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Clinical characteristics, healthcare costs, and resource utilization in hepatitis C vary by genotype

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All authors approved the final version of the manuscript. AGH led study development and design, analyses, and manuscript content development and revision. LR contributed to study development and design, analyses, and manuscript content development and revision. CP contributed to study development and design and manuscript content development and revision. CBP conducted data analysis and assisted in interpretation of results. BAF contributed to study development and design and manuscript content development and revision.

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ABSTRACT

Background: In the United States, approximately 3 million people are infected with hepatitis C virus (HCV). Genotypes of HCV variably affect disease progression and treatment response. However, the relationships between HCV genotypes and liver disease progression, healthcare resource utilization, and healthcare costs have not been fully explored.

Research design and methods: In this retrospective study of patients with chronic hepatitis C (CHC), healthcare claims from a large US health plan were used to collect data on patient demographic and clinical characteristics.

Main outcome measures also include healthcare resource utilization (HCRU) and healthcare costs. Linked laboratory data provided genotype and select measures to determine liver disease severity.

Results: The sample (mean age 50.6 years, 63.5% male) included 10,331 patients, of which 79.1% had genotype (GT)1, 12.8% had GT2, and 8.1% had GT3. Descriptive analyses demonstrated variation by HCV genotype in liver and non-liver related comorbidities, liver disease severity, and healthcare costs. The highest percentage of patients with liver-related comorbidities and advanced liver disease was found among those with GT3. Meanwhile, patients with GT2 had lower HCRU and the lowest costs, and patients with GT1 had the highest total all-cause costs. These differences may reflect differing rates of non-liver-related comorbidities and all-cause care. Multivariable analyses showed that genotype was a significant predictor of costs and liver disease severity: compared with patients having GT1, those with GT3 were significantly more likely to have advanced liver disease. Patients with GT2 were significantly less likely to have advanced disease and more likely to have lower all-cause costs.

Limitations: Results may not be generalizable to patients outside the represented commercial insurance plans, and analysis of a prevalent population may underestimate HCRU and costs relative to a sample of treated patients.

Conclusions: These results suggest that liver disease progression varies by genotype and that CHC patients with GT3 appear to have more severe liver disease. These findings highlight the importance of effective HCV treatment for all patients and support guidelines for treatment of high-risk patients, including those with GT3.

Key words: hepatitis C, liver disease severity, hepatitis C genotype, healthcare administrative claims

Short title: Variation in clinical characteristics by hepatitis C genotype

INTRODUCTION

Approximately 2.7 million residents of the United States (US) are infected with hepatitis C virus (HCV) and 3.6 million people are estimated to have anti-HCV antibodies (Denniston et al., 2014), which indicates prior or current infection. Globally, approximately 130 to 150 million have chronic hepatitis C (CHC; WHO, 2015). Several variant genotypes of HCV exist and are known to variably affect the progression of the disease and response to treatment (Feld et al., 2015). In the US, the HCV genotype (GT) 1 is the most prevalent, affecting 72-73% of patients, while HCV GT2 and GT3 affect 12-13% of patients with HCV (Germer et al., 2011; Manos et al., 2012; Young et al., 2012). However, GT3 is associated with higher risk of liver complications (Probst et al., 2011; Nkontchou et al., 2011; Kanwal et al., 2014; McCombs et al., 2014) and the American Association for the Study of Liver Diseases (AASLD) HCV Guidance panel encourages prompt treatment of high-risk patients, such as those with GT3 (AASLD, 2015). Patients with GT3, having a lower response to treatment and greater risk of complications from liver disease, are of particular interest in the current analyses.

With direct-acting antiviral (DAA) treatments, the prospects for HCV treatment and virologic cure have changed, yet cure rates also vary by HCV genotype based upon the influence of variable comorbidities and complications associated with lower sustained virological response (SVR) (Feld 2015; Cheetham et al., 2015). Recently approved treatments include daclatasvir for patients with GT1 or GT3, to be used with sofosbuvir, with or without ribavirin (BMS, 2016). For all GTs, velpatasvir plus sofosbuvir is the most recently approved combination (Gilead, 2016). While early-use clinical data are becoming available, real-world data regarding healthcare utilization and costs are still lacking.

HCV is a leading cause of chronic liver disease and is associated with high healthcare resource utilization (HCRU), presenting a substantial patient burden and high costs to managed care (Davis et al., 2011; McAdam-Marx et al., 2011). The burden of illness of CHC is expected to grow in coming decades, partly because of the increasing prevalence of advanced liver disease (Razavi et al., 2013). Some studies have evaluated the economic burden of CHC overall (Davis et al., 2011; Gordon et al., 2013; Razavi et al., 2013; LaMori et al., 2016); however, data regarding utilization and healthcare costs associated with specific genotypes of HCV are scarce. Also, to our knowledge, the relationship between HCV genotype, liver disease progression, and health care costs has not been explored.

Because HCV disease severity, progression, and treatment response vary by HCV genotype, analyses regarding HCRU and costs by genotype may help inform treatment decisions. The objectives of the study were to (1) examine variation in patient and clinical characteristics, healthcare resource utilization, and healthcare costs by HCV genotype, and (2) assess the relationships of key clinical characteristics with liver disease severity and increased costs.

METHODS

Study Design and Data Source

This retrospective analysis utilized claims data from the Optum Research Database (ORD). The ORD contains medical and pharmacy claims and enrollment information from a large US health plan, including approximately 12 million patients annually. The underlying information is geographically diverse and fairly representative of the overall US insured population. Medical claims data include *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes, site of service codes, and health plan and patient paid amounts from providers and facilities. Pharmacy claims encompass National Drug Codes for filled prescriptions, days supply, quantity of drug supplied, drug strength, and health plan and patient paid amounts. All study data were de-identified and used in compliance with the Health Insurance Portability and Accountability Act (ref. HIPAA 1996). Within the ORD, outpatient laboratory results are available for subpopulations; logical observations identifiers names and codes (LOINC) are used to identify specific tests and results.

Adult patients with medical claims-based evidence of CHC (Gordon et al., 2012) and laboratory-based genotype test results available between 1/1/2000 and 10/31/2014 were identified. To provide a cross-section of disease progression, a random index date was created to identify a prevalent population. Patients were observed for ≥6 months prior to (baseline) and 12 months following (observation period) the randomly assigned index date (Supplementary Figure S1).

Study Sample

Patients were identified using claims-based criteria for chronic HCV infection (Supplementary Table S1). Patients were required to have ≥18 months of continuous pharmacy and medical plan coverage, encompassing the 6-month pre-index baseline period and the 12-month observation period. Patients with unknown age, sex, geographic region, or health insurance type were excluded, as were patients with no or unknown genotype laboratory results available. Patients were assigned to study cohorts based upon their genotype test results with possible types 1-4 and 6.

Measures

Demographic and clinical characteristics

Demographic characteristics included age, sex, and US Census geographic region (ref. US Census Bureau, 2015) and were obtained from health plan enrollment data on the index date. Baseline diagnoses for key comorbidities were recorded, including cirrhosis, hypertension, human immunodeficiency virus (HIV), hepatitis B virus (HBV), diabetes, and cardiovascular disease (see Supplementary Table S2 for diagnosis codes). The Quan-Charlson comorbidity score was calculated based upon the presence of diagnosis codes on medical claims during the pre-index period (Quan, 2011).

Baseline and observation-period laboratory test results were identified for select liver-related measures. HCV genotype was the independent variable of interest; all included patients were required to have genotype results. Genotype results

may have occurred at any time during which claims data were available for each patient during the study period (2000-2014). If a patient had more than one genotype test result, the one occurring closest to the index date was selected. Results for other laboratory tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count were obtained when available, but were not required for inclusion in the study. Results were used to calculate AST-to-platelet ratio index (APRI) and fibrosis-4 (FIB-4), laboratory measures of liver disease severity [see Supplementary Methods S1 for formulas].

Liver disease severity (based upon ICD-9-CM codes; Supplementary Table S3) was assessed in the baseline and observation periods. Cirrhosis with and without complications was measured based on diagnosis and procedure codes. Cirrhosis with complications included evidence of liver failure, hepatocellular carcinoma, hepatic encephalopathy, portal hypertension, ascites, paracentesis, spontaneous bacterial peritonitis, esophageal varices (with and without bleeding), and/or portal decompression procedures.

Healthcare utilization and costs

HCRU was identified through medical claims for patients having office visits, ambulatory visits, emergency department visits, inpatient admissions (with length of inpatient stay in days), and recorded the proportion of patients using those services during the observation period. All-cause (any diagnosis) and liver-related HCRU are presented; liver-related diagnoses and procedures are described in Supplementary Table S3. Healthcare costs were also defined as all-cause or liver-related and recorded for the observation period. Costs were reported as pharmacy costs, medical costs (which included ambulatory, emergency department, inpatient, and other medical costs), and total (medical + pharmacy) costs. Costs were adjusted to 2014 US dollars using the annual medical care component of the Consumer Price Index (CPI, US Dept Labor) to reflect inflation between 2000 and 2014.

Statistical Analyses

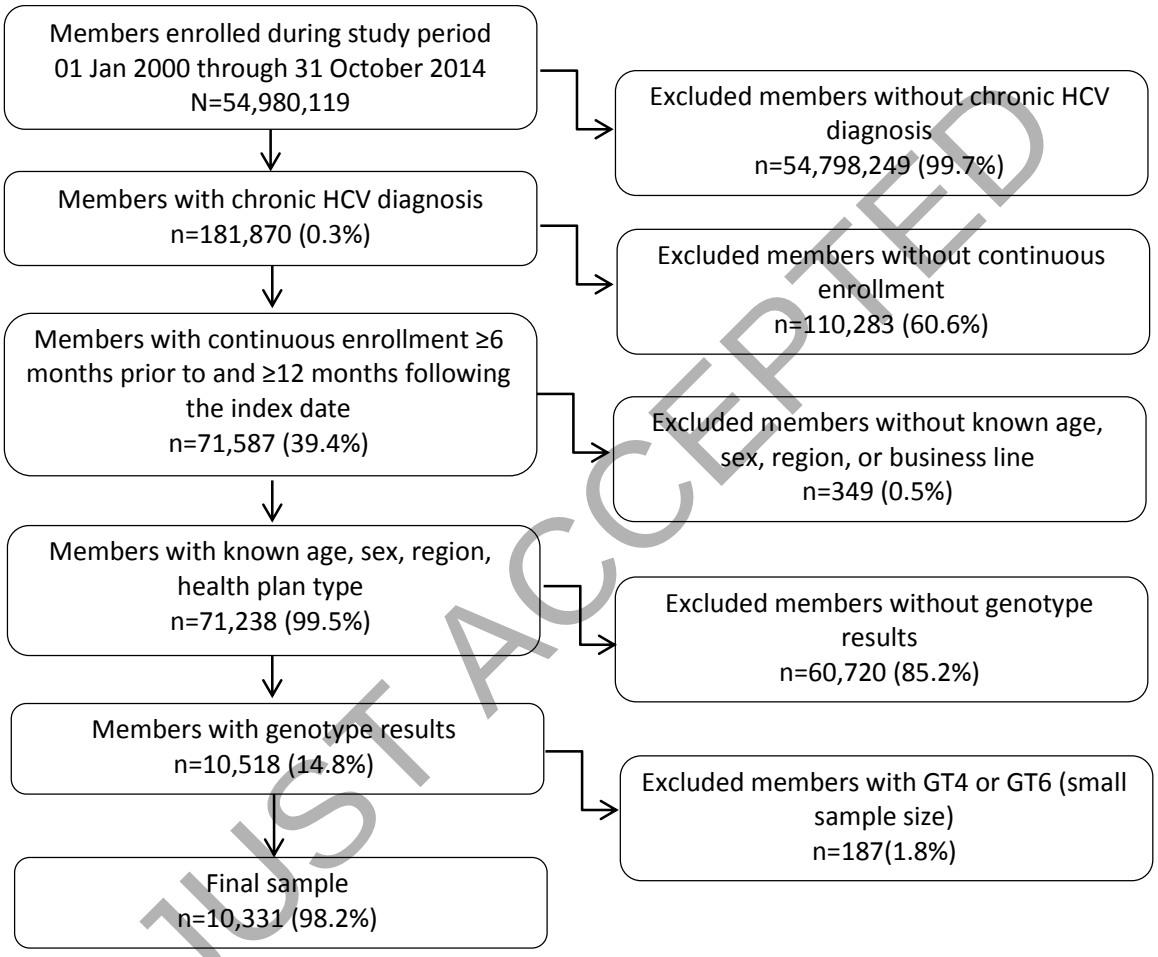
Data were analyzed descriptively by HCV genotype with counts and percentages provided for binary and categorical variables, and means and standard deviations (SD) for continuous variables. To control for possible confounding of the relationship between costs and HCV genotype, total all-cause health care costs and liver disease severity were modeled during the observation period, using a generalized linear model with a gamma distribution and log link and a logistic regression model, respectively. Because liver disease severity was found to be highly correlated with genotype and baseline comorbidities, a conservative approach was taken to the use of clinical disease measures as covariates in the models to limit endogeneity. An earlier version of the models (not shown) tested the use of a continuous Quan-Charlson comorbidity score and baseline liver disease severity covariates. The results were highly correlated at the $p<0.001$ level. To better assess the impact of other important clinical and demographic factors, most baseline health status measures have been removed. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Sample Description

Sample identification criteria were applied as shown in Figure 1, resulting in a final study sample of 10,331 patients. Patients with genotypes 1, 2, and 3 (GT1, GT2, and GT3) were included in the analysis. Genotype 1 subtypes (1a, 1b, and unknown subtype) were combined for analysis, and patients with genotypes 4 and 6 were excluded due to small sample size (n=187). No patients had genotype 5.

Figure 1. Attrition and Sample Selection



Demographic and Clinical Characteristics

Among the total sample of 10,331 patients, 8,176 (79.1%) had GT1 (68% GT1a, 28% GT1b, and 4% unknown subtype); 1,318 (12.8%) had GT2; and 837 (8.1%) had GT3. The majority of patients overall were male (63.5%). The mean age was 50.6 years (SD=8.5). Overall, 19.2% were aged 18-44; 46.9% aged 45-54; and 34.0% ≥55. GT3 patients tended to be

slightly younger, with mean age of 48.4 (SD=8.2) and 27.4% aged 18-44. The proportion of patients with cirrhotic disease with and without complications and liver-related comorbidities was highest among GT3 patients (Table 1).

Overall, the most common baseline comorbidities were hypertension (28.7%), liver disease (24.1%), and type 2 diabetes (13.5%). However, types of comorbidities varied by genotype. Patients with GT1 and GT2 had the highest rates of hypertension, cardiovascular disease, and diabetes. Genotype 3 patients had the highest rates of liver disease sequelae, including steatosis, hepatocellular carcinoma, and liver transplant. The average Quan-Charlson comorbidity scores were similar among GT1 (1.62, SD=1.61) and GT3 (1.59, SD=1.63) patients, and slightly lower among GT2 (1.50, SD=1.50) patients.

Table 1. Demographic Baseline Clinical Characteristics of Study Sample

Demographic Characteristics	**Total (n=10,331)**	**GT1 (n=8,176)**	**GT2 (n=1,318)**	**GT3 (n=837)**
Age, mean (SD)	50.6 (8.5)	50.8 (8.4)	51.0 (8.9)	48.4 (8.2)
Age group, n (%)				
18-44	1,986 (19.2)	1,479 (18.1)	278 (21.1)	229 (27.4)
45-54	4,840 (46.9)	3,881 (47.5)	547 (41.5)	412 (49.2)
55-59	2,279 (22.1)	1,842 (22.5)	291 (22.1)	146 (17.4)
60-64	1,021 (9.9)	822 (10.1)	155 (11.8)	44 (5.4)
65+	205 (2.0)	152 (1.9)	47 (3.6)	6 (0.7)
Gender, n (%)				
Male	6,562 (63.5)	5,205 (63.7)	829 (62.9)	528 (63.1)
Female	3,769 (36.5)	2,971 (36.3)	489 (37.1)	309 (36.9)
Geographic region, n (%)				
Northeast	880 (8.5)	724 (8.9)	87 (6.6)	69 (8.2)
Midwest	901 (8.7)	703 (8.6)	117 (8.9)	81 (9.7)
South	7,538 (73.0)	6,005 (73.5)	959 (72.8)	574 (68.6)
West	1,009 (9.8)	742 9.1)	155 (11.8)	112 (13.4)
Other	3 (0.0)	2 (0.0)	0 (0.0)	1 (0.1)
Clinical Characteristics	**Total (n=10,331)**	**GT1 (n=8,176)**	**GT2 (n=1,318)**	**GT3 (n=837)**
Liver disease severity, n (%)				
Non-cirrhotic disease	9,095 (88.0)	7,194 (88.0)	1,196 (90.7)	705 (84.2)
Cirrhosis without complications*	593 (5.7)	470 (5.8)	59 (4.5)	64 (7.7)
Cirrhosis with complications	643 (6.2)	512 (6.3)	63 (4.8)	68 (8.1)
Conditions indicating cirrhosis with complications, n (%)				
Liver failure	4 (0.0)	3 (0.0)	0 (0.0)	1 (0.1)
Hepatocellular carcinoma	78 (0.8)	58 (0.7)	5 (0.4)	15 (1.8)
Hepatic encephalopathy	253 (2.5)	199 (2.4)	32 (2.4)	22 (2.6)
Portal hypertension	171 (1.7)	137 (1.7)	18 (1.4)	16 (1.9)
Ascites	106 (1.0)	94 (1.2)	7 (0.5)	5 (0.6)
Paracentesis	54 (0.5)	45 (0.6)	5 (0.4)	4 (0.5)
Spontaneous bacterial peritonitis	7 (0.1)	6 (0.1)	0 (0.0)	1 (0.1)
Esophageal varices (with and without bleeding)	199 (1.9)	158 (1.9)	17 (1.3)	24 (2.9)
Portal decompression procedures	2 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)
Comorbid conditions, n (%)				
Hypertension	2,964 (28.7)	2,456 (30.0)	327 (24.8)	181 (21.6)
Liver disease	2,491 (24.1)	1,999 (24.5)	269 (20.4)	223 (26.6)
HIV	339 (3.3)	285 (3.5)	34 (2.6)	20 (2.4)
HBV	232 (2.3)	188 (2.3)	26 (2.0)	18 (2.2)
Diabetes	1,397 (13.5)	1,183 (14.5)	144 (10.9)	70 (8.4)
Cardiovascular disease	954 (9.2)	767 (9.4)	136 (10.3)	51 (6.1)
Steatosis	342 (3.3)	277 (3.4)	28 (2.1)	37 (4.4)
Hepatocellular carcinoma	73 (0.7)	55 (0.7)	5 (0.4)	13 (1.6)
Liver transplant	100 (1.0)	79 (1.0)	8 (0.6)	13 (1.6)
Liver transplant status	99 (1.0)	78 (1.0)	8 (0.6)	13 (1.6)
Liver transplant procedure	14 (0.1)	12 (0.2)	2 (0.2)	0 (0.0)
Quan-Charlson comorbidity score, mean (SD)	1.61 (1.59)	1.62 (1.61)	1.50 (1.50)	1.59 (1.63)

*Cirrhosis with and without complications are mutually exclusive categories

During the 12-month observation period, the proportion of patients with any cirrhosis, including cirrhosis with complications, was highest for those with GT3 (Table 2).

Table 2. Measures of Liver Disease Severity during the 12-Month Observation Period

Liver Disease Severity n (%)	Total (n=10,331)	GT1 (n=8,176)	GT2 (n=1,318)	GT3 (n=837)
Non-cirrhotic disease	8,676 (84.0)	6,822 (83.4)	1,168 (88.6)	686 (82.0)
Any cirrhosis	1,655 (16.0)	1,354 (16.6)	150 (11.4)	151 (18.0)
Cirrhosis without complications	714 (6.9)	592 (7.2)	66 (5.0)	56 (6.7)
Cirrhosis with complications	941 (9.1)	762 (9.3)	84 (6.4)	95 (11.4)

*Cirrhosis with and without complications are mutually exclusive categories; any cirrhosis includes both categories.

Variation in liver disease severity by genotype was also illustrated by laboratory results (Table 3). ALT and AST results were available for about 70% of the sample during the baseline and observation periods. GT3 patients tended to have the highest ALT and AST values during the baseline and observation periods, and GT2 patients had the lowest values. The last baseline mean ALT results (IU/ml) were GT1: 72; GT2: 63; GT3: 78; and last observation period mean ALT results (IU/ml) were GT1: 70; GT2: 59; GT3: 74. The last baseline mean AST results (IU/ml) were GT1: 59; GT2: 50; GT3: 62 and last observation period mean AST results (IU/ml) were GT1: 55; GT2: 41; GT3: 57.

Calculated APRI and FIB-4 results were available for about 75% of patients during the baseline period and 60-65% of patients during the observation period. APRI and FIB-4 showed variation by genotype. GT3 patients had the highest rates of significant fibrosis (APRI >1.5; FIB-4 >3.25) during the baseline and observation periods (Table 3), while GT2 patients had the highest rates of no or minimal fibrosis (APRI <0.5; FIB-4 <1.45) (not shown).

Table 3. Liver Disease Severity Measured by Laboratory Test Results*

Severity Measure	Total (n=10,331)	GT1 (n=8,176)	GT2 (n=1,318)	GT3 (n=837)
Baseline APRI >1.5, n(%)	1,235 (12.0)	990 (12.1)	113 (8.6)	132 (15.8)
Observation period APRI >1.5, n(%)	1,110 (10.7)	921 (11.3)	88 (6.7)	101 (12.1)
Baseline FIB-4 > 3.25, n(%)	1,333 (12.9)	1,072 (13.1)	136 (10.3)	125 (14.9)
Observation period FIB-4 >3.25, n(%)	1,300 (12.6)	1,077 (13.2)	119 (9.0)	104 (12.4)

* Among patients with laboratory test results available to calculate APRI and FIB-4.

Healthcare Utilization and Costs during the 12-Month Observation Period

Overall, most patients had all-cause ambulatory (95.8%) and office (94.9%) visits, but fewer had liver-related ambulatory (71.1%) and office visits (67.9%). All-cause HCRU was fairly similar by genotype. GT1 patients had the highest rates of liver-related HCRU for most types of services, while GT3 patients had the lowest utilization rates for most services. Ambulatory and office visits were the most frequently used types of all-cause and liver-related services.

Table 4. Utilization by Genotype, 12-Month Observation Period

	Total (n=10,331)	**GT1 (n=8,176)**	**GT2 (n=1,318)**	**GT3 (n=837)**
All-Cause Utilization				
Ambulatory visit, n (%)	9,895 (95.8)	7,837 (95.9)	1,267 (96.1)	791 (94.5)
Emergency visit, n (%)	3,233 (31.3)	2,581 (31.6)	394 (29.9)	258 (30.8)
Office visit, n (%)	9,800 (94.9)	7,760 (94.9)	1,253 (95.1)	787 (94.0)
Inpatient admission, n (%)	1,270 (12.3)	1,031 (12.6)	134 (10.2)	105 (12.5)
Inpatient length of stay, days mean (SD)	1.39 (8.0)	1.46 (8.4)	1.09 (6.9)	1.23 (5.7)
Liver-Related Utilization				
Ambulatory visit, n (%)	7,345 (71.1)	5,878 (71.9)	907 (68.8)	560 (66.9)
Emergency visit, n (%)	641 (6.2)	535 (6.5)	66 (5.0)	40 (4.8)
Office visit, n (%)	7,010 (67.9)	5,608 (68.6)	863 (65.5)	539 (64.4)
Inpatient admission, n (%)	933 (9.0)	776 (9.5)	92 (7.0)	65 (7.8)
Inpatient length of stay, days, mean (SD)	1.0 (7.1)	1.1 (7.5)	0.7 (5.1)	0.9 (5.0)

All-cause costs were lowest for GT2 patients and generally highest for GT1 patients for the observation period. Liver-related costs were lowest among GT2 patients for all categories of cost but tended to be similar for GT1 and GT3 patients. Liver-related costs comprised 26.9% of all-cause total costs among all patients (27.4% for GT1 patients; 20.3% for GT2 patients; and 29.9% for GT3 patients).

Figure 2a. All-Cause Costs during the 12-Month Observation Period

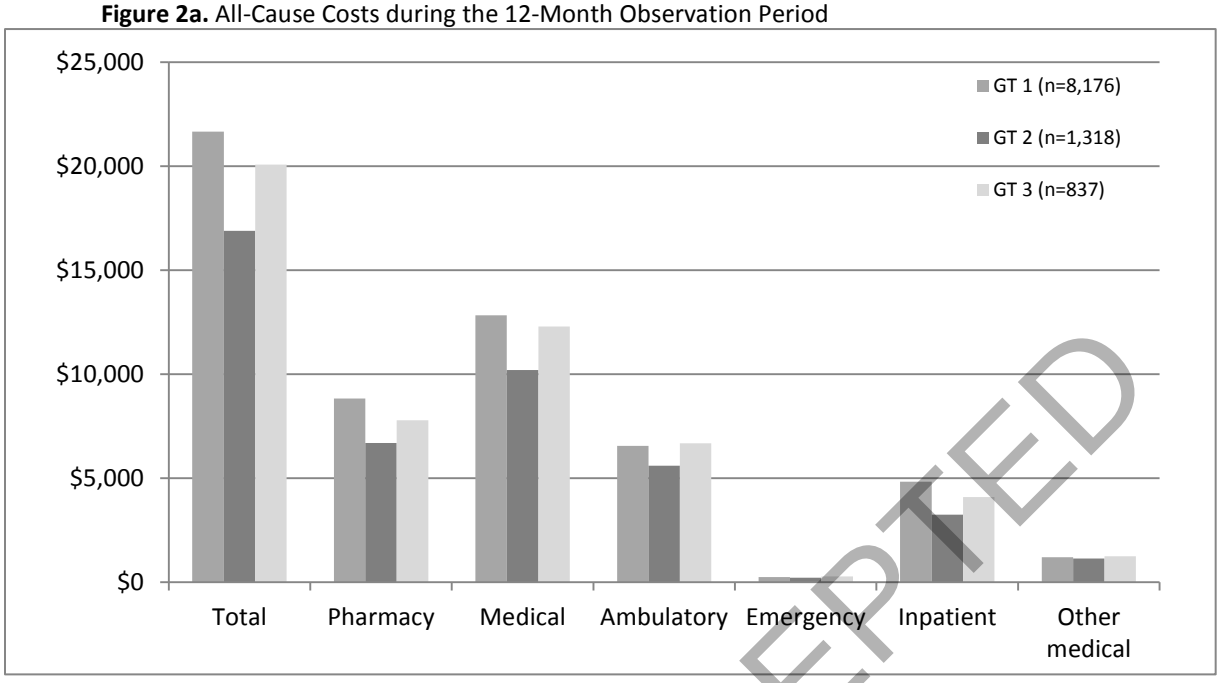
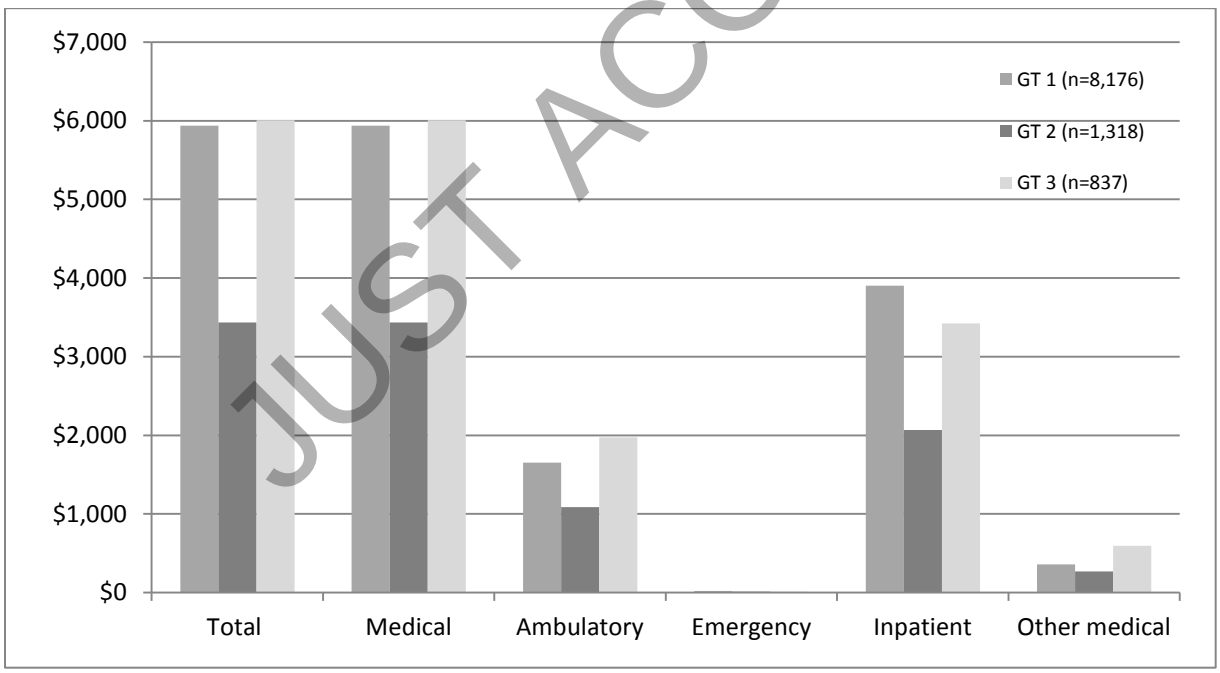


Figure 2b. Liver-Related Costs during the 12-Month Observation Period



Models of Liver Disease Progression and Healthcare Costs

To further assess the relationship of genotype with cost and with liver disease severity, multivariable analyses were conducted. The multivariable model of liver disease severity assessed the impact of the same covariates on the likelihood of having advanced liver disease (i.e., cirrhosis with complications) during the observation period. Compared with GT1 patients, GT3 patients were about one-third more likely (p=0.009) and GT2 patients were about one-third less likely (p=0.001) to have advanced liver disease and (Supplementary Table S5). HBV co-infection conferred a 72% greater likelihood of advanced liver disease (p=0.007). Age was significant predictor of advanced liver disease when compared with the age 45-49 reference group, with lower likelihood among younger patients (OR=0.652; p=0.002) and increasing likelihood as age rose (50-53 years: OR=1.29, p=0.027; 54-57 years: OR=1.603, p<0.001; age 58+: OR=1.742; p<0.001).

The multivariable cost model (Supplementary Table S4) assessed the impact of genotype, treatment prior to the study period, age, gender, and geographic region on total health care costs during the observation period. Consistent with the descriptive data, genotype was a significant predictor of costs. Patients with GT2 had 29% lower all-cause costs as compared with GT1 patients (p=0.001), while the model showed similar costs for GT3 as compared to GT 1 patients. Compared to younger patients, older patients tended to have higher costs. Age 54-57 years was associated with a 26.0% higher cost and age >58 with a 32.5% higher cost, relative to younger patients (p<0.001). Evidence of prior treatment was associated with 17.5% lower costs (p<0.001).

DISCUSSION

High healthcare utilization among patients with CHC presents a high cost burden to US managed care (Davis et al., 2011; Mc-Adam-Marx et al., 2011). As variation by HCV genotype has been understudied in terms of resource utilization, this retrospective analysis of healthcare claims data provided evidence of variation by genotype in liver disease severity and progression and in healthcare costs among CHC patients.

In this study, using both claims-based and laboratory-based measures, GT3 patients had higher rates of liver disease sequelae (highest rates of cirrhosis with and without complications) as compared with GT1 and GT2 patients. These findings are similar to previous studies (Cheetham et al., 2015; Nkontchou et al., 2011; Kanwal et al., 2014; and McCombs et al., 2014) suggesting GT3 patients are more likely to have advanced liver disease. Consistent with descriptive results, multivariate analyses revealed that compared with GT1 patients, GT3 patients were about one third more likely and GT2 patients were about one-third less likely to have advanced liver disease. In addition to overall liver disease status, GT3 patients had the highest rates of hepatocellular carcinoma, steatosis, and liver transplant. These findings support the notion that the GT3 variant of the virus imparts a unique pathophysiology throughout the disease course. They also emphasize the importance of treating GT3 patients early in the disease course in order to improve clinical outcomes and ultimately lower HCRU and costs (Nelson et al., 2015).

Among all patients in this analysis, the all-cause services that the largest proportion of patients used were ambulatory and office visits. Past research has found similar results for all-cause office and ambulatory utilization rates (Gordon et al 2012; Davis et al 2011). When examined by genotype, proportions of patients using each type of service were fairly similar when services were measured as all-cause. GT1 patients had the highest and GT3 patients had the lowest all-cause utilization. Although this finding would not necessarily be predicted by previous work showing costs and utilization increase with advanced liver disease regardless of genotype (Gordon et al., 2012; LaMori et al., 2016), this finding is important in the context of higher rates of advanced liver disease among GT3 patients. Better understanding the impact of liver disease severity with varying genotypes may require a longer observation period to assess comorbidities, cost, and utilization.

Several real-world studies have established the economic burden of CHC overall (Davis et al., 2011; Gordon et al., 2013; LaMori et al., 2016; McAdam-Marx et al., 2011), yet a clear picture of cost burden based upon HCV genotype was not generated and direct comparisons of cost results with this study are not feasible. However, in previous claims-based studies, overall costs for patients with CHC have been shown to increase dramatically as liver disease worsens (McAdam-Marx 2011, Gordon et al., 2013). The clinical characteristics of the GT3 patients suggested more advanced liver disease than patients with GT1 and GT2. Consistent with having the lowest rates of liver-related and comorbid conditions among all genotypes, patients with GT2 also had the lowest healthcare costs, both for all-cause and liver-related care in the descriptive analyses. In multivariable analyses, GT2 significantly predicted 28.8% lower all-cause costs compared with GT1, but the effect relative to GT1 was not significant among patients with GT3. Notably, the liver-related costs for GT2 patients comprised only 20.3% of their all-cause costs, lower than the percentage for GT3 patients (29.9%) and GT1

(27.4%). Although the differences were not tested, these percentages are similar to findings by Davis et al. (2011), who demonstrated nearly one-third of overall costs were HCV-related. In the current study, older age was associated with higher costs, which is also consistent with findings by LaMori et al (2016).

Limitations

Because administrative claims data are collected for the purpose of billing rather than research, certain limitations are associated with the data source: primarily, diagnosis codes may be included as rule-out diagnosis codes and are not verified proof of disease. Also, some medical codes are more general than others (e.g., codes used to assess steatosis also capture other related conditions). Costs from other payers may be important, especially among older patients dually eligible for commercial and Medicare. Costs for patients aged 65 and older may have been underestimated because only patients within the commercial plans were included. Finally, generalization beyond US commercially insured patients or outside the US may not be feasible.

Specific to this study, analysis of a prevalent population is likely to underestimate HCRU and costs when compared with analysis of treated patients. Liver disease severity was determined by claims-based algorithms and was not confirmed by biopsy results. Also, although multivariate results appear to reflect disease progression with age, information was not collected regarding duration of disease. There are likely other factors (e.g., age) that were not the focus of this study but should be considered for future analyses.

Since a random index date was used, no conclusions may be drawn regarding differences in outcomes between the baseline and observation periods. This is particularly relevant to the decision to combine all GT1 subtypes into one group for analysis. The subtypes were not analyzed individually because SVR was not a study outcome and treatments for GT1 tend not to differ by subtype. The majority of patients had GT1a genotype; thus, results are likely most representative of patients with this subtype.

Conclusions

This study provides evidence of variation by HCV genotype in liver and non-liver related comorbidities, liver disease severity, and healthcare costs. The highest proportion of patients with liver-related comorbidities and advanced liver disease was found among patients with GT3.

Patients with GT2 had lower HCRU and the lowest all-cause and liver-related costs, and patients with GT1 had the highest total all-cause costs. However, GT1 and GT3 patients had similar liver-related costs. These differences may reflect differing rates of non-liver-related comorbidities and types of all-cause care. Taken altogether, these results suggest that liver disease progression varies by genotype and that CHC patients with GT3 may have more severe liver disease. These findings highlight the importance of considering genotype in pursuing effective HCV treatment for all patients and support the AASLD guidelines for treatment of high-risk HCV, including GT3 patients.

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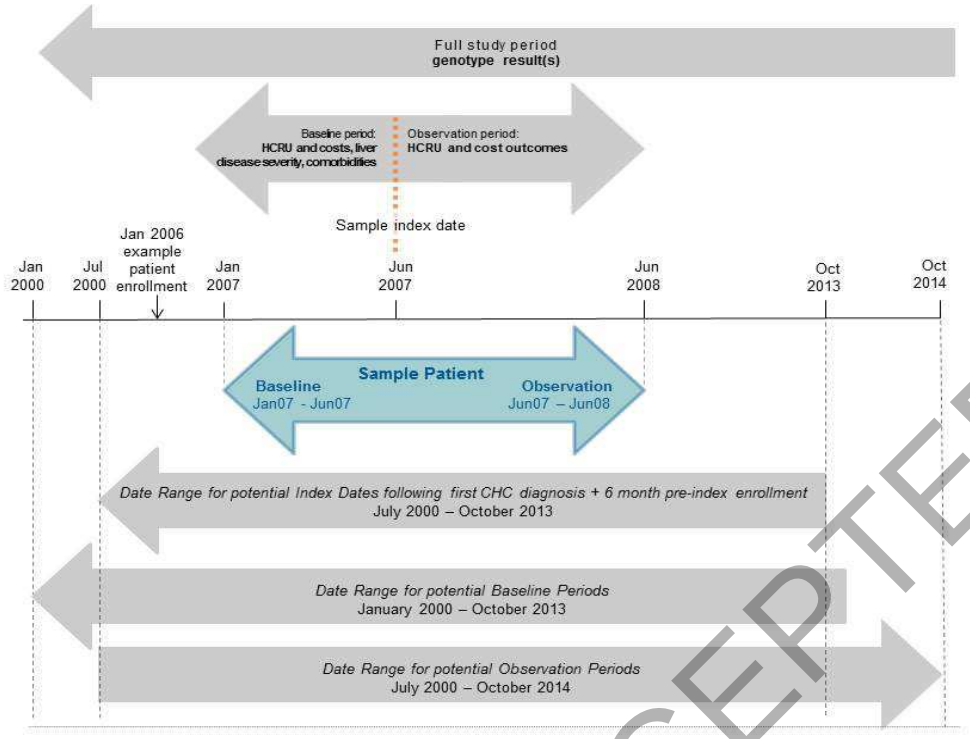
APPENDICES

Supplementary Figure S1. Study Design



Supplementary Table S1. Diagnosis codes used to identify eligible patients

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

Supplementary Methods S1. Formulas for APRI and FIB-4 calculations (Lin et al., 2011). (Wai et al., 2003; Amorim et al., 2012; Sterling et al., 2006)

Aspartate aminotransferase (AST)-to-platelet ratio index (APRI): The APRI is a non-invasive alternative to liver biopsy for detecting liver fibrosis. To calculate this ratio, AST and platelet count laboratory results were captured. AST and platelet results must have occurred within 30 days of each other for ratio calculation. APRI = [AST (IU/L) / normality upper limit] / platelet (109/L) x 100. APRI was classified as no or minimal fibrosis at <0.5, moderate fibrosis at 0.5-1.5, and significant fibrosis at >1.5.

FIB-4: The FIB-4 is also a noninvasive method for evaluation of liver fibrosis based on age, AST, ALT and platelet count. To calculate this score, AST, ALT and platelet count laboratory results were captured. AST, ALT and platelet results must have occurred within 30 days of each other for FIB-4 calculation. FIB-4 = age (years) x AST (IU/L) / [platelets (109/L) x sqrt(ALT [IU/L])]. FIB-4 was classified as no or minimal fibrosis at <1.45, moderate fibrosis at 1.45-3.25, and significant fibrosis at >3.25.

Supplementary Table S2. Codes used for identifying comorbidities of interest

Conditions, Procedures or Treatments	Code Type	Code	Description
HIV	ICD-9-diag	042	Human immunodeficiency virus (HIV)
		079.53	Human immunodeficiency virus, type 2 (HIV 2), in conditions classified elsewhere and of unspecified site
		795.71	Nonspecific serologic evidence of human immunodeficiency virus (HIV)
		V08	Asymptomatic human immunodeficiency virus (HIV) infection status
	Pharmacy	J3485, S0104, S0137, 'S0141, S0140, 'J1324	Abacavir, Amprenavir, Atazanavir, Cobicistat, Dalutegravir, Darunavir, Delavirdine, Didanosine, Efavirenz, Elivitegravir, Emtricitabine, Enfuvirtide, Etravirine, Fosamprenavir, Indinavir, Lamivudine, Lopinavir, Maraviroc, Nelfinavir, Nevirapine, Raltegravir, Rilpivirine, Ritonavir, Saquinavir, Stavudine, Tenofovir, Tipranavir, Zalcitabine, Zidovudine, Atazanavir/Cobicistat, Darunavir/Cobicistat, Abacavir/Dolutegravir/Lamivudine, Lamivudine/Zidovudine, Abacavir/Lamivudine, Abacavir/Lamivudine/Zidovudine, Emtricitabine/Tenofovir DF, Efavirenz/Emtricitabine/Tenofovir DF, Elvitegravir/Cobicistat/Emtracitabine/Tenofovir, Emtricitabine/Rilpivirine/Tenofovir, Lamivudine/Raltegravir
Hepatitis B	ICD-9-diag	070.2x	Viral hepatitis b with hepatic coma
		070.3x	Viral hepatitis b without mention of hepatic coma
		V02.61	Hepatitis b carrier
	Pharmacy		Adefovir, Entecavir, Lamivudine, Telbivudine, Tenofovir
Steatosis	ICD-9-diag	272.8	Other disorders of lipoid metabolism
		429.1	Myocardial degeneration
		593.89	Other specified disorder of kidney and ureter
		571.8	Other chronic nonalcoholic liver disease

Conditions, Procedures or Treatments	Code Type	Code	Description
Diabetes	ICD-9-diag	249.xx	Secondary diabetes
		250.xx	Diabetes mellitus
		251.0	Hypoglycemic coma
		357.2	Polyneuropathy in diabetes
		362.0x	Diabetic retinopathy
		366.41	Diabetic cataract
	Pharmacy		insulins, sulfonylureas, oral hypoglycemic agents, other antidiabetic medications, diabetes treatment supplies: acetohexamide, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide, metformin, pioglitazone, rosiglitazone, acarbose, miglitol, nateglinide, repaglinide, alogliptin, sitagliptin, saxagliptin, linagliptin, glipizide/metformin, glyburide/metformin, glimepiride/pioglitazone, glimepiride/rosiglitazone, pioglitazone/metformin, rosiglitazone/metformin, repaglinide/metformin, alogliptin/metformin, sitagliptin/metformin, saxagliptin/metformin, linagliptin/metformin, alogliptin/pioglitazone, sitagliptin/simvastatin, canagliflozin, dapagliflozin, empagliflozin, canaglifozin/metformin, bromocriptine, pramlintide, exenatide, albiglutide, dulaglutide, liraglutide, insulin lispor, human recombinant analog, insulin aspartate, insulin glulisine, insulin regular human recombinant, insulin nph human recombinant, insulin glargine, human rec. analog, insulin detemir, insulin nph hu s-s/ins rg human rec., insulin nph human rec, insulin rg human rec, insulin npl/insulin lispro, insulin asp prt/insulin aspartate, syringe w-needle, disposable, insulin, needles, insulin disposable, syringe, insulin, reusable, insulin pump reservoir, insulin admin. supplies, insulin administration supplies/lancets, syringe w-o needle, disposable, insulin, needleless access. dev, insulin, syringe w-needle, disposable, insulin 0.5ml, syringe w- needle, disposable, insulin, 1ml, syringe w- needle, disposable, insulin, 3ml, syringe w- needle, disposable, insulin, 2ml, syringe w-needle, disposable, insulin, 0.3ml, syringe w- needle, disposable, insulin, 0.25ml, syringe w- needle, disposable, insulin, 0.333ml, blood-glucose meter/insulin administration supplies, syringe w-o needle, disposable, insulin, 1ml, insulin pump syringe, 1.8ml, insulin pump syringe, 3ml, syringe w-needle, insulin u-40, 1ml, insulin pump cartridge, insulin inhalation chamber, insulin release unit, insulin powder inhaler/chamber, needles, insulin disp., safety, infusion set for insulin pump, subcutaneous insulin pump
Cardiovascular disease	ICD-9-diag	410.xx-414.xx V45.81-V45.82	Ischemic (coronary arterial) heart disease
		426.xx-427.xx V45.0x, V53.3x	Cardiac conduction and rhythm disorders
		425.4, 428.xx	Heart failure
		390.xx-398.xx, 420.xx-425.3x, 425.5-425.9, 429.xx, V12.53, V15.1x, V42.1x-V42.2x,	Other heart disease (e.g., myocarditis, endocarditis, cardiomyopathy, atrioventricular and bundle branch blocks)

Conditions, Procedures or Treatments	Code Type	Code	Description
		V43.2x-V43.3x	
Hepatocellular carcinoma	ICD-9-diag	155.0	Malignant neoplasm of liver, primary
HCV-related hypertension	ICD-9-diag	403.xx	Hypertensive chronic kidney disease
		404.xx	Hypertensive heart and chronic kidney disease
		405.01	Secondary renovascular hypertension, malignant
		405.11	Secondary renovascular hypertension, benign
		405.09	Other secondary hypertension, malignant
		405.19	Other secondary hypertension, benign
		405.91	Secondary renovascular hypertension, unspecified
Additional liver-related codes of interest			
Liver transplant	ICD-9-diag	996.82	Complications of transplanted liver
		V42.7	Liver replaced by transplant
	ICD-9-proc	50.51	Auxiliary liver transplant
		50.59	Other transplant of liver
	CPT/HCPCS	S2053	Transplantation of small intestine and liver allografts
		00796	Anesthesia for intraperitoneal procedures in upper abdomen including laparoscopy; liver transplant (recipient)
		47135	Liver allotransplantation; orthotopic, partial or whole, from cadaver or living donor, any age
		47136	Liver allotransplantation; heterotopic, partial or whole, from cadaver or living donor, any age
Liver transplant status	ICD-9-diag	996.82	Complications of transplanted liver
		V42.7	Liver replaced by transplant
	CPT	00796	Anesthesia for intraperitoneal procedures in upper abdomen including laparoscopy; liver transplant (recipient)

Supplementary Table S3. Liver disease severity codes

Severity Level	Conditions or Procedures	Code Type	Codes	Description
Non-cirrhotic disease	No evidence of cirrhosis with or without complications			
Cirrhosis without complications	No evidence of cirrhosis with complications			
	Cirrhosis	ICD-9-diag	571.2	Alcoholic cirrhosis of liver
			571.5	Cirrhosis of liver without mention of alcohol
			571.6	Biliary cirrhosis
Cirrhosis with complications	Liver failure, including hepatorenal syndrome	ICD-9-diag	572.4	Hepatorenal syndrome
	Hepatocellular carcinoma	ICD-9-diag	155.x	Malignant neoplasm of liver and intrahepatic bile ducts
	Hepatic encephalopathy	ICD-9-diag	572.2	Hepatic encephalopathy
			070.41	Acute hepatitis C with hepatic coma
			070.44	Chronic hepatitis C with hepatic coma
	Portal hypertension	ICD-9-diag	572.3	Portal hypertension
	Ascites	ICD-9-diag	789.59	Ascites (other)
	Spontaneous bacterial peritonitis	ICD-9-diag	567.23	Spontaneous bacterial peritonitis
	Paracentesis	CPT	49080	Peritoneocentesis, abdominal paracentesis, or peritoneal lavage (diagnostic or therapeutic); initial
			49081	Peritoneocentesis, abdominal paracentesis, or peritoneal lavage (diagnostic or therapeutic); subsequent
			49082	Abdominal paracentesis (diagnostic or therapeutic); without imaging guidance
			49083	Abdominal paracentesis (diagnostic or therapeutic); with imaging guidance
			49084	Peritoneal lavage, including imaging guidance, when performed
			49425	Insertion of peritoneal-venous shunt
			49426	Revision of peritoneal-venous shunt
			49427	Injection procedure (e.g., contrast media) for evaluation of previously placed peritoneal-venous shunt
			78291	Peritoneal-venous shunt patency test (e.g., for LeVeen, Denver shunt)
		ICD-9-proc	54.91	Percutaneous abdominal drainage
			39.1	Intra-abdominal venous shunt
	Varices	ICD-9-diag	456.0	Esophageal varices with bleeding
			456.1	Esophageal varices without mention of bleeding
			456.20	Esophageal varices with bleeding in diseases classified elsewhere
			456.21	Esophageal varices without mention of bleeding in diseases classified elsewhere
			456.2x	Esophageal varices in diseases classified elsewhere (Note: this is a roll-up of previous codes)

Severity Level	Conditions or Procedures	Code Type	Codes	Description
		CPT	43204	Esophagoscopy, rigid or flexible; with injection sclerosis of esophageal varices
			43205	Esophagoscopy, rigid or flexible; with band ligation of esophageal varices
			43227	Esophagoscopy, rigid or flexible; with control of bleeding (e.g., injection, bipolar cautery, unipolar cautery, laser, heater probe, stapler, plasma coagulator)
			43243	Esophagogastroduodenoscopy, flexible, transoral; with injection sclerosis of esophageal/gastric varices
			43244	Esophagogastroduodenoscopy, flexible, transoral; with band ligation of esophageal/gastric varices
			43400	Ligation, direct, esophageal varices
			43401	Transection of esophagus with repair, for esophageal varices
			43460	Esophagogastric tamponade, with balloon (Sengstaken type)
		ICD-9-proc	42.91	Ligation of esophageal varices
			44.91	Ligation of gastric varices
			96.06	Insertion of Sengstaken tube
	Portal decompression	CPT	37140	Venous anastomosis, open; portocaval
			37160	Venous anastomosis, open; caval-mesenteric
			37180	Venous anastomosis, open; splenorenal, proximal
			37181	Venous anastomosis, open; splenorenal, distal (selective decompression of esophagogastric varices, any technique)
		CPT	37182	Insertion of transvenous intrahepatic portosystemic shunt(s) (TIPS) (includes venous access, hepatic and portal vein catheterization, portography with hemodynamic evaluation, intrahepatic tract formation/dilatation, stent placement and all associated imaging guidance and documentation)
			37183	Revision of transvenous intrahepatic portosystemic shunt(s) (TIPS) (includes venous access, hepatic and portal vein catheterization, portography with hemodynamic evaluation, intrahepatic tract recanulization/dilatation, stent placement and all associated imaging guidance and documentation)
		HCPCS	C1040	Stent, self-expandable for creation of intrahepatic shunts, wallstent transjugular intrahepatic portosystemic shunt (tips) with unistep plus delivery system (40/42/60/68mm in length), wallstent rp endoprosthesis with unistep plus delivery system (42/68mm in length)

Supplementary Table S4. All-Cause Healthcare Costs during the Observation Period – Generalized Linear Model with Gamma and Log Link

Independent Variables	Dependent Variable				
	cost ratio	lower 95% CI	upper 95% CI	p-value	predicted value
Intercept	–	–	–	<0.001	–
Genotype					
1	ref.	–	–	–	21,462.455
2	0.812	0.714	0.923	0.001	17,428.118
3	0.995	0.850	1.165	0.952	21,359.383
Evidence of prior treatment	0.825	0.750	0.908	<0.001	–
Baseline health status					
HIV co-infection	2.503	1.961	3.194	<0.001	–
HBV co-infection	1.378	1.031	1.841	0.030	–
Age				<0.001	
18-44	0.953	0.831	1.093	0.494	–
45-49	ref.	–	–	–	–
50-53	1.096	0.960	1.251	0.175	–
54-57	1.260	1.100	1.444	<0.001	–
58+	1.325	1.155	1.520	<0.001	–
Gender					
Male	1.038	0.950	1.134	0.408	–
Female	ref.	–	–	–	–
Geographic region				0.335	
Northeast	ref.	–	–	–	–
Midwest	0.838	0.683	1.028	0.090	–
South and Other	0.933	0.800	1.088	0.376	–
West	0.973	0.797	1.187	0.787	–

Observations read = 10,518, Observations used = 10,331
Pearson chi-square=49732.304, DF=10317
Specification link test: p-value=0.602
Park test: estimate = 1.451, gamma distribution p-value = 0.247

Supplementary Table S5. Advanced Liver Disease* during the Observation Period – Logistic Regression Model

Independent Variables	Dependent Variable			
	odds ratio	lower 95% CI	upper 95% CI	p-value
Intercept	–	–	–	<0.001
Genotype				
1	ref.	–	–	–
2	0.669	0.525	0.852	0.001
3	1.372	1.082	1.741	0.009
Evidence of prior treatment	0.939	0.801	1.102	0.444
Baseline health status				
HIV co-infection	0.882	0.583	1.335	0.554
HBV co-infection	1.720	1.157	2.559	0.007
Age				<0.001
18-44	0.652	0.496	0.856	0.002
45-49	ref.	–	–	–
50-53	1.290	1.029	1.618	0.027
54-57	1.603	1.282	2.004	<0.001
58+	1.742	1.394	2.177	<0.001
Gender				
Male	1.387	1.191	1.615	<0.001
Female	ref.	–	–	–
Geographic region				0.098
Northeast	ref.	–	–	–
Midwest	0.769	0.533	1.109	0.160
South and Other	1.082	0.838	1.397	0.546
West	1.152	0.834	1.590	0.391

*Advanced liver disease defined as cirrhosis with complications. Observations read = 10,518, Observations used= 10,331
Specification link test: p-value=0.377