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The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Randomized Clinical Trial

Randomized intervention and outpatient follow-up lowers 30-d readmissions for patients with hepatic encephalopathy, decompensated cirrhosis

Antoinette Pusateri, Kevin Litzenberg, Claire Griffiths, Caitlin Hayes, Bipul Gnyawali, Michelle Manious, Sean G Kelly, Lanla F Conteh, Sajid Jalil, Haikady N Nagaraja, Khalid Mumtaz

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Abstract

BACKGROUND

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

AIM

To study 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 coronavirus disease 2019; 240 patients were randomized into INT and SOC arms. 30-d readmission rate was 33.75%, 35.83% in the INT *vs* 31.67% in the SOC arm ($P = 0.59$). The top reason for 30-d readmission was hepatic encephalopathy (HE, 32.10%). There was a lower rate of 30-d readmissions for HE in the INT (21%) *vs* SOC arm (45%, $P = 0.03$). There were fewer 30-d readmissions in patients who attended early outpatient follow-up ($n = 17$, 23.61% *vs* $n = 55$, 76.39%, $P = 0.04$).

CONCLUSION

Our 30-d 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.

Key Words: Decompensated cirrhosis; Hospital readmissions; Interventions

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Core Tip: Our 30-d readmission rate was higher than the national rate but reduced by interventions in patients with decompensated cirrhosis (DC) with hepatic encephalopathy and early outpatient follow-up. Development of interventions to reduce early readmission in patients with DC is needed.

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INTRODUCTION

Cirrhosis affects approximately 5 million annually[1] and has been reported to be the 8th leading cause of death with more than 40000 deaths annually in the United States[2]. A study on the burden of gastrointestinal (GI), 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-d 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 d, 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*[17] developed a program including a hepatologist follow-up exam within 7 d after discharge. This program resulted in a reduction in 30-d readmissions, 60-d 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-d readmission, 12-mo 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-d 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-d readmission *vs* the SOC arm.

MATERIALS AND 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 coronavirus disease 2019 (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, 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 research electronic data capture (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, coagulopathy, portal hypertension, hepatopulmonary syndrome, hepatocellular carcinoma), and procedures performed during admission [esophago-gastro-duodenoscopy, colonoscopy or flexible sigmoidoscopy, paracentesis, 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 and 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 d 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 d 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 d 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 d 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 National Readmissions Administrative Database, we expected a 30-d readmission rate of 27% among patients meeting inclusion criteria, which yield 114/424 patients with 30-d 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-d 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 χ^2 -test or Fisher's exact test as applicable. Logarithmic transformation was used for comparing the 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 CTP 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 d (median 6, range 1-43 d). The mean cost of index admission was $\$60595 \pm \47174 ($n = 225$, median \$42932, range \$1630-251991). The top five reasons for index admission included volume overload ($n = 111$, 46.25%), AKI ($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$, 6.67%). The top five interventions performed were esophago-gastro-duodenoscopy ($n = 136$, 56.67%), paracentesis ($n = 115$, 47.92%), colonoscopy/flexible sigmoidoscopy ($n = 24$, 10%), HD ($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 d of discharge. The major reasons for first readmission included hepatic encephalopathy ($n = 26$, 32.10%) followed by volume overload ($n = 22$, 27.16%), AKI ($n = 16$, 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 d. The mean time to first readmission was 12.65 ± 7.55 d (median 12 d, range 1-30 d). The mean LOS of first readmission was 8.11 ± 8.98 days. The mean cost of stay of first readmission was $\$55548.29 \pm \65164.91 (Table 2). Those readmitted had a higher MELD-Na score on index admission (23.54 ± 7.80 vs 21.05 ± 8.03 , $P = 0.02$) and index discharge (21.67 ± 7.95 vs 19.39 ± 6.89 , $P = 0.03$) than those not readmitted. Similarly, those readmitted had a higher index admission creatinine (1.80 ± 1.53 vs 1.39 ± 1.16 , $P = 0.03$), index discharge creatinine (1.61 ± 1.34 vs 1.20 ± 0.97 , $P = 0.02$), and higher index admission INR (1.80 ± 0.64 vs 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% vs 45/120, 32.50%) and males in SOC arm (75/120, 62.50% vs 60/120, 50%, $P = 0.03$, Table 3). Index admission characteristics, disposition and index admission were also comparative in two arms (Tables 4 and 5).

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

There was no difference in the readmission rates for patients in the INT ($n = 4$, 35.83%) vs SOC arm ($n = 38$, 31.67%, $P = 0.59$, Table 6). Other outcomes including number of readmissions within 30 d ($P = 0.65$), 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.

Table 1 Characteristic features of index admission by readmission status, *n* (%)

	Total	Not readmitted (<i>n</i> = 159)	Readmitted (<i>n</i> = 81)	<i>P</i> value
Index admission characteristics				
Reasons for admission ¹				
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
SBP	21, 8.75	14, 8.81	7, 8.64	1.00
Complications of cirrhosis during admission ¹				
Presence of AKI	80, 33.33	50, 31.45	30, 37.04	0.39
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
SBP	16, 6.67	12, 7.55	4, 4.94	0.59
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
HPS	15, 6.25	8, 5.03	7, 8.64	0.27
HCC	11, 4.58	6, 3.77	5, 6.17	0.51
Procedures performed during admission ¹				
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 TIPS	10, 4.17	9, 5.66	1, 1.23	0.17
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				
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	

¹Patient can have more than one of variable listed.

SBP: Spontaneous bacterial peritonitis; AKI: Acute kidney injury; HE: Hepatic encephalopathy; HRS: Hepatorenal syndrome; HPS: Hepato-pulmonary syndrome; HCC: Hepatocellular carcinoma; EGD: Esophago-gastro-duodenoscopy; GI: Gastrointestinal; TIPS: Transjugular intrahepatic portosystemic shunt; HD: Hemodialysis; SNF: Skilled Nursing Facility.

Table 2 Characteristics and reasons for readmission

Readmission status	<i>n</i>	%
No	159	66.25
Yes	81	33.75
Number of readmissions within 30 d		
0	159	66.25
1	63	26.25
2	14	5.83
3	3	1.25
5	1	0.42
Location of 1 st readmission		
OSUWMC	59	72.84
Outside hospital	22	27.16
Reason for 1 st 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	3	3.70
LOS of first readmission (<i>n</i> = 81, mean ± SD), median = 5, range = 1 to 69	8.11 ± 8.98	
LOS of all readmissions (<i>n</i> = 105, mean ± SD), median = 4, range = 0 to 124	9.03 ± 14.42	
Cost of first readmission (<i>n</i> = 45, mean ± SD), median = \$31848.95, range \$765-325656.38	\$55548.29 ± 65164.91	
Waiting time for first readmission (<i>n</i> = 81, mean ± SD), median = 12, range = 1-30	12.65 ± 7.55	

¹Patient can have more than one of variable listed.

OSUWMC: The Ohio State University Wexner Medical Center; GI: Gastrointestinal; LOS: Length of stay.

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% *vs* *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 total 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 quality of life and caregiver burden[21]. In the validation of readmission using the liver-renal-risk score or "LIRER score", Freitas *et al*[22] showed that HE was not only a predictor of

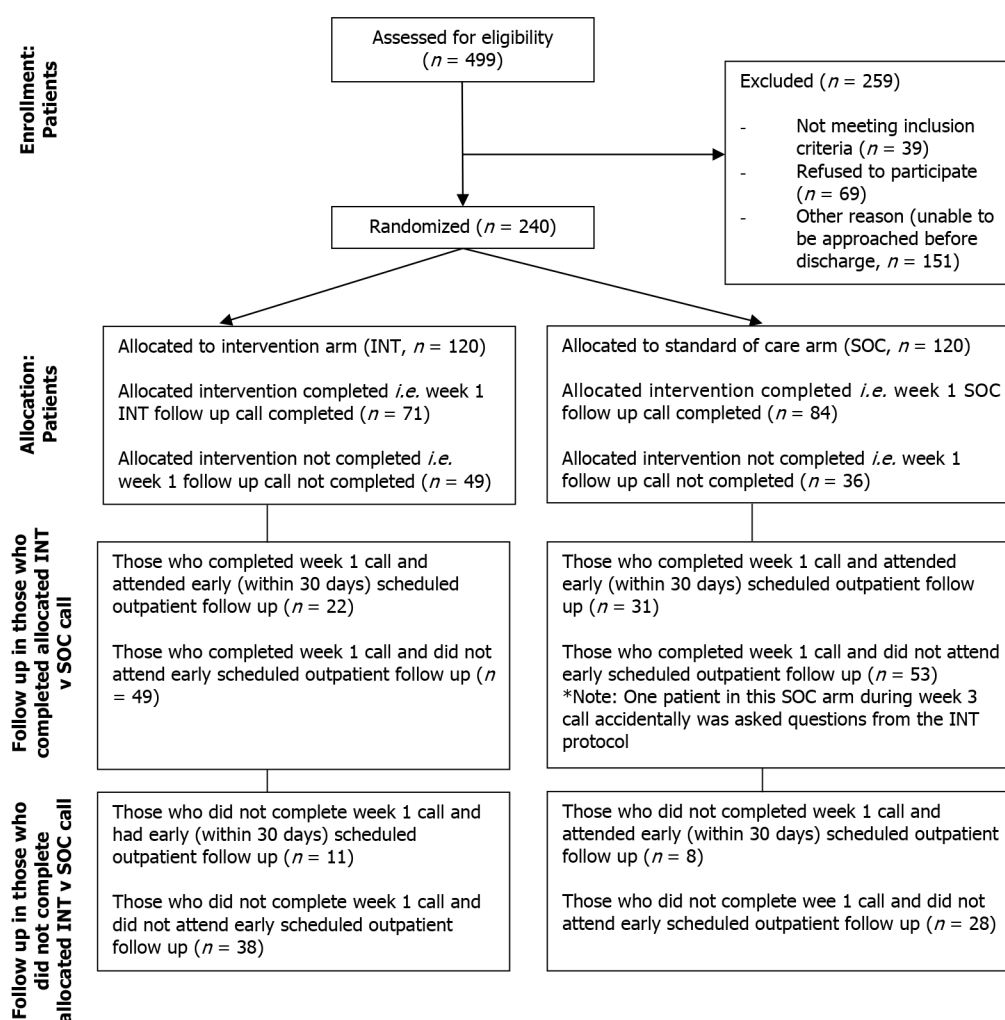
Table 3 Comparison of patient demographics and clinical characteristics by randomization arm, *n* (%)

	Intervention (<i>n</i> = 120)	Standard of care (<i>n</i> = 120)	<i>P</i> value
Patient demographics			
Age (mean ± SD)	56.54 ± 11.21	56.14 ± 11.21	0.78
Age group			
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			
Male	60, 50.00	75, 62.50	0.03
Female	60, 50.00	45, 32.50	
Race			
White	105, 87.50	97, 80.83	0.22
Other	15, 12.50	23, 19.17	
Ethnicity			
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)	\$68045 ± \$21370	\$68455 ± \$21651	0.88
Employment status			
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			
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-Na score admit (mean ± SD)	21.32 ± 8.19	22.47 ± 7.85	0.27
MELD-Na score discharge (mean ± SD, <i>n</i> = 117+118)	20.07 ± 7.74	20.25 ± 6.93	0.84
CTP score admit (mean ± SD)	9.31 ± 2.02	9.41 ± 1.89	0.69
CTP score discharge (mean ± SD)	8.44 ± 1.86	8.73 ± 1.89	0.24
Etiology of cirrhosis (Index admission ¹)			
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			
No	45, 37.50	61, 50.83	0.08
Yes	63, 52.50	53, 44.17	
Unknown	12, 10.00	6, 5.00	

¹Patient can have more than one of variable listed.

OSUWMC: The Ohio State University Wexner Medical Center; DC: Decompensated cirrhosis; MELD-Na: Model of End Stage Liver Disease Score; CTP: Child Pugh Score.



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Figure 1 Modified consort flow diagram of patients eligible for enrollment in study trial. INT: Intervention; SOC: Standard of care.

30 d readmission independent of MELD score, index, first-year, two-years and overall mortality, but also HE at admission had significantly higher mean LIRER scores. 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*[24] found that efforts to reduce medication-precipitated HE, prevent aspiration pneumonia and optimize HE medications on hospital

Table 4 Characteristic features during index admission in two randomization arms, *n* (%)

Index admission characteristics	Intervention (<i>n</i> = 120)	Standard of care (<i>n</i> = 120)	<i>P</i> value
Reasons for admission ¹			
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
Volume overload	59, 49.17	52, 43.33	0.44
Variceal bleed	21, 17.50	21, 17.50	1
Lower GI bleed	8, 6.67	11, 9.17	0.63
SBP	9, 7.50	12, 10.00	0.65
Complications of cirrhosis during admission ¹			
Presence of AKI	39, 32.50	41, 34.17	0.89
HE	25, 20.83	24, 20.00	1
Ascites	70, 58.33	69, 57.50	1
Variceal bleeding	21, 17.50	16, 13.33	0.48
SBP	10, 8.33	6, 5.00	0.44
HRS	7, 5.83	7, 5.83	1
Coagulopathy	32, 26.67	24, 20.00	0.29
Portal hypertension	19, 15.83	27, 22.50	0.25
HPS	10, 8.33	5, 4.17	0.29
HCC	6, 5.00	5, 4.17	1
Procedures performed during admission ¹			
EGD	68, 56.67	68, 56.67	1
Paracentesis	60, 50.00	55, 45.83	0.61
TIPS	7, 5.83	3, 2.50	0.33
HD	5, 4.17	10, 8.33	0.29
Colonoscopy/flex sig	13, 10.83	11, 9.17	0.83
Disposition			
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	

¹Patient can have more than one of variable listed.

SBP: Spontaneous Bacterial Peritonitis; AKI: Acute kidney injury; HE: Hepatic encephalopathy; HRS: Hepatorenal syndrome; HPS: Hepato-pulmonary syndrome; HCC: Hepatocellular carcinoma; EGD: Esophago-gastro-duodenoscopy; TIPS: Transjugular intrahepatic portosystemic shunt; HD: Hemodialysis; SNF: Skilled Nursing Facility; GI: Gastrointestinal.

discharge should be areas of focus to decrease HE readmissions. Tapper *et al*[25] demonstrated that development of a checklist for HE protocols integrated into the EMR and order entry system reduced odds of 30-d readmission for patients with HE (from 39.2% to 27.6%). Thus, our results are congruent with existing evidence that interventions should be invested in post-discharge education and

Table 5 Clinical and laboratory features during index admission and discharge in two randomization arms, *n* (%)

	Intervention (<i>n</i> = 120)	Standard of care (<i>n</i> = 120)	<i>P</i> value
Index admission labs (mean ± SD)			
Sodium	132.59 ± 5.58	132.28 ± 6.28	0.68
Serum creatinine (mg/ dL)	1.42 ± 1.11	1.64 ± 1.47	0.19
Total bilirubin (mg/ dL)	5.90 ± 9.10	6.19 ± 7.80	0.79
Albumin (g/ dL)	2.83 ± 0.59	2.85 ± 0.55	0.72
INR	1.68 ± 0.52	1.70 ± 0.59	0.80
Hemoglobin (g/ dL)	10.22 ± 2.34	10.02 ± 2.04	0.48
Ascites			
Absent	35, 29.17	35, 29.17	0.44
Slight	26, 21.67	34, 28.33	
Moderate	59, 49.17	51, 42.50	
Encephalopathy			
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			
No	117, 97.50	115, 95.83	0.72
Yes	3, 2.50	5, 4.17	
Index admission discharge labs (mean ± SD)			
Sodium (mmol/L)	134.72 ± 4.14	134.95 ± 3.57	0.64
Serum creatinine (mg/ dL)	1.31 ± 1.06	1.37 ± 1.18	0.69
Total bilirubin (mg/ dL, <i>n</i> = 237)	5.50 ± 8.80	5.39 ± 6.96	0.92
Albumin (g/ dL, <i>n</i> = 237)	2.98 ± 0.64	2.94 ± 0.61	0.65
INR (<i>n</i> = 238)	1.71 ± 0.49	1.69 ± 0.45	0.65
Hemoglobin (g/ dL)	9.30 ± 1.69	9.21 ± 1.68	0.68
Ascites			
Absent	42, 35.00	39, 32.50	0.35
Slight	56, 46.67	66, 55.00	
Moderate	22, 18.33	15, 12.50	
Encephalopathy			
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			
No	114, 95.00	110, 91.67	0.44
Yes	6, 5.00	10, 8.33	

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 d 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* [17] in their retrospective program looked at the impact of follow-up of cirrhotics within 7 d after discharge with a hepatologist. They reported reduced 30-d readmission, 60-d mortality

Table 6 Outcomes and reasons of readmission characteristics by randomization arms, *n* (%)

	Intervention (<i>n</i> = 120)	Standard of care (<i>n</i> = 120)	<i>P</i> value
Readmission			
No	77, 64.17	82, 68.33	0.59
Yes	43, 35.83	38, 31.67	
Number of readmissions within 30 d			
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 1 st readmission			
Our institution	36, 83.72	23, 60.53	0.03
Outside hospital	7, 16.28	15, 39.47	
Reason for 1 st readmission ¹			
Acute kidney injury	10, 23.26	6, 15.79	0.58
Hyponatremia	4, 9.30	6, 15.79	0.50
Hepatic encephalopathy	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	2, 4.65	1, 2.63	1.00
Other	20, 46.51	22, 57.89	0.37
Index admission cost (mean ± SD, <i>n</i> = 116 + 109)	61581 ± 47825	59547 ± 46669	0.46
Index admission LOS (mean ± SD)	8.17 ± 5.56	8.08 ± 6.11	0.63
First readmission LOS (<i>n</i> = 43 + 38, mean ± SD)	7.58 ± 7.57	8.71 ± 10.41	0.58
All readmissions LOS (<i>n</i> = 60 + 45, mean ± SD)	9.28 ± 16.88	8.69 ± 10.44	0.82
Waiting time for first readmission (<i>n</i> = 43 + 38, mean ± SD)	11.16 ± 7.10	14.34 ± 7.77	0.06

¹Patient can have more than one of variable listed.

GI: Gastrointestinal; LOS: Length of stay.

and rate of emergency department visits and associated costs in those who followed up within 7 d. Morando *et al*[18] demonstrated that follow up with a “care management check-up” group as opposed to “standard outpatient care” reduced 30-d readmission, reduced 12-mo mortality, and saved almost 1500 euros per patient month of life. While Kanwal *et al*[9] 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. 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 *vs* 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 d, studies should evaluate the use of telehealth visits for follow up, especially in the COVID19 era, as outlined by Stotts *et al*[29].

CONCLUSION

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 *vs* 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 d 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.

ARTICLE HIGHLIGHTS

Research background

Decompensated cirrhosis (DC) is a leading cause of morbidity and mortality in the United States often requiring multiple hospitalizations to manage. Studies show 20%-37% of patients with DC are readmitted within 30 d of index admission, which has significant burden on patients, their families and the healthcare system.

Research motivation

We were motivated to study and reduce readmissions as we see the physical, mental and emotional toll repeated hospitalizations for DC take on our patients and their families.

Research objectives

We sought to enroll patients in a randomized trial seeing if a nurse case manager (CM) ensuring early outpatient follow up, medication compliance and outpatient paracentesis if needed reduced readmissions in patients with DC.

Research methods

We sought to enroll patients in a randomized trial seeing if a nurse CM ensuring early outpatient follow up, medication compliance and outpatient paracentesis if needed reduced readmissions in patients with DC.

Research results

While our calculated sample size was not achieved due to the coronavirus disease 2019 pandemic, we found a 33.75% 30 d readmission rate in our patients admitted with DC. There was no difference in readmission between intervention and standard of care arms. Most patients were re-admitted with hepatic encephalopathy. There was a lower 30 d readmission rate in patients with hepatic encephalopathy in the intervention arm and those who attended early outpatient follow up.

Research conclusions

Our 30 d readmission was higher than the national rate. Further efforts should explore the positive impact of a nurse CM and early outpatient follow up in reducing readmissions for patients with cirrhosis, especially with hepatic encephalopathy.

Research perspectives

Further development of strategies to predict and reduce readmissions for patients with DC should be done.

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FOOTNOTES

Author contributions: Pusateri A and Mumtaz K study design, team administration, training team members for recruiting, recruiting patients for study, interpreting data, drafting manuscript; both approved the final submitted version of this manuscript; Litzenberg K, Griffiths C, Hayes C, Gnyawali B and Manious M recruiting patients for study, drafting manuscript, approved the final submitted version of manuscript; Jalil S, Kelly S and Conteh L reviewed and edited the final draft of the manuscript; Nagaraja K analyzed data, edited manuscript, and approved the final submitted version of this manuscript.

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Institutional review board statement: 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.

Clinical trial registration statement: Since our randomized trial was of a nursing intervention only, it was not an official randomized control clinical trial that needed registering on a national level.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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