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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Nonalcoholic fatty liver disease: impact on healthcare resource utilization, liver transplantation and mortality in a large, integrated healthcare system

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Abstract

Background and aims NAFLD is the most prevalent liver disease globally, affecting 20% of the world population. Healthcare resource utilization (HRU) attributable to NAFLD has been difficult to define.

Methods We performed a case control study on NAFLD patients from 2005 to 2015 in a large integrated healthcare system with an affiliated insurance company that prospectively captures HRU information. Outcomes encompassed costs, liver transplantation and mortality rates.

Results There were 17,085 patients, of which 4512 were NAFLD cases and 12,573 were non-NAFLD controls. The cohorts were similar in age and gender distribution ($p > 0.05$). The NAFLD cohort had a younger mean age of death (60.9 vs. 63.3, $p = 0.004$) and had over twice the number of annual healthcare visits (14.6 vs. 7.1). The increased overall annual overall cost attributable to NAFLD (in 2015 $) was $449/year. Overall, NAFLD was independently associated with 17% higher annual attributable healthcare costs. More advanced NAFLD (FS 3–4) was associated with a 40% increase in median annual healthcare costs (vs. FS 0-2). The strongest predictors of HRU among patients with NAFLD were advanced fibrosis and medical co-morbidities. The rate of liver transplantation was 18 times greater (0.054%/year) in the NAFLD compared with the non-NAFLD cohort, while mortality rate was 1.7 times greater.

Conclusions Within a large, integrated healthcare system a diagnosis of NAFLD is independently associated with a 17% overall excess in HRU and a several-fold increase liver transplantation and mortality. Although the dollar amounts will change over time and between healthcare systems, the proportional need for HRU will have broad applicability and implications.

Keywords Fatty liver · NAFLD · Health economics

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease affecting over 80 million people in the USA, and has an overall global prevalence of over 20% with increasing prevalence in the western Pacific [1]. NAFLD refers to the presence of hepatic steatosis when no other causes for hepatic fat accumulation (e.g., significant alcohol consumption) are apparent [2]. The clinicopathologic spectrum of NAFLD ranges from hepatic steatosis to nonalcoholic steatohepatitis (NASH) which may lead to cirrhosis. There is a strong association between NAFLD and the common conditions of metabolic syndrome, obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension [3]. With no change to the prevalence of obesity and T2DM in an aging population, NAFLD is forecasted to affect 100.0 million people in the USA by 2030, representing an increase in prevalence from 26% in 2016 to 28%. [4] Similar trends have been predicted worldwide, including in Japan where the prevalence is anticipated to increase from 17.9 to 18 8% by 2030. [5].

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A recent study analyzing the trend in cirrhosis-related mortality rates from 2007 to 2016 noted a mortality rate increased to 23.67/100,000 persons in 2016, with an average annual percentage change (APC) of 15.4% for NAFLD, a rate of change three-fold greater than alcohol liver disease (ALD)-related cirrhosis [6]. Moreover, NAFLD has also surpassed hepatitis C virus infection and is close to ALD as the leading cause for liver transplant in the US [7]. This change in listing indication has also been reflected in Europe [8]. Patients with NAFLD have increased mortality compared to the general population, and have significant morbidity [9]. The prevalence of NASH among NAFLD patients ranges from 7 to 30% [1, 4,] and these patients are at higher risk for adverse outcomes such as cirrhosis and liver-related mortality [2]. Given the high likelihood of patients with NAFLD having a number of co-morbidities, and the increasing associated mortality and morbidity, one would expect these patients to utilize significant healthcare resources. However, the burden of NAFLD on healthcare resources is unclear, as healthcare resource utilization (HRU) attributable to NAFLD has been difficult to examine.

Previous studies have tried to ascertain the attributable cost of NAFLD. In the Middle East, a cross-sectional study estimated diagnosis and treatment costs of NAFLD at 5043 purchasing power parity dollar (PPP$) annually [10]. A self-reported HRU cohort study on NAFLD patients (defined by sonographic fatty liver and increased serum ALT levels) from Germany found 26% higher overall healthcare costs at 5-year follow-up compared to other individuals [11]. In the US, a retrospective analysis on Medicare data showed increasing costs of NAFLD, with outpatient charges increasing from US$2624 in 2005 to US$3608 in 2010, and inpatient costs increasing from US$11,769 to US$12,347 in 2010 [12, 13]. This analysis also noted increased prevalence of related co-morbidities [13]. An international study assessing the economic burden of NAFLD, using Markov modeling, estimated that NAFLD accounts for a potential annual direct medical cost of $103 billion ($1613 per patient) in the United States, and €35 billion (from €354 to €1163 per patient) in Europe [14]. Finally, a recent study using a national administrative claims database demonstrated a higher annual cost of care for long-term management of NAFLD patients ($3789 vs. $2298) compared to non-NAFLD patients [15].

Despite this aforementioned research, the true economic impact of NAFLD remains to be directly determined, particularly at a population-level within a broad-based US healthcare system. Intermountain Healthcare (IHC) is an integrated healthcare system with an affiliated insurance company that provides care to more than 2 million individuals. Analysis of patients in IHC's electronic data warehouse therefore provides a unique opportunity to assess actual HRU among patients with NAFLD. The aim of our study was to determine the HRU among patients with NAFLD according to both disease severity and disease definitions (biopsy vs. ICD) and to compare with patients without NAFLD.

Materials and methods

Study setting

Intermountain Healthcare (IHC) is a nonprofit integrated healthcare system of 23 hospitals, 185 clinics and an affiliated insurance company, caring for more than 2 million individuals in Utah, USA. Patients in the IHC system have a high frequency of remaining in the IHC system with relatively little migration, and thus receive the great majority of their care through IHC.

Study design

We performed a case–control study among IHC patients with NAFLD from January 1, 2005 to December 31, 2015. Adult (18 years or older) NAFLD cases were identified by International Classification of Diseases (ICD) codes, liver biopsy, or both. The ICD codes used were: 571.8 (Other Chronic Nonalcoholic Liver Disease), K75.81 (Nonalcoholic steatohepatitis), and K76.0 (Fatty (change of) liver, not elsewhere classified). At IHC, the diagnosis of NAFLD requires fulfillment of the society definition of NAFLD: there must be [1] evidence of hepatic steatosis, either by imaging or histology, and [2] lack of secondary causes of hepatic fat accumulation [2]. NAFLD cases were analyzed overall and according to fibrosis stage (FS, 3-4 vs. F0-2), assessed by NAFLD-Fibrosis Score (NAFLD-FS), a model incorporating age, body mass index (BMI), platelet count, fasting glucose, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and albumin which has been shown to accurately separate patients with NAFLD with and without advanced fibrosis [16]. At the low cutoff score, advanced fibrosis is excluded with high accuracy (negative predictive value of 88–93%) [16]. At the high cutoff score, advanced fibrosis is diagnosed with high accuracy (positive predictive value of 82–90%) [16]. Chronic conditions used in the Charleson Comorbidity Index of ICD codes, such as hypertension, T2DM and hyperlipidemia, were identified in each patient [17]. Once a patient had been identified with a chronic condition, the condition remained assigned to them the following years. Controls were derived from all possible contemporary IHC patients who did not have NAFLD evaluated at routine wellness clinic visits. The total pool of

patients was ~ 2.5 million patients of any age of any visit or encounter during the study timeframe.

The primary study outcomes were annual cost before NAFLD diagnosis, annual post-NAFLD diagnosis, overall annual cost, liver transplant and mortality rates. Regarding costs, the total cost amount from the casemix file for any year from 2005 to 2015 was ascertained, with charges from the outpatient system added. These charges are standardized across payers in this system. Inflation was then accounted for to adjust for all years to 2015 costs using US Federal Reserve medical inflation tables.

Statistical analysis

Continuous variables were summarized with means and standard deviations, and frequencies and percents were used for categorical variables. Comparative analysis of continuous variables was based on two-sample Wilcoxon–Mann–Whitney test (comparison of medians) for samples that failed the Shapiro–Wilk normality test, otherwise, it was based on two sample t test (comparison of means). Comparative analysis of categorical variables was based on two-sided Chi-square test. Propensity matching, via the Matchit package in R, was performed whereby nearest neighbor matching was performed with case patients in each year of the cohort matched to three matches in the control population. Cases were matched on sex, number of comorbidities, cost year prior to diagnosis, age, and year of diagnosis. Resource utilization analysis was a generalized linear model with gamma distribution and a log-link function. Analysis was a negative binomial model using the patient as a random effect. Univariate regression analysis assessed the HRU of individual variables before a multivariate regression model was built and optimized by variables which were statistically significant and improved the model fit. Predictors of mortality were also assessed. A p value of < 0.05 was considered significant for all statistical methods used. The analysis was performed using SAS version 9.3.

Results

Frequency and comparative demographics

There were 17,085 patients in the study cohort encompassing 70,354 person-years of follow-up, of which 4512 (18,512 person-years, for an average of 4.10 years of follow-up) were adult NAFLD cases (3872 by ICD code; 464 by biopsy; 176 by both ICD code and biopsy) (Fig. 1) and 12,573 (51,833 person-years, for an average of 4.12 years of follow-up) were non-NAFLD controls. The demographic and clinical characteristics of the study cohorts are outlined in Table 1. The NAFLD and non-NAFLD cohorts were similar in age and gender distribution (Table 1) ($p > 0.05$). The NAFLD cohort had a higher BMI, transaminase, triglyceride and glucose levels, and lower albumin and platelet levels compared with the non-NAFLD cohort (all p values < 0.05). There was increased prevalence of Hispanic ethnicity in the NAFLD cohort ($p < 0.001$).

Outcomes

While both cohorts had a similar age at diagnosis, the NAFLD cohort had a younger mean age of death (60.9 vs. 63.3, $p = 0.004$). On average, NAFLD patients had over twice the number of healthcare visits over the study period (14.6 vs. 7.1), with 1.9 inpatient visits, 2 emergency room visits, and 10.7 outpatient visits, compared to 0.7 inpatient visits, 0.8 emergency room visits, and 5.6 outpatient visits for the non-NAFLD cohort (Fig. 2). Our cohort of newly-diagnosed NAFLD patients between 2005 and 2015 had significantly higher annual healthcare costs compared to non-NAFLD patients who were evaluated during the same year (Fig. 3). The median annual cost in 2015 USD before NAFLD diagnosis of $970 was 4.8 times higher in the NAFLD cohort, and the median annual cost of $2620 after NAFLD diagnosis was 3.6 times higher in the NAFLD cohort, compared to the non-NAFLD cohort (Fig. 3). The overall median annual cost of $2400 in the NAFLD cohort was 3.3 times higher than the non-NAFLD cohort. NAFLD patients with F3/F4 fibrosis, as determined by the NAFLD-FS, had a median annual cost of $7190, compared to $1880 in patients with F0–F2 fibrosis (Fig. 4).

In univariate (unadjusted) regression analysis, a diagnosis of NAFLD was associated with a 105% (95% CI 97%, 116%) higher median annual healthcare cost (Table 2). Several variables including non-Latino race, albumin and platelet levels, hypercholesteremia, the presence of advanced fibrosis and many co-morbidities including hepatitis C, cerebrovascular disease and diabetes, all predicted higher HRU in patients with NAFLD (Table 2). Ultimately, after adjusting for all pertinent variables and optimizing the regression model fit, NAFLD was independently associated with a 17.35% higher median annual healthcare cost (95% CI 11.63–22.14%, $p = 0.02$) (Table 3). More advanced NAFLD (FS 3–4) was associated with a 40.49% increase in median annual healthcare cost (95% CI 24.61–56.83%, $p < 0.001$) (Table 3). Results were similar when NAFLD cases were identified by liver biopsy and ICD code.

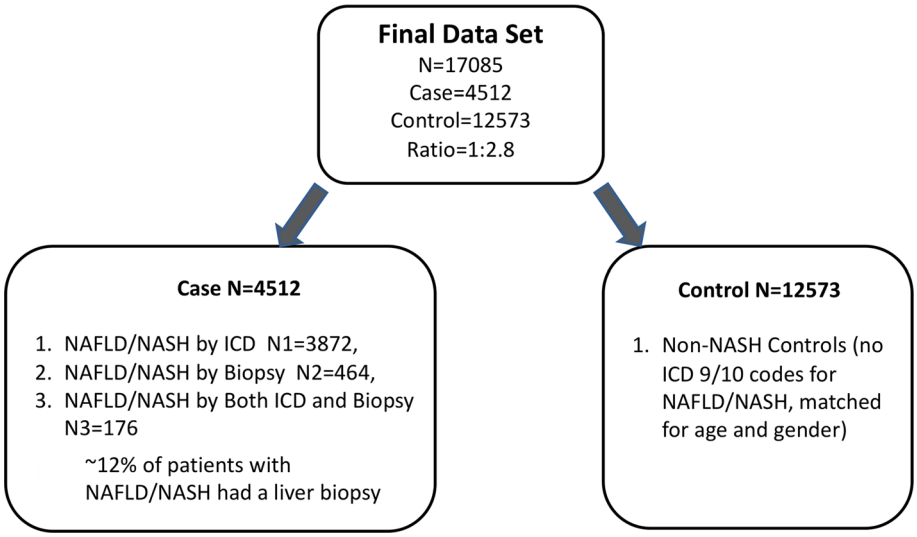

Fig. 1 Data development progression for analysis is shown. Cases included patients with NAFLD/NASH identified by International Classification of Diseases (ICD) code (n = 3842), liver biopsy (n = 464) and by both ICD code and biopsy (n = 176)

Table 1 Demographic and clinical characteristics of the nonalcoholic fatty liver disease (NAFLD) patients (i.e. cases) versus non-NAFLD patients (i.e. controls)

Characteristic	NAFLD patients (N = 4512)	Non-NAFLD patients (N = 12,573)	P value
Age, years	50 ± 13.4	50 ± 12.9	0.090[a]
Gender, n (%)			
Male	2291 (50.8)	6621 (52.7)	0.068[c]
Body mass index, kg/m^2	33.6 ± 7.7	29.7 ± 7.9	< 0.001[a]
BMI categories, n (%)			
< 30 kg/m^2	1404 (34.3)	5126 (60.4)	< 0.001[c]
≥ 30 kg/m^2	2686 (65.7)	3356 (39.6)	
Ethnicity, n (%)			
Hispanic-Latino	594 (13.2)	789 (6.3)	< 0.001[c]
Albumin, g/dL	4.1 (3.7–4.3)	4.1 (3.8–4.4)	< 0.001[a]
Albumin categories, n (%)			
≤ 3.5 g/dL	515 (14.8)	565 (12.3)	0.002[c]
> 3.5 g/dL	2974 (85.2)	4041 (87.7)	
INR	1.1 (1.0–1.3)	1.1 (1.0–1.5)	< 0.001[a]
Bilirubin, mg/dL	0.7 (0.5–1)	0.6 (0.4–0.8)	< 0.001[b]
Creatinine, mg/dL	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.470[b]
Platelet, x10^9/L	223 (177–270)	229 (188–274)	< 0.001[a]
ALT, U/L	57 (36–94)	34 (26–46)	< 0.001[b]
AST, U/L	48 (33–81)	32 (27–43)	< 0.0001[b]
Total cholesterol, mg/dL	194 (167–226)	193 (168–221)	0.074[a]
HDL cholesterol, mg/dL	42 (35–51)	46 (38–56)	< 0.001[a]
LDL cholesterol, mg/dL	112 (87–139)	113 (92–138)	0.093[a]
Triglyceride, mg/dL	178 (127–263)	138 (97–202)	< 0.001[b]
Glucose, mg/dL	112 (95–151)	100 (88–126)	< 0.001[b]

Values are mean ± standard deviation, or median (interquartile range). ALT alanine aminotransaminase, AST aspartate aminotransaminase, NAFLD nonalcoholic fatty liver disease, *BMI* body mass index, *HDL* high-density lipoprotein, *INR* international normalized ratio, *LDL* low-density lipoprotein

[a]Student t test

[b]Wilcoxon-Mann–Whitney test (for samples that failed the Shapiro–Wilk normality test)

[c]Chi-square test

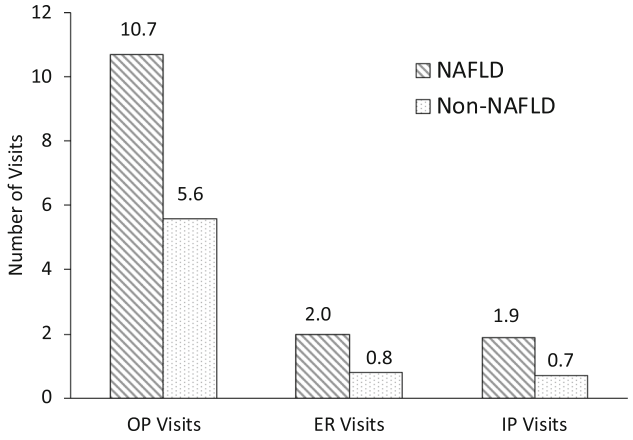

Fig. 2 Annual healthcare visits, including outpatient, inpatient and emergency room are shown for NAFLD cases and non-NAFLD controls. All visit types were higher (1.9–2.5-fold) for patients with NAFLD

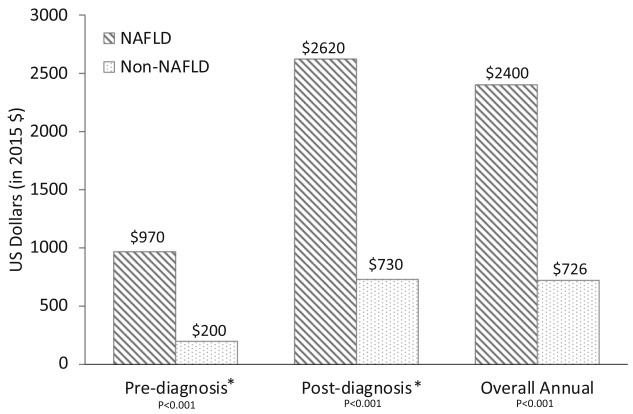

Fig. 3 Median annual costs for cases and controls are shown before (pre), after (post) diagnosis of NAFLD and overall. In multivariate analysis, the increased annual overall cost attributable to NAFLD (in 2015 $) was $449/year

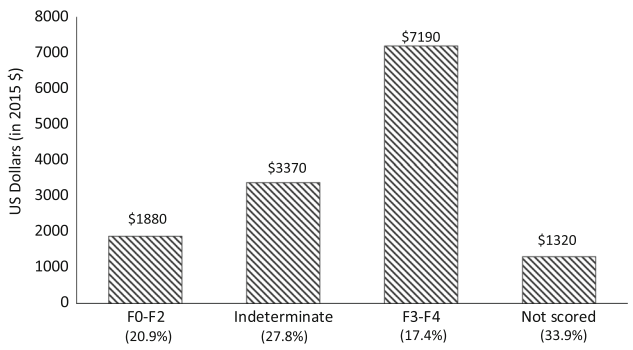

Fig. 4 Variation in median annual costs for cases and controls with estimated fibrosis stage are shown. Approximately one in six patients with NAFLD was estimated to have advanced fibrosis and had a 3.8-fold increase in healthcare cost burden

Liver transplantation and mortality rates

The rate of liver transplantation was 0.054%/year in the NAFLD cohort, 18 times greater than the non-NAFLD cohort ($p < 0.001$). The mortality rate was 8.4% in the NAFLD cohort, 1.7 times greater than the non-NAFLD cohort ($p < 0.001$). Over the 10-year study period, among the patients with NAFLD who died, 51% had F3-F4, 25% had indeterminate scores, 18% were not scored, while only 6% had F0-F2 fibrosis, as adjudged by NAFLD-FS. In the NAFLD cohort, significant predictors of mortality included older age, non-White race, presence of advanced fibrosis and co-morbidities (i.e., hepatitis C, cardiovascular disease, pulmonary disease and alcohol abuse) (Table 4).

Discussion

We were able to define HRU of NAFLD using our population-based cohort within a large, integrated healthcare system. This study yielded several important observations. Most notably, a diagnosis of NAFLD in adults is independently associated with a 17% excess in HRU overall and a several-fold increase liver transplantation and mortality rates compared to patients without NAFLD. Multiple comorbid conditions had significant impact on higher NAFLD-related healthcare costs. Advanced liver fibrosis stage, measured directly and indirectly, was also significantly associated with higher liver transplant and mortality rate in NAFLD patients. When adjusting for comorbidities, based on a national prevalence of 80 million individuals with NAFLD, NAFLD independently accounts for $36bn/year of direct HRU in 2015 USD (1.17 × average annual cost for patients without NAFLD). The most important aspect of these results is the relative cost compared to controls without NAFLD in multivariate analysis, as HRU in the geographic area of the study and in the IHC system is among the lowest in the US. The actual annual cost attributable to NAFLD is almost certainly higher than this estimate. Although the dollar amounts will change over time and between healthcare systems, the proportional need for HRU will have broad applicability and implications.

These findings are interesting from several perspectives. Firstly, the median annual costs for NAFLD patients are substantially higher than non-NAFLD patients who served as appropriate controls (1:2.8 ratio) with similar age and metabolic co-morbidities. The overall median annual cost of $2400 per patient in the NAFLD cohort was 3.3 times higher than the non-NAFLD controls. This is noticeable higher than the estimates from Medicare data in the United States ($1612.18 per patient) and from statistical modeling in Europe (€354-€1163 per patient) [14, 18]. A recent analysis of medical and pharmacy claims data from the

Table 2 Univariate regression analysis of healthcare resource utilization in patients with NAFLD ($N = 4512$)

Variable	Coefficient	Effect of annual costs (%) (95% CI)	p value
Age group (years): ≥ 65 (vs. < 65)	0.60	82.21 (73.33, 93.48)	< 0.001
Sex: female (vs. male)	0.06	6.18 (2.02, 10.52)	< 0.001
Race: White (vs. non-White)	0.15	16.18 (10.52, 22.14)	< 0.001
Ethnicity: Latino (vs. non-Latino)	− 0.04	− 3.92 (− 10.42, 3.05)	0.293
Total number of visits	0.064	6.61 (6.29, 6.82)	< 0.001
BMI* (kg/m^2): ≥ 30 (vs < 30)	0.16	17.35 (11.63, 22.14)	< 0.001
Creatinine* (mg/dL)	0.45	56.83 (50.68, 64.87)	< 0.001
AST* (U/L): ≥ 37 (vs < 37)	0.59	80.40 (71.60, 91.55)	< 0.001
ALT* (U/L): ≥35 (vs < 35)	0.22	24.61 (18.53, 31.00)	< 0.001
Albumin* (g/dL)	− 0.95	− 61.33 (− 62.84, − 59.75)	< 0.001
Platelets* ($10^3/\mu L$): ≥75 (vs. < 75)	− 1.65	− 80.80 (− 83.96, − 77.24)	<0.001
Total bilirubin* (mg/dL)	0.24	27.12 (22.14, 31.00)	<0.001
Total cholesterol* (mg/dl): ≥200 (vs < 200)	− 0.11	− 10.42 (− 16.47, − 5.82)	0.003
HDL cholesterol* (mg/dL): ≥50 (vs < 50)	− 0.13	− 12.19 (− 18.94, − 5.82)	0.001
LDL cholesterol* (mg/dL): ≥100 (vs < 100)	− 0.37	− 30.93 (− 36.24, − 25.92)	< 0.001
Triglyceride* (mg/dL): ≥150 (vs < 150)	0.09	9.42 (2.02, 17.35)	0.014
Glucose* (mg/dL)	0.007	0.70 (0.66, 0.75)	0.001
Fibrosis stage			
F0–F2	Ref		
Indeterminate	0.70	101.38 (87.76, 113.83)	< 0.001
F3–F4	1.54	366.46 (334.92, 405.31)	< 0.001
Comorbidity			
Hepatitis c	1.12	206.49 (171.83, 249.03)	< 0.001
CVD	1.37	293.54 (274.34, 309.60)	< 0.001
PVD	1.20	232.01 (212.68, 252.54)	< 0.001
CKD	1.32	274.34 (245.56, 305.52)	< 0.001
Pulmonary disease	0.81	124.79 (113.83, 133.96)	< 0.001
Diabetes mellitus	1.42	313.71 (297.49, 330.60)	< 0.001
Hypertension	1.09	197.43 (185.77, 209.57)	< 0.001
Hyperlipidemia	0.70	101.38 (93.48, 109.59)	< 0.001
PSC	1.38	297.49 (194.47, 458.45)	< 0.001
Cirrhosis	1.12	206.49 (171.83, 249.03)	< 0.001
Alcohol abuse	0.98	166.45 (145.96, 191.54)	< 0.001
NAFLD	0.72	105.44 (97.39, 115.98)	< 0.001

NAFLD nonalcoholic fatty liver disease, *95% CI* 95% confidence interval, *BMI* body mass index; *AST* aspartate transaminase, *ALT* alanine transaminase, *HDL* High-density lipoprotein, *LDL* low-density lipoprotein, *CVD* cerebrovascular disease, *PVD* peripheral vascular disease, *CKD* chronic kidney disease, *PSC* primary sclerosing cholangitis

*At baseline

OptumLabs Data Warehouse (OLDW), with controls matched at 1:1 ratio, showed substantially higher annual median costs per NAFLD patient, $3789 with commercial insurance and $5363 with Medicare Advantage, 5 years post-diagnosis [15]. Costs were significantly higher than controls, and highest during the first year following the index NAFLD diagnosis with a 72% increase in median costs with commercial insurance and a 38% increase in median costs with Medicare Advantage compared to the year prior to the index NAFLD diagnosis, while the annual costs of non-NAFLD controls only increased by the expected 5–10% [15]. In our study, the index NAFLD diagnosis resulted in a 170% increase in median annual cost, from $970 to $2620.

3 Multivariate regression analysis of health resource utilization in patients with NAFLD ($N = 4512$)

Variable	Coefficient	Effect of annual costs (%) (95% CI)	*P* value
Ethnicity: Latino (vs. Non-Latino)	− 0.17	− 18.28 (− 25.18, − 10.59)	< 0.001
Albumin (g/dL): > 3.5 (vs. ≤ 3.5)	− 0.52	− 40.76 (− 44.45, − 36.85)	< 0.001
Platelets (103/μL): ≥75 vs. < 75	− 0.54	− 41.65 (− 53.79, − 27.25)	< 0.001
Total cholesterol (mg/dL)	0.11	11.77 (5.09, 18.89)	0.004
Fibrosis stage – NAFLD-FS (vs. F0–F2)*			
Indeterminate	0.17	18.53 (9.42, 27.12)	< 0.001
F3–F4	0.34	40.49 (24.61, 56.83)	< 0.001
Comorbidity			
Hepatitis C	0.25	27.80 (10.37, 48.90)	0.001
CVD	0.57	76.83 (64.94, 89.63)	< 0.001
PVD	0.33	39.71(29.68, 50.59)	< 0.001
Hypertension	0.23	26.35 (17.33, 36.03)	< 0.001
Dyslipidemia	− 0.26	− 23.12 (− 28.78, − 17.05)	< 0.001
Alcohol abuse	0.20	22.79 (10.11, 37.44)	< 0.001
Diabetes mellitus	0.36	44.01 (33.60, 55.27)	< 0.001
PSC	0.62	85.39 (28.06, 181.96)	< 0.001
Pulmonary disease	0.08	8.25 (1.39, 15.60)	0.018
NAFLD	0.16	17.35 (11.63, 22.14)	0.020

NAFLD nonalcoholic fatty liver disease, *CI* confidence interval, *NAFLD-FS* nonalcoholic fatty liver disease-fibrosis score, *CVD* cerebrovascular disease, *PVD* peripheral vascular disease, *PSC* peripheral vascular disease

*NAFLD-FS score cutoffs: < − 1.455 = F0–F2; − 1.455 to 0.675 = indeterminate; > 0.675 = F3–F4

Table 4 Multivariate regression analysis of mortality in patients with NAFLD ($N = 4512$)

Variable	Relative risk (95% CI)	*P* value
Age (years) >/= 65 (vs. < 65)	1.93 (1.42, 2.63)	< 0.001
Race: White (vs. non-White)	0.55 (0.39, 0.79)	0.001
ALT (U/L): ≥ 56 (vs < 56)	0.43 (0.31, 0.58)	< 0.001
AST (U/L): ≥ 40 (vs < 40)	2.27 (1.60, 3.23)	< 0.001
Albumin (g/dL) > 3.5 g/dL (vs. ≤ 3.5)	0.45 (0.36, 0.55)	< 0.001
Fibrosis stage		
F3–F4 (vs. F0-F2)	1.79 (1.04, 3.09)	0.035
Comorbidity		
Hepatitis C	1.62 (1.06, 2.48)	0.027
CVD	3.07 (2.28, 4.14)	< 0.001
PVD	1.85 (1.38, 2.48)	< 0.001
Pulmonary disease	1.42 (1.07, 1.88)	0.016
Alcohol abuse	2.75 (2, 3.79)	< 0.001

NAFLD nonalcoholic fatty liver disease, *CI* confidence interval, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CVD* cerebrovascular disease, *PVD* peripheral vascular disease

The relative increased economic burden of NAFLD has been proposed to be as high as 80% when compared to a control with similar age and co-morbidities [15]. However, with the additional granularity of data that our integrated healthcare system provided, we were able to perform multivariate regression analysis to assess for the independent contribution of NAFLD to HRU, which was found to be considerably less and was 17% higher median annual healthcare cost (CI 11.6–22.1%, $p < 0.02$). Notably, more advanced NAFLD (FS 3–4) was associated with a 40% increase in median annual healthcare cost (vs. F0-F2). As expected, our NAFLD cohort had a relative increase in health care visits (14 per year, of which 11 were outpatient visits) with our patients having twice the number of visits compared to non-NAFLD controls. This is higher than the 40% increase in the number of healthcare visits in the recent study using the OLDW claims data which showed NAFLD patients had on average 31 outpatient visits over a 5-year period, or around 6 outpatient visits per year [15]. The higher number of visits we show likely reflects the ability of an integrated healthcare system with comprehensive claims data to provide all encounters, as compared to a national claim database where some visits may not be captured.

Another aspect of our results which merits discussion is the HRU of NAFLD patients with advanced fibrosis (F3/F4). Notably this cohort of patients had a substantially higher median annual cost of healthcare at $7190 per patient, compared to $1880 in patients with F0–F2 fibrosis. This increased economic burden in patients with advanced fibrosis that has been estimated using a Medicare database [14]. They proposed that an analysis focusing only upon patients with NASH and fibrosis, yields an estimated 3–4 million patients in the United States with NASH and fibrosis and an annual expenditure of $10–15 billion [14]. Our findings confirm the increased costs, and provide a more precise estimate of these costs. An additional cost is the mortality rate of 8.4% in the NAFLD cohort, which was 1.7 times greater than the non-NAFLD cohort ($p < 0.001$), with over half of those who died having advanced fibrosis, compared to only 6% who had F0–F2 fibrosis. Indeed, those with advanced fibrosis are at markedly higher risk for adverse outcomes and our results highlight the importance to diagnose and intervene in this subset of patients. The prudent use of testing, to ascertain which patients with NAFLD have advanced liver disease, will no doubt be instrumental in identifying these patients in the most cost-effective manner. The most cost-effective modality to estimate disease severity in NAFLD is an ongoing area of research, and a definitive pathway remains to be elucidated [2]. From our data, it is clear that costs increased substantially once the diagnosis of NAFLD is made and management needs to be improved from a cost effectiveness standpoint, especially considering the ever increasing NAFLD burden, with 100.0 million people expected to be affected in the USA alone by 2030 [4].

A strength of this analysis is that a precise assessment of the HRU of NAFLD within an integrated health system was measured, not estimated. The comprehensive nature to the dataset enabled us to define more precisely the annual costs and to ascertain the cost burden of patients with advanced fibrosis through the NAFLD-FS. This also enabled us to use multivariate regression analysis to ascertain the independent burden of NAFLD, which we found to be noticeably lower than previously published [15]. The use of a 1:2.8 cases to controls' ratio optimized the comparative analysis compared to prior studies [15]. Finally, the study also validates that the NAFLD-FS can identify populations with a diagnosis NAFLD that poses significant economic burden. This study has some limitations which are important to acknowledge. First, the identification of the majority of patients with NAFLD was based on billing codes, thus there is a risk of coding errors which may have resulted in misclassification of a small number of patients. However, the results were similar between NAFLD cases identified by ICD code and liver biopsy, thus helping to validate the accuracy of our patient selection process. Conversely, there may have been some misclassification bias of non-NAFLD controls who may have undiagnosed NAFLD, as all did not have relevant imaging at the time of control selection. Finally, we were also not able to assess additional societal costs from NAFLD such as quality of life, absenteeism and caregiver burden.

In summary, in our population-based cohort, a diagnosis of NAFLD is independently associated with a 17% excess in HRU, and a several-fold increase liver transplantation and mortality rates compared to patients without NAFLD. When adjusting for comorbidities, based on a national prevalence of 80 million individuals with NAFLD, NAFLD independently accounts for $25bn/year of HRU in 2015 USD.

Author contributions TC—study design, interpretation of data; drafting of manuscript. LD, JK, JH—acquisition, analysis and interpretation of data, drafting of manuscript; RG—study design, interpretation of data, critical revision of manuscript for important intellectual content; MC—study concept and design; interpretation of data; critical revision of manuscript for important intellectual content. All authors approved final version to be published.

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Compliance with ethical standards

Conflict of interest TGC, LD, JH, JK have no relevant disclosures. RG has received consultant fees from Salix, Gilead, Novartis; and has been on advisory committees for Salix, Gilead, and Novartis. MC has received grant/research support from Gilead, Conatus, Galectin; consultant fees from Gilead, Metacrine, Enterome, Novartis, AbbVie, Intercept, NGM Bio; and has been on an Advisory Committee for Gilead.

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