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Health Care Use and Costs Among Patients With Nonalcoholic Steatohepatitis With Advanced Fibrosis Using the Fibrosis-4 Score

Stuart C. Gordon,¹ Nandita Kachru,² Emily Parker,³ Stephanie Korner,³ A. Burak Ozbay,² and Robert J. Wong ⁴

Limited evidence exists on the clinical and economic burden of advanced fibrosis in patients with nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) due to the invasiveness of liver biopsies for accurately staging liver disease. The fibrosis-4 (FIB-4) score allows for noninvasive assessment of liver fibrosis by using clinical and laboratory data alone. This study aimed to characterize the comorbidity burden, health care resource use (HCRU), and costs among patients with NAFLD/NASH with FIB-4-defined F3 (bridging fibrosis) and F4 (compensated cirrhosis) fibrosis. Using the Optum Research Database, a retrospective cohort study was conducted among 251,725 commercially insured adult patients with ≥ 1 NAFLD/NASH diagnosis from January 1, 2008, to August 31, 2016, and laboratory data required to calculate FIB-4 scores. Five criteria using varying FIB-4 score cutoffs were identified based on expert clinical opinion and published literature. Date of the first valid FIB-4 score marked the index date. Mean annual HCRU and costs were calculated during the pre-index and post-index periods. The prevalence of FIB-4-based F3 and F4 fibrosis was 0.40%–2.72% and 1.03%–1.61%, respectively. Almost 50% of patients identified with FIB-4-based F3 or F4 had type 2 diabetes, cardiovascular disease, or renal impairment. Total all-cause health care costs increased significantly from pre-index to post-index for patients with FIB-4-based F3 fibrosis across most criteria (17%–29% increase) and patients with FIB-4-based F4 fibrosis across all criteria (47%–48% increase). Inpatient costs were the primary drivers of this increment. **Conclusion:** Significant increases in HCRU and costs were observed following FIB-4-based identification of F3 and F4 fibrosis among U.S. adults with NAFLD/NASH. These data suggest the importance of early identification and management of NAFLD/NASH that may halt or reduce the risk of disease progression and limit the underlying burden. (*Hepatology Communications* 2020;4:998–1011).

Nonalcoholic fatty liver disease (NAFLD) affects approximately 83.1 million American adults and contributes to significant morbidity and mortality. NAFLD is the leading cause of chronic liver disease, and the presence of comorbidities, including obesity, insulin resistance, type 2 diabetes (T2D), metabolic syndrome, hypertension, cardiovascular disease (CVD), and dyslipidemia, may promote the development of NAFLD/nonalcoholic steatohepatitis (NASH) and/or advance fibrosis progression.^(1–4) Conversely, evidence suggests that NAFLD/NASH presence increases the risk of

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate transaminase to platelet ratio; AST, aspartate aminotransferase; CC, compensated cirrhosis; CVD, cardiovascular disease; DCC, decompensated cirrhosis; FIB-4, fibrosis-4; HCC, hepatocellular carcinoma; HCRU, health care resource use; HIV, human immunodeficiency virus; ICD-9-CM/ICD-10-CM, International Classifications of Diseases Ninth/Tenth Revisions Clinical Modification; LT, liver transplant; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PPPM, per patient per month; SD, standard deviation; T2D, type 2 diabetes.

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developing these same comorbidities.⁽¹⁻⁸⁾ While most patients have NAFLD, the prevalence of NASH (steatohepatitis, inflammation, and hepatocyte injury with or without fibrosis) in the U.S. population is estimated at 2%-5%.⁽⁹⁻¹¹⁾ Patients with NASH are at an increased risk of progressing to compensated cirrhosis (CC) or decompensated cirrhosis (DCC) and additional complications, such as liver transplant (LT)/liver failure and hepatocellular carcinoma (HCC).

The presence of fibrosis in NASH is the most important factor in determining disease progression and future complications.⁽¹²⁾ Several studies observed that the presence of advanced fibrosis (stage 3 [F3 or bridging fibrosis] and stage 4 [F4 or CC]) in patients with NAFLD/NASH was associated with significantly increased mortality risk,⁽¹³⁻¹⁶⁾ which increased with advancing fibrosis stage.^(13,16)

The differentiation between NAFLD and NASH is important to identify a high-risk group that may progress to fibrosis and cirrhosis. Liver biopsy remains the standard method; however, the use of biopsy in clinical practice is limited by invasiveness, cost, and potential for sampling error.^(17,18) In a large community-based health care practice, only 0.9% of patients with a NAFLD/NASH diagnosis had a documented liver biopsy.⁽¹⁹⁾ There are no known noninvasive tests that can differentiate between fatty liver and steatohepatitis; however, noninvasive assessments of liver fibrosis using clinical and laboratory data

(e.g., NAFLD fibrosis score,⁽²⁰⁾ aspartate aminotransferase (AST)-to-platelet ratio index [APRI],^(21,22) BARD score,⁽²³⁾ fibrosis-4 score [FIB-4]⁽²⁴⁾) have been used to identify patients at risk of having F3 or F4,⁽¹⁰⁾ potentially avoiding the need for liver biopsy and allowing for closer follow-up. Noninvasive assessments also allow for sequential testing to observe disease progression. One method, FIB-4, uses an algorithm incorporating patient age, platelet count, AST, and alanine aminotransferase (ALT) levels to predict liver fibrosis. In one study, FIB-4 significantly outperformed other tests (Göteborg University cirrhosis index, AST to ALT ratio, APRI, BARD score, and cirrhosis discriminant score) for the prediction of advanced fibrosis versus lower fibrosis stages. Among patients with a FIB-4 index score below 1.30 or above 2.67, FIB-4 identified the absence or presence of advanced fibrosis with 90% and 80% accuracy, respectively.⁽²⁵⁾

Due to the limited use of liver biopsy and absence of specific diagnosis codes for fibrosis stage, little is known on the economic and clinical burden of NASH in the United States, particularly among patients with advanced fibrosis. This study sought to identify patients with NAFLD/NASH with advanced fibrosis based on the noninvasive FIB-4 score and characterize their comorbidity burden, health care resource use (HCRU), and costs. These data are critical to help guide resource planning from a public health perspective.

Potential conflict of interest: Dr. Gordon received grants from AbbVie, Conatus, CymaBay, DURECT, Eiger, Eli Lilly, Genfit, Gilead, GlaxoSmithKline, Intercept, Shire, Merck, and Viking. Dr. Kachru is employed by and owns stock in Gilead. Dr. Parker and Ms. Korrer were employed by Optum at the time the study was conducted and received funding from Gilead to conduct the study. Dr. Parker currently owns stock and is employed by UnitedHealth Group. Dr. Wong consults for, advises, is on the speakers' bureau for, and received grants from Gilead; he received grants from AbbVie and is on the speakers' bureau for Salix. Dr. Ozbay was employed by Gilead during this study.

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Patients and Methods

DATA SOURCES

This retrospective cohort study was conducted using data from U.S. commercial health plan members in the Optum Research database, a nationally representative database containing data on approximately 13.5 million lives annually. Medical claims, pharmacy claims, laboratory data, and enrollment information were collected from July 1, 2007 to February 28, 2017 (study period). International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM/ICD-10-CM) diagnosis and procedure codes, Current Procedural Terminology version 4 procedure codes, health care common procedure coding system codes, and place of service codes were used to classify inpatient and outpatient services. Outpatient pharmacy claims comprised national drug codes for dispensed medications, quantity dispensed, and dose and days' supply. Laboratory data were available for a subpopulation of the database, and the Standard Logical Observation Identifiers Names and Codes was used to define tests and results. Access to protected health information was not needed for this study, thus institutional review board approval or a waiver of authorization was not required.

STUDY SAMPLE SELECTION

Patients aged ≥ 18 years having ≥ 1 nondiagnostic medical claim with a primary or secondary diagnosis code for NAFLD and/or NASH (ICD-9-CM 571.8, 571.9; ICD-10-CM K76.0, K75.81) from January 1, 2008 to August 31, 2016 (identification period) were included in the study. NASH-specific ICD-9/10 diagnosis codes were unavailable before September 30, 2015, so diagnostic codes for NAFLD/NASH were used during this time period. The date of the first medical claim for NAFLD/NASH was the study entry date. Identified patients with NAFLD/NASH were required to have valid laboratory values (AST, ALT, and platelets) within 6 months of each other, sufficient to calculate a FIB-4 score during the identification period. The date of the first valid FIB-4 score was considered the index date. Additionally, continuous enrollment in the health plan for ≥ 6 months before and ≥ 1 month after the study entry date was required.

TABLE 1. COHORT IDENTIFICATION BASED ON FIB-4 SCORE

Criteria	Cohort	FIB-4-Based Fibrosis Stage	Cut-Off Values
Criterion 1 ⁽²⁶⁾	C1	FIB-4-based F3/F4	FIB-4 > 2.67
Criterion 2 ⁽²⁷⁾	C2	FIB-4-based F3	2.67 < FIB-4 \leq 4.12
		FIB-4-based F4*	FIB-4 > 4.12
Criterion 3 ⁽²⁸⁾	C3	FIB-4-based F3	2.67 < FIB-4 \leq 3.5
		FIB-4-based F4 [†]	FIB-4 > 3.5
Criterion 4 ⁽²⁸⁾	C4	FIB-4-based F3	3.25 < FIB-4 \leq 3.5
		FIB-4-based F4 [†]	FIB-4 > 3.5
Criterion 5 ⁽²⁷⁾	C5	FIB-4-based F3	3.25 < FIB-4 \leq 4.12
		FIB-4-based F4*	FIB-4 > 4.12

*Cohorts are identical.

[†]Cohorts are identical.

Patients with a medical claim for other causes of liver disease (viral hepatitis [hepatitis A, B, C, D, E], toxic or autoimmune liver disease, cytomegaloviral infection, mumps, Wilson's disease, Gaucher's disease, lysosomal acid lipase deficiency, alcoholism or alcoholic liver disease, primary biliary/sclerosing cholangitis, or hemochromatosis) and human immunodeficiency virus (HIV) during the study period were excluded. Also excluded were those with ICD-9/10 diagnostic codes for advanced liver disease (CC/DCC/LT/HCC) before the F3/F4 index date. Patients with CC or DCC with evidence of a more severe liver disease stage within 90 days following the respective index date were assigned to the more severe stage to reduce the risk of misclassification.

FIB-4-BASED IDENTIFICATION OF ADVANCED FIBROSIS

Based on expert opinion and published literature, five criteria with varying FIB-4 cutoffs were used to categorize patients with F3/F4 fibrosis (Table 1).⁽²⁶⁻²⁸⁾ If AST, ALT, and platelet laboratory values fell on separate dates, the date of the last laboratory value was used. For multiple scores on the same date, the lowest laboratory values were used to calculate FIB-4.

Pre-index and Post-index Periods

The 6 months before the index date was considered the pre-index period. All eligible patients were followed from the index date to the earliest of 6 months,

progression to advanced liver disease (CC/DCC/LT/HCC), end of coverage, or end of study period (post-index period).

STUDY MEASURES

Pre-index Demographics and Clinical Characteristics

Pre-index measures included patient demographics (age, sex, and geographic region), clinical characteristics (APRI score,⁽²⁹⁾ Charlson comorbidity index,^(30,31) comorbidities of interest), and cardiometabolic comorbidities (T2D, hypertension, CVD, hyperlipidemia, and renal impairment).

Annual All-Cause HCRU

Mean per patient per month (PPPM) all-cause HCRU estimates were calculated during the pre-index and post-index periods. Mean PPPM estimates were annualized and included ambulatory (office and outpatient), emergency, and inpatient care. The mean number of outpatient visits by provider specialty was provided for the pre-index and post-index periods.

Annual All-Cause Health Care Costs

All-cause health care costs were calculated during the pre-index and post-index periods as the mean PPPM combined health plan and patient-paid amounts adjusted for inflation between 2007 and 2016, using the annual medical care component of the Consumer Price Index.⁽³²⁾ Mean PPPM estimates were annualized and included ambulatory (office, outpatient, and other nonemergency/noninpatient costs), emergency, inpatient, and pharmacy costs.

STATISTICAL ANALYSIS

Means and standard deviations (SDs) were calculated for continuous variables, and frequencies and percentages were provided for categorical variables. Appropriate tests of statistical significance were used (two-sample *t* test for pre-index comparisons between different cohorts, paired *t* test for pre-index vs. post-index comparisons, McNemar's test for proportions). The percentage change in health care use

was calculated. All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC), with a statistical significance level of two-tailed $P < 0.05$. A sensitivity analysis was conducted to calculate health care costs over a longer follow-up duration in which patients were followed until the earliest of progression to advanced liver disease (CC/DCC/LT/HCC), end of coverage, or end of the study period (post-index period).

Results

The percentage of patients with NAFLD/NASH identified as FIB-4-based F3 and F4 varied depending on the FIB-4 criteria (C1-C5) applied. Among patients with NAFLD/NASH with sufficient laboratory data to calculate a FIB-4 score, 3.57% ($n = 3,251$) were identified as FIB-4-based F3/F4, 0.40%-2.72% as F3, and 1.03%-1.61% as F4 (Table 2).

PRE-INDEX DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Mean age and sex were comparable across cohorts, with mean age ranging from 56.39 to 57.53 years and a slight minority being female (45.05%-50.37%) (Table 3). The APRI score was higher for FIB-4-based F4 versus F3 cohorts.

The pre-index comorbidity burden was high and comparable among patients with FIB-4-based F3 and F4 across all cohorts (Table 4). A majority had hypertension (F3 range, 57.30%-57.91%; F4 range, 57.55%-58.57%) and hyperlipidemia (F3 range, 51.69%-53.72%; F4 range, 50.27%-50.51%), more than one third had T2D (F3 range, 35.43%-36.64%; F4 range, 34.59%-34.93%), and approximately one fifth had CVD (F3 range, 20.47%-21.76%; F4 range, 18.85%-19.07%). Approximately three-fourths and one-third of patients across all criteria with FIB-4-based F3/F4, F3 and F4 had ≥ 1 and ≥ 3 cardiometabolic comorbidities, respectively.

ANNUAL ALL-CAUSE HCRU

Health care resource use increased from pre-index to post-index for patients with FIB-4-based F3/F4 fibrosis (C1) (Table 5). In the post-index period,

TABLE 2. STUDY SAMPLE SELECTION

	FIB-4-Based F3/F4			FIB-4-BASED F3			FIB-4-Based F4		
	C1	C2	C3	C4	C5	C2/C5	C3/C4	C2/C5	C3/C4
	FIB-4 > 2.67	2.67 < FIB-4 ≤ 4.12	2.67 < FIB-4 ≤ 3.5	3.25 < FIB-4 ≤ 3.5	3.25 < FIB-4 ≤ 4.12	FIB-4 > 4.12	FIB-4 > 3.5	FIB-4 > 4.12	FIB-4 > 3.5
Adult commercial patients with ≥1 medical claim for NAFLD/NASH, continuous health plan enrollment,* complete demographic data, and no claims for other causes of liver diseases [†]	251,725	251,725	251,725	251,725	251,725	251,725	251,725	251,725	251,725
AST, ALT, and platelet laboratory results between 60 days prior to NAFLD/NASH diagnosis date (study entry date) and the end of follow-up (post-index period)	150,732	150,732	150,732	150,732	150,732	150,732	150,732	150,732	150,732
Laboratory data sufficient to compute FIB-4 score [‡]	91,122	91,122	91,122	91,122	91,122	91,122	91,122	91,122	91,122
Laboratory data meeting criterion of interest	4,020	2,835	2,410	589	1,245	1,025	1,563	1,025	1,563
Continuous health plan enrollment ≥6 months before and ≥1 month after index date	3,341	2,573	2,051	393	1,007	990	1,530	990	1,530
No prior diagnosis of advanced liver disease (CC/DCC/LT/HCC)	3,251	2,482	1,965	363	937	939	1,463	939	1,463
Proportion of patients with NAFLD/NASH with valid laboratory data	3.57%	2.72%	2.16%	0.40%	1.03%	1.03%	1.61%	1.03%	1.61%

*Continuous enrollment 6 months before and ≥1 month after the study entry date.

[†]Viral hepatitis (hepatitis A, B, C, D, E), toxic or autoimmune liver disease, cytomegaloviral infection, mumps, Wilson's disease, Gaucher's disease, lysosomal acid lipase deficiency, alcoholism or alcoholic liver disease, primary biliary/sclerosing cholangitis, or hemochromatosis and HIV.

[‡]AST, ALT, and platelet values within 180 days of each other.

TABLE 3. PRE-INDEX DEMOGRAPHICS

	FIB-4-Based F3					FIB-4-Based F4		
	C1	C2	C3	C4	C5	C2/C5	C3/C4	C3/C4
	FIB-4 > 2.67 (n = 3,251)	2.67 < FIB-4 ≤ 4.12 (n = 2,482)	2.67 < FIB-4 ≤ 3.5 (n = 1,965)	3.25 < FIB-4 ≤ 3.5 (n = 363)	3.25 < FIB-4 ≤ 4.12 (n = 937)	FIB-4 > 4.12 (n = 939)		FIB-4 > 3.5 (n = 1,463)
Age, mean (SD)	56.76 (9.41)	56.93 (9.20)	57.04 (9.20)	57.53 (8.63)	56.99 (8.82)	56.39 (9.71)		56.54 (9.52)
Female, n (%)	1,527 (46.97)	1,192 (48.03)	918 (46.72)	169 (46.56)	472 (50.37)	423 (45.05)		689 (47.10)
Geographic region, n (%)								
Northeast	242 (7.44)	188 (7.57)	147 (7.48)	26 (7.16)	68 (7.26)	103 (7.04)		64 (6.82)
Midwest	374 (11.50)	276 (11.12)	219 (11.15)	42 (11.57)	108 (11.53)	178 (12.17)		121 (12.89)
South	2,080 (63.98)	1,606 (64.71)	1,283 (65.29)	246 (67.77)	606 (64.67)	917 (62.68)		580 (61.77)
West	555 (17.07)	412 (16.60)	316 (16.08)	49 (13.50)	155 (16.54)	265 (18.11)		174 (18.53)

TABLE 4. PRE-INDEX CLINICAL CHARACTERISTICS

	FIB-4-Based F3/F4			FIB-4-Based F3			FIB-4-Based F4		
	C1	C2	C3	C4	C5	C2/C5	C3/C4		
	FIB-4 > 2.67 (n = 3,251)	2.67 < FIB-4 ≤ 4.12 (n = 2,482)	2.67 < FIB-4 ≤ 3.5 (n = 1,965)	3.25 < FIB-4 ≤ 3.5 (n = 363)	3.25 < FIB-4 ≤ 4.12 (n = 937)	FIB-4 > 4.12 (n = 939)		FIB-4 > 3.5 (n = 1,463)	
APRI score, mean (SD)	1.01 (1.94)	0.78 (0.37)	0.75 (0.33)	0.83 (0.36)	0.89 (0.45)	1.72 (3.49)		1.40 (2.83)	
Charlson comorbidity index, mean (SD)	1.35 (1.83)	1.31 (1.76)	1.27 (1.69)	1.21 (1.64)	1.41 (1.92)	1.54 (2.02)		1.50 (2.03)	
Comorbid conditions, n (%)									
T2D	1,142 (35.13)	886 (35.70)	706 (35.93)	133 (36.64)	332 (35.43)	328 (34.93)		506 (34.59)	
Obesity	517 (15.90)	403 (16.24)	318 (16.18)	54 (14.88)	146 (15.58)	134 (14.27)		221 (15.11)	
Hypertension	1,860 (57.21)	1,436 (57.86)	1,138 (57.91)	208 (57.30)	538 (57.42)	550 (58.57)		842 (57.55)	
Abdominal pain	620 (19.07)	482 (19.42)	379 (19.29)	55 (15.15)	172 (18.36)	166 (17.68)		272 (18.59)	
Anemia	400 (12.30)	285 (11.48)	217 (11.04)	39 (10.74)	114 (12.17)	153 (16.29)		212 (14.49)	
CVD	645 (19.84)	508 (20.47)	410 (20.87)	79 (21.76)	192 (20.49)	177 (18.85)		279 (19.07)	
Dyspepsia	612 (18.82)	469 (18.90)	365 (18.58)	78 (21.49)	196 (20.92)	179 (19.06)		286 (19.55)	
Hyperlipidemia	1,655 (50.91)	1,283 (51.69)	1,024 (52.11)	195 (53.72)	485 (51.76)	472 (50.27)		739 (50.51)	
Renal impairment	305 (9.38)	231 (9.31)	176 (8.96)	34 (9.37)	100 (10.67)	90 (9.58)		151 (10.32)	
Thyroid disease	584 (17.96)	441 (17.77)	360 (18.32)	59 (16.25)	157 (16.76)	182 (19.38)		272 (18.59)	
Sleep apnea	440 (13.53)	338 (13.62)	279 (14.20)	58 (15.98)	126 (13.45)	121 (12.89)		186 (12.71)	
≥3 Cardiometabolic conditions*	1,029 (31.65)	796 (32.07)	637 (32.42)	126 (34.71)	303 (32.34)	299 (31.84)		460 (31.44)	
≥2 Cardiometabolic conditions*	1,760 (54.14)	1,364 (54.96)	1,086 (55.27)	198 (54.55)	507 (54.11)	508 (54.10)		786 (53.73)	
≥1 Cardiometabolic condition*	2,404 (73.95)	1,856 (74.78)	1,476 (75.11)	267 (73.55)	692 (73.85)	696 (74.12)		1,079 (73.75)	
Renal impairment, T2D, and CVD	75 (2.31)	57 (2.30)	41 (2.09)	10 (2.75)	30 (3.20)	22 (2.34)		39 (2.67)	
Renal impairment, or T2D, or CVD	1,559 (47.95)	1,206 (48.59)	963 (49.01)	174 (47.93)	447 (47.71)	448 (47.71)		697 (47.64)	

*Cardiometabolic conditions consisted of T2D, hypertension, CVD, hyperlipidemia, and renal impairment.

TABLE 5. ANNUAL ALL-CAUSE HCRU

		Pre-Index Mean (SD)	Post-index Mean (SD)	% Change	PValue
Patients with FIB-4-based F3/F4 fibrosis					
C1 F3/F4: FIB-4 > 2.67 (n = 3,251)	Inpatient admissions	0.24 (1.08)	0.36 (1.44)	50%	0.002
	Inpatient days	1.92 (0.82)	2.76 (1.23)	44%	0.001
	Ambulatory visits	17.52 (18.36)	22.08 (19.68)	26%	<0.001
	Emergency visits	1.08 (3.60)	1.32 (4.80)	22%	0.002
Patients with FIB-4-based F3 fibrosis					
C2 F3: 2.67 < FIB-4 ≤ 4.12 (n = 2,482)	Inpatient admissions	0.24 (0.96)	0.36 (1.32)	50%	0.081
	Inpatient days	1.44 (0.59)	2.04 (0.99)	42%	0.021
	Ambulatory visits	17.16 (17.64)	20.76 (18.72)	21%	<0.001
	Emergency visits	1.20 (3.72)	1.32 (5.16)	10%	0.021
C3 F3: 2.67 < FIB-4 ≤ 3.5 (n = 1,965)	Inpatient admissions	0.24 (0.96)	0.24 (1.20)	0%	0.509
	Inpatient days	1.44 (0.58)	1.80 (0.82)	25%	0.233
	Ambulatory visits	16.92 (17.40)	20.16 (18.12)	19%	<0.001
	Emergency visits	1.08 (3.60)	1.32 (5.28)	22%	0.052
C4 F3: 3.25 < FIB-4 ≤ 3.5 (n = 363)	Inpatient admissions	0.24 (0.72)	0.24 (0.96)	0%	0.510
	Inpatient days	1.68 (0.80)	0.84 (0.36)	-50%	0.072
	Ambulatory visits	16.32 (17.16)	20.52 (20.16)	26%	<0.001
	Emergency visits	0.96 (2.76)	1.20 (3.48)	25%	0.336
C5 F3: 3.25 < FIB-4 ≤ 4.12 (n = 937)	Inpatient admissions	0.24 (0.84)	0.36 (1.32)	50%	0.317
	Inpatient days	1.68 (0.68)	2.28 (1.15)	36%	0.211
	Ambulatory visits	17.64 (18.12)	21.48 (19.80)	22%	<0.001
	Emergency visits	1.08 (3.48)	1.20 (4.20)	11%	0.180
Patients with FIB-4-based F4 fibrosis					
C2/C5 F4: FIB-4 > 4.12 (n = 939)	Inpatient admissions	0.36 (1.32)	0.48 (1.44)	33%	0.005
	Inpatient days	3.24 (1.35)	4.44 (1.65)	37%	0.111
	Ambulatory visits	18.96 (19.68)	25.44 (21.96)	34%	<0.001
	Emergency visits	1.08 (3.36)	1.32 (3.60)	22%	0.027
C3/C4 F4: FIB-4 > 3.5 (n = 1,463)	Inpatient admissions	0.36 (1.20)	0.48 (1.44)	33%	0.004
	Inpatient days	2.52 (1.06)	3.84 (1.58)	52%	0.008
	Ambulatory visits	18.60 (19.32)	24.00 (21.00)	29%	<0.001
	Emergency visits	1.08 (3.48)	1.32 (3.96)	22%	0.024

FIB-4, Fibrosis-4; SD, standard deviation.

patients had significantly more inpatient admissions (0.36 vs. 0.24; $P = 0.002$), inpatient stay days (2.76 days vs. 1.92 days; $P = 0.001$), ambulatory visits (22.08 vs. 17.52; $P < 0.001$), and emergency visits (1.32 vs. 1.08; $P = 0.002$).

Among patients with FIB-4-based F3, the number of ambulatory visits increased significantly from pre-index to post-index for all criteria (19%-26%). The mean number of inpatient stay days increased from pre-index to post-index for cohort C2 only. No significant differences were observed for cohorts C3,

C4, or C5. Emergency visits also increased 10%-25% from pre-index to post-index among patients with FIB-4-based F3; however, this difference was only significant in cohort C2 ($P = 0.021$) and approached significance in cohort C3 ($P = 0.052$).

Among patients with FIB-4-based F4, the mean number of inpatient admissions increased 33% ($P \leq 0.005$), ambulatory visits increased 29%-34% ($P < 0.001$), and emergency visits increased 22% ($P \leq 0.027$) from pre-index to post-index across all criteria. The mean number of inpatient stay days

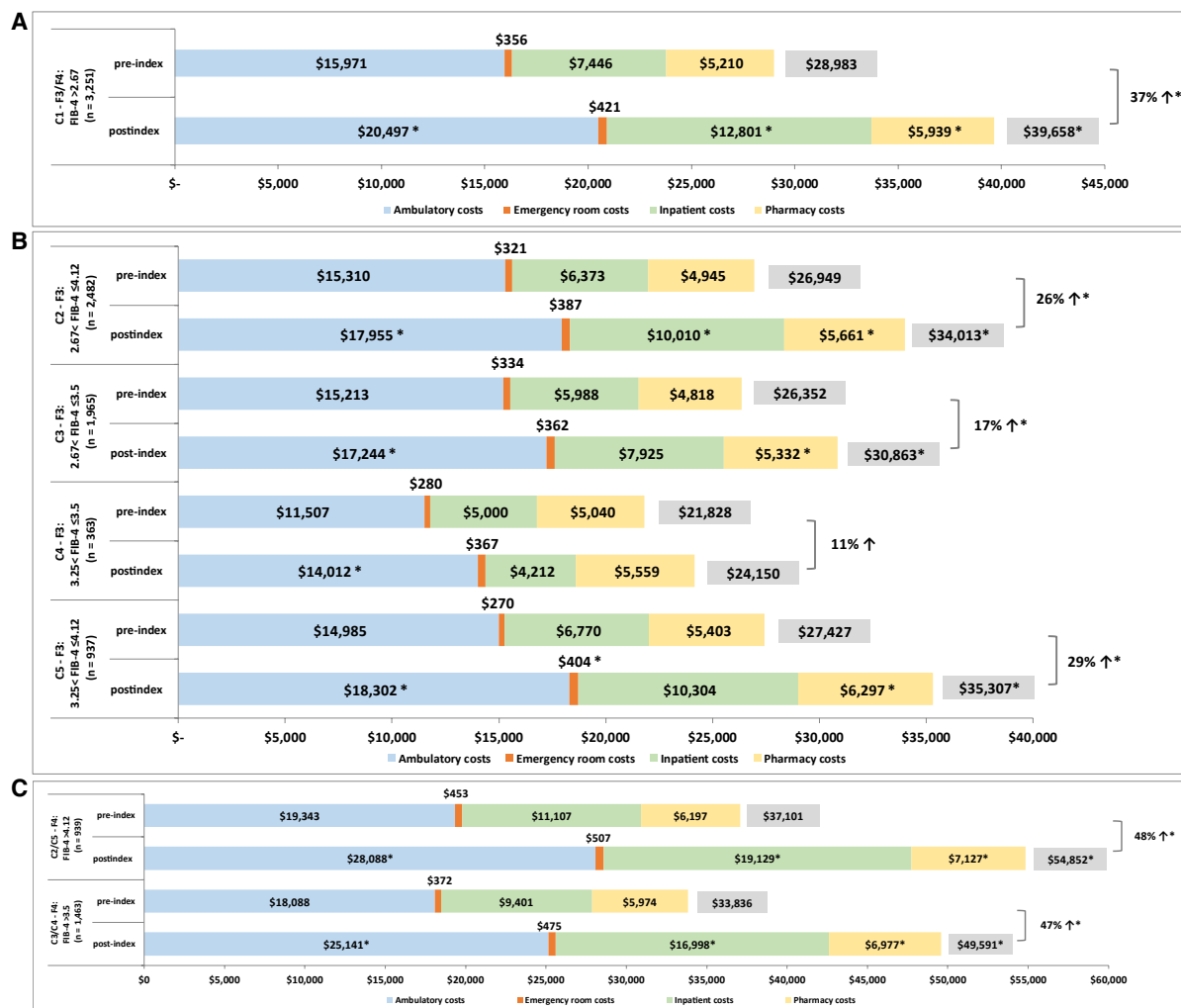


FIG. 1. Annual all-cause health care costs. (A) Patients with FIB-4-based F3/F4 fibrosis. (B) Patients with FIB-4-based F3 fibrosis. (C) Patients with FIB-4-based F4 fibrosis. Combined health plan and patient-paid amounts adjusted for inflation between 2006 and 2016. * $P < 0.05$ for pre-index versus post-index. ↑ reflects increase from pre-index to post-index.

increased 52% ($P = 0.008$) from pre-index to post-index in cohort C3/C4.

Patients were most likely to visit a primary care provider for ambulatory visits as opposed to a gastroenterologist (Supporting Table S1).

ANNUAL ALL-CAUSE HEALTH CARE COSTS

Total all-cause health care costs increased from pre-index to post-index by 37% (\$28,983 vs. \$39,658;

$P < 0.001$) among patients with FIB-4-based F3/F4 (C1) (Fig. 1A). Inpatient costs were the primary driver of the increase in total all-cause health care costs in the post-index period.

Pre-index total all-cause health care costs were similar among patients with FIB-4-based F3 regardless of the criterion used, ranging from \$21,827 to \$27,427 (Fig. 1B). The main cost contributor across all cohorts was ambulatory services, accounting for approximately 53%-58% of total costs. In the post-index period, total all-cause health care costs in

patients with FIB-4-based F3 ranged from \$24,150 to \$35,307, reflecting a significant increase across all cohorts (except C4), ranging from 11% to 29%. Inpatient costs were the primary drivers of this increase across all cohorts (except C3 and C4).

Patients with FIB-4-based F4 appeared to have slightly higher pre-index costs compared with patients with F3 (\$37,101 for patients in cohort C2/C5 and \$33,836 for patients in cohort C3/C4) (Fig. 1C). Similarly, post-index costs for patients with FIB-4-based F4 were slightly higher than patients with F3, ranging from \$49,591 to \$54,852. Total health care costs increased 47%-48% among patients with F4 from pre-index to post-index, with significantly higher ambulatory costs, inpatient costs, and pharmacy costs, regardless of criteria used. Although ambulatory visits were the major cost contributors among all cohorts, inpatient costs had the largest increase from the pre-index to post-index periods (47%-48%).

In the sensitivity analysis, patient follow-up averaged 17-20 months. Health care costs were slightly attenuated but remained consistent with costs presented over the 12-month follow-up period (Supporting Table S2).

Discussion

This study examined patients with NAFLD/NASH with FIB-4-identified F3 and F4 fibrosis within a U.S. payer system and provided real-world data on comorbidity profiles, all-cause HCRU, and associated costs. We found significant increases in HCRU and costs following FIB-4-based identification of advanced fibrosis, particularly among patients with F4. Additionally, HCRU and costs increased with advancing liver fibrosis severity, highlighting the need for targeted interventions, particularly among patients with F3 to prevent progression to CC and CC-related complications.

An accurate estimate of the prevalence of patients with NAFLD/NASH and advanced fibrosis is necessary to assess true disease burden. This study reported F3 prevalence at 0.40%-2.72% and F4 prevalence at 1.03%-1.61% among patients with NAFLD/NASH; however, these estimates could very likely be under-reported compared to the true prevalence, given that only a proportion of diagnosed patients

with NAFLD/NASH had available laboratory data and no definitive noninvasive test can accurately diagnose this condition. These results may also be limited in generalizability to other populations. As the study population is a convenience sample of patients in the database with available laboratory data, it is likely that those patients may have more comorbidities or advanced disease.

Patients with advanced fibrosis had high rates of cardiometabolic comorbidities, with similar rates observed in patients with F3 and F4. More than half of patients had ≥ 2 and approximately one third had ≥ 3 high-risk comorbid conditions (T2D, hypertension, hyperlipidemia, and renal disease). High rates of cardiometabolic comorbidities were also reported in a study of patients with NAFLD/NASH with CC wherein 78.8% had hypertension, 52.6% had T2D, 48.9% had CVD, 47.5% had hyperlipidemia, 36.9% had obesity, and 32.3% had renal impairment.⁽³³⁾ The high prevalence of comorbidities likely contributed to the high rates of all-cause HCRU and costs as patients were treated for these conditions.

Patients with advanced fibrosis had high rates of HCRU and costs, with most patients with F3 averaging more than \$30,000 in annual health care costs and patients with F4 averaging approximately \$50,000 in annual costs over the post-index period. While costs were similar among patients with F3 fibrosis regardless of criterion used, those meeting criterion 4, the most restrictive criterion, had slightly lower costs (\$24,150), while patients meeting criteria 2 and 5, with a higher FIB-4 cutoff had slightly greater costs (\$34,013 and \$35,307, respectively). In a recent study among privately insured patients, those newly diagnosed with NAFLD incurred \$7,804 in health care costs over the course of 1 year compared to \$3,789 for patients with prevalent disease. Patients without NAFLD but with similar comorbidities had costs of \$2,298 annually.⁽³⁴⁾ The higher costs in our study were likely due to more patients with advanced fibrosis and cirrhosis rather than newly diagnosed NAFLD, such as those in the Allen et al. study,⁽³⁴⁾ particularly because cardiometabolic comorbidity rates were similar. Additionally, Allen et al. averaged costs over a much longer period, which likely resulted in lower cost estimates. Costs measured immediately following diagnosis are often much higher than costs averaged over a longer length of time.

Patients categorized with F3 fibrosis had mean annual pre-index costs ranging from \$21,828 to \$28,983 and post-index costs ranging from \$24,150 to \$39,658, depending on the FIB-4 definition used. Patients categorized as F4 had mean pre-index costs ranging from \$28,983 to \$37,101 and post-index costs ranging from \$39,658 to \$54,852. Patients who had FIB-4-based F4 fibrosis had higher overall costs than patients with F3 with precirrhosis. A study by Canbay et al.⁽³³⁾ highlighted the importance of identifying patients before development of cirrhosis. Following a diagnosis of CC, the number of patients requiring an emergency visit doubled and the proportion of patients with a hospitalization rose from 40.9% to 66.9%. Mean annual all-cause health care costs increased 93% after diagnosis (\$14,600 vs. \$7,600), with inpatient costs more than tripling. Patients that progressed to end-stage liver disease had costs that rose even higher, primarily driven by a 411% increase in inpatient costs.⁽³³⁾ Similarly, Boursier et al.⁽³⁵⁾ found that after diagnosis of CC, patients with NAFLD/NASH experienced an increase of 300% in the annual number of hospitalizations and an increase of over 250% in annual hospitalization costs. The higher health care costs over the post-index period in our study likely represented costs associated with diagnostic work-up and follow-up during disease progression. Health care costs would likely decrease further out from diagnosis until the patient progressed to more advanced disease or developed decompensation.

Fibrosis advances histologically with nonspecific symptoms, hence untreated advanced fibrosis may translate to more severe outcomes, leading to higher costs among patients with FIB-4-based F4. This observation could imply a missed opportunity to timely screen, diagnose, and manage patients before fibrosis progression. In the absence of better modalities, widespread use of noninvasive tests to assess fibrosis in clinical practice may help to track fibrosis progression in a timely manner, with subsequent earlier identification of patients with advanced fibrosis. Adoption of this practice may also provide point-of-service information that reduces the need for liver biopsies to confirm fibrosis stage in cases of NAFLD/NASH. Our findings highlight the need for early fibrosis staging to identify patients with NAFLD/NASH, particularly those with F3 fibrosis, for targeted interventions to halt or reduce the risk of progression to cirrhosis and complications related to portal hypertension.

Claims data are subject to inherent limitations because they are based on disease and procedure payment codes. While these limitations do not substantially reduce the strength of the study, they must be considered during interpretation of results. The identification of advanced liver diseases (CC/DCC/LT/HCC) and other comorbidities (such as obesity) were limited to ICD-9/10-CM codes, which may have led to underestimation of the true number of patients. These codes merely reflect the claims submitted for reimbursement and are not necessarily confirmation of actual disease; however, use of these codes has been common practice in the literature. Additionally, ICD-9-CM codes did not provide the level of granularity to distinguish NASH from NAFLD, but it is highly likely that study patients had NASH because other causes of liver disease were excluded and the population was limited to those with biomarker-defined advanced fibrosis. Claims data also did not include historical or laboratory information regarding liver function or liver histology reports. Information on the amount of alcohol consumption was unavailable; however, because alcohol intake may affect the AST/ALT ratio, patients with a diagnosis of alcoholism were excluded from the study. Additionally, some patients who met the criteria for FIB-4-based F3 or F4 cutoffs may have been misclassified because abnormal AST and/or ALT values can occur for reasons other than fibrosis.⁽³⁶⁾ The stringent and comprehensive exclusion criteria followed in the study, however, was meant to exclude patients with other causes of liver diseases, thereby preventing such bias.

Available laboratory information to calculate FIB-4 was part of the inclusion criteria; however, laboratory data were only available for a subset of the population (30%-40%). Among patients with observable laboratory measures, the absence of liver biochemistries may have resulted in potential selection bias because relatively sicker patients with certain comorbid or chronic disease (e.g., hyperthyroidism, hypothyroidism, anemia, hyperlipidemia) may be more likely to obtain routine laboratory work-ups. The reason for ordering laboratory tests could not be determined from the claims data. It is unlikely that physicians screened for NAFLD/NASH using the FIB-4 algorithm, but rather the tests were ordered as part of routine care. While there are other noninvasive methods for the assessment of liver fibrosis that may have higher positive predictive values or greater sensitivity (e.g., NAFLD

score), FIB-4 was chosen as it provided the most comprehensive method to accurately capture patients with advanced fibrosis based on laboratory data alone. Historically, FIB-4 was developed to assess liver fibrosis in patients with HIV and hepatitis C virus coinfection.⁽³⁷⁾ The fact that all the chosen cutoffs have not been validated within the NASH population (except criterion 1, FIB-4 >2.67) is a potential limitation. In a study validating FIB-4 for use in NAFLD, Shah et al.⁽²⁵⁾ found a FIB-4 score ≥ 2.67 had an 80% positive predictive value and a FIB-4 score of ≤ 1.30 had a 90% negative predictive value for advanced fibrosis. These results were corroborated in similar studies comparing the performance of noninvasive markers of advanced fibrosis in NASH^(24,26,38-39); however, a recent study by Wong et al.⁽⁴⁰⁾ provided more robustness around the chosen cutoffs in this study. Nevertheless, future studies are needed to validate different FIB-4 cutoffs in the NAFLD/NASH population.

In conditions such as NAFLD/NASH where there are no available treatments, much of health care use is centered on diagnosis and follow-up. The calculation of annual HCRU and costs from PPM values may have biased the annual estimates away from the null, as follow-up for individuals in the study ranged from 1 to 6 months and costs may have been greater in the first few months following diagnosis. Patients in this study were also required to have a minimum of 1 month of follow-up after the index date. This criterion was explicitly set to identify a more inclusive sample of patients and to reduce the risk of bias that may have been introduced by requiring a longer follow-up that could result in a sample of healthier patients who did not die or progress to advanced liver disease (CC/DCC/LT/HCC). Lastly, a retrospective study design was a limitation for this research question; however, given the issues associated with prospective studies (i.e., long follow-up times for a large number of patients, time-consuming, costly), it was more feasible to conduct a retrospective cohort study. Additional studies with multivariable models are needed to control for the confounding effects of demographics and comorbidities on HCRU and costs to better understand the drivers of this economic burden.

This study documented high rates of comorbidities, HCRU, and costs among patients with NAFLD/NASH with FIB-4-based advanced fibrosis, reflecting the economic burden and urgency to treat this

population. The pre-index comorbidity burden was high and comparable across all cohorts, with almost 50% of patients having T2D, CVD, or renal impairment. Once identified as FIB-4-based F3 or F4, patients experienced significant increases in HCRU and health care costs, with inpatient costs being the major drivers of this increment. This indicates a missed opportunity to be diagnosed and treated in the early stages of liver disease. Further investigation also revealed that a significant minority of patients with FIB-4-identified F3 and F4 progressed to more advanced stages, leading to diagnoses of CC/DCC/LT/HCC. Future research with longer follow-up time is needed to further delineate factors associated with real-world disease progression (e.g., weight attributed to T2D, age >50 years, increased ALT, hypertension)⁽⁴¹⁻⁴⁴⁾ to provide insight for targeting effective treatment strategies as they become available and for resource planning from a public health perspective given the huge clinical burden of patients with NASH. Future work is also needed to identify the utility of noninvasive tests in risk stratification of patients at earlier fibrosis stages for prevention and targeted interventions.

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