Hepatic Encephalopathy is a Strong Predictor of Early Hospital Readmission Among Cirrhosis Patients

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Background & aims: Cirrhosis is a leading cause of morbidity and mortality in the United States. Early readmission to the hospital after discharge increases the clinical and economic burden of cirrhosis patients. We aim to evaluate the prevalence and predictors of early hospital readmission among cirrhosis patients among an underserved safety-net health system. **Methods:** All consecutive adults with cirrhosis seen at the gastroenterology clinics at our safety-net health system from 2014 to 2016 were retrospectively evaluate to determine rates of 30-day readmission after hospital discharge. Comparison of readmission rates between groups used chi-square testing. Overall predictors of 30-day hospital readmission were evaluated using multivariate logistic regression models, with variables included in the model selected a priori based on clinical significance to the outcome. **Results:** Among 230 cirrhosis patients (63.5% men, 80.6% were nonwhite minorities), 27.1% had chronic hepatitis C virus; 16.0%, chronic hepatitis B virus; 34.2%, alcoholic cirrhosis; and 8.0%, nonalcoholic steatohepatitis. Overall 30-day hospital readmission rates were 31.3%. There was a trend towards higher rates of 30-day readmission in men than in women (23.9% vs. 7.4%, $P = 0.075$) and trend towards higher readmission in Hispanics than in non-Hispanic whites (35.3% vs. 14.3%, $P = 0.093$). On multivariate regression, hepatic encephalopathy was the strongest positive predictor of early 30-day hospital readmission (odds ratio 4.40, 95% confidence interval 1.25–7.28, $P = 0.02$). **Conclusions:** Among underserved safety-net cirrhosis patients, 30-day hospital readmission rates were over 30%. Given that presence of hepatic encephalopathy was most strongly correlated with readmissions, targeted interventions to improve management of hepatic encephalopathy may have the greatest impact on improving cirrhosis-related outcomes. (J CLIN EXP HEPATOL 2019;9:484–490)

Cirrhosis and cirrhosis-related complications contribute to significant morbidity and mortality.¹ According to the Centers for Disease Control and Prevention National Health Center for Health Statistics, 3.9 million adults are diagnosed with chronic liver disease in the United States, and approximately 40,326 deaths per year in the United States are attributed to chronic liver disease and cirrhosis.² Cirrhosis is associated with high health-care resource utilization, a major contributor of which is a result of potentially preventable hospitalizations.^{3–8} This increased resource utilization among patients with cirrhosis has been estimated at > \$17 billion per year in the Medicare population.⁷ Patients with decompensated cirrhosis have significantly

higher risk of early hospital readmission within the first month after discharge, with some studies reporting 1-month readmission rates nearing 40%.^{4,7,9} Hospital readmission rates are not only a significant economic burden to the health-care system but recurrent hospitalizations are also associated with increased morbidity and mortality in cirrhosis patients.^{4,7,10}

Increased rates of hospital readmission among cirrhosis patients have been previously reported. Tapper et al⁶ evaluated a large cohort of 130,455 cirrhosis patients who were admitted to hospitals across six regions in the United States in 2011. Overall 30-day and 90-day hospital readmission rates were 12.9% and 21.2%, respectively. Although increasing number of cirrhosis-related complications and comorbidities was associated with higher risk of hospital readmission, the investigators noted that presence of hepatic encephalopathy was the strongest predictor of recurrent hospitalizations. Similar findings were reported in additional cohorts of decompensated cirrhosis patients, all concluding that not only were rates of readmission high but presence of cirrhosis-related complications were strong predictors of risk of readmission.^{4,7,11}

Cirrhosis patients among underserved safety-net health systems are even more vulnerable populations. Although inherent system barriers already contribute to impaired access to care, cirrhosis patients among this complex safety-

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Abbreviations: HBV: hepatitis B virus; HCV: hepatitis C virus

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net system are even more disadvantaged, and we hypothesize that these populations will have high rates of hospital readmission as well. Given the importance of consistent post-hospital discharge follow-up care and maintenance of therapy for managing cirrhosis complications, we hypothesize that, among safety-net settings, cirrhosis-related complications such as ascites and hepatic encephalopathy will be strong predictors of early, potentially preventable hospital readmissions. Furthermore, underserved high-risk populations that utilize safety-net health-care systems are at greatest risk of cirrhosis readmissions, and understanding predictors of readmission among this population may have the greatest potential to improve outcomes. Thus, our study aims to evaluate prevalence of predictors of early hospital readmission among cirrhosis patients at a large safety-net health-care system.

METHODS

We retrospectively evaluated all consecutive adults (age ≥ 18) with cirrhosis from July 1st, 2014 to December 31st, 2016, seen in gastroenterology and hepatology clinics to determine the rates of all-cause hospital readmission after hospital discharge at a large urban safety-net hospital. Our cohort is particularly unique in that the majority of this underserved population lives at or below the national poverty level and the majority are nonwhite minorities. The diagnosis of cirrhosis was determined through a thorough review of the electronic medical records and incorporated data from the clinical history from inpatient and outpatient chart notes, laboratory data, radiographic data, and liver biopsy data if available. Although our goal was to determine all-cause cirrhosis-related readmissions, we also collected presence of liver-related comorbidities at each hospitalization to determine the potential association between the presence of these co-morbidities and the likelihood of all-cause cirrhosis-related hospital readmission.

Overall rates of 30-day hospital re-admission were determined via retrospectively evaluating all clinical encounters of cirrhosis patients within our system. Although there is a possibility that patients utilized hospitals outside of our system, we acknowledge that the majority of our patients are underserved, Medicaid or uninsured populations who utilize the clinical facilities within our system as their primary source of medical care, thus minimizing the impact of this potential ascertainment bias. Hospitalization readmission rates were further stratified by sex, race/ethnicity, insurance status, underlying etiology of liver disease, and severity of cirrhosis as measured by Childs-Pugh score. In addition, we specifically evaluated the impact of concurrent ascites and hepatic encephalopathy or risk of rehospitalization after hospital discharge.

Baseline patient demographic and clinical characteristics were presented proportions (%) and frequencies (N) for categorical variables and mean and standard deviation or median and range for continuous variables. In addition to overall rates of 30-day rehospitalization rates, we evaluated more specific data for each hospitalization including length of hospital stay (days) and time to next hospitalization after discharge (days). Comparison of 30-day rehospitalization rates between groups utilized chi-square testing. Overall predictors of 30-day rehospitalization after discharge were evaluated with multivariate logistic regression analyses. Variables selected for inclusion in the final multivariate model included age and sex (selected a priori) as well as variables that demonstrated significance in the univariate model with $P < 0.10$. Statistical analyses were performed using Stata statistical software package (version 14.0), and statistical significance was met with P -value < 0.05 . This study was approved by the Alameda Health System Institutional Review Board.

RESULTS

Overall, our study included 230 cirrhosis patients (63.5% were male, 80.6% were nonwhite minorities [22.3% African-American, 28.6% Hispanic, 28.0% Asian]) (Table 1). The majority of our cirrhosis patients were insured by Medicaid (48.1%) or Medicare (25.9%). When evaluating by etiology of liver disease, 27.1% had chronic hepatitis C virus (HCV), 16.0% chronic hepatitis B virus (HBV), 34.2% alcoholic cirrhosis, and 8.0% nonalcoholic steatohepatitis. Forty-eight percent of patients had Child's A cirrhosis, and 32.4% had Child's B cirrhosis. Prevalence of major complications included ascites (43.9%), gastroesophageal varices (48.7%), hepatocellular carcinoma (13%), and spontaneous bacterial peritonitis (3.5%). When stratified by liver disease etiology, differences were noted in the severity of liver disease as measured by Childs score (% of patients with Child's C cirrhosis: 10.3% for HCV vs. 8.3% for HBV vs. 29.0% for alcoholic cirrhosis vs. 33.3% for combined HCV and alcoholic cirrhosis, and 16.7% for nonalcoholic steatohepatitis (NASH), $P < 0.05$).

Characteristics of hospitalizations evaluated included mean length of hospitalization and number of discharge medications. Overall, mean length of hospital stay during the first recorded hospitalization was 6.0 days (standard deviation [SD] 6.3) with mean number of discharge medications at 5.5 prescriptions (SD 3.4) (Table 2). Median time to first rehospitalization after discharge was 756 days (range 6–1791) (Table 2). Additional characteristics of subsequent hospitalizations are presented in Table 2.

The observed overall 30-day readmission rate was 31.3% among all cirrhosis patients. There was a trend towards higher rates of 30-day readmission in men than in women

Table 1 Characteristics of the Study Cohort.

Variable	Percent (%)	Frequency (N)
Age, mean (SD)	57.3 (10.1)	
Sex		
Female	36.5	84
Male	63.5	146
Race/ethnicity		
Non-Hispanic white	19.4	34
African-American	22.3	39
Hispanic	28.6	50
Asian	28.0	49
Other	1.7	3
Housing		
Homeless	3.1	7
Housed	96.9	222
Primary insurance		
Medicaid	48.1	65
Medicare	25.9	35
Uninsured	17.8	24
Commercial/private	8.2	11
Etiology of cirrhosis		
Hepatitis C virus	27.1	61
Hepatitis B virus	16.0	36
Alcoholic cirrhosis	34.2	77
Hepatitis C virus and alcoholic cirrhosis	9.3	21
Nonalcoholic steatohepatitis	8.0	18
Other	5.3	12
Childs–Pugh class		
Childs A	48.0	108
Childs B	32.4	73
Childs C	19.6	44
Ascites	43.9	101
Varices	48.7	112
Hepatocellular carcinoma	13.0	30
Spontaneous bacterial peritonitis	3.5	8
Other comorbidities		
Diabetes mellitus	30.0	69
Hypertension	39.6	91
Alcohol use	67.4	155

SD, standard deviation.

(23.9% vs. 7.4%, $P = 0.075$) (Table 3). Compared with non-Hispanic whites with cirrhosis, 30-day readmission rates were lower in African-Americans (7.1% vs. 14.3%, $P = 0.093$) and higher in Hispanics (35.3% vs. 14.3%, $P =$

0.093). Thirty-day hospital readmission rate was 33.3% among cirrhosis patients with alcoholic liver disease, and this group accounted for all of the readmissions among the entire cohort. The observation that all 30-day readmissions were observed only in those patients with alcoholic cirrhosis may be related to these patients having overall more severe liver disease at the time of first hospitalization as determined by Childs score. Although presence of ascites and variceal bleeding was not associated with significantly higher rates of 30-day readmission, cirrhosis patients with hepatic encephalopathy had significantly higher 30-day readmission compared with cirrhosis patients without hepatic encephalopathy (33.3% vs. 10.2%, $P = 0.015$) (Table 3). When stratified by liver disease etiology, 90-day all-cause hospital readmission rates were 37.5% for HCV, 48.5% for alcoholic cirrhosis, and 33.3% for those with combined HCV and alcoholic cirrhosis, $P = 0.10$.

On multivariate logistic regression analyses, presence of hepatic encephalopathy was associated with significantly higher risk of 30-day hospital readmission (OR 4.40, 95% CI 1.25–7.28, $P = 0.02$). No sex-specific and race/ethnicity-specific disparities in risk of 30-day hospital readmission were observed (Table 4).

DISCUSSION

Among a cohort of diverse, underserved cirrhosis patients among a safety-net health-care system, overall 30-day readmission rate was 31.3%. Cirrhosis patients who were previously admitted for hepatic encephalopathy were over four times more likely to be readmitted within 30-days compared with patients without hepatic encephalopathy.

Despite our high-risk safety-net population, our observed rates of early hospital readmission were similar to rates from previous studies.^{4,6,7} The high rates of hospital readmission among cirrhosis patients is not only concerning because of the increased morbidity and mortality associated with recurrent hospitalizations but the significant healthcare economic burden contributed by these potentially preventable hospitalizations are also staggering.^{12–14} The economic burden of caring for cirrhosis patients includes direct costs and indirect costs. Direct costs such as drugs and hospitalizations are significant, whereas indirect costs are even more monumental. In 2004, direct costs associated with management of cirrhosis and chronic liver diseases in the United States were estimated at \$2.5 billion. During this same time, indirect costs were estimated at \$10.6 billion.¹³ These costs are expected to have increased, and along with the aging population of patients with chronic liver disease and cirrhosis, the societal burden of cirrhosis in the United States has grown significantly.^{13,14}

Table 2 Characteristics of Hospitalizations Among Cirrhosis Patients.

	Mean	Standard deviation	Median	Range
1st hospitalization				
Length of stay (days)	6.0	6.3	12	1–40
Number of discharge medications	5.5	3.4	6.5	0–17
Time to next hospitalization (days)	345.8	460.7	756	6–1791
2nd hospitalization				
Length of stay (days)	5.1	7.2	11	1–46
Number of discharge medications	6.1	3.8	7.5	1–22
Time to next hospitalization (days)	178.4	197.3	283	5–793
3rd hospitalization				
Length of stay (days)	7.4	13.3	14.5	1–88
Number of discharge medications	7.0	3.2	7.5	1–13
Time to next hospitalization (days)	166.6	191.6	221	4–731
4th hospitalization				
Length of stay (days)	4.2	4.1	5.5	1–21
Number of discharge medications	7.7	3.3	7	1–18
Time to next hospitalization (days)	115.3	139.4	134	5–603

Similar to previous studies, our present study also demonstrated that the presence of hepatic encephalopathy was the strongest predictor of early readmission to the hospital.^{4,6,7,9,11} This consistent observation across studies and across different cohorts is important for several reasons. First, it validates the important predictive ability of hepatic encephalopathy on recurrent hospitalizations. This emphasizes that not only hepatic encephalopathy is highly prevalent in cirrhosis populations but the symptoms of hepatic encephalopathy have debilitating effects that lead to such significant clinical deterioration that one would need to be hospitalized. Furthermore, these observations identify an important opportunity by which quality improvement interventions could be implemented to improve hepatic encephalopathy management, which would directly translate into improvements in readmission and cirrhosis-related outcomes. For example, Tapper et al⁵ implemented a quality improvement program to improve the management of cirrhosis patients with hepatic encephalopathy. Eight hundred twenty-four unique patients with decompensated cirrhosis admitted to the liver unit from 2010 to 2013 were prospectively evaluated to determine the impact of implementing a graded quality improvement initiative to reduce hepatic encephalopathy-related hospital readmissions. Through first implementation of a checklist to ensure appropriate management of hepatic encephalopathy, including correct medications and dose titrations, the investigators then implemented this checklist into a

provider order entry system in the electronic health records. Incorporation of this quality improvement checklist into the electronic health records decreased cirrhosis admissions for grade 2 or higher hepatic encephalopathy from 48.9% to 26.0% and resulted in overall 40% reduced odds of 30-day readmission compared with the control group. These observations highlight the potential for a systematic targeted quality improvement program to significantly improve hepatic encephalopathy management and overall cirrhosis-related outcomes.^{5,11}

Another important factor influencing hospital readmission rates among cirrhosis patients involves suboptimal patient awareness and understanding of their disease process. A study by Volk et al⁷ reported that 22% of readmissions can be attributed to inadequate patient education about medication dosing (especially in regards to adjusting lactulose) or lack of prompt follow-up labs or clinic visits to adjust diuretics. Among 402 patients with decompensated cirrhosis, 69% of patients had at least one nonelective hospital readmission, with a median time to first readmission of 67 days. By one week after discharge, 14% of subjects had been readmitted, and 37% were readmitted within one month. Among the 165 readmissions within 30 days, the investigators noted that 22% of those were possibly preventable through better patient understanding of medication regimen or by more intensive outpatient monitoring.⁷

Despite the inclusion of an important cohort of high-risk underserved safety-net cirrhosis patients, our study

Table 3 Rates of Early Readmission Within 30-Days of Discharge.

Variables	30-day Readmission (%)	P-Value
Sex		0.075
Female	7.4	
Male	23.9	
Race		0.093
White	14.3	
African/black	7.1	
Hispanic	35.3	
Asian	0	
Other	17.3	
Insurance status		0.201
Medicaid	4.7	
Medicare	22.2	
Uninsured/indigent care	33.3	
Commercial	0	
Etiology of liver disease		0.012
HCV	0	
HBV	0	
Alcoholic liver disease	33.3	
HCV/Alcoholic liver disease	0	
NASH	0	
Childs-Pugh Score		0.81
A	17.7	
B	15.4	
C	22.2	
Cirrhosis-related complications		
Ascites	25	0.205
Hepatic encephalopathy	33.3	0.015
Variceal bleeding	13.0	0.47

HCV, hepatitis B virus; HBV, hepatitis C virus

has limitations that should be acknowledged. As with all observation type studies, although our present study identified significant associations, including a strong association of hepatic encephalopathy with risk of early readmission, these observations cannot necessarily reflect direct causation. We acknowledge that the management of cirrhosis patients is complex and there likely exists many measured and unmeasured confounders that impact risk of early readmission after hospital discharge. As such, it was not possible for us to determine with confidence the exact cause of each hospital readmission. However, our data provide important data about risk factors associated with increased risk of readmission.

Table 4 Multivariate Logistic Regression Model Evaluating Early Hospital Readmission.

Variables	Odds ratio (%)	95% CI	P-value
Male (vs. female)	3.93	0.80–19.30	0.092
Age	1.03	0.97–1.09	0.32
Non-Hispanic White	1.00	Reference	–
African-American	0.46	0.04–5.77	0.55
Hispanic	3.27	0.54–19.75	0.20
Body mass index	1.03	0.27–3.90	0.97
Medicaid	1.00	Reference	–
Medicare	5.71	0.45–73.19	0.18
Uninsured	10.00	0.72–138.68	0.09
Child's A	1.00	Reference	–
Child's B	0.85	0.16–4.37	0.84
Child's C	1.33	0.29–6.23	0.72
MELD Score	1.04	0.95–1.15	0.39
Ascites	2.17	0.64–7.28	0.21
Hepatic encephalopathy	4.40	1.25–7.28	0.02
Diabetes mellitus	0.52	0.13–2.09	0.36

CI, confidence interval; MELD, model for end stage liver disease.

Improved management of these complications may translate into lower rates of hospital readmission. This is particularly relevant for patients with alcoholic cirrhosis who may have been readmitted for encephalopathy from other etiologies such as metabolic encephalopathy or delirium. Thus, although severity of liver disease and underlying etiology of liver disease was included in the multivariate model, these limitations should be considered when evaluating the outcomes of this study. As previously mentioned, it is possible that cirrhosis patients in our cohort may have utilized health-care facilities not within our system. While possible, the impact of this is likely minimal, given that the majority of our cohort are Medicaid or uninsured populations that utilize our safety-net system as their primary source of health care. Even so, if some patients did, in fact, utilize hospitals that were not captured, this would only bias our results towards the null hypothesis, and thus the true rates of early readmission in our cohort would be even higher. Although the analysis of an ethnically diverse safety-net population is a strength of our study, these findings may not be completely generalizable to practice settings that are different from our population. Furthermore, we observed a significant association of hepatic encephalopathy with early readmission. While all patients with hepatic encephalopathy were prescribed both lactulose and rifaximin for secondary prophylaxis,

we were not able to evaluate whether patients were actually taking prescribed therapies. Given that our study population consists of an underserved safety-net population, our relatively high hospital readmission rates among cirrhosis patients may actually reflect high hospital readmission rates for chronic diseases in general. However, we were not able to capture hospital readmission rates for other chronic diseases (e.g. congestive heart failure, chronic obstructive pulmonary disease), and thus, we could not make direct comparisons of hospital readmission rates in our cirrhosis patients compared with patients with other chronic diseases. Furthermore, the decision to admit or not admit patients directly influences our assessment of readmission rates. While decisions related to hospital admission include a comprehensive assessment of the clinical presentation that incorporates hemodynamic stability, presence of comorbidities, laboratory abnormalities, and discussion with specialists, we acknowledge that there may be variations in thresholds to consider hospital admission that may have introduced some degree of bias into our outcomes. Furthermore, while we assessed complications that were present during each hospitalization, given the limitations of the retrospective observational study design, it was challenging to determine with high accuracy the exact precipitating etiology for hospitalization or specific cirrhosis-related complications. It is also important to note that, while our identification of complications such as hepatic encephalopathy was based on review of the clinical records, this type of observational study design does include the possibility of introducing misclassification bias. For example, recurrent hospitalizations in alcoholic cirrhosis patients who were classified as having hepatic encephalopathy may have potentially been confounded by concurrent alcohol intoxication, Wernicke's encephalopathy, or multifactorial delirium. Despite these limitations, our findings provide important data to further add to the literature as it relates to management of cirrhosis patients in the community setting.

In conclusion, among our underserved safety-net cirrhosis population, we observed high rates of 30-day readmission that were similar to previously reported data from different practice settings. We also observed that the presence of hepatic encephalopathy is independently associated with more than four times increased risk of hospital readmission within 30-days of discharge. Implementing a multidisciplinary and targeted intervention to improve quality and consistency of care for management of hepatic encephalopathy in the outpatient settings, particularly in the immediate post-hospital discharge setting, has potential to reduce hospital readmission rates,

reducing morbidity and mortality among high-risk cirrhosis populations, particularly underserved safety-net populations that already experience significant barriers in timely access to medical care.

CONFLICTS OF INTEREST

R.J.W is a member of the advisory board of and speaker's bureau for and received research from grants from Gilead Sciences; received research grants from Abbvie; member of speaker's bureau for Salix, Bayer. The other author has nothing to declare.

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AUTHOR CONTRIBUTION

K.T.S. has contributed in analysis and interpretation of data and critical revision of the manuscript for important intellectual content and has approved the final draft submitted. R.J.W. has contributed in study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, statistical analysis, and study supervision and has approved the final draft submitted.

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