March 22nd, 2023

Dear editors,

Thank you for provisionally accepting our paper entitled, “Randomized Intervention and Outpatient Follow-Up Lowers 30-day Readmissions for Patients with Hepatic Encephalopathy, Decompensated Cirrhosis” to your esteemed journal. We addressed all the advice recommended by the reviewers. Please find below our responses to the reviewers comments.

1. Reviewer 1
    a. Language correction and formatting completed throughout the manuscript. All of these changes can be seen in the track change version of the manuscript below. The clean manuscript follows.
    b. The following citations were added as per the suggestion in the discussion section of manuscript:
        i. Bajaj etal 2019
        ii. Tapper et al 2017
        iii. Chirapongsathorn et al 2016
        iv. Kanwal et al 2016
        v. Frenette et al 2022
2. Reviewer 2
    a. Reviewer has pointed to removing the unnecessary information about the COVID-19 from the manuscript. We removed the unnecessary information and only left pertinent information to show how it limited our ability to recruit patients for our trial.
    b. Grammatical errors including punctuation in Table 3 and 6 have also been fixed.

Of note, our authors signature page is below.

We hope that with addition of information and guidance provided by reviewers, our manuscript quality has further improved. Please let us know if there are any questions.

Sincerely on behalf of all co-authors,

Antoinette Pusateri, MD

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4 SIGNATURES OF ALL AUTHORS

This declaration must be signed by all authors. The manuscript will be rejected immediately if we find the declaration was not signed by authors themselves. The signature list for all authors is as follows:

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TITLE PAGE

Study Title: Randomized Intervention and Outpatient Follow-Up Lowers 30-day Readmissions for Patients with Hepatic Encephalopathy, Decompensated Cirrhosis

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Kevin Litzenberg, Claire Griffiths, Caitlin Hayes, Bipul Gnyawali and Michelle Manious – recruiting patients for study, drafting manuscript; approved the final submitted version of manuscript.

Sajid Jalil, Sean Kelly and Lanla Conteh—Reviewed and edited the final draft of the manuscript.

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Haikady N. Nagaraja– analyzed data, edited manuscript, and approved the final submitted version of this manuscript.

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Potential competing interests:

There no competing interests declared by the authors.

ABSTRACT

Background

We previously reported national 30-day readmission rates of 27% in patients with decompensated cirrhosis (DC).

Aims

We studied prospective interventions to reduce early readmissions in DC at our tertiary center.

Methods

Adults with DC admitted July 2019 to December 2020 were enrolled and randomized into the intervention (INT) or standard of care (SOC) arms. Weekly phone calls for a month were completed. In the INT arm, case managers ensured outpatient follow-up, paracentesis, and medication compliance. Thirty-day readmission rates and reasons were compared.

Results

Calculated sample size was not achieved due to COVID-19; 240 patients were randomized into INT and SOC arms. 30-day readmission rate was 33.75%, 35.83% in the INT versus 31.67% in the SOC arm (p=0.59). The top reason for 30-day readmission was hepatic encephalopathy (HE, 32.10%). There was a lower rate of 30-day readmissions for HE in the INT (21%) versus SOC arm (45%, p=0.03). There were fewer 30-day readmissions in patients who attended early outpatient follow-up (n=17, 23.61% v. n=55, 76.39%, p=0.04).

Conclusions

Our 30-day readmission rate was higher than the national rate but reduced by interventions in patients with DC with HE and early outpatient follow-up. Development of interventions to reduce early readmission in patients with DC is needed.

Keywords: decompensated cirrhosis; hospital readmissions; interventions

INTRODUCTION

Cirrhosis affects approximately 5 million annually[1] and has been reported to be the 8th leading cause of death with more than 40,000 deaths annually in the United States.[2] A study on the burden of gastrointestinal, liver, and pancreatic diseases in the United States revealed that liver diseases had the highest mortality at 3.1%.[3] In addition to high mortality, cirrhosis is also associated with high morbidity. The sequelae of decompensated cirrhosis (DC) are often managed during hospital admissions and include volume overload in the form of ascites, edema or hepatic hydrothorax, portal hypertension leading to bleeding esophageal or gastric varices, as well as hepatic encephalopathy (HE), hyponatremia, acute kidney injury (AKI), and spontaneous bacterial peritonitis (SBP).[4]

Several studies have demonstrated hospital readmissions in DC place a large financial burden on the United State healthcare system. The 30-day readmission rate has been reported to be 20%-37%.[5-14] We have recently published on early readmission rates up to 27% in patients with DC and developed the Mumtaz readmission risk score based on United States data.[15] We also reported that nearly one-third of patients with HE were readmitted within 30 days, and early readmission adversely impacted healthcare utilization and calendar-year mortality.[16]

Interventions to reduce readmissions have been shown to be safe and effective. For instance, Morales et al. developed HEPACONTROL program including a hepatologist follow-up exam within 7 days after discharge. This program resulted in a reduction in 30-day readmissions, 60-day mortality, emergency department visits and associated costs.[17] Similarly, another group demonstrated that follow-up with a “care management check-up” as opposed to “standard

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outpatient care" reduced 30-day readmission, 12-month mortality and saved 1500 euros per patient month of life.[18]

There is a paucity of prospective studies on interventions to reduce early readmission rates in patients with DC. Therefore, we prospectively studied 30-day readmission rates in patients with DC and compared various interventions (INT) with standard of care (SOC) to reduce early readmission rates. We hypothesized that DC patients in the INT arm would have decreased 30-day readmission versus the SOC arm.

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METHODS

This study was conducted at the Ohio State University Wexner Medical Center (OSUWMC), Columbus, Ohio from July 2019 to December 2020. Our study was approved by OSUWMC Institutional Review Board. All aspects of the studying involving human participants including informed consent for enrollment were in accordance with the ethical standards of our Institutional Review Board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Screening

All patients admitted with DC to the hepatology (inpatient or consult) service were screened for enrollment. Patients meeting inclusion criteria were approached for study consent. Of note, due to the global COVID-19 pandemic, beginning March 2020, only COVID negative patients were approached for informed consent. Elective readmissions for inpatient procedures including endoscopy, trans-arterial chemoembolization (TACE), transjugular intrahepatic portosystemic shunt (TIPS), paracentesis or readmissions unrelated to DC such as motor vehicle accidents were excluded.

Randomization and Data Collection

Study data were collected and managed using REDCap hosted at The Ohio State University Wexner Medical Center.[19,20] Informed consent was obtained from all individual participants included in the study. Consented patients were randomly assigned to either the INT arm or the SOC arm in a 1:1 ratio using the RedCap randomization tool. The following data were collected on all patients via RedCap software including demographics (age, sex, insurance type, income

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based on the zip code), hospitalization data (date of index admission defined as initial admission during which patient consented for study, reason for admission, length of stay (LOS) defined as difference in days between index admission date and index admission discharge date, discharge disposition, associated cost of care of admission as obtained through medical record billing tab), etiology of cirrhosis (alcoholic and non-alcoholic including viral, non-alcoholic fatty liver disease, autoimmune, primary biliary cirrhosis, primary sclerosing cholangitis or cryptogenic), complications of cirrhosis {HE, AKI, ascites, variceal bleeding, SBP, hepatorenal syndrome (HRS), coagulopathy, portal hypertension, hepato-pulmonary syndrome (HPS), hepatocellular carcinoma (HCC)}, and procedures performed during admission {esophago-gastro-duodenoscopy (EGD), colonoscopy or flexible sigmoidoscopy, paracentesis, transjugular intrahepatic portosystemic shunt (TIPS) and hemodialysis (HD) on admission and discharge}. We also collected data including Elixhauser comorbidity index, discharge medications, and laboratory data (complete blood counts, serum creatinine, liver function tests including total bilirubin, INR, and sodium). Child Turcotte Pugh (CTP) and Sodium-model for end stage liver disease (MELD-Na) score were calculated from the data. The nurse case manager (CM) also recorded labs & medications at readmission & discharge and associated cost of readmission. Status of early readmission, liver transplantation, and mortality at one year were also collected.

Follow-up

The CM phoned each patient enrolled in either arm weekly for 30 days after index discharge to find out if the patient has been readmitted to OSUWMC or another hospital. In the INT arm, during the call CM also ensured i) early (defined as within 30 days from index admission discharge) outpatient hepatology follow-up ii) compliance of medication, iii) arrangement of

outpatient paracentesis if needed, and reviewed outpatient hepatology clinic follow-up records. SOC arm as per our center's protocol had to be taken care of by the primary inpatient team. This included arranging early outpatient clinic follow-up, providing list of medications, and advice for outpatient paracentesis if needed at the time of discharge. Due to the nature of intervention, the study could not be blinded.

Definition of outcomes

Early readmission was defined as admission within 30 days of index admission discharge. Reasons for readmission were gathered by CM by reviewing the electronic medical record (EMR) of all enrolled patients readmitted at OSUWMC or outside hospital within 30 days of index admission. Predictors of early readmission were also compared in the two arms.

Sample Size

Based on the sample size calculation, target of recruitment for the study was 848 patients, admitted to the hospital with DC under the hepatology (inpatient and consult) services. Patients were randomly assigned in a 1:1 ratio into INT or SOC arms. Based on our previous study using the NRD administrative database, we expected a 30-day readmission rate of 27% among patients meeting inclusion criteria, which yield 114/424 patients with 30-day readmission events, thus meeting the target sample size. Based on this calculation, a total sample size of 848 (424 per group) provided 80% power to detect a 30% decrease in 30-day readmission rate (from 27% to 19%) with a type I error rate of 0.05. However, planned sample size could not be achieved due to the COVID-19 pandemic related restriction started in our center in March 2020. Therefore, we

end up with available sample size of a total of 240 patients. The modified CONSORT Flow diagram for enrollment in our study trial is illustrated in Figure 1.

Statistical analysis:

Means of continuous response variables between two groups were compared using robust t-test (Welch test). Proportions were compared using Chi-square or Fisher's exact test as applicable. Logarithmic transformation was used for comparing the length of stay (LOS) and admission cost across groups. Level of significance was kept at 0.05 for each comparison. JMP Version 15 (SAS Institute, NC) was used for all the analyses.

RESULTS

Initial Screening Data

From July 1, 2019, to December 1, 2020, 1392 patients were screened. Due to the COVID-19 pandemic, recruitment was held from March 2020 to July 2020 and subsequently resumed until December 2020. Out of the patients screened, only 499 (35.85%) were eligible for inclusion; however, 240 patients consented and randomized: 120 each into the INT and SOC arm (Figure 1).

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Patient demographics and clinical characteristics

The mean age of patients was 56.34±11.19 years, majority were males (135, 56.25%), belonged to White race (n=202, 84.17%) and non-Hispanic or Latino ethnicity (n=227, 94.58%). Almost two-thirds of the patients had public insurance (n=76, 31.67% on Medicare and n=70, 29.17% on Medicaid); 73 (30.42%) had private insurance. At admission, the mean MELD-Na score and mean Child Pugh Score were 21.89±8.03 and 9.36±1.96, respectively. Major etiology of cirrhosis was alcohol (n=121, 50.42%) followed by non-alcoholic fatty liver disease (n=79, 32.92%) and viral hepatitis (n=43, 17.92%). Furthermore, 116 (48.33%) patients were actively under evaluation for liver transplantation.

Characteristics of index admissions

The index admission mean LOS was 8.13±5.83 days (median 6, range 1-43 days). The mean cost of index admission was $60,595±$47,174 (n=225, median $42,932, range $1,630-251,991). The top five reasons for index admission included volume overload (n=111, 46.25%), acute kidney injury (n=65, 27.08%), hepatic encephalopathy (n=45, 18.75%), variceal bleed (n=42, 17.50%),

lower GI bleed (n=19, 7.92%) and hyponatremia (n=16, 6.67%). The top five interventions performed were EGD (n=136, 56.67%), paracentesis (n=115, 47.92%), colonoscopy/flexible sigmoidoscopy (n=24, 10 %), hemodialysis (n=15, 6.25%) and TIPS (n=10, 4.17%). Most patients were discharged from index admission to home (n=159, 66.25%) followed by home with health care (n=42, 17.50%) and skilled nursing facility (n=32, 13.33 %, Table 1).

Characteristics and reasons for early readmissions

Overall, 81 (33.75%) patients were readmitted within 30 days of discharge. The major reasons for first readmission included hepatic encephalopathy (n=26, 32.10%) followed by volume overload (n=22, 27.16%), acute kidney injury (n=16, 19.75%), variceal bleed (n=12, 14.82%) and hyponatremia (n=10, 12.35%). 14 patients were readmitted twice, 3 admitted thrice and one admitted 5 times within 30 days. The mean time to first readmission was 12.65±7.55 days (median 12 days, range 1-30 days). The mean length of stay of first readmission was 8.11±8.98 days. The mean cost of stay of first readmission was $55,548.29 ± $65,164.91 (Table 2). Those readmitted had a higher MELD score on index admission (23.54±7.80 v. 21.05±8.03, p=0.02) and index discharge (21.67±7.95 v. 19.39±6.89, p=0.03) than those not readmitted. Similarly, those readmitted had a higher index admission creatinine (1.80±1.53 v 1.39±1.16, p= 0.03), index discharge creatinine (1.61±1.34 v, 1.20±0.97, p=0.02), and higher index admission INR (1.80±0.64 v. 1.63±0.50, p=0.05) than those not readmitted.

Comparison of demographics and clinical characteristics in two intervention arms

Demographics including age, race, ethnicity, income, and insurance were comparable in two groups, as well as etiology of cirrhosis, MELD-Na score, CTP score, status of evaluation for

liver transplant. There were majority females in the INT arm (60/120, 50% v. 45/120, 32.50%) and males in SOC arm (75/120, 62.50% v. 60/120, 50%, p=0.03, Table 3). Index admission characteristics, disposition and index admission were also comparative in two arms (Table 4 and Table 5)

Comparison of reasons of 1st readmission and outcomes in the INT v SOC arm

There was no difference in the readmission rates for patients in the INT (n=4, 35.83%) versus SOC arm (n=38, 31.67%, p=0.59, Table 6). Other outcomes including number of readmissions within 30 days (p=0.65), index admission cost (p=0.49), index admission LOS (p=0.63), 1st readmission LOS (p=0.58), all readmissions' LOS (p=0.82) and waiting time for 1st readmission (p=0.06) were comparable in two arms.

Statistically significant differences were noticed in INT arm in location of 1st readmission (n=36, 83.72% at OSU as compared to n=23, 60.5% outside hospital, p=0.03), and lesser 1st readmission with HE in the INT arm (n=9, 20.9%) vs SOC (n=17, 44.7%, p=0.03). Finally, contingency analysis of readmission data showed fewer readmissions in patients who attended outpatient follow-up within 30 days of discharge from index admission (n=17, 23.61% v. n=55, 76.39%, p=0.04).

At the end of our study, 47 (19.58%) patients received a liver transplant and 62 (25.83%) died; among those who died, 5 patients were post-transplant and 22 died in hospice. Due to the COVID-19 pandemic we were unable to achieve the anticipated sample size. Therefore, multivariate analysis was not performed.

DISCUSSION

This prospective randomized study investigated early readmission rates and healthcare utilization in patients with DC. Our readmission rate of 33.75% is higher than the United States national average (27%). While our nurse CM interventions did not reduce told readmissions, we found that HE was the top reason for readmission and such interventions were helpful in reducing early readmissions in patients with HE. This is an important lesson learned given increased burden of HE on hospitalizations, falls, mortality, impaired QOL and caregiver burden.[21] In the validation of readmission using "LIRER score", Freitas et al, showed that HE was not only a predictor of 30 days readmission independent of MELD score, index, first-year, two-years & overall mortality, but also HE at admission had significantly higher mean LIRER scores.[22] Furthermore HE patients on Medicare and geographically from the South or Midwest have higher in-hospital mortality.[23] Considerable research has been done to address HE readmissions. Bajaj et al found that efforts to reduce medication-precipitated HE, prevent aspiration pneumonia and optimize HE medications on hospital discharge should be areas of focus to decrease HE readmissions.[24] Tapper et al. demonstrated that development of a checklist for HE protocols integrated into the electronic medical record and order entry system reduced odds of 30-day readmission for patients with HE (from 39.2% to 27.6%).[25] Thus, our results are congruent with existing evidence that interventions should be invested in post-discharge education and communication for all patients with cirrhosis, especially with HE.

One of the components of intervention in our study was to arrange appointment of patients in the clinic within a week with their hepatologist. Patients with DC who attended their follow up appointment within 30 days of discharge from index admission had fewer readmissions. This

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We performed a prospective randomized study to understand the fundamentals of early readmission in patients with DC. Our study enrollment was seriously impacted due to COVID-19 global pandemic in the second year of enrollment. Therefore, calculated sample size was not achieved and could not validate our hypothesis. We believe that due to sample size issues, we faced the challenges of type II errors and have false negative findings. Despite inability to enroll patients according to sample size issues, we learned many lessons from this study with pragmatic interventions. ¶

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suggests that overall, in our cohort, outpatient linkage with a hepatologist should be a priority to reduce readmission rates.[26] Morales et al in their retrospective HEPACONTROL program looked at the impact of follow-up of cirrhotics within 7 days after discharge with a hepatologist. They reported reduced 30-day readmission, 60-day mortality and rate of emergency department visits and associated costs in those who followed up within 7 days.[17] Morando et al demonstrated that follow up with a "care management check-up" group as opposed to "standard outpatient care" reduced 30-day readmission, reduced 12-month mortality, and saved almost 1500 euros per patient month of life.[18] While Kanwal et al found early outpatient follow-up after discharge was associated with a small increase in readmissions, they found an lower overall mortality in their patients with cirrhosis admitted to Veterans Affairs hospitals.[9] Thus our results are also consistent with the current evidence that patients with DC likely benefit from early post-hospitalization follow up with specialty providers.[27,28]

One of the major limitations of our study was inability to enroll patients according to the proposed sample size due to the COVID-19 pandemic. Our study was underpowered to perform multiple regression analysis to detect differences in readmission rates in INT versus SOC arm. From March 2020 to July 2020 our recruitment process was put on hold due to hospital regulations to reduce patient and staff exposure. Despite this major limitation, we were able to enroll 80.17% (279 consented out of 348 approached) of patients in our study.

This study was also performed in the setting of a large academic medical center and a high-volume liver transplant center. While our methods and results may be applicable to the clinical

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Deleted: The impact of the pandemic on translational and clinical research has been well described [25-27]. Turner-McGrievy et al described how the pandemic has impacted multiple phases of prospective research including recruitment, assessment, intervention, and retention. Regarding recruitment, authors pointed to lack of trust in the scientific community, ethical issues while interacting with patients for non-essential research during the COVID-19 pandemic [25].

practice of other such centers, the same impact may not be appreciated by smaller, community hospitals that are not liver transplant centers.

Future work in patients with DC should continue to focus on prospective intervention strategies to reduce early readmissions and educate patients and providers. To achieve desired sample size, we would suggest collaborations with various centers to identify and recruit patients with DC into a multicenter prospective cohort. Given our finding that there were fewer readmissions in patients with follow-up within 30 days, studies should evaluate the use of telehealth visits for follows up, especially in the COVID19 era, as outlined by Stotts et al.[29]

In conclusion, this prospective randomized study investigated the impact of various pragmatic interventions to reduce early readmission and healthcare utilization in patients with DC. Our study was underpowered to detect statistically significant differences in readmission rates in INT versus SOC arm. We reported that readmission rate of our medical center was 33.75% and HE was the top reason for readmission. We found a reduction in early readmission in patients with HE in the INT arm and those who attended their follow up appointment within 30 days of discharge from index admission. We demonstrated that simple interventions in patients with DC are pragmatic and there is need for more prospective multicenter trials in this area of research.

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559 **TABLES**
560
561 **Table 1 Characteristic features of index admission by readmission status**

	Total	Not readmitted (n=159)	Readmitted (n=81)	p-value
Index Admission Characteristics				
Reasons for Admission[1] (n, %)				
Acute Kidney Injury	65, 27.08%	41, 25.79%	24, 29.63%	0.54
Hyponatremia	16, 6.67%	11, 6.92%	5, 6.17%	1.00
Hepatic Encephalopathy	45, 18.75%	26, 16.35%	19, 23.46%	0.22
Volume Overload	111, 46.25%	81, 50.94%	30, 37.04%	0.06
Variceal bleed	42, 17.50%	31, 19.50%	11, 13.58%	0.29
Lower GI bleed	19, 7.92%	11, 6.92%	8, 9.88%	0.45
Spontaneous Bacterial Peritonitis (SBP)	21, 8.75%	14, 8.81%	7, 8.64%	1.00
Complications of Cirrhosis During Admission [1] (n, %)				
Presence of acute kidney injury (AKI)	80, 33.33%	50, 31.45%	30, 37.04%	0.39
Hepatic Encephalopathy (HE)	49, 20.42%	31, 19.50%	18, 22.22%	0.62
Ascites	139, 57.92%	95, 59.75%	44, 54.32%	0.49
Variceal bleeding	37, 15.42%	26, 16.35%	11, 13.58%	0.71
Spontaneous Bacterial Peritonitis (SBP)	16, 6.67%	12, 7.55%	4, 4.94%	0.59
Hepatorenal syndrome (HRS)	14, 5.83%	8, 5.03%	6, 7.41%	0.56
Coagulopathy	56, 23.33%	36, 22.64%	20, 24.69%	0.75
Portal hypertension	46, 19.17%	34, 21.38%	12, 14.81%	0.30
Hepato-pulmonary syndrome (HPS)	15, 6.25%	8, 5.03%	7, 8.64%	0.27
Hepatocellular carcinoma (HCC)	11, 4.58%	6, 3.77%	5, 6.17%	0.51
Procedures Performed During Admission[1] (n, %)				
Esophago-gastro-duodenoscopy (EGD)	136, 56.67%	92, 57.86%	44, 54.32%	0.68
Paracentesis	115, 47.92%	73, 45.91%	42, 51.85%	0.41
Emergent Transjugular intrahepatic portosystemic shunt (TIPS)	10, 4.17%	9, 5.66%	1, 1.23%	0.17
Hemodialysis (HD)	15, 6.25%	7, 4.40%	8, 9.88%	0.16
Colonoscopy/flex sig	24, 10.00%	18, 11.32%	6, 7.41%	0.37
Disposition[1] (n, %)				
Home	159, 66.25%	107, 67.30%	52, 64.20%	0.66
Home with Home Health Newly Arranged	39, 16.25%	24, 15.09%	15, 18.52%	
Home with Home Health Previously Arranged	3, 1.25%	2, 1.26%	1, 1.23%	
SNF newly Arranged	21, 8.75%	16, 10.06%	5, 6.17%	
SNF Previously Arranged	11, 4.58%	5, 3.14%	6, 7.41%	
Left Against Medical Advice	2, 0.83%	1, 0.63%	1, 1.23%	
Transfer (long term acute care hospital)	3, 1.25%	2, 1.26%	1, 1.23%	
Homeless	2, 0.83%	2, 1.26%	0, 0.00%	

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Table 2 Characteristics and Reasons for Readmission

Readmission status	N	%
No	159	66.25
Yes	81	33.75
Number of Readmissions within 30 days		
0	159	66.25
1	63	26.25
2	14	5.83
3	3	1.25
5	1	0.42
Location of 1st Readmission		
OSU	59	72.84
Outside Hospital	22	27.16
Reason for 1st Readmission[1]		
Hepatic Encephalopathy	26	32.10
Volume Overload	22	27.16
Acute Kidney Injury	16	19.75
Variceal bleed	12	14.82
Hyponatremia	10	12.35
Lower GI bleed	4	4.94
Spontaneous Bacterial Peritonitis (SBP)	3	3.70
LOS of first Readmission (n=81, mean±SD), median =5, range =1 to 69	8.11±8.98	
LOS of All Readmissions (n=105, mean±SD), median =4, range =0 to 124	9.03±14.42	
Cost of first readmission (n=45, mean±SD), median=$31,848.95, range $765-325,656.38	$55,548.29±65,164.91	
Waiting time for first Readmission (n=81, mean ±SD), median=12, range = 1-30]	12.65±7.55	

[1]indicates patient can have more than one of variable listed

Table 3 Comparison of patient demographics and clinical characteristics by randomization arm

	Intervention (n=120)	Standard of Care (n=120)	p-value
Patient Demographics			
Age (mean±SD)	56.54±11.21	56.14±11.21	0.78
Age Group (n, %)			
65+	32, 26.67%	28, 23.33%	0.79
40-64	75, 62.50%	80, 66.67%	
18-39	13, 10.83%	12, 10.00%	
Gender (n, %)			
Male	60, 50.00%	75, 62.50%	**0.03**
Female	60, 50.00%	45, 32.50%	
Race (n, %)			
White	105, 87.50%	97, 80.83%	0.22
Other	15, 12.50%	23, 19.17%	
Ethnicity (n, %)			
Not Hispanic or Latino	113, 94.17%	114, 95.00%	0.81
Hispanic or Latino	3, 2.50%	1, 0.83%	
Unknown / Not Reported	4, 3.33%	5, 4.17%	
Zip Code Income (mean±SD)	$68,045±$21,370	$68,455±$21,651	0.88
Employment Status (n, %)			
Unemployed	33, 27.50%	30, 25.00%	0.78
Disabled	24, 20.00%	24, 20.00%	
Retired	26, 21.67%	30, 20.00%	
Employed, Part Time	5, 4.17%	3, 2.50%	
Employed, Full Time	23, 19.17%	28, 23.33%	
Other / Unknown	9, 7.50%	14, 11.67%	
Insurance Type (n, %)			
Self-pay	4, 3.33%	3, 2.50%	0.54
No Charge / Other / Unknown	7, 5.83%	7, 5.83%	
Private Insurance	38, 31.67%	35, 29.17%	
Medicare	32, 26.67%	44, 36.67%	
Medicaid	39, 32.50%	31, 25.83%	
Number of admissions at OSU for DC in last 1 year (mean±SD)	1.99±1.61	1.84±1.48	0.45
MELD Score Admit (mean±SD)	21.32±8.19	22.47±7.85	0.27
MELD Score Discharge (mean±SD, n = 117+118)	20.07±7.74	20.25±6.93	0.84
CP Score Admit (mean±SD)	9.31±2.02	9.41±1.89	0.69
CP Score Discharge (mean±SD)	8.44±1.86	8.73±1.89	0.24
Etiology of Cirrhosis (Index Admission[1], n, %)			
Alcoholic	61, 50.83%	60, 50.00%	1.00
Non-alcoholic fatty liver	42, 35.00%	37, 30.83%	0.58
Viral	21, 17.50%	22. 18.33%	1.00
Hep B	1, 4.76%	3, 13.64%	0.80
Hep C	19, 90.48%	18, 81.82%	
Hep B and C	1, 4.76%	1, 4.55%	
Cryptogenic	6, 5.00%	7, 5.83%	1.00
Autoimmune	1, 0.83%	1, 0.83%	1.00
Primary sclerosing cholangitis	2, 1.67%	2, 1.67%	1.00
Hemochromatosis	0, 0.0%	3, 2.5%	0.25
Alpha 1 Anti-Trypsin Deficiency	3, 2.5%	0, 0.0%	0.25
Under Evaluation for Liver Transplant (n, %)			
No	45, 37.50%	61, 50.83%	0.08
Yes	63, 52.50%	53, 44.17%	
Unknown	12, 10.00%	6, 5.00%	

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588 **Table 4 Characteristic features during index admission in two randomization arms**

Index Admission Characteristics	Intervention (n=120)	Standard of Care (n=120)	p-value
Reasons for Admission[1] (n, %)			
Acute Kidney Injury	30, 25.00%	35, 29.17%	0.56
Hyponatremia	10, 8.33%	6, 5.00%	0.44
Hepatic Encephalopathy	22, 18.33%	23, 19.17%	1.00
Volume Overload	59, 49.17%	52, 43.33%	0.44
Variceal bleed	21, 17.50%	21, 17.50%	1.00
Lower GI bleed	8, 6.67%	11, 9.17%	0.63
Spontaneous Bacterial Peritonitis (SBP)	9, 7.50%	12, 10.00%	0.65
Complications of Cirrhosis During Admission [1] (n, %)			
Presence of acute kidney injury (AKI)	39, 32.50%	41, 34.17%	0.89
Hepatic Encephalopathy (HE)	25, 20.83%	24, 20.00%	1.00
Ascites	70, 58.33%	69, 57.50%	1.00
Variceal bleeding	21, 17.50%	16, 13.33%	0.48
Spontaneous Bacterial Peritonitis (SBP)	10, 8.33%	6, 5.00%	0.44
Hepatorenal syndrome (HRS)	7, 5.83%	7, 5.83%	1.00
Coagulopathy	32, 26.67%	24, 20.00%	0.29
Portal hypertension	19, 15.83%	27, 22.50%	0.25
Hepato-pulmonary syndrome (HPS)	10, 8.33%	5, 4.17%	0.29
Hepatocellular carcinoma (HCC)	6, 5.00%	5, 4.17%	1.00
Procedures Performed During Admission[1] (n, %)			
Esophago-gastro-duodenoscopy (EGD)	68, 56.67%	68, 56.67%	1.00
Paracentesis	60, 50.00%	55, 45.83%	0.61
Transjugular intrahepatic portosystemic shunt (TIPS)	7, 5.83%	3, 2.50%	0.33
Hemodialysis (HD)	5, 4.17%	10, 8.33%	0.29
Colonoscopy/flex sig	13, 10.83%	11, 9.17%	0.83
Disposition (n, %)			
Home	83, 69.17%	76, 63.33%	0.44
Home with Home Health Newly Arranged	17, 14.17%	22, 18.33%	
Home with Home Health Previously Arranged	2, 1.67%	1, 0.83%	
SNF newly Arranged	7, 5.83%	14, 11.67%	
SNF Previously Arranged	6, 5.00%	5, 4.17%	
Left Against Medical Advice	1, 0.83%	1, 0.83%	
Transfer (Long term acute care hospital)	3, 2.50%	0, 0.00%	
Homeless	1, 0.83%	1, 0.83%	

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Table 5 Clinical and laboratory features during index admission and discharge in two randomization arms

	Intervention (n=120)	Standard of Care (n=120)	p-value
Index Admission Labs			
Sodium (mmol/L, mean±SD)	132.59±5.58	132.28±6.28	0.68
Serum Creatinine (mg/dL, mean±SD)	1.42±1.11	1.64±1.47	0.19
Total Bilirubin (mg/dL, mean±SD)	5.90±9.10	6.19±7.80	0.79
Albumin (g/dL, mean±SD)	2.83±0.59	2.85±0.55	0.72
INR (mean±SD)	1.68±0.52	1.70±0.59	0.80
Hemoglobin (g/dL, mean±SD)	10.22±2.34	10.02±2.04	0.48
Ascites (n, %)			
Absent	35, 29.17%	35, 29.17%	0.44
Slight	26, 21.67%	34, 28.33%	
Moderate	59, 49.17%	51, 42.50%	
Encephalopathy (n, %)			
None	91, 75.83%	96, 80.00%	0.78
Grade 1-2	22, 18.33%	18, 15.00%	
Grade 3-4	7, 5.83%	6, 5.00%	
Dialysis At Least Twice in Last Week (n, %)			
No	117, 97.50%	115, 95.83%	0.72
Yes	3, 2.50%	5, 4.17%	
Index Admission Discharge Labs			
Sodium (mmol/L, mean±SD)	134.72±4.14	134.95±3.57	0.64
Serum Creatinine (mg/dL, mean±SD)	1.31±1.06	1.37±1.18	0.69
Total Bilirubin (mg/dL, mean±SD, n=237)	5.50±8.80	5.39±6.96	0.92
Albumin (g/dL, mean±SD, n=237)	2.98±0.64	2.94±0.61	0.65
INR (mean±SD, n=238)	1.71±0.49	1.69±0.45	0.65
Hemoglobin (g/dL, mean±SD)	9.30±1.69	9.21±1.68	0.68
Ascites (n, %)			
Absent	42, 35.00%	39, 32.50%	0.35
Slight	56, 46.67%	66, 55.00%	
Moderate	22, 18.33%	15, 12.50%	
Encephalopathy (n, %)			
None	117, 97.50%	112. 93.33%	0.10
Grade 1-2	2, 1.67%	8, 6.67%	
Grade 3-4	1, 0.83%	0, 0.00%	
Dialysis At Least Twice in Last Week (n, %)			
No	114, 95.00%	110, 91.67%	0.44
Yes	6, 5.00%	10, 8.33%	

Table 6 Outcomes and reasons of readmission characteristics by randomization arms

	Intervention (n=120)	Standard of Care (n=120)	p-value
Readmission (n, %)			
No	77, 64.17%	82, 68.33%	0.59
Yes	43, 35.83%	38, 31.67%	
Number of Readmissions within 30 days (n, %)			
0	77, 64.17%	82, 68.33%	0.65
1	31, 25.83%	32, 26.67%	
2	9, 7.50%	5, 4.17%	
3	2, 1.67%	1, 0.83%	
5	1, 0.83%	0, 0.00%	
Location of 1st Readmission (n, %)			
Our institution	36, 83.72%	23, 60.53%	**0.03**
Outside Hospital	7, 16.28%	15, 39.47%	
Reason for 1st Readmission[1] (n, %)			
Acute Kidney Injury (AKI)	10, 23.26%	6, 15.79%	0.58
Hyponatremia	4, 9.30%	6, 15.79%	0.50
Hepatic Encephalopathy (HE)	9, 20.93%	17, 44.74%	**0.03**
Volume Overload	13, 30.23%	9, 23.68%	0.62
Variceal bleed	6, 13.95%	6, 15.79%	1.00
Lower GI bleed	1, 2.33%	3, 7.89%	0.34
Spontaneous Bacterial Peritonitis (SBP)	2, 4.65%	1, 2.63%	1.00
Other	20, 46.51%	22, 57.89%	0.37
Index Admission Cost (mean±SD, n=116+109]	61,581±47,825	59,547±46,669	0.46
Index Admission LOS (mean±SD)	8.17±5.56	8.08±6.11	0.63
First Readmission LOS (n=43+38, mean±SD)	7.58±7.57	8.71±10.41	0.58
All Readmissions LOS (n=60+45, mean±SD)	9.28±16.88	8.69±10.44	0.82
Waiting time for first Readmission (n=43+38, mean±SD)	11.16±7.10	14.34±7.77	0.06

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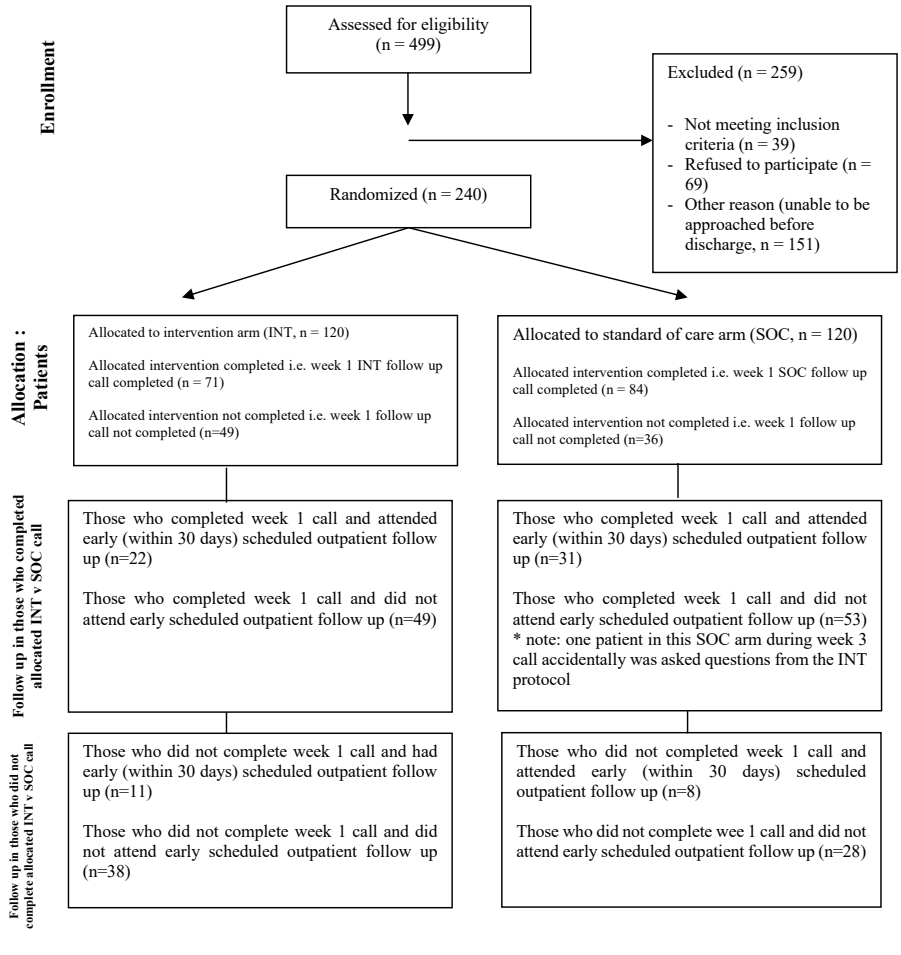
FIGURES

Figure 1. Modified CONSORT flow diagram of patients eligible for enrollment in study trial



TITLE PAGE

Study Title: Randomized Intervention and Outpatient Follow-Up Lowers 30-day Readmissions for Patients with Hepatic Encephalopathy, Decompensated Cirrhosis

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Kevin Litzenberg, Claire Griffiths, Caitlin Hayes, Bipul Gnyawali and Michelle Manious – recruiting patients for study, drafting manuscript; approved the final submitted version of manuscript.

Sajid Jalil, Sean Kelly and Lanla Conteh—Reviewed and edited the final draft of the manuscript.

Haikady N. Nagaraja– analyzed data, edited manuscript, and approved the final submitted version of this manuscript.

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Potential competing interests:

There no competing interests declared by the authors.

ABSTRACT

Background

We previously reported national 30-day readmission rates of 27% in patients with decompensated cirrhosis (DC).

Aims

We studied prospective interventions to reduce early readmissions in DC at our tertiary center.

Methods

Adults with DC admitted July 2019 to December 2020 were enrolled and randomized into the intervention (INT) or standard of care (SOC) arms. Weekly phone calls for a month were completed. In the INT arm, case managers ensured outpatient follow-up, paracentesis, and medication compliance. Thirty-day readmission rates and reasons were compared.

Results

Calculated sample size was not achieved due to COVID-19; 240 patients were randomized into INT and SOC arms. 30-day readmission rate was 33.75%, 35.83% in the INT versus 31.67% in the SOC arm (p=0.59). The top reason for 30-day readmission was hepatic encephalopathy (HE, 32.10%). There was a lower rate of 30-day readmissions for HE in the INT (21%) versus SOC arm (45%, p=0.03). There were fewer 30-day readmissions in patients who attended early outpatient follow-up (n=17, 23.61% v. n=55, 76.39%, p=0.04).

Conclusions

Our 30-day readmission rate was higher than the national rate but reduced by interventions in patients with DC with HE and early outpatient follow-up. Development of interventions to reduce early readmission in patients with DC is needed.

Keywords: decompensated cirrhosis; hospital readmissions; interventions

INTRODUCTION

Cirrhosis affects approximately 5 million annually[1] and has been reported to be the 8th leading cause of death with more than 40,000 deaths annually in the United States.[2] A study on the burden of gastrointestinal, liver, and pancreatic diseases in the United States revealed that liver diseases had the highest mortality at 3.1%.[3] In addition to high mortality, cirrhosis is also associated with high morbidity. The sequelae of decompensated cirrhosis (DC) are often managed during hospital admissions and include volume overload in the form of ascites, edema or hepatic hydrothorax, portal hypertension leading to bleeding esophageal or gastric varices, as well as hepatic encephalopathy (HE), hyponatremia, acute kidney injury (AKI), and spontaneous bacterial peritonitis (SBP).[4]

Several studies have demonstrated hospital readmissions in DC place a large financial burden on the United State healthcare system. The 30-day readmission rate has been reported to be 20%-37%.[5-14] We have recently published on early readmission rates up to 27% in patients with DC and developed the Mumtaz readmission risk score based on United States data.[15] We also reported that nearly one-third of patients with HE were readmitted within 30 days, and early readmission adversely impacted healthcare utilization and calendar-year mortality.[16]

Interventions to reduce readmissions have been shown to be safe and effective. For instance, Morales et al. developed HEPACONTROL program including a hepatologist follow-up exam within 7 days after discharge. This program resulted in a reduction in 30-day readmissions, 60-day mortality, emergency department visits and associated costs.[17] Similarly, another group demonstrated that follow-up with a “care management check-up” as opposed to “standard

outpatient care" reduced 30-day readmission, 12-month mortality and saved 1500 euros per patient month of life.[18]

There is a paucity of prospective studies on interventions to reduce early readmission rates in patients with DC. Therefore, we prospectively studied 30-day readmission rates in patients with DC and compared various interventions (INT) with standard of care (SOC) to reduce early readmission rates. We hypothesized that DC patients in the INT arm would have decreased 30-day readmission versus the SOC arm.

METHODS

This study was conducted at the Ohio State University Wexner Medical Center (OSUWMC), Columbus, Ohio from July 2019 to December 2020. Our study was approved by OSUWMC Institutional Review Board. All aspects of the studying involving human participants including informed consent for enrollment were in accordance with the ethical standards of our Institutional Review Board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Screening

All patients admitted with DC to the hepatology (inpatient or consult) service were screened for enrollment. Patients meeting inclusion criteria were approached for study consent. Of note, due to the global COVID-19 pandemic, beginning March 2020, only COVID negative patients were approached for informed consent. Elective readmissions for inpatient procedures including endoscopy, trans-arterial chemoembolization (TACE), transjugular intrahepatic portosystemic shunt (TIPS), paracentesis or readmissions unrelated to DC such as motor vehicle accidents were excluded.

Randomization and Data Collection

Study data were collected and managed using REDCap hosted at The Ohio State University Wexner Medical Center.[19,20] Informed consent was obtained from all individual participants included in the study. Consented patients were randomly assigned to either the INT arm or the SOC arm in a 1:1 ratio using the RedCap randomization tool. The following data were collected on all patients via RedCap software including demographics (age, sex, insurance type, income

based on the zip code), hospitalization data (date of index admission defined as initial admission during which patient consented for study, reason for admission, length of stay (LOS) defined as difference in days between index admission date and index admission discharge date, discharge disposition, associated cost of care of admission as obtained through medical record billing tab), etiology of cirrhosis (alcoholic and non-alcoholic including viral, non-alcoholic fatty liver disease, autoimmune, primary biliary cirrhosis, primary sclerosing cholangitis or cryptogenic), complications of cirrhosis {HE, AKI, ascites, variceal bleeding, SBP, hepatorenal syndrome (HRS), coagulopathy, portal hypertension, hepato-pulmonary syndrome (HPS), hepatocellular carcinoma (HCC)}, and procedures performed during admission {esophago-gastro-duodenoscopy (EGD), colonoscopy or flexible sigmoidoscopy, paracentesis, transjugular intrahepatic portosystemic shunt (TIPS) and hemodialysis (HD) on admission and discharge}. We also collected data including Elixhauser comorbidity index, discharge medications, and laboratory data (complete blood counts, serum creatinine, liver function tests including total bilirubin, INR, and sodium). Child Turcotte Pugh (CTP) and Sodium-model for end stage liver disease (MELD-Na) score were calculated from the data. The nurse case manager (CM) also recorded labs & medications at readmission & discharge and associated cost of readmission. Status of early readmission, liver transplantation, and mortality at one year were also collected.

Follow-up

The CM phoned each patient enrolled in either arm weekly for 30 days after index discharge to find out if the patient has been readmitted to OSUWMC or another hospital. In the INT arm, during the call CM also ensured i) early (defined as within 30 days from index admission discharge) outpatient hepatology follow-up ii) compliance of medication, iii) arrangement of

outpatient paracentesis if needed, and reviewed outpatient hepatology clinic follow-up records. SOC arm as per our center's protocol had to be taken care of by the primary inpatient team. This included arranging early outpatient clinic follow-up, providing list of medications, and advice for outpatient paracentesis if needed at the time of discharge. Due to the nature of intervention, the study could not be blinded.

Definition of outcomes

Early readmission was defined as admission within 30 days of index admission discharge. Reasons for readmission were gathered by CM by reviewing the electronic medical record (EMR) of all enrolled patients readmitted at OSUWMC or outside hospital within 30 days of index admission. Predictors of early readmission were also compared in the two arms.

Sample Size

Based on the sample size calculation, target of recruitment for the study was 848 patients, admitted to the hospital with DC under the hepatology (inpatient and consult) services. Patients were randomly assigned in a 1:1 ratio into INT or SOC arms. Based on our previous study using the NRD administrative database, we expected a 30-day readmission rate of 27% among patients meeting inclusion criteria, which yield 114/424 patients with 30-day readmission events, thus meeting the target sample size. Based on this calculation, a total sample size of 848 (424 per group) provided 80% power to detect a 30% decrease in 30-day readmission rate (from 27% to 19%) with a type I error rate of 0.05. However, planned sample size could not be achieved due to the COVID-19 pandemic related restriction started in our center in March 2020. Therefore, we

end up with available sample size of a total of 240 patients. The modified CONSORT Flow diagram for enrollment in our study trial is illustrated in Figure 1.

Statistical analysis:

Means of continuous response variables between two groups were compared using robust t-test (Welch test). Proportions were compared using Chi-square or Fisher's exact test as applicable. Logarithmic transformation was used for comparing the length of stay (LOS) and admission cost across groups. Level of significance was kept at 0.05 for each comparison. JMP Version 15 (SAS Institute, NC) was used for all the analyses.

RESULTS

Initial Screening Data

From July 1, 2019, to December 1, 2020, 1392 patients were screened. Due to the COVID-19 pandemic, recruitment was held from March 2020 to July 2020 and subsequently resumed until December 2020. Out of the patients screened, only 499 (35.85%) were eligible for inclusion; however, 240 patients consented and randomized: 120 each into the INT and SOC arm (Figure 1).

Patient demographics and clinical characteristics

The mean age of patients was 56.34±11.19 years, majority were males (135, 56.25%), belonged to White race (n=202, 84.17%) and non-Hispanic or Latino ethnicity (n=227, 94.58%). Almost two-thirds of the patients had public insurance (n=76, 31.67% on Medicare and n=70, 29.17% on Medicaid); 73 (30.42%) had private insurance. At admission, the mean MELD-Na score and mean Child Pugh Score were 21.89±8.03 and 9.36±1.96, respectively. Major etiology of cirrhosis was alcohol (n=121, 50.42%) followed by non-alcoholic fatty liver disease (n=79, 32.92%) and viral hepatitis (n=43, 17.92%). Furthermore, 116 (48.33%) patients were actively under evaluation for liver transplantation.

Characteristics of index admissions

The index admission mean LOS was 8.13±5.83 days (median 6, range 1-43 days). The mean cost of index admission was $60,595±$47,174 (n=225, median $42,932, range $1,630-251,991). The top five reasons for index admission included volume overload (n=111, 46.25%), acute kidney injury (n=65, 27.08%), hepatic encephalopathy (n=45, 18.75%), variceal bleed (n=42, 17.50%),

lower GI bleed (n=19, 7.92%) and hyponatremia (n=16, 6.67%). The top five interventions performed were EGD (n=136, 56.67%), paracentesis (n=115, 47.92%), colonoscopy/flexible sigmoidoscopy (n=24, 10 %), hemodialysis (n=15, 6.25%) and TIPS (n=10, 4.17%). Most patients were discharged from index admission to home (n=159, 66.25%) followed by home with health care (n=42, 17.50%) and skilled nursing facility (n=32, 13.33 %, Table 1).

Characteristics and reasons for early readmissions

Overall, 81 (33.75%) patients were readmitted within 30 days of discharge. The major reasons for first readmission included hepatic encephalopathy (n=26, 32.10%) followed by volume overload (n=22, 27.16%), acute kidney injury (n=16, 19.75%), variceal bleed (n=12, 14.82%) and hyponatremia (n=10, 12.35%). 14 patients were readmitted twice, 3 admitted thrice and one admitted 5 times within 30 days. The mean time to first readmission was 12.65±7.55 days (median 12 days, range 1-30 days). The mean length of stay of first readmission was 8.11±8.98 days. The mean cost of stay of first readmission was $55,548.29 ± $65,164.91 (Table 2). Those readmitted had a higher MELD score on index admission (23.54±7.80 v. 21.05±8.03, p=0.02) and index discharge (21.67±7.95 v. 19.39±6.89, p=0.03) than those not readmitted. Similarly, those readmitted had a higher index admission creatinine (1.80±1.53 v 1.39±1.16, p= 0.03), index discharge creatinine (1.61±1.34 v, 1.20±0.97, p=0.02), and higher index admission INR (1.80±0.64 v. 1.63±0.50, p=0.05) than those not readmitted.

Comparison of demographics and clinical characteristics in two intervention arms

Demographics including age, race, ethnicity, income, and insurance were comparable in two groups, as well as etiology of cirrhosis, MELD-Na score, CTP score, status of evaluation for

liver transplant. There were majority females in the INT arm (60/120, 50% v. 45/120, 32.50%) and males in SOC arm (75/120, 62.50% v. 60/120, 50%, p=0.03, Table 3). Index admission characteristics, disposition and index admission were also comparative in two arms (Table 4 and Table 5)

Comparison of reasons of 1st readmission and outcomes in the INT v SOC arm

There was no difference in the readmission rates for patients in the INT (n=4, 35.83%) versus SOC arm (n=38, 31.67%, p=0.59, Table 6). Other outcomes including number of readmissions within 30 days (p=0.65), index admission cost (p=0.49), index admission LOS (p=0.63), 1st readmission LOS (p=0.58), all readmissions' LOS (p=0.82) and waiting time for 1st readmission (p=0.06) were comparable in two arms.

Statistically significant differences were noticed in INT arm in location of 1st readmission (n=36, 83.72% at OSU as compared to n=23, 60.5% outside hospital, p=0.03), and lesser 1st readmission with HE in the INT arm (n=9, 20.9%) vs SOC (n=17, 44.7%, p=0.03). Finally, contingency analysis of readmission data showed fewer readmissions in patients who attended outpatient follow-up within 30 days of discharge from index admission (n=17, 23.61% v. n=55, 76.39%, p=0.04).

At the end of our study, 47 (19.58%) patients received a liver transplant and 62 (25.83%) died; among those who died, 5 patients were post-transplant and 22 died in hospice. Due to the COVID-19 pandemic we were unable to achieve the anticipated sample size. Therefore, multivariate analysis was not performed.

DISCUSSION

This prospective randomized study investigated early readmission rates and healthcare utilization in patients with DC. Our readmission rate of 33.75% is higher than the United States national average (27%). While our nurse CM interventions did not reduce told readmissions, we found that HE was the top reason for readmission and such interventions were helpful in reducing early readmissions in patients with HE. This is an important lesson learned given increased burden of HE on hospitalizations, falls, mortality, impaired QOL and caregiver burden.[21] In the validation of readmission using "LIRER score", Freitas et al, showed that HE was not only a predictor of 30 days readmission independent of MELD score, index, first-year, two-years & overall mortality, but also HE at admission had significantly higher mean LIRER scores.[22] Furthermore HE patients on Medicare and geographically from the South or Midwest have higher in-hospital mortality.[23] Considerable research has been done to address HE readmissions. Bajaj et al found that efforts to reduce medication-precipitated HE, prevent aspiration pneumonia and optimize HE medications on hospital discharge should be areas of focus to decrease HE readmissions.[24] Tapper et al. demonstrated that development of a checklist for HE protocols integrated into the electronic medical record and order entry system reduced odds of 30-day readmission for patients with HE (from 39.2% to 27.6%).[25] Thus, our results are congruent with existing evidence that interventions should be invested in post-discharge education and communication for all patients with cirrhosis, especially with HE.

One of the components of intervention in our study was to arrange appointment of patients in the clinic within a week with their hepatologist. Patients with DC who attended their follow up appointment within 30 days of discharge from index admission had fewer readmissions. This

suggests that overall, in our cohort, outpatient linkage with a hepatologist should be a priority to reduce readmission rates.[26] Morales et al in their retrospective HEPACONTROL program looked at the impact of follow-up of cirrhotics within 7 days after discharge with a hepatologist. They reported reduced 30-day readmission, 60-day mortality and rate of emergency department visits and associated costs in those who followed up within 7 days.[17] Morando et al demonstrated that follow up with a "care management check-up" group as opposed to "standard outpatient care" reduced 30-day readmission, reduced 12-month mortality, and saved almost 1500 euros per patient month of life.[18] While Kanwal et al found early outpatient follow-up after discharge was associated with a small increase in readmissions, they found an lower overall mortality in their patients with cirrhosis admitted to Veterans Affairs hospitals.[9] Thus our results are also consistent with the current evidence that patients with DC likely benefit from early post-hospitalization follow up with specialty providers.[27,28]

One of the major limitations of our study was inability to enroll patients according to the proposed sample size due to the COVID-19 pandemic. Our study was underpowered to perform multiple regression analysis to detect differences in readmission rates in INT versus SOC arm. From March 2020 to July 2020 our recruitment process was put on hold due to hospital regulations to reduce patient and staff exposure. Despite this major limitation, we were able to enroll 80.17% (279 consented out of 348 approached) of patients in our study.

This study was also performed in the setting of a large academic medical center and a high-volume liver transplant center. While our methods and results may be applicable to the clinical

practice of other such centers, the same impact may not be appreciated by smaller, community hospitals that are not liver transplant centers.

Future work in patients with DC should continue to focus on prospective intervention strategies to reduce early readmissions and educate patients and providers. To achieve desired sample size, we would suggest collaborations with various centers to identify and recruit patients with DC into a multicenter prospective cohort. Given our finding that there were fewer readmissions in patients with follow-up within 30 days, studies should evaluate the use of telehealth visits for follows up, especially in the COVID19 era, as outlined by Stotts et al.[29]

In conclusion, this prospective randomized study investigated the impact of various pragmatic interventions to reduce early readmission and healthcare utilization in patients with DC. Our study was underpowered to detect statistically significant differences in readmission rates in INT versus SOC arm. We reported that readmission rate of our medical center was 33.75% and HE was the top reason for readmission. We found a reduction in early readmission in patients with HE in the INT arm and those who attended their follow up appointment within 30 days of discharge from index admission. We demonstrated that simple interventions in patients with DC are pragmatic and there is need for more prospective multicenter trials in this area of research.

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TABLES

Table 1 Characteristic features of index admission by readmission status

	Total	Not readmitted (n=159)	Readmitted (n=81)	p-value
Index Admission Characteristics				
Reasons for Admission[1] (n, %)				
Acute Kidney Injury	65, 27.08%	41, 25.79%	24, 29.63%	0.54
Hyponatremia	16, 6.67%	11, 6.92%	5, 6.17%	1.00
Hepatic Encephalopathy	45, 18.75%	26, 16.35%	19, 23.46%	0.22
Volume Overload	111, 46.25%	81, 50.94%	30, 37.04%	0.06
Variceal bleed	42, 17.50%	31, 19.50%	11, 13.58%	0.29
Lower GI bleed	19, 7.92%	11, 6.92%	8, 9.88%	0.45
Spontaneous Bacterial Peritonitis (SBP)	21, 8.75%	14, 8.81%	7, 8.64%	1.00
Complications of Cirrhosis During Admission [1] (n, %)				
Presence of acute kidney injury (AKI)	80, 33.33%	50, 31.45%	30, 37.04%	0.39
Hepatic Encephalopathy (HE)	49, 20.42%	31, 19.50%	18, 22.22%	0.62
Ascites	139, 57.92%	95, 59.75%	44, 54.32%	0.49
Variceal bleeding	37, 15.42%	26, 16.35%	11, 13.58%	0.71
Spontaneous Bacterial Peritonitis (SBP)	16, 6.67%	12, 7.55%	4, 4.94%	0.59
Hepatorenal syndrome (HRS)	14, 5.83%	8, 5.03%	6, 7.41%	0.56
Coagulopathy	56, 23.33%	36, 22.64%	20, 24.69%	0.75
Portal hypertension	46, 19.17%	34, 21.38%	12, 14.81%	0.30
Hepato-pulmonary syndrome (HPS)	15, 6.25%	8, 5.03%	7, 8.64%	0.27
Hepatocellular carcinoma (HCC)	11, 4.58%	6, 3.77%	5, 6.17%	0.51
Procedures Performed During Admission[1] (n, %)				
Esophago-gastro-duodenoscopy (EGD)	136, 56.67%	92, 57.86%	44, 54.32%	0.68
Paracentesis	115, 47.92%	73, 45.91%	42, 51.85%	0.41
Emergent Transjugular intrahepatic portosystemic shunt (TIPS)	10, 4.17%	9, 5.66%	1, 1.23%	0.17
Hemodialysis (HD)	15, 6.25%	7, 4.40%	8, 9.88%	0.16
Colonoscopy/flex sig	24, 10.00%	18, 11.32%	6, 7.41%	0.37
Disposition[1] (n, %)				
Home	159, 66.25%	107, 67.30%	52, 64.20%	0.66
Home with Home Health Newly Arranged	39, 16.25%	24, 15.09%	15, 18.52%	
Home with Home Health Previously Arranged	3, 1.25%	2, 1.26%	1, 1.23%	
SNF newly Arranged	21, 8.75%	16, 10.06%	5, 6.17%	
SNF Previously Arranged	11, 4.58%	5, 3.14%	6, 7.41%	
Left Against Medical Advice	2, 0.83%	1, 0.63%	1, 1.23%	
Transfer (long term acute care hospital)	3, 1.25%	2, 1.26%	1, 1.23%	
Homeless	2, 0.83%	2, 1.26%	0, 0.00%	

[1]indicates patient can have more than one of variable listed

485 **Table 2 Characteristics and Reasons for Readmission**

Readmission status	N	%
No	159	66.25
Yes	81	33.75
Number of Readmissions within 30 days		
0	159	66.25
1	63	26.25
2	14	5.83
3	3	1.25
5	1	0.42
Location of 1st Readmission		
OSU	59	72.84
Outside Hospital	22	27.16
Reason for 1st Readmission[1]		
Hepatic Encephalopathy	26	32.10
Volume Overload	22	27.16
Acute Kidney Injury	16	19.75
Variceal bleed	12	14.82
Hyponatremia	10	12.35
Lower GI bleed	4	4.94
Spontaneous Bacterial Peritonitis (SBP)	3	3.70
LOS of first Readmission (n=81, mean±SD), median =5, range =1 to 69	8.11±8.98	
LOS of All Readmissions (n=105, mean±SD), median =4, range =0 to 124	9.03±14.42	
Cost of first readmission (n=45, mean±SD), median=$31,848.95, range $765-325,656.38	$55,548.29±65,164.91	
Waiting time for first Readmission (n=81, mean ±SD), median=12, range = 1-30]	12.65±7.55	

486 [1]indicates patient can have more than one of variable listed
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501 **Table 3 Comparison of patient demographics and clinical characteristics by randomization arm**

	Intervention (n=120)	Standard of Care (n=120)	p-value
Patient Demographics			
Age (mean±SD)	56.54±11.21	56.14±11.21	0.78
Age Group (n, %)			
65+	32, 26.67%	28, 23.33%	0.79
40-64	75, 62.50%	80, 66.67%	
18-39	13, 10.83%	12, 10.00%	
Gender (n, %)			
Male	60, 50.00%	75, 62.50%	**0.03**
Female	60, 50.00%	45, 32.50%	
Race (n, %)			
White	105, 87.50%	97, 80.83%	0.22
Other	15, 12.50%	23, 19.17%	
Ethnicity (n, %)			
Not Hispanic or Latino	113, 94.17%	114, 95.00%	0.81
Hispanic or Latino	3, 2.50%	1, 0.83%	
Unknown / Not Reported	4, 3.33%	5, 4.17%	
Zip Code Income (mean±SD)	$68,045±$21,370	$68,455±$21,651	0.88
Employment Status (n, %)			
Unemployed	33, 27.50%	30, 25.00%	0.78
Disabled	24, 20.00%	24, 20.00%	
Retired	26, 21.67%	30, 20.00%	
Employed, Part Time	5, 4.17%	3, 2.50%	
Employed, Full Time	23, 19.17%	28, 23.33%	
Other / Unknown	9, 7.50%	14, 11.67%	
Insurance Type (n, %)			
Self-pay	4, 3.33%	3, 2.50%	0.54
No Charge / Other / Unknown	7, 5.83%	7, 5.83%	
Private Insurance	38, 31.67%	35, 29.17%	
Medicare	32, 26.67%	44, 36.67%	
Medicaid	39, 32.50%	31, 25.83%	
Number of admissions at OSU for DC in last 1 year (mean±SD)	1.99±1.61	1.84±1.48	0.45
MELD Score Admit (mean±SD)	21.32±8.19	22.47±7.85	0.27
MELD Score Discharge (mean±SD, n = 117+118)	20.07±7.74	20.25±6.93	0.84
CP Score Admit (mean±SD)	9.31±2.02	9.41±1.89	0.69
CP Score Discharge (mean±SD)	8.44±1.86	8.73±1.89	0.24
Etiology of Cirrhosis (Index Admission[1], n, %)			
Alcoholic	61, 50.83%	60, 50.00%	1.00
Non-alcoholic fatty liver	42, 35.00%	37, 30.83%	0.58
Viral	21, 17.50%	22. 18.33%	1.00
Hep B	1, 4.76%	3, 13.64%	0.80
Hep C	19, 90.48%	18, 81.82%	
Hep B and C	1, 4.76%	1, 4.55%	
Cryptogenic	6, 5.00%	7, 5.83%	1.00
Autoimmune	1, 0.83%	1, 0.83%	1.00
Primary sclerosing cholangitis	2, 1.67%	2, 1.67%	1.00
Hemochromatosis	0, 0.0%	3, 2.5%	0.25
Alpha 1 Anti-Trypsin Deficiency	3, 2.5%	0, 0.0%	0.25
Under Evaluation for Liver Transplant (n, %)			
No	45, 37.50%	61, 50.83%	0.08
Yes	63, 52.50%	53, 44.17%	
Unknown	12, 10.00%	6, 5.00%	

502 [1]indicates patient can have more than one of variable listed

503 **Table 4 Characteristic features during index admission in two randomization arms**

Index Admission Characteristics	Intervention (n=120)	Standard of Care (n=120)	p-value
Reasons for Admission[1] (n, %)			
Acute Kidney Injury	30, 25.00%	35, 29.17%	0.56
Hyponatremia	10, 8.33%	6, 5.00%	0.44
Hepatic Encephalopathy	22, 18.33%	23, 19.17%	1.00
Volume Overload	59, 49.17%	52, 43.33%	0.44
Variceal bleed	21, 17.50%	21, 17.50%	1.00
Lower GI bleed	8, 6.67%	11, 9.17%	0.63
Spontaneous Bacterial Peritonitis (SBP)	9, 7.50%	12, 10.00%	0.65
Complications of Cirrhosis During Admission [1] (n, %)			
Presence of acute kidney injury (AKI)	39, 32.50%	41, 34.17%	0.89
Hepatic Encephalopathy (HE)	25, 20.83%	24, 20.00%	1.00
Ascites	70, 58.33%	69, 57.50%	1.00
Variceal bleeding	21, 17.50%	16, 13.33%	0.48
Spontaneous Bacterial Peritonitis (SBP)	10, 8.33%	6, 5.00%	0.44
Hepatorenal syndrome (HRS)	7, 5.83%	7, 5.83%	1.00
Coagulopathy	32, 26.67%	24, 20.00%	0.29
Portal hypertension	19, 15.83%	27, 22.50%	0.25
Hepato-pulmonary syndrome (HPS)	10, 8.33%	5, 4.17%	0.29
Hepatocellular carcinoma (HCC)	6, 5.00%	5, 4.17%	1.00
Procedures Performed During Admission[1] (n, %)			
Esophago-gastro-duodenoscopy (EGD)	68, 56.67%	68, 56.67%	1.00
Paracentesis	60, 50.00%	55, 45.83%	0.61
Transjugular intrahepatic portosystemic shunt (TIPS)	7, 5.83%	3, 2.50%	0.33
Hemodialysis (HD)	5, 4.17%	10, 8.33%	0.29
Colonoscopy/flex sig	13, 10.83%	11, 9.17%	0.83
Disposition (n, %)			
Home	83, 69.17%	76, 63.33%	0.44
Home with Home Health Newly Arranged	17, 14.17%	22, 18.33%	
Home with Home Health Previously Arranged	2, 1.67%	1, 0.83%	
SNF newly Arranged	7, 5.83%	14, 11.67%	
SNF Previously Arranged	6, 5.00%	5, 4.17%	
Left Against Medical Advice	1, 0.83%	1, 0.83%	
Transfer (Long term acute care hospital)	3, 2.50%	0, 0.00%	
Homeless	1, 0.83%	1, 0.83%	

504 [1]indicates patient can have more than one of variable listed
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Table 5 Clinical and laboratory features during index admission and discharge in two randomization arms

	Intervention (n=120)	Standard of Care (n=120)	p-value
Index Admission Labs			
Sodium (mmol/L, mean±SD)	132.59±5.58	132.28±6.28	0.68
Serum Creatinine (mg/dL, mean±SD)	1.42±1.11	1.64±1.47	0.19
Total Bilirubin (mg/dL, mean±SD)	5.90±9.10	6.19±7.80	0.79
Albumin (g/dL, mean±SD)	2.83±0.59	2.85±0.55	0.72
INR (mean±SD)	1.68±0.52	1.70±0.59	0.80
Hemoglobin (g/dL, mean±SD)	10.22±2.34	10.02±2.04	0.48
Ascites (n, %)			
Absent	35, 29.17%	35, 29.17%	0.44
Slight	26, 21.67%	34, 28.33%	
Moderate	59, 49.17%	51, 42.50%	
Encephalopathy (n, %)			
None	91, 75.83%	96, 80.00%	0.78
Grade 1-2	22, 18.33%	18, 15.00%	
Grade 3-4	7, 5.83%	6, 5.00%	
Dialysis At Least Twice in Last Week (n, %)			
No	117, 97.50%	115, 95.83%	0.72
Yes	3, 2.50%	5, 4.17%	
Index Admission Discharge Labs			
Sodium (mmol/L, mean±SD)	134.72±4.14	134.95±3.57	0.64
Serum Creatinine (mg/dL, mean±SD)	1.31±1.06	1.37±1.18	0.69
Total Bilirubin (mg/dL, mean±SD, n=237)	5.50±8.80	5.39±6.96	0.92
Albumin (g/dL, mean±SD, n=237)	2.98±0.64	2.94±0.61	0.65
INR (mean±SD, n=238)	1.71±0.49	1.69±0.45	0.65
Hemoglobin (g/dL, mean±SD)	9.30±1.69	9.21±1.68	0.68
Ascites (n, %)			
Absent	42, 35.00%	39, 32.50%	0.35
Slight	56, 46.67%	66, 55.00%	
Moderate	22, 18.33%	15, 12.50%	
Encephalopathy (n, %)			
None	117, 97.50%	112. 93.33%	0.10
Grade 1-2	2, 1.67%	8, 6.67%	
Grade 3-4	1, 0.83%	0, 0.00%	
Dialysis At Least Twice in Last Week (n, %)			
No	114, 95.00%	110, 91.67%	0.44
Yes	6, 5.00%	10, 8.33%	

Table 6 Outcomes and reasons of readmission characteristics by randomization arms

	Intervention (n=120)	Standard of Care (n=120)	p-value
Readmission (n, %)			
No	77, 64.17%	82, 68.33%	0.59
Yes	43, 35.83%	38, 31.67%	
Number of Readmissions within 30 days (n, %)			
0	77, 64.17%	82, 68.33%	0.65
1	31, 25.83%	32, 26.67%	
2	9, 7.50%	5, 4.17%	
3	2, 1.67%	1, 0.83%	
5	1, 0.83%	0, 0.00%	
Location of 1st Readmission (n, %)			
Our institution	36, 83.72%	23, 60.53%	**0.03**
Outside Hospital	7, 16.28%	15, 39.47%	
Reason for 1st Readmission[1] (n, %)			
Acute Kidney Injury (AKI)	10, 23.26%	6, 15.79%	0.58
Hyponatremia	4, 9.30%	6, 15.79%	0.50
Hepatic Encephalopathy (HE)	9, 20.93%	17, 44.74%	**0.03**
Volume Overload	13, 30.23%	9, 23.68%	0.62
Variceal bleed	6, 13.95%	6, 15.79%	1.00
Lower GI bleed	1, 2.33%	3, 7.89%	0.34
Spontaneous Bacterial Peritonitis (SBP)	2, 4.65%	1, 2.63%	1.00
Other	20, 46.51%	22, 57.89%	0.37
Index Admission Cost (mean±SD, n=116+109|	61,581±47,825	59,547±46,669	0.46
Index Admission LOS (mean±SD)	8.17±5.56	8.08±6.11	0.63
First Readmission LOS (n=43+38, mean±SD)	7.58±7.57	8.71±10.41	0.58
All Readmissions LOS (n=60+45, mean±SD)	9.28±16.88	8.69±10.44	0.82
Waiting time for first Readmission (n=43+38, mean±SD)	11.16±7.10	14.34±7.77	0.06

[1]indicates patient can have more than one of variable listed

FIGURES

Figure 1. Modified CONSORT flow diagram of patients eligible for enrollment in study trial