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# A retrospective study of drug utilization and hospital readmissions among Medicare patients with hepatic encephalopathy

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**Abstract**

Hepatic encephalopathy (HE) is a complication occurring in patients with cirrhosis and is associated with neuropsychiatric and motor abnormalities. Symptomatic HE episodes almost always require hospitalization and the frequent recurrence of episodes is associated with poor prognosis and increased medical costs. The utilization of existing therapies for management of HE and adherence to them has yet to be evaluated using real-world claims data.

The aim of this study was to evaluate HE drug regimens and adherence and their association with hospital readmissions in Medicare Advantage plan patients.

This was a retrospective cohort study of patients discharged from a HE-related hospitalization or emergency room visit. Based on subsequent enrollment in the plan they were categorized into cohorts of 1 month, 3, and 6 months follow-up, and medication regimen was evaluated within the first month. The drugs evaluated included lactulose, rifaximin, and neomycin. Multivariable logistic regression was conducted to evaluate the association of drug regimen and medication adherence measured as proportion of days covered with HE readmissions.

There were 347 patients hospitalized for HE with 184 patients having 30-day enrollment and either a drug refill or an outpatient visit in this duration. Medications were not refilled by 67 (36.4%) patients. Various drug regimens had different adherence with mean (standard deviation) proportion of days covered ranging from 0.56 (0.29) to 0.82 (0.16) at 3 months and 0.48 (0.3) to 0.77 (0.15) at 6 months. The results of logistic regression at 3 and 6 months did not show a significant association of medication use or medication adherence with hospital readmissions.

Despite availability of therapy, medication utilization was alarmingly low after discharge of patients from HE-related hospitalization. Medication adherence was also low, which may affect the rate of recurrence and costs associated with readmissions. Efforts are needed in both care coordination of these patients to ensure they are prescribed appropriate medications and to enhance adherence to them.

**Abbreviations:** CMS = Center for Medicare and Medicaid Services, HE = hepatic encephalopathy, OR = odds ratio, PDC = proportion of days covered, SD = standard deviation.

**Keywords:** adherence, cirrhosis, hepatic encephalopathy, lactulose, readmission, rifaximin

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## 1. Introduction

Hepatic encephalopathy (HE) is a severe complication of cirrhosis presenting a range of symptoms starting with psychomotor changes and progressing to confusion, disorientation, and eventually coma.[1,2] Chronic liver disease affects over 5.5 million patients in the U.S. Despite that, the accurate data for HE incidence is not available due to symptom variability among patients, and approximately 20% to 80% of patients with liver disease experience some form of HE.[3–6]

HE can be either minimal or overt. Patients with minimal HE experience subtle manifestations and may test normally for certain observational examinations for diagnosing HE whereas overt HE is undoubtedly symptomatic and may require hospitalization.[2,7] HE is associated with poor survival ranging between 15% and 42% at 1 year.[8,9] Increasing prevalence of cirrhosis may lead to more patients experiencing HE as a complication over time.[10] HE is associated with a significant economic burden and healthcare utilization especially due to the high rate of hospital readmissions.[5,11,12] According to data from the 2003 Healthcare Cost Utilization Project, HE as a primary diagnosis had a mean length of stay of 5.7 days and mean charge per patient per stay of $23,192.[13] More recent estimates regarding the cost of HE-related hospitalizations were $36,108 per case in 2009.[14] The burden of HE associated with its symptoms extend to increased indirect costs for caregivers and reduced quality of life of the patients as well.[15] Reducing the bouts of HE and its associated hospital readmissions is an important step toward reducing the burden of HE.

According to the 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, treatment of an HE event should be based on resolving the precipitating factor of the episode followed by management of the patients' mental status. Additionally, drug treatment for prevention of recurrence of HE is also a part of the management of HE.[16] Common treatment options for HE include lactulose and rifaximin.[16] Lactulose, a non-absorbable disaccharide, is frequently prescribed to HE patients as a as first line therapy. While adherence to lactulose has been associated with decrease HE recurrence, adherence remains sub-optimal partly because of the dosing complexity of lactulose.[12,17] Rifaximin is a non-absorbable locally acting antibiotic that can be used as an add-on to lactulose or as a first line therapy. Neomycin is an antibiotic used widely in the past for HE and is still prescribed by some practitioners.[16] Rifaximin and lactulose combination is considered the best therapy available to maintain remission and prevent recurrence of overt HE.[18] As compared to other antibiotics, rifaximin has equivalent or superior effects and good tolerability.[16] As with other treatments for patients with cirrhosis, non-adherence to medications is often a concern.[19,20]

While previous literature has demonstrated frequent readmissions and high medical costs of patients with HE, studies investigating the drug regimens and their treatment adherence after an HE-related hospitalization using real world data are scarce. The objective of this study was to evaluate the association of medication regimen, and medication adherence with the risk of hospital readmissions among patients newly discharged from a hospital stay or emergency room visit for HE.

## 2. Methods

### 2.1. Data description

This retrospective cohort study was performed using administrative claims data from 2011 to May 2018 from a regional Medicare Advantage plan in Texas. Medicare is a federal health plan available to people aged 65 and over as well as individuals with disabilities and end-stage renal disease. Medicare Advantage plans are a type of Medicare health plan offered by companies that contract with Medicare to provide services to the beneficiaries.[21] The Managed Care plan provided administrative claims data, which included plan enrollment file, inpatient and outpatient medical files, and pharmacy files. The enrollment file contained membership and demographic information. Inpatient claims had all diagnoses and procedures captured through hospital admissions, and outpatient claims contained information on office-based visits. The pharmacy files included the drug name, prescription fill dates, quantity supplied, as well as dosing information.

This study was approved by the University of Houston Institutional Review Board. As this was a retrospective study of de-identified data obtained from the health plan, it did not involve patient consent.

### 2.2. Study design

The study design is presented in Figure 1. Patients were identified if they had an HE-related hospitalization discharge or emergency room visit identified using the International Classification of Diseases, Ninth and Tenth Revision (ICD-9, ICD-10) codes. The date of discharge was the study index date. Patients were included in the study if they had either a medication refill for HE or an outpatient visit within 30 days of hospital discharge.

### 2.3. Medication regimen

Medications evaluated for patients included lactulose, rifaximin, and neomycin identified within 30 days of the index discharge. For the purpose of analysis, medication exposure was classified as any medication or no medication use. Any medication use was defined as the receipt of lactulose, rifaximin, and neomycin monotherapy or any combination of these medications.[16]

### 2.4. Adherence measurement

Proportion of days covered (PDC) was used to measure adherence to any HE medication in the follow-up (lactulose, neomycin, rifaximin). For patients using combination, patient-days on both the medications were not double-counted in calculating the days covered. Similarly, days spent in hospitals during follow-up were subtracted from the total days' supply, with the assumption that patients had received medication during hospitalization. PDC was dichotomized and patients with a PDC value $\geq$0.8 were considered adherent.[22]

### 2.5. Hospital readmission

HE-related hospital readmission after the index discharge was evaluated as the outcome. The association of medication use with HE-related hospital readmission was assessed. Among patients with medication use within the first 30 days, the association between being adherent and hospital readmissions was also

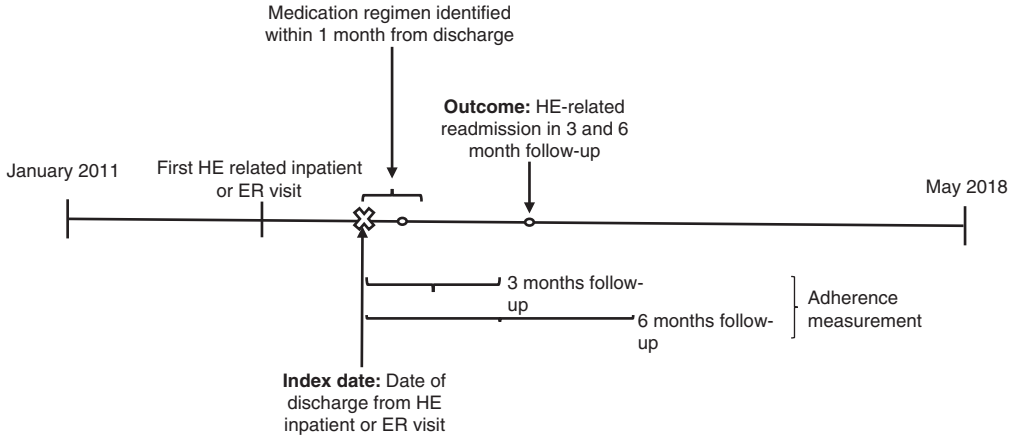


**Figure 1.** Schematic representation of study design.

evaluated. In the 3-month follow-up, 90-day readmissions were assessed, and the 6-month follow-up assessed 180-day readmissions.

### 2.6. Follow-up duration

The follow-up durations varied for different outcome measures. Medication regimen was identified within the first 30 days after discharge, while medication adherence and readmission outcomes were evaluated at 3- and 6-month follow-up from the discharge. Patients who were continuously enrolled in the health plan during these follow-up periods were included in the analytical cohort for evaluating the outcome.

### 2.7. Statistical analysis

Descriptive statistics were compared for baseline characteristics including age, sex, low-income subsidy for pharmacy medications, and Center for Medicare and Medicaid Services (CMS) risk score among patients who received any medication versus no medication after hospitalization. The CMS risk score was obtained from the Managed Care plan and is a single variable that accounts for medication burden and disease severity.[23,24] Proportions of patients who were on each medication regimen were also identified and compared. In order to adjust for the baseline demographic variables age, sex, low-income subsidy status, and CMS risk scores, a propensity-sore adjusted analysis was performed. This allowed controlling for essential covariates despite the small sample size in the study. The propensity score was generated by using a logistic regression model with medication use versus no medication use as the outcome variable. Logistic regression was then performed to assess the association of medication use (vs no use) with hospital readmission adjusting for the propensity score as a co-variable. A multivariable logistic regression was also performed with the same co-variates adjusted for in the propensity score model to compare the results from the 2 methods in order to evaluate the potential impact of the small sample size on the study findings given the limitations of each modeling method. Among patients who were using medications, a subgroup analysis was further conducted to identify the association between medication adherence and hospital readmission during each follow-up durations (3 and 6 months). The subgroup analysis was also performed using both propensity-score adjustment and a multivariable regression model. All analyses were performed using SAS 9.4 (Statistical Analysis Institute, Cary, NC) at an a priori $\alpha$ level of 0.05.

## 3. Results

There were a total of 374 patients with hospital admissions or emergency room visits for HE between 2011 and 2018. Of these, 184 patients met the inclusion criteria of having either a medication use or outpatient visit within the month of discharge and a minimum of 30 days of continuous enrollment with the health plan. The descriptive statistics of these patients are presented in Table 1. There were 117 (63.6%) patients with any

**Table 1**

**Baseline demographics of patients enrolled for 30 days after index discharge.**

| Variable | Any medication (n = 117) | No medication (n = 67) | *P*-value |
|---|---|---|---|
| Age, *mean (SD)* | 68.66 (8.67) | 68.76 (11.40) | .94 |
| Male, *n (%)* | 64 (54.71%) | 40 (59.70%) | .51 |
| Had low-income subsidy, *n (%)* | 29 (24.79%) | 22 (32.84%) | .07 |
| CMS risk score, *mean (SD)* | 3.77 (1.99) | 3.30 (2.19) | .40 |
| Medication regimen, *n (%)* | | | |
| Lactulose | 80 (43.48%) | – | – |
| Rifaximin | 9 (4.89%) | – | – |
| Neomycin | 3 (1.63%) | – | – |
| Combination of lactulose with rifaximin or neomycin | 25 (13.59%) | – | – |

CMS = Centers for Medicare and Medicaid Services, SD = standard deviation.

**Table 2**

**Hepatic encephalopathy (HE)-related exacerbations that required hospitalization or emergency room (ER) visit in the follow-up.**

| Readmission outcome measurement time frame | Readmission in patients with | | *P*-value |
|---|---|---|---|
| | Any medication | No medication | |
| 0–30 d (n=184) | 10 (8.55%) | 6 (8.96%) | .92 |
| 0–90 d (n=164) | 15 (14.42%) | 12 (20.00%) | .39 |
| 0–180 d (n=134) | 23 (25.84%) | 7 (15.56%) | .18 |

HE-medication utilization in this period. Table 1 also presents the number of patients on each medication regimen. Lactulose was the most commonly used medication regimen (68.3%) followed by a combination of lactulose with an antibiotic (21.4%). Antibiotic use, that is, either rifaximin or neomycin, was observed in 10.2% patients. For the analysis, there were 164 patients with 3-month enrollment and 134 patients with 6-month enrollment.

The rates of hospital readmissions in each follow-up duration are presented in Table 2. Chi-Squared tests could not identify any significant difference in the rate of readmission across the patients who had a medication as compared to those who did not. The readmission rate at 3 months was lower in the medication use group (14.5% vs 20%) when compared to patients without medication use. Results of the multivariable and propensity-score adjusted logistic regression models to identify association of medication use with readmission is presented in Table 3. Although the logistic model did not show a significant association between medication use and HE-related readmissions, the direction of the estimate at 90 days favored medication use [odds ratio (OR): 0.62; 95% confidence interval (CI): 0.26–1.45], but flipped in the 6-month follow-up (OR: 1.73; 95% CI: 0.67–4.48).

Among patients who received medication and also had continuous enrollment during 3 and 6 months after the hospital discharge, a majority (43.5%) were using lactulose followed by 13.6% patients using a combination of lactulose with an antibiotic (rifaximin or neomycin). Patients using a combination of lactulose with rifaximin or neomycin had a highest mean PDC 0.82 [standard deviation (SD): 0.16) and 0.76 (SD: 0.23) in the 3- and 6-month follow-up], followed by those who received rifaximin [SD: 0.75 (0.17) and 0.77 (SD: 0.15)], and with the lowest mean PDC observed in patients using lactulose (0.56 (SD: 0.29) at 3 months and 0.48 (SD: 0.30) at 6 months). Only 17 (16.4%) patients during the 3-month follow-up and 9 (10.1%) patients in the 6-month follow-up had a PDC of 0.8 or greater. The results of multivariable and propensity-score-adjusted logistic regression analysis presented in Tables 3 and 4 did not show a significant association of being adherent with hospital readmissions during both 3- and 6-month follow-ups.

## 4. Discussion

This study used administrative claims data to identify the medication regimen and examine hospital readmissions in older adults with HE. Findings indicate that among patients discharged after HE exacerbations, only 64% patients received medication treatment despite recommendations from the European Association for the Study of the Liver and American Association for the Study of Liver Diseases regarding the use of specific drug therapy after correction of the precipitating factors leading to an HE episode.[16] Furthermore, among patients on any medication, the mean 90-day adherence was low, with some variations among medications used by patients.

The inclusion criterion of the study required the patients to have either a medication use or physician visit in the first 30 days to be included in the study. Without this inclusion criterion the medication use among the sample of patients admitted for HE was even lower (approximately 45%). The reason for this criterion was to ensure that patients had visited a physician to provide an opportunity for the guideline recommended medications to be prescribed, in order to reduce selection bias. The adjusted model did not show significant differences even though the direction still favored medication use, possibly due to a low sample size. The low medication use is concerning and presents opportunities for both physician education regarding the guidelines as well as care-coordination among patients who are discharged from the hospital after an HE episode. Even though patients with HE represent a small portion of the overall health

**Table 3**

**Results of multivariable and propensity score adjusted logistic regression models for assessment of 3- and 6-month readmissions with primary exposure being medication use as compared to no use.**

| Variables | Readmission at 90 d | | Readmission at 180 d | |
|---|---|---|---|---|
| | Odds ratio (95% confidence interval) | *P*-value | Odds ratio (95% confidence interval) | *P*-value |
| Multivariable model | | | | |
| Medication use vs no use | 0.61 (0.25–1.47) | .27 | 1.74 (0.67–4.54) | .26 |
| Age | 1.03 (0.98–1.08) | .21 | 1.02 (0.97–1.06) | .49 |
| CMS risk score | 1.09 (0.88–1.34) | .44 | 1.14 (0.93–1.39) | .20 |
| Sex | 0.72 (0.30–1.73) | .46 | 1.31 (0.56–3.04) | .54 |
| Low-income subsidy | 0.32 (0.10–1.01) | .05 | 0.64 (0.25–1.62) | .35 |
| Propensity-score-adjusted model | | | | |
| Medication use vs no use | 0.62 (0.26–1.45) | .27 | 1.73 (0.67–4.48) | .26 |
| Propensity score variable[†] | 0.08 (<0.00–9.42) | .30 | 0.06 (<0.00–9.08) | .27 |

CMS = Centers for Medicare and Medicaid Services.

[†] Propensity score calculation included the variables age, sex, CMS risk score, and low-income subsidy.

**Table 4**

**Results of multivariable and propensity score adjusted logistic regression for assessment of 3- and 6-month readmissions with primary exposure being medication adherence measured as PDC.**

| Variables | Readmission at 90 d | | Readmission at 180 d | |
|---|---|---|---|---|
| | Odds ratio (95% confidence interval) | *P*-value | Odds ratio (95% confidence interval) | *P*-value |
| Multivariable model | | | | |
| PDC≥0.8 vs PDC < 0.8 | 2.00 (0.56–7.12) | .28 | 1.55 (0.52–4.71) | .43 |
| Combination, rifaximin, or neomycin use vs lactulose use only | 1.40 (0.36–5.42) | .62 | 1.55 (0.50–4.87) | .45 |
| Age | 1.10 (1.02–1.19) | .02 | 1.02 (0.97–1.08) | .43 |
| CMS risk score | 0.97 (0.70–1.33) | .84 | 1.08 (0.83–1.41) | .55 |
| Sex | 1.19 (0.36–3.96) | .78 | 1.32 (0.49–3.53) | .59 |
| Low-income subsidy | 0.24 (0.04–1.34) | .11 | 0.72 (0.24–2.27) | .57 |
| Propensity-score-adjusted model | | | | |
| PDC≥0.8 vs PDC < 0.8 | 1.71 (0.52–5.64) | .38 | 1.52 (0.52–4.44) | .45 |
| Propensity score variable[†] | 0.12 (0.00–3.17) | .20 | 0.24 (0.02–3.46) | .29 |

CMS = Centers for Medicare and Medicaid Services, PDC = proportion of days covered.

[†] Propensity score calculation included the variables medication use type (combination, rifaximin or neomycin use vs. lactulose use only), age, sex, CMS risk score and low-income subsidy.

plan, they represent a sample with high healthcare utilization and therefore higher costs.[14,17] Improving evidence-based medication prescribing can translate into cost savings in this high-risk population.

The enrollment at 30 days was 91% of the included sample, which further reduced to 81% at 3-month and 66% during the 6-month follow-up. The annual disenrollment rates from this data source have been reported to be lower at 3% to 5% by the health plan. In the study by Bustamante et al, 74% of patients with an acute HE event died during the follow-up period of 12±17 months. High disenrollment from the plan could be due to death of the patients, which cannot be captured from administrative claims data. This disenrollment can also be used to explain the change in direction of the multivariable logistic regression results for medication use and hospital readmission in the 6-month follow-up as compared to 3-month follow-up. There was a variable attrition between the 2 study groups at the 3- and 6-month follow-up whereby more patients without medication use disenrolled as compared to the patients with medication. To illustrate this point, half of the patients with 3-month readmission outcome in the no medication use group were disenrolled from the study at the 6-month follow-up as compared to 13% patients in the medication use group. A potential explanation could be that the sicker patients died and disenrolled leading to a change in direction of OR at 6-month follow-up, which may reflect an increased survival among the patients using medication.

Medication adherence was low among patients on medication ranging between 48% and 77% at 6 months with variations depending on the medication class the patients were using. A study evaluating precipitating factors for HE found lactulose non-adherence as the most frequently reported factor by 51% to 53% of patients.[25] Adherence to medications also prevents the occurrence of other precipitating factors such as constipation and infection, which the medications are prescribed to address. Efforts are required in emphasizing adherence to HE related medications but also understanding the reasons for non-adherence. Lactulose use can be complex as patients need to self-titrate and overuse can lead to diarrhea causing dehydration, which can precipitate HE as well as be a reason for non-adherence.[17] If poor tolerability is the reason for non-adherence, patients should be switched to other approved medications. Literature has shown better adherence rates and tolerability of rifaximin as compared to lactulose, which was also seen with this study however, we had fewer patients on rifaximin than lactulose.[3,26] The ultimate goal for patients with HE is management of all aspects to prevent recurrence because though the precipitants of HE are inter-related, they can all independently induce HE.

## 5. Limitations

This study had several limitations, most of which arise due to the use of secondary databases. Medication information from claims data only capture refills and therefore, for the patients who were not on medication, it could not be ascertained if they were not prescribed the medications or did not refill the prescriptions. As the data source of the study was a Managed Care Advantage plan in Texas, the generalizability of the study in terms of the rates of medication use as well as hospital readmissions is limited to patients with a similar demographic.

The study incorporated several years of data but the health plan had a small sample of patients who were eligible for the study. The low sample size could be the reason that we could not detect any differences among the study groups and results of the study should be interpreted with caution. However, there are few studies evaluating the effect of HE related care on patient outcomes and this is the first study to our knowledge that uses administrative claims data in a Medicare population. We did not have laboratory information that could be adjusted in the analytic models to adjust for the differences in prognosis of patients from the 2 risk groups. Even though propensity-score analysis adjusting for demographics and the CMS risk score was used for the analysis, there could be unmeasured confounding by severity as this study was not prospective in nature. This may potentially result in sicker patients being more likely to receive medications as well as have greater readmissions due to the underlying pathology of HE. A continuous enrollment criterion was required to be able to assess the adherence as well as readmissions. However, the imposition of continuous enrollment could introduce bias as patients who had readmission but lost enrollment were not included in the study. The direction of this bias can be predicted as we empirically observed more patients who did not refill the medication but had readmission disenroll from the study, leading to an increased proportion of patients in the medication group with the outcome.

Despite these limitations, this study provides an understanding of HE treatment and management in older adults in the real-world setting. Future studies can evaluate the outcomes in a longer follow-up duration and evaluate the differences among patients receiving different medication regimens.

## 6. Conclusion

This study was undertaken to understand the association of hospital readmissions with medication regimen and adherence. Even though there was no difference in hospital readmissions found in this study, the rate of medication use was alarmingly low with poor adherence among patients who were using the medication representing an area of improvement for the providers to optimize outcomes in patients with liver disease experiencing HE.

## Author contributions

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**Formal analysis:** Aisha Vadhariya.
**Funding acquisition:** Susan Abughosh, Hua Chen.
**Investigation:** Susan Abughosh, Hua Chen, Aisha Vadhariya, Omar Serna, Hani Zamil.
**Methodology:** Susan Abughosh, Hua Chen, Aisha Vadhariya, Omar Serna, Hani Zamil.
**Project administration:** Susan Abughosh, Hua Chen.
**Resources:** Susan Abughosh, Hua Chen, Omar Serna.
**Supervision:** Susan Abughosh, Hua Chen.
**Validation:** Susan Abughosh, Hua Chen, Aisha Vadhariya, Omar Serna, Hani Zamil.
**Writing:** Susan Abughosh, Hua Chen, Aisha Vadhariya, Omar Serna, Hani Zamil.

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