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The burden of significant pain in the cirrhosis population: Risk factors, analgesic use, and impact on health care utilization and clinical outcomes

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Abstract

Background: We aimed to characterize pain and analgesic use in a large contemporary cohort of patients with cirrhosis and to associate pain with unplanned health care utilization and clinical outcomes in this population.

Methods: We included all patients with cirrhosis seen in UCSF hepatology clinics from 2013 to 2020. Pain severity and location were determined using documented pain scores at the initial visit; "significant pain" was defined as moderate or severe using established cutoffs. Demographic, clinical, and medication data were abstracted from electronic medical records. Associations between significant pain and our primary outcome of 1-year unplanned health care utilization (ie, emergency department visit or hospitalization) and our secondary outcomes of mortality and liver transplantation were explored in multivariable models.

Results: Among 5333 patients with cirrhosis, 32% had a nonzero pain score at their initial visit and 25% had significant (ie moderate/severe) pain. Sixty percent of patients with significant pain used ≥ 1 analgesic; 34% used opioids. Patients with cirrhosis with significant pain had similar Model for End-Stage Liver Disease-Sodium scores (14 vs. 13), but higher rates of decompensation (65% vs. 55%). The most common pain location was the abdomen (44%). Patients with abdominal pain, compared to pain in other locations, were more likely to have decompensation (72% vs. 56%). Significant pain was independently associated with unplanned health care

This work was presented at the AASLD The Liver Meeting 2022.

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; ICD, International Classification of Diseases; MELD-Na, Model for End-Stage Liver Disease-Sodium; NRS, Numeric Rating Scale; SBP, spontaneous bacterial peritonitis; UCSF, University of California-San Francisco.

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utilization (adjusted odds ratio: 1.3, 95% CI: 1.1–1.5) and mortality (adjusted hazard ratio: 1.4, 95% CI: 1.2–1.6).

Conclusions: Pain among patients with cirrhosis is often not well-controlled despite analgesic use, and significant pain is associated with unplanned health care utilization and mortality in this population. Effectively identifying and treating pain are essential in reducing costs and improving quality of life and outcomes among patients with cirrhosis.

INTRODUCTION

Pain is highly prevalent in patients with cirrhosis. Prior studies have estimated that up to 80% of patients with cirrhosis experience pain, a rate that is significantly higher than in the general population and patients with other chronic diseases.[1–3] However, pain is likely undertreated in this population, due to both provider concerns about multiple analgesic classes, as well as a poor understanding of the types and severity of pain experienced by patients with cirrhosis.[4] Pain in patients with cirrhosis is hypothesized to be related to overlapping risk factors for cirrhosis and chronic pain (eg, substance use disorders and metabolic syndrome), complications of cirrhosis itself (eg, ascites, spontaneous bacterial peritonitis, and muscle cramps), or a combination of the two.[3,5,6] Yet to optimize pain control in patients with cirrhosis—ensuring we are utilizing appropriate management strategies to safely and effectively treat the types of pain experienced by patients with cirrhosis—we must first better understand which patients with cirrhosis are most likely to experience pain and improve characterization of pain in this population.

Moreover, while pain—particularly moderate or severe pain—is known to be associated with poor quality of life and outcomes in the general population, there has been comparatively little research on the impact of pain or its undertreatment on clinical and patient-reported outcomes in patients with cirrhosis.[7] Limited data suggest that pain in this population is associated with higher-than-expected rates of disability and increased outpatient health care utilization.[8,9] Most studies related to pain in cirrhosis have focused on clinical outcomes associated with opioid use, often in the liver transplant setting.[10–13] However, many nontransplant patients with cirrhosis also experience significant pain, which may or may not be managed with opioids.

In the present study, we utilized a contemporary cohort of patients with cirrhosis—including both transplant candidates and nontransplant patients seen in a large outpatient hepatology clinic—to (1) identify demographic and clinical risk factors associated with clinically significant (ie, moderate or severe) pain; (2) characterize pain and analgesic use; and (3) determine the relationships between significant pain, unplanned health care utilization, and clinical outcomes (ie, mortality and liver transplantation) in this population.

METHODS

Data source

This was a retrospective cohort study using University of California-San Francisco (UCSF) Epic-based Clarity data, which includes all structured demographic, laboratory, medication, encounter, and billing variables from the UCSF electronic health record. These data were linked with a dedicated transplant database with machine-automated transfer and manual entry of clinical data.

Study cohort

The study cohort consisted of all patients $\geq$ 18 years old with a cirrhosis diagnosis and an initial visit to one of the UCSF hepatology clinics between January 1, 2013, and December 31, 2020, with a Numeric Rating Scale (NRS) pain score recorded at this initial visit. Cirrhosis was defined by a single inpatient or outpatient International Classification of Diseases, 9th (ICD-9) or 10th (ICD-10) Revision diagnosis code within 1 year of the initial clinic visit (see Supplemental Table S1, http://links.lww.com/HC9/A871), using a set of codes that has been validated previously.[14–17] Follow-up data were collected through July 7, 2022.

Pain definitions

The NRS is a pain screening tool that is commonly used in clinical settings to assess current pain severity with zero meaning “no pain” and 10 meaning “the worst pain imaginable.” The NRS is conducted as a routine part of clinical care for all patients seen in-person at UCSF Hepatology clinics in conjunction with patient vital signs and medication reconciliation. It is typically conducted

TABLE 1 Demographic and clinical characteristics of patients with cirrhosis with and without pain

Characteristics[a]	Overall (N = 5333)	No more than mild pain (N = 4017)	Moderate to severe pain (N = 1316)	*p*
Demographics				
Age at initial visit, y (mean, SD)	58 (11)	59 (11)	58 (10)	0.002
Sex				
Male	61	63	54	< 0.001
Race/ethnicity				
Asian	12	14	8	< 0.001
Black or African American	6	6	7	
Latinx	25	24	27	
Non-Latinx White	45	46	44	
Other	6	6	7	
Unknown	6	5	8	
Non-English speaking	15	15	14	0.2
Insurance				
Medicare	32	31	33	< 0.001
Medi-Cal	25	22	36	
Private	41	45	29	
Other	2	2	2	
Visit details				
Clinic				
Hepatology	60	57	67	< 0.001
Liver transplant	39	42	32	
Clinical characteristics				
Cirrhosis etiology				
Alcohol	35	33	39	< 0.001
Hepatitis B	10	11	7	< 0.001
Hepatitis C	43	42	48	< 0.001
MASLD	25	25	24	0.7
Autoimmune	10	11	8	0.006
Other	8	8	6	0.02
Comorbidities				
Hypertension	54	54	53	0.9
Diabetes	34	34	36	0.1
Chronic kidney disease	16	16	17	0.4
On hemodialysis	4	5	4	0.3
Falls	2	1	3	0.001
Psychiatric diagnosis	22	19	31	< 0.001
Anxiety	9	7	14	< 0.001
Depression	20	17	27	< 0.001
HCC	31	32	25	< 0.001
Substance use				
Current alcohol use	16	18	15	0.08
Current tobacco use	14	12	22	< 0.001
Marijuana use	12	11	15	< 0.001
MELD-sodium score (median, IQR) (n = 3823)	13 (9–19)	13 (9–18)	14 (10–19)	0.002
Decompensated	57	55	65	< 0.001
Cirrhosis complications				
Varices				
Nonbleeding	37	38	37	0.7

TABLE 1. (*continued*)

Characteristics[a]	Overall (N = 5333)	No more than mild pain (N = 4017)	Moderate to severe pain (N = 1316)	*p*
Bleeding	9	9	9	0.8
HE[b]	41	37	51	< 0.001
Ascites	43	41	49	< 0.001
On diuretics	29	27	35	< 0.001
SBP	4	4	5	0.2
Hepatorenal syndrome	4	4	4	0.6
Hepatopulmonary syndrome	1	2	1	0.08

[a]All cells are % unless otherwise indicated.
[b]Defined using ICD-10 code or prescription for lactulose or rifaximin.
Abbreviations: MASLD, metabolic-associated steatotic liver disease; MELD-Na, Model for End-Stage Liver Disease-Sodium; SBP, spontaneous bacterial peritonitis.

verbally by medical assistants before patient visit; interpreters are used for patients whose primary language is not English. In addition to assessing pain severity using the NRS, patients are asked in an open-ended manner to name the primary site of pain; both are documented in the electronic medical record.

We defined pain in 2 ways for the purposes of our analyses. "Active pain" was defined as a nonzero NRS pain score at the time of the initial clinic visit. "Significant pain" was defined as an NRS pain score > 3, corresponding with more than mild pain (ie, moderate or severe pain), at the time of the initial clinic visit. This was based on previously established NRS score cutoffs that have categorized pain as mild (1–3), moderate (4–6), or severe (7–10).[18,19] Pain was further classified as moderate or severe using these cutoffs. In addition, if available, patients were classified by the primary location of pain reported at the time of visit. For our analyses, we chose to focus on those with significant pain compared to those with mild or less pain, as this pain is more likely to be of concern to patients, is more likely to impact daily life and functioning, and suggests pain that is truly not well-treated. We also performed a subgroup analysis in patients with active abdominal pain to identify factors associated with abdominal pain in cirrhosis, as well as patterns of analgesic use in this subpopulation.

Covariate definitions

Demographic covariates collected from the patient medical record included age, gender, race/ethnicity, insurance status, location of primary care provider, and patient zip code. Data were also collected on the date and type of clinic visit (eg, liver transplant, general hepatology, video, and in-person). Clinical covariates included cirrhosis-related labs within 3 months of the clinic visit, etiology, and complications of cirrhosis (based on ICD-9/10 diagnosis codes within the 1-year before the initial clinic visit; see Supplemental Table S1, http://links.lww.com/HC9/A871), and ICD-based comorbidities within the year before the visit. Clinic visit medication lists were used to identify whether patients were on cirrhosis-related medications (eg, diuretics, lactulose, and rifaximin), analgesics (eg, opioids and gabapentin), or other sedating medications (eg, benzodiazepines and antihistamines). A complete list of medications is included in Supplemental Table S2, http://links.lww.com/HC9/A871. In addition to ICD diagnosis codes, patients were considered to have HE if they had either lactulose or rifaximin on their medication lists.

Outcome definitions

Our primary outcome was health care utilization within 1-year of the initial hepatology clinic visit—a binary variable defined by any hospital admission or emergency department visit at UCSF. Admissions were excluded if they were direct admissions for liver transplant. As UCSF is a tertiary referral center, health care utilization at non-UCSF facilities would not be captured in our data set. Therefore, we performed 2 sensitivity analyses to restrict the sample to patients who were most likely to receive unplanned care at UCSF: (1) including only those with UCSF primary care providers and (2) including only patients who live in San Francisco (based on zip code) with non-Kaiser (Health Maintenance Organization) insurance. Our secondary outcomes were captured for a 2-year period and included: (1) transplant, among those who were evaluated and listed for transplant; and (2) mortality (with liver transplant as a competing risk for those who were listed). Our transplant database (which is linked with Epic) included information regarding whether a patient was transplanted elsewhere, and death data were verified by linking Epic data with state death registries.

Statistical analysis

Data were summarized with frequencies and percentages for categorical data, and mean and SD or median and IQR for continuous data. We tested for bivariate associations between pain and covariates using chi-square (χ^2) tests, *t* tests, and Wilcoxon rank sum tests as appropriate. Due to the large number of statistical tests performed, for bivariate associations, we set our α-level

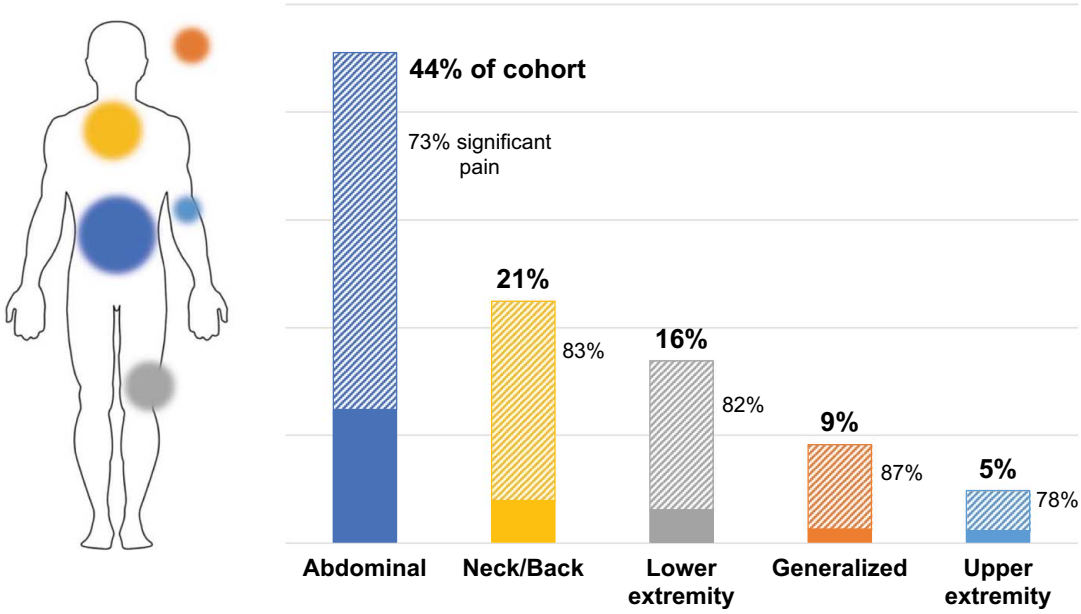

FIGURE 1 Pain location and severity in patients with cirrhosis reporting active pain at the time of their hepatology clinic visit (N = 5333). Shaded represents the proportion of patients reporting significant (ie, moderate or severe) pain, and solid represents the proportion reporting mild pain.

to a conservative 0.001, which is approximately equal to the Bonferroni correction applied for each analysis.[20]

We used simple logistic regression models to examine the unadjusted relationships between our primary outcome and clinically relevant covariates. We included covariates that were significant on unadjusted analysis in our multivariable logistic regression model.

We fit cause-specific hazard models to identify factors associated with the hazard rate of 2 events: all-cause mortality (primary event) and receiving a transplant (semi-competing event). Time-to-event was defined as the time from the initial visit at UCSF to the first event (death or transplant) or end of the study period, which we defined as 2 years after the patient's initial visit.

All statistical analyses were performed using R Statistical Software (v4.2.2; R Core Team, 2022) and RStudio (v2022.12.0; R Studio Team, 2022). This study was approved by the Institutional Review Board at the University of California, San Francisco (IRB #19-28055).

RESULTS

Baseline clinical and demographic characteristics of patients with cirrhosis with and without pain

We identified 5333 unique patients with a diagnosis of cirrhosis and NRS pain score documented during an initial visit to a UCSF hepatology clinic between 2013 and 2020. Nine hundred forty-four patients with cirrhosis were excluded from this study because they were missing pain scores at the initial visit.

The baseline demographics for our overall cohort are shown in Table 1. The mean age of our cohort was 58 years (SD: 10.8). Approximately 40% of our cohort was female, 45% non-Latinx White, and 41% had private insurance. The median Model for End-Stage Liver Disease-Sodium (MELD-Na) score at the time of the initial visit was 13 (IQR: 9–19) and 57% were decompensated at their initial visit.

One-quarter of our cirrhosis cohort (n = 1316, 25%) met our study's definition of significant pain (ie, moderate or severe). Patients with cirrhosis with significant pain were significantly more likely to be female and to have alcohol or hepatitis C etiology. They were less likely to have private insurance and to have hepatitis B cirrhosis compared to those without significant pain (Table 1, $p < 0.001$ for all).

As shown in Table 1, MELD-Na scores were similar between patients with and without significant pain. The proportions of patients with overall decompensation, HE, ascites, and diuretic use were higher among patients with pain compared to patients without pain ($p < 0.001$ for all). Patients with pain were more likely to have concurrent psychiatric disease ($p < 0.001$) and were more likely to smoke and use marijuana ($p < 0.001$ for both) compared to patients without pain.

Pain location

Approximately one-third of patients reported active pain (ie, at least mild pain) at the time of their initial clinic visit (n = 1681), with the majority of these reporting significant pain (41% moderate and 37% severe). Baseline

TABLE 2 Demographic and clinical characteristics of patients with reported pain location at the time of the initial visit

Characteristics[a]	Overall (N = 1567)	Abdominal pain (n = 683)	Other pain locations (n = 884)	*p*
Demographics				
Age at initial visit, y (mean, SD)	58 (10)	56 (10)	59 (10)	< 0.001
Sex				
Male	56	54	58	0.2
Race/ethnicity				
Asian	8	10	7	< 0.001
Black or African American	7	4	9	
Latinx	26	29	23	
Non-Latinx White	45	40	49	
Other	6	9	4	
Unknown	8	9	7	
Non-English speaking	14	18	10	< 0.001
Insurance				
Medicare	34	28	39	< 0.001
Medi-Cal	32	37	28	
Private	32	33	31	
Other	2	2	3	
Clinical characteristics				
Cirrhosis etiology				
Alcohol	37	38	36	0.4
Hepatitis B	7	9	6	0.01
Hepatitis C	47	42	51	0.001
MASLD	25	26	25	0.95
Autoimmune	8	9	8	0.2
Other	7	8	6	0.14
Comorbidities				
Hypertension	54	49	57	< 0.001
Diabetes	36	34	37	0.12
Chronic kidney disease	16	16	15	0.5
On hemodialysis	4	25	32	0.3
Falls	2	2	3	0.4
Psychiatric diagnosis	30	32	29	0.2
Anxiety	14	14	13	0.7
Depression	26	27	25	0.3
HCC	27	29	25	0.1
Substance use				
Current alcohol use (n = 1471)	17	14	18	0.04
Current tobacco use (n = 1512)	20	18	21	0.3
Ever marijuana use	14	14	15	0.4
MELD-Na score (n = 1147), median (IQR)	14 (10–19)	15 (10–19)	12 (9–18)	< 0.001
Decompensated	63	72	56	< 0.001
Cirrhosis complications				
Varices				
Nonbleeding	36	42	32	< 0.001
Bleeding	9	11	8	0.03
HE[b]	48	55	43	< 0.001
Ascites	47	58	39	< 0.001
On diuretics	34	41	28	< 0.001

TABLE 2. (*continued*)

Characteristics[a]	Overall (N = 1567)	Abdominal pain (n = 683)	Other pain locations (n = 884)	*p*
SBP	4	5	4	0.3
Hepatorenal syndrome	4	6	3	0.003
Hepatopulmonary syndrome	1	1	1	0.9
Pain severity				
Mild	22	27	17	< 0.001
Moderate	42	40	43	
Severe	37	33	40	

[a]All cells are % unless otherwise indicated.
[b]Defined using ICD-10 code or prescription for lactulose or rifaximin.
Abbreviations: MASLD, metabolic-associated steatotic liver disease; MELD-Na, Model for End-Stage Liver Disease-Sodium; SBP, spontaneous bacterial peritonitis.

characteristics by pain severity category are shown in Supplemental Table S3, http://links.lww.com/HC9/A871.

Among the subset of patients with active pain who reported a location for their pain (n = 1567), the most common location was the abdomen with 44% (n = 683) reporting abdominal pain; 73% of patients with abdominal pain reported that it was moderate or severe at the time of their visit (Figure 1). The next most common regions of pain were: back or neck pain (21%), lower extremity pain (16%), and generalized pain (9%).

The subgroup of patients with abdominal pain (compared to those with other pain locations) was younger and more likely to be Latinx ($p < 0.001$ for both, Table 2). They were more likely to have Medicaid insurance ($p < 0.001$). Abdominal pain (vs. pain in other locations) was less common in those with hepatitis C cirrhosis and hypertension ($p < 0.001$ for both). Patterns of other comorbidities and substance use were similar between those with abdominal pain and nonabdominal pain. MELD-Na score was higher among those with abdominal pain, as were rates of decompensation and cirrhosis-related complications. Overall, patients with abdominal pain reported milder pain at the initial visit compared to patients with pain in other locations ($p < 0.001$).

Analgesic use among patients with cirrhosis with pain

Over half of the patients with cirrhosis with significant pain were prescribed an analgesic at the time of their initial visit, and 30% were prescribed 2 or more analgesics (Table 3). Nearly 34% were prescribed opioids, 14% were prescribed gabapentin, 10% selective serotonin reuptake inhibitors, and 7% muscle relaxants. The most frequently prescribed opioids in our cohort were hydrocodone and oxycodone. As shown in Table 3, patients with significant pain at the time of their initial visit were more likely to be prescribed most classes of analgesics and were more likely to be prescribed more than one type of analgesic. Compared to patients with cirrhosis without significant pain, those with significant pain were more likely to be prescribed other nonanalgesic sedating medications (24% vs. 15%, $p < 0.001$), including antihistamines, anxiolytics, sedative hypnotics, or antipsychotics.

Patients with active abdominal pain were less likely to be prescribed analgesics compared to those with pain in other locations (52% vs. 62%, $p < 0.001$). Specific types of analgesics were used similarly between the 2 groups, except for muscle relaxants and gabapentanoids, which were used less often among patients with abdominal pain ($p < 0.001$ for both).

Association between pain and health resource utilization

Patients with cirrhosis with significant pain were more likely to have an emergency room visit within 1 year, compared to those with no more than mild pain (7% vs. 5%, $p < 0.001$) and while there was a trend in increased rates of hospitalization within 1 year among those with pain, this was not statistically significant after Bonferroni adjustments (25% vs. 21%, $p = 0.008$, Figure 2).

On simple logistic regression (Table 4), significant pain was associated with nearly 1.5 times the odds of an emergency department visit or hospital admission within 1 year of the initial visit (OR: 1.5, 95% CI: 1.3–1.7, $p < 0.001$). Other factors associated with health care utilization included public insurance, hepatic decompensation at the time of initial visit, ascites, MELD-Na score, opioid use, and psychiatric comorbidities. In multivariable logistic regression, after adjustment for all of these factors, pain remained a strong predictor of health care utilization (aOR: 1.3, 95% CI: 1.1–1.5, $p < 0.001$). In our 2 sensitivity analyses, in which we restricted our sample to patients who were most likely to have emergency department visits or admissions at UCSF, ORs for pain mirrored those found in the original analysis with the full cohort ($aOR_{SF} = 1.4$, $aOR_{PCP} = 1.1$, vs. $aOR_{Full} = 1.3$). However, we lacked sufficient evidence to reject the null hypothesis in both sensitivity analyses (Supplemental Table S4, http://links.lww.com/HC9/A871).

TABLE 3 Analgesic and other sedating medication use among patients with cirrhosis, by pain severity and pain location

	Full cohort				Patients with reported pain location at visit			
Medications[a]	Overall (N = 5333)	No more than mild pain (n = 4017)	Significant pain (n = 1316)	*p*	Overall (N = 1567)	Abdominal pain (n = 683)	Other pain locations (n = 884)	*p*
Overall analgesic use								
One or more medications	41	34	60	< 0.001	58	52	62	< 0.001
Two or more medications	17	13	30	< 0.001	28	23	33	< 0.001
Opioid use								
Any opioid	17	11	34	< 0.001	31	27	34	0.004
Hydrocodone	6	4	11	< 0.001	10	8	12	0.003
Oxycodone	5	3	10	< 0.001	9	9	10	0.6
Tramadol	3	2	6	< 0.001	6	7	6	0.4
Methadone	3	2	5	< 0.001	4	3	5	0.07
APAP opioid combo	7	5	13	< 0.001	13	10	15	0.01
Morphine	2	1	4	< 0.001	3	3	4	0.1
Hydromorphone	1	0.4	2	< 0.001	1	1	2	0.1
Fentanyl	0.3	0.2	1	0.001	0.8	0.7	0.8	0.9
Other	0.3	0.2	0.5	0.05	0.4	0.3	0.6	0.7[b]
Nonopioid use								
Acetaminophen	4	3	5	0.009	5	3	6	0.04
NSAID	3	3	5	< 0.001	5	2	6	0.001
Muscle relaxant	3	2	7	< 0.001	6	4	8	< 0.001
Gabapentanoid	8	6	14	< 0.001	13	10	16	< 0.001
Gabapentin	7	6	13	< 0.001	12	9	14	0.002
Pregabalin	0.6	0.4	1	0.001	1	0.6	2	0.08[a]
Antidepressants	11	10	15	< 0.001	15	15	15	0.6
TCA	2	20	3	0.02	3	2	3	0.3
SSRI	7	7	10	< 0.001	10	10	10	0.7
SNRI	2	2	3	< 0.001	3	3	3	0.6
Other sedating medications								
Any sedating medication	17	15	24	< 0.001	23	22	25	0.1
Antihistamines	8	7	12	< 0.001	11	10	12	0.2
Anxiolytics	7	6	10	< 0.001	9	8	10	0.2
Sedative hypnotics	2	2	3	0.04	3	3	3	0.98
Antipsychotics	3	2	4	0.006	4	4	3	0.5

[a]All cells are %.
[b]Yates' continuity correction applied for small cell sizes.
Abbreviations: APAP, acetaminophen; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants.

Association between pain and clinical outcomes

During the 2 years following patients' first visits at UCSF, there were 256 (16%) deaths on the waitlist among listed patients and 753 (21%) deaths among patients who were not listed for transplant. Overall, 1-year mortality was higher among patients with versus without significant pain (18% vs. 11%, $p < 0.001$). There was no difference in posttransplant mortality by baseline pain status (1% vs. 2%, $p = 0.3$). (Figure 2 and Supplemental Table S5, http://links.lww.com/HC9/A871).

Cause-specific hazard models showed a significant effect of pain on the hazards of mortality and of the transplant itself. Patients with pain had a 50% higher hazard of death within 2 years compared to patients with

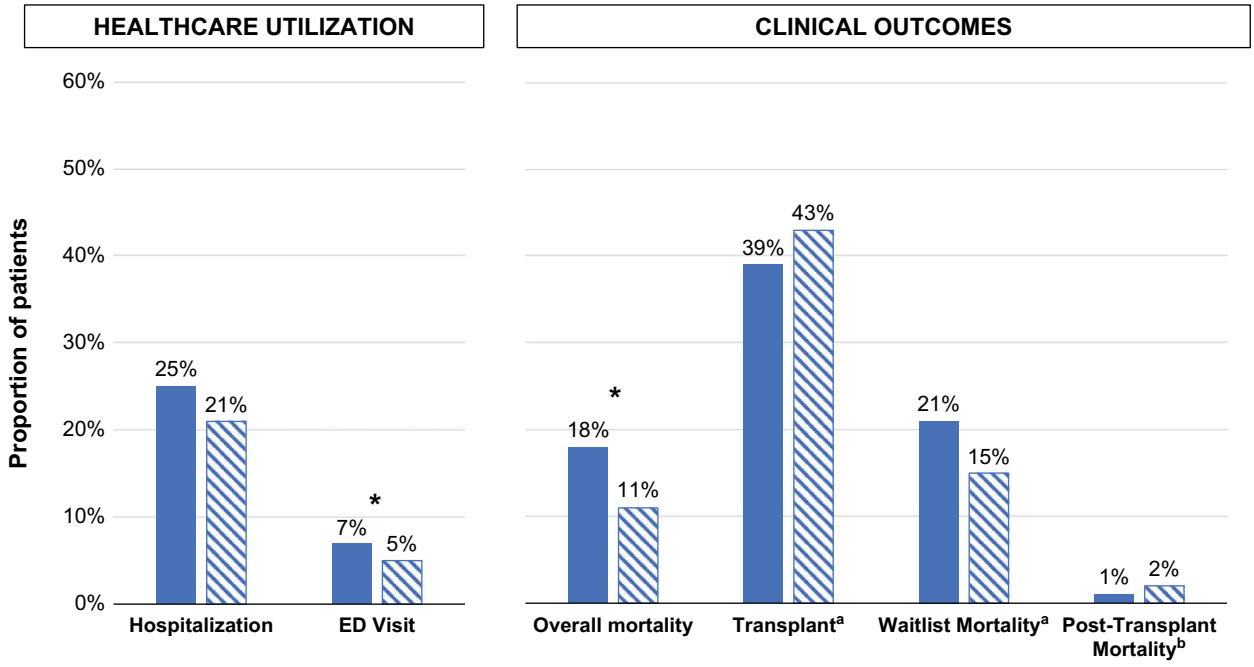

FIGURE 2 One-year health care utilization and 2-year clinical outcomes in patients with cirrhosis with and without pain. Asterisk represents significance at $p < 0.001$. [a]Among the subset of patients listed for transplant. [b]Among the subet that were transplanted.

no more than mild pain (aHR: 1.4, 95% CI: 1.2–1.6) (Figure 3). Cause-specific hazard of death was also higher for older, male, decompensated, and opioid-using patients, as well as for patients with HCC ($p < 0.05$ for all). The pain was not associated with the hazard of transplant (aHR: 0.9, 95% CI: 0.7–1.1). Public insurance and opioid use decreased the cause-specific hazard of receiving a transplant (aHR: 0.4, 95% CI: 0.3–0.5 and aHR: 0.6, 95% CI: 0.4–0.7, respectively) (Table 5).

DISCUSSION

Over the last several decades, the medical field has enhanced its focus on appropriately measuring and treating pain.[21] Yet comparatively little research has focused on patients with cirrhosis and pain, a particularly high-risk population. The present study expands on prior published literature which has suggested high rates of chronic pain in patients with cirrhosis, by utilizing the NRS pain scores, focusing on patients with active pain (ie, nonzero pain score) and those with clinically significant pain (ie, moderate or severe pain) during their hepatology clinic visits. Nearly one-third of patients report active pain, the vast majority of which—nearly 80%—is significant. This is true despite the fact that analgesic prescriptions are quite common in this population, with over 50% of patients with active pain using one or more analgesics, and 25% having an opioid prescription. Significant pain in cirrhosis also appears to be associated with increased health care utilization, as well as increased mortality rates.

Why are rates of active and significant pain so high in this population? One possible explanation is that providers are hesitant to prescribe analgesics to patients with cirrhosis, particularly those with decompensated disease, given concerns about analgesic-related adverse effects. Published recommendations regarding pain management in this population emphasize minimizing analgesic use, highlighting the risks associated with multiple classes of medications in cirrhosis, including opioids, NSAIDs, and acetaminophen.[22–24] However, prior work by our team and others has shown that rates of opioid use among patients with cirrhosis are similar to, if not higher than, patients without cirrhosis.[25–28] It is also possible, as evidenced by high rates of analgesic prescriptions in our cohort, that patients with cirrhosis *are* in fact being prescribed analgesics, but at doses that minimize the risk of adverse effects, which are too low to be effective. While medication doses were not evaluated in the present study, we have shown previously that among Veterans on long-term opioid therapy, those with cirrhosis may in fact receive higher doses of opioids than those without cirrhosis.[27] Additional work should further explore analgesic dosing differences between patients with and without cirrhosis.

It is also possible that the nature of pain in patients with cirrhosis differs from that of the general population. Providers may assume that pain is similar in patients with and without cirrhosis and therefore should be managed similarly. Yet we have shown in the present study that this is not the case. While back pain and headache are the most common causes of pain in the

TABLE 4 Factors associated with nontransplant–related hospital admissions or emergency room visits within 1 year of the initial clinic visit

	Health care utilization within 1 y of initial visit [a]		Estimates from unadjusted bivariate models		Estimates from adjusted multivariable models	
	No admissions or ED visits (n = 4191)	Any admission or ED visit (n = 1142)	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age at initial visit[b] (median, IQR)	59 (53–65)	59 (52–65)	0.99 (0.9–1.1)	0.6	0.97 (0.9–1.0)	0.4
Sex, male	61	62	1.1 (0.9–1.2)	0.5	1.02 (0.9–1.2)	0.7
Race						
Asian	12	13	1.1 (0.9–1.3)	0.6	1.4 (1.1–1.7)	0.003
Black or African American	6	8	1.3 (1.02–1.7)	0.03	1.4 (1.1–1.8)	0.02
Latinx	24	26	1.1 (0.9–1.2)	0.5	0.99 (0.8–1.2)	0.9
Non-Latinx White	45	45	1.0 (reference)	—	1.0 (reference)	—
Other	6	7	1.2 (0.9–1.5)	0.2	1.2 (0.9–1.5)	0.2
Unknown	7	1	0.2 (0.08–0.3)	< 0.001	0.1 (0.08–0.2)	< 0.001
Insurance						
Medicare or Medi-Cal	55	62	1.3 (1.2–1.5)	< 0.001	1.21 (1.1–1.4)	0.003
Private	43	36	1.0 (reference)	—	1.0 (reference)	—
Other	2	2	1.2 (0.8–1.9)	0.4	1.3 (0.8–2.1)	0.3
Decompensation	53	73	2.4 (2.1–2.7)	< 0.001	2.5 (2.2–2.9)	< 0.001
HE	37	54	1.9 (1.7–2.2)	< 0.001	—	—
Ascites	38	61	2.6 (2.3–3.0)	< 0.001	—	—
MELD-Na score (median, IQR) (n = 3823)	12 (9–17)	15 (10–21)	1.1 (1.05–1.07)	< 0.001	—	—
Opioid use	16	22	1.5 (1.2–1.7)	< 0.001	1.3 (1.1–1.6)	0.003
Pain (moderate or severe)	23	31	1.5 (1.3–1.7)	< 0.001	1.3 (1.1–1.5)	0.003
Psychiatric diagnosis	20	29	1.6 (1.4–1.9)	< 0.001	1.6 (1.3–1.8)	< 0.001
HCC	30	34	1.2 (1.1–1.4)	0.01	1.3 (1.2–1.6)	< 0.001

[a]All cells are % unless otherwise indicated.
[b]Age was scaled by decade for regression models.
Abbreviations: ED, emergency department; MELD-Na, Model for End-Stage Liver Disease-Sodium.

general population,[29] we found that abdominal pain was the most common in patients with cirrhosis, with 44% of our pain cohort reporting abdominal pain, compared with 21% reporting back or neck pain and 2% reporting headache. Thus, it is possible that typical pain management strategies are less effective in patients with cirrhosis-related abdominal pain, compared to other locations of pain. The etiology of abdominal pain in cirrhosis has not been well elucidated, though severe abdominal pain is known to be associated with spontaneous bacterial peritonitis.[30] Yet in our cohort, only 5% of patients reporting active abdominal pain had a history of spontaneous bacterial peritonitis. In addition, while 60% of patients with abdominal pain had ascites, there remained a significant proportion of patients with abdominal pain without ascites, suggesting that patients with cirrhosis are predisposed to other types of chronic abdominal pain as well. Prior studies have suggested high rates of nociplastic pain in patients with cirrhosis; this type of pain is associated with central augmentation of nociception (rather than tissue or nervous system damage) and is implicated in conditions such as irritable bowel syndrome and chronic pelvic pain.[31] There is a substantial body of literature suggesting that common pain management strategies, such as opioids, are not effective in treating abdominal pain, and may in fact exacerbate abdominal pain through constipation and gastroparesis (ie, narcotic bowel syndrome).[32–34] Perhaps abdominal pain in cirrhosis needs to be studied further as a unique etiology with unique management strategies.

The present study also highlights that the increased health care utilization associated with pain in the general population is also present in patients with cirrhosis, as rates of emergency room visits and hospitalizations are increased among patients with cirrhosis with pain. This is especially pertinent, as this is already a population at high risk of acute and costly

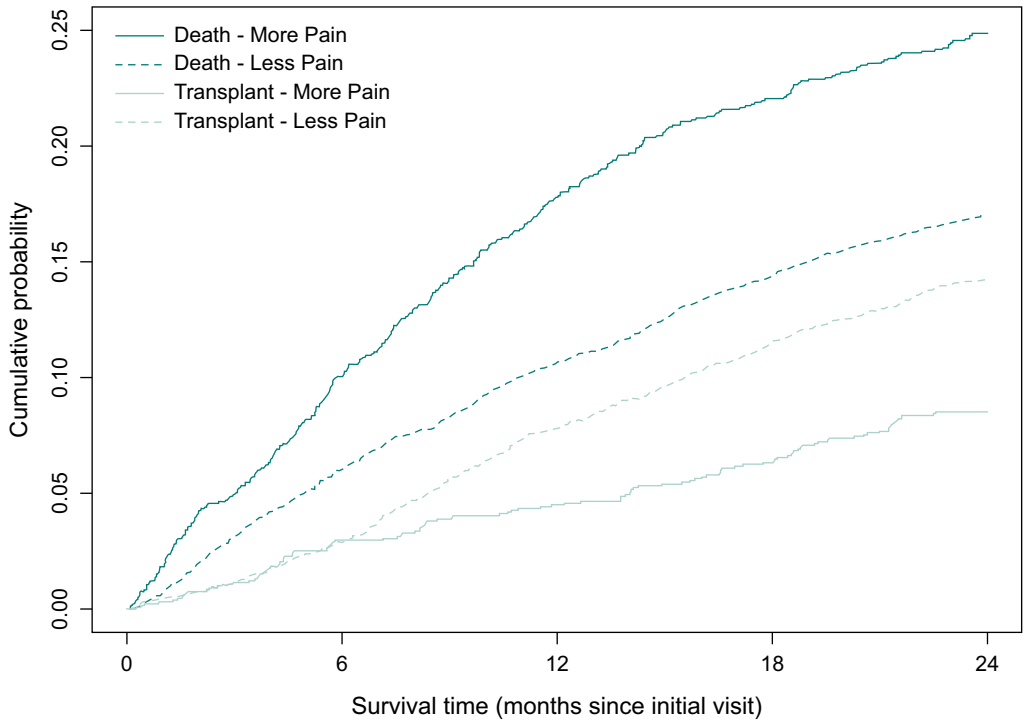

FIGURE 3 Cumulative incidence of death (blue) and transplant (pink) up to 2 years following initial hepatology visit, by significant pain status. Solid lines represent patients with moderate or severe pain at baseline; dotted lines represent patients with no more than mild pain at baseline.

health care utilization. For transplant candidates, health care utilization is associated with worse pretransplant and posttransplant outcomes.[35–37] In the present study, we did not find an association between pain and transplant rates or posttransplant mortality. However, we did find an increased risk of mortality in patients with significant pain among those not listed for transplant, as well as a trend toward increased waitlist mortality among listed patients, although this did not reach statistical significance. These findings may be explained in part by differences in severity of illness or comorbidities that were not captured in our study, but regardless they do suggest a more severe clinical course for patients with pain—perhaps related to differences in underlying disease, risks related to frequent hospitalizations, or adverse effects of polypharmacy/analgesic use. Regardless of the meaning of our observed differences in clinical outcomes, patient quality of life and patient-reported outcomes have become increasingly important metrics within hepatology and the entire medical field, furthering the significance of our findings.[38]

Our study has several limitations. First, given the retrospective and cross-sectional nature of this study, we were unable to explore certain aspects of pain (eg, chronicity, changes over time, and quality of pain) and its management (eg, over-the-counter medication use, analgesic dosing, and nonpharmacologic strategies). In addition, there are likely other confounders not captured in EHR data that could affect the relationship between pain, medication use, and outcomes (eg, behavioral factors, such as adherence). Second, we were only able to capture local EHR data from UCSF's Epic Clarity and transplant databases. Therefore, encounters at health care facilities (ie, hospitals and labs) outside of UCSF were not captured in these data, which also limited our ability to include certain covariates (eg, MELD score) in our multivariable models. We did, however, perform sensitivity analyses among subgroups of patients who were most likely to have complete data captured in our system. While we were able to capture the death data using state death registries, we did not capture cause of death for all patients. Third, UCSF is a transplant center, and ~40% of our cohort included patients referred for transplant; our population may not be representative of the broader US cirrhosis population. However, we did not observe significant differences in rates of pain, medication use, or outcomes between patients seen in transplant versus general hepatology clinics. Finally, we chose to focus our primary analyses on those with active pain that was at least moderate or severe at the time of the patient's initial clinic visit. Thus, we are systematically excluding from our "pain group" patients with mild pain, and those with pain that is well-controlled with pharmacologic or nonpharmacologic therapy, resulting in lower overall rates of pain than other published literature. However, we feel that our study population—those with active "significant pain" represents the highest yield group of patients for additional research and interventions.

TABLE 5 Hazard analyses for all-cause mortality and receipt of liver transplant within 2 years

	Mortality before transplant		Transplant	
	Unadjusted $_{CS}$HR (95% CI)	Adjusted $_{CS}$HR (95% CI)	Unadjusted $_{CS}$HR (95% CI)	Adjusted $_{CS}$HR (95% CI)
Age at initial visit	1.3 (1.1–1.6)*	1.3 (1.2–1.4)*	1.0 (1.0–1.01)	0.9 (0.8–0.96)*
Sex,[a] male	0.8 (0.6–1.03)	1.2 (1.03–1.4)*	0.96 (0.8–1.1)	1.03 (0.9–1.2)
Race				
Asian	0.9 (0.6–1.4)	1.0 (0.8–1.3)	0.99 (0.8–1.2)	1.1 (0.9–1.4)
Black or African American	1.1 (0.6–2.0)	1.1 (0.8–1.4)	0.8 (0.6–1.2)	0.9 (0.6–1.3)
Latinx	1.1 (0.8–1.4)	0.9 (0.8–1.1)	0.96 (0.8–1.1)	1.2 (0.97–1.4)
Non-Latinx White	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Other	1.3 (0.8–2.2)	1.2 (0.95–1.5)	0.9 (0.6–1.2)	0.8 (0.6–1.1)
Unknown	3.1 (1.8–5.4)*	1.6 (1.2–2.0)*	0.1 (0.03–0.6)*	0.1 (0.02–0.24)*
Insurance				
Medicare or Medi-Cal	1.3 (1.03–1.7)*	1.1 (0.98–1.3)	0.6 (0.6–0.8)*	0.4 (0.3–0.5)*
Private	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Other	3.5 (1.7–7.1)*	1.4 (0.99–2.0)	0.5 (0.2–1.3)	0.2 (0.1–0.4)*
MELD	1.08 (1.06–1.1)*	—	1.05 (1.04–1.1)*	—
Decompensated	2.2 (1.6–3.1)*	3.3 (2.8–3.8)*	1.3 (1.1–1.5)*	3.0 (2.5–3.6)*
HE	2.2 (1.7–2.9)*	—	1.4 (1.2–1.7)*	—
Ascites	1.9 (1.5–2.5)*	—	1.3 (1.1–1.5)*	—
Opioid use	1.3 (0.9–1.8)*	1.3 (0.9–1.9)	0.8 (0.6–1.05)	0.6 (0.4–0.7)*
Moderate or severe pain at initial visit	1.4 (1.1–1.9)*	1.4 (1.2–1.6)*	0.9 (0.7–1.1)	0.9 (0.7–1.1)
Psychiatric diagnosis	0.97 (0.7–1.4)	0.95 (0.8–1.1)	1.2 (1.02–1.5)*	1.1 (0.9–1.3)
HCC	1.3 (1.01–1.7)*	1.9 (1.7–2.2)*	1.5 (1.2–1.7)*	4.1 (3.5–4.8)*

*Significant at $\alpha = 0.05$.
[a]Removed single nonbinary patient to generate models.
Abbreviations: $_{CS}$HR, Cause-specific hazard ratio; MELD, Model for End-Stage Liver Disease.

Despite these limitations, our study is one of the largest, most contemporary, and in-depth explorations of pain, its management, and associated outcomes in patients with cirrhosis specifically. Not only does it reinforce the significant burden of pain in this population, but also highlights how poorly pain is controlled in this population. Moreover, our findings suggest that patients with cirrhosis may experience pain differently than the general population. This has important implications for how pain is managed in these patients, particularly considering the effect of liver dysfunction on the metabolism of multiple classes of analgesics. Perhaps instead of commonly used analgesics, such as opioids, NSAIDs, or acetaminophen, we should explore the efficacy and safety of alternative analgesic agents, such as selective serotonin reuptake inhibitors, or nonpharmacologic pain management strategies. An increased focus on understanding and controlling pain in cirrhosis is essential for improving quality of life, and possibly clinical outcomes, for the large proportion of patients with cirrhosis living with pain.

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