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RESEARCH

All-Cause and Incremental Per Patient Per Year Cost Associated with Chronic Hepatitis C Virus and Associated Liver Complications in the United States: A Managed Care Perspective

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ABSTRACT

BACKGROUND: Approximately 3.2-3.9 million U.S. residents are infected with the hepatitis C virus (HCV). Total annual costs (direct and indirect) in the United States for HCV were estimated to be $5.46 billion in 1997, and direct medical costs have been predicted to increase to $10.7 billion for the 10-year period from 2010 through 2019, due in part to the increasing number of HCV patients developing advanced liver disease (AdvLD).

OBJECTIVE: To quantify in a sample of commercially insured enrollees (a) total per patient per year (PPPY) all-cause costs to the payer, overall and by the stage of liver disease, for patients diagnosed with HCV; and (b) incremental all-cause costs for patients diagnosed with HCV relative to a matched non-HCV cohort.

METHODS: This retrospective, matched cohort study included patients aged at least 18 years and with at least 6 months of continuous enrollment in a large managed care organization (MCO) claims database from July 1, 2001, through March 31, 2010. Patients with a diagnosis of HCV (ICD-9-CM codes 070.54, 070.70) were identified and stratified into those with and without AdvLD, defined as decompensated cirrhosis (ICD-9-CM codes 070.44, 070.71, 348.3x, 456.0, 456.1, 456.2x, 572.2, 572.3, 572.4, 782.4, 789.59); hepatocellular carcinoma (HCC, ICD-9-CM code 155); or liver transplant (ICD-9-CM codes V42.7, 50.5 or CPT codes 47135, 47136). For patients without AdvLD, the index date was the first HCV diagnosis date observed at least 6 months after the first enrollment date, and at least 6 months of continuous enrollment after the index date were required. HCV patients without AdvLD were stratified into those with and without compensated cirrhosis (ICD-9-CM codes 571.2, 571.5, 571.6). For patients with AdvLD, the index date was the date of the first AdvLD diagnosis observed at least 6 months after the first enrollment date, and at least 1 day of enrollment after the index date was required. Cases were matched in an approximate 1:10 ratio to comparison patients without an HCV diagnosis or AdvLD diagnosis who met all other inclusion criteria based on gender, age, hospital referral region state, pre-index health care costs, alcoholism, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), and a modified Charlson Comorbidity Index. For the HCV and comparison patient cohorts, PPPY all-cause costs to the payer were calculated as total allowed charges summed across all patients divided by total patient-days of follow-up for the cohort, multiplied by 365, inflation-normalized to 2009 dollars. Because the calculation of PPPY cost generated a single value for each cohort, bootstrapping was used to generate descriptive statistics. Incremental PPPY costs for HCV patients relative to non-HCV patients were calculated as between-group differences in PPPY costs. T-tests for independent samples were used to compare costs between case and comparison cohorts.

RESULTS: A total of 34,597 patients diagnosed with HCV, 78.0% with HCV without AdvLD, 4.4% with compensated cirrhosis, 12.3% with decompensated cirrhosis, 2.8% with HCC, and 2.6% with liver transplant, were matched to 330,435 comparison patients. Mean (SD) age of all HCV cases was 49.9 (8.5) years; 61.7% were male. Incremental mean (SD) PPPY costs in 2009 dollars for all HCV patients relative to comparison patients were $9,681 ($176) PPPY. Incremental PPPY costs were $5,870 ($157) and $5,330 ($491) for HCV patients without liver disease and with compensated cirrhosis, respectively. Incremental PPPY costs for patients with AdvLD were $27,845 ($965) for decompensated cirrhosis, $43,671 ($2,588) for HCC, and $93,609 ($4,482) for transplant. Incremental prescription drug costs, including the cost of antiviral drugs, were $2,739 ($37) for HCV patients overall, $2,659 ($41) for HCV without liver involvement, and $3,102 ($157) for HCV with compensated cirrhosis. These between-group differences were statistically significant at $P < 0.001$.

CONCLUSIONS: Based on a retrospective analysis of data from a large, MCO claims database, patients diagnosed with HCV had annual all-cause medical costs that were almost twice as high as those of enrollees without a diagnosis of HCV. Health care costs increased dramatically with AdvLD. Data from this study may help MCOs project future HCV costs and facilitate planning for HCV patient management efforts.

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What is already known about this subject

- Annual total direct and indirect costs related to infections with the hepatitis C virus (HCV) in the United States were estimated at $5.46 billion in 1997. Davis et al. (2011) estimated that all-cause health care costs for managed care organization (MCO) enrollees with HCV were $20,961 per patient per year (PPPY), of which $6,864 PPPY was HCV-related, from 2002 through 2006.
- The burden of illness for HCV is predicted to grow over the next 2 decades, partly due to increased prevalence of advanced liver disease (AdvLD) in the current HCV population.

What this study adds

- In a retrospective analysis of administrative claims data for approximately 50 million MCO enrollees, the annual direct all-cause health care costs to commercial insurers for patients diagnosed with HCV were estimated to be almost twice as high as costs for matched non-HCV enrollees with similar health statuses, with incremental all-cause costs of more than $9,000 PPPY.
- All-cause PPPY incremental costs were higher for patients diagnosed with AdvLD than for matched comparison group patients, ranging from more than $27,000 PPPY in patients with decompensated cirrhosis to more than $93,000 in patients requiring a liver transplant.

It is estimated that 2%-3% of the worldwide population (130-170 million people) is infected with the hepatitis C virus (HCV)[1-3] including approximately 3.2-3.9 million in the United States.[4,5] In prospective studies of patients who acquired HCV from blood transfusions (duration of time from diagnosis: 8 to 16 years), 7%-16% developed cirrhosis, 0.7%-1.3% developed hepatocellular carcinoma (HCC), and 1.3%-3.7% experienced liver-related death.[6] In retrospective studies primarily in diagnosed HCV patients referred for liver disease (duration of time from diagnosis: 9-29 years), 17%-55% developed cirrhosis, 1%-23% progressed to HCC, and 4%-15% experienced liver-related death.[6] The differences in findings between retrospective and prospective studies are due in part to the notable difference in duration of follow-up and time since infection. Age at the time of infection is also thought to play a role in liver disease progression. It has been estimated that 20% of patients first infected after 40 years of age progressed to cirrhosis within 20 years after infection, versus 3%-8% of those less than 40 years of age at the time of infection.[6]

The majority of HCV infections in the United States occurred in the 1980s and early 1990s, before the identification of the virus and appropriate testing processes.[5] Because HCV is a mainly asymptomatic and slowly progressing disease, most cases remain undiagnosed until the onset of liver disease.[7] While the incidence of new HCV cases has declined over the last 2 decades,[5] it is estimated that significant clinical and economic consequences of HCV will be observed within the next decade, mainly driven by the individuals who have had the virus for 10 to 20 years (or more) and those who progress to AdvLD.[8,9]

The health burden of HCV is driven, in part, by the development of AdvLD,[10] which may also lead to liver transplant.[11] Currently HCV is the leading cause for HCC and liver transplants in the United States,[10,12] and studies suggest that more cases of HCC, decompensated cirrhosis, and liver transplants due to HCV will be observed in the coming years.[13] A recent study suggests that the HCV-related mortality rate increased in the United States from 1995 to 2004 by 123%.[14] In accordance with this finding, Davis et al. (2003) suggest a similar trend in HCV-related mortality and morbidity in the future and estimate that the peak in prevalence of HCV-related cirrhosis in the United States in 2020 will be approximately 1 million cases.[13]

These trends are expected to affect both public and private health insurers in the United States. Health care costs related to HCV are already significant; total annual cost (direct and indirect) in the United States was estimated to be $5.46 billion in 1997.[15] Meanwhile, direct medical expenditures for HCV are predicted to grow to $10.7 billion for the 10-year period from 2010-2019.[9] Other burden-of-illness studies have reported annual amounts paid by managed care plans for HCV-related medical care between 1995 and 1999 to be between $5,100 and $13,000 per HCV patient.[16-18] However, in the most recently published economic analysis of HCV, which was based on a large database of medical and pharmacy claims from 2002-2006, Davis et al. reported that the regression-estimated total PPPY all-cause cost paid by managed care plans was $20,961 for HCV patients compared with $5,451 for patients in a matched non-HCV cohort.[19] HCV-related costs accounted for $6,864 PPPY in the HCV cohort.[19]

Data on the amounts paid for HCV care by MCOs are limited in that current studies do not provide a comprehensive analysis of HCV by stage of liver disease. The burden of AdvLD should be of interest to managed care payers to understand the effects of current and future HCV costs on their plans. Therefore, the purpose of this study was to estimate the all-cause medical costs to payers associated with HCV, both overall and by stage of liver disease. This study focused on enrollees with employer-sponsored health insurance and compared a cohort of HCV patients with a matched comparison cohort of patients without HCV.

Methods

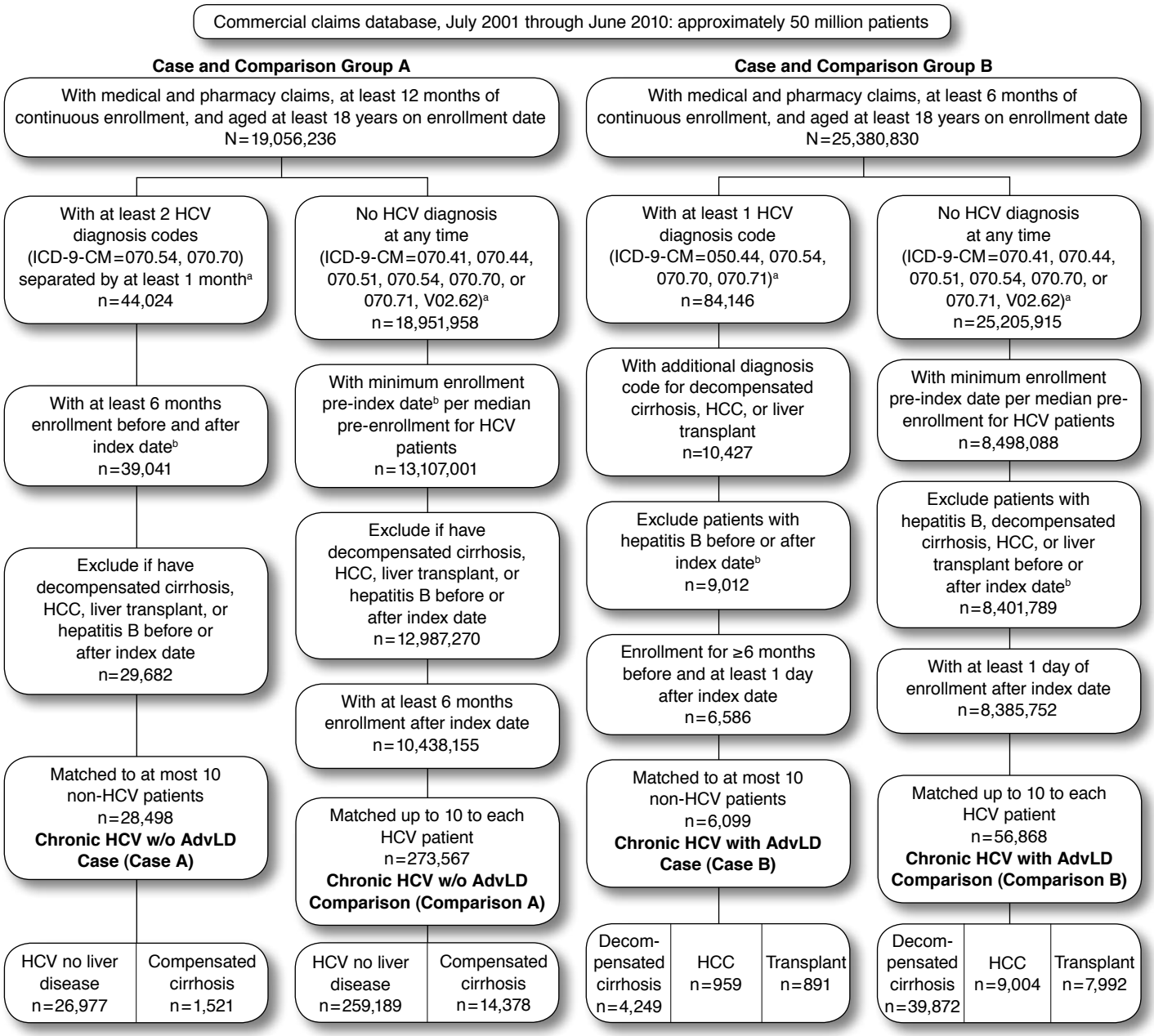
Study Design and Data Source

To estimate HCV-associated PPPY costs, allowed charges for all-cause health care services were collected using a retrospective analysis of administrative claims data in a large commercial insurer database affiliated with OptumInsight.[20,21] The database used for this analysis includes enrollment information and medical and pharmacy claims from July 1, 2001, through June 30, 2010. Of the patients in this database, the study cohorts were drawn from approximately 50 million patients who had both pharmacy and medical coverage. The retrospective matched cohort analysis estimated PPPY health care costs in patients with HCV and a matched comparison cohort for medical services provided from January 1, 2002, through March 31, 2010. The database contains enrollee-level information on demographics (age, geographic region, gender), health plan enrollment, and characteristics of health services utilization including facility revenue codes, place of service, *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnoses and procedures, Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes, and prescription claims data for each individual.

Patient Identification

Four distinct patient cohorts aged 18 years or older were defined: patients who had at least 2 diagnosis codes indicating chronic HCV infection but had no indication of AdvLD during the current enrollment period (i.e., cases A, the non-AdvLD cohort); patients who had diagnosis codes indicating both chronic HCV and AdvLD during the current enrollment period (i.e., cases B, the AdvLD cohort); patients matched to cases A

FIGURE 1



[a]*Based on claims with dates of service from January 1, 2002, through March 31, 2010.*

[b]*For patients without AdvLD, the index date was the first HCV diagnosis date observed at least 6 months after the first enrollment date. For patients with AdvLD, the index date was the first AdvLD diagnosis date observed at least 6 months after the first enrollment date. For comparison group patients, the index date was the date of the first claim for any medical care occurring on or after the median number of pre-index days for the corresponding HCV cohort.*

AdvLD = advanced liver disease; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

(i.e., comparison A); and patients matched to cases B (i.e., comparison B) (Figure 1). All study ICD-9-CM codes are provided in Appendix A. For cases A, the index date was the date of the first HCV ICD-9-CM code occurring in the database after the first 6 months of continuous enrollment. For cases B, the index date was the date of the first AdvLD diagnosis code occurring

after the first 6 months of continuous enrollment. All patients were required to have a minimum of 6 months pre-index date enrollment to identify pre-index cost and comorbidity. Patients were followed after the index date until the end of the eligibility period or until the last day of data provided in the database. Patients with a diagnosis code for infection with hepatitis B virus during the enrollment period were excluded from all cohorts to help isolate the impact of HCV/AdvLD on the study outcomes.

The non-AdvLD HCV cohort (cases A) were required to have at least 2 ICD-9-CM codes indicating chronic HCV (ICD-9-CM codes 070.54, 070.70) documented a month or more apart. Two chronic HCV diagnoses were used to avoid potential false-positive diagnoses within the dataset, as was done in a previous HCV economic study based on a claims database.[16] Patients with a diagnosis of chronic HCV without AdvLD were further stratified into those with and without compensated cirrhosis (ICD-9-CM codes 571.2, 571.5, 571.6). Patients in the non-AdvLD HCV cohort were required to have at least 6 months of enrollment following the index date, for a total of at least 12 months of continuous enrollment.

The AdvLD HCV cohort (cases B) was required to have at least 1 diagnosis code for chronic HCV (ICD-9-CM codes 070.54, 070.70) with a second diagnosis code for decompensated cirrhosis (ICD-9-CM codes 070.44, 070.71, 348.3x, 456.0, 456.1, 456.2x, 572.2, 572.3, 572.4, 782.4, 789.59), HCC (ICD-9-CM code 155), or liver transplant (ICD-9-CM codes V42.7, 50.5 or CPT codes 47135, 47136). For patients with diagnoses indicating 2 or more of these liver disease stages, conditions were prioritized hierarchically, in the order of transplant, HCC, or decompensated cirrhosis diagnosis. Patients in the AdvLD cohort were required to have at least 1 day of enrollment following the index date. Requiring only 1 day of post-index eligibility recognizes that HCV patients with AdvLD have a shortened life expectancy, with the 5-year mortality rate in patients who progress to decompensated cirrhosis estimated to be 50%.[22]

The comparison cohorts for HCV study patients with AdvLD (comparison B) and without AdvLD (comparison A) were based on similar inclusion and exclusion criteria. The primary difference between the inclusion criteria for the comparison cohorts was the minimum duration of enrollment. Comparison patients to the HCV without AdvLD cohort (comparison A) were required to have at least 12 months of continuous enrollment; at least 6 months of the continuous enrollment had to be after the index date, as with the corresponding HCV cohort. In contrast, comparison patients for the HCV with AdvLD cohort (comparison B) were required to have more than 6 months of continuous enrollment, of which at least 1 day had to be after the index date. Comparison patients were excluded if they had any diagnosis of acute or chronic HCV at any time.

The index date for all comparison patients was defined in the following manner. First, the median number of pre-index days for the corresponding HCV cohort was identified. For each comparison patient, the index date was set as the date of the first claim for any medical care occurring on or after that median date.

Matching

Up to 10 comparison patients were matched to each HCV patient. The a priori matching criteria were age on index date (plus or minus 3 years), gender, year of index date, hospital referral region (HRR) based on 5-digit zip codes, as defined in *The Dartmouth Atlas of Health Care*,[23] comorbidities based on ICD-9-CM codes identified in the pre-index date period (see Appendix A) for alcoholism, substance abuse, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), and a modified version of the Charlson Comorbidity index (CCI) Deyo Adaptation[24] in which the comorbidity index was not age-adjusted and excluded comorbidities that were specified as matching criteria (mild and severe liver disease and HIV/AIDS).

Matching can exacerbate selection bias when there are no suitable matches for subgroups, such as more severely ill patients. Thus, 3 approaches for relaxing matching criteria were also defined a priori including (a) relaxing HRR to HRR states; (b) relaxing HRR to states and age from plus or minus 3 years to plus or minus 5 years; and (c) relaxing HRR to states, age to plus or minus 5 years, and index year to 3 year intervals.

After the initial matching process, high pre-index cost variance was noted in both the case and comparison cohorts that was speculated to be due to the large number of matching variables rather than small group size. A large number of matching variables can increase variance if the variables are not sufficiently correlated with the underlying measure, in this case pre-index costs. An additional analysis revealed that age, HRR, index year, and substance abuse were not significantly correlated with pre-index costs. Thus, age was matched on bands based on age distribution in years (18-33, 34-38, 39-41, 42-44, 45-47, 48-49, 50-52, 53-55, 56-58, 59-61, 62-64, and 65 or older); HRR was relaxed to states; and substance abuse and index year were dropped as matching variables. In addition, to maximize the likelihood that the cost outcomes for HCV patients were attributable to HCV and not to other unmeasured characteristics predicting higher utilization, annualized cost in the pre-index period was calculated for each patient as pre-index allowed charges divided by pre-index patient-years (i.e., days enrolled divided by 365) and used for matching purposes only. Five pre-index cost groups (low, medium low, medium, medium high, and high) were determined using percentiles that were defined for HCV without AdvLD and HCV with AdvLD separately. The cut points for these cost strata, which represented the 5th, 33rd, 50th, 66th, and 80th percentiles, were $250, $2,000, $4,000, $7,500, and $15,000, respectively,

for HCV without AdvLD and $500, $5,000, $10,000, $18,000, and $32,000, respectively, for HCV with AdvLD. These choices were made in light of matching to other strata; for example, because high CCI scores are correlated with high costs, a 95th percentile stratum was unnecessary.

The final set of matching criteria included the age bands, gender, geographical location (state), pre-index comorbidities, the modified CCI, and the annualized pre-index costs. This revised matching approach reduced cost variability and resulted in the comparison patients having higher pre-index costs than after the initial matching process; thus, the revised matching approach more accurately paired enrollees to HCV patients of similar health.

Finally, if multiple comparison patients were eligible to match to a given HCV patient, up to 10 comparison enrollees were randomly selected for matching. Up to 10 comparison enrollees were chosen, instead of 1:1 matching, to reduce cost variance in the comparison cohort. Selecting up to 10 comparison enrollees versus exactly 10 to each HCV patient avoided the need to exclude HCV patients for not matching to 10 comparison enrollees. If, in a stratum of HCV patients with the same values for matching, the number of comparison enrollees was more than 10 times the number of HCV patients in the stratum, then comparison enrollees were randomly selected until the total number of randomly selected comparison enrollees was 10 times the number of HCV patients in the stratum. If there were not 10 times the number of HCV patients in the matching comparison stratum, then the largest number of HCV patients in a stratum was identified so there were never more than 9 patients missing from the desired number of comparison enrollees in any stratum. For example, if there were 3 HCV patients in a stratum and 17 comparison enrollees, then including all 3 HCV patients would have resulted in missing 13 desired comparison enrollees in the stratum. Instead, we would have excluded 1 HCV patient and retained all 17 comparison enrollees so only 3 comparison enrollees were missing in the matching stratum.

Classification of Patient Cohorts

The primary independent variable classification was cohort placement (e.g., HCV case versus comparison). All HCV patients were further defined by stage of liver disease. Within the HCV without AdvLD cohort, HCV patients were classified as having HCV without liver disease or compensated cirrhosis (i.e., indication of chronic liver disease and cirrhosis but no indication of decompensated cirrhosis, HCC, or transplant).

Each patient in the HCV with AdvLD cohort was classified by the liver disease diagnosis that defined his or her index date, using the same hierarchy described previously (liver transplant, HCC, or decompensated cirrhosis). Specific diagnosis code criteria for defining stage of liver disease are provided in Appendix A.

Primary Study Outcome and Descriptive Measures

The primary study outcome was PPPY allowed charges for all-cause health care services after the index date. PPPY cost was calculated by cohort, a method commonly used in health economics research.[25,26] All PPPY costs were calculated as the total of allowed charges for patients in a cohort, divided by the total number of days of enrollment in the cohort, multiplied by 365 days. For all patients and their matched comparisons, cost data were captured following the index date for the duration of the patient's enrollment. Costs were inflation-normalized to 2009 U.S. dollars using the Consumer Price Index (CPI) All Urban Consumers for Medical Care Services.[27] Costs per member per month (PMPM) or per member per year (PMPY) for the entire database were not calculated because the total number of member months in the database was not available to the researchers for this study.

Upon review of the findings, a post hoc decision was made to specifically evaluate utilization and PPPY pharmacy costs for HCV antiviral treatments for each of the HCV patient cohorts. Antiviral therapy for this analysis included interferon α-2a, interferon α-2b, interferon Alphacon A, pegylated interferon α-2a, pegylated interferon α-2b, and ribavirin.

Demographic and clinical data were also captured to describe the study cohorts and identify differences between HCV/AdvLD patients and matched comparison patients. Demographic characteristics included age (reported as a continuous variable and also categorized as 18 to 39 years, 40 to 64 years, and aged 65 years or older), gender, and the mean number of days of pre- and post-index date enrollment. Select comorbidities were also identified during the pre-index period based on ICD-9-CM codes including HIV/AIDS, alcoholism, cerebrovascular disease, chronic obstructive pulmonary disease, congestive heart failure, dementia, diabetes, diabetes with complications, hemiplegia or paraplegia, malignancy, metastatic solid tumor, moderate or severe renal disease, myocardial infarction, pancreatitis, peptic ulcer disease, peripheral vascular disease, rheumatologic disease, and substance abuse (ICD-9-CM codes in Appendix A).

Analysis

Direct all-cause PPPY health care costs were evaluated overall and by stage of liver disease. Costs were reported in total and by service categories of inpatient, outpatient, professional services, emergency department, pharmacy including HCV antiviral drugs, and other (ancillary, facility services not included in defined categories). Service categories for emergency department, inpatient, outpatient, and other were classified using the American Medical Association's place of service codes. Pharmacy costs represent only outpatient pharmacy claims because inpatient pharmaceuticals do not appear in the claims in an identifiable manner. Professional fees include all physician claims (i.e., Centers for Medicare & Medicaid Services

TABLE 1 Enrollment Counts by Index Year for Patients with Hepatitis C Virus by Presence of Advanced Liver Disease and for Matched Comparison Patients in a National Medical and Pharmacy Claims Database: 2002-2010

Index Year	HCV without AdvLD[a]	Comparison	HCV with AdvLD[b]	Comparison
2002[c]	3,669	0	284	0
2003	3,461	80,926	523	4,771
2004	3,648	29,962	615	13,592
2005	4,144	31,077	704	6,347
2006	3,885	34,981	797	7,043
2007	3,830	32,572	857	7,680
2008	3,502	37,711	1,032	7,564
2009	2,359	26,338	1,029	7,823
2010[d]			258	2,048
Totals	28,498	273,567	6,099	56,868

[a]*Includes patients without liver disease (n = 26,977) or with compensated cirrhosis (n = 1,521).*

[b]*Includes patients with decompensated cirrhosis (n = 4,249), hepatocellular carcinoma (n = 959), or liver transplant (n = 891).*

[c]*Because comparison enrollees were required to have more than 1 year of enrollment prior to index date per the median pre-index enrollment for their respective HCV cohorts (overall median 408 days), no comparison patients had an index year of 2002.*

[d]*Due to requirement of 6 or more months of enrollment after the index date, none of the HCV patients without advanced liver disease or their comparison enrollees had an index year of 2010.*

AdvLD = advanced liver disease; HCV = hepatitis C virus.

[CMS]-1500s) as well as facility claims where the revenue code indicates a professional fee. Outpatient fees contain the costs from the facility component of independent laboratory, clinic, office, and ambulatory surgical centers.

The incremental direct all-cause health care costs associated with HCV or AdvLD were estimated as the cost differences between HCV/AdvLD and all comparison patients (i.e., PPPY cost for each HCV or AdvLD patient group minus PPPY cost for its matched comparison group). Finally, all-cause PPPY costs for transplant patients were calculated for the first year post-transplant as the total allowed costs for all patients divided by the total patient years. PPPY costs were also calculated for subsequent years in transplant patients with more than 1 year of enrollment after the index date as the total allowed costs after year 1 for all patients divided by the total patient years.

Statistical Analyses

Descriptive statistics (frequency, percent, mean, standard deviation [SD], median) were used to describe the baseline characteristics of the patient cohorts. Baseline characteristics were reported overall for all HCV and comparison patients and for each liver disease cohort. PPPY and incremental costs, as described above, were reported using descriptive statistics (mean, SD, median, minimum, and maximum).

The standard PPPY calculation, the primary outcome measure, provided a single PPPY cost estimate for each cohort; thus, variance information was not directly available. For this reason, bootstrapping with replacement was used to generate descriptive statistics for annualized costs.[28,29] The bootstrapping procedure generated 250 bootstrap samples with replacement of patients within each stratum, with sample size equal to the number of patients in the stratum. For example, there were 34,597 patients in the overall HCV patient group. For that group, the bootstrapping approach drew 250 samples with replacement, each consisting of 34,597 patients. Each measure (e.g., total PPPY cost, outpatient PPPY cost, etc.) was then computed for each of the 250 samples. This process was repeated for patients and comparison enrollees in each liver disease cohort. Using this approach, the minimum/maximum values reported for each cohort represent the minimum/maximum PPPY values observed over the 250 bootstrap samples. Similarly, the SD is the deviation of the 250 means of the bootstrap samples.

Differences in costs between cases and comparison enrollees were assessed using t-tests. The primary motivation for bootstrapping was to generate error estimates for each measure. However, using bootstrap sampling to generate descriptive statistics has the added benefit of generating normally distributed data, which allowed for the use of a more efficient parametric t-test for comparing means in place of the rank-sum test, which is often required to account for skewed cost data.[30]

All statistical analyses were conducted at an a priori significance level of $P < 0.05$ using version 2.11.1 of R: A Language and Environment for Statistical Computing (open source software available at http://www.r-project.org/).

Results

Baseline Characteristics

After matching and prior to classification by liver disease severity, the sample included 34,597 patients diagnosed with HCV and 330,435 comparison enrollees (Figure 1). The mean age for both cohorts was 49.9 years (SD = 8.5 years for HCV patients and SD = 8.9 years for comparisons); 61.7% were male in the HCV cohort versus 61.1% in the comparison group. The mean (median, interquartile range) number of days of follow-up after the index date for HCV patients overall was 837 (650, 362-1,163) days and 909 (713, 359-1,286) days for comparison enrollees.

The distribution of study patients by index year is provided in Table 1. Enrollment was generally steady from 2002 to 2009 for patients who had HCV without AdvLD, but the enrollment of HCV patients with AdvLD increased over the study period. Due to the comparison cohort selection criterion for a minimum duration of enrollment, no comparison patients had an index date in 2002, while an enrollment surge in 2003 or 2004

TABLE 2 Baseline Characteristics for Patients with Hepatitis C Virus Overall and by Stage of Liver Disease and for Matched Comparison Enrollees in a National Medical and Pharmacy Claims Database: 2002-2010

	All HCV	Comparison	HCV without Liver Disease	Comparison	HCV with Compensated Cirrhosis	Comparison
Cohort Size (n)	34,597	330,435	26,977	259,189	1,521	14,378
Age, years mean [SD]	49.9 [8.5]	49.9 [8.9]	49.1 [8.3]	49.1 [8.6]	50.9 [7.9]	50.9 [8.2]
18-39 (%)	9.7	10.2	10.8	11.3	6.7	6.9
40-64 (%)	87.0	86.5	87.0	86.4	89.6	89.4
65 or older (%)	3.3	3.3	2.2	2.2	3.7	3.7
Male (%)	61.7	61.1	60.5	59.8	63.1	62.7
Region						
Northeast (%)	9.1	9.1	9.3	9.3	8.2	7.9
South (%)	55.5	55.6	55.7	55.7	54.2	54.3
Midwest (%)	18.8	18.8	18.6	18.7	22.3	22.6
West (%)	16.6	16.5	16.4	16.3	15.4	15.2
Pre-index enrollment days						
Mean [SD]	618.3 [525.6]	508.7 [205.3]	556.9 [464.2]	451.7 [163.3]	475.7 [434.4]	431.0 [139.6]
Median (interquartile range)	408 (246-798)	416 (380-573)	373 (235-701)	400 (377-458)	288 (205-544)	391 (374-433)
Post-index enrollment days						
Mean [SD]	837.4 [625.3]	908.5 [672.4]	908.3 [624.4]	944.4 [673.9]	827.1 [596.9]	949.3 [679.7]
Median (interquartile range)	650 (362-1,163)	713 (359-1,286)	729 (420-1,241)	724 (384-1,339)	616 (372-1,132)	725 (376-1,359)
≤ 30 days post-index enrollment (%)	1.1	1.2	0.0	0.0	0.0	0.0
Charlson Comorbidity Index mean [SD]	0.36 [0.99]	0.33 [0.90]	0.25 [0.72]	0.23 [0.66]	0.35 [0.84]	0.32 [0.79]
AIDS/HIV (%)	2.0	2.0	2.1	1.5	1.4	1.0
Alcoholism (%)	3.8	2.2	2.4	1.4	3.7	2.0
Cerebrovascular disease (%)	2.6	2.6	1.6	1.8	2.6	2.9
Chronic obstructive pulmonary disease (%)	9.3	8.6	8.3	7.6	9.3	9.0
Congestive heart failure (%)	5.8	5.0	4.0	3.7	6.0	5.1
Dementia (%)	1.4	0.8	0.7	0.5	1.6	0.8
Diabetes (%)	15.1	13.7	12.1	12.0	19.3	14.8
Diabetes with complications (%)	3.0	2.5	2.0	1.8	3.2	2.2
Hemiplegia or paraplegia (%)	2.1	1.8	1.2	1.3	1.3	1.8
Malignancy (%)	0.9	0.6	0.6	0.4	0.7	0.7
Metastatic solid tumor (%)	1.1	1.0	0.4	0.6	0.5	1.0
Moderate/severe renal disease (%)	4.9	2.3	2.5	1.5	3.3	2.2
Myocardial infarction (%)	2.3	3.0	1.7	2.1	2.3	3.6
Pancreatitis (%)	0.4	0.1	0.4	0.1	0.4	0.1
Peptic ulcer disease (%)	2.3	1.2	1.2	1.0	1.8	1.3
Peripheral vascular disease (%)	4.5	3.9	3.1	2.7	3.4	3.8
Rheumatologic disease (%)	3.5	2.6	3.3	2.1	3.6	3.0
Substance abuse (%)	3.0	0.8	2.8	0.6	2.4	0.9
	HCV with Decompensated Cirrhosis	**Comparison**	**HCV with HCC**	**Comparison**	**HCV with Liver Transplant**	**Comparison**
Cohort Size (n)	4,249	39,872	959	9,004	891	7,992
Age, years mean [SD]	52.7 [9.1]	52.9 [9.5]	55.7 [8.7]	55.8 [9.0]	53.3 [7.6]	53.5 [8.3]
18-39 (%)	6.4	6.6	2.8	3.2	4.2	4.5
40-64 (%)	86.0	85.6	86.0	85.3	90.1	89.7
65 or older (%)	7.5	7.9	11.2	11.5	5.7	5.8
Male (%)	64.8	64.8	71.3	70.4	71.4	69.6
Region						
Northeast (%)	8.0	7.9	12.0	12.1	7.0	7.2
South (%)	54.8	55.2	53.6	54.5	56.3	57.1
Midwest (%)	19.6	19.2	16.1	15.7	19.2	18.3
West (%)	17.7	17.7	18.4	17.8	17.5	17.5

TABLE 2 Baseline Characteristics for Patients with Hepatitis C Virus Overall and by Stage of Liver Disease and for Matched Comparison Enrollees in a National Medical and Pharmacy Claims Database: 2002-2010 *(continued)*

	HCV with Decompensated Cirrhosis	Comparison	HCV with HCC	Comparison	HCV with Liver Transplant	Comparison
Pre-index enrollment days						
Mean [SD]	914.8 [673.6]	790.9 [156.1]	1,023.3 [699.2]	791.0 [160.7]	871.6 [621.1]	771.3 [140.5]
Median (interquartile range)	692 (379-1,270)	742 (724-790)	823 (445-1,457)	742 (724-790)	702 (365-1,212)	735 (721-766)
Post-index enrollment days						
Mean [SD]	522.3 [518.5]	736.0 [634.7]	422.0 [498.4]	744.6 [636.8]	658.2 [616.5]	713.6 [636.2]
Median (interquartile range)	358 (145-713)	534 (242-1,102)	238 (84-540)	546 (251-1,104)	454 (196-909)	479 (220-1,088)
≤ 30 days post-index enrollment (%)	6.7	6.3	8.7	6.0	4.6	7.0
Charlson Comorbidity Index mean [SD]	0.85 [1.66]	0.78 [1.52]	0.93 [1.83]	0.83 [1.59]	0.90 [1.46]	0.83 [1.44]
AIDS/HIV (%)	2.3	1.4	2.3	1.1	0.4	0.3
Alcoholism (%)	10.2	6.5	7.6	4.3	13.9	6.1
Cerebrovascular disease (%)	7.6	6.3	6.0	6.4	6.2	7.0
Chronic obstructive pulmonary disease (%)	13.7	12.9	15.1	12.8	11.6	14.8
Congestive heart failure (%)	13.6	10.3	12.4	11.1	16.6	13.9
Dementia (%)	4.9	2.3	2.8	1.9	3.7	3.0
Diabetes (%)	26.9	20.6	27.3	22.8	31.2	21.5
Diabetes with complications (%)	7.5	5.7	5.8	5.7	7.0	5.7
Hemiplegia or paraplegia (%)	7.0	4.5	5.6	4.3	4.0	4.7
Malignancy (%)	2.2	1.4	3.6	1.5	1.8	2.3
Metastatic solid tumor (%)	2.1	2.9	13.9	3.8	3.6	3.6
Moderate or severe renal disease (%)	13.9	5.5	11.8	5.8	32.2	6.7
Myocardial infarction (%)	4.6	6.4	5.0	7.1	5.2	11.5
Pancreatitis (%)	0.6	0.1	0.8	0.1	0.7	0.2
Peptic ulcer disease (%)	6.7	2.2	7.8	2.5	9.7	2.8
Peripheral vascular disease (%)	11.1	8.7	11.8	9.3	10.5	11.5
Rheumatologic disease (%)	5.0	4.4	3.8	4.1	4.5	5.1
Substance abuse (%)	4.7	1.6	2.4	1.1	3.6	2.2

AIDS/HIV = acquired immune deficiency syndrome/human immunodeficiency virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; SD = standard deviation.

occurred because comparison enrollees were selected based on the first date they qualified as comparators. Thus, there is a significantly large set of comparison enrollees in the initial years of the time frame.

For patients with diagnosed HCV (n = 34,597), a majority (78.0%, n = 26,977) did not have indication of cirrhosis, and 4.4% (n = 1,521) of patients had diagnosis codes indicating compensated cirrhosis but no evidence of AdvLD (Figure 1, Table 2). A total of 6,099 (17.6%) had indication of AdvLD, including 4,249 (12.3%) with decompensated cirrhosis without HCC or liver transplant, 959 (2.8%) with HCC and without liver transplant, and 891 (2.6%) with a liver transplant. Of all liver transplant patients, 509 (57.1%) were enrolled in the database for more than 1 year and contributed data for the analyses of cost beyond the first transplant year.

When patients were evaluated by stage of liver disease, differences in baseline characteristics between cases and comparisons were generally similar to those for the full cohort, although differences emerged with advancing liver disease (Table 2). Mean (SD) age ranged from 49.1 (8.3) years for HCV patients without liver disease to 55.7 (8.7) years for patients with HCC. The proportion of male patients similarly increased with liver disease severity, and the prevalence of comorbidities generally increased with advancing stage of liver disease.

PPPY Costs

All between-group differences in PPPY costs were significant ($P < 0.001$) overall and for each place of service or service type, and when classified by stage of liver disease (Table 3). Mean (SD) total PPPY costs, per bootstrap estimates, for all HCV patients were $19,660 ($210) versus $9,979 ($34) for the matched comparison cohort (mean difference of $9,681, SD = $176). Costs for all HCV patients were similarly distributed among inpatient, outpatient, professional, and prescription drugs, whereas emergency department services contributed substantially less. Costs in the category defined as other were nominal (mean $1, SD < $1) and thus are not included in Table 3. The distributions of costs by place of service were also relatively similar for HCV

TABLE 3 Per Patient Per Year All-Cause Health Care Costs[a] for Patients with Hepatitis C Virus Overall and by Stage of Liver Disease Versus Matched Comparison Enrollees in a National Medical and Pharmacy Claims Database: 2002-2010

	All HCV	Comparison	HCV without Liver Disease	Comparison	HCV with Compensated Cirrhosis	Comparison
N	34,597	330,435	26,977	259,189	1,521	14,378
Inpatient place of service ($)						
Observed	5,225	1,867	2,462	1,647	3,119	2,177
Bootstrapped mean [SD]	5,223 [115]	1,897 [16]	2,462 [66]	1,651 [18]	3,122 [267]	2,148 [73]
Median	5,222	1,897	2,460	1,651	3,111	2,142
Range	4,883-5,532	1,844-1,951	2,298-2,678	1,595-1,707	2,419-3,743	1,910-2,343
Outpatient place of service ($)						
Observed	4,901	2,544	4,005	2,293	4,086	3,012
Bootstrapped mean [SD]	4,899 [115]	2,561 [16]	4,000 [139]	2,279 [16]	4,099 [356]	3,018 [80]
Median	4,895	2,560	3,998	2,279	4,067	3,014
Range	4,596-5,354	2,521-2,618	3,728-4,422	2,239-2,316	3,258-5,408	2,804-3,238
Physician services ($)						
Observed	4,136	2,894	3,332	2,701	3,418	3,364
Bootstrapped mean [SD]	4,135 [47]	2,907 [11]	3,331 [48]	2,691 [12]	3,430 [187]	3,337 [56]
Median	4,136	2,907	3,329	2,690	3,433	3,340
Range	3,996-4,280	2,883-2,935	3,202-3,479	2,659-2,725	3,002-4,013	3,183-3,465
Emergency department place of service ($)						
Observed	110	61	96	59	139	65
Bootstrapped mean [SD]	109 [5]	59 [1]	96 [5]	57 [1]	137 [26]	59 [4]
Median	109	59	96	57	138	59
Range	95-121	55-62	82-111	54-61	60-224	50-68
Pharmacy ($)						
Observed	5,291	2,510	5,022	2,356	6,122	3,017
Bootstrapped mean [SD]	5,293 [47]	2,554 [11]	5,025 [52]	2,366 [11]	6,120 [209]	3,018 [52]
Median	5,295	2,554	5,024	2,365	6,116	3,018
Range	5,146- 5,405	2,529-2,585	4,899-5,167	2,339-2,395	5,502-6,820	2,883-3,193
Total ($)						
Observed	19,665	9,877	14,917	9,056	16,887	11,637
Bootstrapped mean [SD]	19,660 [210]	9,979 [34]	14,915 [196]	9,044 [38]	16,911 [659]	11,581 [168]
Median	19,664	9,976	14,916	9,044	16,925	11,577
Range	19,072-20,195	9,889-10,069	14,464-15,686	8,962-9,156	15,313-18,806	11,158-11,978
	HCV with Decompensated Cirrhosis	**Comparison**	**HCV with HCC**	**Comparison**	**HCV with Liver Transplant**	**Comparison**
N	4,249	39,872	959	9,004	891	7,992
Inpatient place of service ($)						
Observed	18,520	3,163	20,358	3,139	64,466	4,612
Bootstrapped mean [SD]	18,560 [787]	3,096 [78]	20,195 [1,443]	2,998 [138]	64,656 [3,828]	4,513 [216]
Median	18,559	3,092	20,070	3,002	64,433	4,519
Range	16,108-20,815	2,864-3,342	16,591-26,174	2,625-3,365	55,630-74,680	3,946-5,070
Outpatient place of service ($)						
Observed	9,608	3,948	16,340	4,320	18,397	5,404
Bootstrapped mean [SD]	9,628 [369]	3,810 [78]	16,276 [1,232]	3,969 [163]	18,353 [1,022]	5,439 [193]
Median	9,589	3,813	16,150	3,980	18,299	5,427
Range	8,748-10,946	3,629-4,059	13,219-19,676	3,585-4,404	16,172-21,485	4,943-5,940
Professional services ($)[b]						
Observed	8,296	3,869	13,623	4,150	16,987	5,396
Bootstrapped mean [SD]	8,303 [262]	3,777 [48]	13,504 [1,291]	4,081 [103]	16,984 [776]	5,287 [131]
Median	8,299	3,780	13,367	4,071	16,989	5,286
Range	7,470-8,978	3,667-3,908	10,485-18,225	3,848-4,406	15,006-19,607	4,923-5,633

TABLE 3 Per Patient Per Year All-Cause Health Care Costs[a] for Patients with Hepatitis C Virus Overall and by Stage of Liver Disease Versus Matched Comparison Enrollees in a National Medical and Pharmacy Claims Database: 2002-2010 *(continued)*

	HCV with Decompensated Cirrhosis	Comparison	HCV with HCC	Comparison	HCV with Liver Transplant	Comparison
Emergency department place of service ($)						
Observed	213	71	152	58	202	94
Bootstrapped mean [SD]	215 [30]	72 [6]	156 [39]	54 [7]	209 [95]	92 [11]
Median	214	71	156	54	198	92
Range	139-311	58-95	70-274	39-79	0-546	65-126
Pharmacy ($)						
Observed	5,239	3,276	8,046	3,465	13,061	4,284
Bootstrapped mean [SD]	5,235 [161]	3,342 [38]	8,068 [690]	3,435 [103]	13,076 [468]	4,341 [105]
Median	5,258	3,345	8,009	3,421	13,082	4,343
Range	4,774-5,596	3,206-3,430	6,277-10,134	3,215-3,780	12,065-14,525	4,024-4,596
Total ($)						
Observed	41,878	14,327	58,529	15,132	113,116	19,791
Bootstrapped mean [SD]	41,943 [1,129]	14,098 [164]	58,208 [2,912]	14,537 [325]	113,282 [4,908]	19,672 [426]
Median	41,832	14,093	57,959	14,547	113,710	19,680
Range	38,670-44,936	13,609-14,562	50,878-66,116	13,729-15,536	101,474-125,998	18,388-20,704

[a]*Descriptive statistics (mean, SD, median, and range) were estimated using bootstrapping with replacement and using 250 draws of patients equal to the number of patients in the stratum to calculate mean PPPY values. Observed mean = total patient allowed charges divided by total patient days × 365. Bootstrapped mean = mean of the 250 bootstrap samples; SD = SD of the 250 sampled means; median = the median value of the 250 means; and range = minimum and maximum values of the 250 sample means. P < 0.001 for case vs. comparison for total costs and for all cost categories. Other-category costs were nominal (all means ≤ $10) and are not reported. All costs are reported in 2009 dollars.*

[b]*Professional services were defined as allowable costs from all CMS-1500 (formerly known as HCFA-1500) claims and from UB-92 claims where the revenue code indicated a professional fee.*

CMS = Centers for Medicare & Medicaid Services; HCC = hepatocellular carcinoma; HCFA = Health Care Financing Administration; HCV = hepatitis C virus; PPPY = per patient per year; SD = standard deviation; UB = Uniform Billing.

patients and matched comparison enrollees.

Total PPPY costs ranged from a mean (SD) $14,915 ($196) for HCV patients without indication of liver disease and $16,911 ($659) for patients with HCV and compensated cirrhosis to $113,282 ($4,908) for patients receiving a liver transplant (Table 3). Costs for these HCV cohorts were significantly higher than those of the matched comparison cohorts with a mean difference of $5,870 ($157) and $5,330 ($491) PPPY for HCV without liver disease and HCV with compensated cirrhosis, respectively, and $93,609 ($4,482) for HCV patients receiving a liver transplant ($P < 0.001$; Table 4).

Incremental all-cause health care costs for transplant patients were further evaluated by time post-transplant on the hypothesis that on average, transplant costs would be higher during the year of transplant than in subsequent years (Table 4). Mean (SD) PPPY total health care costs the first year following transplant for all transplant patients, regardless of post-index enrollment, were $190,995 ($8,022) for transplant patients, which was $168,643 ($7,487) higher than for matched comparison patients. Not surprisingly, inpatient expenses (mean $118,394, SD $6,507) represented the largest proportion of costs the year of transplant (data not shown). Total PPPY health care cost for transplant patients after year 1 for those with at least 1 year of follow-up was less than during the transplant year (mean $54,885, SD $4,409; data not shown), although the incremental difference between these patients and matched comparison enrollees with at least 1 year of follow-up remained high at $38,015 ($3,797).

HCV-related PPPY pharmacy use and costs were evaluated for the HCV cohort during the post-index period (data not shown). Of patients in each of the HCV cohorts, 36.6% with compensated cirrhosis had at least 1 prescription claim for antiviral therapy used to treat HCV, and 30.4% of HCV patients without indication of liver disease had antiviral utilization. Antiviral use was identified in 16.7% of transplant patients, 12.5% of patients with decompensated cirrhosis, and 9.5% of patients with HCC. Mean (SD) PPPY costs for HCV-related antiviral therapy were $2,445 ($30) for HCV without liver involvement, $3,243 ($153) for HCV with compensated cirrhosis, and $1,474 ($85) for HCV with decompensated cirrhosis. HCV antiviral PPPY costs for HCC and transplant patients were $1,599 ($213) and $1,653 ($189), respectively.

Discussion

This study was conducted to evaluate all-cause health care costs associated with HCV and AdvLD from a commercial

TABLE 4 Incremental All-Cause Per Patient Per Year Health Care Costs[a] for Patients with Hepatitis C Relative to Matched Comparison Enrollees in a National Medical and Pharmacy Claims Database: 2002-2010

	HCV without Liver Disease	Compensated Cirrhosis	Decompensated Cirrhosis	HCC	All Liver Transplant	Liver Transplant First Year[b]	Liver Transplant After First Year[b]	All HCV
N	26,977	1,521	4,249	959	891	282	509	34,597
Inpatient place of service ($)								
Mean [SD]	810 [49]	974 [194]	15,464 [710]	17,197 [1,304]	60,143 [3,612]	113,016 [6,216]	20,333 [3,203]	3,326 [99]
Median	809	970	15,466	17,067	59,915	112,829	20,201	3,325
Outpatient place of service ($)								
Mean [SD]	1,721 [123]	1,081 [275]	5,818 [292]	12,307 [1,069]	12,915 [829]	22,383 [1,477]	6,412 [581]	2,338 [99]
Median	1,719	1,053	5,776	12,170	12,872	22,365	6,409	2,335
Professional services ($)[c]								
Mean [SD]	641 [37]	93 [130]	4,526 [213]	9,423 [1,188]	11,697 [646]	22,380 [1,055]	3,870 [518]	1,228 [36]
Median	639	93	4,519	9,296	11,703	22,406	3,876	1,230
Emergency department place of service ($)								
Mean [SD]	39 [4]	78 [23]	143 [24]	102 [32]	116 [84]	262 [196]	2 [8]	50 [4]
Median	38	79	143	102	106	257	(4)	50
Pharmacy ($)								
Mean [SD]	2,659 [41]	3,102 [157]	1,893 [123]	4,632 [587]	8,736 [363]	10,596 [449]	7,402 [395]	2,739 [37]
Median	2,659	3,098	1,913	4,588	8,740	10,575	7,394	2,741
Total ($)								
Mean [SD]	5,870 [157]	5,330 [491]	27,845 [965]	43,671 [2,588]	93,609 [4,482]	168,643 [7,487]	38,015 [3,797	9,681 [176]
Median	5,873	5,348	27,739	43,412	94,030	168,845	38,030	9,688

[a]*Incremental cost was defined as PPPY cost difference (i.e., PPPY cost for each HCV or AdvLD patient group minus PPPY cost for its matched comparison group). Descriptive statistics (mean, SD, median, and range) were estimated using bootstrapping with replacement and using 250 draws of patients equal to the number of patients in the stratum to calculate mean PPPY values. Bootstrapped mean = mean of the 250 bootstrap samples; SD = SD of the 250 sampled means; median = the median value of the 250 means; and range = minimum and maximum values of the 250 sample means. All costs are reported in 2009 dollars.*

[b]*Liver transplant patients were stratified by patients with 1 year or less of enrollment and greater than 1 year of enrollment post-transplant.*

[c]*Professional services were defined as allowable costs from all CMS-1500 (formerly known as HCFA-1500) claims and from UB-92 claims where the revenue code indicated a professional fee.*

AdvLD = advanced liver disease; CMS = Centers for Medicare & Medicaid Services; HCC = hepatocellular carcinoma; HCFA = Health Care Financing Administration; HCV = hepatitis C virus; PPPY = per patient per year; SD = standard deviation; UB = Uniform Billing.

payer perspective using a matched cohort design to control for numerous factors that could influence cost trends including age, prior health care costs, and comorbidities. For the overall HCV cohort of 34,597 patients, the estimated PPPY cost from 2002 to first quarter of 2010 was $19,660 per patient (in 2009 dollars). This amount was almost twice as high as the PPPY cost for the 330,435 matched comparison enrollees ($9,979). An important feature of this study was the evaluation of health care costs based on the stage of liver disease. Costs were substantially higher for the 17.6% of HCV patients who had progressed to AdvLD than for those without AdvLD. These findings confirm the incremental costs of HCV patients within managed care membership and the proportional increase in these costs as patients with HCV advance in their disease.

While this is the first study, to our knowledge, to present costs by stage of liver disease for an entire HCV cohort, the overall health care cost for HCV patients was similar to that reported in a recent study conducted in a large commercial claims database by Davis et al.[19] The study by Davis et al. estimated annual health care costs in all HCV patients to be $20,961. Incremental costs for HCV patients versus comparison patients in the Davis et al. study ($15,510) were higher than in the current study. A potential explanation for this discrepancy is that the Davis et al. study did not match on specific comorbidities or pre-index date costs, nor were these patient characteristics included in their regression analyses.

The PPPY health care cost identified in the current study for patients with HCV but with no indication of liver disease was $14,915. This amount was $5,870 higher than that of matched comparisons and close to twice the U.S. per capita annual health care expenditure of approximately $8,000 in 2009,[5] suggesting that all-cause health care costs for HCV patients are higher than those of non-HCV patients even in the absence of AdvLD. Other studies have found that patients with HCV who have not developed liver disease generally have higher costs after diagnosis than before diagnosis, as well as higher costs

than comparisons.[31,32] In a Canadian study of patients newly diagnosed with HCV, mean per patient all-cause health care costs increased by 34% from $2,630 in the pre-diagnosis year to $3,514 in the first year after diagnosis.[31] Only a small portion of the post-diagnosis costs (10%) in the Canadian study could be explained by liver-related care, which did not distinguish between screening/monitoring and AdvLD. Furthermore, costs for prescription drugs were not included, which suggests that patients with HCV have higher overall health care costs than similar patients, even when the costs of antiviral therapy are not considered.

From an economic perspective, antiviral therapy for HCV is not inconsequential. For instance, 2011 average wholesale prices for a month of antiviral treatment range from approximately $1,500 to $3,200, depending on drug and dose.[33] These antiviral therapies, namely interferon or peg-interferon with ribavirin, have been shown to be reasonably cost-effective when used to prevent progression to AdvLD as a single treatment cycle of 24 or 48 weeks.[34] Specifically, costs per quality adjusted life year (QALY) when compared with no treatment are generally estimated to fall below cost effectiveness thresholds (e.g., <£30,000 per QALY or <U.S.$50,000 per QALY), although one study found that antiviral treatment may not be cost-effective in patients with genotype 1 who have progressed to cirrhosis.[34-37]

In the present study, HCV-related antiviral therapy costs (e.g., interferon α-2a and α-2b, interferon alphacon a, pegylated interferon α-2a and α-2b, and ribavirin), represented a large component of drug costs for HCV patients without AdvLD or with compensated cirrhosis, with PPPY costs for antiviral therapy of $2,445 and $3,243, respectively. HCV antiviral PPPY costs for HCC and transplant patients were less at $1,599 and $1,653, respectively, which represents a smaller proportion of both overall drug costs and incremental drug costs between HCC and transplant patients and their matched comparison enrollees. Lower costs may be attributed to HCC and transplant patients having received antiviral therapy prior to having progressed to a more advanced stage of liver disease or the risk of patients decompensating with HCV treatment. Antiviral therapy was not captured at the patient level by specific treatment regiments. As such, some patients may have been on antiviral therapy for other reasons. Some of the interferon use, for instance, may have been without ribavirin for the treatment of melanoma or other cancers. Thus, this analysis may overstate HCV antiviral drug costs, particularly in the HCC cohort, but given the population and the relatively limited use of interferons in cancer treatment, it is believed that the misclassification of these costs is minimal.

This study provides important information for managed care, because an increased investment in pharmacotherapy early on in HCV may delay the onset of AdvLD and associated costs.[34,38] However, 2 new protease inhibitors, telaprevir and boceprevir, were approved for use in combination with peginterferon/ribavirin in genotype 1 HCV patients in May of 2011.[39] As these combination therapies are more expensive than peginterferon/ribavirin alone, the increased investment up front will need to be weighed against the benefits of further delay in disease progression. In addition, it is likely that identification of appropriate genotypes to optimize treatment efficacy will also assist MCOs.

The current study and the Davis et al. study have provided higher estimates of HCV costs than observed in previous studies, which ranged from approximately $5,000 to $13,000 per patient per year.[16-18] Medical inflation may explain some of this difference, but cost increases over time likely also reflect the HCV "age wave." Recent studies, recognizing this age-related trend in HCV disease severity and related costs, have projected short- and long-term HCV costs overall and have isolated costs driven by AdvLD.[9,40,41] Overall, direct medical costs for HCV in the United States over a 10-year time frame (2010-2019) have been estimated to be $10.7 billion (1999 dollars; range of $6.5 to $13.5 billion) representing approximately $1 billion in direct costs per year.[9] For the current study, and assuming that one-quarter of the estimated 3.5 million HCV-infected persons in the United States are diagnosed, our PPPY cost estimate of approximately $10,000 projects to an annual U.S. burden of $8-$9 billion per year.

Recent nonpeer-reviewed cost estimates have reported costs specifically for private and public payers while also considering the impact of AdvLD. Short-term HCV cost trends from a private payer perspective are projected to increase 88% between 2010 and 2015 (from $21.9 to $41.2 billion) with the proportion of HCV costs related to AdvLD increasing from one-third to more than one-half of total HCV costs by 2015.[40] From a public payer perspective, annual HCV medical costs are projected to increase from $12.2 billion in 2010 to $51.4 billion in 2028 (321% increase).[41] The proportion of costs attributable to AdvLD for public payers is estimated to increase from 19% to 40% over the same time frame.[41] In considering HCV costs, the trend of undiagnosed HCV is also important to monitor because as more HCV-infected patients experience disease progression and are diagnosed, the costs associated with diagnosis and treatment will further amplify the incremental cost differences between those with HCV and those without HCV.

Thus, for MCOs overall, and particularly for those with managed Medicaid beneficiaries, HCV is an important disease to monitor. Cost data from this study, over all HCV patients and stratified by stage of liver disease, can facilitate the projection of short- and long-term costs associated with HCV. While this study addressed the overall and incremental costs associated with HCV and AdvLD, the study did not address cost or cost-effectiveness of treatment, particularly as it relates to agents recently approved (boceprevir and telaprevir). Thus, additional work is encouraged to assist managed care decision makers in making such trade-offs in cost and outcome; however, the current study provides a good foundation of information about health care costs associated with HCV and AdvLD to facilitate this research.

Limitations

First, the estimates of costs associated with HCV infection were based on comparisons of patients with HCV matched to patients of same gender and of similar age and health status. Health status was based on a CCI, plus HIV/AIDS and select conditions that are not part of the CCI calculation. While the approach of matching HCV patients to similar comparison patients can be considered a strength of this study because it helps to isolate HCV-associated costs, the matching process itself introduced several challenges and limitations. Due to high cost variance, several criteria had to be loosened. Widening the age band, relaxing geographic regions to states, and dropping index year and substance abuse as a matched comorbidity were the changes made to the original matching criteria. With this matched cohort design, we estimated HCV-related costs as incremental differences in all-cause costs for HCV patients versus matched comparison enrollees, rather than measuring costs for specific HCV- and AdvLD-related services and treatments.

Second, this study used the CCI to match case and comparison patients based on the presence of common chronic and other less common conditions that significantly influence health. However, using CCI as a measure of health status is imprecise and may not completely reflect the severity of illness in the study cohort, which can lead to residual confounding.[42] Given matching limitations in general, and those related specifically to CCI, there is a risk that observed differences between HCV and comparison patients might be due to health conditions other than HCV. Thus, to address limitations of CCI, we also matched on pre-index health-care costs. However, if pre-index costs among HCV patients were in part due to the process of diagnosing HCV (e.g., liver function and HCV screenings), matching on pre-index costs may lead to underestimation of the true costs of HCV in the post-index period because of higher baseline costs.

Third, this study also depended on ICD-9-CM coding of diseases in establishing case and comparison cohorts and in establishing stage of liver disease in patients infected with HCV. A well-recognized challenge of claims data is that coding errors or omitted diagnosis coding could lead to misclassification of patients by diagnosis and severity, and therefore introduce bias.[43,44] In the present study, patients who were infected with HCV but who did not have a diagnosis in the database were included in the comparison cohort. This potential bias may have led to an underestimation of incremental costs for HCV patients relative to comparison patients if, for example, comparison patients experienced costs associated with liver disease during their post-index observation period but in whom the underlying cause of HCV had not yet been identified. In addition, clinical values, such as histology findings and laboratory values, were not available to validate whether ICD-9-CM coding appropriately classified patients by the presence of liver disease or HCC. It is therefore possible that some HCV patients were misclassified by stage of liver disease. However, due to the severity of AdvLD, the risk of such misclassification is likely small.

Fourth, this study did not require that all patients have 1 full year of cost data after the index date. This was done to avoid selection bias that would be introduced by retaining only those patients healthy enough to survive 1 year after index date. However, the most ill patients, such as patients with HCC or transplant, may have high costs just after diagnosis of AdvLD that taper off over the course of a year; therefore, simply annualizing costs at the patient level likely would have overestimated annual costs. For this reason, the present study combined a standard PPPY calculation with bootstrapping to generate descriptive statistics. There is an inherent assumption in this approach that the bootstrap sample costs represent the costs of the study population, and the minimum and maximum values estimated may not be reliable estimates of the minimum and maximum in the population.[45] However, bootstrap estimates have the benefit of being normally distributed, thereby supporting the use of more robust parametric t-tests as opposed to nonparametric tests generally required for cost data that tend to be skewed.

Finally, this study was based on a sample of patients with commercial health insurance and was conducted from a private payer perspective. It does not consider the costs of HCV borne by the patients, including costs related to over-the-counter therapies, transportation for treatment, governmental expenses, and work loss. Furthermore, the findings may not be generalizable to the uninsured or to those with Medicaid, Medicare, or Department of Veterans Affairs coverage, because patients and cost structures differ among payers. However, the degree of cost differences between HCV patients and comparison enrollees by stage of liver disease could provide insight to other payer types as they consider a range of current and future scenarios related to the cost of treating HCV in their population.

Conclusion

This large, retrospective matched comparison cohort study found that patients diagnosed with HCV infection have PPPY all-cause costs that on average are almost twice as much as those of non-HCV patients. Furthermore, PPPY costs were higher in patients with AdvLD. While a majority (82.4%) of patients in the current study had not progressed to AdvLD, epidemiologic data predict that the number of HCV patients with AdvLD and thus health care costs for the HCV population will increase substantially in the next 2 decades.[8] Data from this study may help MCOs project future HCV costs and facilitate planning for HCV patient management efforts.

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Concept and design were performed by Brixner and Deniz with the assistance of all other authors. Data were collected by Hane and McGarry, and analyzed by Biskupiak, Hane, and Deniz with the assistance of McAdam-Marx and McGarry. The manuscript was written primarily by McAdam-Marx with the assistance of Biskupiak and Deniz. Revisions were made primarily by McAdam-Marx with the assistance of all other authors.

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REFERENCES

1. Baldo V, Baldovin T, Trivello R, Floreani A. Epidemiology of HCV infection. *Curr Pharm Des.* 2008;14(17):1646-54.

2. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis.* 2005;5(9):558-67.

3. Wasley A, Alter MJ. Epidemiology of hepatitis C: geographic differences and temporal trends. *Semin Liver Dis.* 2000;20(1):1-16.

4. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med.* 2006;144(10):705-14.

5. Centers for Disease Control and Prevention. Hepatitis C information for health professionals: Statistics and surveillance. Available at: http://www.cdc.gov/hepatitis/HCV/StatisticsHCV.htm. Accessed August 5, 2011.

6. Seeff LB. Natural history of chronic hepatitis C. *Hepatology.* 2002;36(5 Suppl 1):S35-S46.

7. Beasley RP, Alter HJ, Brandeau ML, et al. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C.* Washington, DC.: Institute of Medicine; 2010. Available at: http://www.iom.edu/Reports/2010/Hepatitis-and-Liver-Cancer-A-National-Strategy-for-Prevention-and-Control-of-Hepatitis-B-and-C.aspx. Accessed August 5, 2011.

8. Pyenson B, Fitch K, Iwasaki K. *Consequences of Hepatitis C Virus (HCV): Costs of a Baby Boomer Epidemic of Liver Disease.* New York, NY: Milliman, Inc.; May 2009. Available at: http://publications.milliman.com/research/health-rr/pdfs/consequences-hepatitis-c-virus-RR05-18-09.pdf. Accessed August 5, 2011.

9. Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health.* 2000;90(10):1562-69. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1446368/?tool=pubmed. Accessed August 5, 2011.

10. Di Bisceglie AM, Lyra AC, Schwartz M, et al. Hepatitis C-related hepatocellular carcinoma in the United States: influence of ethnic status. *Am J Gastroenterol.* 2003;98(9):2060-63.

11. Boyer JL, Chang EB, Collyar DE, et al. Management of hepatitis C: National Institutes of Health consensus conference statement. June 10-12, 2002. Available at: http://consensus.nih.gov/2002/2002HepatitisC2002116html.htm. Accessed August 5, 2011.

12. U.S. Department of Health and Human Services, Health Resources and Services Administration. 2009 OPTN/SRTR Annual Report: Transplant Data 1999-2008. 2009. Available at: http://optn.transplant.hrsa.gov/ar2009/default.htm. Accessed August 5, 2011.

13. Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl.* 2003;9(4):331-38.

14. Wise M, Bialek S, Finelli L, Bell BP, Sorvillo F. Changing trends in hepatitis C-related mortality in the United States, 1995-2004. *Hepatology.* 2008;47(4):1128-35.

15. Leigh JP, Bowlus CL, Leistikow BN, Schenker M. Costs of hepatitis C. *Arch Intern Med.* 2001;161(18):2231-37. Available at: http://archinte.ama-assn.org/cgi/content/full/161/18/2231. Accessed August 5, 2011.

16. Armstrong EP, Charland SL. Burden of illness of hepatitis C from a managed care organization perspective. *Curr Med Res Opin.* 2004;20(5):671-79.

17. Su J, Brook RA, Kleinman NL, Corey-Lisle P. The impact of hepatitis C virus infection on work absence, productivity, and healthcare benefit costs. *Hepatology.* 2010;52(2):436-42.

18. Rosenberg DM, Cook SF, Lanza LL. Health care, treatment patterns and cost of services for patients infected with chronic hepatitis C virus in a large insured New England population. *J Viral Hepat.* Sep 2000;7(5):361-67.

19. Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. *J Clin Gastroenterol.* 2011;45(2):e17-24.

20. Halpern R, Becker L, Iqbal SU, Kazis LE, Macarios D, Badamgarav E. The association of adherence to osteoporosis therapies with fracture, all-cause medical costs, and all-cause hospitalizations: a retrospective claims analysis of female health plan enrollees with osteoporosis. *J Manag Care Pharm.* 2011;17(1):25-39. Available at: http://www.amcp.org/data/jmcp/25-39.pdf.

21. Poordad F, Theodore D, Sullivan J, Grotzinger K. Medical resource utilisation and healthcare costs in patients with chronic hepatitis C viral infection and thrombocytopenia. *J Med Econ.* 2011;14(2):194-206.

22. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology.* 1997;112(2):463-72.

23. The Dartmouth Institute for Health Policy & Clinical Practice. The Dartmouth Atlas of Health Care: Downloads. Available at: http://www.dartmouthatlas.org/tools/downloads.aspx. Accessed August 5, 2011.

24. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45(6):613-19.

25. Begley CE, Annegers JF, Lairson DR, Reynolds TF. Methodological issues in estimating the cost of epilepsy. *Epilepsy Res.* 1999;33(1):39-55.

26. Braman SS. The global burden of asthma. *Chest*. 2006;130(1 Suppl):4S-12S. Available at: http://chestjournal.chestpubs.org/content/130/1_suppl/4S.long. Accessed August 5, 2011.

27. U.S. Department of Labor, Bureau of Labor Statistics. Consumer Price Index—All Urban Consumers. (CUUR0000SAM2). 2010. Available at: http://data.bls.gov/cgi-bin/surveymost. Accessed August 5, 2011.

28. Efron B, Tibshirani R. *An Introduction to the Bootstrap (Chapman & Hall/CRC Monographs on Statistics & Applied Probability)*. Boca Raton, FL: Chapman & Hall/CRC; 1993.

29. Good PI. *Resampling Methods*. Boston, MA: Birkhäuser; 2006.

30. Rascati KL, Smith MJ, Neilands T. Dealing with skewed data: an example using asthma-related costs of Medicaid clients. *Clin Ther*. 2001;23(3):481-98.

31. Nguyen TH, Jacobs P, Hanrahan A, et al. Health care costs of persons with newly diagnosed hepatitis C virus: a population-based, observational study. *J Viral Hepat*. 2008;15(9):634-40.

32. McCombs J, Yu Y, Saab S. A longitudinal database study of the economic consequences of chronic hepatitis C virus (HCV) infections in the U.S. Paper presented at: International Society for Pharmacoeconomics and Outcomes Research Fifteenth Annual International Meeting; May 2010, 2010; Atlanta, GA. Abstract #23901. Available at: http://www.ispor.org/research_study_digest/index.asp. Accessed August 5, 2011.

33. *Red Book*. Ann Arbor, MI: Thompson Reuters; 2010.

34. Sroczynski G, Esteban E, Conrads-Frank A, et al. Long-term effectiveness and cost-effectiveness of antiviral treatment in hepatitis C. *J Viral Hepat*. 2010;17(1):34-50. Available at: http://eurpub.oxfordjournals.org/content/19/3/245.long. Accessed August 5, 2011.

35. Brady B, Siebert U, Sroczynski G, et al. Pegylated interferon combined with ribavirin for chronic hepatitis C virus infection: an economic evaluation [Technology report #82]. Ottawa: Canadian Agency for Drugs and Technologies in Health. March 2007. Available at http://cadth.ca/en/products/health-technology-assessment/publication/697. Accessed August 5, 2011.

36. Fonseca MC, Araújo GT, Araújo DV. Cost effectiveness of peginterferon alfa-2B combined with ribavirin for the treatment of chronic hepatitis C in Brazil. *Braz J Infect Dis*. 2009;13(3):191-99.

37. Grishchenko M, Grieve RD, Sweeting MJ, et al.; Trent HCV Study Group. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. *Int J Technol Assess Health Care*. 2009;25(2):171-80.

38. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49(4):1335-74.

39. U.S. Food and Drug Administration. "Spotlight on Drug Innovation": An ongoing update of FDA's novel new drug approvals of 2011. July 21, 2011. Available at: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm254242.htm. Accessed August 5, 2011.

40. Sullivan JR, Velez F, Deniz B, Iwasaki K, Pyenson B. Projected short-term cost burden of hepatitis C-related advanced liver disease for private payers. Paper presented at: Academy of Managed Care Pharmacy 2010 Educational Conference; October 13-15, 2010; St. Louis, MO. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=8382.

41. Sullivan JR, Velez F, Deniz B, Pyenson B, Iwasaki K. Projected cost burden of hepatitis C-related advanced liver disease for public payers. Paper presented at: Academy of Managed Care Pharmacy 2010 Educational Conference; October 13-15, 2010; St. Louis, MO. Available at: http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=8382.

42. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. *Int J Epidemiol*. 2000;29(5):891-98.

43. Jollis JG, Ancukiewicz M, DeLong ER, Pryor DB, Muhlbaier LH, Mark DB. Discordance of databases designed for claims payment versus clinical information systems. Implications for outcomes research. *Ann Intern Med*. 1993;119(8):844-50.

44. Lewis NJ, Patwell JT, Briesacher BA. The role of insurance claims databases in drug therapy outcomes research. *Pharmacoeconomics*. 1993;4(5):323-30.

45. Mooney CZ, Duval RD. Bootstrapping: *A Nonparametric Approach to Statistical Inference*. Newbury Park, CA: Sage Publications, Inc.; 1993.

APPENDIX Diagnosis Codes for Cohort Identification, Stratifying by Liver Disease Involvement/Severity, and Identifying Comorbidities in a National Medical and Pharmacy Claims Database

	Code[a]	Description	HCV without AdvLD	HCV with AdvLD	Comparison to HCV without AdvLD	Comparison to HCV with AdvLD
Hepatitis-related codes						
HCV	070.44	Chronic hepatitis C with hepatic coma (HCV with AdvLD only)	E	I	E	E
	070.54	Chronic hepatitis C without mention of hepatic coma	I	I	E	E
	070.70	Unspecified viral hepatitis C without hepatic coma	I	I	E	E
	070.71	Unspecified viral hepatitis C with hepatic coma	E	I	E	E
HCV	070.41	Acute hepatitis C with hepatic coma			E	E
	070.51	Acute hepatitis C without mention of hepatic coma			E	E
	V02.62	Hepatitis C carrier			E	E
HBV	070.2x	Viral hepatitis B with hepatic coma	E	E	E	E
	070.3x	Viral hepatitis B without mention of hepatic coma	E	E	E	E
HCV liver disease stratification (mutually exclusive)						
Cirrhosis	571.2	Alcoholic cirrhosis of liver	S	S	E	E
	571.5	Cirrhosis of liver without mention of alcohol (fibrosis stage 4)	S	S	E	E
	571.6	Biliary cirrhosis (fibrosis stage 1-3)	S	S	E	E
Decompensated cirrhosis[b]	070.44	Chronic HCV with hepatic coma	E	S	E	E
	070.71	Unspecified hepatitis with hepatic coma	E	S	E	E
	348.3x	Encephalopathy not otherwise specified	E	S	E	E
	456.0, 456.1, 456.2x	Esophageal varices in diseases classified elsewhere with or without bleeding	E	S	E	E
	572.2	Hepatic encephalopathy	E	S	E	E
	572.3	Portal hypertension	E	S	E	E
	572.4	Hepatorenal syndrome	E	S	E	E
	782.4	Jaundice	E	S	E	E
	789.59	Other ascites	E	S	E	E
Liver cancer	155	Malignant neoplasm of liver and intrahepatic bile duct	E	S	E	E
Liver transplant	V42.7	Liver transplant	E	S	E	E
	47135	Liver allotransplantation; orthotopic, partial or whole, from cadaver or living donor	E	S	E	E
	47136	Liver allotransplantation; heterotopic, partial or whole, from cadaver or living donor	E	S	E	E
	50.5x	Liver transplant	E	S	E	E

Comorbidities (Descriptive for All Cohorts)

Code[a]	Description	Code[a]	Description
042	HIV/AIDS	398.xx, 402.01, 402.11, 402.91, 428.xx	Heart failure/rheumatic heart disease
250.xx	Diabetes (excluding 250.4x-250.6x)		
250.4x-250.6x	Diabetes with complications	401.xx-404.xx	Hypertension
277.0, 277.1	Pancreatitis	403.xx, 404.xx, 580.xx, 581.xx, 582.xx-586.xx	Moderate or severe renal disease
290, 291, 294	Dementia		
291.x, 303.xx	Alcoholism	410.xx, 411.xx	Myocardial infarction and ischemic heart disease
296.2x, 296.3x, 309.0, 309.1, 311.xx	Depression	440-447	Peripheral vascular disease
		491.xx-493.xx	Chronic obstructive pulmonary disease and asthma
304.xx	Other substance abuse	531.xx-534.xx	Peptic ulcer disease
342, 434, 436, 437	Hemiplegia or paraplegia	710, 714, 725	Rheumatologic disease

[a]*ICD-9-CM diagnosis code, ICD-9-CM procedure code, or CPT code.*

[b]*When diagnosed in patients with HCV, these conditions are suggestive of decompensated cirrhosis.*

AdvLD = advanced liver disease; CPT = Current Procedural Terminology; E = exclusion criterion; HBV = Hepatitis B virus; HCV = hepatitis C virus; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; I = inclusion criterion; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; S = liver disease stratification.