HHS Public Access

Author manuscript

J Gastroenterol Hepatol Res. Author manuscript; available in PMC 2021 September 23.

Published in final edited form as:

J Gastroenterol Hepatol Res. 2020 ; 9(3): 3169–3175.

Patterns of Hepatitis C-Related Inpatient Mortality in the United States in the Era of Direct-Acting Antivirals

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Abstract

BACKGROUND & AIMS: Direct-acting antivirals (DAA) have revolutionized the management of hepatitis C virus (HCV) infection. Data on national inpatient mortality in this new era are scarce. This study aimed to evaluate inpatient mortality among HCV-related hospital stays in the United States (US) during the years DAA were available.

METHODS: We conducted a cross-sectional analysis of the National Inpatient Sample (NIS) between 2012 and 2016. Using discharge weights, national estimates of HCV-related hospitalizations were calculated. Simple and multiple logistic regressions were performed to identify factors associated with inpatient mortality.

RESULTS: A total of 67,630 hospitalizations from NIS were HCV-related, accounting for an estimated 338,150 hospitalizations during 2012 – 2016. These hospitalizations have estimated average annual total charges of $4.6 billion, adjusted to 2020 US dollars. The rate of inpatient mortality declined modestly from 5.25% in 2012 to 4.75% in 2016 (P=0.07). Over the 5-year study period, the proportion of in-hospital deaths increased for black patients, Medicaid beneficiaries, and patients with substance-related disorders. Controlling for known predictors, the odds of inpatient mortality were significantly greater among black patients compared to white patients (OR= 1.27 [95% CI=1.16 – 1.39]).

CONCLUSIONS: The burden of HCV infection is substantial given the disease is now curable. Our findings indicate that major disparities in the HCV disease burden exist in the era of DAA.

Keywords

Liver cirrhosis; National Inpatient Sample; Disease burden; Health disparities

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Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

INTRODUCTION

Hepatitis C virus (HCV) infection is the most common blood-borne infection in the U.S[1]. The Centers for Disease Control and Prevention estimate that approximately 2.4 million Americans are chronically infected with HCV[2]. It is particularly prevalent in those born between 1945 and 1965 (i.e. baby boomers);[3] many of who are unaware that they are infected and are also not linked to care[3]. Because this cohort is aging, HCV-related morbidity and mortality rates have been on the rise. The prevalence of HCV infection is disproportionately higher among African Americans, illicit drug users, homeless persons, and individuals of low socioeconomic status[4,5]. Evidence shows that these populations are less likely to be linked to care and are less likely to receive treatment[6,7].

Prior to 2011, the mainstay of HCV infection treatment was the combination of peginterferon alfa and ribavirin. Since 2011, several well-tolerated, highly effective direct-acting antivirals (DAA) have been approved to treat HCV patients with various genotypes and comorbidities. Evidence shows that DAA therapy is associated with lower incidence of hepatocellular carcinoma (HCC) and decompensated cirrhosis in cirrhotic and noncirrhotic patients[8]. However, their high prices have been the main obstacles to their widespread access. As a result of high cost and high demand, many insurance companies and Medicaid programs have established restrictive criteria for DAA authorization. The restrictions are mostly related to type of prescriber, liver fibrosis stage, and abstinence from drugs or alcohol[9].

If left untreated, chronic HCV infection can lead to serious complications and ultimately death. It is the leading cause of liver cirrhosis and HCC in the US[10]. Persons infected with HCV have an estimated all-cause mortality rate greater than twice that of HCV-negative persons[11]. In addition, the number of HCV-related deaths are much greater than those related to hepatitis B virus (HBV) and to human immunodeficiency virus (HIV)[12]. In the pre-DAA era, several studies reported significant increases in the national inpatient mortality among HCV patients[13,14]. To date, there is little data providing a comprehensive view on the national patterns of HCV-related inpatient mortality in the new era of DAA. In the current study we provide national estimates for the inpatient mortality rate among HCV-related hospital stays and identify sociodemographic and clinical factors that are associated with inpatient mortality.

METHODS

Study Design and Data Source

A cross-sectional study using National Inpatient Sample (NIS) 2012 – 2016 databases was conducted. NIS is the largest publicly available all-payer database of hospital inpatient care in the US. It is a part of several databases developed for the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ)[15]. NIS is a stratified sample of approximately 20% of all discharge records from U.S. community hospitals, excluding long-term care and rehabilitation hospitals. The 2016 NIS includes inpatient data from 46 states and District of Columbia, covering more than 97% of the US population. The unit of observation in NIS is a hospital stay record and

contains clinical and nonclinical information. Data elements for each hospital stay include patient demographic data, up to 30 diagnoses, expected source of payment, length of stay, total charges, and discharge status, among others.

Outcome Measurement and Identification of HCV-Related Hospitalizations

The outcome of interest in this study was in-hospital death during an HCV-related hospitalization. The outcome was measured as a binary outcome using the variable DIED in the NIS database. An HCV-related hospitalization was defined as one in which the principal diagnosis contained an ICD-9-CM or ICD-10-CM diagnosis code for HCV infection (see table 1 for the complete list of diagnosis codes). Hospitalizations with HCV infection as the principal diagnosis refers to hospitalizations that are primarily due to HCV infection. To better estimate the burden of HCV infection, we also included discharge records that had a liver-related complication as the principal diagnosis and HCV infection was listed among the secondary diagnoses. Liver-related complications included liver cirrhosis, portal hypertension, ascites, jaundice, spontaneous bacterial peritonitis (SBP), esophageal varices, hepatic encephalopathy, HCC, hepatic failure, and hepatorenal syndrome.

Covariates

For each hospital stay, we identified patient's age, gender, race, insurance type, and geographic region. Age was assessed as a continuous and as a categorical variable. The categorical age variable was classified as younger than 48 years, 48 years – 70 years, and older than 70 years. The age group 48 years – 70 years was grouped in order to capture the age range of baby boomers during the study period. Race was recoded into white, black, Hispanic, and others. Geographic census region is based on the actual location of the hospital, and is categorized as Northeast, Midwest, South, and West. Expected source of payment was recoded into insurance type with 5 categories- private, Medicare, Medicaid, uninsured, and others. Median household income for patient's zip code, which is a quartile classification that indicates the poorest to wealthiest zip codes, was also included.

Several clinical factors were identified and considered for analysis. Decompensated cirrhosis was included in the analysis, and it was defined as the presence of cirrhosis along with variceal bleeding, ascites, jaundice, or hepatic encephalopathy. We included HBV coinfection based on the presence of ICD-9-CM or ICD-10-CM codes for HBV infection among the secondary diagnoses. Using the single-level Clinical Classifications Software (CCS)[16], we included HIV coinfection, comorbid cancer, alcohol-related disorders, and substance-related disorders. To adjust for comorbidities, we included the severity of illness measure available in the NIS. This measure for the extent of functional deterioration is based on the All Patient Refined Diagnosis-Related Groups (APR-DRGs) classification system. This measure has four severity levels, ranging from minor to severe. For the purpose of this study, it was recoded into minor/moderate and major/severe.

Statistical Analysis

Descriptive analysis of demographic and clinical characteristics of HCV-related hospitalizations over the study period was conducted. The weighted number of HCV-related hospitalizations was calculated for each year. We calculated the proportion of inpatient

mortality among HCV-related hospitalizations, and the differences over the years were assessed using chi-square test for trend. Bivariable association with inpatient mortality was evaluated using the Rao-Scott chi-square test to identify potential predictors. Factors that were significantly associated with inpatient mortality ($p < 0.05$) in the bivariable analysis were considered for analysis in the multivariable model. HBV coinfection and HIV coinfection were predetermined to enter the adjusted model regardless of their bivariable association with inpatient mortality. Simple and multiple logistic regressions were performed to identify significant predictors of inpatient mortality among HCV-related hospitalizations. Odds ratios (OR) and 95% confidence intervals were calculated. *P* values of less than 0.05 (two-tailed) were considered statistically significant. All statistical analyses were conducted using SAS software version 9.4.

RESULTS

Characteristics of HCV-Related Hospital Stays

A total of 67,630 hospitalizations from NIS were related to HCV infection from 2012 to 2016. Weighted, this represented an estimated 338,150 HCV-related hospital stays in the US during this time. These hospitalizations have estimated average nationwide total charges of $4.6 billion annually, adjusted to 2020 US dollars. Characteristics of the HCV-related hospitalizations are shown in table 2. The majority of these hospitalizations were by patients who were male, white, and aged 48 years – 70 years. More than two thirds of all hospitalized patients were covered by either Medicare or Medicaid. Nearly 40% of all HCV-related hospitalizations were by patients coming from the poorest zip codes in the US. About 42% of all HCV-related hospitalizations were in the South. Approximately 59% of all HCV-related hospital stays had a liver-related complication as the principal diagnosis. Liver cirrhosis was listed as primary or secondary diagnosis in nearly 85% of all HCV-related hospitalizations. Patients with alcohol-related disorders and substance-related disorders represented 40.37% and 22.48% of all HCV-related hospitalizations, respectively.

Mortality occurred in 5.16% of all HCV-related hospital stays, accounting for an estimated 17,455 in-hospital deaths in the US between 2012 and 2016. Stratified by race, the rate of inpatient mortality was 4.89% among whites, 6.79% among blacks, 4.51% among Hispanics, and 5.34% among other races. Of all in-hospital deaths, baby boomers (ages 48 – 70) represented more than 85% and male patients represented nearly 71% (Table 2). Hospital stays in which mortality occurred were significantly different from other HCV-related hospital stays in terms of clinical presentation. Decompensated cirrhosis, SBP, hepatorenal syndrome, hepatic failure, HCC, and comorbid cancer were significantly higher among hospital stays in which mortality occurred. On average, hospital stays in which mortality occurred had significantly higher total charges per stay and higher length of stay.

Trends of HCV-Related Hospitalizations and Mortality

The incidence rate of HCV-related hospitalizations declined nationwide from 0.2% of all hospitalizations in 2012 to 0.15% in 2016 ($p < 0.01$). Figure 1 shows the estimated number of HCV-related hospital stays in the US, from 2012 to 2016. The nationwide number of HCV-related hospitalizations in the US was almost steady at around 70,000 from 2012

to 2014. By the end of study period in 2016, the number of hospital stays declined by about 20% to nearly 55,000 hospitalizations. A similar downtrend was manifested across the four US regions, with the South having the highest number of hospitalizations throughout the study. The rate of inpatient mortality among HCV-related hospitalizations declined modestly, from 5.25% in 2012 to 4.75% in 2016 (Figure 2). This trend was not statistically significant ($p = 0.07$). Although the average length of stay for HCV-related hospitalizations remained almost unchanged at 5.5 days throughout the study period, the inflation-adjusted average total charges per stay increased 4% from $66,000 in 2012 to $69,000 in 2016.

Figure 3 shows the change in the proportions of HCV-related inpatient mortality from 2012 to 2016 by demographics and clinical characteristics. Over the 5-year study period, the proportion of in-hospital deaths declined significantly for those younger than 47 years, Hispanics, privately insured patients, and hospitalizations in Northeast. In contrast, the proportion of in-hospital deaths increased significantly for black patients, those older than 70 years, Medicaid beneficiaries, and hospital stays in the South. The percentage of in-hospital deaths for baby boomers remained steady at approximately 85% throughout the study period. HCC accounted for 38.10% of all in-hospital deaths in 2016, compared to 27.18% of all in-hospital deaths in 2012. The percentage of in-hospital deaths increased for patients with alcohol-related disorders from about 39% in 2012 to 43% in 2016. For patients with substance-related disorders, the proportion of in-hospital deaths increased substantially from 11% in 2012 to nearly 35% in 2016.

Predictors of Inpatient Mortality Among HCV-Related Hospitalizations

The results of the simple and multiple logistic regression models predicting inpatient mortality are shown in table 3. The multivariable model showed that baby boomers and those older than 70 years had greater odds of inpatient mortality than those younger than 47 years. Controlling for known predictors, blacks were more likely to die during an HCV-related hospitalization compared to whites. The multivariable analysis also showed that Medicaid beneficiaries and uninsured patients were more likely to die than patients with Medicare. The diagnosis of hepatorenal syndrome was associated with five-fold increase in the odds of inpatient mortality. In addition, the adjusted odds of inpatient mortality were significantly higher among hospitalizations that involved SBP, HCC, hepatic failure, and comorbid cancer. Severity of illness was positively associated with inpatient mortality. The adjusted odds of inpatient mortality were greater among hospitalizations in the Northeast and in the West than those in the South. Year of admission was not a significant predictor of inpatient mortality.

DISCUSSION

In this study, we evaluated the patterns of HCV-related inpatient mortality using a nationally representative inpatient data. From 2012 to 2016, our study showed an encouraging downtrend in the incidence of HCV-related hospitalizations nationally. Several previous studies reported significant increases in hospitalizations among HCV patients in the US[13,17–19]. We found that the decline in the number of HCV-related stays started in 2015 (Figure 1). One potential explanation for this time trend is that the first interferon-free

regimen, ledipasvir–sofosbuvir, was introduced in late 2014. While we found that HCV-related hospitalizations declined, the rate of inpatient mortality remained almost steady at around 5% throughout the study period. In addition, our study revealed that the average inflation-adjusted total charges per stay increased during the study period. In the pre-DAA era, several studies reported increases in the rate of inpatient mortality and total charges among HCV patients[13,14,19]. Considering that DAA have provided a safe and effective treatment option for HCV patients, there was hope they can increase the historically low treatment rate and lower complications of cirrhosis.

Our study explored the association between several sociodemographic characteristics and inpatient mortality among HCV-related hospital stays. Expectedly, older age groups were associated with greater odds of inpatient mortality. In our study, baby boomers represented the majority of in-hospital deaths (85.79%) and were more likely to die compared to the younger age group. It is estimated that about three fourths of all HCV patients in the U.S were born between 1945 and 1965[3]. We also found that Hispanic patients were associated with lower inpatient mortality compared to whites. A similar finding was reported in a previous study of inpatient data during 1998 – 2003[7]. We found that being uninsured was positively associated with inpatient mortality. A previous study also found that uninsured patients have greater odds of inpatient mortality[14]. Our study indicated that having Medicaid was significantly associated with inpatient mortality, and that patients covered by Medicaid represented the highest proportion (34.42%) of all in-hospital deaths in 2016 (Figure 3). A recent study found that the median time to DAA fill was longer for Medicaid beneficiaries than Medicare or privately insured patients, and having Medicaid insurance was associated with absolute denial[20]. Medicaid policies related to pre-authorization of DAAs are different from one state to another. Among 42 states with known Medicaid policies in 2014, about three fourths restricted DAA access to patients with fibrosis stage 3 or cirrhosis, all states had criteria related to drug or alcohol use (i.e. screening, counseling, and/or abstinence), and half of states required drug or alcohol abstinence for a certain period.[21] However, many states have recently eased their sobriety and liver damage restrictions[21].

An important finding of our study was that black patients have greater odds of mortality during an HCV-related hospitalization even after controlling for known predictors of inpatient mortality. We also found that the rate of inpatient mortality among blacks (6.79%) was higher than among their white (4.89%) or Hispanic (4.51%) counterparts. The disease burden of HCV infection remains substantial among black patients in the era of DAA. A recent report from the CDC revealed that the mortality rate with HCV listed as a cause of death in 2016 was 7.89 per 100,000 for blacks, compared to 4.19 per 100,000 for whites[22. Several factors may have contributed to this racial disparity. The prevalence of HCV infection is disproportionately higher among blacks, with an estimated prevalence rate among blacks at least twice as high as among whites[4]. Previous studies found that black patients infected with HCV were less likely to be linked to care[6,7]. In addition, recent studies reported that black patients were less likely to receive DAA treatment[23,24]. Lack of linkage to care and lack of access to DAA treatment can accelerate the rate in which the disease progress to cirrhosis and other sequelae of HCV infection.

Several clinical factors were evaluated for their association with inpatient mortality. The multivariable analysis showed that hepatorenal syndrome was the strongest predictor of death during an HCV-related hospitalization. This finding was in parallel with findings from previous studies that evaluated inpatient mortality among HCV patients[13,25], HIV coinfection was not associated with inpatient mortality, but previous studies in the pre-DAA era found that HIV coinfection was significantly associated with inpatient mortality[13,25], The multivariable analysis also showed that the odds of inpatient mortality were lower among patients with substance-related disorders. However, we found that the proportion of in-hospital deaths for this population more than tripled from 2012 to 2016 (Figure 3), coinciding with the recent opioid epidemic in the US. The prevalence of HCV infection among injection drug users is very high, with an estimated prevalence rate of about 53%[26], Along with high prevalence rate, most public and private health insurances restrict access to DAA treatment for this population until patients abstain from drugs. Screening and treatment of HCV infection among this population is a key for eradication of HCV. Future studies addressing the opioid epidemic impact on HCV infection outcomes are warranted.

Our study has some limitations. Although NIS is the largest publicly available inpatient database in the US, it does not include Veterans Administration hospitals. The prevalence rate of HCV infection is disproportionately high among veterans compared to the general population[27]. However, it has been reported that more than 75% of HVC infected veterans who receive care from the Veterans Administration have received DAA therapy[28]. As with any study relying on administrative data, the accuracy of our findings depends on the completeness and accuracy of diagnosis codes in the NIS database. In addition, due to the switch to ICD-10-CM diagnosis coding in the 4th quarter of 2015, there is a potential risk of misclassification bias. Thus, our findings may underestimate the true burden of HCV infection in the US. Lastly, it is important to emphasize that the unit of analysis in our study is a hospital discharge record not an individual patient, and thus multiple hospitalizations by the same patient during the study period is possible. Despite these limitations, this is among the first studies that provide a national perspective on HCV-related inpatient mortality in the new era of DAA.

CONCLUSION

In conclusion, our study indicates that the clinical and economic burden of HCV infection remain substantial in the era of DAA. There are major racial disparities in the disease burden of HCV infection that need to be addressed and solved. In addition to screening for HCV infection, linkage to care and eliminating barrier to DAA treatment are critical areas for successful treatment and essential key for HCV eradication in the US.

ACKNOWLEDGMENTS

This project was partially funded by the HRSA Center of Excellence Grant number D34HP16042 and by the National Institute on Minority Health and Health Disparities of the National Institutes of Health under Award Number G12MD007597.

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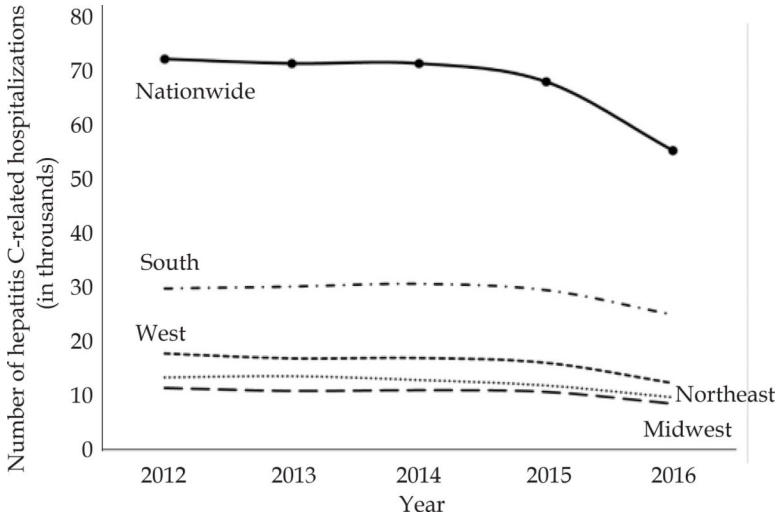

Figure 1.

Estimated number of hepatitis C-related hospitalizations in the United States, nationwide and by regions, 2012 – 2016.

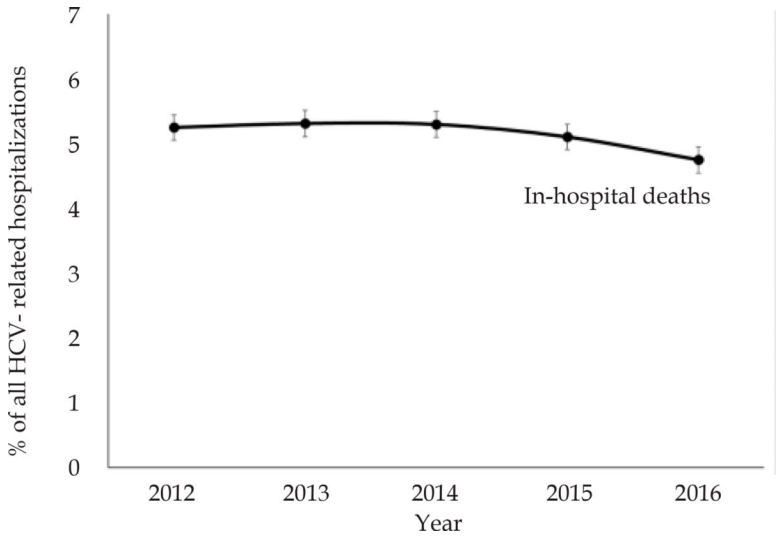

Figure 2.

Trends in mortality rates among hepatitis C-related hospitalizations in the US, during 2012 – 2016.

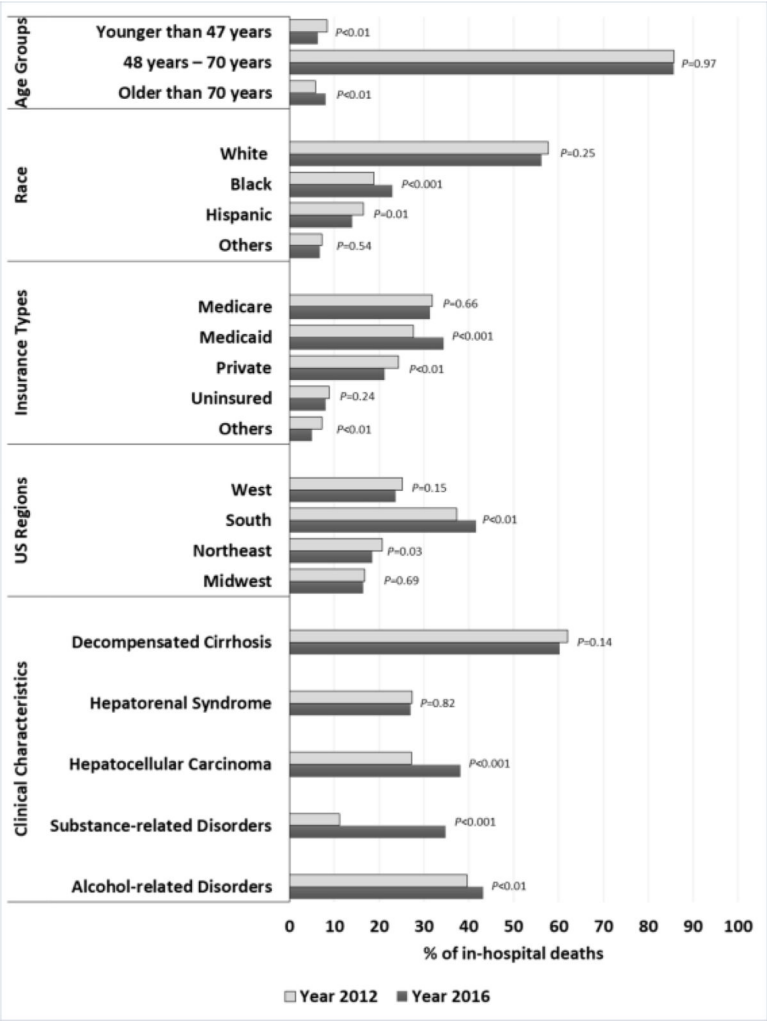

Figure 3.

Change in the proportions of hepatitis C-related inpatient mortality between 2012 and 2016, by demographics and clinical characteristics.

Table 1

Diagnosis Codes for Hepatitis C Virus Infection and Comorbidities

Condition	ICD-9-CM or CCS diagnosis codes	ICD-10-CM or CCS diagnosis codes
HCV infection	070.41, 070.44, 070.51, 070.54, 070.70, 070.71, V02.62	B17.10, B17.11, B17.8, B18.2, B19.20, B19.21, Z22.50, Z22.52
HBV infection	070.20, 070.21, 070.22, 070.23, 070.30, 070.31, 070.32, 070.33, 07042, 070.52, V02.61	B16.0, B16.1, B16.2, B16.9, B17.0, B18.0, B18.1, B19.10, B19.11, Z22.51
Cirrhosis	571.2, 571.5	K70.30, K70.31, K74.60, K74.69
Esophageal varices without bleeding	456.1, 456.21	I85.00, I85.10
Esophageal varices with bleeding	456.0, 456.20	I85.01, I85.11
SBP	567.23	K65.2
Jaundice	782.4	R17
Ascites	789.59	R18.8
Portal hypertension	572.3	K76.6
Hepatic encephalopathy	572.2	K72.90, K72.91
Hepatorenal syndrome	572.4	K76.7
Hepatic failure	572.8	K72.10, K72.11
HCC	155.0, 155.2	C22.0, C22.7, C22.8, C22.9
HIV	CCS: 5	
Comorbid cancer	CCS: 11 – 44 (excluding CCS: 16)	
Substance-related disorders	CCS-MHSA: 661	
Alcohol-related disorders	CCS-MHSA: 660	

Abbreviations: CCS=clinical classifications software, HCV=hepatitis C virus, HBV= hepatitis B virus, SBP= spontaneous bacterial peritonitis, HCC= hepatocellular carcinoma, CCS-MHSA= the clinical classifications software for mental health and substance abuse, HIV=human immunodeficiency virus.

Table 2

Characteristics of HCV-related hospital stays in the US, from 2012 to 2016.

Characteristics	All HCV-Related Hospitalizations	Mortality Status†		
		Yes	No	P-value
Number of hospitalizations (weighted)	338,150	17,455	320,370	-
Male, %	68.7	70.93	68.58	0.004
Age, mean	56.05	58.35	55.93	<.0001
Age groups, %				
Older than 70 years	5.42	6.96	5.33	<.0001
48 years – 70 years	80.52	85.79	80.24	
Younger than 48 years	14.06	7.25	14.43	
Race, %				
White	60.94	58.18	61.09	<.0001
Black	14.56	19.25	14.3	
Hispanic	18.19	16.01	18.31	
Others	6.31	6.56	6.3	
Insurance type, %				
Medicare	34.16	33.99	34.18	<.0001
Medicaid	33.88	30.29	34.09	
Private	18.6	21.78	18.42	
Uninsured	8.45	7.7	8.49	
Others	4.91	6.24	4.82	
Patient's zip code median income, %				
1st quartile	39.45	39.8	39.43	0.672
2nd quartile or higher	60.55	60.2	60.57	
U.S Regions, %				
Northeast	18.13	19.79	18.02	0.001
Midwest	15.48	14.67	15.52	
South	42.78	39.96	42.95	
West	23.6	25.58	23.51	
Decompensated Cirrhosis, %	55.98	62.96	55.6	<.0001
Portal hypertension‡, %	35.84	36.29	35.81	0.565
SBP ‡, %	5.97	10.46	5.74	<.0001
Hepatorenal syndrome‡, %	6.18	27.76	5.01	<.0001
Hepatic failure ‡, %	8.85	16.61	8.43	<.0001
HCC ‡, %	18.53	30.79	17.87	<.0001
Severity of illness, %				
Minor/Moderate	29.94	5.9	31.25	<.0001
Major/Severe	70.06	94.1	68.75	

Characteristics	All HCV-Related Hospitalizations	Mortality Status†		
		Yes	No	P-value
Alcohol-related disorders, %	40.38	40.99	40.34	0.444
Substance-related disorders, %	22.48	16.07	22.83	<.0001
HBV co-infection, %	3.05	3.55	3.02	0.077
HIV co-infection, %	2.37	2.58	2.36	0.399
Comorbid cancer§, %	8.66	14.49	8.33	<.0001
Total charges per stay, mean ($)	58,159.91	113,530	55,163.30	<.0001
Length of stay, mean (days)	5.49	8.41	5.33	<.0001

Abbreviations: HCV=Hepatitis C Virus, HBV= Hepatitis B Virus, SBP= spontaneous bacterial peritonitis, HCC= hepatocellular carcinoma, HIV=Human Immunodeficiency Virus.

†Data on in-hospital death were missing in 75 discharge records (weighted N=325).

‡Listed as primary or secondary diagnosis.

§Excluding hepatocellular carcinoma.

Table 3

Predictors of Inpatient Mortality among HCV-related Hospitalizations.

Characteristics	Unadjusted OR (95% CI)	P value	Adjusted OR (95%CI)	P value
Age groups				
Younger than 47 years	Ref		Ref	
48 years – 70 years	2.13 (1.89 – 2.39)	<.0001	1.46 (1.29 – 1.65)	0.077
Older than 70 years	2.59 (2.20 – 3.07)	<.0001	1.79 (1.48 – 2.16)	<.0001
Male	1.12 (1.04 – 1.20)	0.003	0.99 (0.93 – 1.08)	0.963
Race				
White	Ref		Ref	
Black	1.41 (1.29 – 1.54)	<.0001	1.27 (1.16 – 1.39)	<.0001
Hispanic	0.92 (0.84 – 1.00)	<.0001	0.88 (0.79 – 0.97)	0.000
Others	1.09 (0.96 – 1.25)	0.957	0.94 (0.81 – 1.08)	0.163
Insurance type				
Medicare	Ref		Ref	
Medicaid	0.89 (0.82 – 0.97)	<.0001	1.11 (1.01 – 1.21)	0.000
Private	1.19 (1.09 – 1.30)	0.000	1.19 (1.08 – 1.32)	0.146
Uninsured	0.91 (0.81 – 1.03)	0.005	1.48 (1.29 – 1.69)	0.004
Others	1.30 (1.12 – 1.52)	0.000	1.66 (1.40 – 1.96)	<.0001
Decompensated cirrhosis	1.36 (1.27 – 1.45)	<.0001	0.99 (0.93 – 1.07)	0.930
Hepatorenal syndrome	7.29 (6.74 – 7.88)	<.0001	5.20 (4.77 – 5.66)	<.0001
Hepatic failure	2.17 (1.98 – 2.37)	<.0001	1.82 (1.65 – 2.01)	<.0001
HCC	2.05 (1.90 – 2.20)	<.0001	1.79 (1.65 – 1.94)	<.0001
SBP	1.92 (1.73 – 2.14)	<.0001	1.29 (1.15 – 1.46)	<.0001
HBV co-infection	1.18 (0.99 – 1.41)	0.065	1.18 (0.98 – 1.42)	0.090
Substance-related disorders	0.65 (0.59 – 0.71)	<.0001	0.79 (0.72 – 0.87)	<.0001
HIV co-infection	1.09 (0.89 – 1.35)	0.393	1.17 (0.93 – 1.46)	0.178
Comorbid cancer	1.87 (1.69 – 2.05)	<.0001	1.41 (1.27 – 1.57)	<.0001
Severity of illness				
Minor/moderate	Ref		Ref	

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Characteristics	Unadjusted OR (95% CI)	P value	Adjusted OR (95%CI)	P value
Major/sever	7.25 (6.33 – 8.29)	<.0001	5.07 (4.40 – 5.83)	<.0001
Regions				
South	Ref		Ref	
Midwest	1.02 (0.92 – 1.12)	0.045	0.94 (0.85 – 1.04)	0.001
Northeast	1.18 (1.08 – 1 .30)	0.013	1.16 (1.05 – 1.28)	0.009
West	1.17 (1.07 – 1 .28)	0.018	1.16 (1.06 – 1.28)	0.007
Calendar year				
2012	Ref		Ref	
2013	1.01 (0.91 – 1.12)	0.309	0.98 (0.88 – 1.09)	0.533
2014	1.01 (0.91 – 1.11)	0.336	0.93 (0.83 – 1.04)	0.430
2015	0.97 (0.88 – 1.08)	0.837	0.91 (0.82 – 1.02)	0.230
2016	0.90 (0.81 – 1.01)	0.028	0.96 (0.85 – 1.08)	0.917

Abbreviations: OR=odds ratio, CI=confidence interval, HBV= hepatitis B virus, SBP= spontaneous bacterial peritonitis, HCC= hepatocellular carcinoma, HIV=human immunodeficiency virus.