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FIB-4 stage of liver fibrosis is associated with incident heart failure with preserved, but not reduced, ejection fraction among people with and without HIV or hepatitis C

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Abstract

Background—Liver fibrosis, is independently associated with incident heart failure (HF). Investigating the association between liver fibrosis and type of HF, specifically HF with reduced ejection fraction (EF; HFrEF) or HF with preserved ejection fraction (HFpEF), may provide mechanistic insight into this association. We sought to determine the association between liver fibrosis score (FIB-4) and type of HF, and to assess whether HIV or hepatitis C status modified this association.

Methods—We included patients alive on or after 4/1/2003 from the Veterans Aging Cohort Study. We followed patients without prevalent cardiovascular disease until their first HF event, death, last clinic visit, or 9/30/2015. We defined liver fibrosis as: likely advanced fibrosis (FIB-4 > 3.25), indeterminate (FIB-4 range 1.45–3.25), unlikely advanced fibrosis (FIB-4 < 1.45). Primary outcomes were HFrEF and HFpEF (defined using ICD-9 diagnoses for HF, and EF extracted from electronic medical records using natural language processing). Cox proportional hazards models were adjusted for potential confounders and used to estimate hazard ratios (HR).

Results—Among 108,708 predominantly male (96%) participants mean age was 49 years. Likely advanced fibrosis was present in 4% at baseline and was associated with an increased risk of HFpEF [HR (95% confidence interval)] [1.70 (1.3–2.3)]; and non-significantly with HFrEF [1.20 (0.9–1.7)]. These associations were not modified by HIV or hepatitis C status.

Conclusion—Likely advanced fibrosis was independently associated with incident HFpEF but not HFrEF. This suggests that risk factors and/or mechanisms for liver fibrosis may have greater overlap with those for HFpEF than HFrEF.

Keywords

Liver fibrosis; Heart failure; Ejection fraction; HIV; Hepatitis; Cohort

Introduction

Liver cirrhosis, a late stage of liver disease, contributes to the development of hyperdynamic circulation, electrophysiologic abnormalities, and systolic and diastolic dysfunction in a syndrome termed cirrhotic cardiomyopathy.[1] There is an association between liver fibrosis and incident heart failure (HF).[2] The mechanisms for this association, currently unclear, may be of particular importance for people living with human immunodeficiency virus (HIV) and/or hepatitis C, both of which are chronic infections with hepatic and cardiac involvement.[3–6]

HF is a complex disease with different sub-types, including HF with reduced ejection fraction (EF; HFrEF) or preserved EF (HFpEF), which arise from different pathophysiologic mechanisms. HFrEF typically occurs due to an injury to the heart (e.g., myocardial infarction), which leads to an adaptive neurohormonal response to compensate for the injury and enables the heart to continue pumping blood adequately throughout the body. These changes, over the long term become maladaptive beginning the process of HF. In contrast, the etiology of HFpEF is poorly understood but thought to be of extra-myocardial origin with comorbidities like obesity, arterial hypertension, and renal insufficiency driving left ventricular remodeling through systemic inflammation.

Knowledge about the impact of liver fibrosis on type of heart failure may help narrow the gaps in knowledge about the mechanisms driving HF risk in HIV or hepatitis C. For example, liver fibrosis secondary to steatohepatitis could be an indicator of visceral adiposity and systemic inflammation, which are associated with HFpEF. Alternatively, liver injury could have a more integral role wherein cirrhosis drives systemic inflammation, endothelial dysfunction and HFpEF.

We hypothesized that liver fibrosis is associated with both HFpEF and HFrEF. Further, we assessed whether HIV and hepatitis C status modified the association of liver fibrosis and type of HF.

Methods

Cohort

Patients were from the Veterans Aging Cohort Study (VACS), which has been previously described.[7] Briefly, the VACS is a cohort of Veterans with HIV who are matched on age, sex, race/ethnicity and geographic location to two Veterans without HIV but who are also receiving clinical care at a Veterans Health Administration (VA) medical center.

We defined baseline as a patient's first VA clinic visit on or after 4/1/ 2003; follow up ended on 9/30/2015, the last date a patient was seen at the VA, or on the date of death.[3] To investigate the incidence of HFpEF and HFrEF, we excluded those with an ICD-9 diagnosis of HF or cardiomyopathy at baseline and up to 180 days after baseline. We also excluded those with other cardiovascular diseases (CVD) including acute myocardial infarction (MI), stroke, coronary heart disease, unstable angina or cardiac revascularization procedures to maximize the likelihood that HF events occurring during follow up were incident events.

Independent variables – liver fibrosis by FIB-4 score

The primary exposure was FIB-4 score.[8] FIB-4 is a validated noninvasive tool to assess hepatic fibrosis in HIV and chronic hepatitis C virus co-infection, hepatitis C mono-infection and non-alcoholic fatty liver disease (NAFLD) populations.[8,9] FIB-4 is calculated as: $\frac{Age(years) \times Aspartateaminotransferase\ (U/L)}{\times \sqrt{Alanine\ aminotransferase\ (U/L)}}$ $Platelet(10^9/L)$. FIB-4 is typically categorized as follows: FIB-4 b 1.45 (no advanced fibrosis likely), 1.45–3.25 (indeterminate level of fibrosis), and N 3.25 (advanced fibrosis likely) as per prior work.[10] ALT, AST, and

platelets from the same day, were obtained from VA laboratory records. The lab values selected were the closest and prior to, or up to 180 days after the baseline date.

Covariates

We used covariates measured closest and prior to, or up to 180 days after baseline date unless otherwise described below. Sociodemographic data included age, sex, and race/ethnicity. Framingham CVD risk factors, including diabetes, hypertension (HTN), and total and high-density lipoprotein (HDL) cholesterol were extracted from electronic health record data.[3] Diabetes was defined using glucose measurements, hemoglobin A1c, use of insulin or oral hypoglycemic agents, and/or ≥1 inpatient and/or 2 outpatient ICD-9 codes, as previously described.[11] HTN was defined as systolic blood pressure (SBP) N140 mm Hg or use of antihypertensive medication. Lipid levels were categorized based on National Cholesterol Education Program Adult Treatment Panel III criteria.[12] Smoking status, from VA Health Factors data,[13] was categorized into current, past, and never smoking. Body mass index (BMI; weight (kg) divided by height (m) squared) was dichotomized at 30 kg/m^2 with values at or above this threshold indicating obesity. Antecedent acute MI diagnosis (i.e., not present up to 180 days after baseline, but occurred during follow up and prior to the HF event) was defined using the inpatient 410 ICD-9 code. History of cocaine or alcohol abuse or dependence was defined using ICD-9 codes.[14]

HIV infection was present if a participant had at least one inpatient and/or two outpatient ICD-9 codes for HIV infection.[7] We also collected data on HIV-1 RNA, CD4+ T-lymphocyte counts (CD4 cell counts), and current use of antiretroviral therapy (ART). Hepatitis C virus (HCV) infection was categorized as uninfected (HCV antibody undetectable, HCV RNA undetectable, no ICD-9 code for HCV), chronic (detectable HCV RNA or genotype), and exposed (HCV antibody detectable and HCV RNA undetectable or unknown or ICD-9 code for HCV). We included all ART medications that were on VA formulary during the study period. We have previously shown in a nested VACS sample that 98% of Veterans with HIV on ART obtain their medications from the VA pharmacy.[7] HIV-1 RNA and CD4 cell counts were obtained from VA laboratory before and up to 180 days after baseline. ART use was determined 180 days before up to 7 days after baseline.

Dependent variables – type of HF

The primary outcome was type of HF (HFrEF or HFpEF). HF was identified by the presence of 1 inpatient or at least 2 outpatient ICD-9 codes (402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx) as previously described.[2,4] EF of participants with an ICD-9 diagnosis of HF was extracted from the VA VistAEchocardiogram file, VistA Radiology/Nuclear medicine file and the VistA Text Integration Utilities file. Extraction was performed with natural language processing as previously described.[15] HFrEF was defined as having an ICD-9 diagnosis of HF and an EF below 40% or in the absence of a numerical EF, clinical notes indicative of reduced EF.[4,15] HFpEF was similarly defined but with an EF above 50% or in the absence of a numerical EF, clinical notes indicative of preserved EF.[4,15] Participants with HF with EF from 40% to 50% were classified as HFmEF (HF with mid-range EF). Those with HF who did not have EF data were classified as HF with no known EF (HFnoEF).

Statistical analyses

Descriptive analyses were performed for all continuous and categorical variables stratified by FIB-4. We further stratified these descriptive analyses by type of HF among those who had incident HF. Next, we calculated incidence rates of HFrEF and HFpEF by FIB-4 category. In all analyses, only the first occurrence of HF during the observation period was considered.

For the primary analysis, we used Cox proportional hazards models to estimate the association of FIB-4 category with HFrEF and HFpEF. Models were initially unadjusted, then adjusted for age and race/ethnicity and then for all covariates. We assessed the linearity of the association of FIB-4 and HFpEF and HFrEF risk using restricted cubic splines (three knots, Stata 13 mkspline package default knot positions) of FIB4 to capture non-linear associations. To assess whether the association of FIB-4 and type of HF was altered by HIV or hepatitis C status, we included interaction terms between HIV status and FIB-4 and between hepatitis C status and FIB-4. A significant interaction was defined as having a *p*-value <0.10.

Multiple imputation techniques were used to address missing covariate data by generating five datasets with complete covariate values.[16] Relative risk estimates using imputed data were consistent with those from the complete case analyses. Regression results presented are based on imputed datasets. All covariates had complete data except the following: HDL cholesterol (69%), triglycerides (70%), SBP (86%), smoking (60%) BMI (84%), CD4 count (75%), and HIV-1 RNA (77%). All analyses were conducted with Stata 13.

Results

Baseline characteristics

Among 108,708 predominantly male (96%) Veterans eligible for this study, mean age was 49 years (standard deviation 10 years). Almost half the participants were black (48%) and 31% of the cohort had HIV (Table 1).

Four percent of the cohort had FIB-4 > 3.25 at baseline while 64% had FIB-4 < 1.45. Sixty percent of those with FIB-4 > 3.25 had HIV; a prevalence twice as high as for those with FIB-4 < 1.45. For veterans with HIV, prior exposure to any ART was similar across FIB-4 categories. Those with higher FIB-4 had lower CD4 T-cell count and higher HIV-1 RNA. Chronic hepatitis C was almost six times more prevalent among those with FIB-4 > 3.25 compared to those with FIB-4 < 1.45. Total cholesterol and obesity prevalence were lowest among those with FIB4 > 3.25 while current smoking, history of alcohol abuse dependence, and history of cocaine abuse/dependence were highest in this group (Table 1).

Compared to individuals with HFrEF, those with HFpEF on average, were two years older, had a higher prevalence of diabetes (38 vs. 27%), obesity (44 vs. 32%) and advanced liver fibrosis (7 vs. 4%) and lower occurrence of antecedent MI (6 vs. 9%) (Appendix Table 1).

Rates and risk of HF

During the observation period, there were 4018 incident HF events (1298 HFpEF, 1220 HFrEF, 483 HFmEF and 1017 HFnoEF; Table 2). HF incidence rates increased consistently with FIB-4 score category for HFpEF but inconsistently for HFrEF (i.e., overlapping 95% confidence intervals; Table 3). This pattern persisted among those without HIV or chronic hepatitis C (Table 3).

In unadjusted models, FIB-4 between 1.45 and 3.25 or FIB-4 > 3.25 were associated with increased risk of HFpEF, HFrEF, HFmEF and HFnoEF (Table 4). After adjustment for covariates, these associations only persisted for FIB-4 > 3.25 and HFpEF and HFnoEF (Table 4); compared to those with FIB-4 < 1.45, adjusted hazard ratio (95% confidence interval) for HFpEF was 1.1 (1.0–1.3; $p = 0.09$) among those with FIB-4 between 1.45 and 3.25 and 1.5 (1.1–1.9; $p = 0.003$) for those with FIB4 N 3.25. For HFrEF, these values were 1.1 (0.9–1.2; $p = 0.43$) and 1.1 (0.8–1.4; $p = 0.55$) respectively.

Spline models assessing FIB-4 as a continuous variables suggested a non-linear association of FIB-4 and HF risk (Fig. 1). The rate of increase in HF risk appeared greater below a FIB-4 threshold of 1.45 than above this threshold. However, tests for non-linearity were only statistically significant for heart failure (p = 0.01), but not for HFpEF (p = 0.10) or HFrEF (p = 0.61).

Interactions by HIV and/or hepatitis C status

The associations of FIB-4 category and heart failure types did not differ by HIV or hepatitis C status (all interaction p-values >0.1).

Discussion

This study found that advanced liver fibrosis as estimated by FIB-4 score was associated with an increased risk of HFpEF but not HFrEF. Notably, the association with type of HF did not differ by HIV or hepatitis C status.

No prior studies have assessed whether liver fibrosis is associated with incidence of HFpEF and HFrEF though our prior work has shown an association between liver fibrosis and risk of any type HF.[2] The current study extends this literature by providing evidence suggesting that this association is primarily driven by an association between liver fibrosis and HFpEF.

These findings suggest that HFpEF has a greater overlap in etiology with liver fibrosis than does HFrEF. HFpEF is more directly linked with systemic inflammation,[17] increased collagen dependent stiffness, increased extracellular matrix fibrillar collagen content,[18] and longer duration HTN and metabolic syndrome; HFrEF, in contrast, is more directly linked to prior MI.[19] Liver fibrosis, excessive accumulation of extracellular matrix proteins e.g., collagen, is preceded and promoted by inflammation following repeated liver injury.[20] Further, the liver has a key role in circulating blood volume and metabolic regulation.[1,21]

While this study was not designed to investigate mechanisms linking liver fibrosis to type of HF, we note that those with HFpEF (versus HFrEF) were slightly older, had a higher

prevalence of diabetes and obesity, and a lower prevalence of antecedent MI (i.e., occurred after baseline but before HF incidence). Likewise, those with FIB-4 > 3.25 (versus <1.45) were older, had a higher prevalence of type 2 diabetes despite a lower prevalence of obesity, and similar prevalence of antecedent MI. This finding also suggests that there is greater overlap in etiology for HFpEF (vs. HFrEF) and liver fibrosis.

We did not find evidence suggesting that HIV or HCV status modifies the association between FIB-4 and type of HF. This lack of interaction could suggest that liver fibrosis per se, rather than chronic infections accelerating liver fibrosis progression or promoting chronic inflammation is contributing to increased HFpEF risk.

The potential non-linearity we identified in the association between FIB-4 and HF highlights the need for improved discrimination of liver health in lower FIB-4 categories not indicative of advanced fibrosis. 82% of the cohort had FIB-4 values below the threshold for advanced fibrosis (FIB-4 < 3.25) while 64% of cohort had FIB-4 < 1.45 i.e. no advanced fibrosis. The rate of increase in HF risk (Fig. 1d) appeared greater below a FIB-4 threshold of 1.45 than above this threshold. A better understanding of alterations in liver health as FIB-4 increases below this threshold may explain the non-linear association we observed.

The potential implications of this work are threefold. First, it supports the need to screen for and reduce HF risk among people with liver disease, particularly among people with conditions like HIV or hepatitis C that enhance the overall risk of HF. Second, it supports the need for basic research focusing on the liver fibrosis as a mechanism driving incident HF, particularly HFpEF. Third, it supports the need to improve clinically available liver fibrosis risk stratification in the lower range of FIB-4 (<1.45) and in the indeterminate range of FIB-4 (between 1.45 and 3.25).

Important limitations to this analysis warrant discussion. VACS is a predominantly male cohort, which may limit generalizability of these findings to women who unlike men, tend to have higher prevalence of HFpEF. We did not have adjudicated HF outcomes. However, available EF data further minimized misclassification of the previously validated ICD-9 diagnoses used to identify HF. We did not have imaging or biopsy data to confirm liver fibrosis staging. It is conceivable that a participant with undiagnosed cirrhosis at baseline who decompensates and presents with HF symptoms (e.g., lower extremity edema, ascites) and a normal EF on echocardiography may be misdiagnosed as HFpEF if a careful history and physical exam were not obtained or a paracentesis was not performed for diagnostic evaluation. HF diagnoses were restricted to those within the VA and did not include Medicare and Medicaid diagnoses. This was because EF data were only available and extracted from VA medical records. In addition to the potential for residual confounding, the sensitivity of some of our measures of confounders was low e.g., alcohol consumption assessed by ICD 9 codes for alcohol abuse dependence. Despite the shortcomings of FIB-4 for identifying moderate fibrosis, it is a validated measurement that can be easily calculated in most clinical settings making it a very useful tool for large population epidemiologic research involving liver fibrosis.

In summary, FIB-4, a marker of liver fibrosis was independently associated with incident HFpEF but not HFrEF. Future studies should be conducted among women, include quantified and/or biological measures of alcohol exposure, and consider additional modalities of liver health ascertainment e.g., imaging, to ascertain whether it is fibrosis, steatosis, or steatohepatitis driving the association of liver injury and HFpEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Statement of conflict of interest

Joseph K. Lim has received consulting fees from Bristol-Myers Squibb and Gilead. Adeel A. Butt has received investigator initiated research grants (to the institution) from Gilead, Merck, and AbbVie. Vincent C. Marconi has received research grants from the Centers for Disease Control and Prevention and unrestricted grants and contracts from ViiV. Matthew J. Budoff has received research grants and contracts from General Electric.

Abbreviations and acronyms

HIV	human immunodeficiency virus
HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
VACS	Veterans Aging Cohort Study
CVD	cardiovascular disease
VHA	Veterans Health Administration
ICD-9	International Classification of Disease 9th Revision
FIB-4	Liver fibrosis index 4
NAFLD	non-alcoholic fatty liver disease
ALT	alanine aminotransferase
AST	aspartate aminotransferase
HDL	high-density lipoprotein
SBP	systolic blood pressure
BMI	body mass index
HCV	hepatitis C

HFmEF	heart failure with mid-range ejection fraction
HFnoEF	heart failure with no known ejection fraction

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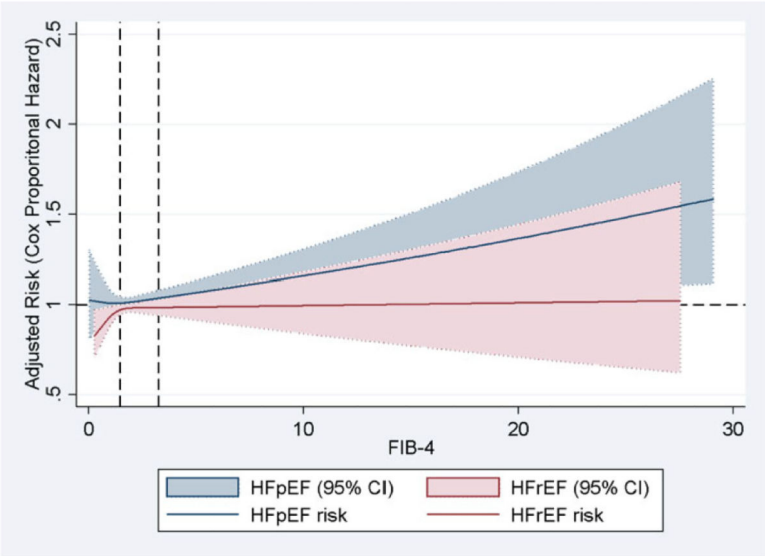

Fig. 1.

Association of FIB-4 (from spline models) and HFpEF and HFrEF risk. Vertical dashed lines indicate FIB-4 at 1.45 and 3.25. FIB-4 truncated at 30 (HFpEF) and 29 (HFrEF) for ease of viewing.

Table 1

Baseline characteristics of study population.

Data Are Column Percent Unless Otherwise Noted	FIB-4 (category of liver fibrosis)			Missing FIB-4
	<1.45 (No Advanced Fibrosis Likely)	1.45–3.25 (Indeterminate)	>3.25 (Advanced Fibrosis Likely)	
Demographics				
N(%)	69,175 (64)	19,367 (18)	4105 (4)	16,061 (15)
Mean age (SD)	47 (10)	55 (9)	54(8)	47 (10)
Male				
Race	96	98	99	98
White	41	37	38	38
Black	46	51	48	47
Hispanic	9	8	11	8
Other	4	4	3	7
HIV-related				
HIV	28	47	60	17
Mean RNA log copies/ml	7.3 (3.1)	7.9 (3.3)	8.4 (3.3)	7.2 (3.1)
HIV-1 RNA ≥500 copies/ml % of HIV+)	46	51	54	14
Mean CD4+ T-cell count cells/mm^3	478 (305)	374 (272)	310 (261)	466 (298)
CD4+ T-cell count<500 cells/mm^3 (% of HIV+)	51	64	70	17
On HIV antiretroviral therapy (% of HIV+)	44	43	43	21
Liver				
Hepatitis C: uninfected	72	57	33	54
Hepatitis C: chronic	9	23	53	8
Hepatitis C: exposed	3	5	9	4
Unknown HCV status	15	11	4	34
CVD risk factors				
Diabetes	14	15	17	5
Systolic blood pressure (BP)/mm Hg				
Mean (SD)	131 (14)	134 (16)	132 (17)	131 (15)
<140 no BP medication	41	34	32	47
<140 on BP medication	35	38	38	14

Data Are Column Percent Unless Otherwise Noted	FIB-4 (category of liver fibrosis)			Missing FIB-4
	<1.45 (No Advanced Fibrosis Likely)	1.45–3.25 (Indeterminate)	>3.25 (Advanced Fibrosis Likely)	
≥140 on BP medication	18	22	23	10
≥140 no BP medication	6	6	6	11
Total cholesterol ≥200 mg/dL	36	27	17	13
HDL cholesterol <40 mg/dL	36	36	40	11
Smoking				
Never smoker	25	22	15	15
Current smoker	37	38	47	24
Former smoker	12	14	11	7
Body mass index				
Mean (SD)	28.7 (5.9)	27.0 (5.4)	25.6 (5.2)	28.2 (5.6)
Obese > 30 kg/m^2	35	24	17	23
Cocaine use	14	20	25	15
Alcohol abuse/dependence (ever)	23	31	50	21
Antecedent incident acute myocardial infarction	2.0	2.4	2.1	1.7

All covariates had complete data except the following: HDL cholesterol (75543), triglycerides (76046), SBP (92961), smoking (65118) BMI (91534), CD4 count (25197), and HIV-1 RNA (25828).

Table 2

Number of incident heart failure events by type and overall stratified by FIB-4.

	FIB-4				Total
	<1.45	1.45–3.25	>3.25	Missing	
Cohort	69,175	19,367	4105	16,061	108,708
HFpEF	748	343	87	120	1298
HFrEF	736	302	54	128	1220
HFmEF	290	116	26	51	483
HFnoEF	574	273	62	108	1017
All HF	2348	1034	229	407	4018

Abbreviation: FIB-4 – liver fibrosis 4 index.

Table 3

Crude incidence rates of heart failure types (per 1000 person years [95% CI]) stratified by FIB-4, HIV and HCV status.

Heart Failure Type	HIV/HCV Status	FIB-4			
		<1.45	1.45–3.25	>3.25	Missing
HFpEF	All	1.3 (1.3–1.4)	2.4 (2.2–2.7)	3.7 (3.0–4.6)	0.9 (0.8–1.1)
HFrEF		1.3 (l.2–1.4)	2.1 (1.9–2.4)	2.3 (1.8–3.0)	1.0 (0.8–1.2)
HFmEF		0.5 (o.5–0.6)	0.8 (0.7–1.0)	1.1 (0.8–1.6)	0.4 (0.3–0.5)
HFnoEF		1.0 (1.0–1.1)	1.9 (1.7–2.2)	2.6 (2.1–3.4)	0.8 (0.7–1.0)
All HF		4.1 (3.9–4.3)	7.4 (6.9–8.0)	10.1 (8.7–11.8)	3.7 (3.4–4.1)
HFpEF	No HCV No HIV	1.5 (1.3–1.6)	2.1 (1.8–2.6)	3.9 (2.3–6.6)	1 (0.8–1.3)
	No HCV	1.3 (1.2–1.4)	2 (1.7–2.4)	3.2 (2.2–4.7)	1 (0.8–1.3)
	HCV chronic	1.9 (1.6–2.3)	3.2 (2.7–3.8)	4.3 (3.3–5.6)	1.7 (1.1–2.6)
	No HIV	1.4(1.3–1.6)	2.5 (2.2–2.9)	4.1 (3.0–5.6)	0.9 (0.7–1.1)
	HIV	1.1 (0.9–1.3)	2.3 (2.0–2.7)	3.4 (2.5–45)	1.2 (0.8–1.9)
HFrEF	No HCV No HIV	1.3 (1.1–1.4)	1.7 (1.4–2.2)	1.4 (0.6–3.3)	1 (0.8–1.3)
	No HCV	1.3 (1.2–1.4)	1.9 (1.6–2.2)	2.5 (1.6–3.9)	1.1 (0.9–1.4)
	HCV chronic	1.8 (1.4–2.1)	2.6 (2.2–3.1)	2.2 (1.6–3.2)	1.5 (1.0–2.4)
	No HIV	1.3 (1.2–1.4)	1.9 (1.7–2.3)	1.9 (1.2–3.0)	0.9 (0.8–1.1)
	HIV	1.5 (1.3–1.7)	2.3 (2.0–2.7)	2.6 (1.9–3.6)	1.4 (0.9–2.0)
HFmEF	No HCV No HIV	0.5 (0.4–0.6)	0.8 (0.6–1.2)	0.6 (0.1–2.2)	0.4 (0.3–0.6)
	No HCV	0.6 (0.5–0.7)	1.0 (0.8–1.2)	1.4 (0.8–2.5)	0.5 (0.4–0.7)
	HCV chronic	0.9 (0.7–1.2)	1.1 (0.8–1.4)	1.2 (0.7–1.9)	0.9 (0.5–1.6)
	No HIV	0.5 (0.5–0.6)	0.8 (0.6–1.1)	0.4 (0.2–1.1)	0.4 (0.3–0.5)
	HIV	0.5 (0.4–0.7)	0.8 (0.6–1.1)	1.6 (1.1–2.4)	0.3 (0.1–0.7)
HFnoEF	No HCV No HIV	1.0 (0.9–1.2)	1.9 (1.5–2.4)	2.5 (1.3–4.8)	0.9 (0.7–1.2)
	No HCV	1.0 (0.9–1.1)	1.9 (1.6–2.2)	2.2 (1.4–3.4)	0.9 (0.7–1.1)
	HCV: chronic	1.4(1.2–1.9)	2.0 (1.6–2.4)	2.8 (2.1–3.9)	1.3 (0.8–2.1)
	No HIV	1.1 (1.0–1.2)	1.8 (1.5–2.1)	2.9 (2.0–4.2)	0.8 (0.7–1.0)
	HIV	1.0 (0.8–1.1)	2.1 (1.8–2.5)	2.4 (1.7–3.4)	0.8 (0.5–1.3)

Number of participants: All (108,708); No HCV, No HIV (48,116); No HCV (71,037); HCV (15,016); No HIV (74,736); HIV (33,972).

Abbreviations: HIV – human immunodeficiency virus, HCV – hepatitis C, FIB-4 – liver fibrosis index 4.

Table 4

Risk of heart failure by FIB-4.

		Hazard Ratio (95% Confidence Interval)		
Heart Failure Type	**FIB4**	**Unadjusted**	**Adjusted For Age, Race, HIV**	**Fully Adjusted**
Preserved EF	<1.45	1 (ref)	1 (ref)	1 (ref)
	1.45–3.25	1.7 (1.5–1.9)	1.2 (1.0–1.3)	1.1 (1.0–1.3) $p = 0.09$
	>3.25	2.1 (1.7–2.7)	1.6 (1.3–2.1)	1.5 (1.1–1.9)
Reduced EF	<1.45	1 (ref)	1 (ref)	1 (ref)
	1.45–3.25	1.5 (1.3–1.7)	1.1 (0.9–1.2)	1.1 (0.9–1.2)
	>3.25	1.5 (1.2–1.9)	1.1 (0.9–1.4)	1.1 (0.8–1.4)
Moderate EF	<1.45	1 (ref)	1 (ref)	1 (ref)
	1.45–3.25	1.5 (1.2–1.8)	1.1 (0.8–1.3)	1.0 (0.8–1.3)
	>3.25	1.7 (1.0–3.0)	1.3 (0.7–2.3)	1.3 (0.7–2.3)
Missing EF	<1.45	1 (ref)	1 (ref)	1 (ref)
	1.45–3.25	1.8 (1.5–2.0)	1.3 (1.1–1.5)	1.3 (1.1–1.5)
	>3.25	2.0 (1.5–2.7)	1.6 (1.2–2.1)	1.5 (1.1–2.1)
All	<1.45	1 (ref)	1 (ref)	1 (ref)
	1.45–3.25	1.6 (1.5–1.8)	1.1 (1.1–1.2)	1.1 (1.0–1.2) $p = 0.002$
	>3.25	1.8 (1.6–2.1)	1.4 (1.2–1.6)	1.3 (1.2–1.6)