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The incidence and outcome of postoperative hepatic encephalopathy in patients with cirrhosis

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Abstract

Background: Cirrhosis is associated with increased perioperative risks related to hepatic decompensation. However, data are lacking regarding the incidence and outcomes of postoperative hepatic encephalopathy (HE).

Objective: To determine the incidence of HE postoperatively, factors associated with its development, and its association with in-hospital mortality.

Methods: Retrospective cohort study of 583 patients with cirrhosis undergoing non-hepatic surgery over a 10-year period. Outcomes included postoperative HE and in-hospital mortality and were, respectively, evaluated using multi-state modeling and Fine-Gray competing risk regression (with postoperative HE as a time-varying covariate).

Results: Overall, the median Model for End-Stage Liver Disease Sodium was 10, 61.7% had a history of ascites, 49.9% esophageal varices, and 34.6% HE. The most common surgeries including abdominal/non-bowel (33.3%), orthopedic (18.0%), and bowel (12.2%). A total of 42 (7.2%) patients developed HE postoperatively during admission. The cumulative risk of HE was 7.2%, which was most associated with a history of HE, ASA class, postoperative AKI, and postoperative infection. In-hospital mortality occurred in 34 (5.8%) individuals. Only ASA class was independently associated (HR 2.46, 95%CI 1.21–5.02), but there was a trend for postoperative HE (HR 1.71, 95%CI 0.73–3.98).

Discussion: HE is an uncommon but not rare postoperative complication that increases the risk of patient harm. This study implies its development is predictable. Consequently, at-risk patients should have consultation with a hepatologist before undergoing elective surgery.

KEYWORDS

HE, hepatic decompensation, hepatic encephalopathy, manuscript info section: liver cirrhosis, MELD-na, mortality, outcome, perioperative risk, postoperative, surgery

INTRODUCTION

The perioperative risks of surgery are raised in persons with cirrhosis. Risk is determined in part by disease severity,[1,2] the presence of portal hypertension, comorbidities,[3–7] as well as the type and urgency of surgery.[3,4,8] Understanding the specific risks incurred by patients undergoing surgery can inform perioperative planning and potentially reduce postoperative complications. For example, ascites increases the risk of postoperative wound healing, infection, and renal failure; however, with preoperative volume status optimization, persons with cirrhosis undergoing colectomy can experience reduced postoperative complications.[9] Similarly, hepatic encephalopathy (HE) may benefit from optimization perioperatively with respect to lactulose dosing, adjunctive co-therapies, or avoidance of triggers such as benzodiazepines. It is suspected that HE is a common and modifiable cause of postoperative delirium in patients with cirrhosis,[10] and postoperative delirium in general is associated with poor outcomes.[11] Additionally, HE can lead to numerous inpatient complications, such as falls[12] and increased mortality.[13–15] Data are lacking regarding whom will develop postoperative HE and whether this development is independently associated with poor outcomes.

Patients with cirrhosis undergoing surgery encounter clinicians with various experience anticipating and managing postoperative cirrhotic complications. It is thus important to understand the risk of and risk factors for postoperative HE in order to define the population who could benefit from interventions to mitigate those risks. We seek to evaluate the risk and impact of HE on patients requiring surgery by assessing the incidence of HE postoperatively and factors associated with its development. Herein, we examine the risk of postoperative HE as well as the association of postoperative HE on in-hospital mortality.

Key Summary

1. Summarize the established knowledge on this subject
   - Patients with cirrhosis have increased perioperative risks when undergoing surgery
   - HE is a known complication of cirrhosis and contributes to inpatient morbidity and mortality
   - Data are lacking regarding the factors associated with developing postoperative HE and the effect it has on outcomes
2. What are the significant and/or new findings of this study
   - 7.2% of patients with cirrhosis undergoing surgery developed postoperative HE
   - Risk factors associated with development of postoperative HE include history of HE, increasing ASA classification, postoperative AKI, and postoperative infection
   - Multivariable cox regression revealed a trend toward increased risk of in-hospital mortality with the development of postoperative HE

METHODS

Patient selection

We retrospectively evaluated patients ≥18 years of age with cirrhosis (using diagnosis codes) admitted to Michigan Medicine between 01/01/2009 and 01/01/2019 for surgery. The surgeries included intrabdominal, cardiac, head and neck, orthopedic, skin and soft-tissue, thoracic, and vascular procedures. Central nervous system procedures were not included given the difficulty in assessing etiology of alerted mental status in this patient population. Urological and obstetrics/gynecologic procedures were not included due to their sex-specific nature. Patients were excluded if they underwent any liver- or biliary-related surgery or underwent transjugular intrahepatic portosystemic shunt (TIPS) placement during the admission. The diagnosis of cirrhosis was confirmed using histological, imaging, and clinical criteria. A search of the electronic medical record with these criteria yielded 728 unique hospitalizations, 104 of which involved patients without cirrhosis, 26 patients who did not undergo a procedure from the above categories or also underwent hepatobiliary or TIPS-related procedures during the same admission, 8 of age <18 years, and 7 patients who were never extubated following surgery. A total of 583 patients met the above criteria and were included in the analysis.

Study design

We collected demographic information and clinical information including cirrhosis etiology and prior complications (ongoing and/or resolved), home medications, history of TIPS placement, selected preoperative and postoperative medication administration (lactulose, rifaximin, non-selective beta blockers, diuretics, opioids, acetaminophen, NSAIDs, anti-psychotics, and benzodiazepines), disease severity scoring (Model for End-Stage Liver Disease Sodium [MELD-Na],[16] Child-Turcotte-Pugh [CTP] scoring system, Charlson Comorbidity Index, and American Society of Anesthesiologists [ASA] physical status classification), and Mayo Operative Risk Score.[3] Surgical procedures were grouped into one of the following categories: abdominal; abdominal/nonbowel; cardiac; head & neck; incision and drainage; orthopedic; spine; thoracic; vascular. Data regarding the nature of the surgery (elective, urgent, emergent) and anesthesia type were also collected. Postoperative courses were reviewed for the development of HE (defined as gross disorientation that was clinically diagnosed as HE by an attending physician, documented in the electronic health record, and associated with a corresponding change in therapy or management) and time to onset. Postoperative courses were also analyzed for the development of postoperative

complications, such as infection, acute kidney injury (AKI), and hypoglycemia (serum glucose <70 mg/dL). Data were extracted utilizing EMERSE.[17] Finally, data regarding patients' hospital length of stay (LOS) and in-hospital mortality were extracted from the electronic health record.

Statistical analysis

The primary outcome was the risk of postoperative HE. To calculate the risk of postoperative HE, we used a multi-state model to account for the competing events of being discharged without HE and in-hospital death without preceding HE.[18] In this 4-state model, patients could transition from the postoperative state (state 1) to three potential absorbing states: discharge without postoperative HE (state 2), the development of postoperative HE (state 3), and death without postoperative HE (state 4). Covariates included in the competing risk regression model were selected a priori and included age, MELD-Na, ASA class, history of HE, and history of ascites. We intended to analyze postoperative medications, such as benzodiazepines and opioids, however they did not show an association on univariable analysis.

We further sought to analyze factors associated with the risk of postoperative in-hospital mortality. Specifically, we assessed the risk of in-hospital mortality after the development of postoperative HE using Cox regression with postoperative HE as a time-dependent covariate. A history of overt HE was not included in the multivariable model to avoid multicollinearity with the development of postoperative HE. This study was approved by the University of Michigan Medical School Institutional Review Board on July 29, 2019, which includes conformation to 1975 Declaration of Helsinki where appropriate. Consent was not required for this deidentified retrospective chart review. Statistical analysis was performed using RStudio (version 1.2).[19]

RESULTS

Demographics and patient characteristics

Baseline characteristics for the 583 patients are included in Table 1. Patients had a median age of 60 years and were predominantly White (85.4%), with a male predominance (61.9%). The two most common etiologies of cirrhosis were alcohol-related (34.8%) and chronic hepatitis C infection (18.5%), while 17.8% were cryptogenic/unknown etiologies. The median MELD-Na was 10 (IQR 8–17), median CTP score was 7 (IQR 6–8), and the median ASA classification of III (frequencies: ASA II (22), III (352), IV (197), V (9), unlisted (3)). A history of ascites, esophageal varices, and HE was present in 61.7%, 49.9% of patients, 34.6%, respectively. Overall, 65.4% of patients examined had decompensated cirrhosis. Approximately 21% had an outpatient prescription for lactulose and 10% for rifaximin.

Surgical details

The most common categories of surgical procedures performed were abdominal/non-bowel (33.3%) and orthopedic (18.0%) (Table 3, a detailed breakdown can be found in Supplemental Figure S1). Surgeries were elective in 52.1% of the operations examined. In the preoperative period, less than 6% of patients received lactulose, rifaximin, diuretics, or nonselective beta-blockers. Table 2 details some of the perioperative details. General anesthesia was administered in approximately 91% of the patients in each group. Analgesics were the most commonly administered postoperative medications, opioids (65.0%), acetaminophen (42.9%), and NSAIDs (10.1%). Benzodiazepines (11.7%), diuretics (13.4%), and nonselective beta blockers (2.9%) were administered infrequently postoperatively. Lactulose and rifaximin were administered postoperatively in 10.1% and 6.5% of patients, respectively. In terms of complications amongst all patients, 12.2% developed AKI, 3.6% developed hypoglycemia, and 20.8% developed an infection during their postoperative course.

The risk of postoperative hepatic encephalopathy

A total of 42 (7.2%) patients experienced in-hospital HE in the postoperative setting (Table 3). On postoperative day 15, the cumulative risk of postoperative HE was 6.0% overall. The risk increased to 12.9%, 7.2%, and 9.8% if there was a prior history of hepatic encephalopathy (Figure 1), ascites, or TIPS placement, respectively. Additionally, the risk of postoperative HE was increased with increasing ASA class (0% ASA II, 4.0% ASA III, 9.6% ASA IV, and 22.2% ASA V) and MELD-Na (7.9% MELD-Na $\geq$ 10 vs. 3.7% MELD-Na < 10). The unadjusted subdistribution hazard ratios for the development of postoperative HE was significantly associated with markers of disease severity including MELD-Na, ASA class, history of HE, history of ascites, and Mayo 30-day postoperative risk score (Table 4). Additionally, while CTP Class C patients comprised only 10.8% of the overall study population, they accounted for one third of all postoperative HE cases. Conversely, 43.4% of all patients were Class A, however, only 19% of Class A patients developed postoperative HE (Table 1).

Neither opioids (subdistribution HR 0.88, 95%CI 0.47–1.63) nor benzodiazepines (subdistribution HR 1.55, 95%CI 0.69–3.46) administered in the 48-h postoperative period significantly modified the risk of postoperative HE. Postoperative diuretics (subdistribution HR 1.32, 95%CI [0.59–2.99]), and nonselective beta blockers (subdistribution HR 1.75, 95%CI 0.41–7.43) were also not associated with increased risk of HE. Fine and Gray multivariable competing risk regression revealed a history of HE (subdistribution HR 4.12, 95%CI 2.07–8.21) and ASA class (subdistribution HR 2.12, 95%CI 1.25–3.60) as significant factors associated with postoperative HE (Table 4).

In terms of postoperative complications, 23% developed AKI, 2% developed hypoglycemia, and 45% developed an infection in the HE group, compared with 11%, 4%, and 19%, respectively, in the non-HE group. The most commonly diagnosed infections in the HE group

TABLE 1 Patient characteristics

	N (%) or Median (IQR)			
	All Patients N = 583	Develop HE N = 42	Did not Develop HE N = 541	*P*-value
Demographics				
Age	60 (13)	60 (14)	60 (13)	0.71
Sex, male	361 (61.9%)	24 (57.1%)	337 (62.3%)	
Race, non-white/non-Caucasian	85 (14.6%)	4 (9.5%)	81 (15.0%)	
BMI	28.3 (9.0)	27.3 (7.8)	28.4 (9.0)	0.69
Baseline laboratory values				
Platelets	128 (102)	98 (97)	129 (101)	0.21
Na	138 (5)	137 (6)	138 (5)	<0.05
Creatinine	0.98 (0.62)	1.09 (0.49)	0.96 (0.62)	0.80
Albumin	3.6 (1.0)	3.0 (0.6)	3.6 (1.1)	<0.05
Bilirubin, total	1.0 (1.2)	1.7 (2.5)	0.9 (1.0)	<0.05
INR	1.1 (0.3)	1.3 (0.3)	1.1 (0.3)	<0.05
MELD-Na	10.0 (9.0)	15.5 (10.7)	10.0 (9.0)	<0.05
CTP score	7 (2.0)	8 (3.0)	7 (2.0)	<0.05
—CTP Class A	253 (43.4%)	8 (19.0%)	245 (45.3%)	
—CTP class B	258 (44.3%)	20 (47.6%)	238 (44.0%)	
—CTP class C	63 (10.8%)	14 (33.3%)	49 (9.1%)	
Cirrhosis details				
Etiology, alcohol-related	203 (34.8%)	16 (38.1%)	187 (34.6%)	
History of complications				
—Ascites	360 (61.7%)	32 (76.2%)	328 (60.6%)	
—Hepatic encephalopathy	202 (34.6%)	29 (69.0%)	173 (32.0%)	
—Varices	291 (49.9%)	30 (71.4%)	261 (48.2%)	
—TIPS	61 (10.5%)	6 (14.3%)	55 (10.2%)	
Disease severity scoring				
—Median CCI	5 (5)	8 (4)	5 (5)	<0.05
—Median ASA classification	3 (1)	4 (1)	3 (1)	<0.05
—Median mayo surgical risk score, 30-day	7% (10%)	12% (22%)	6% (9%)	<0.05
Decompensated cirrhosis	381 (65.4%)	34 (81.0%)	347 (64.1%)	
Home medications				
Lactulose	122 (20.9%)	22 (52.4%)	100 (18.5%)	
Rifaximin	57 (9.8%)	16 (38.1%)	41 (7.6%)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index; CTP, Child-Turcotte-Pugh; HE, hepatic encephalopathy; INR, international normalized ratio; IQR, interquartile range; MELD-Na, model for end-stage liver sisease; Na, sodium; TIPS, transjugular intrahepatic portosystemic shunt.

were sepsis (19%) and urinary tract infection (10%), and the most common in the non-HE group were urinary tract infection (5.9%) and sepsis (5.4%, Table 2). Both postoperative AKI (subdistribution HR 2.27, 95%CI 1.12–4.57) and infection (subdistribution HR 1.28, 95% CI 0.31–5.22) were associated with an increased risk of postoperative HE (Table 4).

Postoperative hepatic encephalopathy and in-hospital mortality

In-hospital mortality occurred in 34 (5.8%) individuals. On multivariable cox regression with postoperative HE as a time-dependent covariate, there was a trend towards an increased risk of in-

TABLE 2 Perioperative data

	N (%) or Median (IQR)		
	All Patients N = 583	**Develop HE N = 42**	**Did not Develop HE N = 541**
Preoperative medications, 48 h preoperatively			
Lactulose	34 (5.8%)	10 (23.8%)	24 (4.4%)
Median total dose	46 (80)	70 (74)	40 (65)
Rifaximin	20 (3.4%)	6 (14.3%)	14 (2.6%)
Diuretics	24 (4.1%)	2 (4.8%)	22 (4.1%)
Nonselective beta blockers	6 (1.0%)	1 (2.4%)	5 (0.9%)
Intraoperative anesthesia			
General anesthesia	531 (91.1%)	38 (90.5%)	493 (91.1%)
Postoperative medications, 48 h postoperatively			
Lactulose	59 (10.1%)	14 (33.3%)	45 (8.3%)
—Median total dose, 24 h postoperatively	20 (40)	5 (40)	20 (40)
—Median total dose, 48 h postoperatively	40 (65)	50 (115)	40 (60)
Rifaximin	38 (6.5%)	11 (26.2%)	27 (5.0%)
Opioids	379 (65.0%)	26 (61.9%)	353 (65.2%)
Acetaminophen	250 (42.9%)	9 (21.4%)	241 (44.5%)
NSAIDs	59 (10.1%)	3 (7.1%)	56 (10.4%)
Anti-psychotics	0 (0.0%)	0 (0.0%)	0 (0.0%)
Benzodiazepines	68 (11.7%)	7 (16.7%)	61 (11.3%)
Diuretics	78 (13.4%)	7 (16.7%)	71 (13.1%)
Nonselective beta blockers	17 (2.9%)	2 (4.8%)	15 (2.8%)
Postoperative complications			
Development of AKI[b]	71 (12.2%)	10 (23.8%)	61 (11.3%)
Development of hypoglycemia[b]	21 (3.6%)	1 (2.4%)	20 (3.7%)
Development of postoperative infection[a]	121 (20.8%)	19 (45.2%)	102 (18.9%)

Abbreviations: AKI, acute kidney injury; HE, hepatic encephalopathy; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs.
[a]Refers to development of infection during the postoperative course, prior to the development of hepatic encephalopathy.
[b]Within five days postoperatively, or prior to the development of postoperative HE, whichever occurred first.

hospital mortality after the development of postoperative HE (adjusted HR 1.71, 95%CI 0.73–3.98). Higher ASA class significantly increased risk of in-hospital mortality (adjusted HR 2.46, 95%CI 1.21–5.02) (Table 5).

DISCUSSION

The postoperative period is a uniquely vulnerable time for patients with cirrhosis. HE is a morbid complication that interferes with the patient's capacity to follow postoperative instructions, meet nutritional goals, and increases the risk of nosocomial complications. Identifying risk factors for postoperative HE is important to improving care for patients with cirrhosis through risk stratification, developing informed postoperative expectations, and, speculatively, strategizing prophylactic approaches. To date, however, it is neither clear how many or which patients develop postoperative HE nor what the impact of HE on outcomes could be. Our study extends on the literature on postoperative risk assessment in multiple ways.

Postoperative HE is uncommon

The incidence of postoperative HE is approximately 7.2% in patients with cirrhosis. Postoperative HE has received little attention. A study of the association between MELD-Na and postoperative outcomes in the National Surgical Quality Improvement Program through 2014 did not assess the incidence or impact of HE but concluded that MELD-Na alone underestimated risk.[20] A recent national sample of 8,193 veterans with cirrhosis undergoing surgery did not evaluate HE

TABLE 3 Overall outcomes and by procedure type

	Overall	Develop HE	Did Not Develop HE[b]	Procedure Type								
				Abdominal	Abdominal Non-bowel	Cardiac	Head & Neck	I&D	Orthopedic	Spine	Thoracic	Vascular
N (%)	583	42 (7.2%)	541 (92.8%)	71 (12.2%)	194 (33.3%)	99 (17.0%)	35 (6.0%)	5 (0.9%)	105 (18.0%)	26 (4.5%)	14 (2.4%)	34 (5.8%)
Median LOS, days (IQR)	7.0 (12.0)	26.5 (25.7)	7.0 (9.0)	7.0 (12.0)	6.0 (9.0)	12.0 (14.0)	8.0 (8.0)	14.0 (19.0)	5.0 (5.0)	8.0 (11.7)	5.0 (8.5)	10.0 (25.8)
In-hospital mortality	5.8%	23.8%[a]	4.4%[a]	7.0%	7.2%	8.1%	0.0%	0.0%	3.8%	0.0%	0.0%	8.8%

Abbreviations: HE, hepatic encephalopathy; I&D, incision and drainage; IQR, interquartile range; LOS = length of stay.

[a] $P < 0.05$.

[b] Includes patients discharged without developing HE (517%, 88.7%) and patients who died without developing HE (24%, 4.1%).

FIGURE 1 History of hepatic encephalopathy and risk of postoperative hepatic encephalopathy. Abbreviations: HE, Hepatic Encephalopathy

as a complication but did find prior HE increased the risk of mortality.[21] Although a third of our study sample had a history of HE, few developed postoperative HE. This study was largely comprised of CTP Class A and B patients (89.2%), which likely contributed to the low prevalence of HE overall within the cohort, seeing as one-third of CTP Class C patients went on to develop HE postoperatively. If prior HE is used as a selection criterion for operative candidacy, it must be refined for to avoid excluding good candidates. We therefore provide risk factors for the development of postoperative HE.

Postoperative HE may be predictable

We used multistate modeling to determine risk factors for postoperative HE that account for the competing risk of in-hospital mortality without postoperative HE or discharge without postoperative HE. HE was most likely to occur in the patients with prior HE, high (≥10) MELD-Na, and with increasing ASA class. Infections and AKI were both associated with an increased risk of HE. We also show that patients with a history of HE mostly developed HE rapidly within the first five postoperative days while those without prior HE experienced more linear risk of postoperative HE, likely with a risk that parallels the complexity of their postoperative course (Figure 1). Understanding the patient's risk of HE informs clinical management. Patients with advanced disease, a history of cirrhosis complications, or high scores on existing models, may benefit from (1) increased vigilance for HE symptoms postoperatively, (2) appropriate HE prophylaxis prior to and after surgery (lactulose, rifaximin), and (3)

TABLE 4 Unadjusted and adjusted hazard ratios for postoperative HE

	Postoperative HE	
	Unadjusted Subdistribution Hazard Ratio (95%CI)	**Adjusted Subdistribution Hazard Ratio (95%CI)**
Age (per 10 years)	0.96 (0.78–1.18), $p = 0.69$	1.04 (0.82–1.33), $p = 0.78$
MELD-Na	1.07 (1.04–1.11), $p = <0.001$	1.03 (0.99–1.07), $p = 0.058$
ASA class	2.7 (1.7–4.3), $p = <0.001$	2.12 (1.25–3.60), $p = 0.0065$
History of HE	4.49 (2.35–8.59), $p = <0.001$	4.12 (2.07–8.21), $p = <0.001$
History of ascites	2.03 (1.0–4.12), $p = 0.048$	0.79 (0.37–1.70), $p = 0.59$
TIPS	1.48 (0.62–3.53), $p = 0.38$	
Intraoperative general anesthesia	0.91 (0.32–2.58), $p = 0.86$	
Postoperative benzodiazepine	1.55 (0.69-3.46), $p = 0.29$	
Postoperative opioid	0.88 (0.47–1.63), $p = 0.68$	
Postoperative diuretics	1.32 (0.59–2.99), $p = 0.50$	
Postoperative beta blocker	1.75 (0.41–7.43), $p = 0.45$	
Postoperative AKI	2.27 (1.12–4.57), $p = 0.022$	
Postoperative hypoglycemia	1.28 (0.31–5.22), $p = 0.73$	
Postoperative infection	3.25 (1.78–5.94), $p = <0.001$	
Nonelective procedure	2.51 (1.31–4.81), $p = 0.0056$	
30-Day mayo risk score (unit 1%)	1.03 (1.01–1.04), $p = <0.001$	

Abbreviations: AKI, acute kidney injury; ASA, American Society of Anesthesiologists; CI, confidence interval; HE, hepatic encephalopathy; MELD-Na, Model for End-Stage Liver Disease Sodium; TIPS, transjugular intrahepatic portosystemic shunt.

TABLE 5 Unadjusted and adjusted hazard ratios for postoperative in-hospital mortality

	Postoperative Death	
	Unadjusted Hazard Ratio (95%CI)	**Adjusted Hazard Ratio (95%CI)**
Age (per 10 years)	1.08 (0.82–1.42), $p = 0.58$	1.09 (0.80–1.49), $p = 0.58$
MELD-Na	1.04 (1.01–1.08), $p = 0.022$	1.0 (0.95–1.04), $p = 0.84$
ASA class	2.59 (1.44–4.65), $p = 0.0014$	2.46 (1.21–5.02), $p = 0.013$
Postop HE	2.12 (0.94–4.76), $p = 0.070$	1.71 (0.73–3.98), $p = 0.22$
History of ascites	1.37 (0.58–3.21), $p = 0.47$	1.30 (0.50–3.38), $p = 0.59$

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; HE, hepatic encephalopathy; MELD-Na, Model for End-Stage Liver Disease Sodium.

consideration of optimization with subspecialty consultation prior to elective procedures. Consultation with gastroenterologists/hepatologists prior to planned operations for persons with cirrhosis is associated with improved postoperative outcomes.[9] The role of inpatient consultation in the perioperative period would benefit from multicenter/national database studies.

Contextual factors

Our data was derived over a 10-year period at a single-center academic health system and may not reflect the characteristics and risk factors of the broader population. Additionally, some of the risk factors have inherent limitations, such as the subjective nature of ASA physical classification grading and inability to input values of II or V into the Mayo risk score. Patients who developed HE prior to surgery were not included as they did not *develop* HE postoperatively, which limits the ability of this study to assess for *worsening* of HE postoperatively. The retrospective nature of the data and assessing a diagnosis of HE as documented in the electronic medical record by different physicians is another limitation. Additionally, it is difficult to draw conclusions based on preoperative lactulose or rifaximin usage, given that only medications given during the admission would be recorded in the electronic health record. Another limitation is the nature of surgery, many procedures were done nonelectively, which limits pre-procedural interventions that can be

taken to minimize the risk of developing postoperative HE. Finally, we had hypothesized that exposure to opioids or benzodiazepines would increase risk. No association was detected in this study. However, we cannot exclude the possibility that sample exposed was too small or confounded by indication to observe an effect. This is especially true in the case of benzodiazepines, where the point estimate hazard ratio is 1.55 and prior research would suggest they do confer an increased risk for HE.[22]

CONCLUSIONS

Postoperative HE is neither common nor rare but it substantially increases the risk of patient harm. The prevalence identified in this study is largely reflective of CTP Class A and B patients who were not having ongoing encephalopathy prior to their procedure. The prevalence of postoperative HE in CTP Class C patients may be increased, as seen within the small subset of Class C patients in this study. Multicenter data are needed to confirm these findings. However, interventions including monitoring protocols and prophylactic therapies merit further study.

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AUTHORS CONTRIBUTIONS

Zachary M Saleh: Conceptualization, Data Acquisition, Analysis, Writing Quintin P Solano: Data Acquisition, Writing Jeremy Louissaint: Data Acquisition, Analysis, Writing PeterJepsen: Writing Elliot B. Tapper: Conceptualization, Analysis, Writing

CONFLICTS OF INTEREST

Elliot Tapper has served as a consultant to Norvartis, Kaleido, and Allergan, has served on advisory boards for Mallinckrodt, Rebiotix, and Bausch Health, and has received unrestricted research grants from Gilead.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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