Hospitalization Rates in a Longitudinal US Cohort of Insured Patients with Cirrhosis

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Conflict of Interest Statement

Dr. VanWagner serves as an advisor for Numares, Novo-Nordisk and Gerson Lehrman Group, receives grant support from W.L. Gore & Associates and provides expert witness services outside the submitted work.

Other authors have no conflicts of interests to disclose.

Declaration of Funding Source

This study was supported by R01DK131164 (Ladner/Manski). Dr. Hasjim was supported by NIH grant T32DK077662-15 (PD: Ladner/Green). Dr. VanWagner was supported by the National Heart, Lung, and Blood Institute K23 HL136891 and R56 HL155093 grant. Praneet Polineni was supported by the Steven J. Stryker, MD, Gastrointestinal Surgery Research and Education Endowment. Dr. Duarte was supported by NIH grant R01DK130294

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Statistical analysis: Gmeiner, Manski, Zhao
Obtained funding: Ladner, Manski
Administrative, technical, or material support: Banea, Doll
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ABSTRACT

Background: Hospitalization rates are not well described among patients with cirrhosis compared to those with other leading non-cancerous chronic diseases such as chronic obstructive pulmonary disease (COPD) and heart failure (HF). We aim to describe the hospitalization rates, risk factors, and indications for admission among insured US patients with cirrhosis.

Methods: In this longitudinal, retrospective cohort study of 352,227 adult patients with cirrhosis from 2011-2021 identified by claims data from a large national insurer were compared with random samples of over one million COPD and HF patients. Hospitalizations were identified from claims data. Risk factors were estimated by multivariate logistic regression. Causes of admission were organized using the Healthcare Cost and Utilization Project (HCUP) Clinical Classification Software. Analyses were stratified by compensated and decompensated cirrhosis states, by the presence of clinical decompensations (ascites, HE, SBP, variceal bleeding, HPS, or HRS).

Findings: Among 352,227 patients with cirrhosis the mean [SD] follow-up time was 4·7 [3·1] years; age 63·1 [13·0] years, 158,230 [44·9%] female, and 154,202 [43·8%] commercially insured. 160,644 (46%) experienced hepatic decompensation during the observation period. Annually, 27·8% of the total cirrhotic population was hospitalized, compared to 21·6% for COPD and 28·0% for HF. Patients with decompensated cirrhosis were hospitalized at over twice the rate of those with compensated cirrhosis (18·8% vs. 42·5%, p<0·001). Compared to patients with alcohol-related cirrhosis, those with HCV cirrhosis (OR 0·70, 95%CI 0·68-0·72, P<0·001) and NASH cirrhosis (OR 0·69, 95%CI 0·68-0·71, P<0·001) had reduced risk of hospitalizations. The leading cause of admission among patients with cirrhosis was septicemia (10·5% of admissions), similar to COPD (9·6%) and HF (9·7%).

Interpretation: Patients with cirrhosis have high hospitalization rates, in comparison to other common, burdensome chronic diseases. Improving care for patients with cirrhosis and reducing hospitalizations should be a focus for quality improvement efforts and policymakers.

Research in Context

Evidence before this study

While the prevalence of liver cirrhosis in the US rapidly increases, their rates of hospitalizations poses a large healthcare burden. While single-center analyses have noted the high hospitalization rate of patients with cirrhosis, these studies often only focus on acutely ill patients who were recently hospitalized or have hepatic decompensations. Comparatively, little is known of the healthcare utilization of patients with compensated cirrhosis, who make up the majority of the cirrhosis population, and the causes of their hospitalization in the modern US.

Added value of this study

This study of 352,227 patients – the largest longitudinal cohort of patients with cirrhosis in the US – describes the high hospitalization rate of patients with cirrhosis and the hospitalization-associated risk factors. It further establishes that patients with compensated cirrhosis are hospitalized at rates nearing that of patients with other leading chronic diseases such as heart failure (HF) and chronic obstructive pulmonary disease (COPD). Finally, we find that sepsis, HF, decompensations, and alcohol-related disorders were the leading causes of admission among patients with cirrhosis.

Implications of all the available evidence

At present, patients with cirrhosis are hospitalized more frequently than those with HF or COPD. As the prevalence of cirrhosis increases, hospitalized care for patients with cirrhosis will likely increase and constitute a significant burden on the US health system. This study underscores the need for policy attention, research, and intervention for patients with compensated and decompensated cirrhosis. Immediate work along these lines focusing on risk factors such as alcohol-related etiology, multiple decompensations, or specific leading causes of admission may improve quality of care and future morbidity.

INTRODUCTION:

Liver cirrhosis is a burdensome chronic disease affecting 2-5 million adults in the US.[1,2] Its prevalence and mortality rates have increased by 200% and 65%, respectively in the past decade.[3,4] Approximately 5-7% of patients with cirrhosis suffer a decompensation event each year, which decreases the median survival from over 12 years to less than two years.[5] In patients with cirrhosis, hospitalizations may signal worsening health as 60% were readmitted and 30% died within one year from discharge.[6,7] Despite their severe impact on patients, research on cirrhosis-related hospitalizations has been limited by the lack of large, longitudinal cohorts of cirrhosis patients.

National and single-center cross-sectional studies have estimated a 21%-92% increase in the proportion of liver-related hospitalizations between 2004-2016.[8,9] However, these studies are limited by their single-center experience and cross-sectional design. Although longitudinal studies exist, these studies are often restricted to a cohort of patients with decompensated cirrhosis, high comorbidity burdens, or small sample sizes.[8–10] Thus, it is less generalizable to the majority of patients with compensated cirrhosis. There remains a gap in knowledge in the hospitalization rate, risk factors for hospitalizations, and causes of admission for the general cirrhosis population in the US.

We used a longitudinal, administrative claims dataset from 2011-2021 from a large national insurer to characterize the hospitalization rate, risk factors, and causes of admission of patients with cirrhosis. For context, we compared hospitalization rates for cirrhosis with two prominent chronic diseases: chronic obstructive pulmonary disease (COPD) and heart failure (HF) which have similar disease complexity, demographics, and inpatient burden.[9]

METHODS:

This retrospective longitudinal cohort study was deemed exempt from review by the Northwestern University Institutional Review Board. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Data Source

Deidentified data from a large national payor between 1/1/2011 and 12/31/2021 were analyzed. Data such as demographic information, diagnoses codes (International Classification of Disease 9th/10th revision [ICD-9/10]), procedures (Current Procedural Terminology [CPT]), hospitalization events, laboratory results, and associated administrative claims data were analyzed for all patients included in this study.

Patient Population

From a total sample of 92,150,632 adult patients (≥18-years-old) enrolled in commercial insurance or Medicare Advantage plans between January 1, 2011 and December 31, 2021, we included 352,227 patients who were diagnosed with cirrhosis through validated ICD-9 and ICD-10 inclusion codes (Table S1).[11–14] Comparison to other chronic disease cohorts involved a randomly sampling of one million COPD (from an eligible pool of 3·3 million) and 1,125,543 HF patients (from an eligible pool of 5 million) using ICD inclusion codes (Table S1). Patients were included at the earliest occurrence of the respective inclusion code and were censored at the end of observation or respective organ transplant (liver, lung, heart).

Patients were considered to have compensated cirrhosis from the time of inclusion to the time of first decompensation event: ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), esophageal variceal bleeding, hepatorenal syndrome (HRS), or hepatopulmonary syndrome (HPS) defined by previously published ICD and CPT codes (Table S2) or the end of observation.[11–14] Cirrhosis patients were considered decompensated from time

of first decompensation to their end of observation. If a decompensation event preceded inclusion (N=41,771 patients, 11·9%, median time 36 days until inclusion), the length of time a patient was considered as decompensated was calculated from the time of decompensating event rather than the time of inclusion.

Outcomes

The primary outcome was the annual hospitalization rate - calculated by dividing the number of patients who had ≥1 hospitalization in a year by the total number of patients enrolled in a year and reported as a percentage. A hospitalization was defined as an inpatient admissions of ≥1 calendar day. A hospitalization event rate was calculated by dividing the total number of hospitalizations by the total patient-years and reported as hospitalizations per patient-year for the respective cohorts. Hospitalizations involving an acute decompensation event was counted towards the decompensated hospitalization rate. Length of stay (LOS) was defined as the number of days from date of admission to date of discharge for a given hospitalization. Cause of admission for cirrhosis patients was determined by primary discharge diagnosis codes based on Healthcare Resource and Utilization Project (HCUP) Clinical Classification Software (CCS), which groups diagnosis codes into clinically meaningful categories as described in the literature.[9,10] ICD codes pertaining to decompensation events (Table S2) were categorized alongside HCUP CCS.[9,10]

Demographic and Clinical Covariates

Demographics information such as age, sex, insurance and the Charlson Comorbidity Index were reported.[15] Etiology of cirrhosis, decompensations, hepatocellular carcinoma (HCC), transjugular intrahepatic shunt (TIPS), and liver transplant were also defined by ICD and CPT codes (Table S2). Cirrhosis etiology of interest includes alcohol-related, hepatitis C virus (HCV), hepatitis B virus (HBV), non-alcoholic steatohepatitis (NASH), primary biliary cirrhosis (PBC), cardiac,

genetic, autoimmune (AIH), primary sclerosing cholangitis (PSC) and other. Sodium, creatinine, International Normalized Ratio (INR), total bilirubin, platelets, and albumin were relevant laboratory information reported at inclusion into the cohort.

Statistical Analysis

Descriptive statistics were reported using means and medians with their respective standard deviations (±SD) or interquartile ranges (IQR). Two tailed Student's T-test was used to compare categorical and continuous variables respectively between two groups of interests: cirrhosis vs. COPD, cirrhosis vs. HF, decompensated vs. compensated, never hospitalized vs. hospitalized.

Multivariable logistic regression analysis calculating the probability of hospitalization within one year follow-up adjusted for age, sex, insurance, and Charlson Comorbidity Index, etiology, decompensation, and laboratory results at inclusion to the cohort. Odds ratios (OR) were reported with 95% confidence intervals (CI) for model covariates. For modelling, mutually exclusive meaningful categories of etiology and decompensation were created based on clinical relevance. Cirrhosis, COPD, and HF hospitalization event rates (hospitalizations per patient-year) were modelled by multivariate ordinary least square linear regression at the patient-year and adjusted for age, sex, insurance, and Charlson Comorbidity Index. MELD-Na was calculated for patients with available labs (N=76,690 patients [21·8%]). Age was treated as a piece-wise linear spline with linear segments (18-45, 45-64, 65-84, ≥85 years). All statistical analysis were performed using STATA software version 14·1 (StataCorp LLC, TX, USA).

RESULTS:

Cohort Characteristics

During the study period, 352,227 patients with cirrhosis were identified. Cirrhosis patients had a mean age of 63·1 (SD±13·0) years, 158,230 (44·9%) were female, and mean length of follow-up

was 4·7 (SD±3·1) years. Patients were enrolled in Medicare Advantage (N=180,725, 51·3%), commercial insurance (N=154,202, 43·8%), and both (N=17,300, 4·9%). Common etiologies of cirrhosis include alcohol-related liver disease (38·0%), HCV (23·1%), and NASH (19·5%) cirrhosis. The median MELD-Na was 9 (IQR 7–16), mean Charlson comorbidity index was 7·6 (SD±4·6), and 26,372 patients had HCC (7·5%). Throughout follow-up, 191,570 (54·4%) remained compensated and 160,657 (45·6%) experienced a decompensating event. The most common decompensating events were ascites (N=133,967, 83·4%), HE (N=79,245; 49·3%), and variceal bleeding (N=33,883; 21·1%). Among the comparator group of patients with COPD, the mean age was 67·0 (SD±14·5) years, 528,551 (52·9%) were female, and mean length of follow-up was 5·1 (SD±3·2) years. Of patients with HF, the mean age was 71·4 (SD±13·7) years, 568,735 (50·5%) were female, and mean length of follow-up was 5·1 (SD±3·4) years (Table 1).

Hospitalized Cirrhosis Cohort Characteristics

In the observed enrollment follow-up period, 206,606 (58·7%) of patients with cirrhosis were hospitalized, while 145,621 (41·3%) were never hospitalized. Hospitalized patients were older (64·8 [SD±12·9] vs. 60·7 [SD±12·9] years, P<0·001), more frequently male (56·5% vs. 53·0%, P<0·001), had alcohol-related cirrhosis (46·8% vs. 25·5%, P<0·001), and had more decompensating events such as ascites (53·6% vs. 16·0%, P<0·001), HE (32·3% vs. 8·6%, p<0·001), and variceal bleeding (13·2% vs. 4·5%, P<0·001). Hospitalized patients also had higher rates of HCC (9·1% vs. 5·2%, P<0·001), and higher MELD-Na (median 11 [8, 19] vs. 8 [6, 10], P<0·001) compared to those not hospitalized (Table 2).

Annual Hospitalization Rate and Logistic Regression Modelling

The mean annual hospitalization rate of patients with cirrhosis was 27·8% with 51·4 (SD±112·7) hospital admissions/100 patients per year. Of these, the annual hospitalization rates for patients with compensated and decompensated cirrhosis were 18·8% and 42·5% respectively (P<0·001).

Patients with compensated and decompensated cirrhosis had 29·4 (SD±79·0) and 85·8 (SD±144·5) hospital admissions/100 patients per year respectively (P<0.001). In comparison, the annual hospitalization rates for COPD and HF were 21·6% and 28·0% respectively (P<0·001, Figure 1). COPD and HF had 33·9 (SD±82·8) and 45·6 (SD±95·6) hospitalizations/100 patients per year respectively on average (P<0.001, Table 1).

In our multivariable analysis, female sex (OR 1·07, 95% CI 1·05-1·09, P<0·001) had higher annual odds of hospitalization compared to male sex. Compared to compensated patients, patients with ascites (OR 1·59, 95% CI 1·55-1·63, P<0·001), HE (OR 1·44, 95% CI 1·38-1·49, P<0·001), and esophageal variceal bleeding (OR 1·34, 95% CI 1·28-1·41, P<0·001) were associated with greater annual odds of hospitalization. HCV (OR 0·70, 95% CI 0·68-0·72, P<0·001) and NASH (OR 0·69, 95% CI 0·68-0·71, P<0·001) were associated with decreased annual odds of hospitalization, compared to alcohol-related cirrhosis (Table 3). In adjusted analyses, patients with cirrhosis had 24·2 and 21·1 more hospital admissions per 100 patient-years than patients with COPD or HF, respectively (P<0·001). Mean LOS was 6.1 days for cirrhosis patients overall, compared to 5·6 days for COPD patients and 6·0 days for HF patients. Mean LOS for decompensated patients was 6·6 days vs. 5·4 days for compensated patients (Table 1).

Cause of Admission

Overall, the leading causes of hospitalization for cirrhosis patients were septicemia (10·5%), HF (6·1%), and general, non-specific, cirrhosis-related issues (3·6%). Patients with compensated cirrhosis vs. decompensated cirrhosis were admitted for septicemia (9·8% vs. 11·0%), HF (5·9% vs. 6·2%), alcohol-related disorders (3·9% vs. 2·2%) (Table 4).

DISCUSSION:

There are 2-5 million people living with cirrhosis in the US, whose disease burden on health systems will only worsen as its prevalence increases.[1,2] Our contemporary, longitudinal cohort study showed that 27·8% of patients with cirrhosis were hospitalized annually with a mean LOS of 6.1 days, a high public health burden, comparable to COPD or HF. Although patients with decompensated cirrhosis were hospitalized more frequently than those with compensated cirrhosis, patients with compensated cirrhosis suffer a very high hospitalization burden – 18·8% of patients were hospitalized each year with a mean LOS of 5·4 days. For every 100 patients with compensated cirrhosis, there were nearly 30 hospital admissions annually. Leading causes of admission among patients with compensated cirrhosis include septicemia (9·8%), HF (5·9%), and alcohol-related disorders (3·9%). These findings suggest that these hospitalizations could be preventable through outpatient specialty care and that interventions aimed at mitigating risk factors for hospitalization such as alcohol-related cirrhosis and specific decompensation events may be beneficial.

Cirrhosis is an increasingly prevalent chronic disease which exhibits similar trends in hospitalization rate over time compared to COPD and HF. However, cirrhosis is the most burdensome of the three, with 24·2 and 21·1 more hospitalizations per 100 patient-years in adjusted analyses compared to COPD and HF patients respectively. This increased burden is further reflected in healthcare costs, with annual inpatient expenditures totaling $20·4 billion for cirrhosis, compared to $9·8 billion for COPD and $17·1 billion for HF.[16] Despite this, cirrhosis does not garner the same public health policy attention as other chronic illnesses. Though COPD and HF are frequently the focus of quality improvement initiatives, such as the Agency for Healthcare Research and Quality's Prevention Quality Indicators or the Hospital Readmission Reduction Program (HRRP), cirrhosis-related complications are often not covered by such policies.[17,18] Identifying hospitalizations due to ambulatory care-sensitive conditions (ACSCs) among patients with cirrhosis could be an important proactive step in reducing this anticipated

burden. However, such policies should be carefully vetted prior to implementation to prevent unintended consequences, like the observed increase in 1-year mortality among HF patients under the HRRP.[19]

The subclinical nature of compensated cirrhosis poses unique challenges when describing its hospitalization burden. This gap in knowledge is especially difficult as large, national data repositories of patients with cirrhosis do not currently exist. Prior research has predominantly focused on severely ill patients or those with only decompensated events.[8–10] We found that patients with compensated cirrhosis, which constitute the majority of the cirrhosis population, have annual hospitalization rates greater than 2·5-times those of the general US population (18·8% vs. 7·4%).[20] Patients with compensated cirrhosis may project towards hospitalization rates much higher than their baseline 29·4 hospitalizations per 100 patient-years as they age, obtain more comorbidities, and become Medicare eligible.[21]

At present, cirrhosis-specific guideline-recommended care has low adherence, with low rates of hepatitis vaccination and screening for varices and HCC.[22] While patients with established specialist care have improved outcomes, the majority of cirrhosis patients do not receive such specialized care.[23] In fact, the anticipated rise in cirrhosis prevalence will only exacerbate work force shortages among gastroenterologists and hepatologists.[24] Understanding which patients are at greatest risk for hospitalizations, decompensation, and other adverse clinical outcomes would tremendously facilitate the prioritization of specialty care for these patients. Additionally, leveraging the electronic health record (EHR) towards automated decision support modules with integrated infrastructures of care, have shown to be effective in improving maintenance strategies in chronic disease.[25] Furthermore, successful care coordination with a multidisciplinary team of primary and specialty care clinicians have had some success in HF.[23] Such strategies have been shown to reduce hospitalizations by as much as 13% among patients with HF.[26]

Not surprisingly, patients with cirrhosis presented most frequently with sepsis. Patients with cirrhosis have higher risk for infections due to immune dysfunction and alterations in gut barrier permeability.[27] Patients with cirrhosis may be at further risk of HF related sequalae due to volume overload or cirrhotic cardiomyopathy.[28,29] Addressing these specific risks for patients with cirrhosis can be mitigated through targeted prophylaxis against infections (e.g., vaccines, antibiotics) and optimal medical treatment (e.g., diuretics).[30–32] Although patients with decompensated cirrhosis have dominated the attention of cirrhosis management interventions, our study emphasizes the importance of vigilant care for patients with compensated cirrhosis and also attention all those who were hospitalized.

Alcohol-related hospitalizations were the third leading cause of admission among patients with compensated cirrhosis. Even prior to the COVID-19 pandemic, rates of alcohol-related cirrhosis were steadily rising and have worsened as the rate of alcohol consumption and alcohol-use disorders (AUD) increased through the pandemic.[33,34] In this study, alcohol-related etiology for cirrhosis was associated with the highest odds of hospitalizations compared to all other cirrhosis etiology. However, curtailing alcohol use remains challenging due to low utilization of pharmacologic and behavioral interventions, and prevailing judgment towards patients struggling with AUD remains steadfast.[35] In a VA cohort, a dismal 14% of eligible patients with AUD received pharmacologic or behavioral treatment.[36] Yet, among patients who received treatment, a 37% and 13% reduction in risk of decompensation and mortality respectively were observed.[36] Such intervention with multidisciplinary teams should be considered when caring for patients with cirrhosis suffering from AUD.

Patients with decompensated cirrhosis had frequent admissions for ascites, HE, and other cirrhosis-related issues. This aligns with prior studies that estimated 22%-37% of 30-day

readmissions among hospitalized patients with these decompensation events were preventable.[7,37] In our study, ascites or HE were associated with 59% and 44% increased odds of hospitalizations respectively, compared to compensated patients. These two complications have been previously identified as risk factors for readmission and targets for quality improvement initiatives spearheaded by the American Association for the Study of Liver Diseases (AASLD).[17] A prospective study implementing an EHR alert to prescribe lactulose and rifaximin at discharge for patients with HE led to a 23% decreased risk of readmission.[38] Leveraging the EHR highlights a possible area for improved management of cirrhosis patients.

LIMITATIONS:

Our study has several limitations. Because our study is based on secondary data, our report relies on the accuracy of the assigned diagnosis and associated procedure codes. Although validated ICD-9/10 algorithms were used to define clinical covariates, miscoding and underdiagnosis may have occurred.[14] Thus, our report may underestimate its true hospitalization rates. Second, this study focuses on patients who were insured through commercial insurance and Medicare Advantage plans. Our cohort does not include patients who were uninsured and our report cannot be generalized to this subpopulation. Non-privately insured patients may have higher rates of hospitalization, which further underscores that our results may be a lower bound of the true rate.[10] However, the uninsured population only constitute an estimated 9·7% of the total US population compared to the approximately 70% who are enrolled in either commercial insurance or Medicare Advantage plans.[39] Lastly, this study is a retrospective analysis which cannot claim causality and may capture more stable patients who survive over time. Hence, we may be underestimating risk factors of hospitalization of patients with more acute trajectories. Yet, our report leverages this dataset's strength as one of the largest longitudinal and contemporary cohorts on insured patients with cirrhosis with a mean patient follow-up of 4·7 years.

CONCLUSIONS:

Patients with cirrhosis have a higher hospitalization burden. The overall burden of patients with compensated and decompensated cirrhosis are higher on average than those of COPD and HF patients. Alcohol-related etiology and prior decompensation events were particularly strong predictors for hospitalization. However, patients with compensated cirrhosis have much higher hospitalization rates than the general US adult population, a concerning observation given the increasing prevalence of cirrhosis in the US. Access to specialty care for those hospitalized should be considered to reduce further healthcare burden. Future studies are needed to identify those at highest risk for hospitalizations among patients with compensated cirrhosis and to implement effective interventions for them.

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TABLES:

Table 1: Patient Demographics and Disease Characteristics

Characteristics	All Cirrhosis (N=352,227)	Compensated (N=191,570)	Decompensated(N=160,657)	COPD (N=1,000,000)	HF (N=1,125,543)
Follow-up (years); mean (SD)	4·7 (3·1)	5·0 (3·2)***	4·5 (3·1)	5·1 (3·2) ***	5·1 (3·4) ***
Age; mean (SD)	63·1 (13·0)	62·4 (13·5) ***	63·9 (12·4)	67·0 (14·5) ***	71·4 (13·7) ***
Female; N (%)	158,230 (44·9%)	91,530 (47·8%)***	66,700 (41·5%)	528,551 (52·9%) ***	568,735 (50·53%) ***
Insurance					
Commercial; N (%)	154,202 (43·78%)	89,315 (46·62%)***	64,887 (40·39%)	369,200 (36·92%) ***	335,019 (29·77%) ***
Medicare; N (%)	180,725 (51·31%)	93,139 (48·62%)***	86,586 (54·52%)	573,080 (57·31%) ***	716,946 (63·70%) ***
Both; N (%)	17,300 (4·91%)	9,116 (4·76%)	8,184 (5·09%)	57,720 (5·77%)	73,578 (6·54%)
Charlson Comorbidity; mean (SD)	7·6 (4·6)	6·0 (4·2) ***	9·5 (4·3)	5·7 (4·0) ***	7·0 (3·8) ***
Etiology					
Alcohol-related; N (%)	133,833 (38·00%)	48,491 (25·31%)***	85,342 (53·12%)		
NASH; N (%)	68,653 (19·49%)	36,847 (19·23%)***	31,806 (19·80%)		
HCV; N (%)	81,295 (23·08%)	43,638 (22·78%)***	37,657 (23·44%)		
PBC; N (%)	35,559 (10·10%)	22,847 (11·93%)***	12,712 (7·91%)		
HBV; N (%)	18,767 (5·33%)	9,669 (5·05%)	9,098 (5·66%)		
Cardiac; N (%)	4,016 (1·14%)	856 (0·45%)***	3,160 (1·97%)		
AIH; N (%)	11,750 (3·34%)	6,616 (3·45%)***	5,134 (3·20%)		
Genetic/Metabolic; N (%)	8,170 (2·32%)	4,115 (2·15%)***	4,055 (2·52%)		
PSC; N (%)	4,462 (1·27%)	2,356 (1·23%)**	2,106 (1·31%)		
Other; N (%)	14,160 (4·02%)	10,968 (5·73%)***	3,192 (1·99%)		
Compensated with pHTN; N (%)	129,659 (36·81%)	33,283 (17·37%)***	96,376 (59·99%)		
Decompensation Events; N (%)	160,657 (45·61%)		160,657 (100%)		
Ascites; N (%)	133,967 (38·03%)		133,967 (83·39 %)		
HE; N (%)	79,245 (22·50%)		79,245 (49·33%)		
Variceal Bleed; N (%)	33,883 (9·62%)		33,883 (21·09%)		
HRS; N (%)	16,293 (4·63%)		16,293 (10·14%)		
SBP; N (%)	12,727 (3·61%)		12,727 (7·92%)		
HPS; N (%)	1,213 (0·34%)		1,213 (0·76%)		

>1 decompensated complication; N (%)	76,234 (21·64%)		76,234 (47·45%)		
HCC; N (%)	26,372 (7·49%)	7,400 (3·86%)***	18,972 (11·81%)		
MELD-Na; median [IQR]	9 [7, 16]	7 [6, 10]***	12 [8, 19]		
TIPS; N, (%)	4,393 (1·25%)	47 (0·02%) ***	4,346 (2·71%)		
Hospitalizations/100 patients per year, mean (SD)	51·4 (112·7)	29·4 (79·0) ***	85·8 (144·5)	33·9 (82·8) ***	45·6 (95·6) ***
LOS, mean (SD), days	6·09 (8·89)	5·38 (7·57) ***	6·64 (9·98)	5·59 (8·63) ***	6·00 (9·71) ***
Liver Transplant; N, (%)	15,532 (4·41%)	7,503 (3·92%) ***	8,029 (5·00%)		

AIH: Autoimmune Hepatitis, COPD: Chronic Obstructive Pulmonary Disease, HCV: Hepatitis C Virus, HF: Heart failure, HBV: Hepatitis B Virus, HE: hepatic encephalopathy, HRS: hepatorenal syndrome, HPS: hepatopulmonary syndrome, HCC: hepatocellular carcinoma, LOS: length of stay, MELD-Na: Model for End-Stage Liver Disease – Sodium, N: Number of Patients, NASH: Non-alcoholic steatohepatitis, PBC: Primary Biliary Cirrhosis, pHTN: portal hypertension, PSC: Primary Sclerosing Cholangitis, SBP: spontaneous bacterial peritonitis, TIPS: transjugular intrahepatic portosystemic shunt.

Statistical testing for significance between compensated and patients with decompensated cirrhosis and all cirrhosis patients to COPD patients and all cirrhosis patients to HF patients.
** Statistically significant p-value to <0·05*
*** Statistically significant p-value to <0·01*
**** Statistically significant p-value to <0·001*

Table 2: Cirrhosis Patients Demographics by Hospitalization Frequency

Characteristics	Never Hospitalized (N=145,621)	Hospitalized (N=206,606)	p-values
Follow-up (years); mean (SD)	4·6 (3·2)	4·8 (3·1)	<0.001
Age; mean (SD)	60·70 (12·90)	64·81 (12·88)	<0.001
Female; N (%)	68,446 (47·0%)	89,784 (43·5%)	<0.001
Insurance			<0.001
Commercial; N (%)	77,146 (52·98%)	77,056 (37·30%)	<0.001
Medicare; N (%)	62,510 (42·93%)	118,215 (57·22%)	<0.001
Both; N (%)	5,965 (4·10%)	11,335 (5·49%)	<0.001
Charlson Comorbidity; mean (SD)	5·28 (3·75)	9·30 (4·39)	<0.001
Etiology			<0.001
Alcohol-related; N (%)	37,139 (25·50%)	96,694 (46·80%)	<0.001
NASH; N (%)	24,748 (16·99%)	43,905 (21·25%)	<0.001
HCV; N (%)	36,560 (25·11%)	44,735 (21·65%)	<0.001
PBC; N (%)	18,025 (12·38%)	17,534 (8·49%)	<0.001
HBV; N (%)	8,056 (5·53%)	10,711 (5·18%)	<0.001
Cardiac; N (%)	454 (0·31%)	3,562 (1·72%)	<0.001
AIH; N (%)	5,641 (3·87%)	6,109 (2·96%)	<0.001
Genetic/Metabolic; N (%)	3,559 (2·44%)	4,611 (2·23%)	<0.001
PSC; N (%)	1,689 (1·16%)	2,773 (1·34%)	<0.001
Other; N (%)	10,678 (7·33%)	3,482 (1·69%)	<0.001
Compensated with pHTN; N (%)	112,875 (77·51%)	78,695 (38·09%)	<0.001
Decompensation Events; N (%)	37,827 (25·98%)	91,832 (44·45%)	<0.001
Ascites; N (%)	23,323 (16·02%)	110,644 (53·55%)	<0.001
HE; N (%)	12,552 (8·62%)	66,693 (32·28%)	<0.001
Variceal Bleed; N (%)	6,572 (4·51%)	27,311 (13·22%)	<0.001
HRS; N (%)	835 (0·57%)	15,458 (7·48%)	<0.001
SBP; N (%)	587 (0·40%)	12,140 (5·88%)	<0.001
HPS; N (%)	187 (0·13%)	1,026 (0·50%)	<0.001
>1 decompensated complication; N (%)	9,004 (6·18%)	67,230 (32·54%)	<0.001
HCC; N (%)	7,615 (5·23%)	18,757 (9·08%)	<0.001
MELD-Na; median [IQR]	8 [6, 10]	11 [8, 19]	<0.001
TIPS; N, (%)	248 (0·17%)	4,145 (2·01%)	<0.001
Liver Transplant; N, (%)	9,048 (6·21%)	6,484 (3·14%)	<0.001

AIH: Autoimmune Hepatitis, HCV: Hepatitis C Virus, HBV: Hepatitis B Virus, HE: hepatic encephalopathy, HRS: hepatorenal syndrome, HPS: hepatopulmonary syndrome, HCC: hepatocellular carcinoma, LOS: length of stay, MELD-Na: Model for End-Stage Liver Disease – Sodium, N: Number of Patients, NASH: Non-alcoholic steatohepatitis, PBC: Primary Biliary Cirrhosis, pHTN: portal hypertension, PSC: Primary Sclerosing

Cholangitis, SBP: spontaneous bacterial peritonitis, TIPS: transjugular intrahepatic portosystemic shunt.

Table 3. Multivariable logistic regression analysis for probability of hospitalization per patient-year

Characteristics	OR (95% CI)	p-value
Gender		
Male	**Reference**	
Female	1·07 (1·05 - 1·09)	<0·001
Insurance		
Medicare	**Reference**	
Commercial	0·82 (0·80 - 0·83)	<0·001
HCC	1·03 (0·98 - 1·08)	0·228
Etiology		
Alcohol-related	**Reference**	
HCV	0·70 (0·68 - 0·72)	<0·001
NASH	0·69 (0·68 - 0·71)	<0·001
PBC	0·60 (0·57 - 0·62)	<0·001
HBV	0·46 (0·43 - 0·49)	<0·001
Cardiac	0·82 (0·71 - 0·95)	0·008
Genetic	0·70 (0·65 - 0·76)	<0·001
AIH	0·69 (0·65 - 0·74)	<0·001
2+ Etiology	0·79 (0·77 - 0·82)	<0·001
Other	0·32 (0·29 - 0·36)	<0·001
Decompensation Status		
Compensated	**Reference**	
HE	1·44 (1·38 - 1·49)	<0·001
Ascites	1·59 (1·55 - 1·63)	<0·001
Variceal Bleed	1·34 (1·28 - 1·41)	<0·001
HPS	1·25 (0·83 - 1·89)	0·277
HRS	1·03 (0·75 - 1·41)	0·864
HE & Ascites	1·63 (1·56 - 1·70)	<0·001
HE & HRS	1·14 (0·72 - 1·80)	0·576
SBP	1·67 (1·46 - 1·92)	<0·001
2 Decompensations	1·69 (1·61 - 1·77)	<0·001
≥3 Decompensations	1·77 (1·68 - 1·86)	<0·001

AIH: Autoimmune Hepatitis, HBV: Hepatitis B Virus, HCC: hepatocellular carcinoma, HCV: Hepatitis C Virus, HE: hepatic encephalopathy, HRS: hepatorenal syndrome, HPS: hepatopulmonary syndrome, NASH: Non-alcoholic steatohepatitis, PBC: Primary Biliary Cirrhosis, SBP: spontaneous bacterial peritonitis

Table 4: Top 15 Causes of Admission for Cirrhosis and NIS

Rank	All Cirrhosis (N=395,508 admissions)	Compensated (N=156,020 admissions)	Decompensated (N=239,488 admissions)	COPD (N=980,079 admissions)	HF (N=1,454,634 admissions)
1	Septicemia (10·5%)	Septicemia (9·8%)	Septicemia (11·0%)	Septicemia (9·6%)	Heart failure (10·0%)
2	Heart failure (6·1%)	Heart failure (5·9%)	Heart failure (6·2%)	Heart failure (7·3%)	Septicemia (9·7%)
3	General cirrhosis related (3·6%)	Alcohol-related disorders (3·9%)	Ascites (5·6%)	Chronic obstructive pulmonary disease and bronchiectasis (5·1%)	Cardiac dysrhythmias (4·0%)
4	Ascites (3·4%)	Acute and unspecified kidney injury (2·7%)	General cirrhosis related (5·6%)	Pneumonia (except tuberculosis) (4·0%)	Acute myocardial infarction (3·8%)
5	Hepatic Encephalopathy (3·2%)	Gastrointestinal hemorrhage (2·5%)	Hepatic Encephalopathy (5·3%)	Respiratory failure; insufficiency; arrest (3·8%)	Pneumonia (except tuberculosis) (3·2%)
6	Acute and unspecified kidney injury (3·0%)	Pneumonia (except tuberculosis) (2·4%)	Hepatic failure (3·7%)	Cardiac dysrhythmias (2·8%)	Chronic obstructive pulmonary disease and bronchiectasis (3·1%)
7	Alcohol-related disorders (2·9%)	Chronic obstructive pulmonary disease and bronchiectasis (2·4%)	Acute and unspecified kidney injury (3·2%)	Acute myocardial infarction (2·6%)	Acute and unspecified renal failure (3·0%)
8	Gastrointestinal hemorrhage (2·8%)	Diabetes mellitus with complication (2·3%)	Gastrointestinal hemorrhage (3·0%)	Osteoarthritis (2·6%)	Respiratory failure; insufficiency; arrest (3·0%)
9	Hepatic failure (2·4%)	Cardiac dysrhythmias (2·3%)	Alcohol-related disorders (2·2%)	Acute and unspecified kidney injury (2·5%)	Cerebral infarction (2·4%)
10	Diabetes mellitus with complication (1·9%)	Respiratory failure; insufficiency; arrest (2·2%)	Fluid and electrolyte disorders (1·7%)	Cerebral infarction (2·0%)	Diabetes mellitus with complication (2·3%)
11	Pneumonia (except tuberculosis) (1·9%)	Osteoarthritis (2·1%)	Diabetes mellitus with complication (1·7%)	Urinary tract infections (1·8%)	Osteoarthritis (2·0%)
12	Respiratory failure; insufficiency; arrest (1·9%)	Urinary tract infections (1·9%)	Respiratory failure; insufficiency; arrest (1·7%)	Diabetes mellitus with complication (1·8%)	Urinary tract infections (2·0%)

13	Cardiac dysrhythmias (1·7%)	Skin and subcutaneous tissue infections (1·8%)	Pneumonia (except tuberculosis) (1·5%)	Fracture of the neck of the femur (hip), initial encounter (1·7%)	Coronary atherosclerosis and other heart disease (1·9%)
14	Fluid and electrolyte disorders (1·6%)	Biliary tract disease (1·7%)	Pancreatic disorders (excluding diabetes) (1·4%)	Spondylopathies/spondyloarthropathy (including infective) (1·5%)	Fracture of the neck of the femur (hip), initial encounter (1·6%)
15	Skin and subcutaneous tissue infections (1·5%)	Acute MI (1·7%)	Skin and subcutaneous tissue infections (1·3%)	Coronary atherosclerosis and other heart disease (1·5%)	Gastrointestinal hemorrhage (1·6%)
Other	51·6%	54·5%	44·8%	49·4%%	46·4%%

COPD: Chronic Obstructive Pulmonary Disease, HF: Heart failure

FIGURES:

Figure 1. Annual Hospitalization Rates

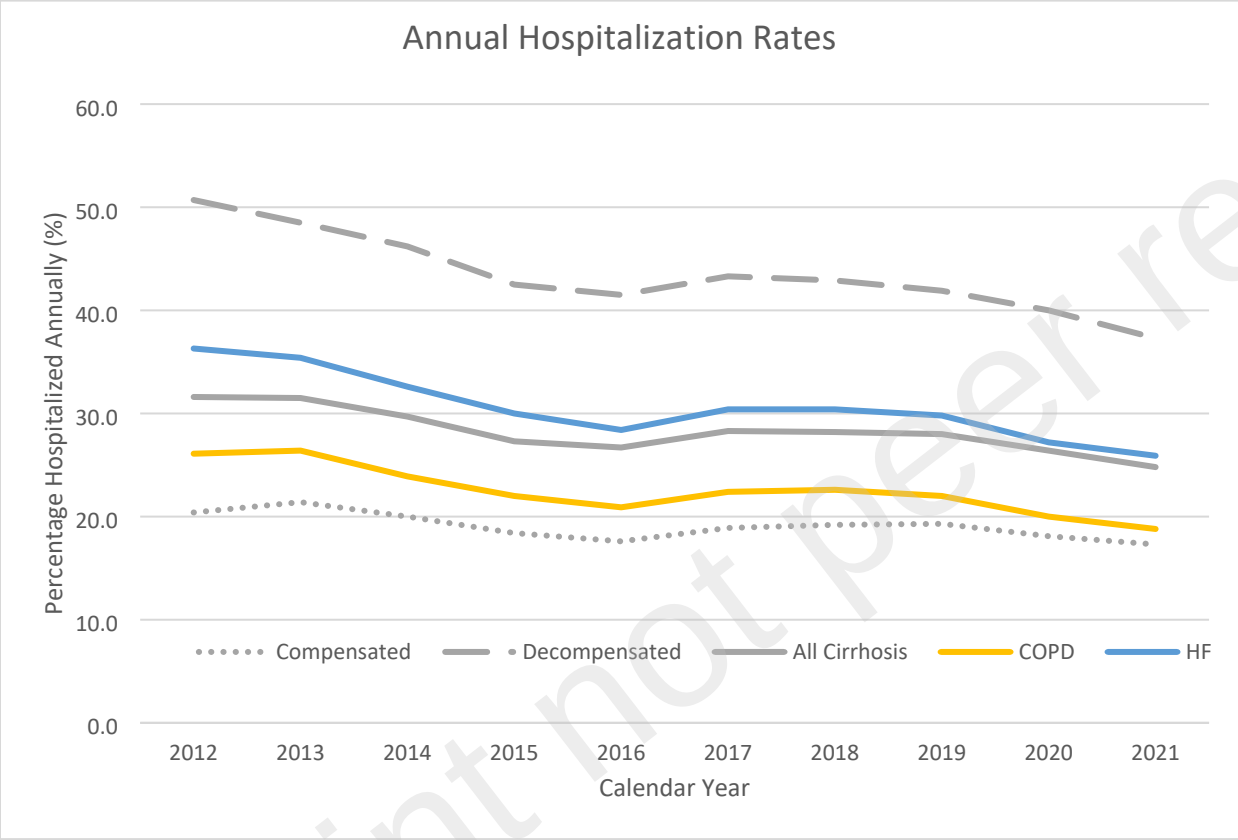

Figure 1 Legend:
COPD: Chronic Obstructive Pulmonary Disease. For differences in mean between cirrhosis and HF (P<0·001) and for differences in mean between cirrhosis and COPD (P<0·001). Annually, 27·8% of the total cirrhotic population was hospitalized, compared to 21·6% for COPD and 28·0% for HF. Patients with decompensated cirrhosis were hospitalized at over twice the rate of those with compensated cirrhosis (18·8% vs. 42·5%, p<0·001).