OPEN

Variables Associated With Inpatient and Outpatient Resource Utilization Among Medicare Beneficiaries With Nonalcoholic Fatty Liver Disease With or Without Cirrhosis

Mehmet Sayiner, MD, Munkhzul Otgonsuren, MS, MPH,**
Rebecca Cable, BS,† Issah Younossi, BA,‡ Mariam Afendy, BS,†
Pegah Golabi, MD, Linda Henry, PhD,‡*
and Zobair M. Younossi, MD, MPH†*

Background: Nonalcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease worldwide with tremendous clinical burden. The economic burden of NAFLD is not well studied.

Goal: To assess the economic burden of NAFLD.

Study: Medicare beneficiaries (January 1, 2010 to December 31, 2010) with NAFLD diagnosis by International Classification of Diseases, Ninth Revision codes in the absence of other liver diseases were selected. Inpatient and outpatient resource utilization parameters were total charges and total provider payments. NAFLD patients with compensated cirrhosis (CC) were compared with decompensated cirrhosis (DC).

Results: A total of 976 inpatients and 4742 outpatients with NAFLD were included—87% were white, 36% male, 30% had cardiovascular disease (CVD) or metabolic syndrome conditions, and 12% had cirrhosis. For inpatients, median total hospital charge was $36,289. NAFLD patients with cirrhosis had higher charges and payments than noncirrhotic NAFLD patients ($61,151 vs. $33,863 and $18,804 vs. $10,146, $P < 0.001$). Compared with CC, NAFLD patients with DC had higher charges and payments ($P < 0.02$). For outpatients, median total charge was $9,011. NAFLD patients with cirrhosis had higher charges and payments than noncirrhotic NAFLD patients ($12,049 vs. $8,830 and $2,586 vs. $1,734, $P < 0.001$). Compared with CC, DC patients had higher total charges ($15,187 vs. $10,379, $P = 0.04$). In multivariate analysis, variables associated with increased inpatient resource utilization were inpatient mortality, DC, and CVD; for outpatients, having CVD, obesity, and hypertension (all $P < 0.001$).

Conclusions: NAFLD is associated with significant economic burden to Medicare. Presence of cirrhosis and CVD are associated with increased resource utilization.

Key Words: NAFLD, cirrhosis, resource utilization, cost

(*J Clin Gastroenterol* 2017;51:254–260)

Received for publication December 18, 2015; accepted May 9, 2016.
From the *Betty and Guy Beatty Center for Integrated Research, Inova Health System; †Department of Medicine, Center for Liver Disease, Inova Fairfax Hospital, Falls Church, VA; and ‡Center for Outcomes Research in Liver Diseases, Washington DC.
The authors declare that they have nothing to disclose.
Address correspondence to: Zobair M. Younossi, MD, MPH, Betty and Guy Beatty Center for Integrated Research, Claude Moore Health Education and Research Building, 3300 Gallows Road, Falls Church, VA 22042 (e-mail: zobair.younossi@inova.org).

DOI: 10.1097/MCG.0000000000000567

Nonalcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease worldwide.[1,2] NAFLD is defined as presence of hepatic steatosis, in the absence of secondary causes such as excessive alcohol intake, medications, some hereditary disorders, and infections. NAFLD is generally an asymptomatic disease, and the most common cause of elevated serum aminotransferase levels (ALT), which is, in most cases, the only laboratory abnormality found in patients with NAFLD.[3,4] The prevalence of NAFLD is estimated to be between 20% and 40% in the general population, but exceeds 80% in specific groups such as the morbidly obese patients.[5] In many cases, NAFLD presents in the context of metabolic syndrome or its components such as obesity, diabetes (DM), insulin resistance, and dyslipidemia which are also the common risk factors for NAFLD development.[6] Parallel to the increased incidence of obesity, NAFLD is projected to be a major cause of liver-related morbidity and mortality in the next decades.[7,8]

Pathologically, NAFLD encompasses a range of liver disorders, starting from simple hepatic steatosis, to nonalcoholic steatohepatitis (NASH), which can lead to cirrhosis and hepatocellular carcinoma (HCC).[9,10] In this context, NAFLD contributes significantly to the burden of cirrhosis in the United States.[11,12] In fact, recent data suggest that NASH has become the second leading cause for liver transplantation in the United States.[13] Beside the clinical burden of NAFLD (cirrhosis and HCC), NAFLD could potentially have enormous impact on resource utilization contributing to the societal economic burden of this disease and other obesity related diseases.[14–17] In fact, in our previous study of outpatient Medicare recipients with NAFLD enrolled from 2005 to 2010, we showed that the resource utilization related to NAFLD is on the rise.[18] However, this study was limited to the outpatient setting and did not provide detailed information about the resource utilization in cirrhotics and noncirrhotics with NAFLD. Therefore, the aim of this study is to investigate and quantify the economic burden of NAFLD and related cirrhosis among the Medicare beneficiaries who sought inpatient and outpatient care in 2010.

MATERIALS AND METHODS

Data Source and Study Population

This is a retrospective cohort study pertaining to Medicare claims among inpatients and outpatients during 2010. Medicare is a US government sponsored health insurance program for US residents aged 65 years and older, for younger patients with disabilities and those with end-stage

renal disease or amyotrophic lateral sclerosis. A 5% random sample of all Medicare claims were obtained from the Denominator Files provided by the Centers for Medicare and Medicaid Services. The 5% sample was created based on selecting records with 05, 20, 45, 70, or 95 in positions 8 and 9 of the Health Insurance Claim number. For inclusion in this cohort patients had a diagnosis code for NAFLD [the International Classification of Diseases, Ninth Revision (ICD-9) codes of 571.8 as NAFLD without mention of alcohol or 571.9 as unspecified chronic liver disease]. Further, patients had to have at least 12 months (or until death) of continuous enrollment in Medicare Part A and B. Patients were excluded if they had other chronic liver diseases without NAFLD [070 viral hepatitis; 155.0 and 155.2 HCC; 155.2 cholangiocarcinoma; 275.0 disorders or iron metabolism; 570 acute and subacute necrosis of liver; 571.0 alcoholic liver disease; 571.1 acute alcoholic hepatitis; 571.2 alcoholic cirrhosis of liver; 571.3 alcoholic liver damage, unspecified; 571.4 chronic hepatitis (including 571.42 autoimmune hepatitis); 571.6 biliary cirrhosis; 573.3 toxic hepatitis; 573.8 hepatoptosis], cancer codes 140 to 209, human immunodeficiency virus infection code 042, or renal disorders (582 chronic glomerulonephritis code; 585 chronic kidney disease; 586 renal failure; V42.0 kidney transplant; V45.1 renal dialysis; V56 encounter for dialysis and dialysis catheter care); or incurred a negative charge. For more details on inpatient inclusion see Figure 1 and for outpatient see Figure 2. ICD-9 code for health conditions were considered to be always present if they were coded at least once.

Outcomes

The resource utilization parameters included total charges and total provider payments. The total provider payments were calculated as the sum of Medicare reimbursement amount plus the primary insurance payment plus the beneficiary-paid amounts (copay and deductibles). For the time-varying variables, a unique variable was created for each healthcare utilization episode during 2010. For example, total health care charges vary by claim, so we created a variable for each beneficiary representing annual total health care charges for each claim: further, an average annual charge was calculated by dividing annual total charges by annual total health care visits.

Variables

The following variables were available: The following 7 diagnoses were also considered covariates and were identified using any of the up to 10 listed ICD codes: (1) hepatic cirrhosis was identified by ICD-9 code 571.5 as hepatic cirrhosis without mention of alcohol; (2) decompensated cirrhosis (DCC) codes 789.5 as ascites, 567.23 as spontaneous bacterial peritonitis, 456.0 as esophageal varices with bleeding, 456.2 as esophageal varices in disease classified elsewhere, code underlying cause are cirrhosis of liver and portal hypertension, and 572.2 as hepatic encephalopathy; (3) cardiovascular disease (CVD) codes 410, 412 as myocardial infarction, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428 as congestive heart failure, 093.0, 437.3, 440, 441, 443.1-443.9, 447.1, 557.1, 557.9, 43.4 as peripheral vascular disease, 362.34, 430-438 as cerebrovascular disease; (4) diabetes code 250; (5) hypertension codes 401-405; (6) Hyperlipidemia codes 272.0-272.2, and 272.4; and (7) obesity codes 278.00, 278.01, V85.3, V85.4.

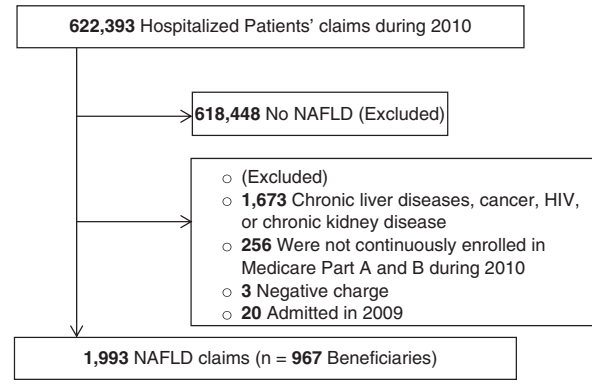

FIGURE 1. Flow chart of study cohort selection, inpatient Medicare, 2010. HIV indicates human immunodeficiency virus; NAFLD, nonalcoholic fatty liver disease.

Statistical Analysis

Study characteristics are presented with interquartile ranges (IQRs) for continuous variables or proportions for categorical variables. Descriptive characteristics were compared between NAFLD with compensated cirrhosis (CC) and DCC by t test for numerical variables and χ^2 tests for categorical variables. Log-linked γ-generalized regression was used to generate β coefficients with P-values for each highly skewed outcome variables. To separately describe the amount of increases and decreases in annual total charges/payments associated with a unit change in the explanatory variable for inpatient care cohort and in outpatient care cohort, exponentiated coefficients were reported as percentages. In the inpatient cohort, we analyzed the causes of hospitalizations among patients with NAFLD, according to the presence or absence of cirrhosis. In order to minimize a misclassification bias, we further narrowed the inpatient population to patients with NAFLD, where NAFLD was primary, secondary or tertiary diagnosis, and analyzed the leading causes of hospitalization again. Finally, using the primary ICD-9 diagnosis code, we selected the following conditions: NAFLD, nonalcoholic hepatic cirrhosis, hepatic encephalopathy, portal hypertension, esophageal varices with/without bleeding, ascites, and spontaneous bacterial peritonitis as NAFLD-related inpatient/outpatient utilization. Data analyses were conducted for a beneficiary level not a claim level. SAS

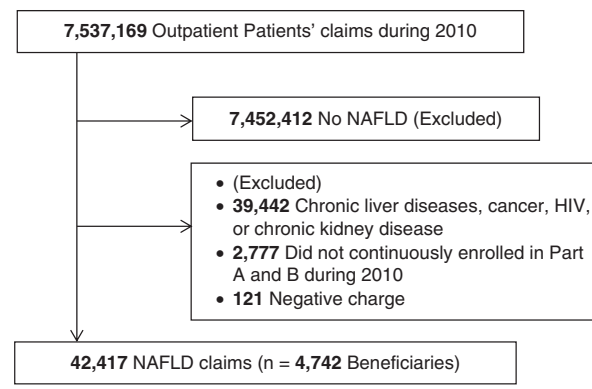

FIGURE 2. Flow chart of study cohort selection, outpatient Medicare, 2010. HIV indicates human immunodeficiency virus; NAFLD, nonalcoholic fatty liver disease.

v.9.3 (SAS Institute Inc., Cary, NC) software was used for the statistical analysis. This study was approved by the Inova Institutional Review Board.

RESULTS

After applying strict inclusion and exclusion criteria, between January 1, 2010 and December 31, 2010, we were able to include 976 NAFLD patients who received care in the inpatient setting while 4742 NAFLD patients sought care in the outpatient setting (Figs. 1 and 2). Overall, approximately 87% were white, 36% were male, and nearly 30% had CVD or metabolic syndrome conditions (DM, hypertension, hyperlipidemia) (Table 1). Of the entire NAFLD cohort, about 12% had compensated or DCC.

Total Hospital Charges and Payments for the Inpatients With NAFLD

Among NAFLD inpatients, the median annual total hospital charges were $36,289 (IQR: $18,359-$71,225] (Table 1). As expected, total charges for the NAFLD patients without cirrhosis were significantly lower than those for NAFLD patients with cirrhosis ($33,863 vs. $61,151; $P < 0.001$). Furthermore, charges for the NAFLD patients with DCC were significantly higher than patients with CC ($66,554 vs. $34,860; $P = 0.019$) (Table 2). In multivariate adjusted analyses, inpatient mortality (258%, $P < 0.001$), presence of CC (90%, $P < 0.001$), and presence of CVD (51%, $P < 0.001$) were associated with increased inpatient total charges (Table 3).

Among inpatients with NAFLD, the median annual total payment was $11,043 (IQR: $6,103-$21,345). Again, for NAFLD patients without cirrhosis, total payment was

TABLE 1. Characteristics of Study by Cirrhosis Status, Inpatient and Outpatient Medicare, 2010

	Total (Overall NAFLD)	NAFLD Without Cirrhosis	NAFLD With Cirrhosis	*P*
Inpatient—annual hospital utilization per beneficiary	N = 967	N = 850	N = 117	
Total number of visits	1 (1-2)	1 (1-2)	2 (1-4)	< 0.0001
Total charge ($)	36,289 (18,359-71,225)	33,863 (17,619-65,238)	61,151 (29,706-124,133)	< 0.0001
Average charge ($)	23,836 (13,720-37,866)	23,449 (13,453-37,373)	25,656 (15,254-45,137)	0.0564
Total payment ($)	11,043 (6103-21,345)	10,146 (5712-19,139)	18,804 (11,576-35,430)	< 0.0001
Average payment ($)	6854 (4954-10,570)	6670 (4863-10,309)	8864 (6257-11,116)	< 0.0001
Age (y)				0.0547
< 65	382 (39.5)	347 (40.6)	35 (29.7)	
Male	349 (36.1)	317 (37.1)	34 (28.8)	0.0783
Race				0.2531
White	836 (86.2)	732 (85.8)	104 (88.9)	
Nonwhite	134 (13.9)	118 (14.2)	13 (11.1)	
Died (by December 2010)	40 (4.1)	17 (2.0)	23 (19.5)	< 0.0001
Died in hospital	11 (1.1)	3 (0.4)	8 (6.8)	< 0.0001
Comorbidity				
CVD	354 (36.4)	299 (35.0)	55 (46.6)	0.0141
Diabetes mellitus	414 (42.6)	341 (39.9)	73 (61.9)	< 0.0001
Hypertension	653 (67.2)	579 (67.8)	74 (62.7)	0.2700
Hyperlipidemia	383 (39.4)	350 (41.0)	33 (28.0)	0.0067
Obesity	261 (26.9)	236 (27.6)	25 (21.2)	0.1385
Outpatient—annual outpatient utilization per beneficiary	**N = 4742**	**N = 4432**	**N = 310**	
Total number of visits	6 (3-11)	6 (3-11)	9 (5-16)	< 0.0001
Total charge ($)	9011 (4030-18577)	8830 (3924-18220)	12049 (6479-23238)	< 0.0001
Average charge ($)	1376 (677-2653)	1377 (673-2670)	1353 (776-2407)	0.7259
Total payment ($)	1777 (785-4043)	1734 (761-3946)	2586 (1278.16-5301)	< 0.0001
Average payment ($)	267 (145-486)	266 (144-487)	274 (179-478)	0.1818
Age (y)				0.8804
< 65	1638 (34.9)	1537 (34.7)	101 (32.6)	
Male	1750 (36.9)	1640 (37.0)	110 (35.5)	0.5919
Race				0.4014
White	4136 (87.4)	3871 (87.6)	265 (85.5)	
Nonwhite	595 (12.6)	561 (12.4)	36 (14.5)	
Died (by December 2010)	71 (1.5)	50 (1.1)	21 (6.8)	< 0.0001
Comorbidity				
CVD	1389 (29.3)	1285 (29.0)	104 (33.5)	0.0885
Diabetes mellitus	1660 (35.0)	1491 (33.6)	169 (54.5)	< 0.0001
Hypertension	2686 (56.6)	2501 (56.4)	185 (59.7)	0.2647
Hyperlipidemia	2092 (44.1)	1977 (44.6)	115 (37.1)	0.0100
Obesity	566 (11.9)	526 (11.9)	40 (12.9)	0.5869

Data were represented as median (interquartile range) for numerical variables and N (%) for categorical variables.
CVD indicates cardiovascular disease; NAFLD, nonalcoholic fatty liver disease.
P-values reported by *t* tests for numerical variables and χ^2 tests for categorical variables.

TABLE 2. Characteristics of Study by Cirrhosis Type, Inpatient and Outpatient Medicare, 2010

	NAFLD With Compensated Cirrhosis	NAFLD With Decompensated Cirrhosis (N = 95)	*P*
Inpatient—annual hospital utilization per beneficiary,	N = 22	N = 95	
Total number of visits	2 (1-3)	2 (2-4)	0.0752
Total charge ($)	34,860 (15,145-80,873)	66,554 (37,216-12,7892)	0.0199
Average charge ($)	17,011 (11,342-34,448)	28,274 (17,008-46,832)	0.0509
Total payment ($)	11,699 (7167-25,928)	19,767 (12,713-37,787)	0.0189
Average payment ($)	7226 (5788-10,355)	9233 (6446.05-11,442)	0.0861
Age (y)			
< 65	9 (40.9)	26 (27.4)	0.2113
Male	5 (22.7)	29 (30.5)	0.4678
Race			
White	22 (100.0)	81 (86.2)	0.0642
Nonwhite	0 (0.0)	13 (13.8)	0.0642
Died (by December 2010)	2 (9.1)	21 (21.9)	0.1722
Died in hospital	0 (0.0)	8 (8.3)	0.1608
Comorbidity			
CVD	8 (36.4)	47 (49.0)	0.2855
Diabetes mellitus	11 (50.0)	62 (64.6)	0.2040
Hypertension	13 (59.1)	61 (63.5)	0.6970
Hyperlipidemia	6 (27.3)	27 (28.1)	0.9360
Obesity	4 (18.2)	21 (21.9)	0.7022
Outpatient—annual outpatient utilization per beneficiary	**N = 181**	**N = 129**	
Total number of visits	9 (5-15)	9 (5-16)	0.6119
Total charge ($)	10,379 (5394-21,362)	15,187 (7457-24,283)	0.0431
Average charge ($)	1258 (729-2321)	1474 (997.81-2579.85)	0.0366
Total payment ($)	2389 (1067-5117)	2701 (1401-5454)	0.3403
Average payment ($)	261 (165-481)	300 (197-458)	0.2186
Age (y)			
< 65	60 (33.1)	43 (33.3)	0.9729
Male	62 (34.3)	48 (37.2)	0.5919
Race			
White	153 (84.5)	112 (86.8)	0.5724
Nonwhite	28 (15.5)	17 (13.2)	0.5724
Died (by December 2010)	3 (1.7)	18 (14.0)	< 0.0001
Comorbidity			
CVD	59 (32.6)	45 (34.9)	0.6742
Diabetes mellitus	107 (59.1)	62 (48.1)	0.0540
Hypertension	118 (65.2)	67 (51.9)	0.0190
Hyperlipidemia	76 (42.0)	39 (30.2)	0.0347
Obesity	22 (12.2)	18 (14.0)	0.6414

Data were represented as median (interquartile range) for numerical variables and N (%) for categorical variables.
CVD indicates cardiovascular disease; NAFLD, nonalcoholic fatty liver disease.
P-values reported by t tests for numerical variables and chi-square tests for categorical variables.

significantly lower compared with patients with advanced disease ($10,146 vs. $18,804, $P < 0.001$) (Table 1). Furthermore, NAFLD patients with DC had approximately $8000 higher annual total hospital payment than NAFLD with CC ($19,767 vs. $11,699, $P = 0.018$) (Table 2). In multivariate analyses, inpatient mortality (148%, $P < 0.001$), presence of DC (89%, $P < 0.001$), and presence of CVD (53%, $P < 0.001$) were again associated with increased total inpatient payment (Table 3).

Total Hospital Charges and Payments for the Outpatients With NAFLD

The median annual total outpatient care charge was $9,011 ($4,030-$18,577) for patients with NAFLD for a total of 6 outpatient visits (range: 3 to 11) (Table 1). Compared with NAFLD patients with cirrhosis, NAFLD patients without cirrhosis had significantly lower outpatient charges ($8,830 vs. $12,049, $P < 0.001$). Similar to the inpatient setting, total charges increased in the outpatient setting in parallel to the severity of the liver disease. Patients with DCC had approximately a $5,000 higher charges than patients with CC ($15,187 vs. $10,379, $P = 0.043$) (Table 2). In multivariate adjusted analyses, presence of CVD (66%), hypertension (61%), and obesity (53%, all $P < 0.001$) were associated with increased outpatient charges (Table 3).

Among NAFLD patients, the median total annual outpatient care payment was $1,777 ($785-$4,043) (Table 1). Again, NAFLD patients without cirrhosis had significantly lower payments than NAFLD patients with cirrhosis ($1,734 vs. $2,586, $P < 0.001$). Although NAFLD patients with DCC had higher payments than patients with CC, it was not statistically significant ($2,701 vs. $2,389, $P = 0.34$) (Table 2). Similar to outpatient charges, presence

TABLE 3. Multivariate Adjusted Associations of Hospital Utilization With Covariates Among Medicare Beneficiaries With NAFLD, Inpatient and Outpatient Medicare, 2010

	Percentage Change (*P*)			
	Inpatient Care		Outpatient Care	
Covariates	**Total Charge**	**Total Payment**	**Total Charge**	**Total Payment**
Age (y)				
< 65	Reference	Reference	Reference	Reference
65 +	−21.229 (0.001)	−27.363 (< 0.001)	−25.625 (< 0.001)	−33.860 (< 0.001)
Male	17.015 (0.016)	24.862 (< 0.001)	−8.118 (0.004)	NS
Race				
White	Reference	Reference	Reference	Reference
Nonwhite	29.214 (0.006)	NS	−15.994 (< 0.001)	−18.524 (< 0.001)
Died (by December 2010)	NS	NS	NS	30.412 (0.023)
Died in hospital	258.426 (< 0.001)	148.178 (< 0.001)	—	—
Comorbidity				
CVD	50.659 (< 0.001)	52.637 (< 0.001)	65.645 (< 0.001)	61.972 (< 0.001)
Diabetes mellitus	NS	NS	12.229 (< 0.001)	14.486 (< 0.001)
Hypertension	NS	NS	61.424 (< 0.001)	61.476 (< 0.001)
Hyperlipidemia	29.106 (< 0.001)	13.024 (0.028)	NS	10.911 (< 0.001)
Obesity	18.664 (0.017)	NS	53.317 (< 0.001)	52.436 (< 0.001)
Hepatic cirrhosis	NS	NS	NS	24.306 (< 0.001)
Decompensated cirrhosis	90.927 (< 0.001)	88.893 (< 0.001)	34.918 (< 0.001)	NS

NS indicates not significant ($P < 0.05$).
CVD indicates cardiovascular disease; NAFLD, nonalcoholic fatty liver disease.

of CVD (62%), hypertension (61%), and obesity (52%, all $P < 0.001$) were associated with increased outpatient payments in NAFLD patients with Medicare (Table 3).

NAFLD-related Total Hospital Charges and Payments

In order to assess the NAFLD-related resource utilization more clearly, we selected inpatients and outpatients where NAFLD and related diseases (cryptogenic cirrhosis, etc.) were the primary diagnosis. In addition, in order to exclude the impact on an expensive confounder, we excluded patients with CVD (Table 4). As expected, the number of patients in each group was smaller than the original analysis. Compared with the total cohort, total cumulative charges ($74,276 vs. $36,289) and payments ($20,450 vs. $11,043) almost doubled in this NAFLD-related analysis in the inpatient setting. In contrast, total cumulative charges ($6390 vs. $9011) and payments ($1400 vs. $1777) were found to be slightly lower in the NAFLD-related analysis as compared with total cohort in the outpatient setting.

Causes of Hospitalizations Among the Inpatients With NAFLD

We also analyzed the leading causes of hospitalizations among total inpatient cohort. In patients with the diagnosis of cirrhosis, hepatic encephalopathy (16%) was the most common diagnosis, followed by the diagnosis of "cryptogenic cirrhosis" and the diagnostic code for "NAFLD." In the cohort without diagnosis of cirrhosis, the most common diagnoses leading to hospitalization were acute pancreatitis, morbid obesity, and pneumonia.

In order to assess NAFLD-related hospitalizations more clearly, we reanalyzed the data for inpatients where NAFLD was the primary, secondary or tertiary diagnoses. This reanalysis showed that in those who were admitted with diagnosis of cirrhosis, NAFLD (16%) and hepatic encephalopathy (14%) were the most common diagnoses,

TABLE 4. Charges and Payments of Inpatients and Outpatients With NAFLD, Where NAFLD and Related Diseases (Cryptogenic Cirrhosis, etc.) are the Primary Diagnosis in the Absence of CVD

	Inpatient		Outpatient	
	Primary D×NAFLD—Without CVD (N = 30) (3.1%)	**Total Cohort (N = 967)**	**Primary D×NAFLD—Without CVD (N = 1013) (21%)**	**Total Cohort (N = 4742)**
Total number of visits	3 (2-4)	1 (1-2)	6 (4-11)	6 (3-11)
Total cumulative charge ($)	74,276 (38,903-131,650)	36,289 (18,359-71,225)	6390 (2902-13,434)	9011 (4030-18,577)
Average charge per episode ($)	27,833 (18,352-34,191)	23,836 (13,720-37,866)	957 (530-1965)	1376 (677-2653)
Total cumulative payment ($)	20,450 (14,949-34,620)	11,043 (6103-21,345)	1400 (611-3183)	1777 (785-4043)
Average payment per episode ($)	9466 (6846-10,378)	6854 (4954-10,570)	203 (116-350)	267 (145-486)

CVD indicates cardiovascular disease; NAFLD, nonalcoholic fatty liver disease.

followed by chronic bronchitis. In contrast, in patients who were hospitalized without cirrhosis, acute pancreatitis remained the leading cause of hospitalization, followed by morbid obesity and acute bronchitis.

DISCUSSION

NAFLD is a growing health problem around the world, affecting patients and the society not only with its clinical consequences, but also with its economic burden. Although NAFLD impacts all age groups, the prevalence of NAFLD increases with age,[1–4] making it especially pertinent to the Medicare services in the United States.

Our study showed that Medicare patients with NAFLD posed substantial inpatient and outpatient health care utilization. As liver disease progressed to cirrhosis and its complications, the total charges and payments from Medicare in both the inpatient and outpatient setting increased. In fact, NAFLD with DCC was associated with higher costs, with 90% and 70% increases for total charge and payment in the inpatient setting, and 46% and 13% increases in the outpatient setting, when compared with noncirrhotic NAFLD patients. In addition to the actual cost per patient, the total number of patients with NAFLD in the United States can make these costs potentially enormous. It is estimated that about 25% of US population has NAFLD. Further, approximately 10% to 12% of these patients will transition to a more severe disease state, NASH, which can then progress to cirrhosis.

The findings of this study were in agreement with previous studies that reported the increased resource utilization among NAFLD patients.[18–20] In a recent study among outpatients with NAFLD who were Medicare beneficiaries, it was found that the annual average charge and payment significantly increased between 2005 and 2010. The outpatient charge increased nearly a thousand dollars, with an annual increase rate of 5%.[18] This is an important finding indicating not only an increasing prevalence of NAFLD but also an increase in the cost of each patient with NAFLD over the study time period. In another study, Baumeister et al[19] investigated the cost of presumed fatty liver in the inpatient and outpatient setting. They reported their findings according to liver hyperechogenicity on the ultrasound and ALT levels. The authors concluded that compared with those with normal liver echogenity and normal levels of ALT, presence of liver hyperechogenity with elevated ALT levels increased overall costs 32%, with a 15% increase in outpatient costs and a 38% in inpatient costs. In our study, in order to assess resource utilization caused by NAFLD more clearly, we reanalyzed the total cohort and selected inpatient and outpatient groups where NAFLD and other related diagnostic codes (NAFLD-related cirrhosis, hepatic encephalopathy, portal hypertension, etc.) were the primary diagnosis. From one of the subanalysis, we excluded an important confounder associated with NAFLD which could be driving the cost (CVD). These reanalyses showed that total charges and payments almost doubled for inpatients when NAFLD-related conditions were the primary diagnosis in comparison to the total cohort. On the contrary, in the outpatient setting, total charges and payments were slightly lower than the total NAFLD cohort. These data suggest that when NAFLD is the primary diagnosis in the inpatient setting, these patients have more severe disease accounting for the higher costs.

It is also important to remember that most patients with NAFLD are asymptomatic and undiagnosed. In this context, a large number of these patients may silently progress and then present with cirrhosis for liver transplantation or present with the diagnosis of advanced HCC.[12,21,22] Presence of cirrhosis is important because the median survival of CC is about 6.5 years, which falls to 2.5 years for those in the decompensated stage.[23,24] In our study, 22% of inpatient and 14% of outpatient NAFLD patients with DCC died during the study period of only 12 months, whereas these rates were 9% and 1.7% in patients with CC, respectively. This data reiterates the poor prognosis of NAFLD-related DCC. In addition to the high mortality, cirrhotic patients are known to have significant morbidities such as variceal bleeding, ascites and hepatic encephalopathy which could lead to not only increased resource utilization but also significant negative impact on patients' health-related quality of life.[25]

Our study also confirmed the strong association between NAFLD and the risk of CVD. Previous studies reported that the prevalence of coronary, cerebrovascular and peripheral vascular disease were remarkably higher among patients with NAFLD.[26–28] In our study, CVD was an important driver of resource utilization. In fact, in Medicare patients with NAFLD, presence of CVD was an independent predictor of charges and payments in both inpatient and outpatient settings, with $>50\%$ increase in inpatients charges and payments, and $>60\%$ in the outpatient setting. In addition to CVD, our study also confirmed the close association of NAFLD with metabolic syndrome components and obesity. In fact, among NAFLD patients with CC, $>65\%$ had hypertension and nearly 60% had diabetes. Similar to CVD, in multivariate analysis, presence of these comorbidities was found to increase inpatient and outpatient charges and payments in different rates. Obesity was another factor for increased resource utilization increasing total outpatient charges and payments by $>50\%$. In fact, as a future projection, Finkelstein et al[29] reported that obesity prevalence will be 42% in the year 2030 and if it remained at 2010 levels, nearly $440 billion in medical expenditures would be saved in the next 2 decades. These findings are in agreement with the study by Ghamar Chehreh et al, [30] showing the average treatment cost of NAFLD patients with obesity and hypertension was higher than for treatment of NAFLD patients without metabolic conditions.

There were some limitations to our study. First, because of lack of accessibility of recent data, we utilized inpatient and outpatient data for the year 2010 only. By limiting the study period to a year, we were unable to make estimations about the changing pattern of the economic burden of NAFLD, as noted in other publications.[18,31] Second, although charges and payments for procedures, imaging and other costs were included in the total amounts, we were unable to itemize individual amounts of these procedures among cirrhotic and noncirrhotic NAFLD patients. Also, as this was a retrospective study on Medicare database, we could not determine if patients utilized any type of healthcare plan other than Medicare, which may have changed our findings. Finally, we used ICD-9 coding and a very strict criteria to select our study cohort. Although this approach assured us that we have only patients with NAFLD, it certainly may have underestimated the number of NAFLD patients with Medicare.

In summary, NAFLD is associated with a significant economic burden to Medicare. Presence of DC due to

NAFLD is associated with more resource utilization compared with CC and noncirrhotic NAFLD patients. It can be suggested that as long as the prevalence of obesity and NAFLD continue to grow, this economic burden of NAFLD on Medicare expenditures will continue to rise.

ACKNOWLEDGMENTS

The authors would like to thank Deena Hallaji, Manirath Srishord, and Brian Lam for their great support during the study process.

REFERENCES

1. Mishra A, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. *J Clin Exp Hepatol*. 2012;2:135–144.
2. Ahmed A, Wong RJ, Harrison SA. Nonalcoholic fatty liver disease review: diagnosis, treatment, and outcomes. *Clin Gastroenterol Hepatol*. 2015;13:2062–2070.
3. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA*. 2015;313:2263–2273.
4. Younossi ZM, Henry L. Economic and quality-of-life implications of non-alcoholic fatty liver disease. *Pharmacoeconomics*. 2015;33:1245–1253.
5. Milic S, Lulic D, Stimac D. Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations. *World J Gastroenterol*. 2014;20:9330–9337.
6. Weiss J, Rau M, Geier A. Non-alcoholic fatty liver disease: epidemiology, clinical course, investigation, and treatment. *Dtsch Arztebl Int*. 2014;111:447–452.
7. Golabi P, Sayiner M, Fazel Y, et al. Current complications and challenges in nonalcoholic steatohepatitis screening and diagnosis. *Expert Rev Gastroenterol Hepatol*. 2016;10:63–71.
8. Birerdinc A, Younossi Z. Can NASH lipidome provide insight into the pathogenesis of obesity-related non-alcoholic fatty liver disease? *J Hepatol*. 2015;62:761–762.
9. Otgonsuren M, Estep MJ, Hossain N, et al. Single non-invasive model to diagnose non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). *J Gastroenterol Hepatol*. 2014;29:2006–2013.
10. Stepanova M, Rafiq N, Makhlouf H, et al. Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). *Dig Dis Sci*. 2013;58:3017–3023.
11. Kelley CE, Brown AJ, Diehl AM, et al. Review of nonalcoholic fatty liver disease in women with polycystic ovary syndrome. *World J Gastroenterol*. 2014;20:14172–14184.
12. Michelotti GA, Machado MV, Diehl AM. NAFLD, NASH and liver cancer. *Nat Rev Gastroenterol Hepatol*. 2013;10:656–665.
13. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148:547–555.
14. Ward BW, Schiller JS, Goodman RA. Multiple chronic conditions among US adults: a 2012 update. *Prev Chronic Dis*. 2014;11:E62.
15. Hernandez C, Jansa M, Vidal M, et al. The burden of chronic disorders on hospital admissions prompts the need for new modalities of care: a cross-sectional analysis in a tertiary hospital. *QJM*. 2009;102:193–202.
16. Centers for Disease Control (CDC). The cost of chronic diseases and health risk behaviours. Chronic Disease Overview, 2014. Available at: www.cdc.gov/chronicdisease/overview/index.htm. Accessed May 27, 2016.
17. Finkelstein EA, Trogdon JG, Cohen JW, et al. Annual medical spending attributable to obesity: payer-and service-specific estimates. *Health Aff (Millwood)*. 2009;28:w822–w831.
18. Younossi ZM, Zheng L, Stepanova M, et al. Trends in outpatient resource utilizations and outcomes for Medicare beneficiaries with nonalcoholic fatty liver disease. *J Clin Gastroenterol*. 2015;49:222–227.
19. Baumeister SE, Volzke H, Marschall P, et al. Impact of fatty liver disease on health care utilization and costs in a general population: a 5-year observation. *Gastroenterology*. 2008;134:85–94.
20. Davis GL, Roberts WL. The healthcare burden imposed by liver disease in aging Baby Boomers. *Curr Gastroenterol Rep*. 2010;12:1–6.
21. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology*. 2011;140:124–131.
22. Bambha K, Belt P, Abraham M, et al. Ethnicity and nonalcoholic fatty liver disease. *Hepatology*. 2012;55:769–780.
23. Zipprich A, Garcia-Tsao G, Rogowski S, et al. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. *Liver Int*. 2012;32:1407–1414.
24. Poordad FF. Presentation and complications associated with cirrhosis of the liver. *Curr Med Res Opin*. 2015;31:925–937.
25. Berzigotti A, Seijo S, Reverter E, et al. Assessing portal hypertension in liver diseases. *Expert Rev Gastroenterol Hepatol*. 2013;7:141–155.
26. Paredes AH, Torres DM, Harrison SA. Nonalcoholic fatty liver disease. *Clin Liver Dis*. 2012;16:397–419.
27. Corrado RL, Torres DM, Harrison SA. Review of treatment options for nonalcoholic fatty liver disease. *Med Clin North Am*. 2014;98:55–72.
28. Younossi ZM, Otgonsuren M, Venkatesan C, et al. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. *Metabolism*. 2013;62:352–360.
29. Finkelstein EA, Khavjou OA, Thompson H, et al. Obesity and severe obesity forecasts through 2030. *Am J Prev Med*. 2012;42:563–570.
30. Ghamar Chehreh ME, Vahedi M, Pourhoseingholi MA, et al. Estimation of diagnosis and treatment costs of non-alcoholic fatty liver disease: a two-year observation. *Hepat Mon*. 2013;13:e7382.
31. Younossi ZM, Zheng L, Stepanova M, et al. Clinical outcomes and resource utilisation in Medicare patients with chronic liver disease: a historical cohort study. *BMJ Open*. 2014;4:e004318.