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ORIGINAL RESEARCH

Nonalcoholic Fatty Liver Disease and Risk of Heart Failure Among Medicare Beneficiaries

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BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) and heart failure (HF) are increasing in prevalence. The independent association between NAFLD and downstream risk of HF and HF subtypes (HF with preserved ejection fraction and HF with reduced ejection fraction) is not well established.

METHODS AND RESULTS: This was a retrospective, cohort study among Medicare beneficiaries. We selected Medicare beneficiaries without known prior diagnosis of HF. NAFLD was defined using presence of 1 inpatient or 2 outpatient claims using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), claims codes. Incident HF was defined using at least 1 inpatient or at least 2 outpatient HF claims during the follow-up period (October 2015–December 2016). Among 870 535 Medicare patients, 3.2% (N=27 919) had a clinical diagnosis of NAFLD. Patients with NAFLD were more commonly women, were less commonly Black patients, and had a higher burden of comorbidities, such as diabetes, obesity, and kidney disease. Over a mean 14.3 months of follow-up, patients with (versus without) baseline NAFLD had a significantly higher risk of new-onset HF in unadjusted (6.4% versus 5.0%; $P<0.001$) and adjusted (adjusted hazard ratio [HR] [95% CI], 1.23 [1.18–1.29]) analyses. Among HF subtypes, the association of NAFLD with downstream risk of HF was stronger for HF with preserved ejection fraction (adjusted HR [95% CI], 1.24 [1.14–1.34]) compared with HF with reduced ejection fraction (adjusted HR [95% CI], 1.09 [0.98–1.2]).

CONCLUSIONS: Patients with NAFLD are at an increased risk of incident HF, with a higher risk of developing HF with preserved ejection fraction versus HF with reduced ejection fraction. The persistence of an increased risk after adjustment for clinical and demographic factors suggests an epidemiological link between NAFLD and HF beyond the basis of shared risk factors that requires further investigation.

Key Words: heart failure ■ heart failure with preserved ejection fraction ■ heart failure with reduced ejection fraction ■ nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) encompasses hepatic steatosis, nonalcoholic steatohepatitis, and nonalcoholic steatohepatitis–related cirrhosis. NAFLD is often asymptomatic and underdiagnosed, but is assumed to affect 10% to 30% of the general US population.[1] The incidence of NAFLD in the United States has increased 5-fold over the past 2 decades.[2] Cardiovascular disease is a leading cause of mortality among patients with NAFLD and to a greater degree than in the general population, and growing evidence suggests that NAFLD is an independent risk factor for cardiovascular disease.[3]

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CLINICAL PERSPECTIVE

What Is New?

- Over a follow-up period of 14 months, patients with (versus without) baseline nonalcoholic fatty liver disease had a significantly higher risk of new-onset heart failure (HF).
- The association with HF and preserved ejection fraction was stronger than for HF with reduced ejection fraction.

What Are the Clinical Implications?

- Our findings suggest an epidemiological link between nonalcoholic fatty liver disease and HF beyond shared risk factors.
- Our findings support further clinical investigation into nonalcoholic liver disease in patients with HF with preserved ejection fraction.

Nonstandard Abbreviations and Acronyms

HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
NAFLD	nonalcoholic fatty liver disease

Similar to NAFLD, heart failure (HF) is marked by high morbidity and mortality and has reached epidemic proportions. NAFLD, independent of other established risk factors for HF, is associated with adverse cardiac remodeling and diastolic dysfunction.[4,5] Specifically, a link between NAFLD and HF with preserved ejection fraction (HFpEF) has been proposed on the basis of shared pathophysiologic characteristics.[6–9] However, epidemiological evidence linking NAFLD to downstream risk of incident HF, including HF subtypes, is lacking. Better understanding of the epidemiological association of NAFLD and HF is essential to develop future public health interventions aimed at preventing and treating HF. Accordingly, in this Medicare claims-based cohort study, we evaluated the association between presence of NAFLD and downstream risk of incident HF among Medicare beneficiaries.

METHODS

This retrospective cohort study represents a secondary analysis of deidentified data, is considered exempt from informed consent, and is approved by the institutional review board of the University of Texas Southwestern Medical Center.

Data Source and Study Population

The present analysis used a subset of the national 5% sample of all fee-for-service Medicare beneficiaries (Part A and Part B) with no prior HF, followed up from October 2015 to December 2016. The data source has been described previously and included fee-for-service claims submitted from inpatient and outpatient encounters, as well as physician or carrier claims.[10] The start of study period coincided with the availability of *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes in the Medicare claims data to allow for the evaluation of HF subtypes (HFpEF and HF with reduced ejection fraction [HFrEF]). Beneficiaries with prevalent HF were identified by presence of any HF claims (Table S1 for specific diagnosis codes) over a 2-year look-back period from the start of the study (October 2015) and excluded from the present analysis.[11]

The data that support the findings of this study are available from the corresponding author on reasonable request.

Identification of Clinical NAFLD and Other Relevant Comorbidities at Baseline

The presence of clinical NAFLD at the start of the study period was determined by presence of 1 inpatient or 2 outpatient claim codes for NAFLD at baseline through 2-year look back (Table S2 for specific *International Classification of Diseases, Ninth Revision* [*ICD-9*], codes). Patients diagnosed with other liver diseases with any *ICD-9* codes for viral, alcoholic, or cholestatic liver disease were excluded from the clinical NAFLD group. These diagnostic codes identify clinical NAFLD cases with 85% accuracy.[2] A sensitivity analysis defined the presence of NAFLD using with only 1 inpatient or 1 outpatient claim code (instead of 2 outpatient codes) (Tables S3 and S4 and Figure S1). Presence of relevant HF risk factors was ascertained on the basis of presence of 1 inpatient or 2 outpatient/carrier file claims during the 2-year look back from October 1, 2015, using specific claims codes consistent with prior studies (Table S1 for specific *ICD-9* codes).

Assessment of Incident HF Outcome

Consistent with prior studies, the incident HF outcome was ascertained using either 1 inpatient or 2 outpatient/carrier file claims for HF diagnosis on follow-up (Table S1 for specific *ICD-9* codes). Starting October 2015, time to HF event was calculated using the date for first HF diagnosis encountered on follow-up. Incident HFpEF and HFrEF outcomes were captured using HF subtype-specific *ICD-10* codes (I50.3x for HFpEF and I50.2x for HFrEF).

Statistical Analysis

Clinical characteristics of participants with versus without NAFLD were compared using χ^2 test and Wilcoxon rank sum test for categorical and continuous variables, respectively. The unadjusted risk of HF outcomes among patients with versus without NAFLD was assessed using cumulative incidence curves. Cox proportional hazard models were constructed to evaluate the association between NAFLD and risk of HF. Models included the following covariates selected a priori based on biologic plausibility and prior work[12]: age, sex, race, region, hypertension, diabetes, obesity, prior myocardial infarction, atrial fibrillation, kidney disease, and valvular disease. Separate models were constructed for overall HF, HFpEF, and HFrEF, with death and other HF subtype treated as censoring events. HF with missing subtype diagnosis and HF with other subtype diagnosis were considered censoring events for HFpEF and HFrEF outcome models. Interaction between presence of NAFLD and sex, race, and obesity for the risk of HF was also assessed by adding multiplicative interaction terms to the model (NAFLD status×sex, NAFLD status×race, and NAFLD status×obesity). The 2-sided level of statistical significance was set at $P<0.05$ for all analyses. Statistical analysis was performed using R, version 3.6.0.

RESULTS

There were 870 535 unique beneficiaries with continuous Medicare enrollment for at least 2 years before October 1, 2015. Of them 3.2% (N=27 919) had the claims-based diagnosis of clinical NAFLD. Beneficiaries with (versus without) NAFLD were more commonly women, were less commonly Black individuals, and had a higher burden of HF risk factors (Table 1).

During a mean follow-up duration of 14.3±2.5 months, 5% (N=43 667) were newly diagnosed with HF, of whom 25% (N=10 923) had a claims-based diagnosis of HFrEF, 37% (N=16 062) had a diagnosis of HFpEF, and the rest (N=16 682) had a missing HF subtype diagnosis. The cumulative incidence of HF was higher among patients with NAFLD versus no NAFLD (6.4% versus 5.0%; $P<0.001$) (Table 2 and the Figure). In adjusted Cox models, NAFLD was significantly associated with a higher risk of HF, independent of other potential confounding factors (hazard ratio, 1.23; 95% CI, 1.18–1.29; $P<0.001$; Table 2). For HF subtypes, the cumulative incidence of HFpEF and HFrEF was numerically higher among patients with versus without NAFLD, with a statistically significant difference noted only for HFpEF. In adjusted Cox models, NAFLD was significantly associated with the risk of HFpEF but

Table 1. Baseline Characteristics

Variables	Total	No baseline NAFLD (N=842 616; 96.8%)	With baseline NAFLD (N=27 919; 3.2%)	*P* values
Age, mean (SD), y	74.5 (7.1)	74.6 (7.1)	72.4 (5.7)	<0.001
Sex				<0.001
Women	494 904 (56.9)	478 414 (56.8)	16 490 (59.1)	
Race or ethnicity				<0.001
White	757 690 (87)	733 362 (87)	24 328 (87.1)	
Black	59 075 (6.8)	57 668 (6.8)	1407 (5)	
Others*	45 204 (5.2)	43 308 (5.1)	1896 (6.8)	
Region				<0.001
Northeast	155 582 (17.9)	150 494 (17.9)	5088 (18.2)	
Midwest	197 541 (22.7)	192 222 (22.8)	5319 (19.1)	
South	347 067 (39.9)	334 918 (39.7)	12 149 (43.5)	
West	166 195 (19.1)	160 936 (19.1)	5259 (18.8)	
Others	4150 (0.5)	4046 (0.5)	104 (0.4)	
Myocardial infarction	38 273 (4.4)	36 862 (4.4)	1411 (5.1)	<0.001
Peripheral vascular disease	113 330 (13)	108 034 (12.8)	5296 (19)	<0.001
Cerebrovascular disease	102 659 (11.8)	98 482 (11.7)	4177 (15)	<0.001
Chronic pulmonary disease	148 256 (17)	141 141 (16.8)	7115 (25.5)	<0.001
Diabetes	450 900 (51.8)	430 598 (51.1)	20 302 (72.7)	<0.001
Chronic kidney disease	78 368 (9)	74 917 (8.9)	3451 (12.4)	<0.001
Hypertension	707 309 (81.2)	681 517 (80.9)	25 792 (92.4)	<0.001
Obesity	222 618 (25.6)	209 876 (24.9)	12 742 (45.6)	<0.001
Atrial fibrillation	114 269 (13.1)	110 116 (13.1)	4153 (14.9)	<0.001

Data are given as number (percentage), unless otherwise indicated. NAFLD indicates nonalcoholic fatty liver disease.
*Others includes Asian, Hispanic, Native American, and others.

Table 2. Cox Regression on NAFLD Versus Study Outcomes

Incident outcome	Cohort with NAFLD, No. of events/No. at risk (%)	Cohort without NAFLD, No. of events/No. at risk (%)	Adjusted HR (95% CI) of NAFLD vs no NAFLD	*P* value
Overall HF	1800/27 919 (6.4)	41 867/842 616 (5)	1.23 (1.18–1.29)	<0.001
HFpEF*	677/27 919 (2.4)	15 385/842 616 (1.8)	1.24 (1.14–1.34)	<0.001
HFrEF*	384/27 919 (1.4)	10 539/842 616 (1.3)	1.09 (0.98–1.2)	0.12

HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; and NAFLD, nonalcoholic fatty liver disease.

*The heart failure (HF) subtype-specific diagnosis codes were available in 62% of all incident HF cases and included in the HF subtype analysis. HF with missing subtype diagnosis and HF with other subtype diagnosis were considered censoring events for HFpEF and HFrEF outcome models. Model adjusted for age, sex, race, region, baseline hypertension, diabetes, obesity, acute myocardial infarction, atrial fibrillation, chronic kidney disease, and valvular disease.

not HFrEF (Table 2). The association of NAFLD with risk of HF outcomes was not modified by sex, race, or obesity status (*P*-interaction>0.1 for all).

The results of a sensitivity analysis using only 1 inpatient or 1 outpatient claim code to define NAFLD (instead of 2 outpatient codes) are presented in Tables S3 and S4 and Figure S1. The incidence of NAFLD increased from 3.2% to 3.5% without significantly affecting baseline characteristics or the relationship between NAFLD and incident HF and its subtypes.

DISCUSSION

In this cohort of 5% Medicare beneficiaries, we observed that patients with NAFLD were at ≈20% higher risk of developing HF when compared with patients without NAFLD. Over an average of 14.3 months of follow-up, 6.4% of patients with NAFLD developed HF. The increased risk of HF appeared to be independent of risk factors commonly associated with both NAFLD and HF. Finally, NAFLD was associated with a higher risk for HFpEF than HFrEF. Our study provides an epidemiological link between NAFLD and incident HF, particularly HFpEF that requires further mechanistic exploration.

Despite the observational nature of our investigation, our findings support the hypothesis that HF (particularly HFpEF) is not merely associated with NAFLD but rather a potential consequence of NAFLD.[4,5,13,14] NAFLD impacts cardiorenal metabolism, which may explain NAFLD-associated subclinical changes of left ventricular structure and function and precipitate the onset of distinct HF phenotypes.[4,13–15] Although metabolic disease and obesity appear to account for a large portion of those early cardiac changes,[14] we found that incident HF was independent of common cardiometabolic risk factors, including obesity.

The apparent discrepancy between the estimated prevalence of NAFLD in the US population (10%–30%) and the incidence of 3.2% that we found in our cohort has likely several reasons. The estimates of a high prevalence of NAFLD in the US population refer to NAFLD globally, and encompass clinical and subclinical disease. In our analysis, the inclusion and exclusion criteria for NAFLD were stringent to include what is likely to be clinical NAFLD (inpatient claim code or ongoing outpatient evaluation [2 outpatient claim codes]). At the same time, patients with other liver diseases with any history of *ICD-9* codes for viral, alcoholic, or cholestatic liver disease were excluded from the clinical NAFLD group.

Furthermore, the primary focus of the analysis was the risk of incident HF in this cohort of clinical NAFLD. The analysis of incident rate among the chosen NAFLD cohort should remain valid, even though we might underestimate the true prevalence of NAFLD in the Medicare population.

This study has several limitations. We used previously validated administrative claims data to define comorbidities[2,16] but could not independently confirm them. The use of *ICD-9* codes underestimates prevalent NAFLD because the vast majority of NAFLD is subclinical. Whether missing some true but silent NAFLD would change the true risk of associated HF is unknown. Furthermore, we could not definitively exclude prevalent HF among the original study population. However, a 2-year look-back period to define prevalent HF minimized inadvertent inclusion of patients with HF. HF was classified using claims data and not on the basis of ejection fraction, as this information was not available. Because follow-up was limited to only ≈14 months and the Medicare data do not provide cause-specific mortality data, we did not analyze mortality as an outcome. Finally, our data set did not allow adjustment for laboratory values, such as liver function test results or markers of liver fibrosis, which have been closely associated with HF-related morbidity and mortality.[17,18]

Our findings suggest an epidemiological link between NAFLD and HF beyond shared risk factors. Thus, the current epidemic of NAFLD[19] could significantly drive the changing landscape of HF epidemiological features, where HFpEF is set to become the predominant HF subtype in the upcoming 2 decades.[20]

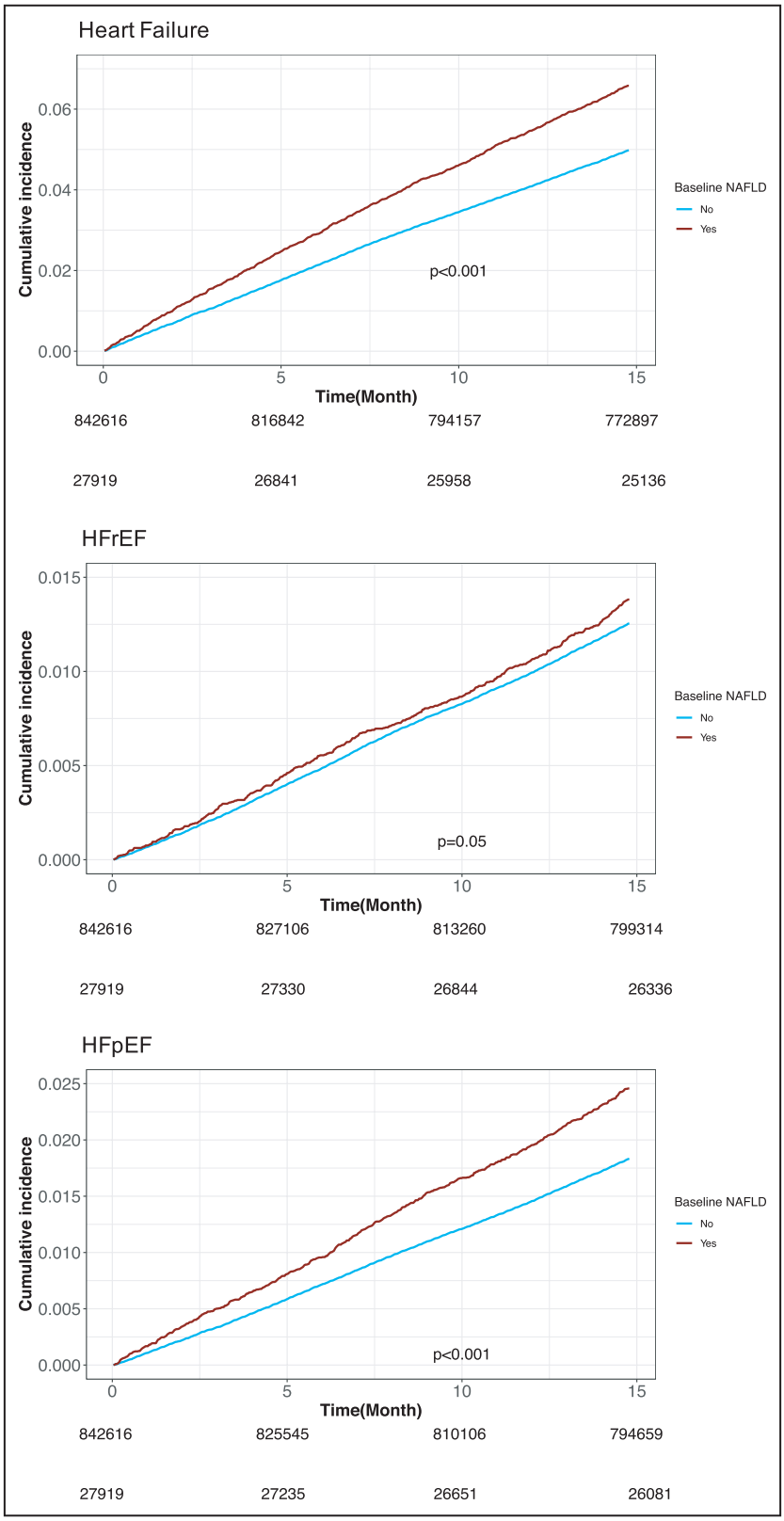

Figure 1. Cumulative incidence of the onset of heart failure (HF), HF with reduced ejection fraction (HFrEF), and HF with preserved ejection fraction (HFpEF).
NAFLD indicates nonalcoholic fatty liver disease.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Tables S1–S4
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. International Classification of Disease (ICD) 9 & 10 Codes Used to Identify Heart Failure and Comorbidities Amongst Medicare Beneficiaries.

Heart Failure	The ICD-9 CM codes including 428.x, 402.x1, 404.x1, and 404.x3 ICD-10 CM codes including I50x, I11.0, I13, and I13.2
Heart Failure with Preserved Ejection Fraction	ICD-10 codes: 150.3
Heart Failure with Reduced Ejection Fraction	ICD-10 codes: 150.2
Acute Myocardial Infarction	ICD9 substrate CD1. 1,3) in ('410') and substrate CD1,5,5) not in ('2') or ICD 10 CCS diagnosis group '100'
Atrial Fibrillation	ICD9 diagnoses including '42731' or ICD 10 diagnosis I48.xx
Chronic Kidney Disease	ICD 9 codes: 585.1–585.6 ICD10 code N18.x
Diabetes	ICD9 diagnoses including '24900','25000','25001','7902','79021','79022','79029','7915','7916','V4585','V5391','V6546','24901','24910','24911','24920','24921','24930','24931','24940','24941','24950','24951','24960','24961','24970','24971','24980','24981','24990','24991','25002','25003','25010','25011','25012','25013','25020','25021','25022','25023','25030','25031','25032','25033','25040','25041','25042','25043','25050','25051','25052','25053','25060','25061','25062','25063','25070','25071','25072','25073','25080','25081','25082','25083','25090','25091','25092','25093') or ICD 10 CC diagnosis groups '49','50'
Hypertension	ICD9 diagnoses including '4011','4019','4010','40200','40201','40210','40211','40290','40291','4030','40300','40301','4031','40310','40311','4039','40390','40391','4040','40400','40401','40402','40403','4041','40410','40411','40412','40413','4049','40490','40491','40492','40493','40501','40509','40511','40519','40591','40599','4372' or ICD10 CC diagnosis groups I10-I16
Obesity	ICD9 diagnoses including '2780','27800','27801','27802','27803','79391','V8521','V8522','V8523','V8524','V8525','V8530','V8531','V8532','V8533','V8534','V8535','V8536','V8537','V8538','V8539','V854','V8541',''

	V8542','V8543','V8544','V8545','V8554','Z6841','Z6842','Z6843','Z6844','Z6845' or ICD 10 diagnosis group with E66
Valvular Disease	ICD-9 codes 395.x, 396.x, 398.9, 424.1, 7463, and 7464 (aortic valve disease); 394.x, 396.x, 398.9, 424.0, 7465, and 7466 (mitral valve disease); 397.0, 398.9, 424.2, and 746.1 (tricuspid valve disease); and 397.1, 424.3, 746.00, 746.02, and 746.09 (pulmonary valve disease).

Table S2. **Inclusion and exclusion International Classification of Diseases-9 Codes (ICD-9) codes used in the algorithm of NAFLD cases identification.**

INCLUSION
571.8 other chronic nonalcoholic liver disease
571.9 unspecified chronic liver disease without alcohol
571.5 cirrhosis without alcohol
EXCLUSION
HEPATITIS (VIRAL AND AUTOIMMUNE)
070.0 viral hepatitis A with hepatic coma
070.1 viral hepatitis A without hepatic coma
070.20 viral hepatitis B with hepatic coma acute or unspecified without hepatitis delta
070.21 viral hepatitis B with hepatic coma acute or unspecified with hepatitis delta
070.22 chronic viral hepatitis B with hepatic coma without hepatitis delta
070.23 chronic viral hepatitis B with hepatic coma with hepatitis delta
070.30 viral hepatitis B without hepatic coma acute or unspecified without hepatitis delta
070.31 viral hepatitis B with hepatic coma acute or unspecified with hepatitis delta
070.32 chronic viral hepatitis B without hepatic coma without hepatitis delta
070.33 chronic viral hepatitis B without hepatic coma with hepatitis delta
070.41 acute hepatitis C with hepatic coma
070.42 hepatitis delta without active hepatitis B with hepatic coma
070.43 hepatitis E with hepatic coma
070.44 chronic hepatitis C with hepatic coma
070.49 other specified viral hepatitis with hepatic coma
070.51 acute hepatitis C without mention of hepatic coma
070.52 hepatitis delta without active hepatitis B disease or hepatic coma
070.53 hepatitis E without hepatic coma
070.54 chronic hepatitis C without hepatic coma
070.59 other specified viral hepatitis without hepatic coma
070.6 unspecified viral hepatitis with hepatic coma
070.70 unspecified viral hepatitis C without hepatic coma
070.71 unspecified viral hepatitis C with hepatic coma
070.9 unspecified viral hepatitis without hepatic coma
V02.60 carrier or suspected carrier of viral hepatitis unspecified
V02.61 carrier or suspected carrier of hepatitis B
V02.62 carrier or suspected carrier of hepatitis C
V02.69 carrier or suspected carrier of other viral hepatitis
571.40 chronic hepatitis unspecified
571.41 chronic persistent hepatitis
571.42 autoimmune hepatitis
571.49 chronic hepatitis
573.1 hepatitis in viral diseases classified elsewhere
573.2 hepatitis in other infectious diseases classified elsewhere
ALCOHOLIC LIVER DISEASE
571.0 alcoholic fatty liver disease
571.1 acute alcoholic hepatitis
571.2 alcoholic cirrhosis of liver
571.3 alcoholic liver damage
OTHER
571.6 biliary cirrhosis

Table S3. Baseline characteristics for the cohort using a sensitivity analysis. The sensitivity analysis defined the presence of NAFLD using with only 1 inpatient or 1 outpatient claim code (instead of 2 outpatient) the full study cohort.

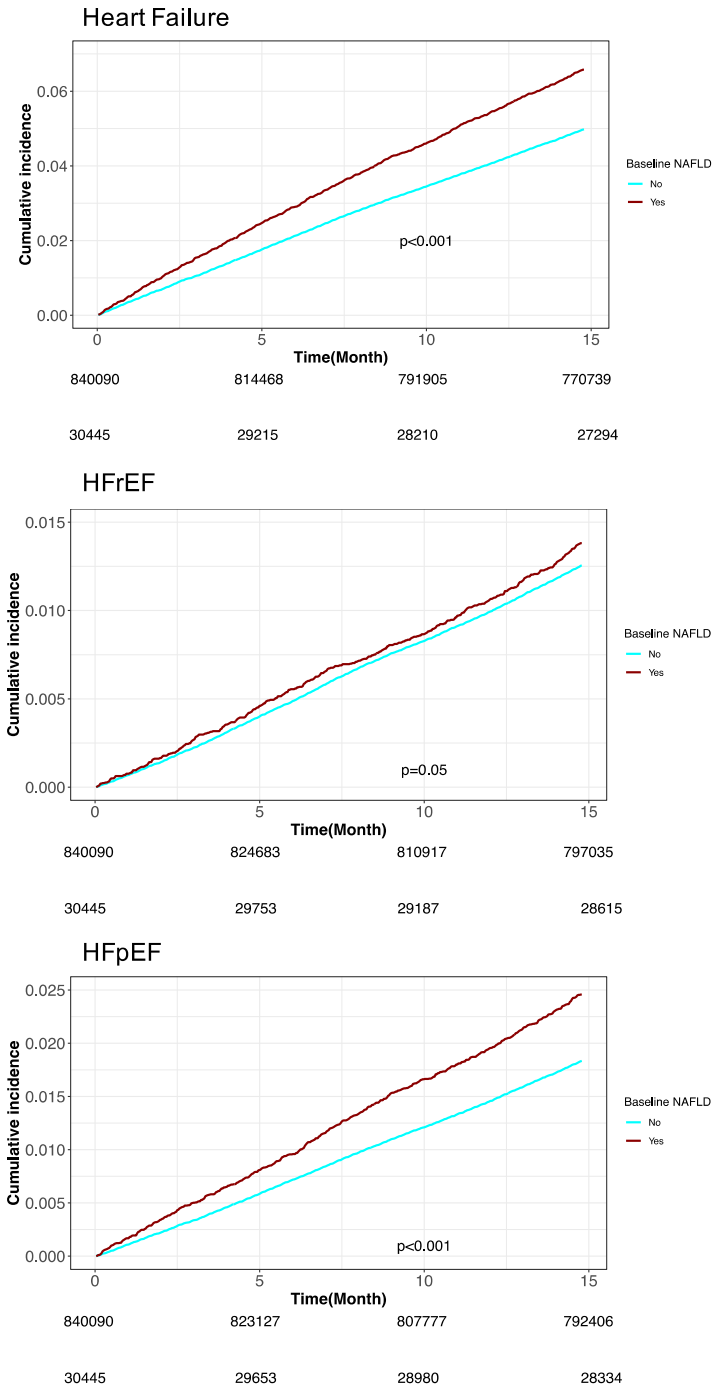
Variables	**Total**	**No baseline NAFLD** (N=840,090, 96.5%)	**With baseline NAFLD** (N=30,445, 3.5%)	**p values**
Age (mean, SD)	74.5 (7.1)	74.6 (7.1)	72.3 (5.7)	<0.001
Sex				<0.001
Female	494,904 (56.9%)	477,133 (56.8%)	17,771 (58.4%)	
Race				<0.001
White	757,690 (87%)	731,527 (87.9%)	26,163 (86.8%)	
Black	59,075 (6.8%)	57,375 (6.9%)	1,700 (5.6%)	
Others	45,204 (5.2%)	42,938 (5.2%)	2,266 (7.5%)	
Region				<0.001
Northeast	155,582 (17.9%)	150,031 (17.9%)	5,551 (18.2%)	
Midwest	19,7541 (22.7%)	191,788 (22.8%)	5,753 (18.9%)	
South	347,067 (39.9%)	333,963 (39.8%)	13,104 (43%)	
West	166,195 (19.1%)	160,273 (19.1%)	5,922 (19.5%)	
Others	4,150 (0.5%)	4,035 (0.5%)	115 (0.4%)	
Myocardial Infarction	38,273 (4.4%)	23,546 (2.8%)	1,245 (4.1%)	<0.001
Peripheral Vascular Disease	113,330 (13%)	107,567 (12.8%)	5,763 (18.9%)	<0.001
Cerebrovascular Disease	102,659 (11.8%)	98,095 (11.7%)	4,564 (15%)	<0.001
Chronic Pulmonary Disease	148,256 (17%)	140,451 (16.7%)	7,805 (25.6%)	<0.001
Diabetes	450,900 (51.8%)	428,961 (51.1%)	21,939 (72.1%)	<0.001
Chronic Kidney Disease	78,368 (9%)	74,541 (8.9%)	3,827 (12.6%)	<0.001
Hypertension	707,309 (81.2%)	679,281 (80.9%)	28,028 (92.1%)	<0.001
Obesity	222,618 (25.6%)	209,049 (24.9%)	13,569 (44.6%)	<0.001
Atrial Fibrillation	114,269 (13.1%)	109,752 (13.1%)	4,517 (14.8%)	<0.001

Table S4. Cox regression on NAFLD vs. study outcomes for the cohort using a sensitivity analysis. The sensitivity analysis defined the presence of NAFLD using with only 1 inpatient or 1 outpatient claim code (instead of 2 outpatient) the full study cohort.*

Incident Outcome	**Cohort with NAFLD No of events/No. at risk (%)**	**Cohort without NAFLD No of events/No. at risk (%)**	**Adjusted HR (95% CI) NAFLD vs. no NAFLD**	**P-value**
Overall HF	1985/28460 (6.5%)	43425/861969 (5%)	1.26 (1.21 – 1.32)	<0.001
HFpEF*	743/29702 (2.4%)	15986/861969 (1.9%)	1.27 (1.18 – 1.36)	<0.001
HFrEF*	418/30027 (1.4%)	10858/861969 (1.3%)	1.1 (1.0 – 1.21)	0.078

HF subtype specific diagnosis code were available in 62% of all incident HF cases and included in the HF subtype analysis. HF with missing subtype diagnosis as well as other subtype diagnosis were considered censoring events for HFpEF and HFrEF outcome models. Model adjusted for age, sex, race, region, baseline hypertension, diabetes, obesity, AMI, AF, CKD and valvular disease.
Abbreviations: HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction, NAFLD- non-alcoholic fatty liver disease

Figure S1. Cumulative incidence on the onset of HF, HFrEF and HFpEF for the cohort using a sensitivity analysis. The sensitivity analysis defined the presence of NAFLD using with only 1 inpatient or 1 outpatient claim code (instead of 2 outpatient) the full study cohort.



Abbreviations: HFrEF- heart failure with reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction, NAFLD- non-alcoholic fatty liver disease