \times \sqrt{\text{ALT}}]$) [7–10]. FIB-4 has demonstrated the ability to “rule out” advanced fibrosis in numerous studies and MASLD care recommendations use advanced fibrosis risk as an inflection point for referring patients with MASLD to hepatology for specialty care [7,8,11]. Current guidelines recommend that patients with MASLD at low risk for advanced fibrosis ($\text{FIB-4} < 1.3$, the established threshold for “ruling out” advanced fibrosis) remain in primary care for ongoing management [7,8,12–14].

Primary care strategies for managing MASLD entail addressing cardiometabolic conditions that often occur in concert with MASLD, including type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome [7,8,10,11]. Interventions for MASLD focus on weight loss, exercise, glycemic control, dyslipidemia treatment, and cardiovascular disease (CVD) prevention; however, specific guidelines for delaying or preventing the progression of advanced fibrosis risk are not well delineated [7,15]. T2DM is a well-established risk factor for advanced fibrosis in MASLD, and routine liver fibrosis risk assessment with FIB-4 is recommended in affected patients [7,16]. Despite CVD’s close relationship with metabolic dysfunction, there are no current recommendations for modifying advanced fibrosis risk surveillance in patients with comorbid CVD. How CVD associates with progression from low-risk MASLD to advanced fibrosis is not fully understood [17,18].

This study evaluated the association of CVD with time to high risk of advanced fibrosis in primary care patients with initially low-risk MASLD. We hypothesized that CVD diagnoses would be associated with an increased hazard of transitioning from low to high risk for advanced fibrosis in patients with MASLD.

2. Methods

We performed a retrospective cohort study of patients with low-risk MASLD to determine the association of CVD with time to progression to MASLD with a FIB-4 score at high risk for advanced fibrosis using Cox regression models. This study was approved by the Institutional Review Board at the Medical University of South Carolina.

2.1. Setting

This retrospective study of electronic health record (EHR, EPIC[®]) data comes from a University-based internal medicine, primary care clinic between 1 July 2012 and 31 December 2021. Data was collected from the Enterprise Data Warehouse (EDW) at the Medical University of South Carolina (MUSC). The Institutional Review Board at MUSC approved this project.

2.2. Patients

Cohort inclusion required: (i) evidence of hepatic steatosis on at least one abdominal image during the study period; (ii) laboratory inputs for FIB-4 calculation (age, aspartate aminotransferase [AST], platelet count [Plt], and alanine aminotransferase [ALT]) at the time of steatosis identification, or within the preceding year; and (iii) a FIB-4 score ($\text{FIB-4} = [(\text{Age} \times \text{AST}) / (\text{Plt} \times \sqrt{\text{ALT}})] < 1.3$, at low risk for advanced fibrosis [8,9,11]. We excluded patients with documentation of competing chronic liver diseases or with diagnoses of cirrhosis, complications of cirrhosis, hepatocellular carcinoma, or liver transplant at the time of, or prior to, steatosis identification (Supplementary Table S1).

2.3. Outcome

Time to a FIB-4 score at high risk for advanced fibrosis ($\text{FIB-4} \geq 2.67$) was the primary outcome of interest. Beginning with the index FIB-4 (identified at the time of steatosis

identification), FIB-4 scores were calculated longitudinally for each qualifying set of amino-transferase and platelet results. FIB-4 scores were computed for each pair of AST and ALT values ≤ 350 IU/L, if there was a platelet count at the time of, or within 6 months of, the AST and ALT results [19,20]. We required at least 6 months between each FIB-4 value to ensure unique AST, ALT, and platelet count inputs. The low-risk FIB-4 score used for cohort inclusion served as the beginning of follow-up, and patients were followed until the occurrence of a FIB-4 ≥ 2.67 , or the end of the study period (31 December 2021).

2.4. Primary Independent Variable

Diagnosis of CVD, a composite of coronary artery disease (CAD), cerebrovascular disease, and peripheral vascular disease (PVD), placed prior to the index FIB-4 score was the primary exposure of interest. We used Elixhauser coding algorithms to detect ICD-9/10 codes for CAD, cerebrovascular disease, and PVD from the EHR data [21,22].

2.5. Other Covariates

Other predictor variables of interest included demographic variables of age (continuous), sex (Female/Male), race (non-White/White), marital status (married/unmarried), and smoking status (ever/never). We also included a body mass index (BMI) measurement (continuous) obtained at the time of the index FIB-4 score. Comorbidities other than cardiovascular disease were also obtained and included hypertension, T2DM, hyperlipidemia, hypothyroidism, and chronic kidney disease. All comorbidities were identified using Elixhauser coding algorithms [21,22].

2.6. Statistical Analysis

Means and proportions of patient characteristic variables were computed for the overall cohort and by CVD status. Patient variables between CVD status groups were compared using two sample *t*-tests and Mann–Whitney U tests for continuous variables and Chi square tests for categorical variables. The mean number of FIB-4 scores available per patient during follow-up were calculated and compared by CVD status. The proportions of patients with CVD overall, and each individual component (coronary artery, cerebrovascular, and peripheral arterial disease), were calculated and compared by outcome status (high-risk FIB-4 in follow-up or not). Other patient-level variables were compared by high-risk FIB-4 outcome status with two sample *t*-tests used for continuous variables and Chi square tests used for categorical variables.

We developed a Kaplan–Meier curve for the outcome of time to high-risk FIB-4 by CVD status. We also developed an unadjusted Cox regression model to assess the association of CVD with time to high-risk FIB-4. We developed a second model adjusting for demographic covariates including sex, race, marital status, and smoking history. We then developed a third model also adjusting for the comorbidity variables of hypertension, T2DM, hyperlipidemia, hypothyroidism, and chronic kidney disease. The specific variables, and the number of variables, were chosen a priori based on their clinical relationship with MASLD outcomes [23]. The proportionality of hazards assumption was tested visually using the Kaplan–Meier curves and by testing the interaction of CVD and time with the time to event outcome. Multicollinearity was assessed in the models using variance inflation factor (VIF). There were no missing data in this cohort. We tested for interactions between CVD and the hypertension, T2DM, and hyperlipidemia variables. For a sensitivity analysis, we developed similar models (unadjusted, adjusted for demographic covariates, and fully adjusted) with each element of our composite predictor (coronary artery, cerebrovascular, and peripheral arterial disease) as the primary predictor variable. We also repeated all analyses for the outcome of time to indeterminate-risk for advanced fibrosis (FIB-4 ≥ 1.3). SAS version 9.4 was used for all statistical analyses.

3. Results

The overall cohort included 859 unique patients with MASLD at low risk for advanced fibrosis (Figure 1). Included patients had a mean age of 49.6 years and were 70.0% female, 41.0% non-White, and 12.3% had previously or currently smoked (Table 1). Cohort patients had a mean BMI of 34.1 kg/m² and 74.4%, 36.1%, and 61.5% had hypertension, T2DM, and hyperlipidemia, respectively. Of the study subjects, 276 (32.1%) were diagnosed with CVD prior to their index FIB-4 score. Patients with CVD diagnoses were older (51.9 vs. 48.6, $p = 0.002$) and a higher proportion were non-White (46.0% vs. 38.6%, $p = 0.039$) and unmarried (53.3% vs. 45.6%, $p = 0.037$) compared to those without CVD. Patients with CVD had higher burdens of hypertension (83.3% vs. 70.2%, $p < 0.001$), T2DM (52.9% vs. 28.1%, $p < 0.001$), hyperlipidemia (72.5% vs. 56.3%, $p < 0.001$), and chronic kidney disease (27.9% vs. 10.8%, $p < 0.001$) compared to their non-CVD counterparts. For the overall sample, the mean index FIB-4 score was 0.82, and there was no statistically significant difference between the mean index FIB-4 score in patients with (0.84) and without CVD (0.81, $p = 0.147$).

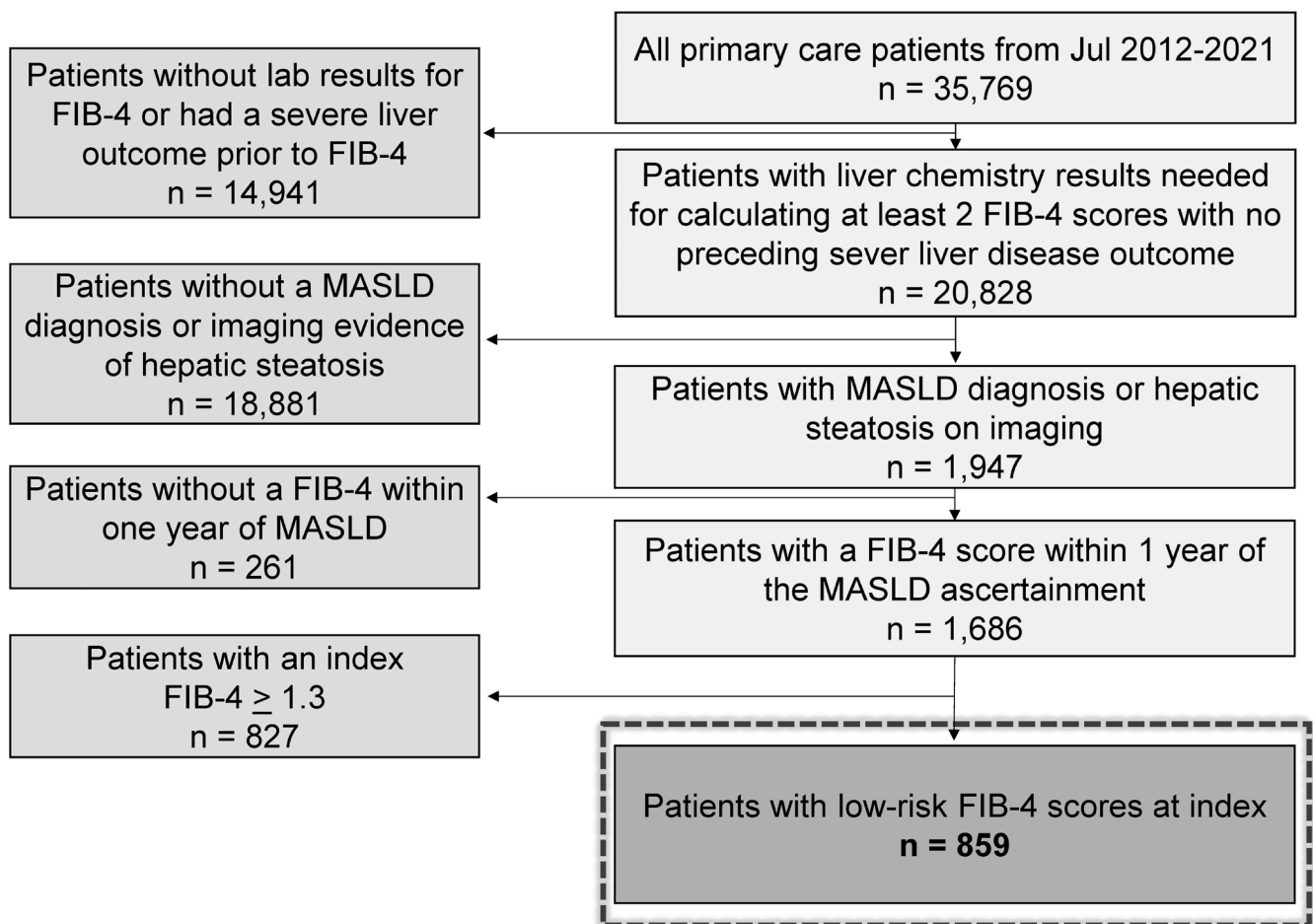


Figure 1. Flow diagram.

Table 1. Cohort characteristics overall and by diagnosis of cardiovascular disease (CVD) prior to the index FIB-4.

	CVD			
	Overall	Yes	No	<i>p</i> -Value
Characteristics	n = 859	n = 276	n = 583	
Demographics % (n)				
Age, mean (SD)	49.6 (13.7)	51.9 (14.6)	48.6 (13.1)	0.002 *
Sex				0.115 †
Female	70.0% (601)	73.6% (203)	68.3% (398)	
Male	30.0% (258)	26.5% (73)	31.7% (185)	
Race				
Non-White	41.0% (352)	46.0% (127)	38.6% (225)	0.039 †
White	59.0% (507)	54.0% (149)	61.4% (358)	
Unmarried	48.1% (413)	53.3% (147)	45.6% (266)	0.037 †
Smoking history	12.3% (106)	12.3% (34)	12.4% (72)	0.990 †
Comorbidities % (n)				
BMI, mean (SD)	34.1 (8.3)	33.6 (8.8)	34.4 (8.0)	0.187 *
Hypertension	74.4% (639)	83.3% (230)	70.2% (409)	<0.001 †
Type 2 diabetes mellitus	36.1% (310)	52.9% (146)	28.1% (164)	<0.001 †
Hyperlipidemia	61.5% (528)	72.5% (200)	56.3% (328)	<0.001 †
Hypothyroidism	18.7% (161)	22.1% (61)	17.2% (100)	0.083 †
Chronic kidney disease	16.3% (140)	27.9% (77)	10.8% (63)	<0.001 †
Index FIB-4 Scores				
Mean (SD)	0.82 (0.28)	0.84 (0.29)	0.81 (0.27)	0.147 *
Median (IQR)	0.83 (0.60–1.05)	0.87 (0.60–1.10)	0.81 (0.59–1.02)	0.115 ‡

* Two sample *t*-test. † Chi square test. ‡ Mann–Whitney U test. BMI = body mass index (kg/m²). CVD = cardiovascular disease. SD = standard deviation.

Patients were followed for a mean 3.8 ($\pm$ 2.7) years and 80 (9.3%) experienced a transition to a FIB-4 score at high risk for advanced fibrosis (FIB-4 $\geq$ 2.67, Figure 2). Overall, the cohort had a mean of 7.58 (SD 10.97) FIB-4 scores during follow-up. Patients with CVD had a mean of 11.7 FIB-4 scores in follow-up compared to 7.1 FIB-4 scores in patients without CVD (p < 0.001). Of patients with a high-risk FIB-4 during follow-up, 55.0% had a CVD diagnosis compared to 29.8% (p < 0.001) of patients without a high-risk FIB-4 (Table 2). Compared to patients without a high-risk FIB-4, patients with the high-risk outcome had a higher proportion of CAD (28.8% vs. 8.6%, p < 0.001) and PVD (31.3% vs. 15.0%, p < 0.001). There was no significant difference in cerebrovascular disease diagnoses (p = 0.396) by high-risk FIB-4 outcome groups. There were no significant differences in demographic variables by FIB-4 outcome group. Higher proportions of patients with a FIB-4 $\geq$ 2.67 had hypertension (86.3% vs. 73.2%, p = 0.011), T2DM (50.0% vs. 34.7%, p = 0.007), and chronic kidney disease (33.8% vs. 14.5%, p < 0.001) compared to subjects without a high-risk FIB-4. Patients with a FIB-4 at high risk for advanced fibrosis had a lower mean BMI (32.2 kg/m²) than patients without a FIB-4 $\geq$ 2.67 (34.3 kg/m², p = 0.029).

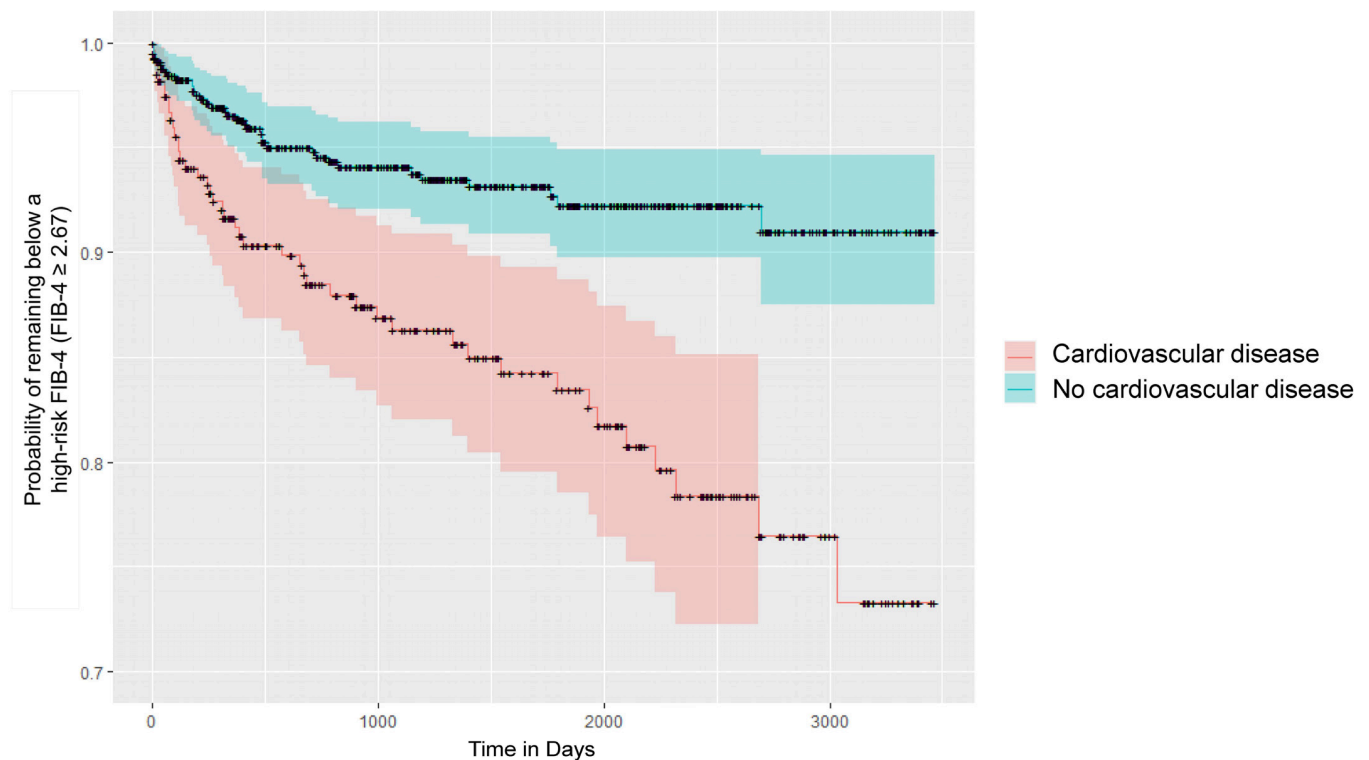


Figure 2. Kaplan–Meier curve for time to transition to high-risk FIB-4 score (FIB-4 ≥ 2.67).

Table 2. Characteristics for the cohort of primary care patients with MASLD and a FIB-4 score at low risk for advanced fibrosis by progression to high-risk FIB-4 (≥ 2.67).

	High-Risk FIB-4 (≥ 2.67)			<i>p</i> -Value
	Overall	Yes	No	
Characteristics, % (n)	n = 859	n = 80	n = 779	
Cardiovascular disease	32.1% (276)	55.0% (44)	29.8% (232)	<0.001 [†]
Coronary artery disease	10.5% (90)	28.8% (23)	8.6% (67)	<0.001 [†]
Cerebrovascular disease	15.5% (133)	18.8% (15)	15.2% (118)	0.396 [†]
Periph. arterial disease	16.5% (142)	31.3% (25)	15.0% (117)	<0.001 [†]
Demographics				
Age, mean (SD)	49.6 (13.7)	51.1 (13.2)	49.5 (13.7)	0.312 [*]
Sex				0.203 [†]
Female	70.0% (601)	63.8% (51)	70.6% (550)	
Male	30.0% (258)	36.3% (29)	29.4% (229)	
Race				0.085 [†]
Non-White	41.0% (352)	50.0% (40)	40.0% (312)	
White	59.0% (507)	50.0% (40)	60.0% (467)	
Unmarried	48.1% (413)	56.3% (45)	47.2% (368)	0.125 [†]
Smoking history	12.3% (106)	16.3% (13)	11.9% (93)	0.264 [†]
Comorbidities				
BMI, mean (SD)	34.1 (8.3)	32.2 (8.08)	34.3 (8.3)	0.029 [*]
Hypertension	74.4% (639)	86.3% (69)	73.2% (570)	0.011 [†]

Table 2. Cont.

	High-Risk FIB-4 (≥ 2.67)			
	Overall	Yes	No	p-Value
Type 2 diabetes mellitus	36.1% (310)	50.0% (40)	34.7% (270)	0.007 [†]
Hyperlipidemia	61.5% (528)	60.0% (48)	61.6% (480)	0.777 [†]
Hypothyroidism	18.7% (161)	11.3% (9)	19.5% (152)	0.071 [†]
Chronic kidney disease	16.3% (140)	33.8% (27)	14.5% (113)	<0.001 [†]

[†] Chi square test. * Two sample *t*-test. FIB-4 = Fibrosis-4 Index. Periph = peripheral. SD = standard deviation.

The unadjusted Cox regression model demonstrated an association between CVD diagnoses (HR 2.60; 95%CI 1.67–4.03) and transition to a FIB-4 score at high risk for advanced fibrosis (Table 3). After adjusting for demographic covariates, CVD remained significantly associated with time to a FIB-4 ≥ 2.67 (HR 2.56; 95%CI 1.64–3.98). The fully adjusted Cox regression model, which included potentially confounding comorbidity diagnoses, also showed a significant association between CVD and a high-risk FIB-4 (HR 2.13; 95%CI 1.33–3.40). In this fully adjusted model, chronic kidney disease diagnoses were also associated with time to high-risk FIB-4 scores (HR 2.05; 95%CI 1.23–3.42). The proportional hazard assumption was met visually and by testing the interaction term of CVD status with time for the primary outcome ($p = 0.267$). No significant interactions or multicollinearity were detected among the variables in the final, fully adjusted Cox regression model (Supplementary Table S2). Sensitivity analyses demonstrated similar results when looking at single components of the composite predictor (CVD) for CAD and PVD in the unadjusted models (PVD was not significant in the fully adjusted model, Supplementary Table S3). Diagnoses of cerebrovascular disease were not associated with time to a high-risk FIB-4 score in the unadjusted or adjusted models. The results were similar in models developed for the outcome of time to indeterminate- or high-risk FIB-4 (FIB-4 ≥ 1.3) score (Supplementary Figure S1, Supplementary Tables S4 and S5).

Table 3. Unadjusted and adjusted Cox regression models evaluating the association of cardiovascular disease with the time to transition from low-risk to high-risk FIB-4.

	Regression Models		
	Unadjusted	Adjusted	Adjusted
	HR 95% CI	HR 95% CI	HR 95% CI
Covariates			
Cardiovascular disease	2.60 1.67–4.03	2.56 1.64–3.98	2.13 1.33–3.40
Demographics			
Male sex		1.54 0.97–2.46	1.19 0.74–1.93
Non-white race		1.39 0.87–2.20	1.12 0.69–1.81
Unmarried		1.23 0.77–1.97	1.15 0.72–1.85
Smoker		1.34 0.73–2.44	1.38 0.75–2.52

Table 3. Cont.

	Regression Models		
	Unadjusted	Adjusted	Adjusted
Comorbidities			
BMI			0.97 0.94–1.00
Hypertension			1.86 0.93–3.73
Type 2 diabetes mellitus			1.24 0.76–2.02
Hyperlipidemia			0.63 0.39–1.03
Hypothyroidism			0.51 0.25–1.05
Chronic kidney disease			2.05 1.23–3.42

Age was not included as it is in the calculation for the outcome (FIB-4 score). BMI = body mass index (kg/m²). CI = confidence interval. HR = hazard ratio.

4. Discussion

Our study of primary care patients with MASLD at initially low risk for advanced fibrosis demonstrated a high burden of comorbid CVD (32% of the cohort affected) and an association between CVD and progression to a FIB-4 score at high risk for advanced fibrosis in MASLD patients after adjusting for comorbid conditions (HR 2.13; 95%CI 1.33–3.40). Known CVD, like T2DM, may prompt more aggressive advanced fibrosis risk assessment in primary care patients with MASLD [7,16].

MASLD often coexists with chronic conditions of metabolic dysfunction, including T2DM, obesity, and dyslipidemia, that have well-established relationships with CVD outcomes [3,24]. Thus, it is no surprise that this cohort of primary care patients with MASLD has a heavy burden of metabolic dysfunction comorbidities and a high prevalence of CVD. A previous meta-analysis of 16 observational studies examining the relationship between CVD and MASLD revealed a higher risk of CVD events (OR 1.64; 95%CI 1.26–2.13) in patients with MASLD [25]. But another retrospective study of a large, primary care dataset refutes this relationship, demonstrating no significant association between MASLD and incident acute myocardial infarction or stroke (HR 1.04; 95%CI 0.99–1.09) after adjusting for T2DM, hypertension, total cholesterol level, and statin use [26]. In our study, though the composite CVD variable was associated with time to a high-risk FIB-4 score, the sensitivity analyses with only cerebrovascular disease did not demonstrate that relationship. It is possible that the mechanisms for cerebrovascular disease captured are broader than those captures for CAD (e.g., hemorrhagic stroke), which may not fully align with the cardiometabolic risk pathway likely shared by CAD and MASLD. Whether MASLD is an independent risk factor for CVD, or if CVD risk is driven by other comorbid conditions (e.g., T2DM and hypertension), is worth further study, but it is clear that CVD is highly prevalent in patients with MASLD.

The relationship between CVD and advanced fibrosis in patients with MASLD is less well understood. Our results show that CVD at baseline is associated with an increased risk of progressing to a high risk for advanced fibrosis by FIB-4. A study of Medicare claims data explored the natural history of then NAFLD and NASH over time, and found that CVD (along with T2DM, dyslipidemia, and chronic kidney disease) was an independent

predictor of NAFLD progression to cirrhosis [27]. Measures of advanced fibrosis have also been linked to incident cardiovascular events (CVEs), with a FIB-4 ≥ 2.67 having a greater hazard of incident CVEs (aHR 4.57; 95%CI 1.60–12.98), compared to low- and indeterminate-risk FIB-4 scores [28]. Both of these studies demonstrate a potential relationship between advanced fibrosis and CVD, but they are limited by MASLD underdiagnosis, coding limitations, and cardiovascular event rates [27,28].

Clinically, establishing CVD as a risk factor for future chronic liver disease progression could significantly impact primary care delivery for patients with MASLD. Current MASLD management strategies include an emphasis on weight loss, alcohol avoidance, and exercise, all of which are hallmarks of historical CVD risk reduction in primary care [7,29,30]. More recently, emerging evidence demonstrates that foundational medication in CVD management, statins and aspirin, can prevent and delay fibrosis progression in chronic liver disease [31,32]. Future research can address whether proactive management of cardiovascular risk factors can reduce fibrosis risk in patients with MASLD.

We recognize limitations of our study, including the use of FIB-4 as an outcome variable. FIB-4 is a proxy for advanced fibrosis in this study, but it is not as good of an outcome as liver histology or liver stiffness measurement. However, FIB-4 can accurately detect advanced fibrosis and it is a fibrosis risk assessment that is far more accessible and available in primary care than liver histology or liver stiffness measurements [12,33]. Additionally, FIB-4 includes age in the numerator of the calculation; thus, increases in FIB-4 could theoretically happen with the simple passage of time. However, we used a high-risk FIB-4 risk category as the outcome, and that FIB-4 ≥ 2.67 threshold for a high-risk assessment is validated for patients younger and older than 65 years of age [8,34]. The passage of time would have had a bigger impact if the outcome was FIB-4 as a continuous measure. Also, this dataset did not include variables for medication therapies like glucagon-like peptide-1 receptor agonists, sodium glucose transporter-2 inhibitors, statins, or aspirin, all of which could impact the incidence of cardiovascular disease and the progression of liver disease [31,32,35–37]. Surveillance bias may impact the study's findings. Patients with CVD, CKD, or other comorbidities are likely to get more frequent lab testing than patients without these comorbidities and thus have more opportunities to have a high-risk FIB-4 score. This was observed in our data, as patients with CVD had significantly more FIB-4 scores during the follow-up period. Environmental and lifestyle factors may play a key role in the CVD and liver fibrosis relationship, but our EHR data has limited smoking intensity, alcohol use, and other exposure data. This is also a single center study, which does threaten generalizability. However, we feel that the distribution of cardiometabolic risk factors in this cohort is representative of primary care practices throughout the U.S [38]. We also relied on ICD-9/10 codes for detecting CVD, the primary exposure in the study. ICD-9/10 codes do have limitations in their sensitivity for identifying clinical conditions from administrative data.

5. Conclusions

In this study, we aimed to evaluate the association of CVD with time to a FIB-4 score at high-risk for advanced liver fibrosis in primary care patients with initially low-risk MASLD. MASLD often coexists with chronic conditions of metabolic dysfunction that have well-established relationships with CVD outcomes. Our study showed a high burden of comorbid CVD (32%) in our cohort and that CVD was associated with an increased risk of progression from a low- to high-risk FIB-4 score in MASLD patients. Future work is needed to fully understand how the detection and management of cardiometabolic comorbidities may impact the progression of MASLD.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/livers6050098/s1>, Figure S1: Kaplan Meier curve for time to transition to indeterminate- or high-risk FIB-4 score (FIB-4 $\geq$ 1.3). Table S1: ICD-9/10 codes for severe liver disease outcomes and chronic liver disease diagnoses; Table S2: Variance inflation factor (VIF) results for the fully adjusted Cox regression model evaluating the association of cardiovascular disease with the time to transition from low-risk to high-risk FIB-4; Table S3: Unadjusted and adjusted Cox regression models evaluating the association of the components of the cardiovascular disease composite outcome (coronary artery disease, cerebrovascular disease, and peripheral vascular disease) with the time to transition from low-risk to high-risk FIB-4; Table S4: Characteristics for the cohort of primary care patients with MASLD and a FIB-4 score at low-risk for advanced fibrosis by progression to indeterminate-risk or greater FIB-4 ($\geq$ 1.30); Table S5: Unadjusted and adjusted Cox regression models evaluating the association of cardiovascular disease with the time to transition from low-risk to indeterminate- or high-risk FIB-4.

Author Contributions: Conceptualization, A.D.S., M.Q., J.M., J.Z. and K.P.A.; methodology, J.Z., J.M. and A.D.S.; software, J.M.; validation, J.Z. and J.M.; formal analysis, J.Z.; investigation, J.Z. and A.D.S.; resources, J.M. and A.D.S.; data curation, J.Z. and J.M.; writing—original draft preparation, M.Q.; writing—review and editing, all authors; supervision, A.D.S.; project administration, C.B.; funding acquisition, A.D.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was reviewed and approved by the Institutional Review Board (IRB) at the Medical University of South Carolina (MUSC, Pro00056541). The initial approval date was 24 August 2016, and the expiration date is 17 May 2027. All research was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent Statement: Informed consent for participation is not required as per local legislation [Institutional Review Board at the Medical University of South Carolina]. This was a retrospective analysis of existing data and did not involve prospective enrollment or interaction with participants.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest. Dr. Schreiner has consulted for Novo Nordisk.

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