

Real-world healthcare utilization and costs among patients with nonalcoholic fatty liver disease are substantial and increase with advanced disease

Mohammad S. Siddiqui,¹ Joel Myers,² Clare Byrne,³ Yuexi Wang,³ Jackson Tang,³ Adesuwa Ogbomo,³ Ying Qiu²

¹Virginia Commonwealth University, Richmond, VA; ²Bristol Myers Squibb, Princeton, NJ; ³STATinMED Research, Ann Arbor, MI



Introduction

- The prevalence of nonalcoholic fatty liver disease (NAFLD)/ nonalcoholic steatohepatitis (NASH) is growing worldwide; in the United States (US), it is currently estimated that 30% of the population has NAFLD and 5% has NASH¹
- The most commonly used histologic scoring system for NAFLD/ NASH, defined by the NASH Clinical Research Network², classifies fibrosis into stages 1-4; stages ≥ 2 are considered significant fibrosis, while stages 3 (bridging fibrosis) and 4 (cirrhosis) are considered advanced fibrosis³
- Liver biopsy is the standard modality to establish the diagnosis and stage disease; however, due to its invasive nature, a number of noninvasive biomarkers have been evaluated in NAFLD to stage liver disease⁴
- Historically, there have not been International Classification of Disease (ICD) codes to classify the degree of fibrosis in patients with NAFLD/NASH, which has limited the study of healthcare resource utilization (HCRU) and costs associated with different stages of fibrosis through analysis of retrospective real-world datasets
- In this real-world study, fibrosis stages were indirectly quantified using Fibrosis-4 (FIB-4) scores in a longitudinal repeated measures design to determine the HCRU and costs associated with NAFLD/NASH and advancing fibrosis

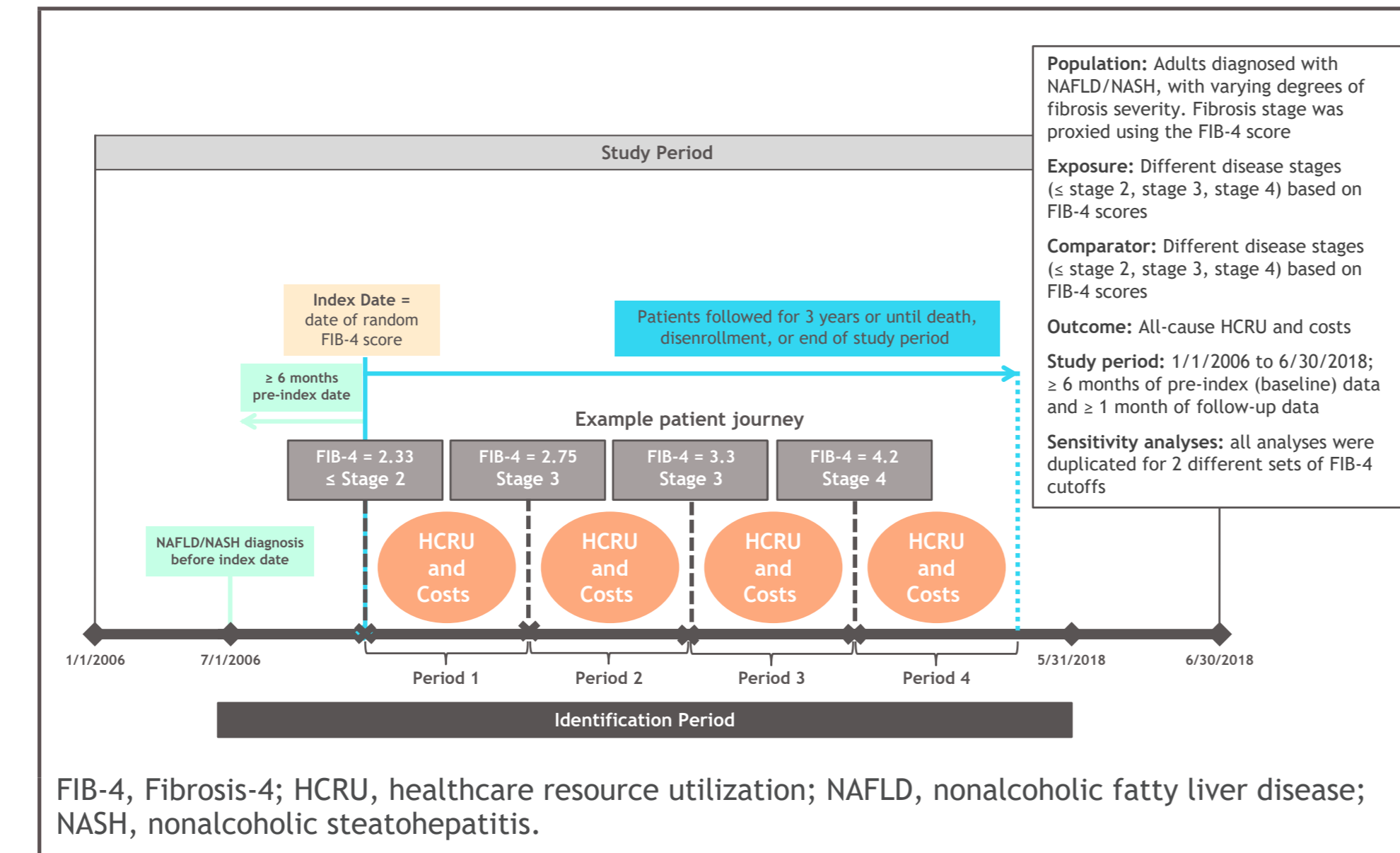
Methods

Study design

- This analysis used data from Optum Clinformatics® Data Mart (Optum, Eden Prairie, MN), a large administrative claims database of commercially insured patients in the US
- Eligible patients were adults with ≥ 1 claim with a diagnosis code for NAFLD/NASH (ICD-9-CM: 571.8, 571.9; ICD-10-CM: K76.0, K75.81) between January 1, 2006 and June 30, 2018 (Figure 1)
 - Patients were required to have available laboratory data for FIB-4 score calculation (ALT, AST, and platelet count, all measured within a 14 day time period) at ≥ 1 time point
 - For each patient, following first NASH/NAFLD diagnosis, a randomly selected FIB-4 score during the identification period (July 1, 2006 - May 31, 2018) was used as the index score; random scores were chosen in order to select patients with varying levels of disease severity
 - Patients were also required to have continuous insurance enrollment for ≥ 6 months prior to the index date and ≥ 1 month after the index date
- Patients were followed for up to 3 years, until the end of insurance enrollment, or until the end of the study period, whichever came first; FIB-4 scores were assessed repeatedly at all time points for which data were available
- Fibrosis stage was estimated using FIB-4 scores and classified as \leq stage 2 (< 2.67), stage 3 (2.67-4.12), or stage 4 (> 4.12), based on a comprehensive review of the published literature and expert opinion. Sensitivity analyses were undertaken to assess the impact of varying the FIB-4 cut-off values as shown below:

Analysis	\leq Stage 2 fibrosis	Stage 3 fibrosis	Stage 4 fibrosis
Primary	< 2.67	2.67-4.12	> 4.12
Sensitivity 1	< 2.67	2.67-3.50	> 3.50
Sensitivity 2	< 3.25	3.25-4.12	> 4.12

Figure 1. Study design



Study Variables

- Patient demographics, including age, gender, and geographic region were collected on the index date
- Charlson Comorbidity Index (CCI), comorbid conditions, and HCRU and costs were measured in the 6-month baseline period
- Per patient per month (PPPM) HCRU and costs associated with each FIB-4 score over the study period were calculated and compared

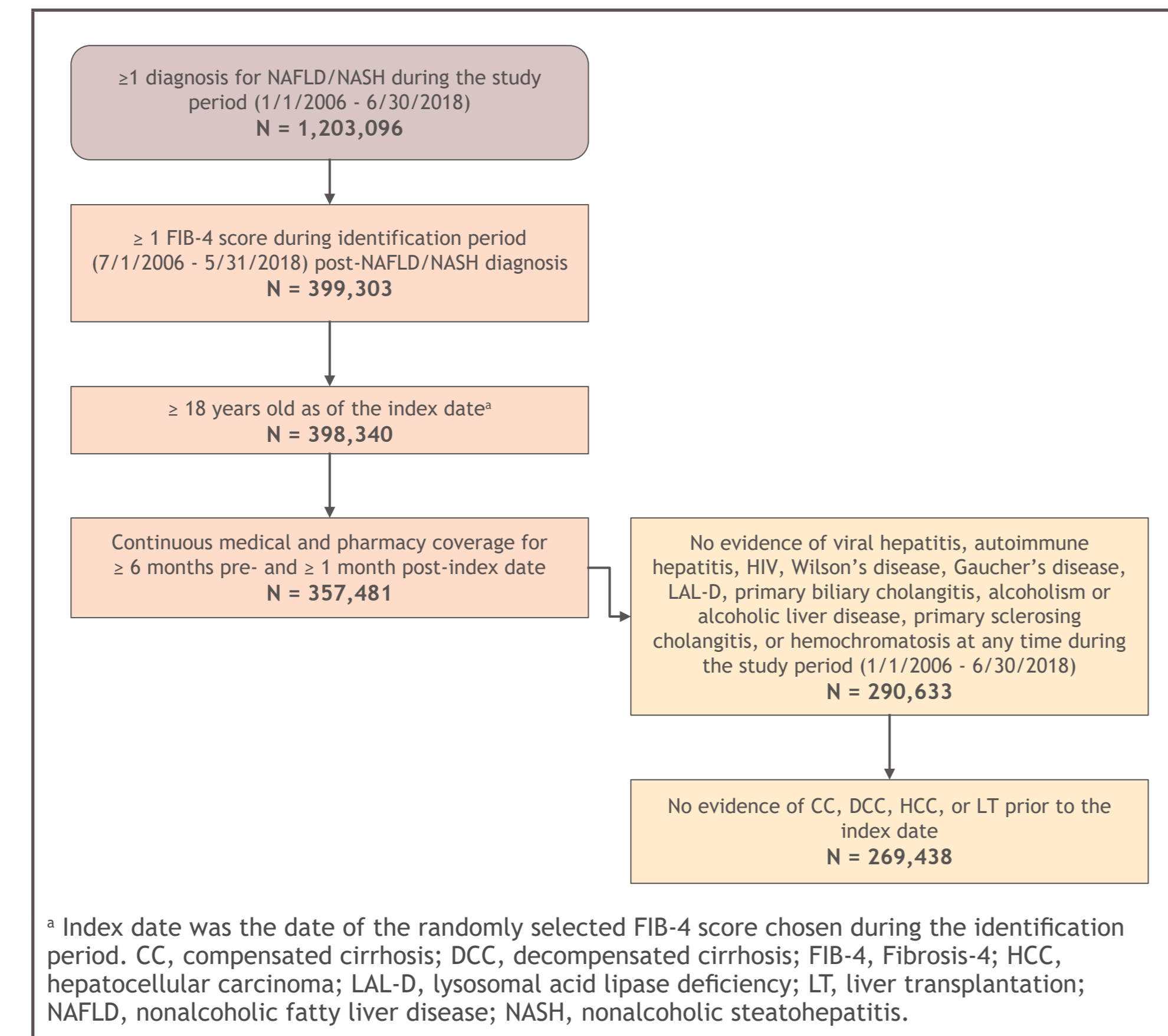
Statistical Analysis

- Linear regressions with generalized estimating equations were performed to adjust for fibrosis stage, age, geographic region, comorbidities, and baseline HCRU
- Marginal effects and 95% confidence intervals were calculated for each fibrosis stage; P values were calculated to examine the significance of difference in HCRU and costs between fibrosis stages

Results

- From January 1, 2006 to June 30, 2018, there were 269,438 patients that met all study criteria to be included in this analysis (Figure 2)

Figure 2. Patient flow diagram



* Index date was the date of the randomly selected FIB-4 score chosen during the identification period. CC, compensated cirrhosis; DCC, decompensated cirrhosis; FIB-4, Fibrosis-4; HCC, hepatocellular carcinoma; LAL-D, lysosomal acid lipase deficiency; LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

- The mean age of the study population was 58.5 years and a majority of participants were women (Table 1)
- Overall, 489,117 FIB-4 scores were calculated throughout the study period; most (93.9%) corresponded to stage 2 fibrosis or lower, while 4.6% were stage 3 fibrosis and 1.5% were stage 4 fibrosis in the primary analysis

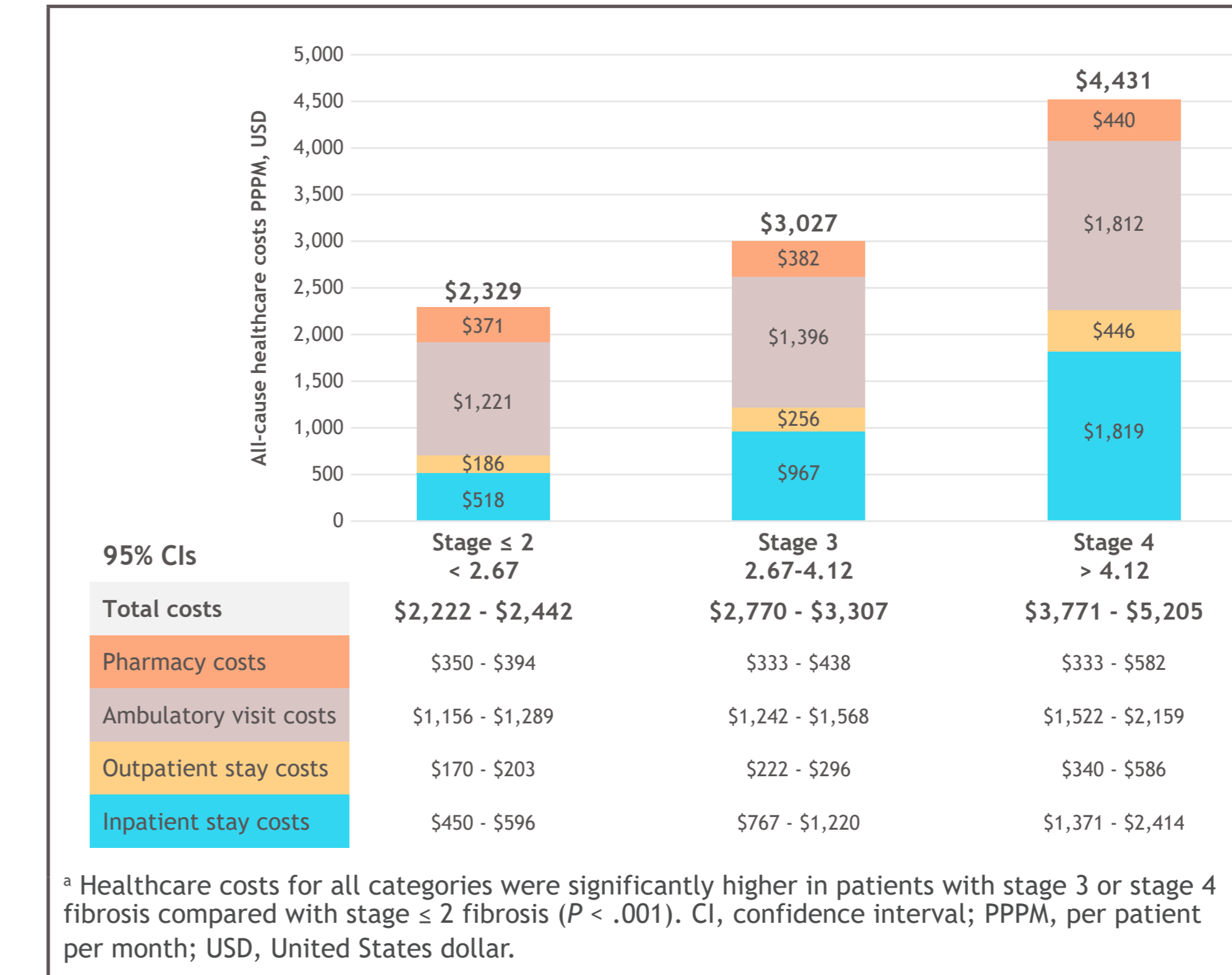
Table 1. Baseline patient characteristics

Parameters	All Patients (N = 269,438)
Age, mean (SD), years	58.5 (14.5)
Age range, n (%)	
18-34	15,921 (5.9)
35-54	88,362 (32.8)
55-64	64,173 (23.8)
65+	100,982 (37.5)
Sex ^a , n (%)	
Male	113,804 (42.2)
Female	155,576 (57.7)
CCI, mean (SD)	1.18 (1.68)
CCI, n (%)	
0	120,972 (44.9)
1-2	108,428 (40.2)
≥3	40,038 (14.9)
Comorbidities, n (%)	
Abdominal pain	54,769 (20.3)
Hypertension	140,247 (52.0)
Hyperlipidemia	128,801 (47.8)
Obesity	61,860 (23.0)
Renal dysfunction	46,563 (17.3)
CHD	10,522 (3.9)
T2DM	88,692 (32.9)

^a Percentage does not equal 100 because 0.02% of patients were not classified due to missing data. CCI, Charlson comorbidity index; CHD, congestive heart disease; T2DM, type-2 diabetes mellitus; SD, standard deviation.

- Unadjusted mean total healthcare cost PPPM increased with increasing fibrosis stage; additionally, such increases were observed across all healthcare service types examined
- A significant stepwise increase was noted in the adjusted mean total healthcare cost PPPM according to fibrosis stage: \$2,339 for \leq stage 2 fibrosis, \$3,027 for stage 3 fibrosis, and \$4,431 for stage 4 fibrosis (Figure 3)
 - In those patients with lower fibrosis stages, ambulatory visits were the major contributor to costs, while inpatient costs were markedly increased in patients with stage 4 fibrosis compared with those with lower fibrosis stages

Figure 3. Adjusted healthcare costs (PPPM) by fibrosis stage: primary analysis^a



^a Healthcare costs for all categories were significantly higher in patients with stage 3 or stage 4 fibrosis compared with stage ≤ 2 fibrosis ($P < .001$). CI, confidence interval; PPPM, per patient per month; USD, United States dollar.

- Similarly, HCRU increased with increasing fibrosis stage (Table 2)

Table 2. Adjusted HCRU by fibrosis stage: primary analysis^a

All-cause HCRU, PPPM	Stage ≤ 2 fibrosis (< 2.67)		Stage 3 fibrosis (2.67-4.12)		Stage 4 fibrosis (> 4.12)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Patients with ≥ 1 inpatient stay, %	10.4	10.0-10.8	12.2	11.6-12.9	15.9	14.9-16.9
Number of inpatient stays	0.03	0.02-0.03	0.07	0.05-0.09	0.10	0.07-0.14
Length of inpatient stay	0.22	0.17-0.26	0.51	0.43-0.59	1.01	0.82-1.20
Patients with ≥ 1 outpatient ER visit, %	26.0	25.4-26.6	27.0	26.1-27.8	28.8	27.5-30.0
Number of outpatient ER visits	0.09	0.09-0.10	0.12	0.11-0.14	0.17	0.14-0.21
Patients with ≥ 1 ambulatory visit, %	98.6	98.5-98.8	98.3	98.0-98.5	97.9	97.5-98.3
Number of ambulatory visits	1.97	1.94-2.00	2.11	2.06-2.16	2.34	2.25-2.43

^a All HCRU differences between patients with stage 3 or stage 4 fibrosis compared with stage ≤ 2 fibrosis were statistically significant ($P < .001$). CI, confidence interval; ER, emergency room; HCRU, healthcare utilization; PPPM, per patient per month; USD, United States dollar.

- The sensitivity analyses, which used alternate FIB-4 cutoff values, demonstrated similar increases in total healthcare costs as were observed in the primary analysis (Table 3)

Table 3. Sensitivity analysis summary

Cutoff set	Mean total healthcare cost, PPPM			P value ^a
	Stage ≤ 2 fibrosis	Stage 3 fibrosis	Stage 4 fibrosis	
Primary analysis	\$2,329	\$3,027	\$4,431	$< .001$
Sensitivity 1	\$2,329	\$3,051	\$3,887	$< .001$
Sensitivity 2	\$2,329	\$3,168	\$4,352	$< .001$

^a All differences in costs between patients with stage 3 and stage 2 fibrosis, and stage 4 and stage 2 fibrosis were statistically significant ($P < .001$). PPPM, per patient per month.

Study limitations

- Claims databases created for payment purposes may have missing values, coding errors, and/or lack of clinical accuracy that could potentially affect the results of the study
- Patients analyzed in this study had insurance coverage from private US health plans, so the findings may not be generalizable to the overall US NAFLD/NASH patient population or to patients who live in countries other than the US
- Patients were followed for a maximum of 3 years because of the potential for changes in patient characteristics over time; however, this may have led to underestimation of costs, because disease progression often occurs over a long time period in NAFLD/NASH
- Finally, owing to the lack of specific ICD codes for NAFLD disease stages, staging was estimated based on FIB-4 scores. Although the choice of FIB-4 score cut-offs to define each stage in this study was based on extensive research and the best available evidence, and sensitivity analyses were employed to test the impact of using alternative criteria, the patient cohorts identified will not correspond exactly to liver biopsy-staged cohorts

Summary & Conclusions

- The real-world economic burden associated with NAFLD/ NASH is substantial, even among patients with early stage liver fibrosis, and increases with more advanced disease
- We observed significant incremental increases in the adjusted mean total healthcare costs PPPM of \$697 (30%) from \leq stage 2 fibrosis to stage 3 fibrosis and \$1,404 (46%) from stage 3 fibrosis to stage 4 fibrosis
- Similarly, HCRU increased with increasing fibrosis stage; ambulatory costs were a major cost driver in patients with lower fibrosis stages, while increased inpatient costs were the major cause of the substantial increase in total costs observed in patients with stage 4 fibrosis
- Although the approach has limitations, estimation of fibrosis stage using FIB-4 scores provides insights into the economic and clinical burden associated with more advanced fibrosis in patients with NAFLD/NASH

References

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