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FIB-4 stage of liver fibrosis predicts incident heart failure among HIV infected and uninfected patients

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Abstract

Liver fibrosis is common, particularly in human immunodeficiency virus infected (HIV+) people. HIV+ people have excess congestive heart failure (CHF) risk compared to uninfected people. It remains unknown if stage of liver fibrosis influences the CHF risk or if HIV or hepatitis C virus (HCV) infection modifies this association. Our objectives were to assess whether: 1) stage of liver fibrosis is independently associated with incident CHF; 2) the association between stage of liver fibrosis and incident CHF is modified by HIV/HCV status. Participants alive on or after 4/1/2003 in the Veterans Aging Cohort Study were included. Those without prevalent cardiovascular disease (CVD) were followed until their first CHF event, death, last follow-up date or 12/31/2011. Liver fibrosis was measured by FIB-4, calculated using age, aminotransferases and platelets. Outcome: incident CHF (ICD-9 codes). Cox proportional hazards regression models were adjusted for CVD risk factors. Among 96,373 participants over 6.9 years, 3,844 incident CHF events occurred. FIB-4 between 1.45–3.25 (moderate fibrosis) and FIB-4>3.25 (advanced fibrosis/cirrhosis) were associated with CHF (HR (95% CI)=1.17 (1.07–1.27); 1.65(1.43–1.92)). The association of advanced fibrosis/cirrhosis and incident CHF persisted regardless of HIV/HCV status.

Conclusions—Moderate and advanced liver fibrosis/cirrhosis are associated with an increased risk of CHF. The association for advanced fibrosis/cirrhosis persists even among participants without hepatitis C and/or HIV infection. Assessing liver health may be important for reducing the risk of future CHF events, particularly among HIV and hepatitis C infected people among whom CVD risk is elevated and liver disease is common.

Keywords

cirrhosis

Introduction

Liver disease is among the leading causes of death among people living with human immunodeficiency virus (HIV) infection.(1) Advances in direct-acting antiviral and antiretroviral therapies have helped to reduce the risk of liver-related and acquired immune deficiency syndrome (AIDS)-related adverse outcomes, respectively, among people living with hepatitis C virus (HCV) infection and human immunodeficiency virus (HIV).(2) Consequently, extra-hepatic non-AIDS-related complications, particularly cardiovascular disease, now represent an increasingly important proportion of morbidity and mortality risk in these populations. (3, 4) Understanding traditional and novel mechanisms driving these complications is essential to quantifying and minimizing their risk among chronic HCV-infected, HIV-infected, and other populations at risk for liver disease.

Several plausible mechanisms connect liver disease and cardiovascular disease. For example, cirrhosis contributes to the development of hyperdynamic circulation, electrophysiologic abnormalities, and systolic and diastolic dysfunction in a syndrome termed cirrhotic cardiomyopathy.(5) Cirrhosis is also associated with altered synthesis of coagulant and anti-coagulant factors that could lead to thrombosis or hemorrhage (6) thereby increasing ischemic heart disease risk. Bacterial translocation from the intestinal lumen to extra-intestinal sites is common among people with cirrhosis (7) and is associated with immune system activation and inflammation (8) which further drive atherosclerosis and ischemic heart disease, and ultimately result in congestive heart failure (CHF). (9) Congestive hepatopathy occurs when heart failure leads to increased systemic venous pressure, hepatocyte atrophy and perisinusoidal edema, which, drive hypoperfusion and hypoxia in hepatocytes. (10) The mechanisms connecting liver and cardiovascular diseases are bi-directional such that liver disease may cause heart disease and heart disease may cause liver disease.(5) This study is designed to focus on the former mechanism – liver disease leading to heart disease – and minimize potential confounding by the latter mechanism. Specifically, we sought to examine whether subclinical liver disease (stages of liver fibrosis) assessed non-invasively would be associated with incident CHF events.

Elucidating the mechanisms of CHF risk is important because heart disease is among the 10 leading causes of death in the general population (11) and a growing cause for concern among aging HIV infected men and women. (12, 13) Liver fibrosis is potentially reversible (14) and can be measured non-invasively using routine clinical laboratory tests, such as the FIB-4 score. (15) If liver fibrosis is associated with incident CHF events, this could have implications for research and clinical practice. First, it would improve our understanding of the mechanisms driving excess cardiovascular disease risk in the setting of HIV infection. Second, it may prompt clinicians to screen for CHF among HIV infected and uninfected patients at risk for liver fibrosis or liver fibrosis progression.

Our primary hypothesis is that increasing liver fibrosis, determined by FIB-4, (15) is independently associated with incident CHF events accounting for Framingham and other established cardiovascular disease risk factors. We assessed whether this association is modified by HIV or hepatitis C (HCV) status. We tested this hypothesis in the Veterans Aging Cohort Study (VACS), a longitudinal prospective cohort of HIV+ Veterans each matched on age, race/ethnicity, and clinical site to two uninfected Veterans in care.

Methods

Data source

Participants were selected from the VACS, which has been described previously.(16) VACS participants have been continuously enrolled each year since 1998 using a validated existing algorithm from United States Department of Veterans Affairs (VA) national electronic medical record system. Institutional review boards at Yale University, West Haven VA Medical Center and Vanderbilt University approved this study. We had full access to all data in the study and take responsibility for its integrity and data analyses.

Study Participants

All participants who were alive and enrolled in VACS on or after 4/1/2003 were eligible for this study. Participants were excluded if they had prevalent cardiovascular disease based on ICD-9 codes for CHF, cardiomyopathy, acute myocardial infarction (AMI), unstable angina, coronary artery revascularization, ischemic or hemorrhagic stroke. (13, 17–19) Prevalent cardiovascular disease included events occurring up to six months after baseline. Data on prevalent cardiovascular disease included ICD-9 diagnoses from Veterans Health Administration electronic health records, Medicare, Medicaid, and VA Fee for Service records. VA Fee for Service represents care provided to Veterans who receive care outside the VA healthcare system that is not covered by Medicare.

Baseline was defined as a patient's first clinical encounter on or after 4/1/2003 and follow up ended after an incident CHF event (see dependent variables), death, last follow-up date or 12/31/2011.

Dependent variable

The outcome was time to first CHF event defined using International Classification of Diseases, Ninth Revision (ICD-9) diagnoses (402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx). At least one inpatient or two outpatient codes on different days were required for a CHF event to be confirmed. ICD-9 data were obtained from VA electronic health records, Medicare, and VA fee-for-service records.

Independent variables

The primary exposure was three mutually exclusive liver fibrosis categories defined by FIB-4 score. FIB-4 is calculated as the product of age (years) and aspartate aminotransferase (AST, U/L) divided by the product of platelet count ($10^9/L$) and the square root of alanine aminotransferase (ALT, U/L). The categories were: FIB-4 <1.45 (from here referred to as minimal fibrosis), 1.45–3.25 (moderate fibrosis), and >3.25 (advanced fibrosis/cirrhosis).

Those with missing FIB-4 data were included a fourth category for descriptive analyses and subsequently imputed as described below. In HIV and HCV infected populations, FIB-4 ≥ 3.25 correctly identifies advanced hepatic fibrosis 71% of the time (i.e., positive predictive value, PPV); sensitivity 31%, specificity 93%. FIB-4 ≤ 1.45 correctly rules out advanced fibrosis 83% of the time (negative predictive value, NPV); sensitivity 73%, specificity 70%. (20) Prior work among HIV/HCV uninfected populations with non-alcoholic fatty liver disease (NAFLD), FIB-4 ≥ 3.25 had a PPV of 53% (sensitivity 48%, specificity 95%) for advanced fibrosis; for FIB-4 ≤ 1.45 NPV was 98% (sensitivity 90%, specificity 64%). (21) ALT, AST, and platelets, were obtained from VA laboratory records before and up to 180 days after baseline.

Covariates

Covariate data closest to baseline date were used. Sociodemographic data included age, sex, and race/ethnicity. Framingham cardiovascular disease risk factors including diabetes, hypertension, and total and high-density lipoprotein (HDL) cholesterol were measured using electronic health record data. (13) Diabetes was diagnosed using glucose measurements, use of insulin or oral hypoglycemic agents, and/or 1 inpatient and/or 2 outpatient ICD-9 codes, as previously validated. (22) Hypertension was defined as systolic blood pressure (SBP) greater than 140 mmHg or use of antihypertensive medication. (23) Lipid levels were categorized based on National Cholesterol Education Program Adult Treatment Panel III criteria. (24) Smoking was measured from the VA Health Factors data repository. (25) Smoking was categorized into current, past, and never smoking. Body mass index (BMI; weight (kg) divided by height (m) squared) was dichotomized at 30 kg/m² with values at or above this threshold indicating obesity. Antecedent incident AMI (i.e., an AMI that was not present at baseline, but occurred during follow up prior to the CHF event) was defined using the inpatient 410 ICD-9 code.

HIV infection was present if a participant had at least one inpatient and/or two outpatient ICD-9 codes for HIV infection. (16) HCV infection was defined as a positive HCV antibody or RNA test or at least one inpatient and/or two outpatient ICD-9 codes for this diagnosis. (26) We also collected data on HIV-1 RNA, CD4+ T-lymphocyte counts (CD4 cell counts), and current use of antiretroviral therapy (ART). We included all ART medications that were on VA formulary during the study period. We have previously shown in a nested sample that 98% of HIV+ Veterans on ART obtain their medications from the VA. (16) HIV-1 RNA, CD4 cell counts and antiretroviral therapy data were obtained from VA laboratory and pharmacy records before and up to 180 days after baseline.

History of cocaine or alcohol abuse or dependence was defined using ICD-9 codes. (27)

Statistical analysis

Descriptive statistics for all variables by FIB-4 categories were assessed using the Kruskal-Wallis test for continuous variables and chi-square test for categorical variables. We calculated rates of CHF per 1,000 person-years (py) stratified by FIB-4 categories. We further assessed CHF rates and risk across FIB-4 categories stratified by HIV/HCV status.

We calculated mortality rates stratified by FIB-4 categories to enable us to assess the potential competing risk of death with elevated FIB-4 occurring prior to a CHF event. (28)

We examined the association between FIB-4 and incident CHF using six Cox proportional hazard models: 1) unadjusted; 2) adjusted for age, and race-ethnicity; 3) adjusted for Framingham 30-year cardiovascular disease risk factors (age, treated or untreated systolic blood pressure, smoking, diabetes, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides) plus race-ethnicity; 4) adjusted for Model 2 covariates plus antecedent incident acute myocardial infarction; 5) adjusted for Model 3 covariates plus HIV and HCV status; and 6) adjusted for covariates in model 5 plus BMI and history of substance use (alcohol dependence/abuse, cocaine). We repeated the sixth model stratifying by HIV/HCV status instead of adjusting for it.

Sensitivity analyses were conducted to minimize confounding and the impact of reverse causality on our results. First, we excluded participants with conditions at baseline that are likely to drive liver fibrosis and/or are associated with CHF: diabetes, alcohol abuse/dependence, hepatitis C, and obesity. Second, we assessed incident CHF events occurring at least two years (as opposed to six months in the primary analysis) after baseline FIB-4 measurement. This further increased separation between FIB-4 measurement and incident CHF making it more likely that our results would reflect the effect of liver fibrosis on CHF and not vice versa (i.e., reverse causality by congestive hepatopathy). Congestive hepatopathy occurs when heart failure (often right-sided) leads to increased venous pressure including in the hepatic veins and sinusoids, which could ultimately lead to hepatocellular injury, liver enzyme and FIB-4 alterations (10, 29, 30). Third, we excluded participants with hepatic decompensation (31) prior to incident CHF diagnosis or censoring. This was done to further minimize reverse causality by congestive hepatopathy. Hepatic decompensation was defined based on previously validated ICD-9 diagnoses of ascites, portal hypertension, spontaneous bacterial peritonitis and/or esophageal variceal hemorrhage,(31) relevant features in congestive hepatopathy. (32, 33)

Regression models were run using multiple imputation techniques that generated five datasets with complete covariate values. (34) Relative risk estimates using imputed data were consistent with those from the missing category analyses. Regression results presented are based on imputed datasets.

Results

After excluding people with pre-existing cardiovascular disease, the 96,373 people free of cardiovascular disease at baseline were included in these analyses.

In this cohort of HIV infected and uninfected veterans, 59% of patients (N=57,309) had minimal fibrosis, 17% (N=16,360) had moderate fibrosis, and 4% (N=3,679) had advanced fibrosis/cirrhosis. Compared to those with minimal fibrosis, those with advanced fibrosis/cirrhosis were more likely to be older, and have HIV or HCV (Table 1). Those with advanced fibrosis/cirrhosis were less likely to be female or white. Participants with advanced

fibrosis/cirrhosis had a greater prevalence of diabetes, current smoking, and alcohol or cocaine abuse/dependence, but lower total cholesterol and BMI (Table 1).

Those missing FIB-4 (N=19,025) were similar to those with minimal fibrosis. Overall, compared to those with non-missing FIB-4, those with missing FIB-4 had lower prevalence of HIV infection, HCV, diabetes, hypertension, HDL <40 mg/dL, and current smoking (Table 1).

Over a median of 6.9 (interquartile range 3.2–8.6) years of follow up, there were 3,844 incident CHF events. Elevated FIB-4 was associated with increasing rates of incident CHF despite competing risk of higher mortality among those with higher FIB-4 (Figure 1).

Moderate and advanced fibrosis/cirrhosis were strongly associated with CHF risk in unadjusted models (hazard ratio (HR)= 1.78 95% confidence interval (CI)=1.65–1.92; and HR (95% CI)=2.77 (2.38–3.22)). Adjustment for age and race/ethnicity attenuated these associations (1.20 (1.11–1.30) and 1.89 (1.62–2.19)). Further for Framingham cardiovascular disease risk factors and antecedent incident AMI had minimal effect on risk estimates. After additional adjustment HIV/HCV status, substance use and obesity, moderate fibrosis and advanced fibrosis/cirrhosis were associated with 17% (HR (95% CI)=1.17 (1.07–1.27) and 65% (1.65 (1.43–1.92)) increased risk of CHF respectively compared to those with minimal fibrosis (Table 2). The pattern of increasing risk of CHF with increasing FIB-4 remained when the analyses were stratified by HIV and HCV status (Table 3). The association of advanced fibrosis/cirrhosis and incident CHF persisted regardless of HIV/HCV status (Table 3). The association of moderate fibrosis and incident CHF remained statistically significant only among those with either HIV or HCV infection (Table 3). We did not find evidence of statistical interaction between HIV/HCV status and FIB-4 stage on CHF risk (p=0.94). FIB-4 remained associated with incident CHF even after excluding participants with diabetes, alcohol abuse/dependence, hepatitis C or obesity at baseline (1.16 (0.99–1.37) and 1.73 (1.23–2.44)). Results were similar to those of the primary analyses after excluding participants with incident CHF within two years of FIB-4 measurement or excluding participants with hepatic decompensation prior to incident CHF diagnosis or censoring (Table 4).

Discussion

In this study, higher FIB-4 scores, including those indicative of moderate liver fibrosis, were significantly associated with an increased risk of incident CHF. The association between FIB-4 and incident CHF was present even after adjustment for traditional cardiovascular disease risk factors and antecedent AMI, regardless of HIV/HCV status, and despite increased total mortality among those with higher FIB-4.

Previous studies examining associations between liver disease and incident cardiovascular disease events focused on the etiologies of the underlying liver disease (e.g. viral hepatitis, obesity leading to fatty liver disease) and not severity of hepatic fibrosis (i.e., no/minimal, moderate or advanced fibrosis/cirrhosis, as measured by FIB-4). (35–38) This focus on etiology does not address whether the extent of hepatic fibrosis is an important determinant

of CHF risk. Our cohort is large, has a high proportion of non-whites, and includes people without diabetes, which extends generalizability beyond previous studies. (39–42) Further extending prior work, (40, 41, 43, 44) our analyses also accounted for alcohol dependence/abuse, HIV, and HCV as well as other comorbid conditions linked to liver fibrosis such as obesity and smoking.

To our knowledge this is the first large study to report that moderate liver fibrosis is associated with 17% increased risk of CHF after adjustment for possible confounders. Importantly, participants with prevalent cardiovascular disease were excluded from the analysis, and only the first occurrence of CHF was considered. This methodology minimized the possibility of reverse causality due to congestive hepatopathy i.e. finding a significant association that reflects the effect of heart disease on the liver rather than the effect of liver disease on the heart.(5) Moreover, results from sensitivity analyses excluding patients who developed hepatic decompensation prior to an incident CHF event or censoring were consistent with those of the primary analyses. Clinical features of hepatic decompensation overlap with features of congestive hepatopathy; thus, by eliminating hepatic decompensation, we further minimize the likelihood of reverse causality due to congestive hepatopathy. Adjusting for antecedent AMI did not alter the association between FIB-4 and incident CHF, suggesting that this association is independent of AMI events occurring prior to CHF diagnosis. The association of advanced liver fibrosis/cirrhosis with increased CHF risk persisted among those without HIV and HCV suggesting an association that is independent of HIV and HCV.

Our findings are also consistent with a prior study using data from the National Health and Nutrition Examination Survey (NHANES) that reported increased risk of cardiovascular mortality associated with higher NAFLD fibrosis scores. (45) Taken together, these data provide evidence that the etiology (e.g., NAFLD), type and severity (e.g., moderate fibrosis), of liver disease contribute to CVD risk.

The mechanisms driving the association between FIB-4 and incident CHF are understudied, particularly in relation to intermediate levels of liver fibrosis. Earlier work reports an association between cirrhosis and hyperdynamic circulation, electrophysiologic abnormalities and systolic and diastolic dysfunction that culminate in cirrhotic cardiomyopathy. (5) It may be that similar hemodynamic and electrophysiologic alterations are occurring, albeit to a lesser extent in those who have not yet progressed to cirrhosis, and contributing over time to increased risk of clinical CHF. Whether improving liver health reduces the risk of future CHF warrants further study.

These results may have important implications for health care providers. While clinicians are very familiar with traditional CHF risk factors such as diabetes, understanding that even moderate liver fibrosis may independently contribute to the increased risk of heart failure may be important for reducing the risk of heart failure events. The fact that vulnerable populations, like those infected with HIV, hepatitis C, or both, already have an increased risk of cardiovascular disease events, makes assessing liver health a potentially important part of any cardiovascular disease risk reduction strategy in these groups. FIB-4 is calculated using routinely available clinical lab results. Thus clinicians could incorporate FIB-4 assessment

into their heart failure risk stratification procedures and prioritize interventions to improve liver health (e.g., alcohol use reduction, weight loss, glycemic control, successful treatment of HCV, viral suppression of HIV) as appropriate.

Limitations

This study has important limitations that merit discussion. First, CHF outcomes were not adjudicated. However, we did utilize validated ICD-9 codes that have been used in prior work. Moreover, these ICD-9 codes were obtained from multiple data sources i.e. VA, Medicare, and VA Fee for service data, thus minimizing the possibility of missing CHF events that occurred outside the VA health care system. (17) Second, though the FIB-4 score was originally developed among HIV/HCV co-infected people with clinically diagnosed liver disease that called for liver biopsy, subsequent studies have assessed this measure in several other populations including HCV uninfected individuals and others without an indication for liver biopsy. (46–48) These studies suggest that FIB4 score can be used as an accurate indication of liver fibrosis in a cohort such as the VACS. Third, while FIB-4 is considered an acceptable surrogate marker of liver fibrosis, there are non-invasive (e.g., FibroScan, magnetic resonance elastography, Enhanced Liver Fibrosis score) and invasive measures (i.e., liver biopsy) that may better discriminate stages of liver fibrosis. However, these other fibrosis measures are not routinely collected on all patients within a health care system and in the case of liver biopsy, have a risk-benefit ratio that may be unacceptable for patients at low risk for liver fibrosis. (49) Fourth, the associations between FIB-4 and incident CHF could have been attributable to reverse causality by congestive hepatopathy; however, we excluded individuals with prevalent cardiovascular disease up to two years after FIB-4 measurement; analyzed only the first occurrence of new heart failure; and found similar results after exclusions of individuals with a diagnosis of hepatic decompensation prior to incident CHF diagnosis or censoring. Fifth, only baseline values of FIB-4 used in analyses and thus we cannot comment on changes in liver health during the follow up period. Sixth, only baseline covariates were used in analyses and thus we cannot comment on whether changes in covariates (e.g., hepatitis status) explain some or all of the association of FIB-4 with CHF risk. Seventh, the population was predominantly male so these findings may not generalize to women. Lastly, as with all observational studies, there is potential for unmeasured confounding.

Summary

In conclusion, participants with moderate and severe liver fibrosis/cirrhosis as measured by FIB4 score had an increased risk of CHF compared to participants with no liver fibrosis. This association persisted even among participants who did not have hepatitis C and or HIV infection. Moreover, this increased risk of CHF was present even though those with moderate and severe liver fibrosis had significantly higher mortality rates than those without liver fibrosis. The results suggest that assessing liver health may be important for reducing the risk of future CHF events, particularly among HIV and hepatitis C infected people where cardiovascular disease risk is elevated and liver disease is common.

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Abbreviations

CHF	Congestive heart failure
HIV	Human immunodeficiency virus
FIB-4	Liver fibrosis index-4
HCV	Hepatitis C
VACS	Veterans Aging Cohort Study
VA	U.S. Department of Veterans Affairs
ICD-9	International classification of Disease, Ninth Revision
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
PPV	Positive predictive value
NPV	Negative predictive value
NAFLD	Non-alcoholic fatty liver disease
AMI	Acute myocardial infarction
HDL	High density lipoprotein
SBP	Systolic blood pressure
BMI	Body mass index
RNA	Ribonucleic acid
py	Person-years
HR	Hazard ratio
CI	Confidence interval

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Figure 1. Unadjusted rates (95% confidence intervals) of incident CHF events and total mortality by liver fibrosis.

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 (Minimal)	1.45–3.25 (Moderate)	>3.25 (Advanced)	
Demographics				
N (%)	57,309 (59)	16,360 (17)	3,679 (4)	19,025 (20)
Mean age (SD)	47 (9)	54 (9)	53 (8)	48 (10)
Male	96	98	99	97
Race				
<i>White</i>	40	35	37	38
<i>Black</i>	47	53	50	47
<i>Hispanic</i>	8	7	9	7
<i>Other</i>	5	5	4	8
HIV				
HIV infected	29	50	61	16
HIV-1 RNA <500 copies/ml (% of HIV+)	48	53	56	22
CD4+ T-cell count <500 cells/mm ³ (% of HIV+)	54	65	71	17
On any ART (% of HIV+)	75	78	78	35
Liver				
HCV	13	35	65	8
CVD risk factors				
Diabetes	13	15	18	8
Systolic blood pressure (BP)/mmHg				
<140 no BP medication	40	35	33	44
<140 on BP medication	34	36	37	20
140 on BP medication	18	22	22	12
140 no BP medication	6	6	6	10
LDL cholesterol <160 mg/dL	10	6	3	5
HDL cholesterol <40 mg/dL	37	37	40	16
Triglycerides <200 mg/dL	23	21	19	9
Smoking				
<i>Never smoker</i>	23	20	13	17
<i>Current smoker</i>	37	38	46	27
<i>Former smoker</i>	11	13	11	9
Obese, BMI >30 kg/m ²	34	23	16	27
Cocaine	15	21	25	15
Alcohol abuse/dependence (ever)	24	32	51	23
Antecedent incident AMI	1.5	2.0	1.6	1.0

All variables had complete data except the following: LDL cholesterol data were available for 74559, HDL cholesterol (75543), triglycerides (76046), SBP (92961), smoking (65118) BMI (91534), CD4 count (25327), and HIV-1 RNA (26048).

p-values across FIB-4 groups (excluding missing FIB-4 group) were all <0.01

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Table 2

Hazard ratio (95% confidence interval) for the association between liver injury and incident congestive heart failure

Variables	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Liver fibrosis						
<i>FIB-4</i> < 1.45	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
<i>FIB-4</i> 1.45–3.25	1.78 (1.65–1.92)	1.20 (1.11–1.30)	1.27 (1.17–1.38)	1.27 (1.17–1.38)	1.17 (1.07–1.27)	1.17 (1.07–1.27)
<i>FIB-4</i> > 3.25	2.74 (2.39–3.13)	1.89 (1.62–2.19)	1.93 (1.67–2.22)	1.93 (1.68–2.22)	1.66 (1.43–1.93)	1.65 (1.43–1.92)
Age (per 10 years)		1.99 (1.92–2.06)	1.79 (1.72–1.86)	1.75 (1.69–1.82)	1.78 (1.72–1.85)	1.84 (1.76–1.91)
Race/ethnicity						
<i>White</i>		1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
<i>Black</i>		1.29 (1.21–1.39)	1.21 (1.13–1.3)	1.22 (1.14–1.31)	1.20 (1.11–1.28)	1.17 (1.09–1.25)
<i>Hispanic</i>		0.75 (0.66–0.87)	0.73 (0.63–0.84)	0.73 (0.64–0.84)	0.72 (0.63–0.83)	0.72 (0.63–0.83)
<i>Other</i>		0.77 (0.64–0.93)	0.86 (0.71–1.04)	0.88 (0.72–1.06)	0.89 (0.74–1.08)	0.91 (0.75–1.1)
Systolic blood pressure (BP)/mmHg						
<140 no BP meds			1 (ref)	1 (ref)	1 (ref)	1 (ref)
<140 on BP meds			1.54 (1.4–1.7)	1.53 (1.39–1.69)	1.56 (1.42–1.72)	1.53 (1.39–1.68)
140 on BP meds			2.33 (2.12–2.57)	2.29 (2.08–2.52)	2.37 (2.15–2.60)	2.27 (2.06–2.5)
140 no BP meds			1.56 (1.32–1.85)	1.57 (1.33–1.85)	1.61 (1.36–1.91)	1.58 (1.34–1.87)
Smoking						
<i>Never smoker</i>			1 (ref)	1 (ref)	1 (ref)	1 (ref)
<i>Current smoker</i>			1.59 (1.43–1.76)	1.57 (1.41–1.76)	1.52 (1.36–1.70)	1.5 (1.33–1.68)
<i>Former smoker</i>			1.14 (0.98–1.32)	1.14 (0.98–1.33)	1.13 (0.97–1.31)	1.12 (0.96–1.3)
Diabetes			2.26 (2.10–2.43)	2.22 (2.06–2.39)	2.24 (2.09–2.41)	2.19 (2.03–2.36)
LDL cholesterol 160 mg/dL			1.04 (0.96–1.12)	1.03 (0.95–1.12)	1.00 (0.92–1.09)	0.99 (0.91–1.07)
HDL cholesterol <40 mg/dL			1 (0.89–1.13)	0.99 (0.88–1.11)	1.01 (0.90–1.14)	1.01 (0.9–1.14)
Triglycerides 200 mg/dL			1.13 (1.05–1.22)	1.11 (1.03–1.2)	1.10 (1.02–1.18)	1.08 (1–1.17)
Antecedent incident AMI				3.04 (2.7–3.43)	2.98 (2.64–3.35)	2.99 (2.66–3.37)
HIV/Hepatitis C (HCV)						
<i>HIV & HCV uninfected</i>					1 (ref)	1 (ref)
<i>HCV infected only</i>					1.15 (1.03–1.28)	1.1 (0.98–1.23)

Variables	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
<i>HIV infected only</i>					1.20 (1.10–1.31)	1.29 (1.18–1.41)
<i>HIV & HCV co-infected</i>					1.62 (1.46–1.80)	1.66 (1.49–1.85)
Alcohol abuse or dependence						1.19 (1.09–1.31)
Cocaine abuse or dependence						1.07 (0.96–1.19)
Body mass index 30/kg/m ²						1.27 (1.18–1.37)

Model 1: unadjusted

Model 2: adjusted for age and race/ethnicity

Model 3: adjusted for Model 2 covariates plus Framingham cardiovascular disease risk factors (treated or untreated systolic blood pressure, smoking, diabetes, LDL cholesterol, HDL cholesterol and triglycerides)

Model 4: adjusted for Model 3 covariates plus antecedent incident acute myocardial infarction

Model 5: adjusted for Model 4 covariates plus HIV/HCV status

Model 6: adjusted for Model 5 covariates plus alcohol and cocaine abuse or dependence and body mass index

Table 3

Hazard ratios (95% confidence intervals) for the association between liver injury and incident congestive heart failure stratified by HIV and hepatitis C status

	HIV and HCV uninfected	HCV infected only	HIV infected only	HIV and HCV co-infected
N (# of CHF events)	57594 (2097)	8354 (424)	21449 (760)	8976 (563)
Liver fibrosis				
<i>FIB-4</i> <1.45	1 (ref)	1 (ref)	1 (ref)	1 (ref)
<i>FIB-4</i> 1.45–3.25	1.08 (0.96–1.22)	1.30 (1.05–1.62)	1.27 (1.05–1.52)	1.15 (0.93–1.41)
<i>FIB-4</i> >3.25	1.56 (1.19–2.05)	1.81 (1.34–2.44)	1.74 (1.30–2.33)	1.66 (1.30–2.12)

All models adjusted for age, race-ethnicity, systolic blood pressure and blood pressure medication, smoking, diabetes, LDL- cholesterol, HDL- cholesterol, triglycerides, antecedent incident AMI, alcohol abuse/dependence, cocaine abuse/dependence, body mass index. Models including HIV infected participants additionally adjusted for HIV-1 RNA, CD4+ T cell count, and antiretroviral therapy regimen

Table 4

Hazard ratios (95% confidence intervals) for the association between liver injury and incident congestive heart failure in the full cohort compared to relevant subsamples

	Hazard ratio of CHF (95% confidence interval)	
	Unadjusted	Adjusted*
Full cohort (N=96,373)		
<i>FIB-4</i> <1.45	1 (ref)	1 (ref)
<i>FIB-4</i> 1.45–3.25	1.78 (1.65–1.92)	1.17 (1.07–1.27)
<i>FIB-4</i> >3.25	2.74 (2.39–3.13)	1.65 (1.43–1.92)
Cohort excluding participants with CHF up to 2 years after baseline (n=80,170)		
<i>FIB-4</i> <1.45	1 (ref)	1 (ref)
<i>FIB-4</i> 1.45–3.25	1.57 (1.45–1.70)	1.15 (1.05–1.26)
<i>FIB-4</i> >3.25	2.18 (1.87–2.54)	1.46 (1.21–1.75)
Cohort excluding participants with hepatic decompensation (N=94,601)		
<i>FIB-4</i> <1.45	1 (ref)	1 (ref)
<i>FIB-4</i> 1.45–3.25	1.76 (1.63–1.91)	1.15 (1.05–1.25)
<i>FIB-4</i> >3.25	2.62 (2.21–3.10)	1.56 (1.33–1.84)

* Models adjusted for age and race/ethnicity, Framingham cardiovascular disease risk factors (treated or untreated systolic blood pressure, smoking, diabetes, LDL cholesterol, HDL cholesterol and triglycerides), antecedent incident acute myocardial infarction, HIV/HCV status, alcohol abuse or dependence, cocaine abuse or dependence and body mass index