Increasing Economic Burden in Hospitalized Patients With Cirrhosis: Analysis of a National Database

Archita P. Desai, MD[1], Prashanthinie Mohan, MBA[2], Brandon Nokes, MD[3], Deekksha Sheth, MBBS[4], Shannon Knapp, PhD[5], Malaz Boustani, MD, MPH[6], Naga Chalasani, MD[1], Michael B. Fallon, MD[7] and Elizabeth A. Calhoun, PhD, MEd[2]

INTRODUCTION: **The prevalence of cirrhosis is increasing despite advances in therapeutics, and it remains an expensive medical condition. Studies examining the healthcare burden of inpatient cirrhosis-related care regardless of etiology, stage, or severity are lacking. This study aims to describe the current drivers of cost, length of stay (LOS), and mortality in hospitalized patients with cirrhosis.**

METHODS: **Using the National Inpatient Sample (NIS) data from 2008 to 2014, we categorized admissions into decompensated cirrhosis (DC), compensated cirrhosis (CC), and NIS without cirrhosis. Descriptive statistics and regression analysis were used to analyze the association between patient characteristics, comorbidities, complications, and procedures with costs, LOS, and mortality in each group.**

RESULTS: **The hospitalization costs for patients with cirrhosis increased 30.2% from 2008 to 2014 to $7.37 billion. Cirrhosis admissions increased by 36% and 24% in the DC and CC groups, respectively, compared with 7.7% decrease in the NIS without cirrhosis group. DC admissions contributed to 58.6% of total cirrhotic admissions by 2014. Procedures increased costs in both DC and CC groups by 15%–152%, with mechanical ventilation being associated with high cost increase and mortality increase. Complications are also key drivers of costs and LOS, with renal and infectious complications being associated with the highest increases in the DC group and infections and nonportal hypertensive gastrointestinal bleeding for the CC group.**

DISCUSSION: **Economic burden of hospitalized patients with cirrhosis is increasing with more admissions and longer LOS in DC and CC groups. Important drivers include procedures and portal hypertensive and nonportal hypertensive complications.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A67

Clinical and Translational Gastroenterology 2019;10:e-00062. https://doi.org/10.14309/ctg.0000000000000062

INTRODUCTION

Liver cirrhosis is a significant source of mortality and morbidity in the United States (1,2). The societal burden is likely to increase in the next 10–20 years due to an increasing prevalence of alcoholic liver disease, nonalcoholic fatty liver disease, and hepatocellular cancer (1,3,4). Patients with cirrhosis have more hospitalizations, longer stays, more readmissions, and poorer outcomes when compared with patients with other chronic diseases such as congestive heart failure and chronic obstructive pulmonary disease (5). Cirrhosis can also affect the outcome of non–liver-related comorbidities requiring hospitalizations (6). Several studies estimate the burden of chronic liver disease in the United States to be in the range of $2.5 billion, with the indirect cost of $10.6 billion (7–9). However, expensive medications that have altered the treatment regimens for patients with cirrhosis have been launched over the past few years (10), thus requiring us to reassess the burden of cirrhosis and the drivers for the costs. Therefore, our study aims to estimate the costs of hospitalizations in patients with cirrhosis using a recent national database and assess the drivers for such costs among patients with decompensated cirrhosis (DC) and compensated cirrhosis (CC).

METHODS

Data source

The National Inpatient Sample (NIS) database is the largest all-payer inpatient database within the United States. The database

[1]Division of Gastroenterology, Department of Medicine, Indiana University, Indianapolis, Indiana, USA; [2]College of Public Health, University of Arizona, Tucson, Arizona, USA; [3]Division of Pulmonary, Critical Care, and Sleep Medicine, University of California, San Diego, San Diego, California, USA; [4]Kasturba Medical College and Hospital, Manipal University, Manipal, India; [5]Statistics Consulting Laboratory, BIO5 Institute, University of Arizona, Tucson, Arizona, USA; [6]Department of Medicine, Center for Health Innovation and Implementation Science, Indiana University School of Medicine, Indianapolis, Indiana, USA; [7]Department of Medicine, College of Public Health, University of Arizona, Phoenix, Arizona, USA. **Correspondence:** Archita P. Desai, MD. E-mail: desaiar@iu.edu.

Received January 28, 2019; accepted May 16, 2019; published online July 23, 2019

includes information on more than 7 million hospital stays each year, with discharge weights to help produce national estimates. In 2015, the sampling frame for NIS included more than 96% of discharges from US community hospitals (11).

Inclusion criteria

Admission records between 2008 and 2014 for all patients aged ≥18 years were included in the study. Two previous studies using the NIS have used inclusion criteria restricting the primary diagnosis to cirrhosis, portal hypertension (PHTN), or complication of PHTN (12,13). However, this may not capture all patients admitted with cirrhosis such as those primarily admitted for an infection or acute kidney injury which is now considered an important complication of cirrhosis. Thus, we considered both primary and secondary diagnosis to identify admission records for patients with cirrhosis. Primary and secondary diagnoses are coded in the NIS using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnostic and procedural codes for all years included in this study. Admissions were separated into 3 mutually exclusive groups for all analyses.

DC group included admissions with a primary or secondary diagnosis of cirrhosis (*ICD-9* codes 571.2, 571.5, 571.6) along with complications (PHTN [572.3], ascites [789.59], hepatic encephalopathy [572.2], upper gastrointestinal [GI] bleed [456.0, 456.20, 578.0, 578.1, 578.9], and hepatorenal syndrome [572.4]).

CC group included individuals with a primary or secondary diagnosis of cirrhosis but without any of the portal hypertensive complications used to define the DC group. The remaining admissions were included in a third group, "NIS without cirrhosis" and included all admissions without a cirrhosis-related *ICD-9* code. The reason for admission, etiology, and complications of liver disease were extracted from the *ICD-9* codes used for the primary and secondary diagnoses (see Appendix A and B, Supplementary Digital Content 1, http://links.lww.com/CTG/A67). Comorbidities were assessed both as a dichotomous variable (present or not) and using Elixhauser Comorbidity Index to understand their contribution to costs and length of stay (LOS) (14).

Statistical analysis

Economic burden of hospitalizations was assessed using descriptive statistics. Continuous variables were assessed as weighted median with interquartile range (IQR), and categorical variables were reported using weighted proportions. Cost-to-charge ratio files published by the Healthcare Utilization Project were used to calculate the costs from the charges provided in the NIS database. Each file contains hospital-specific cost-to-charge ratios based on all-payer inpatient costs for nearly every hospital in the NIS. Cost information was obtained from the hospital accounting reports collected by the Centers for Medicare & Medicaid Services. All costs are reported using 2014 average inflation-adjusted dollars.

Multivariable regression was used to assess the association of each of the outcomes with patient demographics, comorbidities, and hospital characteristics. For the outcomes inpatient mortality, LOS, and cost, we used logistic, negative binomial and inverse Gaussian regression, respectively. Each model was analyzed separately for the DC group and the CC group. In the regression analysis, specific comorbidities were grouped together as comorbidity classes to assess their association with the outcomes (see Appendix C, Supplementary Digital Content 1, http://links.lww.com/CTG/A67). All data management and analysis were conducted using SAS statistical software (version 9.4; SAS Institute Inc), R Core Team (2016), and Microsoft Excel (15,16).

RESULTS

In 2014, the total number of weighted admissions for cirrhosis was 570,730 or 1.92% of all admissions (Table 1). The total number of admissions for patients with cirrhosis increased 30.8% from 2008 to 2014, whereas the total number of admissions for other NIS patients decreased 7.7% during the same period. Of the 2014 cirrhosis admissions, 58.6% had a portal hypertensive complication (DC). Mean in-hospital mortality in the DC group was higher during the study period at 6.7% when compared with that in the CC group (3.4%) and other NIS admissions (2.1%). The median LOS was also longer for the DC group (4 days) and

Table 1. Specific outcome measures by group

Outcome variable	Patients with DC	Patients with CC	All NIS without cirrhosis
No. of admissions (2014)	334,370	236,360	29,181,233
Percentage increase in the no. of admissions between 2008 and 2014	35.89	24.22	−7.72
Total cost of hospitalization (2014)	$4,570,431,130	$2,801,813,569	$333,194,350,525
Percentage increase in the total cost of admissions between 2008 and 2014	33.4	25.33	3.98
Median cost per admission (IQR)[a]	$8,596 ($9,633)	$7,738 ($8,998)	$7,141 ($9,137)
Medicare (IQR)	$8,618 ($9,586)	$7,922 ($9,028)	$8,183 (9,714)
Medicaid (IQR)	$8,801 ($10,568)	$7,266 ($8,625)	$5,073 ($6,023)
Private pay (IQR)	$9,086 ($11,179)	$7,962 ($9,881)	$6,535 ($8,651)
Median LOS (Q1–Q3)	4 (2–7)	4 (2–6)	3 (2–5)
In-hospital mortality (%)[b]	6.66	3.37	2.13

CC, compensated cirrhosis; DC, decompensated cirrhosis; IQR, interquartile range; LOS, length of stay; NIS, National Inpatient Sample.
[a]Median cost calculated for all years (2008–2014) combined and adjusted to 2014 dollars.
[b]Percentage of patients died before discharge.

Table 2. Demographics of patients admitted between 2008 and 2014[a]

Discharge and hospital characteristic	Patients with DC	Patients with CC	All NIS without cirrhosis
Age (in yr), mean (SD)	58.3 (12.1)	59.3 (12.6)	57.2 (20.8)
18–44	10.5%	9.9%	29.8%
45–64	61.4%	58.7%	28.7%
65–84	26.0%	28.5%	31.8%
85+	2.1%	2.9%	9.7%
% Male	62.5	58.9	40.1
Race (%)			
White	60.6	60.6	61.7
Black	8.8	11.4	13.1
Hispanic	16.7	14.4	9.3
Asian or Pacific Islander	1.8	1.8	2.2
Native American	1.3	1.1	0.6
Other	2.9	2.7	2.8
Missing	7.9	7.9	10.4
Median income by patient zip code[b] (%)			
Quartile 1 (lowest income)	31.8	33.3	28.5
Quartile 2	25.7	25.4	25.7
Quartile 3	22.3	21.5	23.2
Quartile 4 (highest income)	16.9	16.1	20.2
Admissions by payer type (%)			
Medicare	41.3	46.3	45.5
Medicaid	23.0	22.1	15.5
Private/HMO	22.3	19.7	29.7
Other	13.2	11.6	9.1
Origin of admission (%)			
Emergency department	74.2	69.5	53.5
Transfer	6.8	5.3	4.9
Disposition of the patient (%)			
Home	58.3	61.9	66.8
Transfer to another hospital	3.8	2.8	2.1
Transfer to SNF, intermediate care, or another facility	15.5	16.2	15.6
Home health care	13.4	13.0	12.1
Teaching hospital[c] (%)	54.5	53.2	49.2
Rural hospital (%)	8.8	9.7	11.9
Hospital region[d] (%)			
Northeast	18.5	20.0	19.6
Midwest	18.9	18.6	23.0
South	38.9	39	38.5
West	23.8	22.5	18.8

CC, compensated cirrhosis; DC, decompensated cirrhosis; HMO, health maintenance organization; NIS, National Inpatient Sample; SNF, skilled nursing facility.
[a]Mean and proportions present in the table are weighted as per NIS discharges.
[b]Income by zip code included in each quartile varies by year. For dollar amounts included in each quartile each year, refer to http://www.hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nisnote.jsp.
[c]All rural hospitals are classified as nonteaching as per https://www.hcup-us.ahrq.gov/db/vars/nis_stratum/nisnote.jsp.
[d]For 2012–2014, the NIS data include divisions instead of regions. However, the 9 divisions in the data were grouped into regions as per https://www.hcup-us.ahrq.gov/db/vars/nis_stratum/nisnote.jsp.

CC group (4 days) compared with other NIS admissions (3 days; Table 1). Similar trends were seen when admissions related to pregnancy (10.1% of all non-cirrhosis NIS admissions) were excluded (see Appendix D, Supplementary Digital Content 1, http://links.lww.com/CTG/A67). Patient demographics and hospital characteristics by the group for the study period are listed in Table 2. In the DC group, the average patient was 58 years old, male (62.5%), and white (60.6%), compared with the average patient in the NIS without cirrhosis group who was 57 years old, female (59.8%), and white (61.7%). Most of the admissions in the cirrhosis groups were for patients in the 45–64 age category (61.4% and 58.7% for DC and CC groups, respectively) compared with more even age distribution in admissions for patients without cirrhosis. Among minorities, Hispanics constituted a larger portion of the DC and CC group, whereas blacks were a higher proportion of the non-cirrhotic admissions. Those in the DC and CC groups were more likely to live in zip codes in the lowest median income quartile and in urban settings compared with the non-cirrhosis group (Table 2; see Appendix E, Supplementary Digital Content 1, http://links.lww.com/CTG/A67). The reason for admission in the cirrhosis groups was largely related to liver disease in the DC group (53.8%), followed by GI causes (10.7%) and infections (7.2%) (Figure 1a; see Appendix B, Supplementary Digital Content 1, http://links.lww.com/CTG/A67). In comparison, the top 3 causes of admission in the CC group were infections (15%), liver disease (12.2%), and GI causes (11.5%) (Figure 1a; see Appendix B, Supplementary Digital Content 1, http://links.lww.com/CTG/A67). There was a significantly higher burden of cirrhosis due to alcohol without concomitant hepatitis C in those with DC compared with those with CC (39% vs 27%). More than 50% of the admissions in the DC group constituted those with alcoholic liver disease with or without hepatitis C. Of note, nonalcoholic steatohepatitis (NASH) is not specifically accounted for due to lack of an associated *ICD-9* code throughout the study period (see Appendix A, Supplementary Digital Content 1, http://links.lww.com/CTG/A67).

Appendix C (see Supplementary Digital Content 1, http://links.lww.com/CTG/A67) lists the weighted proportion of admissions, with each of the comorbidities across the 3 groups. Fluid and electrolyte disorders were among the top 3 comorbidities in all 3 groups. Although hypertension was the most common comorbidity among non-cirrhotic admissions, it ranked second among CC admissions (49.9%) and fourth among DC admissions (38.6%). When summarized as Elixhauser Index, 20.8% of the NIS population without cirrhosis had an Elixhauser Index of 0, whereas only 1% of DC admissions and 0.5% of CC admissions had a 0 index (Figure 1b). Furthermore, most admissions in the cirrhosis groups had an Elixhauser Comorbidity Index of 3 or greater (79.2% in DC group vs 83.6% in CC group vs 39.6% in non-cirrhotic group).

Drivers of cost in cirrhosis admissions

The total annual cost of hospitalization in patients with cirrhosis was $7.37 billion in 2014, with $4.57 billion for the DC group and $2.80 billion for the CC group (Table 1). Patients with cirrhosis contributed to 2.16% of the total hospitalization costs incurred by the NIS sample in 2014. The median cost of hospitalization in 2014 for patients with DC was $8,596 (IQR: $9,633), whereas it was $7,738 (IQR: $8,998) for patients with CC and $7,141 (IQR: $9,137) for other NIS patients. Over the study period, hospitalization costs for cirrhosis admissions increased 30.2% compared with 3.98% increase for non-cirrhotic NIS admissions. The costs for the DC group increased 33.4% and that for the CC group increased 25.3% (Table 1; see Appendix D, Supplementary Digital Content 1, http://links.lww.com/CTG/A67). In the regression model, all procedures were associated with significant

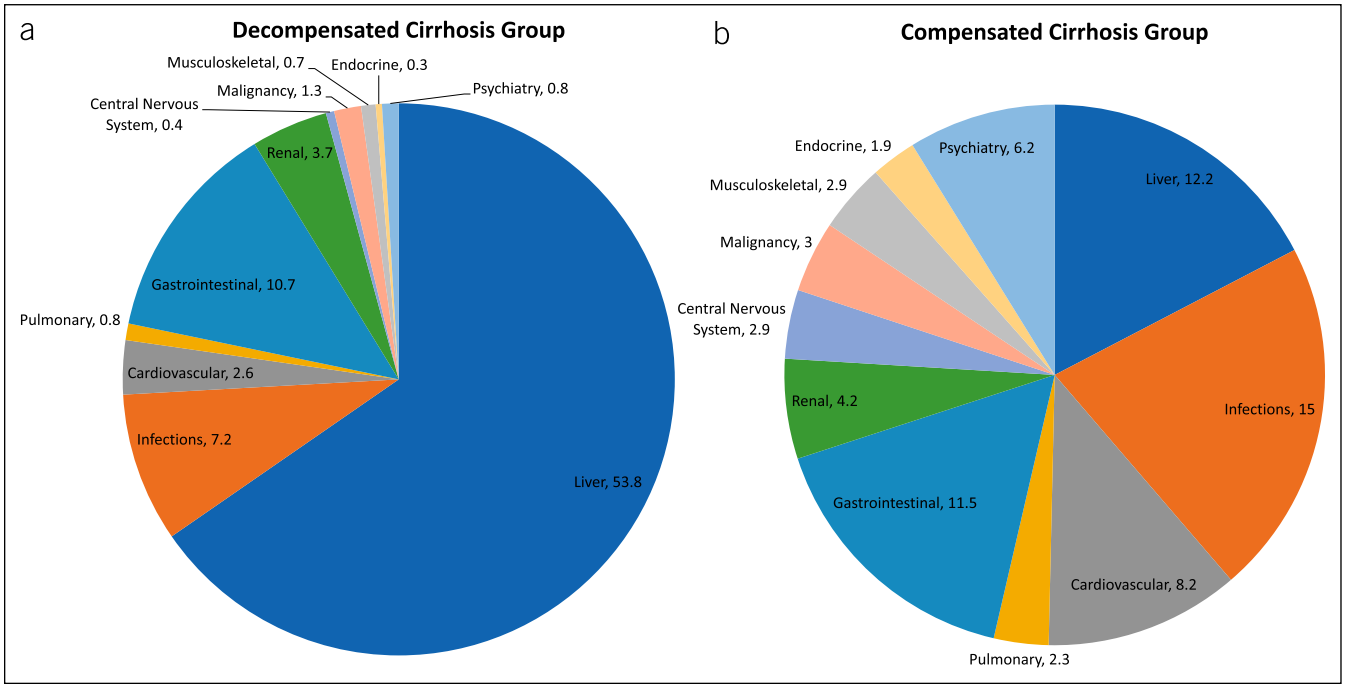

Figure 1. Primary diagnosis for admission by group reveals distinct reasons for admission between those with (a) decompensated cirrhosis, and (b) compensated cirrhosis. Analysis done on admissions from 2008 to 2011 on primary diagnosis codes with prevalence of ≥0.1%.

Table 3. Results of the regression analysis

Variable	DC group						CC group					
	Mortality odds ratio	95% CI	Change in cost (%)	95% CI	Change in LOS (%)	95% CI	Mortality odds ratio	95% CI	Change in cost (%)	95% CI	Change in LOS (%)	95% CI
Age (in yr)[a]												
45–64	1.5	1.47, 1.54	−1.9	−2.76, −1.03	−0.67	−0.67, −1.43	1.78	1.7, 1.86	8.07	6.91, 9.25	3.58	2.56, 4.6
64–84	2.38	2.32, 2.46	−3.13	−4.18, −2.06	1.67	1.67, 0.69	3.88	3.69, 4.08	10.76	9.31, 12.24	4.4	3.19, 5.63
85+	4.26	4.07, 4.46	−6.3	−8.2, −4.37	7.13	7.13, 5.21	7.97	7.47, 8.5	0.73	−1.54, 3.05	5.72	3.67, 7.81
Gender												
Female	0.99	0.97, 1	−1.68	−2.23, −1.13	−0.27	−0.27, −0.76	0.96	0.94, 0.99	−6.39	−7.04, −5.74	−4.63	−5.19, −4.06
Race[b]												
Black	1.14	1.12, 1.17	2.73	1.73, 3.74	4.25	4.25, 3.37	1.08	1.04, 1.11	3.23	2.09, 4.39	5.36	4.39, 6.34
Hispanic	0.91	0.9, 0.93	−0.35	−1.1, 0.4	−0.95	−0.95, −1.61	0.96	0.93, 0.99	−0.29	−1.29, 0.71	−1.22	−2.07, −0.37
Other	1	0.97, 1.02	2.75	1.57, 3.94	0.72	0.72, −0.26	1.05	1.01, 1.1	3.45	1.9, 5.03	−0.38	−1.6, 0.87
Etiology												
ALD	1.2	1.15, 1.25	−0.1	−1.85, 1.68	0.9	0.9, −0.71	1.43	1.34, 1.52	−10.03	−11.68, −8.34	2.5	0.88, 4.14
Hepatitis C	0.97	0.95, 0.99	0.25	−0.59, 1.1	−0.43	−0.43, −1.18	0.77	0.75, 0.79	−6.11	−6.97, −5.24	−5.44	−6.18, −4.69
ALD and Hepatitis C	0.95	0.92, 0.98	−1.39	−2.53, −0.24	1.32	1.32, 0.28	1.17	1.12, 1.23	2.81	1.32, 4.31	4.07	2.76, 5.4
Other NOS	1	0.95, 1.04	−3.8	−5.38, −2.19	−3.77	−3.77, −5.22	1.43	1.35, 1.52	−4.19	−5.81, −2.54	0.62	−0.85, 2.12
Comorbidity												
Alcohol and drug abuse	0.85	0.84, 0.87	−7.02	−7.69, −6.34	−6.36	−6.36, −6.94	0.87	0.85, 0.9	−0.23	−1.08, 0.64	0.71	−0.01, 1.45
Anemia	0.7	0.69, 0.72	−4.04	−4.57, −3.5	−3.31	−3.31, −3.8	0.73	0.71, 0.75	1.04	0.23, 1.85	5.12	4.42, 5.82
Cancer	1.36	1.32, 1.4	6.11	4.75, 7.48	2.82	2.82, 1.68	2.17	2.1, 2.24	17.92	16.14, 19.73	7.64	6.42, 8.87
Chronic pulmonary disease	1.02	1, 1.04	5.12	4.36, 5.89	3.73	3.73, 3.06	0.89	0.87, 0.92	7.15	6.29, 8.02	5.02	4.31, 5.74
Diabetes	0.66	0.64, 0.67	−5.02	−5.57, −4.47	−6.56	−6.56, −7.05	0.74	0.72, 0.76	−0.84	−1.56, −0.12	−3.89	−4.49, −3.29
Heart disease	1.08	1.06, 1.1	9.54	8.69, 10.4	9.91	9.91, 9.18	1.16	1.13, 1.19	9.5	8.48, 10.53	10.02	9.19, 10.84
Hypertension	0.71	0.7, 0.72	−3.24	−3.77, −2.71	−4.57	−4.57, −5.04	0.6	0.59, 0.61	0.16	−0.52, 0.84	−3.66	−4.22, −3.1
Renal failure and fluid disorders	1.36	1.34, 1.38	9.98	9.32, 10.65	9.14	9.14, 8.56	1.47	1.44, 1.51	9.21	8.44, 9.99	12.93	12.25, 13.61
Mental illness	0.64	0.62, 0.66	−2.05	−2.77, −1.32	3.37	3.37, 2.66	0.62	0.59, 0.64	−4.37	−5.15, −3.58	1.56	0.82, 2.3
Neurologic disorders	0.94	0.92, 0.97	8.01	6.89, 9.14	12.18	12.18, 11.16	0.88	0.85, 0.91	4.57	3.41, 5.74	14.48	13.42, 15.55
Median income by zip code[c]												
Quartile 2	0.94	0.92, 0.95	3.89	3.19, 4.59	−1.06	−1.06, −1.67	0.99	0.97, 1.02	4.36	3.48, 5.26	−0.95	−1.68, −0.21
Quartile 3	0.9	0.88, 0.92	8.32	7.53, 9.12	−1.2	−1.2, −1.84	0.87	0.85, 0.9	8.18	7.17, 9.2	−1.96	−2.75, −1.18
Quartile 4	0.9	0.88, 0.92	16.14	15.15, 17.13	0.1	0.1, −0.62	0.88	0.85, 0.91	15.83	14.56, 17.11	−0.42	−1.31, 0.48

Table 3. (*continued*)

Variable	DC group						CC group					
	Mortality odds ratio	95% CI	Change in cost (%)	95% CI	Change in LOS (%)	95% CI	Mortality odds ratio	95% CI	Change in cost (%)	95% CI	Change in LOS (%)	95% CI
Payer[d]												
Medicaid	1.16	1.14, 1.19	0.73	−0.06, 1.52	7.09	7.09, 6.34	1.26	1.22, 1.3	0.59	−0.38, 1.58	8.93	8.02, 9.84
Other	1.7	1.66, 1.74	−1.51	−2.38, −0.63	1.33	1.33, 0.51	1.74	1.68, 1.8	−0.82	−1.93, 0.32	0.14	−0.87, 1.16
Private	1.16	1.13, 1.18	5.36	4.54, 6.19	0.33	0.33, −0.35	1.53	1.48, 1.58	7.45	6.37, 8.54	−2.45	−3.26, −1.63
Urban hospital	0.83	0.81, 0.85	1.32	0.42, 2.23	9.08	9.08, 8.1	0.81	0.78, 0.84	3.31	2.18, 4.46	11.66	10.48, 12.84
Hospital region[e]												
Northeast	1.04	1.02, 1.06	−8.05	−8.89, −7.21	17.48	17.48, 16.64	1.17	1.13, 1.21	−13.68	−14.65, −12.7	15.03	14.02, 16.05
Midwest	0.82	0.81, 0.84	−19.34	−20.04, −18.63	−4.26	−4.26, −4.98	0.93	0.9, 0.96	−21.27	−22.16, −20.37	−2.6	−3.51, −1.67
South	0.94	0.93, 0.96	−23	−23.56, −22.44	4.37	4.37, 3.72	1.14	1.11, 1.17	−24.08	−24.79, −23.36	5.11	4.3, 5.93
Hospital characteristics												
Teaching hospital	0.82	0.81, 0.83	20.37	19.67, 21.07	5.95	5.95, 5.41	0.88	0.86, 0.9	20.26	19.38, 21.15	3.54	2.9, 4.18
ED admission	1.02	1, 1.04	−17.35	−17.96, −16.74	−11.94	−11.94, −12.46	0.97	0.94, 0.99	−23.25	−23.91, −22.59	−11.81	−12.4, −11.22
Hospital transfer	1.22	1.19, 1.25	3	1.63, 4.39	17.5	17.5, 16.34	1.62	1.55, 1.69	−3.97	−5.65, −2.27	41.57	39.78, 43.38
Primary diagnosis: liver disease	0.84	0.83, 0.85	−19.96	−20.42, −19.51	−15.04	−15.04, −15.46	1.72	1.67, 1.78	−5.22	−6.19, −4.25	−8.58	−9.39, −7.76
Complications												
AKI	2.31	2.28, 2.35	20.12	19.2, 21.04	16.2	16.2, 15.52	2.49	2.43, 2.55	16.25	14.94, 17.58	15.48	14.5, 16.46
Infection	0.84	0.83, 0.86	28.04	27.1, 28.98	41.18	41.18, 40.38	0.76	0.74, 0.78	16.14	15.15, 17.15	36.26	35.33, 37.19
Non-PHTN GI bleed	1.36	1.34, 1.38	5.34	4.61, 6.09	−3.96	−3.96, −4.55	0.61	0.59, 0.64	25.51	23.6, 27.46	3.09	1.96, 4.24
Ascites	1.18	1.17, 1.2	7.58	6.93, 8.23	8.59	8.59, 7.99	NI	NI	NI	NI	NI	NI
HRS	3.45	3.38, 3.51	33.07	31.1, 35.07	18.88	18.88, 17.73	NI	NI	NI	NI	NI	NI
Variceal bleed	1.54	1.5, 1.58	9.59	8.41, 10.79	−3.58	−3.58, −4.44	NI	NI	NI	NI	NI	NI
HCC	1.56	1.51, 1.61	23.33	21.47, 25.21	0.78	0.78, −0.49	NI	NI	NI	NI	NI	NI
HE	1.51	1.49, 1.54	6.81	6.15, 7.48	22.91	22.91, 22.25	NI	NI	NI	NI	NI	NI
Hyponatremia	0.96	0.94, 0.98	7.19	6.34, 8.04	13.29	13.29, 12.56	NI	NI	NI	NI	NI	NI
Malnutrition	0.9	0.87, 0.93	3.38	2.21, 4.55	8.1	8.1, 7.03	NI	NI	NI	NI	NI	NI
SBP	1.71	1.67, 1.76	18.39	16.58, 20.23	13.37	13.37, 12.09	NI	NI	NI	NI	NI	NI
Procedure												
Fluid removal	0.7	0.69, 0.71	15.63	14.88, 16.39	22.34	22.34, 21.65	1.15	1.1, 1.19	40.57	37.85, 43.34	47.5	45.59, 49.43
Mechanical ventilation	14.85	14.62, 15.09	152.83	148.05, 157.7	52.17	52.17, 50.82	27.69	27.05, 28.34	171.79	164.05, 179.76	69.48	67.28, 71.71
Non-RBC transfusion	1.78	1.75, 1.81	46.27	44.71, 47.83	18.93	18.93, 18.09	2.22	2.15, 2.3	62.34	58.83, 65.93	22.01	20.46, 23.58

Table 3. (*continued*)

Variable	DC group					CC group				
	Mortality odds ratio	95% CI	Change in cost (%)	95% CI	Change in LOS (%)	Mortality odds ratio	95% CI	Change in cost (%)	95% CI	Change in LOS (%)
RBC transfusion	0.91	0.89, 0.92	28.42	27.46, 29.39	17.27	0.97	0.95, 1.01	39.99	38.12, 41.89	24.43
Varices treatment	0.42	0.41, 0.43	24.1	23.14, 25.07	20.23	0.56	0.53, 0.59	20.61	18.87, 22.38	16.86
Hemodialysis	1.57	1.54, 1.61	41.61	39.41, 43.84	33.58	1.73	1.66, 1.8	25.41	22.86, 28.01	15.45

Only results of model 4 are presented in this table.
AKI, acute renal injury; ALD, alcoholic liver disease; CC, compensated cirrhosis; CI, Charlson Index; DC, decompensated cirrhosis; ED, emergency department; GI, gastrointestinal; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; LOS, length of stay; NI, not included; NOS, not otherwise specified; PHTN, portal hypertension; RBC, red blood cell; SBP, spontaneous bacterial peritonitis.
[a]Age group of 18–44 is the reference age group.
[b]Whites are the reference group for race.
[c]Quartile 1 is the reference group for median income by zip code.
[d]Medicare is the reference group for payer.
[e]West is the reference group for hospital region.

cost increases (Tables 3 and 4). The top 3 procedures associated with the highest cost increase were mechanical ventilation, non–red blood cell (RBC) transfusions, and hemodialysis. However, these procedures were also associated with higher odds for mortality in both DC and CC groups. The odds ratio (OR) for mortality for mechanical ventilation in DC admissions is 14.85, whereas for CC admissions it is 27.69 (Table 3). Hemodialysis was also associated with higher mortality odds (1.57 in the DC group and 1.73 in the CC group) and 41.6% and 25.4% increase in the costs per admission for DC and CC, respectively. Fluid removal (defined by paracentesis and/or thoracentesis) (see Appendix A, Supplementary Digital Content 1, http://links.lww.com/CTG/A67), while costly (15.63% increase in cost), was the most common procedure in the DC group and was associated with lower mortality odds (OR: 0.70). The other procedures included in the study (RBC transfusion and varices treatment) were also associated with lower OR for mortality and higher costs for both DC and CC admissions (Table 3; see Appendix A, see Supplementary Digital Content 1, http://links.lww.com/CTG/A67). All complications of cirrhosis resulted in significant cost increases in the DC group. Based on the regression analysis, renal-related complications (hepatorenal syndrome and acute renal injury) were associated with the maximum increase in the odds for mortality and costs in the DC group. This was followed by infection (28.0% increase in the costs) and liver cancer (23.3% increase in the costs; Table 3). Notably, in the CC group, 34.7% of the admissions had 1 or more of the nonportal hypertensive complications such as infection (20.2%), renal injury (12.5%), nonportal hypertensive GI bleed (7.53%) but contributed to 45% of the costs for total CC admissions. The total cost of hospitalizations for admissions with nonportal hypertensive complications in the CC group increased by 42.6% to $1.3 billion over the study period, whereas the costs for CC hospitalizations without these complications increased only by 14% to $1.5 billion for the same period. In both DC and CC groups, none of the comorbidity classes were in the top 5 variables associated with increased odds for mortality or percentage increase in LOS and costs. Renal and fluid disorders and heart conditions were associated with the most increase in costs in the DC group (9.98% and 9.54%, respectively).

Drivers of LOS in cirrhosis admissions

The median LOS for both DC and CC admissions was 4 days, whereas the IQR for DC admissions (5 days) was longer than that for CC admissions (4 days). In the regression model, all advanced procedures were associated with increased LOS in both DC and the CC groups (Tables 3 and 4). In the DC group, mechanical ventilation and hemodialysis were associated with the highest increase among procedures in the LOS (52.2% and 33.6% longer LOS, respectively). Similarly, all procedures were associated with higher LOS in the CC group, with mechanical ventilation being associated with the highest increase (69.5% increase in the LOS). Based on the regression model, all complications, except for non-PHTN GI bleed and varices with bleeding, were associated with an increase in the LOS in the DC group. Infection and hepatic encephalopathy were associated with the maximum increase in the LOS in the DC group (41.1% and 22.9% increased LOS, respectively). In the CC group, all nonportal hypertensive complications were associated with increased LOS, with infection ranking the highest (36.3% increase). Admissions through hospital transfers were also associated with a significant increase in

Table 4. Mean LOS and mean cost of hospitalization for admissions with and without specific procedures and complications

	DC group				CC group			
	Weighted mean cost		Weighted mean LOS		Weighted mean cost		Weighted mean LOS	
Complications/ procedure	With variable	Without variable	With variable	Without variable	With variable	Without variable	With variable	Without variable
Complications								
AKI	20,144.74	12,856.28	8.12	5.54	16,313.11	11,612.24	6.84	5.04
Infection	19,290.99	13,177.99	8.56	5.48	14,312.12	11,660.03	6.88	4.86
Non-PHTN GI bleed	16,690.02	13,531.77	6.17	6.02	18,662.58	11,670.72	6.25	5.19
Ascites	15,263.46	13,087.10	6.54	5.43	NI	NI	NI	NI
HRS	27,285.18	13,528.64	9.75	5.83	NI	NI	NI	NI
Variceal bleed	17,194.55	13,991.24	5.95	6.07	NI	NI	NI	NI
HCC	17,453.50	14,156.30	5.97	6.06	NI	NI	NI	NI
HE	15,885.17	13,581.11	6.98	5.62	NI	NI	NI	NI
Hyponatremia	16,951.93	13,685.55	7.52	5.70	NI	NI	NI	NI
Malnutrition	12,985.04	14,406.42	6.34	6.04	NI	NI	NI	NI
SBP	19,990.12	14,091.57	8.13	5.97	NI	NI	NI	NI
Procedures								
Fluid removal	16,721.81	13,086.43	7.25	5.44	20,832.48	11,801.28	8.38	5.12
Mechanical ventilation	41,269.22	12,469.73	11.38	5.69	36,866.80	11,132.50	10.72	5.03
Non-RBC transfusion	25,515.98	12,696.84	8.41	5.72	25,934.65	11,475.62	7.69	5.14
RBC transfusion	20,651.56	12,294.63	7.47	5.61	20,999.43	11,042.49	7.33	5.00
Varices treatment	16,860.18	13,526.72	6.54	5.91	14,930.59	11,995.17	6.35	5.19
Hemodialysis	30,493.37	13,460.21	10.04	5.85	19,690.88	11,885.06	7.21	5.18

Only procedures and complications included in the regression analysis are listed in this table.
AKI, acute renal injury; CC, compensated cirrhosis; DC, decompensated cirrhosis; GI, gastrointestinal; HCC, hepatocellular carcinoma; HRS, hepatorenal syndrome; LOS, length of stay; NI, not included; PHTN, portal hypertension; RBC, red blood cell; SBP, spontaneous bacterial peritonitis.

the LOS in both CC and DC groups (41.6% and 17.5% increase in the LOS, respectively).

DISCUSSION

Our study found that the economic burden of hospitalized patients with cirrhosis is increasing with more admissions and longer LOS in the DC and CC groups. Procedures and PHTN and non-PHTN complications were the key drivers for such burden in both patients with CC and DC. From 2008 to 2014, our study found 31% increase in the prevalence of all cirrhosis-related hospitalizations in comparison with 8% reduction in the prevalence of non–cirrhosis-related admissions.

Although there was no predominant primary diagnosis for CC admissions, the top 3 diagnoses were infection, liver disease, and GI-related diagnoses. Figure 1a highlights the variety of reasons patients with cirrhosis are admitted. The drivers of cost in the CC population included procedures such as mechanical ventilation and hemodialysis and nonportal hypertensive complications such as infection, nonportal hypertensive GI bleeding, and acute renal failure. Despite our effort to carefully define the CC group by excluding any *ICD-9* codes related to known cirrhosis complications, the high prevalence of renal failure and infection during the compensated phase of cirrhosis requires further investigation because these may be early indicators of future healthcare utilization (HCU).

These trends in the CC group do not discount the significant contribution of DC on healthcare costs. Those with DC experienced even higher increases in the number of hospitalizations than those with CC, 35.89% vs 24.22%. As with the CC group, the rise in hospitalizations for the DC group contributes to a 33.4% increase in the total healthcare costs. These significant increases are put into context when we compare with those without cirrhosis for whom hospitalization costs increased by only 3.98% during the same period. In both CC and DC groups, our analysis also highlights the burden of cirrhosis-related inpatient care on individuals at the prime of their life, with about two-thirds of admissions in both groups occurring in those aged 45–64 years compared with only one-third of admissions in the NIS without cirrhosis cohort. In addition, our data describe a higher burden in those at the lowest quartile of income in these groups. Furthermore, alcohol-related cirrhosis is disproportionately represented in the DC group compared with the CC group, highlighting the changing landscape of chronic liver disease (17). Programs and interventions that allow for earlier diagnosis in this group stand to significantly affect HCU in the cirrhosis population. In addition to such interventions, our results highlight the role of teaching hospitals in the care of cirrhosis population. As with previous literature, we show lower mortality rates in both DC and CC groups despite higher costs and LOS (12). This association may be

explained by access to specialists and transplantation, although those undergoing transplant remain the extreme minority (<0.001% in the DC group) (Table 3; see Appendix A, Supplementary Digital Content 1, http://links.lww.com/CTG/A67). Beyond the primary diagnoses, our data also highlight the role of chronic comorbid conditions in those with cirrhosis. Whereas there was not a predominant comorbid condition, almost all admissions in the CC group had at least 1 comorbidity and 83.6% had more than 3 comorbidities. Furthermore, 8.2% of all CC admissions carried a primary diagnosis of cardiovascular disease. These data support the hypothesis that whereas individual comorbid conditions may not be a significant driver of HCU, specific combinations of comorbidities may differentially affect the HCU (18). Models of care used to manage patients with cirrhosis who are the most costly and at highest risk of dying need to keep comorbid conditions in mind. An important trend we noted is lower odds of mortality with certain prevalent comorbid conditions such as type II diabetes mellitus and hypertension. We are not the only study to notice this trend (19–21). It is clinically more plausible that during data abstraction of complex hospitalizations, comorbid conditions are undercoded when only the first 15 diagnoses are included. Other hypotheses include the association of these comorbidities with the causes of cirrhosis such as NASH which may provide to have different drivers of cost, LOS, and inpatient mortality than seen in alcohol- or hepatitis C-related cirrhosis.

The trends noted in our study may help inform future interventions aimed at improving the cost effectiveness of therapies provided to patients with end-stage liver disease. For example, we find that for patients with cirrhosis, not only did procedures raise the cost significantly as expected but some of these procedures were also associated with the highest odds of mortality. Here, a comparison can be made between the procedures. Although both mechanical ventilation and fluid removal are considered lifesaving but costly procedures, mechanical ventilation increased the odds of inpatient death by 14.85 in the DC group, whereas fluid removal was associated with lower odds of mortality. Despite the high mortality and costs associated with mechanical ventilation, it is used near twice as more often in patients with DC compared with all other admissions. These data indicate that interventions at the individual level through improved goal setting during critical illness are key to controlling healthcare costs. At the hospital level, quality measures that can trigger interventions for those at risk for respiratory failure would affect a high-risk group of patients with cirrhosis (22–24). Conversely, individuals with cirrhosis in need of fluid removal via procedures such as dialysis, thoracentesis, and paracentesis should receive these procedures without delay (25). This is also true of patients with cirrhosis who present with GI bleeding. These patients often require endoscopy and blood transfusion for management. Because these costly procedures are associated with lower mortality, making quality improvement projects that identify this cohort early and set up processes to allow the procedures to occur efficiently are key to further improving outcomes. In the case of non-RBC transfusions, an example would be the use of thromboelastography which may curtail the number of transfusions and reduce transfusion-related complications without adverse effects on patient outcomes (26).

Our study provides an all-payer perspective on drivers of inpatient HCU for cirrhosis-related admission. These national-level data were specifically created to represent national estimates of HCU. Combined with our broad inclusion of cirrhosis admissions through the analysis of secondary *ICD-9* codes and creation of DC and CC cohorts through validated definitions, our study uniquely defines the trends and drivers of inpatient HCU for end-stage liver disease. With HCU increasing for patients with cirrhosis much faster than for other NIS patients, our analysis provides data to guide future healthcare delivery research targeted at improving HCU in cirrhosis population.

We acknowledge several limitations to our study. The NIS lacks traditional methods to stage liver disease such as Model for End-Stage Liver Disease-Sodium score or Child Pugh score. In addition, although the use of discharge codes has been validated to identify groups of patients with cirrhosis in the compensated and decompensated stages, only the first 15 diagnostic codes are captured in this dataset. Therefore, assessments of other drivers of poor outcomes in advanced cirrhosis such as frailty may not be coded and underrepresented in this analysis (27,28). Future studies using pharmacy data that are not available in the NIS may also improve our understanding of the drivers of HCU in end-stage liver disease. Finally, the lack of longitudinal data only allows for comments on associations between exposure variables analyzed and outcomes. Futures studies using cohorts with multiple data points over time may allow for inferences on the association between our proposed exposure variables and HCU. Despite these limitations, our findings have important implications. Our data provide key national estimates of inpatient mortality and healthcare use in both DC and CC, define trends in the healthcare burden of hospitalized patients with cirrhosis, and identify drivers of inpatient mortality, LOS, and costs in this vulnerable population.

Interventions that allow more efficient use of procedures in patients with cirrhosis are likely to yield significant reductions in inefficient healthcare use. Future studies that better align healthcare delivery for the prevention and management of infection and renal failure in those with CC will similarly have a significant impact on healthcare use by those with chronic liver disease. In addition, studies looking at the impact of comorbid conditions on future healthcare use by cirrhosis population may improve our ability to deliver more tailored and efficient care.

CONFLICTS OF INTEREST

Guarantor of the article: Archita P. Desai, MD.

Specific author contributions: All authors wrote the article and have approved the final submission. A.P.D.: obtained funding, study concept and design, analyzed and interpreted the data, drafted the manuscript, critically revised the manuscript, and approved the final submission. P.M.: analyzed and interpreted the data, wrote the manuscript, and approved the final submission. B.N. and D.S.: analyzed and interpreted the data and approved the final submission. S.K.: performed statistical analysis and approved the final submission. M.B. and N.C.: critically revised the manuscript, maintained study supervision, and approved the final submission. M.B.F.: study concept and design, critically revised the manuscript, and approved the final submission. E.A.C.: study concept and design, critically revised the manuscript, maintained study supervision, and approved the final submission.

Financial support: The study was funded by 2017 AASLD Clinical and Translational Research Award (A.P.D.).

Potential competing interests: None.

REFERENCES

1. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999–2016: observational study. BMJ 2018;362:k2817.

2. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990–2010: Burden of diseases, injuries, and risk factors. JAMA 2013;310(6):591–608.
3. Peery AF, Crockett SD, Barritt AS, et al. Burden of gastrointestinal, liver, and pancreatic diseases in the United States. Gastroenterology 2015; 149(7):1731–41.e3.
4. Kim D, Li AA, Perumpail BJ, et al. Changing trends in etiology- and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. Hepatology 2019;69(3):1064–74.
5. Asrani SK, Kouznetsova M, Ogola G, et al. Increasing health care burden of chronic liver disease compared with other chronic diseases, 2004–2013. Gastroenterology 2018;155(3):719–29.e4.
6. Schmidt ML, Barritt AS, Orman ES, et al. Decreasing mortality among patients hospitalized with cirrhosis in the United States from 2002 through 2010. Gastroenterology 2015;148(5):967–77.e2.
7. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. Gastroenterology 2009;136(4): 1134–44.
8. Allen AM, Kim WR, Moriarty JP, et al. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. Hepatology 2016;64(6):2165–72.
9. Neff GW, Duncan CW, Schiff ER. The current economic burden of cirrhosis. Gastroenterol Hepatol (N Y) 2011;7(10):661–71.
10. Moon AM, Green PK, Berry K, et al. Transformation of hepatitis C antiviral treatment in a national healthcare system following the introduction of direct antiviral agents. Aliment Pharmacol Ther 2017; 45(9):1201–12.
11. Introduction to HCUP National Inpatient Sample (NIS). https://www.hcupus.ahrq.gov/db/nation/nis/NIS_Introduction_2015.pdf. Published 2015. Accessed December 20, 2018.
12. Mellinger JL, Richardson CR, Mathur AK, et al. Variation among United States hospitals in inpatient mortality for cirrhosis. Clin Gastroenterol Hepatol 2015;13(3):577–84.
13. Nguyen GC, Segev DL, Thuluvath PJ. Nationwide increase in hospitalizations and hepatitis C among inpatients with cirrhosis and sequelae of portal hypertension. Clin Gastroenterol Hepatol 2007;5(9):1092–9.
14. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Med Care 1998;36(1):8–27.
15. SAS Software Version 9.4. Cary, NC: SAS Institute, Inc., 1999.
16. R: The R Project for Statistical Computing. https://www.r-project.org/. Accessed December 20, 2018.
17. Mellinger JL, Scott Winder G, DeJonckheere M, et al. Misconceptions, preferences and barriers to alcohol use disorder treatment in alcohol-related cirrhosis. J Subst Abuse Treat 2018;91:20–7.
18. Lee CS, Chien CV, Bidwell JT, et al. Comorbidity profiles and inpatient outcomes during hospitalization for heart failure: An analysis of the U.S. Nationwide inpatient sample. BMC Cardiovasc Disord 2014;14:73.
19. Myers RP, Quan H, Hubbard JN, et al. Predicting in-hospital mortality in patients with cirrhosis: Results differ across risk adjustment methods. Hepatology 2009;49(2):568–77.
20. Hughes JS, Iezzoni LI, Daley J, et al. How severity measures rate hospitalized patients. J Gen Intern Med 1996;11(5):303–11.
21. Jencks SF, Williams DK, Kay TL. Assessing hospital-associated deaths from discharge data. JAMA 1988;260(15):2240.
22. Han X, Edelson DP, Snyder A, et al. Implications of Centers for Medicare & Medicaid Services severe sepsis and septic shock early management bundle and initial lactate measurement on the management of sepsis. Chest 2018;154(2):302–8.
23. Gong MN, Schenk L, Gajic O, et al. Early intervention of patients at risk for acute respiratory failure and prolonged mechanical ventilation with a checklist aimed at the prevention of organ failure: Protocol for a pragmatic stepped-wedged cluster trial of PROOFCheck. BMJ Open 2016;6(6):e011347-7.
24. Alam N, Hobbelink EL, van Tienhoven AJ, et al. The impact of the use of the Early Warning Score (EWS) on patient outcomes: A systematic review. Resuscitation 2014;85(5):587–94.
25. Gaetano JN, Micic D, Aronsohn A, et al. The benefit of paracentesis on hospitalized adults with cirrhosis and ascites. J Gastroenterol Hepatol 2016;31(5):1025–30.
26. De Pietri L, Bianchini M, Montalti R, et al. Thrombelastography-guided blood product use before invasive procedures in cirrhosis with severe coagulopathy: A randomized, controlled trial. Hepatology 2016;63(2): 566–73.
27. Goldberg D, Lewis J, Halpern S, et al. Validation of three coding algorithms to identify patients with end-stage liver disease in an administrative database. Pharmacoepidemiol Drug Saf 2012;21(7):765–9.
28. Tapper EB, Finkelstein D, Mittleman MA, et al. Standard assessments of frailty are validated predictors of mortality in hospitalized patients with cirrhosis. Hepatology 2015;62(2):584–90.