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Impact of Disease Severity on Healthcare Costs in Patients With Chronic Hepatitis C (CHC) Virus Infection

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Hepatitis C virus (HCV) infection increases total healthcare costs but the effect of the severity of liver disease associated with chronic hepatitis C (CHC) on healthcare costs has not been well studied. We analyzed the demographics, healthcare utilization, and healthcare costs of CHC patients in a large U.S. private insurance database (January, 2002 to August, 2010), with at least 1 year of baseline enrollment and 30 days of continuous follow-up. Patients were stratified by liver disease severity: noncirrhotic liver disease (NCD), compensated cirrhosis (CC), and endstage liver disease (ESLD), as defined by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) codes. Mean all-cause and HCV-related healthcare costs per-patient-per-month (PPPM) during follow-up (mean 634 days) are reported in 2010 U.S.$ from the payer's perspective. A total of 53,796 patients with CHC were included (NCD: 41,858 [78%]; CC: 3,718 [7%]; and ESLD: 8,220 [15%]). Mean all-cause PPPM healthcare costs were 32% and 247% higher for patients with CC and ESLD compared to those with NCD ($1,870 and $4,931 versus $1,420; $P < 0.001$) and were independent of age or comorbid conditions. Pharmacy, ambulatory, and inpatient care collectively accounted for 90% of NCD costs and 93% of CC and ESLD costs. The largest cost components were inpatient costs for those with ESLD (56%) and ambulatory costs for those with CC and NCD (37% and 36%, respectively). Overall, 56% of costs were HCV-related and this proportion increased with severity (46%, 57%, and 71% for patients with NCD, CC, and ESLD, respectively). *Conclusion*: The direct healthcare costs associated with CHC are high, increase in association with the progression of liver disease, and are highest in those with ESLD. (HEPATOLOGY 2012;56:1651-1660)

Approximately 1.8% of the U.S. population (3.9 million people) are infected with hepatitis C virus (HCV),[1] of whom ~70% are unaware that they are infected.[2] There is a large cohort of aging patients who were infected between 1960 and 1980,[3] with a resultant increase in the current number of patients with compensated cirrhosis (CC) and, subsequently, endstage liver disease (ESLD). Between 1996 and 2006 the proportion of patients with HCV-related cirrhosis increased from 9% to 19%, and the prevalence of decompensated cirrhosis increased from 5% to 11%.[4] The prevalence of hepatocellular carcinoma (HCC) and HCV-related mortality has also increased considerably.[4,5] Chronic HCV infection is the leading indication for liver transplantation in the U.S., and the disease is estimated to cause ~5,000 to 10,000 deaths each year.[6,7] Between 1999 and 2007 HCV-associated mortality increased significantly and, in 2007, the number of HCV-related deaths surpassed the number of HIV-related deaths for the first time.[8]

Progression of liver fibrosis does not occur at a constant rate.[9] Rather, disease progression is highly variable and is accelerated by, among other factors, alcohol consumption, obesity, and metabolic syndrome. Current treatment guidelines suggest clinicians consider withholding treatment in patients with mild fibrosis

Abbreviations: CC, compensated cirrhosis; CHC, chronic hepatitis C; ESLD, endstage liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NCD, noncirrhotic liver disease; OLT, orthotopic liver transplantation; PPPM, per-patient-per-month.

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Table 1. HCV Diagnostic Codes Used to Identify Patients With Chronic HCV Infection

ICD-9-CM Code	Description	Inclusion Criteria* (1 of the Following)
	1. Chronic HCV diagnosis codes	A single claim with one of
070.44	Chronic hepatitis C with hepatic coma	these diagnosis codes
070.54	Chronic hepatitis C without mention of hepatic coma	OR
	2. Unspecified HCV diagnosis codes	2 claims with one of these
V02.62	Hepatitis C carrier	diagnosis codes on separate
070.70	Unspecified viral hepatitis C without hepatic coma	dates of service
070.71	Unspecified viral hepatitis C with hepatic coma	OR
	3. Acute and unspecified HCV diagnosis codes	2 claims with one of these diagnosis
070.41	Acute hepatitis C with hepatic coma	codes spaced at least 6 months apart
070.51	Acute hepatitis C without mention of hepatic coma	
070.62	Hepatitis C carrier	
070.70	Unspecified viral hepatitis C without hepatic coma	
070.71	Unspecified viral hepatitis C with hepatic coma	

ICD-9-CM = International Classification of Diseases, 9th Edition, Clinical Modification.
*During the patient identification period: 1 January 2003 to 31 August 2010.

because of the low likelihood of disease progression and complications, and because of the high cost of treatment.[10] However, once advanced fibrosis develops, the rate of liver-related disease progression is high: it is estimated that, each year, 10% of patients with bridging fibrosis progress to cirrhosis, and 5% of patients with cirrhosis die or undergo liver transplantation.[11]

Treatment of chronic hepatitis C (CHC) is associated with significant costs and delaying or forgoing treatment incurs additional costs associated with caring for patients with advanced HCV-related liver disease. HCV infection increases healthcare costs overall,[9,12,13] and treatment of HCC and liver transplantation are undoubtedly associated with very high healthcare costs,[14] but the specific impact of the progression of liver disease on healthcare costs has not been well studied. The purpose of this study was to analyze the demographic characteristics, healthcare utilization, and healthcare costs of patients with HCV in a large U.S. private insurance database as stratified by liver disease severity: noncirrhotic liver disease (NCD), compensated cirrhosis (CC), and ESLD.

Methods

Medical and pharmacy claims data, enrollment information, and linked laboratory results and mortality information from commercial health plan enrollees for the period January 1, 2002 to August 31, 2010 were analyzed.

Patients. Patients eligible for this analysis were commercial health plan members with both pharmacy and medical benefits who had evidence of chronic HCV infection during the patient identification period (January 1, 2003 to August 31, 2010). Specifically, to be included in the analysis patients were required to have an HCV diagnosis code based on the presence of International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM) codes during the patient identification period and at least one nondiagnostic code for HCV during the study period (in order to exclude patients who only had rule-out codes for HCV). Further, in order to limit the study population to include patients with chronic HCV infection and to exclude patients with acute HCV infection, patients had to meet one of three different criteria that were highly supportive of the diagnosis of chronic HCV infection (Table 1).

All patients were assigned to one of three liver disease severity cohorts on the basis of diagnosis or procedure codes (Table 2). Patients with ESLD were subdivided into those with and without HCC and with and without liver transplantation (Supporting Table S1). A consensus panel of three clinical hepatologists (S.G., P.P., and N.T.) defined the ICD-9 codes used to assign patients to the three disease severity strata and substrata. Patients were assigned to the highest severity category for which they had a qualifying code.

The index date for patients with NCD was the date on which the first claim with an HCV diagnostic code occurred during the patient identification period, after a minimum of 1 year of continuous enrollment.

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Additional Supporting Information may be found in the online version of this article.

Table 2. Criteria for Assignment to Liver Disease Severity Cohorts

Disease Severity Cohort	Conditions or Procedures*
Noncirrhotic disease (NCD)	No listed conditions or procedures
Compensated cirrhosis (CC)	Cirrhosis
	Liver transplant
	Hepatocellular carcinoma
	Liver failure, including hepatorenal syndrome
	Hepatic encephalopathy
	Portal hypertension
	Esophageal varices
Endstage liver disease (ESLD)	Other gastrointestinal hemorrhage
	Ascites
	Other sequelae of chronic liver disease
	Abdominal paracentesis procedures
	Shunts and catheter procedures
	Treatment of varices
	Portal decompression procedures

*Assignment to a liver disease severity cohort was based on diagnosis or procedure codes. Patients were assigned to the highest level severity category for which they had a qualifying condition or procedure.

The index date for patients with CC or ESLD was the date of the first claim for a condition or service in their assigned severity level. Patients with CC or ESLD who had a claim for a condition or service in their severity level during the year prior to their index date were excluded. This limited the analysis to individuals who were just entering that severity category.

Patients with more severe disease may have had a shorter enrollment period following the index date because of death or disability-related health plan changes, which could have biased the results by limiting the analysis to less severe patients if all patients were required to have the same amount of follow-up enrollment. To minimize the risk of this potential bias, patients were allowed to have variable durations of follow-up. Patients were observed for a 1-year fixed period prior to the index date (baseline period), and for a minimum of 30 days after the index date (follow-up period) until disenrollment, death, or the end of the study period (August 31, 2010).

Claims Data. The analysis used a deidentified commercial healthcare claims database, including electronic pharmacy and medical claims and enrollment data, from U.S. managed care providers affiliated with OptumInsight (Optum). The constituent health plans were primarily fee-for-service independent practice association model plans.

The database included claims for all prescription medications and all medical services that were submitted to the health plans for payment. Medical claims and encounter data were collected from all available healthcare sites (physician's office, emergency room, hospital inpatient and outpatient, etc.) for all types of services, including specialty, preventive, and office-based.

Medical claims included ICD-9-CM diagnosis codes, ICD-9-CM procedure codes, Current Procedure Terminology (CPT), the Healthcare Common Procedure Coding System (HCPCS), site of service codes, provider specialty codes, revenue codes (for facilities), and paid amounts.

Claims analyses were based upon amounts paid by the health plans, rather than billed or standardized costs, as well as patient responsibility amounts; costs paid by other health plans and Medicare were not included. Cost and healthcare utilization were considered HCV-related if any HCV-related ICD-9-CM codes or CPT codes (i.e., codes indicating HCV, liver disease, or HCV treatment) occurred in a primary or secondary position in a claim. The costs of evaluation of patients for orthotopic liver transplantation (OLT) and of OLT were included provided that claims for procedures contained HCV-related codes.

Pharmacy claims were submitted electronically by pharmacies at the time of dispensing. The pharmacy claims history comprised the outpatient prescription drug profile and included drug name, dosage form, strength, date of fill, number of days supplied, financial information, and deidentified patient and prescriber codes, which allowed for longitudinal tracking of medication refills and changes in medications. HCV-related pharmacy claims included the costs of antiviral therapy (pegylated or consensus interferon and ribavirin) and the costs of drugs used to treat side effects of antiviral therapy (the consensus panel of three clinical hepatologists defined and agreed upon the medications that were considered to be HCV-related). Mortality data were obtained from Social Security Administration (SSA) death tapes which, with a proper linkage, allowed for the establishment of the date of death, but not the cause of death.

Statistical Analysis. The analyses were conducted from a health plan perspective. Healthcare utilization and costs were compared for patients with ESLD versus patients with NCD, and for patients with CC versus patients with NCD. Costs and healthcare utilization were analyzed using multivariate models with liver disease severity as the primary predictor of interest in two ways: one unadjusted statistical model and one adjusted model with demographic, comorbidity, and treatment variables as covariates. Because of the small number of patients aged 0-17 with chronic HCV ($n = 234$), patients <18 years of age were excluded from the sample used for multivariate analysis.

Cost and utilization outcomes were analyzed using generalized linear models with a gamma distribution (gamma regression) and log link. Utilization outcomes

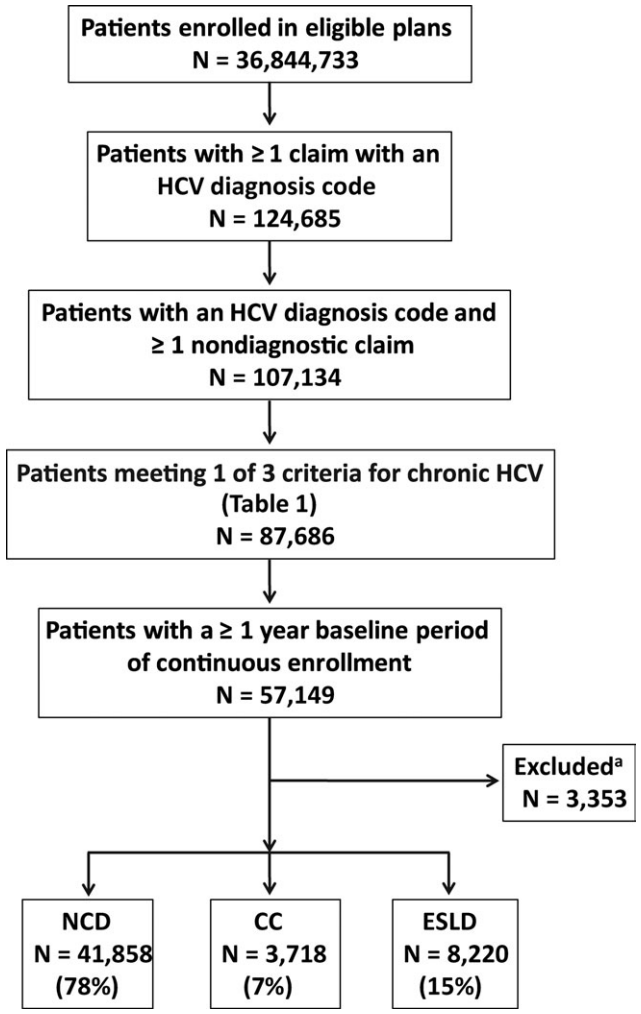

Fig. 1. Identification of the study population with eligible claims during the study period (1 January 2002 to 31 August 2010). [a]Reasons for exclusion included: >1 death date in SSA death tapes (n = 4); evidence of death prior to the index date (n = 171); patients with <30 days of continuous enrollment during the follow-up period and without evidence of death in the first 30 days following the index date (n = 388); patients with claims ≥90 days following the first instance of death (n = 356); patients with baseline evidence of the same or higher level of liver disease severity than their assigned severity level (n = 2,434).

with a small number of zero counts were modeled using a one-part model. Utilization outcomes with a large number of zero counts were modeled using two-part models, specifically, a logit model to estimate the probability of having any visit, and a gamma regression model with a log link was used to estimate the number of visits among those individuals with at least one visit. The predicted number of visits for all patients in the sample was estimated by multiplying the predicted probability of having any visit by the predicted number of visits among those with at least one visit.[15] Using the parameter estimates from the multivariate models, predicted costs and utilization counts for each severity level were estimated using recycled predictions.[16]

The following covariates were evaluated in the adjusted cost and utilization models as potential confounders: age, gender, geographic region/division, index year, Charlson comorbidity score, other HCV-related comorbidities, baseline healthcare utilization, baseline medications, and baseline HCV antiviral treatments. All cost and utilization models were analyzed using Stata 10.1 (StataCorp, College Station, TX).

Mean all-cause and HCV-related healthcare costs were expressed on a per-patient-per-month (PPPM) basis. Costs were adjusted to 2010 U.S.$ using the annual medical care component of the consumer price index to account for inflation between 2001 and 2010.

Results

A total of 53,796 patients with chronic HCV infection met all inclusion criteria: 41,858 (78%) with NCD, 3,718 (7%) with CC, and 8,220 (15%) with ESLD (Fig. 1).

Overall, the mean age of patients was 49.6 years, 61.6% were male, and the mean duration of follow-up was 633.7 days (Table 3). Statistically significant differences were detected between patients with NCD and CC and between patients with NCD and ESLD for the mean age and age distribution, the proportion of male patients, the mean Charlson comorbidity score and distribution of Charlson comorbidity scores, and the mean duration of follow-up (all $P < 0.001$, Table 3). Among patients with ESLD, 1,086 (13%) had HCC (486 of whom had portal hypertension [PHTN]), and 574 (7%) had a history of liver transplantation.

The death rate was significantly higher among patients with ESLD than among patients with NCD (600.8/10,000 versus 58.9/10,000; rate ratio 10.19; 95% confidence interval [CI] 9.07-11.46, $P < 0.001$). In contrast, the death rate in patients with CC was not significantly different from patients with NCD (69.8/10,000 versus 58.9/10,000, rate ratio 1.18; 95% CI 0.85-1.61, $P = 0.277$). The mean time from index date to death was significantly shorter in patients with ESLD than in NCD (1.16 versus 1.35 years, $P = 0.014$), but was not statistically different between patients with CC and NCD (1.69 versus 1.35 years, $P = 0.101$).

Healthcare Costs (Statistical Model Without Demographics, Comorbidities, Healthcare Utilization, or Treatment Covariates). Mean (±SD) PPPM all-cause healthcare costs during the follow-up period were $1,987 ± $6,460 overall in patients with HCV infection with statistically significant differences by liver

Table 3. Patient Demographics, Duration of Follow-up, and Charlson Comorbidity Score by Disease Severity

		Total N=53,796	NCD N=41,858	CC N=3,718	ESLD N=8,220	CC vs. NCD *P*-value	ESLD vs. NCD *P*-value
Mean age ± SD		49.6 ± 9.3	48.9 ± 9.4	51.0 ± 8.3	52.1 ± 8.9	$P < 0.001$	$P < 0.001$
Age category, N (%)	<18	234 (0.4)	212 (0.5)	11 (0.3)	11 (0.1)		
	18-34	3,177 (5.9)	2,800 (6.7)	135 (3.6)	242 (2.9)		
	35-44	8,955 (16.7)	7,511 (17.9)	462 (12.4)	982 (12.0)	$P < 0.001$	$P < 0.001$
	45-54	26,404 (49.1)	20,560 (49.1)	1,918 (51.6)	3,926 (47.8)		
	55-64	13,339 (24.8)	9,709 (23.2)	1,076 (28.9)	2,554 (31.1)		
	≥65	1,687 (3.1)	1,066 (2.6)	116 (3.1)	505 (6.1)		
Gender, N (%)	Male	33,124 (61.6)	25,283 (60.4)	2,399 (64.5)	5,442 (66.2)	$P < 0.001$	$P < 0.001$
	Female	20,672 (38.4)	16,575 (39.6)	1,319 (35.5)	2,778 (33.8)		
Mean follow-up, days ± SD		633.7 ± 582.6	622.9 ± 582.1	646.7 ± 559.2	683.0 ± 593.0	$P = 0.013$	$P < 0.001$
Mean Charlson comorbidity score ± SD		1.24 ± 1.10	1.10 ± 1.52	1.59 ± 1.53	1.81 ± 1.99	$P < 0.001$	$P < 0.001$
Charlson comorbidity score	0	19,038 (35.4)	16,738 (40.0)	515 (13.9)	1,785 (21.7)		
category, N (%)	1	20,943 (38.9)	15,955 (38.1)	1,905 (51.2)	3,083 (37.5)		
	2	7,147 (13.3)	4,932 (11.8)	727 (19.6)	1,488 (18.1)	$P < 0.001$	$P < 0.001$
	3-5	4,437 (8.3)	2,695 (6.4)	425 (11.4)	1,317 (16.0)		
	≥6	2,231 (4.2)	1,538 (3.7)	146 (3.9)	547 (6.7)		

disease severity (Table 4). Mean PPPM all-cause healthcare costs were 32% and 247% higher for patients with CC and ESLD, respectively, compared to those with NCD ($1,870 ± $4,448 and $4,931 ± $11,911 versus $1,420 ± $4,689 PPPM; $P < 0.001$).

Similar statistically significant differences were observed for mean HCV-related healthcare costs during the follow-up period (Table 4). Mean PPPM HCV-related all-cause healthcare costs were $1,115 ± $5,083 overall, and among patients with NCD, CC, and ESLD they were $650 ± $2,714, $1,067 ± $2,941, and $3,505 ± $10,996, respectively ($P <$ 0.001 for CC versus NCD and for ESLD versus NCD). Overall, 56% of total costs were HCV-related and this proportion increased with disease severity (46%, 57%, and 71% for patients with NCD, CC, and ESLD, respectively).

A breakdown of total medical costs by disease severity showed that the largest cost components were inpatient costs for those with ESLD and ambulatory costs for those with CC and NCD (Table 4). Inpatient costs comprised 62% of all medical costs for patients with ESLD compared to 38% and 33% for patients with NCD and CC, respectively. All medical cost components were significantly higher for those with ESLD when compared to those with NCD, but only ambulatory costs were significantly higher for those with CC when compared to those with NCD (Table 4).

Among patients with ESLD the highest total mean healthcare costs were incurred by patients who underwent OLT ($12,087.12 versus $4,393.81 PPPM in patients who had not undergone OLT, $P < 0.001$; Supporting Table S2) and among those with HCC ($9,378.05 versus $4,254.07 PPPM in patients without ESLD, $P < 0.001$; Supporting Table S2). Both medical and pharmacy costs were significantly higher in patients with OLT and HCC compared with all other patients with ESLD. Patients with HCC and PHTN also had significantly higher total healthcare costs than those with HCC and without PHTN ($10,790.51 versus $8,233.95 PPPM, respectively, $P = 0.004$; Supporting Table S2). The significant difference in total medical costs in this subgroup was associated with significantly higher ambulatory medical costs, with no significant differences in all other cost components included in the analysis.

Healthcare Cost and Utilization Statistical Models Adjusted for Demographics, Comorbidities, Healthcare Utilization, and Treatment Covariates. After adjustment for demographic characteristics, comorbidities, baseline healthcare utilization, and treatments, there were statistically significant differences in incremental cost ratios for all-cause healthcare costs between liver disease severity groups (Table 5). Patients with CC and ESLD were estimated to have total healthcare costs that were 1.40-fold higher (cost ratio 1.40; 95% CI 1.31-1.49) and 3.33-fold higher (cost ratio 3.33; 95% CI 3.12-3.56), respectively, than those for patients with NCD. The estimated cost ratios were also significantly higher for both medical costs and pharmacy costs for patients with CC and ESLD when compared with patients with NCD (Table 5). Other factors that were found to be statistically significantly associated with healthcare costs in this model included age 18-34 years (cost ratio 1.40; 95% CI 1.16-1.69) and age >65 years (cost ratio 0.72; 95% CI 0.62-0.83) as compared with the reference category of 35-44 years, male gender (cost ratio 1.164 versus female gender; 95% CI 1.11-1.22), an index year of 2010 relative to 2003 (cost ratio 1.270; 95% CI 1.10-1.47), baseline Charlson comorbidity score (cost ratio 1.08; 95% CI 1.05-1.10), HIV coinfection (cost ratio 1.75;

Table 4. Mean Follow-up PPPM Costs (USD 2010) by Liver Disease Severity (*t*-test)

		Total N=53,796	NCD N=41,858	CC N=3,718	ESLD N=8,220	CC vs. NCD *P*-value	ESLD vs. NCD *P*-value
All-cause costs							
Total healthcare costs		1987.44 (6,459.84)	1,419.77 (4,689.36)	1,870.46 (4,448.25)	4,931.01 (11,911.22)	<0.001	<0.001
Medical costs	Total	1572.96 (6,331.99)	1,043.99 (4,538.99)	1,253.46 (4,246.60)	4,411.10 (11,824.50)	0.004	<0.001
	Inpatient	749.34 (5,020.60)	391.66 (3,005.17)	417.85 (3,509.02)	2,720.63 (10,432.26)	0.659	<0.001
	Ambulatory	647.97 (1,861.22)	509.75 (1,516.17)	698.61 (1,371.89)	1,328.93 (3,090.80)	<0.001	<0.001
	Emergency	24.26 (114.76)	19.05 (83.20)	20.38 (91.72)	52.52 (214.93)	0.394	<0.001
	Other	151.39 (2,506.35)	123.53 (2,476.15)	116.61 (1,255.81)	309.02 (3,024.58)	0.772	<0.001
Pharmacy costs	Total	414.48 (865.39)	375.78 (845.33)	617.01 (1,011.63)	519.93 (873.19)	<0.001	<0.001
HCV-related costs							
Total healthcare costs		1,115.37 (5,083.45)	650.31 (2,713.82)	1,067.47 (2,941.49)	3,505.20 (10,995.61)	<0.001	<0.001
Medical costs	Total	917.48 (5,052.51)	466.68 (2,647.95)	663.31 (2,814.75)	3,328.05 (10,996.25)	<0.001	<0.001
	Inpatient	665.06 (4,772.80)	312.85 (2,587.05)	334.09 (2,674.37)	2,608.33 (10,359.53)	0.642	<0.001
	Ambulatory	210.70 (809.87)	129.92 (443.59)	303.95 (587.35)	579.85 (1,720.85)	<0.001	<0.001
	Emergency	3.98 (48.95)	1.57 (24.31)	2.28 (29.54)	17.02 (109.91)	0.154	<0.001
	Other	37.75 (964.34)	22.35 (235.08)	22.99 (126.68)	122.86 (2,406.12)	0.787	<0.001
Pharmacy costs	Total	197.88 (630.31)	183.63 (611.72)	404.16 (847.41)	177.15 (590.91)	<0.001	<0.001

95% CI 1.49-2.05), a diagnosis of cancer (other than HCC, superficial skin cancer or cancer in situ) (cost ratio 1.13; 95% CI 1.06-1.21), and alcohol and substance abuse (cost ratio 1.130; 95% CI 1.06-1.21). Although these factors were statistically significant in the model, they had little effect on the estimated cost ratios when comparing patients with CC and ESLD to patients with NCD. Results of the covariate-adjusted models were very similar to results from the unadjusted models, suggesting that liver disease severity is the major driver of all-cause healthcare costs, and the observed cost differences between patients with CC and ESLD compared to patients with NCD cannot be attributed to confounding by age or other factors controlled for in the adjusted analysis.

Incremental cost ratios for total HCV-related costs and HCV-related medical costs adjusted for demographics and other factors also differed between disease strata (Table 5). Patients with CC and ESLD were estimated to have total HCV-related costs that were 1.85-fold higher (cost ratio 1.85; 95% CI 1.69-2.01) and 5.32-fold higher (cost ratio 5.32; 95% CI 4.88-5.81), respectively, than those for patients with NCD. HCV-related pharmacy costs were significantly higher in patients with CC compared with NCD (cost ratio 2.86; 95% CI 2.61-3.13), but were not significantly different between patients with ESLD compared to those with NCD (cost ratio 1.01; 95% CI 0.99-1.19).

Nearly all patients (99%) had at least one ambulatory visit during the follow-up period and thus ambulatory visits were modeled using a one-part model. The covariate-adjusted analyses showed that individuals with CC and ESLD had 1.18-fold (count ratio 1.18; 95% CI 1.15-1.21) and 1.55-fold (count ratio 1.55; 95% CI 1.52-1.59), respectively, more ambulatory visits when compared to NCD patients (Table 6).

In contrast, fewer patients had an emergency room visit (39%) or an inpatient visit (23%) during the follow-up period; therefore, a two-part modeling procedure was used in which the probability of having a visit was modeled first, followed by an estimate of the number of PPPM visits among those patients who had at least one visit.

Table 5. Healthcare Cost Models Adjusted for Demographics and Comorbidities

	NCD (Reference)	CC		ESLD	
	Predicted Cost USD 2010	Cost Ratio (95%CI)	Predicted Cost USD 2010	Cost Ratio (95%CI)	Predicted Cost USD 2010
All-cause healthcare costs					
Total	1,572.04	1.40 (1.31-1.49)	2,196.23	3.33 (3.12-3.56)	5,234.75
Medical	1,303.76	1.26 (1.15-1.38)	1,642.08	4.14 (3.84-4.46)	5,390.49
Pharmacy	387.29	1.83 (1.72-1.94)	707.80	1.44 (1.37-1.50)	556.03
HCV-related costs					
Total	691.46	1.85 (1.69-2.01)	1,276.87	5.32 (4.88-5.81)	3,681.64
Medical	670.44	1.58 (1.40-1.78)	1,056.13	7.06 (6.42-7.75)	4,730.15
Pharmacy	201.71	2.86 (2.61-3.13)	576.45	1.09 (0.99-1.19)	219.45

Covariates adjusted for in the analysis included: age, gender, geographic region, index year, baseline comorbidities, baseline healthcare utilization, and baseline treatment for chronic hepatitis C.

Similarly, in the two-part covariate adjusted analyses of hospital admissions there were statistically significant differences in both the probability of any visit and the number of admissions between patients with CC or ESLD and patients with NCD (Table 6). However, after combining these two estimates the predicted number of admissions was very similar among patients with NCD (0.023 PPPM) and CC (0.022 PPPM), but was 3.8-fold higher among patients with ESLD (0.087 PPPM) as compared to patients with NCD.

Annual Cost Estimates. Under the assumption that follow-up time was not associated with disease severity, PPPM all-cause cost measures can be roughly translated into annual cost estimates by multiplying the PPPM estimates by 12.167. Using this formula, annual all-cause healthcare costs were estimated to be $24,176 for patients with chronic HCV infection. When stratified by cohort, mean annual costs are estimated to be $17,277 for patients with NCD; $22,752 for patients with CC; and $59,995 for patients with ESLD.

Discussion

The results of this retrospective analysis demonstrate the costs associated with the care of patients with CHC are substantial and are driven largely by disease severity. The present study has several strengths. First, the definitions of liver disease severity (and associated ICD-9 codes) were developed by a consensus panel of three practicing clinical hepatologists. Second, we used actual amounts paid rather than charges to determine healthcare costs, thus reflecting a more realistic estimate of the costs of this disease in the U.S. Third, to our knowledge, no other study of patients with CHC enrolled in a U.S. managed care database has included a geographically and demographically more diverse cohort of patients (57,149), or had a longer duration of follow-up (more than 8 years). Another unique feature of our analysis is the estimate of both costs and resource use as stratified by liver disease severity. These results demonstrate that direct all-cause healthcare costs and HCV-related healthcare costs increased as chronic HCV infection progresses, and were lowest in patients with NCD, highest in patients with ESLD, and intermediate in patients with CC. Consistent with these findings, our statistical model showed that healthcare utilization increased with progressive liver disease severity and was highest in patients with ESLD.

The stepwise increase in direct healthcare costs with increasing liver disease severity highlights the imminent crisis that CHC infection poses in an aging population for the U.S. healthcare system. The proportion of patients with cirrhosis and ESLD, the incidence of HCC, and the rate of liver-related deaths are all increasing.[4,9,17,18] Moreover, the greatest increase in the incidence of HCC is occurring in those aged 45 to 60 years, and approximately three-quarters of HCC deaths attributable to HCV infection is occurring between the ages of 45 and 64 years.[8,18] The mean age of patients with NCD, CC, and ESLD in our analysis falls within these ranges. The subgroup analysis of patients with ESLD demonstrates that the cost of caring for patients with OLT is ~3 times greater than in patients without OLT and the cost of caring for patients with HCC is approximately twice that of caring for patients without HCC.

The results of this analysis add to previous analyses that have shown that patients with HCV infection have higher direct healthcare costs compared with patients who do not have HCV infection.[9,12,13] Our estimate of the annual cost of caring for a patient with CHC ($24,176) is similar to that reported in other recent studies ($19,665[12] to $20,961[9]), but greater than that reported for patients without HCV infection ($9,979).[12] Our estimates of the annual cost of care for patients with ESLD and either HCC ($112,537) or OLT ($145,045) are somewhat higher than estimates in another analysis conducted on the same database. McAdam-Marx et al.[12] estimated the annual cost of care for a patient with advanced liver disease and HCC or OLT to be $58,529 and $113,116, respectively. The differences between these estimates are likely due to the codes used to define the populations and differences in the index dates. For example, our estimate of the cost of care for patients with HCC applies only to patients who first met our criteria for ESLD. In contrast, McAdam-Marx et al.[12] included all patients with HCV infection and HCC in their estimate, regardless of liver disease severity. This difference most likely explains the higher number of patients with HCC in their estimate. Patients included in our analysis were required to have at least 1 year of baseline enrollment and 30 days of continuous follow-up. In contrast, McAdam-Marx et al.[12] required patients to have 6 months of baseline enrollment and 1 day of follow-up. This difference in definitions likely explains the lower number of patients with OLT and the higher cost of care for these individuals in our analysis.

Observational studies with claims data are valuable for examining patterns of healthcare utilization and expenditures in a "real-world" setting. However, there

Table 6. Healthcare Utilization Models Adjusted for Demographics and Comorbidities

	NCD (Reference)	CC		ESLD	
	Predicted number of visits (PPPM)	Count ratio (CR) or odds ratio (OR) (95%CI)	Predicted number of visits (PPPM)	Count ratio (CR) or odds ratio (OR) (95%CI)	Predicted number of visits (PPPM)
All-cause ambulatory visits (PPPM)	1.66	–	1.96	–	2.58
Number of ambulatory visits (PPPM) (n=53,562)		CR: 1.18 (1.15-1.21)		CR: 1.55 (1.52-1.59)	
All-cause ER visits (PPPM)	0.0795	–	0.0775	–	0.1397
Any ER visit (n=53,562)		OR: 1.17 (1.08-1.26)		OR: 2.44 (2.32-2.57)	
Number of ER visits (PPPM) in patients with at least 1 visit (n=20,675)		CR: 0.89 (0.81-0.97)		CR: 1.11 (1.06-1.17)	
All-cause inpatient visits (PPPM)	0.0225	–	0.0217	–	0.0872
Any inpatient visit (n=53,562)		OR 1.14 (1.04-1.25)		OR 4.223 (4.00-4.46)	
Number of inpatient visits (PPPM) in patients with at least 1 visit (n=12,186)		CR 0.88 (0.80-0.96)		CR 1.57 (1.49-1.65)	

Covariates adjusted for, in the analysis, included: age, gender, geographic region, index year, baseline comorbidities, baseline healthcare utilization, and baseline treatment for chronic hepatitis C.

are limitations inherent to a study of this type. Claims data are collected for the purpose of payment rather than research. Patients with NCD or CC may have been misclassified because clinical information on liver fibrosis (i.e., the results of liver biopsy or noninvasive tests) was not available to confirm the diagnosis of cirrhosis. Misclassification of patients with CC as having NCD would have resulted in an overestimation of the costs associated with NCD and an underestimation of the true cost difference between these two patient groups. However, the risk of misclassifying patients with ESLD was minimized by including both diagnosis and procedural codes in the classification algorithm.

A claims database does not contain any information about the reason why a medication is prescribed (or not) and whether a medication is actually taken as prescribed. Our definition of HCV-related pharmacy costs was narrow and included only those drugs used for the treatment of HCV and management of the side effects of HCV treatment. Less frequent use of antiviral drugs was likely the major reason for the lower pharmacy costs in patients with ESLD. However, much of the pharmacy costs for these individuals would have been incurred in-hospital and thus would have resulted in higher inpatient hospital costs. The costs of drugs prescribed to manage HCV-related complications such as diabetes were not included in this definition. As a result the pharmacy costs are likely underestimates in each of the three strata. There is also a lack of information regarding medications purchased outside of the healthcare pharmacy system, which would result in an underestimate of total costs. Cost estimates for patients aged older than 65 years and those on Social Security Disability Insurance may be underestimates because costs paid by other care plans (e.g., Medicare) were not included in this analysis. Finally, the data may also not be easily generalized to nonmanaged-care populations.

We observed a consistent increase in healthcare costs and utilization with progression of HCV-related liver disease, yet only a small proportion of patients in this analysis (18%) received combination antiviral therapy of pegylated interferon with ribavirin. This finding implies that a majority of patients who might have benefited from antiviral therapy were either not offered treatment, were not eligible, or did not consent to treatment. This observation is consistent with the finding that only a small proportion of chronic HCV patients (i.e., less than 30%) receive treatment with peginterferon plus ribavirin.[19-22] The nature of a claims database prevents us from determining why such a low percentage of patients received treatment.

Although decompensated cirrhosis represents a contraindication to treatment with interferon-based therapy, the results of this analysis suggested that treatment for patients with less severe forms of CHC (NCD and CC) should be considered in order to potentially prevent liver disease progression and to limit direct healthcare costs. Clearly, treatment should be offered before the development of comorbid conditions that preclude such therapy. Benefits associated with successful treatment for CHC (sustained virological response) include durable eradication of HCV infection, improved health-related quality of life, regression of hepatic fibrosis, and reduction in the incidence of HCC, liver-related mortality, and all-cause mortality.[23-28]

Our study did not consider screening for HCV among those at high risk, or include the costs of the recently approved protease inhibitors (boceprevir and telaprevir, which were not approved until after this

study was conducted). However, our data intuitively demonstrate that, in the future, the costs of screening and treatment must be offset by the costs of ignoring these options and allowing chronic HCV disease to progress from NCD to CC and ESLD. We have clearly shown that the direct costs associated with chronic HCV are considerable, averaging over $24,000 annually for all patients and $60,000 for those with advanced liver disease. A recent study showed that birth-cohort screening of all patients born between 1945 and 1965 is cost-effective, averaging $2,874 per new case identified. If the costs of treatment are included, this adds $15,700 per quality-adjusted life-year (QALY) assuming peginterferon plus ribavirin is used, or $35,700 per QALY saved assuming that a protease inhibitor is used in combination with peginterferon plus ribavirin.[29] We have shown that the current cost of HCV disease management would likely offset these expenses.

In conclusion, this retrospective analysis of a medical and pharmacy claims database demonstrates that the direct healthcare costs associated with CHC infection are high, increase in association with the progression of liver disease, and are highest in those with ESLD. Given the increasing age and disease severity, and the low rate of awareness of infection status in patients with CHC, priority should be given to identifying and treating patients with this disease. Early intervention has the potential to avoid healthcare costs associated with progressive liver disease.

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