Original Article

Hospital Opioid Usage and Adverse Events in Patients With End-Stage Liver Disease

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Abstract

Context. Patients with end-stage liver disease (ESLD) commonly experience pain and other symptoms that result in a poor quality of life. Few studies have examined opioid usage, adverse events (AEs), and other outcomes in ESLD patients receiving opioid analgesia.

Objectives. This study aimed to compare outcomes in ESLD patients who received opioids to those who did not and to determine risk factors for AEs.

Methods. This was a retrospective case-cohort study of 270 hospitalized patients with ESLD that used administrative and clinical data from the electronic medical record.

Results. Two-thirds of patients with ESLD admitted during the study period received at least one opioid analgesic. Patients who received opioids presented with a greater number of liver related complications and higher rates of anxiety (32% vs. 17%, $P= 0.007$), had substantially worse initial and average pain scores (both $P< 0.001$), and received more palliative care consultations. The opioid group had somewhat more respiratory (22.2% vs. 11.1%, $P= 0.02$) and gastrointestinal (38.5% vs. 25.2%, $P= 0.03$) AEs, but no increase in CNS adverse events which included hepatic encephalopathy. Anxiety and disease severity (i.e., the number of liver related complications) but not opioid administration were risk factors for the number of AEs.

Conclusion. Opioid administration was not an independent risk factor for the number of AEs in hospitalized patients with ESLD, whereas anxiety and more liver-related complications increased AE risk. Our findings suggest that opioids have an appropriate and reasonably safe role in alleviation of pain in patients with ESLD. J Pain Symptom Manage 2023;65:326–334.

Key words

Cirrhosis,opioids, analgesia, adverse events, palliative care anxiety

Key Message

This retrospective case-cohort study found that two-thirds of hospitalized patients with end-stage liver disease (ESLD) were prescribed opioids. Opioids were appropriately used for those ESLD patients with more severe pain. Review of adverse events indicated a reasonable benefit to risk ratio for opioid use in the palliative care of ESLD.

Introduction

End-stage liver disease (ESLD) was the 10th leading cause of death in American males in 2017 and its incidence is increasing.[1] It is defined as advanced, irreversible fibrosis of the liver with one or more liver related decompensations of ascites, esophageal varies, or hepatic encephalopathy. Patients can also suffer from liver related

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Accepted for publication: 26 November 2022.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2022.11.026

complications such as hepatocellular carcinoma, hepatorenal syndrome, hepatopulmonary syndrome, spontaneous bacterial peritonitis and hepatic hydrothorax.[2] ESLD is a progressive disease, and the only cure is transplantation and that is only given to a select few.[3] Patients with advanced disease suffer from a poor quality of life and high physical and psychological symptom burden.[4,5] Pain is a common complaint reported in up to 79% of patients with ESLD with the abdomen being the most common site of pain.[6,7] Abdominal pain is thought to be due to ascites, spontaneous bacterial peritonitis, splenomegaly, and liver capsule distension.[8] There is limited evidence-based guidance on standard of care for pain management in this population.[9] Non-opioid analgesics are utilized, but are often limited due to possible side effects such as increased risk of bleeding, worsening hepatic encephalopathy and renal function.[10] When non-opioid analgesics options are not effective or considered unsafe, this patient population utilizes opioid therapy for analgesia even though they also carry the risk of adverse effects.[11,12]

Despite a high percentage of patients with ESLD that suffer from pain, there is very little empirical evidence in the literature to guide the use of opioids. Several studies discuss pain management in patients with liver disease based on pharmacokinetics and suggest cautious or even minimal use of opioids in this complex patient population due to risk of over sedation and worsening hepatic encephalopathy.[13] However, empirical evidence is limited and the few studies that have addressed opioid use in patients with liver disease, no study has focused on the end-stage population and the adverse events are rates not well characterized despite known poor quality of life and heightened symptom burden.[14–17]

As with all medications some risk of adverse events can be expected, but the risks to benefits must be weighed in patients with serious illness. The aims of this study were to characterize opioid use and adverse events rates in patients with ESLD. We address the frequency and characteristics of opioid use among hospitalized patients with ESLD, the incidence of adverse events typically related to opioid use, and health care outcomes for patients receiving opioid therapy. Although clinicians are commonly cautioned about the use of opioid therapy in patients with ESLD, these patients frequently suffer from pain and clinical guidance is needed to help this palliative patient population. To our knowledge this is the largest sample of patients with ELSD receiving opioids aimed at identifying the frequency and characteristics of opioid use and the first to characterize adverse events often attributed to opioid administration.

Methods

Study Design

This retrospective case-cohort study used administrative and clinical data from the Cerner electronic medical record (EMR) system at a major mid-west urban academic health system that is a comprehensive liver transplant center. Data were obtained from International Classification of Disease, 10th edition (ICD-10) codes for each visit, individual chart review of the admission notes, daily progress notes, discharge notes, laboratory data, and the medication administration log. This study was approved by the Indiana University institutional review board.

Study Population

This study included hospitalized patients with ESLD admitted over a 12-month period from January 1 toDecember 31 ,2019. Patients were identified by having at least 1 of 88 ICD-10 diagnoses that were related to cirrhosis or one of its complications coded during the index hospitalization. This list was based on a previously published list and was updated for this study and is presented in Supplementary Table 1.[18] Patients 18 years or older were included when the individual chart review of the admission history and physical note confirmed they had cirrhosis and at least one liver related complication (ascites, hepatic encephalopathy, or esophageal varices). Patients were excluded if they: 1) received buprenorphine/naloxone because there is no agreed upon opioid conversion factor for buprenorphine as it is a partial agonist and is most often used for substance use disorder rather than pain; 2) received a continuous opioid infusion; or 3) were admitted for liver transplantation surgery. Only the first hospitalization was used if the patient was admitted more than once during the study time frame.

Measures

Patient demographic data was collected electronically and included age, sex, gender, race, and insurance status. Clinical variables collected included height and weight for body mass index calculation and creatinine, bilirubin, INR and sodium to calculate the Model for End-Stage Liver Disease- Sodium (MELD-Na).[19] The presence of previous liver transplant, ICU length of stay, location of discharge, and 30 day readmissions to our hospital system were recorded. The admitting team type (hepatology teaching service, hospitalist, medical intensive care (MICU), surgical team or transplant surgery team, or interventional radiology) was collected as well as the occurrence of a palliative care consult.

ICD-10 codes from the index hospitalization and individual chart reviews of the admission note and discharge summary were used to identify the etiology of ESLD, complications such as renal failure, ascites, hepatic encephalopathy, esophageal varices, hepatocellular carcinoma, and other comorbidities including substance abuse, depression, anxiety, as well as the variables that make up the Charlson comorbidity index.

The Charlson comorbidity index is a validated score that has been shown to predict 10-year mortality.[20] Opioid-related adverse events (ORADEs) are typically used to identify adverse events commonly associated with opioids.[21–23] Respiratory adverse events included acute respiratory failure, hypoxia, bradypnea and any respiratory complication. Central nervous system adverse events included confusion, altered mental status, delirium, dizziness/vertigo or use of naloxone. Genital urinary adverse events included urinary retention and oliguria. Gastrointestinal adverse events included dry mouth, ileus, constipation, nausea and vomiting. Other adverse events included rash, itching, bradycardia, and fall. As none of these adverse events are specific to opioids, in our study these events were coded for both the opioid and non-opioid treated groups (Table 1). Adverse events were determined by reviewing the primary team's daily notes and ICD-10 codes for the hospitalization. Charts were reviewed by four individual reviewers. Each reviewers had random charts audited by the primary author to give feedback and assure consistency.

For those receiving 1 or more opioid doses during the hospitalization, the opioid type, dose, and frequency was collected. Also, prescriptions within 30 days of admission and prescriptions at discharge for opioids and benzodiazepines were collected. The average morphine milligram equivalents (MME), the minimum and maximum MME per day, and the number of days opioids administered were all calculated. The patients' first, last and average pain scores were obtained.

For all patients the use of nonopioid analgesics and psychotropic medications that can be used for analgesia was extracted. These analgesics included gabapentinoids, acetaminophen, non-steroidal anti-inflammatory (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). Data on benzodiazepine administration was also extracted.

Table 1
Potentially Opioid Related Adverse Drug Events (ORADEs) by Organ System

Respiratory	Urinary
Acute respiratory failure	Urinary retention
Pulmonary insufficiency	Oliguria
Bradypnea	Gastrointestinal
Hypoxemia	Dry mouth
Respiratory complications	Ileus
Hypoxia	Constipation
Central Nervous System	Nausea
Confusion	Vomiting
Delirium	Others
Altered mental status	Rash/itching
Dizziness/vertigo	Bradycardia
	Fall

Statistical Analysis

In the 12-month study period, the sample comprised 270 ESLD patients, of whom 135 received an opioid during their hospitalization and 135 did not receive an opioid medication. Only 135 patients with ESLD admitted did not receive an opioid and in order to maintain a 1:1 ratio of the study groups, the135 patients in the opioid group were chosen randomly from the 269 patients. Descriptive statistics were used to compare patients who did and did not receive opioid therapy. T-test and Wilcoxon tests were conducted to compare continuous characteristics between groups. Chi-square test was performed to compare categorical characteristics, unless values in any cell were < 5, in which case Fisher's exact test was performed instead. To identify potential predictors of adverse events, an ordinal logistic regression model was conducted with the number of adverse events (0-1, 2, 3 or more) as the dependent variable. In addition to opioid group, variables that were plausible confounders and that differed at a $P < 0.10$ between the opioid and non-opioid groups on bivariate analyses were entered into the multivariable model. The number of liver-related complications rather than etiology of liver disease was entered because in ESLD it is disease severity rather than etiology that is clinically important. Ordinal logistic regression yields proportional odds ratios (OR), and variables with an OR for which the 95% CI does not include 1 are considered independent predictors of the number of AEs.

Results

Patient Characteristics

There were 540 patients with ESLD admitted during our 12-month study time frame (Fig. 1). After excluding 78 patients admitted for liver transplantation, 56 who received a continuous opioid infusion, and 2 who received buprenorphine/naloxone, a total of 404 ESLD patients were eligible. During the study period, a total of 269 patients had at least one opioid analgesic administered during the hospitalization and 135 did not. To maintain a 1:1 case-control ratio, 135 patients receiving an opioid were randomly selected from the 269 to compare to the 135 patients who did not receive an opioid analgesic.

Baseline patient characteristics are summarized in Table 2. Compared to the non-opioid group, patients in the opioid group were younger (56.2 vs. 60.2, $P = 0.003$), had a higher prevalence of anxiety disorders (32% vs. 17%, $P = 0.007$), and had higher concurrent benzodiazepine administration (48.9% vs 30.4%, $P = 0.003$). Over half of the patients in the opioid group had 3 or more liver related complications at the time of admission

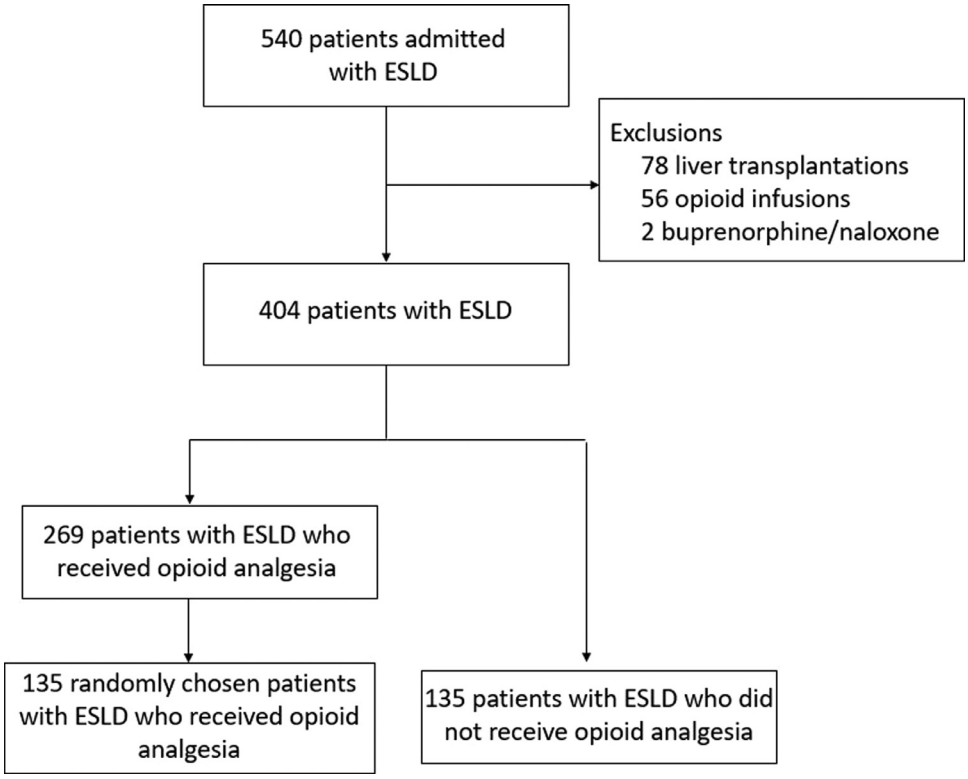

Fig. 1. Flow diagram of patients admitted with end-stage liver disease (ESLD).

Opioid Characteristics

Two-thirds of hospitalized patients with ESLD received at least one opioid analgesic (Fig. 1). Theproportion of patients admitted on chronic opioids was similar between the groups receiving and not receiving opioids during hospitalization (15% vs. 9%, $P = 0.29$). Among the 135 patients who received an opioid the average MME dose did not exceed 24mg/day (Supplementary Table 2). As seen in Table 3, nearly half of the patients received oral oxycodone and over one-third received IV hydromorphone. Forty (29.6%) patients received at-least 3 different opioid agents while 84 (62.2%) received at least one non-opioid analgesic. Almost half of the patients who received an opioid also received at least one benzodiazepine. Fifty-one (37.8%) of those in the opioid group received an opioid prescription at discharge and only 6 (4.4%) were given a script for a benzodiazepine at discharge.

Adverse Events

Patients receiving opioids tended to have more overall adverse events ($P = 0.05$) with significant differences in any respiratory (22.2% vs. 11.1%, $P = 0.022$) and any gastrointestinal (38.5% vs. 25.2%, $P = 0.026$) events, but no difference in central nervous system adverse events which included hepatic encephalopathy (32.6% vs. 37%, $p = 0.52$) (Table 4). Opioid use was not a predictor of the number of AEs in bivariate analyses (odds ratio = 1.06; 95% CI, 0.69 to 1.64; $P = 0.79$). When adjusting for potential confounders (Table 5), opioid use remained a nonsignificant risk factor (odds ratio = 0.84; 95% CI, 0.53 to 1.34, P=0.47). The two factors that emerged as independent predictors of AEs were patient anxiety and the number of liver-related complications. Within the opioid group, patients with and without adverse events did not differ significantly on any variable except there were more patients who received fentanyl in the adverse event group) (36.8% vs. 11.9%, $P = 0.002$), Supplementary Table 2. There was no difference in the average daily MME for patients with adverse events vs. those without (23.7 vs. 22, $P = 0.77$), but there was a nonsignificant trend towards higher adverse events the more days a patient received an opioid (6.8 vs. 5.0 days, $P = 0.07$) (Supplementary Table 2).

Patient Outcomes

As shown in Table 6, patients in the opioid group had substantially worse ($P< 0.001$) initial and average pain scores (approximately 3 points higher on a 0 to 10 scale) and had over a 1 point improvement in their final pain scores.Patients in the opioid group averaged 3 additional days in the hospital ($P< 0.001$) and were more likely to receive a palliative care consult (27.4% vs. 16.3%, $P = 0.039$), undergo an invasive procedure (91.1% vs. 80.0%, $P = 0.015$), and be prescribed an

Table 2
ESLD Patient Demographics and Characteristics

Patient Characteristic	No-Opioid Group (*n* = 135)	Opioid Group (*n* = 135)	*P*-value
Age at admission, mean (SD)	60.2 (10.5)	56.2 (10.9)	.003
Women, *n* (%)	48 (35.6)	60 (44.4)	0.172
Race, *n* (%)			0.278
White	123 (91.1)	120 (88.9)	
Black	3 (2.2)	8 (5.6)	
Other	9 (6.7)	7 (5.2)	
Insurance			0.070
Medicaid/Dual	7 (5.2)	17 (12.6)	
Medicare	62 (45.9)	56 (41.5)	
Other Government	16 (11.9)	22 (16.3)	
Private/Managed	38 (28.1)	31 (23)	
Self-Pay	3 (2.2)	6 (4.4)	
Special contract	9 (6.7)	3 (2.2)	
Liver Disease Etiology, *n* (%)			0.017
NAFLD/NASH	48 (35.6)	36 (26.7)	
Alcohol	38 (28.1)	42 (31.1)	
Hepatitis C	5 (3.7)	18 (13.3)	
Hepatitis C and Alcohol	13 (9.6)	18 (13.3)	
Other	31 (23.0)	21(15.6)	
Liver-related Complications, *n* (%)			
Ascites	105 (77.8)	114 (84.4)	0.214
Hepatic Encephalopathy	82 (60.7)	90 (66.7)	0.376
Esophageal Varices	55 (40.7)	68 (50.4)	0.143
Esophageal Varices with bleed	20 (14.8)	22 (16.3)	0.867
Hepatocellular Cancer	12 (8.9)	11(8.1)	>0.999
Hepatorenal Syndrome	10 (7.4)	3 (2.2)	0.088
Spontaneous Bacterial Peritonitis	8 (5.9)	18 (13.3)	0.063
Hepatopulmonary	0 (0)	2 (1.5)	0.498
Hepatic hydrothorax	7 (5.2)	15 (11.1)	0.119
Number of Liver-related Complications, *n* (%) [a]			0.079
1	36 (26.7)	24 (17.8)	
2	47 (34.8)	42 (31.1)	
≥ 3	52 (38.5)	69 (51.1)	
Hemodialysis in the last 7 days, *n* (%)	7 (5.2)	17 (12.6)	0.054
Charlson Comorbidity Index, mean (SD)	6.45 (2.25)	5.84 (2.3)	.027
MELD-Na, mean (SD)	24.6 (12.4)	23.8 (8.34)	.560
Psychiatric Comorbidity, *n* (%)			
Substance Misuse	13 (9.6)	25 (18.5)	0.054
Alcohol Misuse	68 (50.4)	74 (54.8)	0.542
Depression	41 (30.4)	51 (37.8)	0.248
Anxiety	23 (17.0)	43 (31.9)	0.007
Admitting Team, *n* (%)			0.080
Hospitalist	57 (42.2)	57 (42.2)	
Liver teaching team	60 (44.4)	45 (33.3)	
Surgical/Interventional Radiology/Other	8 (5.9)	17 (12.6)	
Medical ICU	10 (7.4)	16 (11.9)	
Concurrent analgesics, *n* (%)			
Pain scores, mean (SD)			
Initial	1.14 (2.22)	4.56 (3.60)	<.001
Benzodiazepine	41 (30.4)	66 (48.9)	.003
Acetaminophen	31 (23.0)	40 (29.6)	.269
NSAID	0 (0)	5 (3.7)	.060
Gabapentinoid	7 (5.2)	19 (14.1)	.023
SSRI antidepressant	25 (18.5)	31 (23.0)	.453
SNRI antidepressant	2 (1.5)	6 (4.4)	.282
Other	26 (19.3)	20 (14.8)	.418
No alternative analgesic/ psychotropics	66 (48.9)	48 (35.6)	.036

[a]Number of liver related complications per patient (ascites, hepatic encephalopathy, esophageal varices, esophageal varices with bleed, hepatocellular carcinoma, hepatorenal syndrome, spontaneous bacterial peritonitis, hepatopulmonary, hepatic hydrothorax)

Table 3
Medications Used in Patients who Received Opioid Analgesia (*n* = 135)

Medication	N	(%)
Opioid Medication (n, %)		
Oral Tramadol	41	(30.4)
Oral Hydrocodone[a]	27	(20.0)
Oral Oxycodone[a,b]	66	(48.9)
Oral Hydromorphone	11	(8.2)
Oral Morphine[b]	8	(5.9)
Transdermal Fentanyl	1	(0.7)
IV Hydromorphone	50	(37.0)
IV Morphine	28	(20.7)
IV Fentanyl	35	(25.9)
Other	5	(3.7)
Number of opioid agents (*n*, %)		
1	50	(37.8)
2	45	(33.3)
≥3	40	(29.6)
Long-acting opioid	8	(5.9)
Non-opioid analgesic (n, %)	84	(62.2)
Benzodiazepine use (*n*, %)	66	(48.9)
Prescription at admission (*n*, %)		
Opioid	15	(11.1)
Benzodiazepine	2	(1.5)
Prescription at discharge (*n*, %)		
Opioid	51	(37.7)
Benzodiazepine	6	(4.4)

[a]Includes combination medications
[b]includes extended-release preparations

opioid on hospital discharge (37.8% vs. 6.7%, p < 0.001). There were no differences in readmission rates and benzodiazepine prescription at discharge. There were 7 deaths in the opioid group vs. 1 death in the non-opioid group. However, the average admission MELD-Na score among the patients who died in the opioid group was 34 (a score associated with a > 50% mortality), and all these patients transitioned to comfort care due to expected death during the hospitalization. The patient in the non- opioid group who died had a MELD-Na of 36 at admission.

Discussion

In our study patients with ESLD who reported clinically significant pain received both opioid and non-

Table 4
Adverse Event Incidence

Adverse Events	No opioid group (*n*=135)	Opioid Group (*n*=135)	*P*-value
Type of adverse event, n (%)			
Respiratory	15 (11.1)	30 (22.2)	0.022
Central Nervous System	50 (37.0)	44 (32.6)	0.523
Urinary	12 (8.9)	12 (8.9)	>0.999
Gastrointestinal	34 (25.2)	52 (38.5)	0.026
Other	18 (13.3)	11 (8.1)	0.238
Number of adverse events, n (%)			0.050
0	52 (38.5)	59 (43.7)	
1	48 (35.6)	28 (20.7)	
2	15 (11.1)	22 (16.3)	
≥ 3	20 (14.8)	26 (19.3)	

Table 5
Multivariable Ordinal Logistic Regression Model of Adverse Events

Predictor	Odds Ratio (95% CI)	*P*-value
Opioid administered during hospital stay	0.84 (0.53, 1.34)	0.47
Number of liver-related complications[a]		
2	1.15 (0.62, 2.16)	0.65
≥ 3	1.77 (1.00, 31.6)	0.05
Anxiety	1.76 (1.03, 3.01)	0.04
Hemodialysis with the last 7 days	1.36 (0.57, 3.19)	0.48
Benzodiazepine use during hospital stay	1.13 (0.71, 1.81)	0.61
Age	1.00 (0.97, 1.02)	0.74
Charlson comorbidity score	0.94 (0.83, 1.06)	0.33
Substance misuse	0.83 (0.42, 1.62)	0.59

[a]Patients with 0 to 1 liver-related complications constitute the reference group

opioid analgesics despite theoretical risks. Patients who received opioid analgesics had a modest increase in respiratory and gastrointestinal adverse events (AEs), but also had more disease related complications and palliative care consultations suggesting a clinically sicker population despite no difference in MELD-Na scores and lower Charlson comorbidity scores. Importantly, receipt of opioids was not associated with the overall number of AEs after adjusting for potential confounders in a multivariable model. The two independent predictors of overall AEs were documented anxiety at admission and the number of liver-related complications.

To our surprise, two-thirds of patients with ESLD received at least one opioid during their hospitalization, indicating frequent opioid prescribing despite theoretical concerns expressed by some experts.[24] Our findings were similar to previous published data that found 62% of patients with all stages of cirrhosis received at least one opioid during hospitalization.[25-] This clinical use probably reflects the paucity of empiric data regarding opioid risks in ESLD and the clinical need of pain control. Notably, patients receiving opioids had much higher initial pain scores suggesting that prescribing was appropriate for alleviation of pain. Pain scores were 3 points higher in those receiving opioids on a 0 to 10 numeric rating scale where a 1-point difference is considered clinically meaningful, and a 2-point difference is considered large.[26] Final pain scores in the opioid group improved by over one point suggesting improvement of overall pain. Although the indication for opioid use could not be easily determined, presumably most prescriptions would be for pain or discomfort. Moreover, the purpose of our study was to examine the association between opioid use and adverse events regardless of indication for opioid use. Further, there are also greater safety concerns about the use of non-opioid analgesics in patients with ESLD making decisions about the benefits and risks of opioid prescribing different than in patients without ESLD.[27]

Table 6
Patient Outcomes

Outcome	No Opioid Group	Opioid Group	*P*-value
Pain scores, mean (SD)			
Initial	1.14 (2.22)	4.56 (3.60)	<.001
Final	0.38 (1.27)	3.38 (3.30)	<.001
Average	0.56 (0.92)	3.32 (2.31)	<.001
Length of stay, mean (SD)			
Hospital days	5.39 (3.94)	8.58 (7.69)	<.001
Intensive care unit days	0.32 (1.08)	0.96 (3.41)	.038
Palliative care consult, *n* (%)	22 (16.3)	37 (27.4)	0.039
Recent procedure, *n* (%)	108 (80.0)	123 (91.1)	0.015
Recent surgery, *n* (%)	1 (0.7)	6 (4.4)	0.120
Readmission within 30 days, *n* (%)	30 (22.2)	32 (23.7)	0.885
Death during admission, *n* (%)	1 (0.7)	7 (5.2)	0.066
Opioid prescription, n (%)			
Within 30 days of admission	9 (6.7)	15 (11.1)	0.285
At discharge	9 (6.7)	51 (37.8)	<0.001
Benzodiazepine prescription, n (%)			
Within 30 days prior to admission	3 (2.2)	2 (1.5)	>0.999
At discharge	4 (3.0)	6 (4.4)	0.747

Six out of 10patients in the opioid group also received at least one non-opioid analgesic or psychotropic medication, including a few who received NSAIDs which are strongly contraindicated in ESLD due to bleeding risk and renal failure.[28] Only 30% of patients received acetaminophen which is recommended as the first line analgesic, suggesting that the pain was either considered moderate to severe thus requiring a more potent analgesic or physicians were concerned about prescribing acetaminophen to patients with ESLD.[12] Gabapentin was used more in the opioid group (14.1% vs. 5.2%), $P = 0.023$, but overall less than expected.

Opioid medications are associated with known adverse events and in patients with ESLD the risk of neurological events is cited as a reason for cautious use.[14] Counterintuitive to previously reported studies, our patients in the opioid group had slightly fewer central nervous system adverse events than the non-opioid group, which included hepatic encephalopathy, but did experience modestly higher rates of respiratory and gastrointestinal events. Overall, opioid administration was not a predictor of the number of adverse events in our study. Adverse events in patients with ESLD appear to be better predicted by the patient's clinical condition, namely the number of liver related complications and concurrent anxiety.

Nearly half of the patients in the opioid group received at least one benzodiazepine during the hospitalization and one-third had a documented anxiety disorder at admission. This is similar to previous studies that have shown up to 50% of patients with cirrhosis have moderate to severe anxiety.[15] It has also been

shown that patients with pain and co-existing psychiatric comorbidity have higher pain severity than those with pain alone, which is highlighted in our study.[29,30] Anxiety and its association with pain warrants further exploration in patients with ESLD. Notably, anxiety is associated with increased reporting of a wide range of somatic symptoms across many medical conditions.[31–33] This could be one explanation for our finding that anxiety was an independent predictor of AEs in our ESLD sample.

Studies provide mixed recommendations for opioid analgesic medication in patients with liver disease due to perceived adverse events caused by altered pharmacodynamics.[11,16,34] In our study oxycodone was the most used oral opioid despite theoretical concerns of decreased clearance and prolonged half-life; however, it was not associated with a heightened risk compared to other opioids in our sample.[9,17] Instead, the highest adverse events were in patients receiving IV fentanyl which was an unexpected finding as it has been shown to have the same hepatic clearance as healthy controls in well-compensated cirrhosis.[35] However, this unexpected finding regarding fentanyl should be considered preliminary and warrants further investigation. Indeed, future studies would be required to determine if safety varies among individual opioid agents.

Our study highlights a clinically vulnerable population as the average MELD-Na score was 24.2, which is associated with a 35 percent risk of 6-month mortality.[36] This patient population suffers from poor quality of life and there has been a call for more palliative care involvement in the past decade.[37,38] Palliative care is a type of medical care that focuses on symptom management, including pain control, and on elucidating patients' health care goals in light of their advanced illnesses. Opioids are therapy for analgesia in patients receiving palliative care when non-opioid analgesics are either not effective or pose safety concerns in the setting of ESLD. The risks of opioid utilization are well known and when balanced with safety and patients' health care goals they may improve quality of life in patients with ESLD. This has been seen in a previous study that found hospitalized patients with ESLD were more likely to receive regular opioid administration when compared to those with compensated cirrhosis.[16] Unfortunately, there is limited guidance for analgesic prescribing in patients with ESLD, and this study provides some initial direction for clinicians caring for this seriously ill patient population. Our study is unique in that the EMR review allowed for greater delineation of clinical details compared to other studies that have only used administrative data sets. Moreover, the case-cohort design facilitated a more rigorous examination of opioid effects adjusting for potential confounders. However, several limitations should be acknowledged. The sample size was moderate although larger than some previous studies in this area.It was conducted at a single liver transplantation center and may not be generalizable to non-transplant centers. Because it was a retrospective EMR review it was difficult to determine the indication for opioid use and the causality of the opioid use leading to an adverse event which was partly addressed by comparing adverse events in patients not receiving opioid analgesia.

Conclusion

This is the first study to review opioid usage and adverse events in patients with ESLD, including palliative care and end-of-life care patients. Patients with ESLD who suffer from pain should be treated judiciously with non-opioid and opioid analgesics. Our findings suggest that opioid use per se is not independently associated with the overall number of AEs after controlling for anxiety and the number of liver-related complications. If an opioid is needed for analgesia, most oral and IV opioids appeared to have similar safety profiles except for a possibly greater risk of adverse events with IV fentanyl; this latter finding should be considered preliminary and warrants further investigation. Future research can further inform the safe and appropriate use of analgesics, including opioids, for the treatment of pain in patients with ESLD.

Author Contributions

A.W.J.: Conceptualization (lead), analysis/interpretation of data (equal), statistical analysis (supporting), drafting manuscript (lead), and critical revision of the manuscript (lead)L.G.A.: Conceptualization (supporting), analysis/interpretation of data (lead), statistical analysis (lead), drafting manuscript (supporting), and critical revision of the manuscript(equal)N.M.: Conceptualization (supporting), acquisition of data, drafting manuscript (supporting), and critical revision of the manuscript (equal)J.H.: Conceptualization (supporting), acquisition of data (equal), and critical revision of the manuscript (equal)K.K.: Conceptualization (supporting), analysis/interpretation of data (equal), drafting manuscript (equal), critical revision of the manuscript, study supervision (lead)Disclosures and Acknowledgments

Disclosure

This work was funded by the "Advanced Scholarship Program for Internists in Research and Education," Indiana University School of Medicine, Indianapolis, IN, USA. Study data were collected and managed using REDCap electronic data capture tools hosted at the Indiana Clinical and Translational Sciences Institute

(Indiana CTSI) funded, in part by Grant Numbers UL1TR001108, KL2TR001106, or TL1TR001107 from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award and at the Indiana University Pervasive Technology Institute (https://pti.iu.edu/) which supports REDCap with IT infrastructure and consulting resources. All authors deny any conflicts of interest.

Acknowledgments

Amy W Johnson wishes to express her sincere appreciation to Ms. Sarah Roth, Ms. Sara Koch, Dr. Ann Cottingham and Dr. Richard Frankel.

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Supplementary Table 1
Liver Related Diagnoses Based ICD 10[a]

ICD 10	Description
K74	Fibrosis and cirrhosis of liver
K74.0	Hepatic fibrosis
K74.1	Hepatic sclerosis
K74.2	Hepatic fibrosis with hepatic sclerosis
K74.3	Primary biliary cirrhosis
K74.4	Secondary biliary cirrhosis
K74.5	Biliary cirrhosis
K74.6	Other and unspecified cirrhosis of liver
K74.60	Unspecified cirrhosis of liver
K74.69	Other cirrhosis of liver
K70.3	Alcoholic cirrhosis of liver
K70.30	Alcoholic cirrhosis of liver without ascites
K70.31	Alcoholic cirrhosis of liver with ascites
K70.4	Alcoholic hepatic failure
K70.40	Alcoholic hepatic failure without coma
K70.41	Alcoholic hepatic failure with coma
K70.9	Alcoholic liver disease, unspecified
K72.01	Acute and subacute hepatic failure with coma
K70.2	Alcoholic fibrosis and sclerosis of liver
K70.11	Alcoholic hepatitis with ascites
K76.1	Chronic passive congestion of liver
K76.5	Hepatic veno-occlusive disease
K76.6	Portal hypertension
K76.7	Hepatorenal syndrome
K76.8	Other specified diseases of liver
K76.81	Hepatopulmonary syndrome
K76.89	Other specified diseases of liver
K76.9	Liver disease, unspecified
K71.11	Toxic liver disease with hepatic necrosis, with coma
K71.51	Toxic liver disease with chronic active hepatitis with ascites
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K71.7	Toxic liver disease with fibrosis and cirrhosis of liver
K71.8	Toxic liver disease with other disorders of liver
K71.9	Toxic liver disease
K74.3	Primary biliary cirrhosis
K74.4	Secondary biliary cirrhosis
K74.5	Biliary cirrhosis, unspecified
K74.6	Other and unspecified cirrhosis of live
K74.60	Unspecified cirrhosis of liver
K74.69	K74.69 Other cirrhosis of liver
K74.1	Hepatic sclerosis
K72	Hepatic failure, not elsewhere classified
K72.0	Acute and subacute hepatic failure
K72.00	Acute and subacute hepatic failure without coma
K72.01	Acute and subacute hepatic failure with coma
K72.1	Chronic hepatic failure
K72.10	Chronic hepatic failure without coma
K72.11	Chronic hepatic failure with coma
K72.9	Hepatic failure, unspecified
K72.90	Hepatic failure, unspecified without coma
K72.91	Hepatic failure, unspecified with coma
B19	Unspecified viral hepatitis
B19.0	Unspecified viral hepatitis with hepatic coma
B19.1	Unspecified viral hepatitis Bincludes
B19.11	Unspecified viral hepatitis B with hepatic coma
B19.2	Unspecified viral hepatitis C
B19.20	Unspecified viral hepatitis C without hepatic coma
B19.21	Unspecified viral hepatitis C with hepatic coma
K92	Other diseases of digestive system
K92.0	Hematemesis
K92.1	Melena
K92.2	Gastrointestinal hemorrhage, unspecified
B18.2	Chronic viral hepatitis C
B18.8	Other chronic viral hepatitis
B18.9	Chronic viral hepatitis, unspecified
K73	Chronic hepatitis, not elsewhere classified
K73.0	Chronic persistent hepatitis, not elsewhere classified
K73.1	Chronic lobular hepatitis, not elsewhere classified
K73.2	Chronic active hepatitis, not elsewhere classified
K73.8	Other chronic hepatitis, not elsewhere classified
K73.9	Chronic hepatitis, unspecified
E88.01	Alpha-1-antitrypsin deficiency
E83.0	Disorders of copper metabolism
E83.00	Disorder of copper metabolism, unspecified
E83.01	Wilson's disease
E83.09	Other disorders of copper metabolism
E83.11	Hemochromatosis
E83.110	Hereditary hemochromatosis
E83.111	Hemochromatosis due to repeated red blood cell transfusions
E83.118	Other hemochromatosis
E83.119	Hemochromatosis, unspecified
K75.4	Autoimmune hepatitis
K75.8	Other specified inflammatory liver diseases
K75.81	Nonalcoholic steatohepatitis (NASH)
K75.89	Other specified inflammatory liver diseases
K75.9	Inflammatory liver disease, unspecified
K83.01	Primary sclerosing cholangitis
K83.09	Other cholangitis

Supplementary Table 1
Continued

[a]ICD 10, nternational classification of diseases, tenth revision

Supplementary Table 2
Comparison of Patients in Opioid Group with and without Adverse Events

Variable	No Adverse vent (*n*=59)	Adverse Event (*n*=76)	*P*-value
Number of opioids, *n* (%)			0.603
1	24 (40.7)	26 (34.2)	
2	20 (33.9)	25 (32.9)	
≥ 3	15 (25.4)	25 (32.9)	
Number of non-opioid analgesics, n (%)			
0	24 (40.7)	27 (35.5)	0.150
1	25 (42.4)	29 (38.2)	
2	10 (16.9)	14 (18.4)	
≥ 3	0 (0)	6 (7.9)	
Number of liver-related complications, n (%)			0.384
1	10 (16.9)	14 (18.4)	
2	22 (37.3)	20 (26.3)	
≥ 3	27 (45.8)	42 (55.3)	
Opioid type			
Oral tramadol	22 (37.3)	19 (25.0)	0.177
Oral hydrocodone[a]	11 (18.6)	16 (21.1)	0.896
Oral morphineb	2 (3.4)	6 (7.9)	0.465
Oral oxycodone[a,b]	29 (49.2)	37 (48.7)	>0.999
Oral Hydromorphone	4 (6.8)	7 (9.2)	0.755
Transdermal fentanyl	1 (1.7)	0 (0)	0.437
IV morphine	8 (13.6)	20 (26.3)	0.110
IV fentanyl	7 (11.9)	28 (36.8)	0.002
IV hydromorphone	26 (44.1)	24 (31.6)	0.190
Other	2 (3.4)	3 (3.9)	>0.999
Opioid amount			
Daily average MME, mean (SD)	22.0 (36.0)	23.7 (31.6)	.769
Average median, mean (SD)	21.5 (35.2)	22.8 (33.6)	.827
Average minimum, mean (SD)	9.1 (17.5)	6.2 (12.1)	.287
Average maximum, mean (SD)	40.1 (57.9)	46.0 (48.6)	.531
Number of days, mean (SD)	5.00 (4.32)	6.78 (7.07)	.074
Pain score, mean (SD)			
Initial	4.12 (3.72)	4.91 (3.5)	.212
Final	3.47 (3.31)	3.30 (3.31)	.765
Average	3.28 (2.24)	3.35 (2.37)	.860
Age at admission, mean (SD)	56.2 (10.8)	56.2 (11.1)	.972
Female, *n* (%)	23 (39.0)	37 (48.7)	0.342
Race			0.277
White	54 (91.5)	66 (86.8)	
African-American	4 (6.8)	4 (5.3)	
Other	1 (1.7)	6 (7.9)	
Insurance			0.405
Medicaid/Dual	9 (15.3)	8 (10.5)	
Medicare	23 (39)	33 (43.4)	
Other Government	6 (10.2)	16 (21.1)	
Private/Managed	17 (28.8)	14 (18.4)	
Self pay	3 (5.1)	3 (3.9)	
Special contract	1 (1.7)	2 (2.6)	
Liver disease etiology			0.544
NAFLD/NASH	15 (25.4)	21 (27.6)	
Alcohol	18 (30.5)	24 (31.6)	
Hepatitis C	11 (18.6)	7 (9.2)	
Hepatitis C and Alcohol	6 (10.2)	12 (15.8)	
Other	9 (15.3)	12 (15.8)	
Liver-related complications, *n* (%)			
Ascites	50 (84.7)	64 (84.2)	>0.999
Hepatic encephalopathy	36 (61.0)	54(71.1)	0.297
Esophageal varices	26 (44.1)	42 (55.3)	0.264
Esophageal varices with bleed	13 (22.0)	9(11.8)	0.175
Hepatocelluar cancer	5 (8.5)	6(7.9)	>0.999
Hepatorenal syndrome	1 (1.7)	2(2.6)	>0.999
Spontaneous bacterial peritonitis	8 (13.6)	10(13.2)	>0.999
Hepatopulmonary	0 (0)	2(2.6)	0.504
Hepatic hydrothorax	4 (6.8)	11(14.5)	0.256
Hemodialysis in the last 7 days, *n* (%)	10 (16.9)	7(9.2)	0.279
Charlson Index (SD)	6.03 (2.60)	5.68 (2.03)	.397
MELD-Na (SD)	22.5 (7.97)	24.8 (8.52)	.107
Psychiatric comorbid conditions, *n* (%)			
Substance misuse	11 (18.6)	14 (18.4)	>0.999
Alcohol misuse	31 (52.5)	43 (56.6)	0.769
Depression	18 (30.5)	33 (43.4)	0.175
Anxiety	14 (23.7)	29 (38.2)	0.110
Recent procedure, *n* (%)	54 (91.5)	69 (90.8)	>0.999
Recent Surgery, (%)	2 (3.4)	4 (5.3)	0.696
Readmission within 30 days, *n* (%)	17 (28.8)	15 (19.7)	0.305
Death during admission, *n* (%)	1 (1.7)	6 (7.9)	0.136
Script for opioid within 30 days of admission, *n* (%)	4 (6.8)	11 (14.5)	0.256
Script for opioid at discharge, *n* (%)	21 (35.6)	30 (39.5)	0.778
Script for benzodiazepine, *n* (%)within 30 days of admission	1 (1.7)	1 (1.3)	>0.999
Script for benzodiazepine at discharge, *n* (%)	2 (3.4)	4 (5.3)	0.696
Benzodiazepine, *n*(%)	26 (44.1)	40 (52.6)	0.416
Acetaminophen, *n*(%)	17 (28.8)	23 (30.3)	>0.999
NSAID, *n*(%)	2 (3.4)	3 (3.9)	>0.999
Gabapentinoid, *n*(%)	9 (15.3)	10 (13.2)	0.922
SSRI, *n*(%)	11 (18.6)	20 (26.3)	0.398
SNRI, *n* (%)	1 (1.7)	5 (6.6)	0.231
Other (add TCA), *n* (%)	5 (8.5)	15 (19.7)	0.113
No alternative analgesic, *n* (%)	21 (35.6)	27 (35.5)	>0.999
Admitting Team, n (%)			0.204
Hospitalist	31 (52.5)	26 (34.2)	
Liver teaching team	16 (27.1)	29 (38.2)	
Surgical/ Interventional Radiology/Other	6 (10.2)	11 (14.5)	
Medical ICU	6 (10.2)	10 (13.2)	

[a]Includes combination medications,
[b]includes extended-release preparations.