Research Article
Viral Hepatitis

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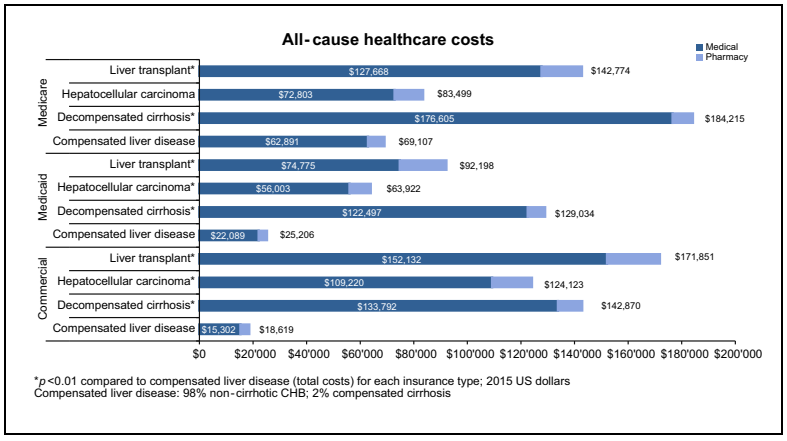
Healthcare resource utilization and costs by disease severity in an insured national sample of US patients with chronic hepatitis B

Graphical abstract



Highlights

- All-cause inpatient admissions (average stay 6–10 days) were more frequent in advanced liver disease states.
- Across all payers, patients with decompensated cirrhosis used the emergency department most (1.6–2.8 annual visits).
- HCC and liver transplant patients had highest proportion of outpatient hospital-based visits and annual visits.
- Advanced liver disease cohorts experienced 6–10× higher costs than patients with compensated liver disease.
- Compensated liver disease patients with CHB incurred 3× the cost of non-CHB controls.

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Lay summary

Hepatitis B virus can be a progressive disease leading to cirrhosis, hepatocellular carcinoma, liver transplant, and death. These progressive disease states are associated with a higher rate of hospitalizations, emergency room visits, outpatient visits, and costs compared to similar patients without hepatitis B. The most ill patients have the highest costs, but even patients who are less sick experience higher costs than patients without hepatitis B.

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Healthcare resource utilization and costs by disease severity in an insured national sample of US patients with chronic hepatitis B

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Background & Aims: Chronic hepatitis B (CHB) affects over 2 million people in the US, with little reported on healthcare utilization and cost. We aimed to quantify annual CHB utilization and costs by disease severity and payer type.

Methods: Using Commercial, Medicare, and Medicaid databases from 2004 to 2015 and ICD9 codes, we retrospectively identified adults with CHB, analyzing all-cause inpatient, outpatient, and pharmaceutical utilization and costs by disease severity. We compared healthcare utilization and costs between patients with CHB, without advanced liver disease, and matched non-CHB controls. All-cause inpatient, outpatient, and pharmaceutical utilization and costs were reported for each year and adjusted to 2015 dollars.

Results: Our sample consisted of 33,904 CHB cases and 86,072 non-CHB controls. All-cause inpatient admissions (average stay 6–10 days) were more frequent in advanced liver disease states. Across all payers, patients with decompensated cirrhosis had the highest emergency department utilization (1.6–2.8 annual visits) and highest mean annual costs. The largest all-cause cost components for Commercial and Medicaid were inpatient costs for all advanced liver disease groups (Commercial: 62%, 47%, 68%; Medicaid: 81%, 72%, 74%, respectively), and decompensated cirrhosis and hepatocellular carcinoma groups for Medicare (Medicare 49% and 48%). In addition, patients with compensated liver disease incurred costs 3 times higher than non-CHB controls.

Conclusion: Patients with CHB, regardless of payer, who experienced decompensated cirrhosis, hepatocellular carcinoma, or a liver transplant incurred the highest annual costs and utilization of healthcare resources, but even patients with CHB and compensated liver disease incurred higher costs than those without CHB. All stakeholders in disease management need to combine efforts to prevent infection and advanced liver disease through improved vaccination rates, earlier diagnosis, and treatment.

Lay summary: Hepatitis B virus can be a progressive disease leading to cirrhosis, hepatocellular carcinoma, liver transplant, and death. These progressive disease states are associated with a higher rate of hospitalizations, emergency room visits, outpatient visits, and costs compared to similar patients without hepatitis B. The most ill patients have the highest costs, but even patients who are less sick experience higher costs than patients without hepatitis B.

Introduction

Chronic hepatitis B (CHB)-induced liver disease can progress to compensated cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and death; and such progression occurs over many years for most patients. CHB currently affects approximately 240 million individuals worldwide, including 2 million individuals within the US, and is associated with substantial healthcare utilization.[1–4]

Currently, there is no cure for CHB, though newer treatments with nucleos(t)ide-based medications demonstrate effective viral suppression, consequently slowing disease progression. HBV vaccination became available over 30 years ago and is now the primary method of HBV prevention. The original targeted populations for vaccination were people at high risk of blood-borne infections through sexual contact or in the provision of health care, but in the mid-1990s universal vaccination was recommended for all infants.[5,6]

As a result of the change in vaccination recommendations, a report from the Centers for Disease Control and Prevention in 2014 indicated that 92% of kindergarteners and over 70% of healthcare workers were fully vaccinated for HBV; but only 24.6% of adults (>19 years of age) had been vaccinated, leaving a large pool of adults at risk of HBV infection.[7] Importantly, the population previously diagnosed with CHB has continued to age, and if untreated, may progress to more advanced liver disease with higher healthcare resource demands.[8,9] Currently, there are limited data on the healthcare utilization and costs associated with CHB in the US. Therefore, the aim of this study was to estimate the annual healthcare resource utilization and costs of liver disease associated with CHB in a large diverse population of patients with CHB in the US, with three types of insurance coverage, compared to matched non-CHB controls.

Keywords: CHB; Medicare; Commercial; Insurance; Cirrhosis; Medicaid.
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Table 1. Study sample – selection of CHB cases and matched non-CHB controls.

Attrition	Commercial		Medicaid		Medicare	
	n	%	n	%	n	%
Selection criteria CHB cases with variable post-period follow-up						
Adults with ≥1 inpatient or ≥2 outpatient non-rule-out medical claims (on different days and at least 30 days apart) with a diagnosis of CHB (ICD-9-CM diagnosis codes 070.22. 070.23, 070.32, 070.33, 070.30 or 070.31) in any diagnostic position between January 1, 2004, and June 30, 2015. (The index date will be the date of the first non-rule-out claim for CHB)	78,793	100.0	34,051	100.0	6,681	100.0
At least 6 months of continuous enrollment in medical and pharmacy benefits prior to and following the index date*	31,700	40.2	12,564	36.9	3,109	46.5
Matched to a non-CHB control patient	31,236	39.6	12,184	35.8	3,089	46.2
No evidence of hepatitis delta co-infection	29,585	37.5	11,503	33.8	2,938	44.0
Patients with CHB Severity Index Dates during 7/1/2004–6/30/2015 and at least 30 days of enrollment after CHB Severity Index Date (n)	29,363	37.3	11,290	33.2	2,881	43.1
No evidence of HIV or Hepatitis C in 6 months prior to and variable length period (at least 30 days) following the CHB Severity index date	24,818	31.5	6,616	19.4	2,470	37.0.4
CHB severity level (n, %)						
Compensated liver disease patients	23,504	94.7	6,057	91.6	1,987	80.4
Decompensated cirrhosis patients	750	3.0	415	6.3	353	14.3
HCC patients	309	1.2	86	1.3	86	3.5
Liver transplant patients	225	0.9	58	0.9	44	1.8
Selection criteria for non-CHB controls with variable post-period follow-up						
Patients ages 18+ without a diagnosis of CHB during the study period (1/1/2004–12/31/2015) and randomly selected as 1 of 6 matches for cases and no exclusionary drug or drug/dx combination	188,699	100.0	74,319	100.0	18,473	100.0
At least 6 months of continuous enrollment in medical and pharmacy benefits prior to and following the index date*	119,342	63.2	41,369	55.7	14,480	78.4
Controls matched to compensated liver disease patients	64,821	34.4	15,450	20.8	5,801	31.4

CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; HIV, Human immunodeficiency virus.
* Medicaid patients with dual eligibility excluded. Bold numbers represent patients included in final analysis. Compensated liver disease includes non-cirrhotic and compensated cirrhosis patients.

Patients and methods

This retrospective, observational study used the Truven Health MarketScan® Commercial, Medicare, and Medicaid databases from 2004 to 2015. The Commercial database contained 41 million commercial enrollees from the general population. The Medicare database contained approximately 4 million patients (ages 65 and older) with employer-sponsored Medicare supplemental insurance. The Medicaid database contained approximately 8 million low-income enrollees in 10–12 geographically dispersed states. All three databases included medical and pharmacy claims for healthcare services performed in the inpatient and outpatient settings, as well as enrollment and demographic data for covered individuals. Supplemental Appendix provides further details on these databases.

Patients with CHB were identified using ICD-9 codes (070.22. 070.23, 070.32, 070.33, 070.30 or 070.31) and were included if they were adults (≥18 years) with at least one inpatient or two outpatient non-rule-out claims (claims not associated with a diagnostic workup used to rule out the presence of a condition, such as laboratory tests for CHB). Eligible patients had at least 6 months of continuous medical and prescription coverage before and after the earliest CHB diagnosis (index date), continuous enrollment for at least one full calendar year during 2006–2015, no claims for hepatitis delta co-infection (ICD-9-CM diagnosis codes 070.23, 070.31, or 070.33), and no co-infection with either or both hepatitis C virus (HCV; ICD-9 codes 070.41, 070.44, 070.51, 070.54, or 070.7) or human immunodeficiency virus (HIV, ICD-9 codes 042 or 079.53). Medicaid patients with dual eligibility (those who receive health care benefits from both Medicare and Medicaid) were also excluded.[10]

Patients with CHB were assigned to 1 of 4 liver disease severity cohorts: (1) compensated liver disease (CLD), (2) decompensated cirrhosis, (3) HCC, and (4) liver transplant (in order of increasing severity) using diagnosis or procedure codes from the dates of July 1, 2006 to June 30, 2015 (Table S1). Due to the small sample size of patients with compensated cirrhosis (n = 837, 2%), these patients were grouped together with the non-cirrhotic patients, which comprised the CLD group. Liver transplant status was assigned the highest severity, since this population included patients with CHB and the most advanced forms of liver disease – end-stage liver disease and/or HCC. All other patients with CHB were assigned to the highest severity category for which they had qualifying claims determined by either: (1) the date associated with the first claim and with the highest liver disease severity or (2) the CHB diagnosis date. All included patients with CHB were also required to have at least 30 days of continuous enrollment after their CHB severity level index date (Table 1).

Non-CHB controls (without a diagnosis of CHB during the study period) were selected from the same payer databases and matched to patients with CHB and CLD by CHB index year, age, gender, geographic region, and race (Medicaid only).

Clinical characteristics evaluated included the Deyo-Charlson comorbidity Index (DCCI), comprised of 19 comorbidities identified by ICD codes such as heart disease, diabetes, chronic lung disease combined to generate a score between 0–32 with higher scores indicating sicker patients,[11] and other comorbidities were identified by ICD-9-CM and ICD-10-CM diagnosis codes which were reported for the 6-month baseline period prior to the CHB severity index date.

Study outcomes

All-cause and CHB-specific inpatient, outpatient, and pharmaceutical healthcare utilization and costs were reported as per patient per year adjusted to 2015 US dollars, where all dollar estimates were inflated to 2015 dollars using the Medical Care

Table 2. Patient characteristics in patients with CHB by disease severity and in non-CHB controls.

Demographic and clinical characteristics	CHB patients				Non-CHB control patients[†]
	Compensated liver disease	Decompensated cirrhosis	HCC	Liver transplant	
Commercial					
Patients (n)	23,504	750	309	255	64,821
Age (Mean, SD)	44.1 (11.0)	53.1 (8.8)[*]	51.8 (9.1)[*]	53.3 (8.3)[*]	44.5 (10.8)
Age (Median)	44	54	53	55	45
Male (%)	53.4%	67.9%[*]	71.5%[*]	76.1%[*]	53.3%
Follow-up (months) (Mean, SD)	38.7 (29.1)	24.1 (21.7)[*]	24.0 (22.3)[*]	37.0 (29.4)	39.4 (30.0)[**]
DCCI (Mean, SD)	0.3 (0.9)	2.0 (2.3)[*]	1.9 (2.7)[*]	2.2 (2.4)[*]	0.2 (0.6)[**]
Comorbid conditions (%)					
Diabetes	6.8%	23.5%[*]	14.2%[*]	26.7%[*]	5%[**]
Hyperlipidemia	7.6%	13.6%[*]	11.3%[*]	11%[*]	7%[**]
Cardiovascular disease	3.7%	21.2%[*]	8.1%[*]	12.2%[*]	2.2%[**]
Hypertension	12.8%	37.1%[*]	25.2%[*]	25.5%[*]	10.9%[**]
Renal impairment	4.3%	25.5%[*]	13.3%[*]	44.3%[*]	1.5%[**]
Medicaid					
Patients (n)	6,057	415	85	58	15,450
Age (Mean, SD)	42.7 (13.0)	50.4 (10.5)[*]	56.3 (9.6)[*]	47.8 (13.5)[*]	43.2 (13.0)[**]
Age (Median)	43	52	56	49	44
Male (%)	41.0%	55.9%[*]	70.6%[*]	56.9%[*]	40.7%
Follow-up (months) (Mean, SD)	26.1 (23.1)	19.2 (17.6)[*]	14.2 (17.5)[*]	21.9 (17.8)	25.4 (22.9)[**]
DCCI (Mean, SD)	0.5 (1.1)	2.2 (2.2)[*]	2.8 (2.7)[*]	2.2 (2.6)[*]	0.4 (0.9)[**]
Comorbid conditions (%)					
Diabetes	12.8%	27.7%[*]	27.1%[*]	27.6%[*]	11.2%[**]
Hyperlipidemia	8.9%	14.9%[*]	11.8%	3.4%	8.7%
Cardiovascular disease	8.0%	28%[*]	11.8%	12.1%	6%[**]
Hypertension	22.4%	48.2%[*]	37.6%[*]	24.1%	19.4%[**]
Renal impairment	7.5%	34.2%[*]	18.8%[*]	37.9%[*]	3.5%[**]
Medicare					
Patients (n)	1,987	353	86	44	5,801
Age (Mean, SD)	72 (7.1)	74.7 (7.7)[*]	73.5 (6.6)	69.1 (3.6)[*]	72.1 (7.0)
Age (Median)	71	74	73	70	71
Male (%)	55.2%	62.3%[*]	73.3%[*]	70.5%[*]	55.4%
Follow-up (months) (Mean, SD)	34.5 (26.1)	19.0 (17.6)[*]	22.3 (37.3)[*]	37.3 (24.4)	38.1 (27.7)[**]
DCCI (Mean, SD)	1.7 (2.1)	3.7 (2.7)[*]	2.5 (2.6)[*]	2.2 (2.4)	0.8 (1.3)[**]
Comorbid conditions (%)					
Diabetes	30.6%	45.6%[*]	29.1%	40.9%	18.4%[**]
Hyperlipidemia	24.0%	30.3%[*]	24.4%	13.6%	19.1%[**]
Cardiovascular disease	30.9%	58.9%[*]	20.9%	25.0%	19.6%[**]
Hypertension	48.8%	62%[*]	46.5%	40.9%	18.4%[**]
Renal impairment	29.9%	58.9%[*]	24.4%	40.9%	8%[**]

CHB, chronic hepatitis B; DCCI, Deyo-Charlson Comorbidity Index; HCC, hepatocellular carcinoma.
[†]Non-CHB Control Patients: compensated liver disease control group.
[*]p <0.05 for comparisons between compensated liver disease *vs.* decompensated cirrhosis, *vs.* hepatic carcinoma, and *vs.* liver transplant patients.
[**]p <0.05 for comparisons of compensated liver disease *vs.* non-CHB controls. Compensated liver disease: 98% non-cirrhotic CHB; 2% compensated cirrhosis.

Component of the Consumer Price Index (CPI). The CPI is collected by the Bureau of Labor Statistics for which a time series of this index can be found at http://research.stlouisfed.org/fred2/series/CPIMEDNS and an index description at http://www.bls.gov/cpi/cpifact4.htm. CHB-specific utilization and costs were defined by the presence of a diagnosis or procedure code for CHB, compensated cirrhosis, decompensated cirrhosis, HCC, or liver transplant (inpatient admissions required a primary diagnosis code). Each payer was evaluated separately.

Statistical analysis

Categorical variables were presented as the count and percentage of patients in each category; continuous variables were summarized by providing the means and standard deviations. Continuous variables of two independent study groups were compared by the Student's t tests if data followed a normal distribution; otherwise, non-parametric methods were used. Comparisons of categorical variables such as proportions of patients with different age groups or comorbidities in 2006 *vs.* 2015 were performed using the asymptotic Pearson chi-square and Fisher's exact tests. The p value considered to be significant was <0.05 (2-tailed). All statistical tests were performed using the program SAS (SAS version 9.4, SAS Institute Inc, Cary, NC). This study was determined as exempt due to the study use of de-identified data only by the Institutional Review Board at Stanford University, Palo Alto, CA.

Results

Patient sample

After applying our inclusion/exclusion criteria the final Commercial CHB insurance cohort consisted of 24,818 patients, the Medicare CHB cohort of 2,470 patients, and the Medicaid CHB cohort of 6,616 patients (Table 1). Over 80% of the patients across all insurance groups had CLD; and a minority of patients had decompensated cirrhosis, ranging from 3.0% (Commercial) to 14.3% (Medicare), or HCC, ranging from 1.2% (Commercial) to 3.5% (Medicare). Less than 1% of patients received a liver

transplant in either the Commercial or Medicaid cohorts compared to 1.8% of patients with Medicare (Table 1).

The number of non-CHB matched patients is also displayed (Table 1). Of non-CHB patients, there were 64,821 patients in the Commercial cohort, 5,801 patients in the Medicare cohort, and 15,450 patients in the Medicaid cohort.

Patient characteristics

Patient characteristics by stage of liver disease among the three insurance coverages and the non-CHB controls (Table 2). Among patients with CHB from the Commercial cohort, CLD patients were younger, less likely to be male, generally healthier with lower DCCI scores, and with fewer comorbid conditions than patients with advanced liver disease. Diabetes mellitus (26.7%) and renal impairment (44.3%) were greater in the liver transplant group, while hypertension (37.1%), hyperlipidemia (13.6%), and cardiovascular disease (21.2%) were highest in the decompensated group. The range of follow-up time was 24.1 months (decompensated cirrhosis) to 38.7 months in the CLD group which is somewhat less than the overall follow-up time for all decompensated patients (60.2 months) and all CLD (96.7 months) patients in the database (Table S2).

Similarly, Medicaid patients with CHB in the CLD group were generally healthier (fewer comorbidities) than those with advanced liver disease. The prevalence of comorbidities followed the same pattern as for those with Commercial coverage, though overall, the Medicaid group was more ill across all liver disease stages than the Commercial group, as indicated by DCCI scores. The range of follow-up time was 14.2 months (HCC group) to 26.1 months (CLD group) with a similar trend of a shorter length of time in the database compared to all patients with CLD (Table 2, Table S2).

Overall, the Medicare group was the most ill group by DCCI score. Comorbidities of diabetes (>30%), hypertension (>40%), and renal impairment (>25%) were common in Medicare patients with CHB, irrespective of liver disease severity. The

Table 3. All-cause resource utilization in patients with CHB by disease severity and in non-CHB controls.

All-cause healthcare utilization	CHB patients				Non-CHB control patients[†]
	Compensated liver disease	Decompensated cirrhosis	HCC	Liver transplant	
Commercial					
Patients (n)	23,504	750	309	255	64,821
Patients with inpatient admission (%)	27.2%	60.0%[*]	60.8%[*]	62.0%[*]	13.2%[**]
Annual number of inpatient admissions (mean, SD)	0.2 (0.7)	1.9 (3.9)[*]	1.6 (3.1)[*]	1.2 (2.1)[*]	0.1 (0.3)[**]
Length of stay per admission, in days (mean, SD)	4.0 (6.6)	8.3 (10.0)[*]	5.3 (4.2)[*]	10.8 (16.8)[*]	3.4 (4.1)[**]
Patients with ER visits (%)	31.2%	52.1%[*]	41.1%[*]	58.0%[*]	30.4%[**]
Annual number of ER visits (mean, SD)	0.3 (1.4)	1.6 (4.4)[*]	1.1 (2.6)[*]	1.1 (2.1)[*]	0.2 (0.7)[**]
Patients with OP hospital-based visits (%)	16.6%	33.6%[*]	54.0%[*]	53.7%[*]	9.5%[**]
Annual number of OP hospital-based visits (mean, SD)	0.5 (2.7)	1.8 (5.0)[*]	5.2 (11.5)[*]	2.2 (4.6)[*]	0.2 (1.1)[**]
Patients with pharmacy claims (%)	92.5%	94.7%[*]	94.2%	97.3%[*]	86.3%[**]
Annual number of pharmacy claims (mean, SD)	14.8 (20.5)	39.9 (35.6)[*]	28.6 (28.3)[*]	53.6 (38.4)[*]	13.0 (17.7)[**]
Medicaid					
Patients (n)	6,057	415	85	58	15,450
Patients with inpatient admission (%)	47.5%	80.7%[*]	75.3%[*]	60.3%	22.8%[**]
Annual number of inpatient admissions (mean, SD)	0.7 (1.5)	3.3 (4.8)[*]	2.4 (2.7)[*]	1.7 (3.7)[*]	0.3 (1.1)[**]
Length of stay per admission, in days (mean, SD)	4.6 (4.6)	9.3 (13.7)[*]	4.8 (3.2)	7.4 (7.5)[*]	5.1 (6.4)[**]
Patients with ER visits (%)	51.7%	70.4%[*]	43.5%	62.1%	37.3%[**]
Annual number of ER visits (mean, SD)	1.6 (3.8)	3.3 (6.9)[*]	2.8 (5.9)[*]	1.3 (1.9)	0.8 (1.8)[**]
Patients with OP hospital-based visits (%)	33.8%	43.6%[*]	58.8%[*]	67.2%[*]	15.0%[**]
Annual number of OP hospital-based visits (mean, SD)	1.5 (4.0)	2.7 (5.8)[*]	5.6 (9.6)[*]	5.0 (8.2)[*]	0.7 (3.3)[**]
Patients with pharmacy claims (%)	96.6%	94.7%[*]	96.5%	98.3%	81.5%[**]
Annual number of pharmacy claims (mean, SD)	40.7 (46.9)	72.4 (67.5)[*]	58.4 (51.4)[*]	85.3 (43.2)[*]	41.6 (50.5)
Medicare					
Patients (n)	1,987	353	86	44	5,801
Patients with inpatient admission (%)	66.6%	75.6%[*]	67.4%	63.6%	34.1%[**]
Annual number of inpatient admissions (mean, SD)	0.8 (1.1)	2.3 (3.7)[*]	1.5 (2.7)[*]	1.0 (1.7)	0.3 (0.6)[**]
Length of stay per admission, in days (mean, SD)	5.4 (7.2)	7.3 (6.8)[*]	4.9 (3.5)	5.8 (3.9)	4.6 (4.3)[**]
Patients with ER visits (%)	60.4%	76.5%[*]	57.0%	61.4%	45.2%[**]
Annual number of ER visits (mean, SD)	1.0 (1.8)	2.8 (3.5)[*]	1.4 (2.3)[*]	0.8 (1.5)	0.4 (1.0)[**]
Patients with OP hospital-based visits (%)	32.8%	36.5%	50.0%[*]	59.1%[*]	22.6%[**]
Annual number of OP hospital-based visits (mean, SD)	1.5 (4.5)	2.5 (5.8)[*]	3.0 (5.5)[*]	3.4 (7.4)[*]	0.8 (2.9)[**]
Patients with pharmacy claims (%)	96.5%	91.5%[*]	94.2%	97.7%	94.0%
Annual number of pharmacy claims (mean, SD)	37.6 (31.2)	45.8 (39.6)[*]	31.8 (23.5)	47.9 (26.8)[*]	28.1 (25.0)[**]

CHB, chronic hepatitis B; ER, emergency room; HCC, hepatocellular carcinoma; OP, outpatient.
[*] p <0.05 for comparisons between compensated liver disease vs. decompensated cirrhosis, vs. hepatic carcinoma, and vs. liver transplant patients.
[**] p <0.05 for comparisons of compensated liver disease vs. non-CHB controls.
[†] Non-CHB Control Patients: compensated liver disease control group. Compensated liver disease: 98% non-cirrhotic CHB; 2% compensated cirrhosis.

range of follow-up time was 19.0 months in the decompensated cirrhosis group compared to 37.3 months for the liver transplant group.

Across all groups, the non-CHB control patients were less ill and had significantly fewer comorbidities (p <0.05) except for hyperlipidemia. The non-CHB control group also had an average follow-up of 39.4 months (Table 2). The trend in length of time in the database was also shorter for both the Medicare group and the control non-CHB group compared to the overall length of time in patients with CLD (Table S2).

Inpatients stays and length of stay

All-cause inpatient admission was more frequent in patients with more advanced liver disease, with about two-thirds to three-quarters of patients with decompensated cirrhosis (n = 567/750), HCC (n = 208/309), or liver transplant (n = 162/255) requiring inpatient hospitalization (>65% Commercial, >76% Medicaid, >69% Medicare) (Table 3). Average inpatient length of stay was also highest in decompensated cirrhosis and liver transplantation (Commercial 8.3 and 10.8 days, Medicaid 9.3 and 7.4 days, Medicare 7.3 and 5.8 days, respectively) (Table 3).

Outpatient visits

The proportion of patients with outpatient hospital-based visits and the annual number of visits were highest in HCC and liver transplant patients across all payer types (Table 3). Conversely, the proportion of patients visiting the emergency room was different per insurance coverage group. Within the Commercial insurance cohort, the CLD group had the lowest proportion of patients visiting the emergency room (31.2%, p <0.05), while among the Medicare and Medicaid cohorts the proportion of patients with HCC experienced the fewest emergency room visits (57.0% *vs.* 43.5%, respectively). For Medicare and Medicaid, HCC was ranked second behind the decompensated group for the highest annual number of emergency room visits per person across all insurance carriers (Commercial: 1.1 *vs.* 1.6; Medicare: 1.4 *vs.* 2.8 and Medicaid: 3.3 *vs.* 2.8, respectively) (Table 3).

Prescriptions

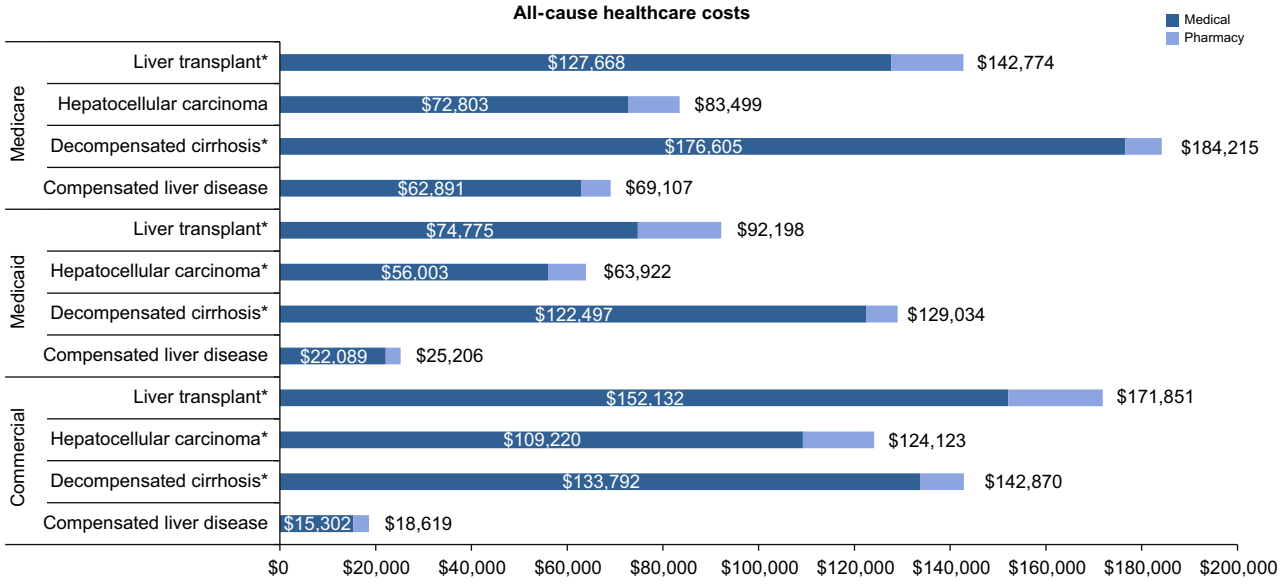
Across payers, patients with CLD had fewer average annual prescriptions compared to those with higher disease severity (all p <0.05), except for the HCC group among Medicare patients (Table 3).

Healthcare costs

Total mean all-cause annual healthcare costs were highest in patients with decompensated cirrhosis, HCC or receiving liver transplant compared to patients with CLD across insurance types (all p <0.05 except Medicare HCC) (Fig. 1), (*e.g.*, for Commercial: $142,870, $124,123 and $171,851 *vs.* $18,619, respectively). In Commercial patients, annual healthcare costs for decompensated cirrhosis, HCC, and liver transplant were 6–10 times higher compared to costs for patients with CLD (all p <0.05) (Fig. 1).

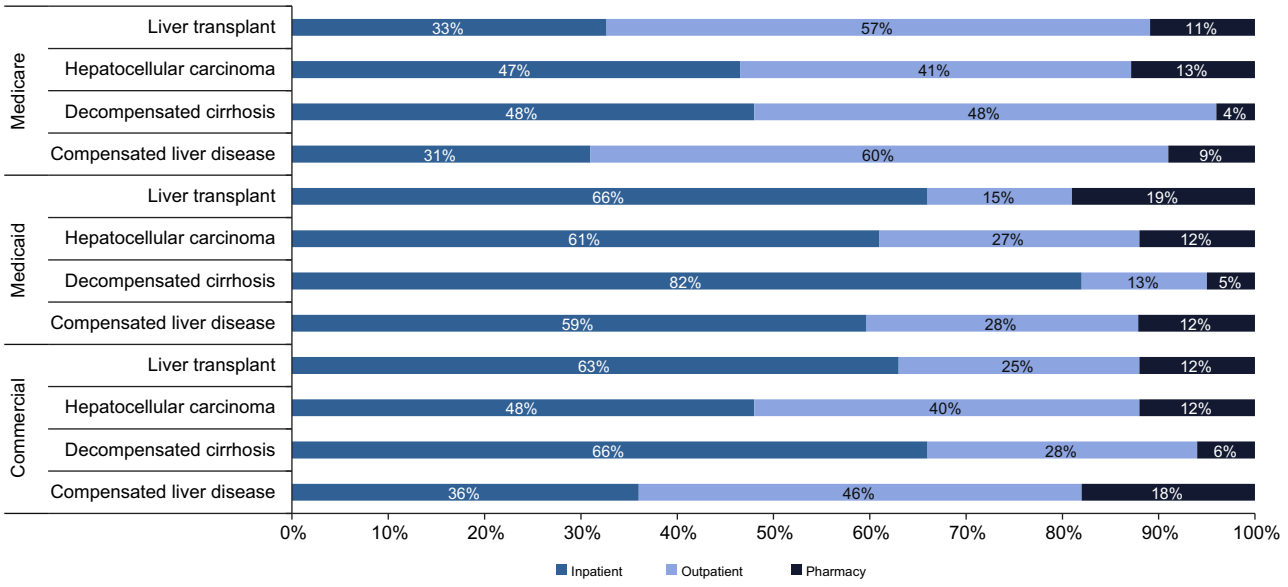
The largest all-cause cost components were inpatient for Commercial and Medicaid patients with decompensated cirrhosis, HCC and liver transplant (Commercial: 66%, 48%, 63%; Medicaid: 82%, 61%, 66%, respectively), and Medicare patients with decompensated cirrhosis and HCC (48% and 47%) (Fig. 2).

Regarding CHB-specific costs, patients with higher disease severity had higher costs across all payer types (all p <0.05) (Fig. 3). This was especially evident when comparing the costs of patients without cirrhosis and those with compensated cirrhosis to those who underwent a liver transplant. Specifically, for the non-cirrhotic or compensated cirrhotic patients their costs ranged from $1,393 to $2,609 (dependent on payer group) compared to $30,849 to $130,139 for those with a history of liver transplant and again dependent on payer group (all p <0.05) (Fig. 3). The total all-cause healthcare costs among CHB patient groups of CLD, decompensated liver disease, HCC, and liver transplant were significantly higher than non-CHB



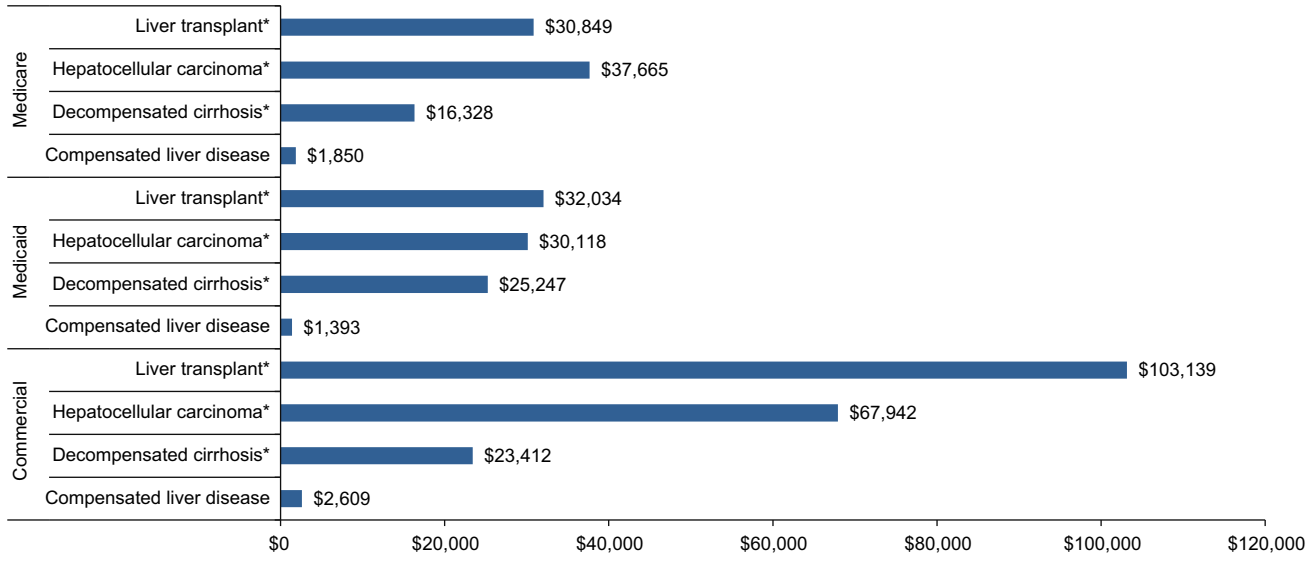
*p <0.01 compared to compensated liver disease (total costs) for each insurance type; 2015 US dollars
Compensated liver disease: 98% non-cirrhotic CHB; 2% compensated cirrhosis

Fig. 1. All-cause healthcare costs (per person per year in 2015 US dollars) in patients with CHB by disease severity.



Compensated liver disease: 98% non-cirrhotic CHB; 2% compensated cirrhosis

Fig. 2. Service/care components of all-cause healthcare costs in patients with CHB by disease severity.



*p <0.01 compared to compensated liver disease for each insurance type; 2015 US dollars
Compensated liver disease: 98% non-cirrhotic CHB; 2% compensated cirrhosis

Fig. 3. CHB-specific healthcare cost in patients (per person per year) by disease severity.

controls across all payers (all p <0.05) (Fig. 4). Advanced liver disease cohorts heavily utilized high-cost inpatient care, outpatient hospital-based care, and pharmacy services (6–10 times higher than the costs in patients with CLD). However, even patients with CLD had three times the annual healthcare cost of matched non-CHB controls across payers (all p <0.05) (Fig. 4).

Discussion

This analysis represents one of the first studies to quantify the healthcare utilization and costs of an aging CHB population within the United States using data from a large, diverse, and nationally representative sample of patients with CHB (n = 27,949) and matched non-CHB controls (n = 86,072). We found that, as expected, patients with CHB and end-stage liver disease (decompensated cirrhosis, HCC, or liver transplant) had significantly higher healthcare utilization and costs compared to patients with CLD; however, the comorbid burden, healthcare utilization, and cost burden was high for all patients with CHB irrespective of liver disease severity.

Compared to non-CHB control patients, patients with CHB and CLD (98% non-cirrhotic, 2% compensated cirrhosis) were more ill, based on DCCI scores, had significantly higher healthcare utilization, and 3 times the costs. This finding is in line with results from another recent study in which investigators using the National Inpatient Sample found that costs for treating HBV almost doubled from 2000 to 2012.[12]

Therefore, besides primary prevention of new HBV infection through vaccination and other public health measures, patients

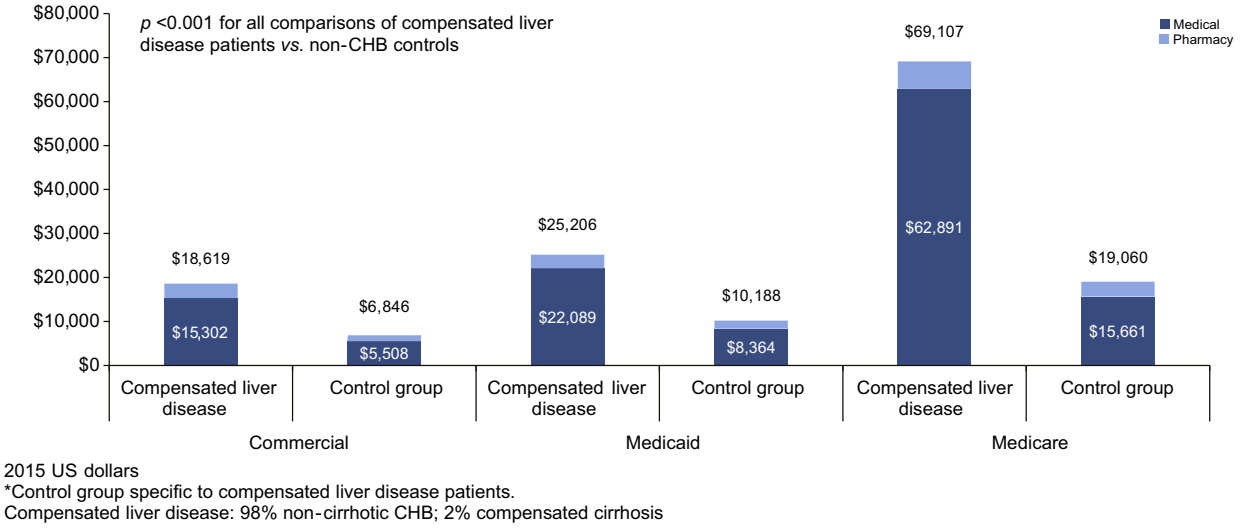


Fig. 4. All-cause health care cost (per person per year) in compensated liver disease patients with CHB compared to non-CHB controls.

already chronically infected with HBV who are at high risk of disease progression should also be targeted and initiated on antiviral therapies that have been proven to prevent HCC and end-stage liver disease.[13] This is particularly relevant as a recent study found that the CHB population is aging with increasing liver and non-liver comorbidities, a finding that was consistent in both community and academic settings.[14]

There were also significant differences in total healthcare cost and utilization patterns among the different payer types. We found within the Medicare cohort that patients with decompensated cirrhosis experienced an average annual all-cause healthcare cost of $184,215 per person, which is over $50,000 more than patients with decompensated cirrhosis in the Medicaid or Commercial cohorts.

Interestingly, the costs for decompensated cirrhosis within Medicare were evenly distributed between inpatient (48%) and outpatient (48%) care, while the costs for decompensated cirrhosis among the Medicaid or Commercial cohorts were predominantly associated with inpatient care (82% and 66%, respectively), despite higher levels of comorbidity (DCCI 3.7 [Medicare] *vs.* 2.2 [Medicaid] *vs.* 2.0 [Commercial]). One explanation may be that a larger proportion of Medicare patients used the emergency room for follow-up care resulting from a shortened length of stay compared to patients in the other insurance cohorts (Medicare = 7.3 days; Medicaid = 9.3 days; Commercial = 8.3 days).[15] In fact, 57–77% of Medicare patients visited the emergency room compared to 44–70% of Medicaid patients and 31–58% of Commercially-insured patients. In addition, previous studies have demonstrated that Medicare enrollees were up to 2 times more likely to be frequent users of the emergency room relative to the general population.[16]

Recognizing these economic burdens of CHB is particularly important for the Medicare population, as healthcare delivery in this population shifts from fee-for-service to value based care in an effort to "rein in" costs. Medicare costs are expected to grow 6.0 percent per year through 2023 comprising 17.5% of total federal spending by the year 2027.[9,17–20] Therefore, although patients with CHB comprise a relatively small percentage of hospitalizations overall, treatment of CHB contributes to increased healthcare utilization because of higher rates of inpatient admissions and ER visits, creating a substantial economic burden for the government and individual especially as the CHB population ages.

In addition, looking at total costs, the burden of disease can be conceptualized into disability-adjusted life years (DALYs). DALYs assist in choosing particular interventions and assessing the success or failure of such interventions. One study suggested that the disease burden due to CHB infection was estimated at 2,763 DALYs/year overall (95% CI 2,428–3,097).[21] Specifically, compensated liver cirrhosis and decompensated liver cirrhosis were associated with an estimated 651 DALYs/year (95% CI 551–754) and 2,182 DALYs/year (95% CI 1,791–2,594), respectively, while HCC was associated with 2,795 DALYs/year (95% CI 1,833–3,810).[21]

Although we did not quantify DALYs in this study, we did identify a high number of comorbidities among patients with CHB relative to non-CHB controls. The number of comorbidities was especially pertinent in those who had decompensated cirrhosis, HCC or liver transplant, conditions that were prevalent in all payer groups but most prevalent in the Medicare cohort, as these conditions were potentially associated with increased DALYs translating to a higher number of years living with a disability and a greater economic burden.[21] Therefore, continual effort is needed to identify patients at risk of CHB as well as patients with CHB at risk for disease progression so that they are treated accordingly, especially given the growing evidence of the preventive effect of antiviral therapies and availability of effective and well-tolerated medications.[13]

As such, a strength of this study is that we have provided dollar amounts associated with all-cause and liver-related CHB hospitalizations. These figures can be used in future economic analyses to put an exact dollar amount to the disease burden of CHB, which will provide decision and policy makers with the economic information that is needed when making decisions about covering treatments and interventional approaches. However, it is important to note that not all comorbidity-associated costs may be averted when treating HBV, as many of the comorbidities may have been present before HBV was diagnosed and/or were unrelated to CHB. In addition, the costs for the liver transplant patient may appear low (Fig. 3); however, these costs are a per person per year average so the costs take into account both the patient that

may have been a new transplant recipient of a liver, as well as a patient who may be a stable 10-year liver transplant survivor. Therefore, these costs should be interpreted with caution as they are average costs. However, they do provide a basis for future cost-effectiveness analysis as noted previously.

There were several limitations to this study. The first, as with any claims databases, was that the MarketScan Research Databases relied on administrative data for clinical detail – such data are subject to data coding limitations, data entry error, and misclassification of CHB. However, stringent data quality checks were in place to reduce coding errors for all data entered.

Secondly, the study results may not be generalizable to the entire US population, especially the uninsured, but the data are given certain weights which allow the data and subsequent results to be generalizable, at least to the population with similar insurance coverage. Thirdly, with the small number of patients coded as having cirrhosis without decompensation or HCC, they were analyzed together with non-cirrhotic cases. This could increase the cost reported for non-cirrhotic patients. However, as the sample size of this group is small (2%), it was unlikely to cause substantial changes in the results for non-cirrhotic patients.

Clinical diagnosis of cirrhosis often depends on signs of portal hypertension or hepatic insufficiency, both of which are often subclinical in compensated cirrhosis. Therefore, compensated cirrhosis was likely underdiagnosed, leading to the smaller number of cases relative to decompensated cases in our study. In addition, patients were assigned to the highest severity category for which they had qualifying claims. By doing this, we may have over-simplified the level of liver severity. For example, while compensated and decompensated cirrhosis are two mutually exclusive conditions, HCC can co-exist with either compensated or decompensated cirrhosis. As a result, within the HCC group, the healthcare utilization and cost of HCC with compensated cirrhosis and HCC with decompensated cirrhosis may have differed.

We also realized that there are both advantages and limitations to our matching strategy. By not matching for comorbidity, we were able to include the effect of comorbidities on healthcare utilization and cost difference between CHB and non-CHB patients.[22] However, by not matching for comorbidity, we were not able to conclude that the observed healthcare utilization and cost differences between CHB and non-CHB patients were independent of any comorbidities. Finally, CHB-specific utilization and costs may have been underestimated due to possible pharmacy claims for CHB-specific diagnoses, but not CHB antiviral specific medications.

In summary, healthcare costs associated with CHB are high, even in patients without advanced liver disease and particularly high in patients with decompensated cirrhosis, HCC, and those requiring liver transplant. In this study, we found that higher healthcare costs were associated with inpatient services, emergency room visits, and outpatient service utilization for patients with more severe liver disease across payer types. Notably, the highest costs were associated with decompensated cirrhosis within the Medicare group due to emergency room, inpatient, and outpatient visits. As Medicare spending is increasing, it is imperative that earlier identification and treatment is initiated to prevent progression of CHB and specifically prevent progression of CHB patients to advanced liver disease. In order to prevent the current rates of progression to more severe liver disease and associated costs, efforts should focus on identification of barriers to early screening, diagnosis, and linkage to care. For patients who are already diagnosed and linked to care, appropriate management should be prioritized to reduce downstream complications that result in increased resource utilization and cost to the health care system.

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Conflict of interest

MN: Research support; BMS, Gilead, Janssen. Advisory board/consulting; BMS, Gilead, Janssen, Roche. BO: Employee of Gilead Sciences, Inc. IL: None. NM: Employee of IBM Watson Health. SG: Grant/Research support; Abbvie Pharmaceuticals, Conatus, CymaBay, Genfit, Gilead, Intercept Pharmaceuticals, Merck. Consulting; Abbvie Pharmaceuticals, Intercept, Gilead, Merck. GD: Advisory board: Gilead Sciences; Abbott, Abbvie, Bristol-Myers Squibb, Janssen, and Roche. JL: Research support; AbbVie, Conatus, Genfit, Gilead, Intercept. Consulting; BMS, Gilead.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

MN: study design, data analysis and interpretation, drafting of the manuscript and study supervision. BO: study design, data analysis and interpretation, and participated in the drafting of the manuscript. IL: study design, data analysis and interpretation, and revision of the manuscript. NM: study design, data analysis and interpretation, and review of the manuscript. SG: study design, data analysis and interpretation, and review of the manuscript. GD: study design, data analysis and interpretation, and review of the manuscript. JL: study design, data analysis and interpretation, and participated in the drafting of the manuscript.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.09.021.

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