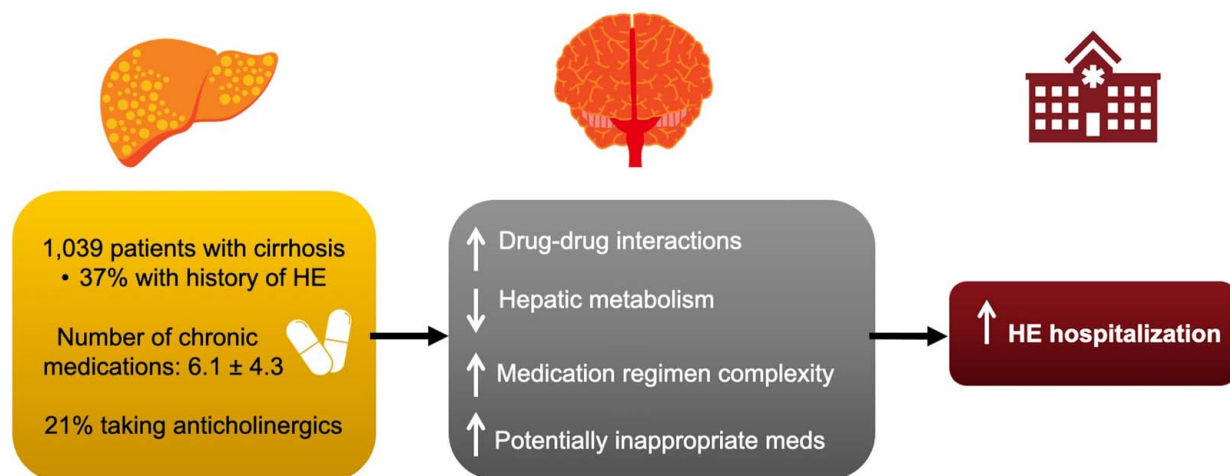


# Medication burden and anticholinergic use are associated with overt HE in individuals with cirrhosis

## VISUAL ABSTRACT


### Medication Burden and Anticholinergic Use in Cirrhosis



## ORIGINAL ARTICLE

OPEN

# Medication burden and anticholinergic use are associated with overt HE in individuals with cirrhosis

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**Abstract**

**Background:** Polypharmacy and anticholinergic medications are associated with cognitive decline in elderly populations. Although several medications have been associated with HE, associations between medication burden, anticholinergics, and HE have not been explored. We examined medication burden and anticholinergics in patients with cirrhosis and their associations with HE-related hospitalization.

**Methods:** We conducted a retrospective cohort study of patients aged 18–80 with cirrhosis seen in hepatology clinics during 2019. The number of chronic medications (medication burden) and anticholinergic use were recorded. The primary outcome was HE-related hospitalization.

**Results:** A total of 1039 patients were followed for a median of 840 days. Thirty-seven percent had a history of HE, and 9.8% had an HE-related hospitalization during follow-up. The mean number of chronic medications was  $6.1 \pm 4.3$ . Increasing medication burden was associated with HE-related hospitalizations in univariable (HR: 1.09, 95% CI: 1.05–1.12) and multivariable (HR: 1.07, 95% CI: 1.03–1.11) models. This relationship was maintained in those with baseline HE but not in those without baseline HE. Twenty-one percent were taking an anticholinergic medication. Anticholinergic exposure was associated with increased HE-related hospitalizations in both univariable (HR: 1.68, 95% CI: 1.09–2.57) and multivariable (HR: 1.71, 95% CI: 1.11–2.63) models. This relationship was maintained in those with baseline HE but not in those without baseline HE.

**Abbreviations:** AKI, acute kidney injury; EMR, electronic medical record; ICD, International Classification of Diseases; INPC, Indiana Network for Patient Care; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD-Na, Model for End-Stage Liver Disease; PPI, proton pump inhibitor; RR, risk ratio.

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**Conclusions:** Anticholinergic use and medication burden are both associated with HE-related hospitalizations, particularly in those with a history of HE. Special considerations to limit anticholinergics and minimize overall medication burden should be tested for potential benefit in this population.

## INTRODUCTION

HE is a defining characteristic of end-stage liver disease. It can present across a wide spectrum of neuropsychiatric deficits, ranging from subclinical impairment to gross disorientation, confusion, and coma.<sup>[1]</sup> In its clinically apparent form, overt HE is a burden on individuals and the health care system. It causes >100,000 hospitalizations annually in the United States at a cost of nearly \$12 billion, and it leads to poor quality of life, disability, and caregiver burden.<sup>[2–5]</sup> In at-risk individuals, overt HE can be precipitated by infections, gastrointestinal bleeding, kidney injury, electrolyte abnormalities, and medications.<sup>[6,7]</sup>

Medications with neuropsychiatric effects in particular can increase the risk of HE; opioids, benzodiazepines, benzodiazepine receptor agonists, and gabapentinoids have all been associated with overt HE.<sup>[8–11]</sup> In addition, some medications that are not central depressants (eg, proton pump inhibitors [PPIs]) have also been linked to HE.<sup>[12]</sup> However, the cumulative burden of these (and other) chronic medications on HE has not been explored. This topic is important, as polypharmacy is common in the cirrhosis population, and increased numbers of chronic medications for an individual can increase the risk of cognitive adverse events owing to drug interactions and synergism of medication side effects.<sup>[13,14]</sup> In other populations, polypharmacy has been linked to an increased risk of neurocognitive degenerative disorders (eg, delirium and dementia).<sup>[15,16]</sup>

Delirium and dementia have also been associated with the use of medications with anticholinergic effects.<sup>[17–20]</sup> Such medications are used for a variety of indications, including pruritis (eg, diphenhydramine), depression (eg, paroxetine), pain (eg, amitriptyline), muscle spasm (eg, methocarbamol), and irritable bowel syndrome (eg, hyoscyamine), among others. Many patients with cirrhosis suffer from these conditions and take anticholinergic medications, but the impact of anticholinergics on HE has not been examined.

Given the above gaps in the literature and the clinical importance of this topic, we sought to examine whether medication burden may be a marker of increased risk for overt HE and also whether anticholinergics are associated with HE. To achieve these goals, we performed a cohort study of patients with cirrhosis seen at a large tertiary care liver transplant center.

## METHODS

### Cohort definition

This retrospective cohort study was approved by the Indiana University Institutional Review Board. We included individuals aged 18–80 with a diagnosis of cirrhosis without a previous liver transplant seen consecutively at Indiana University Health Hepatology Clinics in 2019. Potentially eligible patients with an outpatient hepatology clinic encounter during 2019 were identified using International Classification of Diseases (ICD), 10th edition codes for cirrhosis: K70.30, K70.31, K74.60, K74.69, K74.3, K74.4, and K74. Eligibility was then confirmed through a detailed chart review. Cirrhosis was diagnosed based on liver histology or characteristic clinical, laboratory, imaging, and endoscopic features. The first clinic visit in 2019 was considered the baseline visit. Patients were followed from the baseline visit until liver transplant, death, or administrative censoring on December 31, 2021. All study data were extracted by manual chart review from the primary electronic medical record (EMR) and the Indiana Network for Patient Care (INPC). The INPC is a large statewide health information exchange, connecting data from over 20 million patients across >120 hospitals from 38 health systems across the state of Indiana, allowing for the capture of outcome data from multiple hospitals.<sup>[21]</sup>

### Exposures

Medication exposure was collected at the time of the clinic visit through the EMR's medication reconciliation. The primary medication class of interest was anticholinergics, defined as medications with an anticholinergic burden score of 2 or 3 as described elsewhere (those with established and clinically relevant cognitive anticholinergic effects).<sup>[22]</sup> Anticholinergics were also examined as a binary time-varying covariate. The duration of exposure was calculated based on prescription fill dates and quantities from the EMR. Because this exposure duration could not be calculated for nonprescription medications (eg, diphenhydramine, one of the more commonly used anticholinergics), this time-varying covariate analysis was not the primary analysis. We also examined additional medication classes known to be associated with HE: opioids, benzodiazepines,

benzodiazepine receptor agonists, gabapentinoids, and PPIs.<sup>[8,11,12]</sup> Statins, which have been associated with reduced HE risk, were also examined.<sup>[23]</sup> We further identified medications used to treat complications of liver disease: diuretics, nonselective beta-blockers, spontaneous bacterial peritonitis prophylaxis, lactulose, and rifaximin. A complete list of medications examined is listed in Supplemental Table S1, <http://links.lww.com/HC9/A924>. Medication burden was examined based on the total number of chronic medications (those started at least 30 days before the visit with a  $\geq 30$ -day prescription excluding those prescribed “PRN”) excluding those used to manage cirrhosis complications listed above. In defining anticholinergic exposure, both scheduled and PRN anticholinergics were included.

## Outcomes

The primary outcome was hospitalization for HE. Secondary outcomes included hospitalizations for ascites, gastrointestinal bleeding, acute kidney injury (AKI), and infections. Hospitalizations were identified from the EMR and the INPC, and the primary cause was identified through manual chart review. HE as the primary cause of hospitalization was based on initial presentation with acute altered mental status and improvement with HE-specific treatment (ie, lactulose and/or rifaximin). We did not include emergency department visits without inpatient admission as an outcome. Liver transplant and all-cause mortality were also examined.

## Variables

Demographic information included age, sex, race, and ethnicity (Black or African American, Latino or Spanish Origin, Other, and White), and insurance (Medicare, Medicaid, private, and other). The comorbidity burden was collected using the Charlson Comorbidity Index.<sup>[24]</sup> The presence of HCC was also collected.

Primary liver disease etiology was classified as alcohol, viral, metabolic dysfunction–associated steatotic liver disease (MASLD),<sup>[25]</sup> or other. Liver disease severity at baseline was collected, including a history of ascites, HE, and laboratory values to calculate the Model for End-Stage Liver Disease (MELD-Na) score and Child-Pugh classification.<sup>[26,27]</sup> Those with a previous history of HE at the baseline visit were considered to have baseline HE.

## Statistical analysis

Patient characteristics were compared by medication burden status and anticholinergic status. Continuous variables were presented as mean  $\pm$  SD or median

with IQR, and the Pearson R coefficient was used to compare continuous variables where appropriate. Categorical variables were presented as percentages. Differences across groups with respect to categorical variables were analyzed using chi-square and Fisher exact tests, whereas continuous variables were analyzed using *t* test among 2 groups, or ANOVA among 3 groups. Liver transplant and death were considered competing risks for the primary outcome of HE and secondary outcomes of ascites, gastrointestinal bleeding, AKI, and infection. Death was considered a competing risk for the liver transplant outcome. The relationships between the exposure variables (medication burden and anticholinergic use) and the outcomes were assessed using cause-specific multiple Cox proportional hazard models. All baseline variables were considered for inclusion in multivariable models. Backward selection was done by removing the least significant covariate one at a time until only a significant set of covariates was left. The likelihood ratio test was done to verify that the reduced model was not inferior to the full model. HRs and their corresponding 95% CIs were reported. In addition, Cumulative Incidence Competing Risk estimates for HE by anticholinergic status were plotted. Subgroup analyses were performed in those with and without HE at baseline. The main analyses examined the presence of anticholinergics at the time of the baseline clinic visit. In a secondary analysis, anticholinergic exposure was examined as a binary time-varying covariate from the time of the clinic visit through the study follow-up. For medication burden, a sensitivity analysis was also performed, where medications used to treat the complications of cirrhosis were included in the number of chronic medications. To examine the relationship between medication exposures and repeated hospitalizations, negative binomial regression was used with the number of HE hospitalizations as the outcome. For negative binomial regression, rate ratios (RRs) with 95% CIs were reported. The statistical significance level was set to 0.05 and *p* values were 2-sided. All analyses were performed in R (4.2.1) or in SAS (9.4).

## RESULTS

Of 1236 patients screened, 1039 met the inclusion criteria and were followed for a median of 840 days (IQR: 596–956) (Supplemental Figure S1, <http://links.lww.com/HC9/A925>). The mean age was  $59 \pm 11.8$  years and the majority were White (85.8%) and male (53%) (Table 1). The most common etiologies of cirrhosis were MASLD (36.9%) and alcohol (27.0%). The mean MELD-Na score was  $13.3 \pm 6.2$  and 56% had Child-Pugh class B or C cirrhosis. Thirty-seven percent had a history of HE at baseline. 9.8% experienced an HE hospitalization at a median of

**TABLE 1** Patient characteristics and anticholinergic exposure

Characteristic	Total	Anticholinergic (n = 223)	No anticholinergic (n = 816)	p
Age	58.8 ± 11.8	58.6 ± 10.9	58.9 ± 12.1	0.74
Sex, female	488 (47.0)	137 (61.7)	351 (43.0)	<0.001
Race				0.08
Black or African American	66 (6.4)	21 (9.5)	45 (5.5)	
Latino or Spanish origin	39 (3.8)	5 (2.3)	34 (4.2)	
Other	43 (4.2)	5 (2.3)	38 (4.6)	
White	891 (85.8)	191 (86.0)	700 (85.7)	
Insurance				0.12
Medicaid	197 (19.0)	47 (21.2)	150 (18.4)	
Medicare	432 (41.6)	103 (46.4)	329 (40.3)	
Private	346 (33.3)	61 (27.5)	285 (34.9)	
Other	64 (6.2)	11 (5.0)	53 (6.5)	
CCI	3.5 ± 2.0	3.8 ± 2.1	3.4 ± 2.1	0.004
Etiology of cirrhosis				0.013
Alcohol	277 (27.0)	54 (24.4)	223 (27.7)	
Viral	224 (21.9)	44 (19.9)	180 (22.4)	
MASLD	378 (36.9)	101 (45.7)	277 (34.5)	
Other	146 (14.2)	22 (10.0)	124 (15.4)	
MELD-Na	13.3 ± 6.2	13.4 ± 6.7	13.2 ± 6.0	0.75
Child-Pugh				0.72
A (5–6)	424 (44.0)	93 (45.1)	331 (43.7)	
B (7–9)	384 (39.8)	77 (37.4)	307 (40.5)	
C (10–15)	156 (16.2)	36 (17.5)	120 (15.8)	
HE	387 (37.2)	86 (38.7)	301 (36.8)	0.66
Ascites	565 (54.4)	119 (53.6)	446 (54.6)	0.85
HCC	85 (8.2)	13 (5.9)	72 (8.8)	0.20
Diabetes mellitus	440 (42.3)	122 (54.7)	318 (39.0)	<0.001

Note: Values reported as mean ± SD or n (%).

Abbreviations: CCI, Charlson Comorbidity Index; MASLD, metabolic dysfunction–associated steatotic liver disease; MELD-Na, Model for End-Stage Liver Disease.

176 days after their clinic visit (IQR: 65–345 d). In those with a history of HE at baseline, 18.6% had an HE hospitalization after a median of 154 days (IQR: 61–331).

## Medication burden

The mean number of chronic medications for the cohort was 6.1 ± 4.3. Fifty-nine percent were taking ≥ 5 medications chronically. The comparison of a number of medications according to patient characteristics is shown in Table 2. Medication burden had a weak correlation with age and MELD-Na and a moderate correlation with the Charlson Comorbidity Index. Medication burden was associated with all baseline variables except HCC. Medication burden was greatest in females, White patients, those with Medicare insurance, those with MASLD, Child-Pugh B or C cirrhosis, those with diabetes mellitus, and in those with HE and ascites at baseline.

Accounting for liver transplant and death, increasing medication burden was associated with increased HE hospitalizations in both univariable (HR: 1.03; 95% CI: 1.00–1.07) and multivariable models (HR: 1.05; 95% CI: 1.01–1.10) (Table 3). In other words, adjusting for potential confounding variables, with each additional chronic medication, the risk of an HE-related hospitalization increased by 5%. In the subgroup of those with HE at baseline, this relationship was maintained, but in those without baseline HE, the relationship was not statistically significant.

71.5% were taking medications used for the treatment of cirrhosis complications (diuretics, nonselective beta-blockers, spontaneous bacterial peritonitis prophylaxis, lactulose, and rifaximin). After including these medications, patients were taking 7.9 ± 4.6 chronic medications. A greater number of total chronic medications was also associated with increased HE hospitalizations in univariable (HR: 1.09; 95% CI: 1.05–1.12) and multivariable models (HR: 1.07; 95% CI: 1.03–1.11) (Table 3).

**TABLE 2** Patient characteristics and medication burden

Continuous variables	Pearson <i>R</i>	<i>p</i>
Age	<i>R</i> = 0.17	< 0.001
CCI	<i>R</i> = 0.36	< 0.001
MELD-Na	<i>R</i> = 0.09	0.004
Categorical variables	Number of chronic medications, mean (SD)	
Sex		< 0.001
Female	8.7 (5.0)	
Male	7.1 (4.1)	
Race		0.04
Black or African American	7.7 (5.6)	
Latino or Spanish origin	6.8 (5.3)	
Other	4.8 (4.4)	
White	8.0 (4.5)	
Insurance		< 0.001
Medicaid	7.2 (4.3)	
Medicare	9.3 (4.9)	
Private	6.4 (3.9)	
Other	7.9 (4.5)	
Etiology of cirrhosis		< 0.001
Alcohol	7.0 (4.1)	
Viral	6.6 (4.5)	
MASLD	9.6 (4.6)	
Other	7.8 (5.0)	
Child-Pugh		< 0.001
A (5–6)	7.1 (4.8)	
B (7–9)	8.5 (4.4)	
C (10–15)	8.6 (4.3)	
HE	9.5 (4.4)	< 0.001
No HE	6.9 (4.5)	
Ascites	8.5 (4.5)	< 0.001
No ascites	7.1 (4.6)	
HCC	7.4 (4.5)	0.31
No HCC	7.9 (4.6)	
Diabetes mellitus	9.7 (4.8)	< 0.001
No diabetes mellitus	6.5 (3.9)	

Abbreviations: CCI, Charlson Comorbidity Index; MASLD, metabolic dysfunction–associated steatotic liver disease; MELD-Na, Model for End-Stage Liver Disease.

## Anticholinergic medications

Characteristics of patients with and without exposure to anticholinergic medications are compared in [Table 1](#). Twenty-one percent of the cohort had exposure to anticholinergics. Of those with anticholinergic exposure, 15% had exposure to 2 and 2% had exposure to 3 medications. Specific anticholinergic medication frequency is listed in Supplemental Table S2, Supplemental Digital

Content 1, <http://links.lww.com/HC9/A924>. The most frequently used anticholinergics were hydroxyzine (19%), cyclobenzaprine (17%), diphenhydramine (12%), promethazine (12%), and dicyclomine (7%). Patients with anticholinergic exposure were more likely to be female (62% vs. 38%,  $p < 0.001$ ). There were no significant differences between age or race. However, those with exposure to anticholinergics had a greater Charlson Comorbidity Index (3.8 vs. 3.4,  $p = 0.004$ ) and were more likely to have diabetes. Those with MASLD were more likely to be taking anticholinergics (46% vs. 35%,  $p = 0.01$ ). Disease severity was similar between those with and without exposure to anticholinergics with no significant differences in MELD-Na or Child-Pugh class. The prevalence of HE at baseline was similar in those taking and not taking anticholinergics.

The 1-year unadjusted cumulative incidence of HE hospitalization in those taking anticholinergics was 14% compared to 7% in those not taking anticholinergics ( $p = 0.02$ ) ([Figure 1A](#)). Among those with baseline HE, the 1-year incidence of HE in those taking anticholinergics was 26% compared to 15% in those not taking anticholinergics ( $p = 0.02$ ) ([Figure 1B](#)). In contrast, in those without baseline HE, the 1-year incidence in those taking anticholinergics was 6% versus 3% in those not taking anticholinergics ( $p = 0.38$ ) ([Figure 1C](#)). Accounting for liver transplant and death, anticholinergics were associated with increased HE hospitalizations in both univariable (HR: 1.68; 95% CI: 1.09–2.57) and multivariable models (HR: 1.71; 95% CI: 1.11–2.63) ([Table 4](#)). In the subgroup of those with HE at baseline, this relationship was maintained, but in those without baseline HE, there was no statistically significant relationship. Treating anticholinergic use as a time-varying covariate, anticholinergics were associated with HE hospitalization in both univariable (HR: 1.80; 95% CI: 1.12–2.90) and multivariable models (HR: 1.67; 95% CI: 1.02–2.75) ([Table 4](#)).

## Repeat HE hospitalizations

The median number of HE hospitalizations was 1 (IQR: 1,2). Of the 102 patients with at least 1 HE hospitalization, 64 (63%) had only 1, 23 (23%) had a second hospitalization, 10 (10%) experienced a third, and 5 (5%) experienced  $\geq 4$  hospitalizations. Increasing medication burden trended toward an association with more HE hospitalization (RR: 1.04, 95% CI: 0.95–1.06). When including medications used to treat cirrhosis, increasing medication burden was associated with more HE hospitalizations (RR: 1.13, 95% CI: 1.07–1.18) as was anticholinergic exposure (RR: 2.48, 95% CI: 1.48–4.13).

## Other medication classes

Sixty-nine percent were on at least one of the following medication classes known to be associated with

**TABLE 3** Associations between medication burden and clinical outcomes

Outcome	Univariable HR (95% CI)	Multivariable HR (95% CI)
HE	1.03 (1.00, 1.07)	1.05 (1.01, 1.12)
Baseline HE subgroup	1.05 (1.01, 1.11)	1.07 (1.02, 1.12)
No baseline HE subgroup	0.99 (0.92, 1.07)	1.02 (0.95, 1.09)
Child-Pugh Class A	0.93 (0.80, 1.09)	0.99 (0.87, 1.12)
Child-Pugh Class B	1.07 (1.02, 1.13)	1.08 (1.03, 1.13)
Child-Pugh Class C	1.10 (1.02, 1.18)	1.08 (1.00, 1.17)
With diabetes mellitus	1.02 (0.96, 1.07)	1.04 (0.98, 1.10)
Without diabetes mellitus	1.05 (0.99, 1.11)	1.08 (1.02, 1.15)
Including cirrhosis medications	1.09 (1.05, 1.12)	1.07 (1.03, 1.11)
Ascites	1.00 (0.96, 1.04)	1.02 (0.98, 1.06)
GIB	0.98 (0.93, 1.03)	0.98 (0.93, 1.04)
AKI	0.98 (0.92, 1.03)	0.98 (0.93, 1.04)
Infection	1.03 (1.00, 1.07)	1.01 (0.97, 1.05)
Transplant	0.91 (0.86, 0.96)	0.96 (0.90, 1.02)
Mortality	1.02 (1.00, 1.03)	1.00 (0.98, 1.01)

Note: Covariates in the multivariable models for HE: baseline HE, baseline ascites, and baseline esophageal varices. Baseline HE was not included in models in the subgroups stratified by baseline HE. Covariates for ascites: MELD-Na and baseline ascites. Covariates for GIB: MELD-Na and baseline esophageal varices. Covariates for AKI: baseline HE and baseline ascites. Covariates for infection: insurance, MELD-Na, and CCI. Covariates for transplant: insurance, cirrhosis etiology, MELD-Na, CCI, baseline esophageal varices, and HCC. Covariates for mortality: age, insurance, MELD-Na, CCI, baseline HE, ascites, esophageal varices, and HCC. Abbreviations: AKI, acute kidney injury; CCI, Charlson Comorbidity Index; GIB, gastrointestinal bleed; MELD-Na, Model for End-Stage Liver Disease.

HE<sup>[8–12]</sup>: opioids (22%), benzodiazepines (9.5%), benzodiazepine receptor agonists (2.6%), gabapentinoids (16.7%), PPIs (50%), and anticholinergics (21%). HE hospitalization was associated with opioids (HR: 2.41, 95% CI: 1.61–3.60) and PPIs (HR: 2.70, 95% CI: 1.75–4.17). However, associations with HE were not significant for benzodiazepines (HR: 1.36, 95% CI: 0.74–2.50), benzodiazepine receptor agonists (HR: 1.95, 95% CI: 0.79–4.81), and gabapentinoids (HR: 1.13, 95% CI: 0.69–1.87). Statins were not significantly associated with reduced HE hospitalizations (HR: 0.85, 95% CI: 0.53–1.37).

### Other outcomes

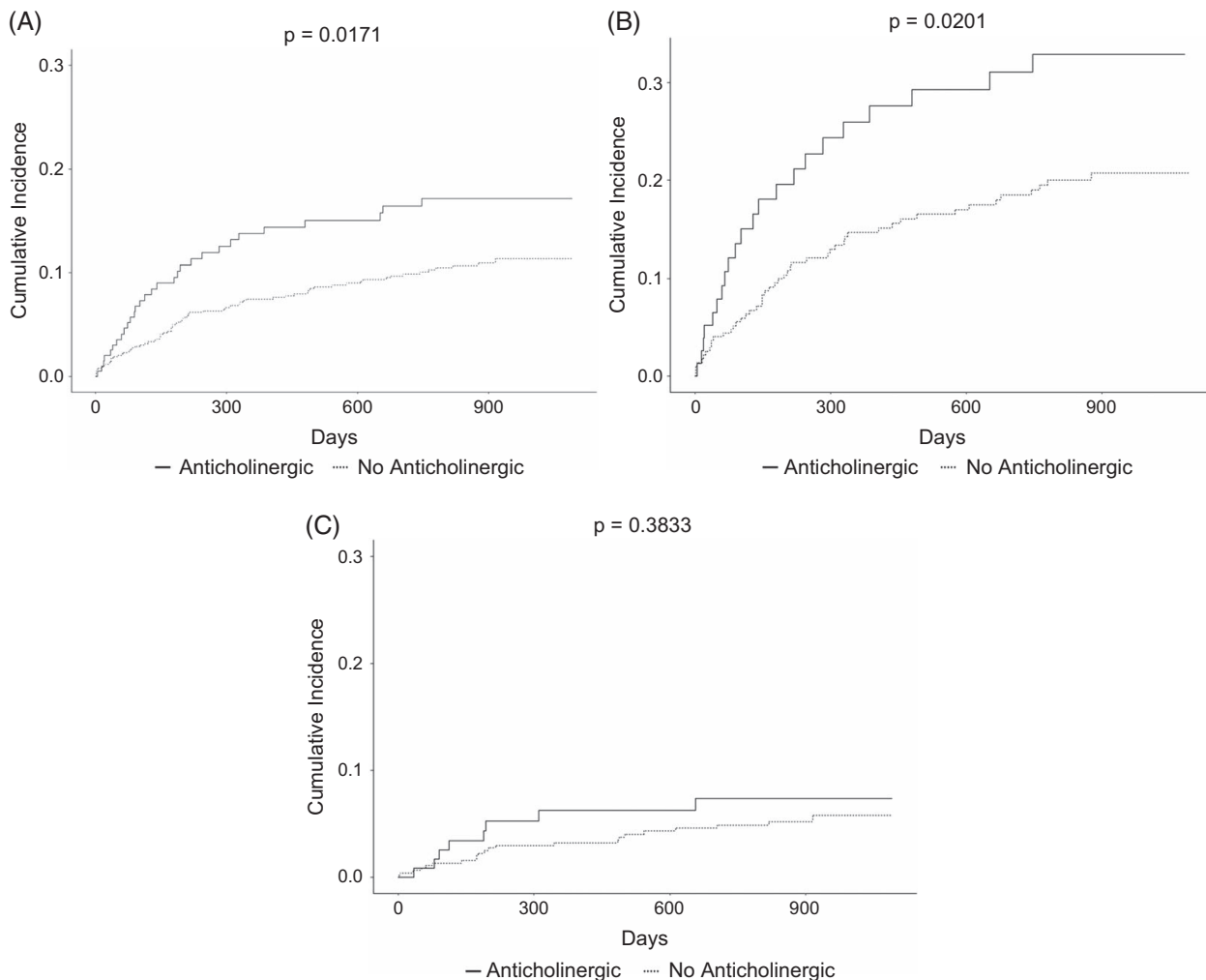
During follow-up, 12% were hospitalized for ascites, 8% for gastrointestinal bleeding, 8% for AKI, and 12% for infections. Ten percent underwent liver transplants, and 18% died. Univariable and multivariable models examining the relationships between medication burden and these other outcomes are shown in Table 3. In univariable cause-specific Cox models accounting for liver transplant and death, medication burden was not associated with gastrointestinal bleeding or AKI-related hospitalizations. However, it was associated with hospitalization for ascites and infection. In cause-specific Cox models accounting for death, medication burden was not associated with liver transplant. In univariable analysis, medication burden was associated with increased mortality. On multivariable analysis, none of these relationships were statistically significant.

Anticholinergics were associated with increased hospitalizations for infection in univariable and multivariable models but were not associated with any of the other outcomes (Table 4).

## DISCUSSION

Older adults and those with multiple chronic conditions often require multiple medications to manage these conditions, resulting in high rates of polypharmacy across populations.<sup>[28,29]</sup> Individuals with cirrhosis are particularly susceptible to this phenomenon, as they have a high burden of comorbidity and often require multiple medications to manage the causes and complications of cirrhosis.<sup>[30]</sup> In this large cohort study, we confirmed a high medication burden in cirrhosis, and this burden persisted even after excluding the medications used to manage cirrhosis. In addition, we found that 1 in 5 were taking anticholinergic medications, which have been associated with a host of adverse effects in multiple populations<sup>[31,32]</sup> and are a critical component of several medication appropriateness criteria, such as the Beers Criteria.<sup>[33,34]</sup> Both medication burden and anticholinergics were associated with an increased risk of HE-related hospitalization, novel findings which to our knowledge have not been demonstrated previously.

There are multiple mechanisms by which medication burden can lead to HE. We demonstrated significant proportions of patients taking medications previously identified as associated with HE: opioids,



**FIGURE 1** (A) Cumulative incidence function curve comparing HE-related hospitalizations based on anticholinergic exposure in the whole cohort. (B) Cumulative incidence function curve comparing HE hospitalizations based on anticholinergic exposure in those with HE at baseline. (C) Cumulative incidence function curve comparing HE hospitalizations based on anticholinergic exposure in those without HE at baseline.

benzodiazepines, gabapentinoids, and PPIs.<sup>[8–12]</sup> Those taking more medications are more likely to be on one of these (or other) potentially inappropriate medications, resulting in poor outcomes.<sup>[35]</sup> Many of these medications have mechanisms that can interrupt attention, memory, and processing abilities that may lead to HE.<sup>[36,37]</sup> Some sedating medications (eg, benzodiazepines) also have mechanisms of action that rely on pathways shared with HE pathophysiology, triggering decompensation.<sup>[38]</sup> Increased medication burden can also lead to more drug-drug interactions. Combined with the decreased hepatic metabolism of some medications, these phenomena may further contribute to HE risk. Along with an increased number of medications, increased medication regimen complexity (exemplified in cirrhosis by frequently adjusted diuretic regimens and lactulose dose titration requirements) has also been associated with nonadherence and hospitalization.<sup>[39]</sup> Our sensitivity analysis including

cirrhosis medications in the medication burden highlights this point.

Along with increased medication burden, anticholinergics were also associated with increased HE hospitalizations. This novel finding is in keeping with multiple studies documenting an increase in cognitive decline, dementia, and delirium with anticholinergics.<sup>[32,40,41]</sup> As with the other high-risk medication classes, anticholinergics may be considered potentially inappropriate in cirrhosis, particularly in those with a history of HE, and consideration should be made to reduce their use in this population.

In addition to our primary findings, several other results provide direction in identifying and intervening in those at the highest risk. First, the associations between medication exposures and HE were only significant in the subgroup with a history of HE at baseline. Although reducing medication burden in all patients with cirrhosis may be an important future goal, in the near term

**TABLE 4** Associations between anticholinergics and clinical outcomes

Outcome	Univariable HR (95% CI)	Multivariable HR (95% CI)
HE	1.68 (1.09, 2.57)	1.71 (1.11, 2.63)
Time-varying exposure	1.80 (1.12, 2.90)	1.67 (1.02, 2.75)
With baseline HE	1.82 (1.10, 3.02)	1.90 (1.15, 3.15)
Without baseline HE	1.43 (0.64, 3.20)	1.28 (0.58, 2.84)
Child-Pugh Class A	0.47 (0.06, 3.76)	0.51 (0.05, 4.88)
Child-Pugh Class B	2.00 (1.14, 3.53)	1.84 (1.02, 3.32)
Child-Pugh Class C	1.39 (0.63, 3.08)	1.52 (0.69, 3.39)
With diabetes mellitus	1.63 (0.91, 2.92)	1.82 (0.99, 3.35)
Without diabetes mellitus	1.66 (0.87, 3.16)	1.64(0.86, 3.12)
Ascites	1.29 (0.86, 1.94)	1.37 (0.90, 2.10)
GIB	1.19 (0.72, 1.96)	1.20 (0.71, 2.02)
AKI	1.26 (0.76, 2.08)	1.25 (0.76, 2.08)
Infection	2.01 (1.39, 2.90)	1.81 (1.24, 2.65)
Transplant	0.64 (0.36, 1.12)	0.79 (0.44, 1.41)
Mortality	0.94 (0.81, 1.09)	0.97 (0.83, 1.12)

Covariates in the multivariable models for HE: CCI, baseline HE, and baseline ascites. Baseline HE was not included in models in the subgroups stratified by baseline HE. Covariates for ascites: MELD-Na and baseline ascites. Covariates for GIB: MELD-Na and baseline esophageal varices. Covariates for AKI: baseline HE and baseline ascites. Covariates for infection: insurance, CCI, and baseline ascites. Covariates for transplant: insurance, cirrhosis etiology, MELD-Na, CCI, baseline esophageal varices, and HCC. Covariates for mortality: age, insurance, MELD-Na, CCI, baseline HE, ascites, esophageal varices, and HCC. Abbreviations: AKI, acute kidney injury; CCI, Charlson Comorbidity Index; GIB, gastrointestinal bleed; MELD-Na, Model for End-Stage Liver Disease.

focusing resources on those with a history of HE is more likely to yield improved outcomes. We also found that anticholinergic use disproportionately impacted women, with a trend toward increased use in Black patients and in those with MASLD cirrhosis. The medication burden also appeared greater in women and in those on Medicare and with MASLD. Special attention should be given to these patient groups to identify those on high-risk medication regimens.

In multivariable analysis, anticholinergics were associated with an increased risk for infection-related hospitalization. In community-dwelling older adults, anticholinergics have been linked to community-acquired pneumonia, possibly because of anticholinergic-induced sedation leading to aspiration and atelectasis.<sup>[42]</sup> Infections are very common in cirrhosis and are a leading cause of death in this population. Reductions in anticholinergic use may therefore benefit patients beyond a reduced burden of HE. In contrast, other outcomes were not associated with medications (eg, ascites and bleeding). These findings provide an important “negative control” for the results and support the notion that medication burden uniquely impacts HE.

In addition to including these other outcomes as negative controls, this study has numerous strengths. The large sample size and long follow-up time provide adequate power to detect differences in the outcomes while controlling for multiple confounders and allowing for subgroup analyses. We also repeated sensitivity analyses including cirrhosis medications and examined rates of repeated hospitalizations. Both yielded similar

results, suggesting robust associations for the main study questions. We also examined medications previously identified as associated with HE, providing some measure of external validity for the cohort. Although benzodiazepines, benzodiazepine receptor agonists, and gabapentinoids were not significantly associated with HE, these medications were used in relatively few patients as compared to opioids, PPIs, and anticholinergics. It is possible our study was underpowered to test these associations. Importantly, for the primary analyses, medication exposures were verified by direct chart review and did not rely on orders or pharmacy records. We do acknowledge several study limitations. Although chart review ascertainment of medications is likely more accurate than other medication measures, we are not able to ascertain medication adherence. There may also be errors in the EMR medication record. In particular, over-the-counter medications could be omitted. However, such misclassification of medication exposure is likely to be nondifferential, which would bias the results toward the null. Another limitation is a lack of information on indications for anticholinergics, and confounding by indication is a potential concern. However, we considered several robust markers of liver disease severity in our models to minimize residual confounding. One potential bias is that earlier medication exposure could influence covariates at the time of study entry. A new user design could mitigate this bias, but such an approach is not feasible in this study as it would further reduce sample size and HE outcomes. The primary outcome was HE hospitalization only, and

episodes of overt HE not requiring hospitalization may also be relevant to the study question. Lastly, a potential limitation is the difficulty in distinguishing HE and delirium; however, we used a strict definition for HE hospitalization requiring a response to HE-specific treatment.<sup>[43,44]</sup>

This study provides novel data showing a high medication burden and high prevalence of anticholinergic use in those with cirrhosis. It also links medication burden and anticholinergic use to HE-related hospitalizations, especially in those with a previous history of HE. Although validation of these results in other cohorts would be helpful to confirm the findings, the hepatology community should start considering the potential for deprescribing interventions to improve HE care and reduce the burden of liver disease on patients and the health care system.

### AUTHOR CONTRIBUTIONS

Study concept and design: All authors. Data extraction: Jonathan A. Montrose. Data analysis: Yingjie Qiu and Matthew E. Hays. Interpretation of data: All authors. Manuscript preparation: Jonathan A. Montrose and Eric S. Orman. Critical manuscript review: All authors.

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### CONFLICTS OF INTEREST

Eric S. Orman consults for Sitero and advises Biovie. Naga Chalasani declares no direct or significant conflicts of interests with this paper. For full disclosure, he reports ongoing paid consulting agreements with Madrigal, Zydus, Pfizer, Merck, Ventyx, Altimmune, Foresite, and GSK. He receives research support from DSM and Exact Sciences. He reports equity ownership in Avant Sante, a contract research organization. Noll L. Campbell consults for Blue Agilis and advises Urovant Sciences. The remaining authors have no conflicts to report.

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