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Cirrhosis inpatients receive more opioids and fewer nonopioid analgesics than patients without cirrhosis

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Abstract

Goals/Background: Pain is common among cirrhosis patients, particularly those hospitalized with acute illness. Managing pain in this population is challenging due to concern for adverse events and lack of guidelines for analgesic use. We sought to characterize analgesic use among inpatients with cirrhosis compared to matched noncirrhosis controls, as well as hospital-level variation in prescribing patterns.

Study: We utilized the Vizient Clinical Database, which includes clinical and billing data from hospitalizations at >500 US academic medical centers. We identified cirrhosis patients hospitalized in 2017-2018, and a matched cohort of noncirrhosis patients. Types of analgesic given—acetaminophen (APAP), nonsteroidal anti-inflammatories (NSAIDs), opioids, and adjuvants (e.g. gabapentinoids, antidepressants) were defined from inpatient prescription records. Conditional logistic regression was used to associate cirrhosis diagnosis with analgesic use.

Results: Of 116,363 cirrhosis inpatients, 83% received at least one dose of an analgesic and 58% had regular inpatient analgesic use, rates that were clinically similar to noncirrhosis controls. Cirrhosis inpatients were half as likely to receive APAP (26% vs 42%,p<0.01) or NSAIDs (3% vs 7%,p<0.01), but were more likely to receive opioids (59% vs 54%, p<0.01), particularly decompensated patients (60%). There was notable variation in analgesic prescribing patterns between hospitals, especially among cirrhosis patients.

Conclusions: Analgesic use was common among inpatients, with similar rates among patients with and without cirrhosis. Cirrhosis patients—particularly decompensated patients—were less

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likely to receive APAP and NSAIDs and more likely to receive opioid analgesics. Because of lack of evidence-based guidance for management of cirrhosis patients with pain, providers may avoid nonopioid analgesics due to perceived risks, and consequently may overutilize opioids in this high-risk population.

Keywords

Analgesics; Pain; Opioids; Medication safety; Health services research

Introduction

Pain is common among patients with cirrhosis, but analgesic options in this population are limited due to concerns regarding impaired drug metabolism and susceptibility to adverse events.[1–4] Providers often avoid commonly used over-the-counter (OTC) analgesics in cirrhosis patients—acetaminophen (APAP) because of its potential for hepatoxicity at high doses,[5] and non-steroidal anti-inflammatories (NSAIDs) because they are thought to precipitate renal injury and increase the risk of bleeding in this population.[6–8] However, alternatives, namely opioids and other neuropsychiatric medications (e.g. skeletal muscle relaxants), are also considered high-risk in cirrhosis patients as they may worsen hepatic encephalopathy and can be associated with dependence and abuse.[9–11] the setting of risks associated with all of these classes of analgesics in this population, cirrhosis patients are also particularly vulnerable to undertreatment of pain and resulting poor quality of life.[1,12–14]

Because of these risks, there is likely variation in how cirrhosis patients with pain are managed, but there is little evidence confirming this. Additionally, the minimal data that exist on analgesic-related harms in patients with cirrhosis are pharmacokinetic studies of drug metabolism or small single-center studies, often focusing on the highest-risk patients – those with decompensated cirrhosis.[8,15–20] The contemporary real-world effects of analgesics among all cirrhosis patients—both compensated and decompensated—remain largely unknown. Studying patterns of analgesic use is additionally challenging because it is difficult to collect data on commonly used OTC medications from outpatient prescription records. The inpatient setting provides a unique environment to study utilization of analgesic agents because inpatient pain is exceedingly common, and because all doses of medications are recorded, including OTC agents. In the present study, we utilized a contemporary national hospitalization cohort to help understand differences in the frequency and patterns of analgesic use – APAP, NSAIDs, opioids, and adjuvant agents (e.g. antidepressants, gabapentanoids, muscle relaxants) – among inpatients with and without cirrhosis, as well as hospital-level variability in analgesic prescribing.

METHODS

Data source

This was a retrospective cohort study using deidentified inpatient data from the Vizient Clinical Data Base/Resource Manager (CDB/RM). Vizient is a consortium of 3,000 hospitals across the United States; over 150 academic medical centers and 400 affiliate hospitals participate in the CBD/RM, which provides clinical, discharge, procedure, cost,

and outcome data for each hospital encounter. Data are extracted from hospital billing systems approximately 30 days after discharge, and are de-identified to conform with requirements of the Health Insurance Portability and Accountability Act.

Study population

The study population consisted of all inpatient non-surgical admissions in the Vizient CDB/RM with hospital discharges from January 1, 2017 to December 31, 2018 for patients ≥18 years old at admission (Figure 1). Surgical admissions were excluded because of the high likelihood for acute post-surgical pain in this cohort, resulting in differing analgesic requirements. Excluded surgical admissions were those with operating-room based procedures, defined using the Agency for Healthcare Research and Quality's (AHRQ) Procedure Class Definitions for International Classification of Diseases, 10th Revision-Clinical Modification (ICD-10) procedure codes.[21,22] Given differing patterns of analgesic use at the end-of-life, we excluded admissions if patients died during hospitalization, or if they were discharged with hospice care. We also removed admissions in which length of stay was less than one day, or if the discharge provider was an emergency medicine physician. Stays >45 days (determined to be outliers, >99th percentile) were excluded. Encounters were also excluded if they represented a 30-day readmission following an index hospitalization in the Vizient database, to ensure we captured unique patients to the extent possible.

Cirrhosis patients were identified from within this medical cohort by presence of one of nine ICD-10 diagnosis codes for cirrhosis (Table, Supplemental Digital Content 1), whether principal or secondary. A subset of 7 of these ICD-10 codes has been validated previously, with >90% positive predictive value.[23] Two additional ICD-10 codes were added to increase sensitivity of identifying patients with cirrhosis.

Covariate definitions

We were interested in demographic, clinical, and hospitalization factors associated with inpatient analgesic use among patients with and without cirrhosis. Demographic factors included in Vizient data and tested as covariates in our analyses included gender, patient age group (precise age is not provided to ensure data remains de-identified), race/ethnicity, primary payer, and hospital region.

Clinical factors (e.g. comorbidities and cirrhosis-related complications) were defined using ICD-10 diagnosis codes. We used the administrative data-derived Charlson Comorbidity Index as a proxy for patient comorbidity.[24,25] Cirrhosis complications were defined as: ascites, varices, variceal bleed, hepatic encephalopathy, hepatorenal syndrome (HRS), and spontaneous bacterial peritonitis (SBP) (see Table, Supplemental Digital Content 2). Codes for ascites and esophageal varices have been validated previously, with positive predictive value >90%.[23,26] Hepatic encephalopathy was defined as either having an ICD-10 code for liver disease "with coma", or at least one inpatient charge for *both* lactulose and rifaximin (using medication charges available in the Vizient CDB/RM, as described below). While lactulose and rifaximin can each be used for non-hepatic encephalopathy indications, use of both medications is strongly suggestive of treatment for hepatic encephalopathy. HRS

and SBP are each defined using single specific ICD-10 codes. In an effort to utilize the most sensitive definition of hepatic decompensation, a diagnosis code for *any* one of these cirrhosis-related complications (excluding nonbleeding varices) categorized a patient as having decompensated cirrhosis.[26] To minimize confounding by decompensation status, we performed secondary analyses in which we stratified patients as: no cirrhosis, compensated cirrhosis, or decompensated cirrhosis.

As chronic pain prior to admission was thought to be an important predictor of inpatient analgesic use, we identified the proportion of patients with a one of 4 ICD-10 diagnosis codes for chronic pain that have been previously validated in the literature.[27,28]

Hospitalization-specific covariates included: admission status (emergency, urgent, elective, trauma), admission source (emergency room, transfer, other), length of stay, and intensive care unit stay, all of which were variables in the Vizient CDB/RM. Physician specialty was defined as the specialty of the primary discharging provider, categorized as general medicine, liver/gastroenterology specialist, and other. Hospital characteristics (i.e. size, teaching status, liver transplant center) were available in the database.

Prevalence and patterns of analgesic use

In order to identify patients who received analgesics during hospitalization, we utilized inpatient prescription charges by hospital day, which were available in the Vizient CDB/RM. Charges are only recorded if the medication is administered to the patient. Medications were categorized as opioids or nonopioids; nonopioids were further categorized into APAP, NSAIDs, or adjuvant analgesics, which included antidepressants, gabapentinoids, and muscle relaxants (Table, Supplemental Digital Content 3). As antidepressants are often used to treat ailments other than pain, we also performed sensitivity analyses excluding this class of medications. Opioid combinations with APAP or NSAIDs were included in both relevant categories.

We identified inpatient analgesic use in multiple ways: (1) any analgesic use, defined as any charge for an analgesic during hospitalization; (2) regular analgesic use, defined as a charge for the same class of analgesic on more than half of hospital days; and (3) new analgesic use (which is a subset of Group 2), defined as regular inpatient analgesic use in patients *without* an ICD-10 code for long-term use of NSAIDs (Z79.1) or opiate analgesic (Z79.891) and without analgesic use within 24 hours of admission. To evaluate patterns of and risk factors for inpatient analgesic use among the group of patients that was most likely to have “persistent pain”, we focused on the second of these definitions, those with regular analgesic use.

Hospital-level variation in analgesic use

In our analysis of hospital variation in analgesic prescribing, we also wantd to focus on patients with persistent pain during their hospital stay. Thus, we only included those that had regular analgesic use (i.e. second definition above). We excluded hospitals with fewer than 50 patients per subgroup with regular analgesic use. Given patients were matched by site (see details below), we did not adjust for patient characteristics in this analysis. We then

calculated the proportion of patients with and without cirrhosis that received each analgesic by site, and summary statistics were reported.

Statistical analysis

To ensure that baseline characteristics were similar between cirrhosis and non-cirrhosis patients, we utilized a propensity score model to match patients on clinically relevant demographic and clinical characteristics, defined a priori, which were hypothesized to be associated with in-hospital analgesic use (noted in Table 1). Propensity scores were calculated for each subject to identify the conditional probability of having cirrhosis using a logistic regression model with cirrhosis as the dependent variable, stratified by hospital. One hospital that did not admit any cirrhosis patients over the two-year study period was excluded. Patients with and without cirrhosis were then matched in a 1:1 ratio using caliper matching without replacement with a caliper size of 0.1 times the pooled standard deviation of the logit of the propensity score. The *psmatch2* program was applied for matching,[29] and the *pstest* command was used to evaluate the success of matching by comparing the differences in baseline characteristics before and after matching. The double-adjustment method was used for all matching covariates given large sample size, which also accounted for any imbalances in matching variables.[30]

Categorical variables were presented as percentages and compared between unmatched groups by χ^2 and Fisher's exact tests. Continuous variables were presented as medians with interquartile ranges (IQR) and compared between unmatched groups by Wilcoxon Rank-Sum tests, given non-normal distributions. Conditional logistic regression models grouped by matched pairs and clustered by hospital were used to identify associations between cirrhosis and analgesic use. Using the covariates from the cirrhosis subgroup multivariable model (Table 2), in models including both cirrhosis and noncirrhosis patients, we tested for interaction between a cirrhosis diagnosis and all other covariates to determine how predictors of our outcomes differed in cirrhosis compared with noncirrhosis patients. Backward selection was used to develop all multivariable models. Potential confounders with $p < 0.1$ in univariable analysis were selected for inclusion in multivariable models. Covariates not reaching a significance of $p < 0.05$ were sequentially eliminated. Two-sided *P* values <0.05 were considered statistically significant. All *P* values reported from the matched cohort analyses are from double-adjusted conditional logistic regression models, unless otherwise specified. We used a paired Bartlett's test to compare variance between hospitals in rates of analgesic use among patients with and without cirrhosis. Analyses were performed using Stata/MP 16.1 statistical software (College Station, TX).

RESULTS

Of 9,348,723 hospitalizations in the 2017-2018 Vizient CDB/RM, 117,957 cirrhosis patients and 3,106,452 patients without cirrhosis met our inclusion criteria (Figure 1). A final cohort of 232,726 patients was generated after matching; select demographic and clinical characteristics of the cohorts after matching are shown in Table 1. Cirrhosis patients were statistically more likey to be non-White (29.5% vs 29.0%, p<0.01), have chronic pain (10.7% vs 10.2%, p<0.01), and have more comorbidities (p<0.01), though these were not

clinically significant differences. Our cohort was 40.2% female, 70.7% non-Hispanic white and 32.0% aged 65 years or older. Among cirrhosis patients, over half had decompensated disease; 43.2% had ascites and 23.1% had hepatic encephalopathy. Approximately 40% of cirrhosis patients had alcohol-related disease.

Overall, 82.6% of cirrhosis patients received at least one dose of an analgesic medication during hospitalization. Among cirrhosis patients, 58.4% had regular inpatient analgesic use (>50% of hospital days), and of these, 3.7% had new in-hospital analgesic use. Cirrhosis patients were 14% less likely to have any analgesic use (OR 0.86, $p<0.01$) and 12% less likely to have regular inpatient analgesic use compared to controls without cirrhosis (OR 0.88, $p<0.01$), but were 42% more likely to have new analgesic use during admission (OR 1.42, $p<0.01$). However, absolute percentage point differences for all of these definitions of analgesic use were small (<2%). On subgroup analysis, rates of pain medication use (using all 3 definitions) were similar among patients with compensated cirrhosis and those without cirrhosis. Patients with decompensated cirrhosis were significantly *less* likely to have any analgesic use or regular analgesic use compared with compensated and noncirrhosis patients, yet they were nearly twice as likely to have new analgesic use during hospitalization (Figure 2).

Among patients with persistent pain (i.e. those with regular inpatient analgesic use), there were significant differences in patterns of pain medication use in patients with versus those without cirrhosis (Figure 3). Cirrhosis patients were nearly half as likely to receive APAP (26% vs 42%, $p<0.01$) or NSAIDs (3% vs 7%, $p<0.01$) compared with noncirrhosis patients. However, cirrhosis patients were slightly more likely than noncirrhosis patients to have regular inpatient opioid use (59% vs 54%, $p<0.01$). Patients with decompensated cirrhosis were significantly more likely to have regular opioid use than compensated patients or those without cirrhosis (60% vs 55%, $p<0.01$), and significantly less likely to regularly use all other analgesics. Among patients with regular opioid use, 72% of noncirrhosis patients received APAP at least once in addition to a trial of opioids, compared with 53% of compensated cirrhosis patients and 47% of decompensated cirrhosis patients (p-values <0.01). Overall, adjuvant analgesics were used regularly in approximately 30% of patients and 50% of patients with regular analgesic use, with similar rates between patients with and without cirrhosis. On sensitivity analysis excluding antidepressants, while rates of adjuvant analgesic use were lower (resulting in slightly lower overall rates of regular analgesic use in our cohort), they remained similar in patients with and without cirrhosis.

There was notable variation in rates of use of all analgesics by hospital among patients with persistent pain, as shown in Figure 4A. Among these patients, rates of regular opioid use by hospital ranged from 34.1% to 93.0% (median 56.5%, IQR 51.1%-62.5%). By comparison, rates of regular APAP use ranged from 0.4% to 56.7% (median 34.8%, IQR 28.3%-41.7%). There was a trend towards more between-hospital variation in opioid use ($p = 0.1$) and APAP use ($p = 0.07$) in cirrhosis patients compared to noncirrhosis patients as shown in Figures 4B and 4C.

Risk factors for opioid use (versus nonopioid use) among the subgroup of cirrhosis patients with persistent pain are shown in Table 2. On multivariable logistic regression, demographic

factors most strongly associated with regular opioid use included younger age, black race, and public insurance. Hospitalization-specific risk factors for regular opioid use included being on a surgical service, transferred from an outside facility, and at a nonteaching hospital. These covariates were similar to risk factors for opioid use in patients without cirrhosis (data not shown). Regarding cirrhosis-specific factors, patients with hepatitis C cirrhosis were significantly more likely to use opioids, as were those with ascites. Patients with hepatic encephalopathy were 24% less likely to have regular opioid use. A diagnosis of decompensated cirrhosis was significantly associated with opioid use on univariable, but not multivariable analysis.

DISCUSSION

Up to 80% of cirrhosis patients experience pain, which is reported to be poorly controlled in the majority of this population.[1,3,12,14] There is a paucity of data on optimal pain management strategies in cirrhosis, which we hypothesize results in variable patterns of analgesic use. We utilized a large contemporary national cohort of nonsurgical inpatients to characterize patterns of both opioid and nonopioid analgesic use in patients with cirrhosis. We found that rates of inpatient analgesic use, as well as rates of prior chronic pain diagnoses, were clinically similar between patients with and without cirrhosis. However, patients with cirrhosis—particularly those with decompensated disease—were significantly *less* likely than matched controls without cirrhosis to receive nonopioid analgesics, including acetaminophen, NSAIDs, and other adjuvant analgesics, but were *more* likely to receive opioids. Additionally, we identified notable variation in patterns of analgesic use by hospital among those requiring regular analgesics, with a trend toward more variation in prescribing rates among patients with cirrhosis than among controls without cirrhosis.

What explains these differences in analgesic use patterns in inpatients with cirrhosis compared to those without cirrhosis? Liver dysfunction is well-known to alter drug pharmacokinetics and metabolism, leading to increased risk of toxicity from multiple classes of medications in cirrhosis patients.[4,31] In particular, previous studies have shown that providers often avoid commonly used over-the-counter analgesics in cirrhosis patients, such as APAP and NSAIDs.[32,33] The present study confirmed that concerns regarding these classes of medications likely affected provider decision-making in cirrhosis inpatients with pain, as patients *without* cirrhosis were nearly twice as likely to receive APAP or NSAIDs as patients *with* cirrhosis. In contrast, or perhaps consequently, cirrhosis patients were significantly more likely than noncirrhosis patients to receive opioids – a class of medications that may be especially risky in this population, as they have been shown to alter gut flora leading to hepatic encephalopathy, and can be associated with dependence and abuse, even when started for acute pain in the inpatient setting.[9–11,34–36] In our study, cirrhosis patients on opioids were also less likely than patients without cirrhosis to receive multimodal pain management (i.e. combination of opioid plus a nonopioid agent), despite evidence that this strategy is more efficacious than opioids alone, and can reduce cumulative opioid doses.[37,38] These differences in pain management patterns between inpatients with and without cirrhosis were even further pronounced when comparing patients with decompensated cirrhosis to patients without cirrhosis, suggesting that the patients at

highest risk of opioid-related adverse events may be more, rather than less, likely to receive this class of medications.

The patterns we observed may be driven by provider perceptions about analgesic risks in cirrhosis patients that are often not data-driven. For example, while APAP—the most commonly used first-line analgesic in the inpatient and outpatient settings—is associated with hepatotoxicity at high doses, limited evidence and clinical experience suggest that it is likely safe in therapeutic doses in patients with chronic liver disease. In fact, it is often recommended as the first-line analgesic in this population.[4,14,39,40] However, we observed that APAP was often not prescribed at all during hospitalization to patients with cirrhosis and pain, suggesting that provider misconceptions about the risks of therapeutic APAP doses in cirrhosis patients may result in its complete avoidance in this population, as has been suggested previously.[33] Similarly, data on the harms of other analgesics in cirrhosis patients are often extrapolated from pharmacokinetic studies of drug metabolism, many conducted in healthy volunteers rather than cirrhosis patients or from small single-center studies.[6,15–17,41] These limited data and resulting lack of evidence-based guidelines for pain management in this high-risk population may explain why we observed significant hospital-level variation in analgesic use among cirrhosis patients.

Our study has several limitations. First, because the Vizient CDB/RM is an administrative dataset, it lacks clinical details which would allow for better characterization of nature and severity of pain which may explain some of the differences in analgesic patterns we observed between patients with and without cirrhosis. However, given our large sample size, matched cohort, and adjustment for multiple covariates, we believe our cirrhosis patients and matched controls likely had similar types and reasons for pain. Second, this analysis did not include medication dosage information; it is possible that although cirrhosis patients had higher rates of opioid use, they received lower doses of these medications. Lack of dosage information, however, would not explain the differences in rates of APAP and NSAID use that we observed. Third, the lack of pre-admission outpatient medications precludes analysis of chronic versus new analgesic users, although we did use analgesic use on day of admission and ICD-10 codes for long-term opioid and NSAID therapy as a proxy for this. Additionally, even if these differences in analgesic patterns were determined by outpatient, rather than inpatient providers, we should still be aware of them and ensure that we are not subjecting cirrhosis patients to increased risk of medication-related adverse events or ineffective pain control. Finally, differences in analgesic use between site may have been determined by hospital policies and default electronic order sets, rather than by individual provider decisions, which may explain some of the variation between hospitals we observed, yet this would not explain the differences in hospital-level variation we observed among patients with cirrhosis compared to those without cirrhosis. We hypothesize that these differences may instead be related to provider specialty or experience with cirrhosis patients.

Despite these limitations, our study is the first to use a large contemporary dataset to explore analgesic use patterns among hospitalized cirrhosis patients, and to compare these patterns to those in the general population. Additionally, utilizing an inpatient database provided us with a unique ability to capture patterns of OTC analgesic use in this population as well. We found that while overall rates of pain and analgesic use are clinically similar

between inpatients with and without cirrhosis, cirrhosis patients receive different types of analgesics than patients without cirrhosis. The differences we observed in analgesic prescribing patterns, as well as the significant hospital-level variation in analgesic use patterns in high-risk cirrhosis patients, highlights the need for more evidence-based guidance on how to safely and effectively manage pain in this population. Although there has been an increased national focus on pain as the “fifth vital sign” and on improving pain management strategies in the general population in the wake of the opioid epidemic, there remains a paucity of literature on pain and analgesic use specifically in the high-risk population of patients with cirrhosis.[42–44] Future studies should explore the true efficacy and harms of analgesics in cirrhosis patients across clinical settings, in order to arm clinicians with the tools they need to safely and effectively manage pain in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Sources of Funding

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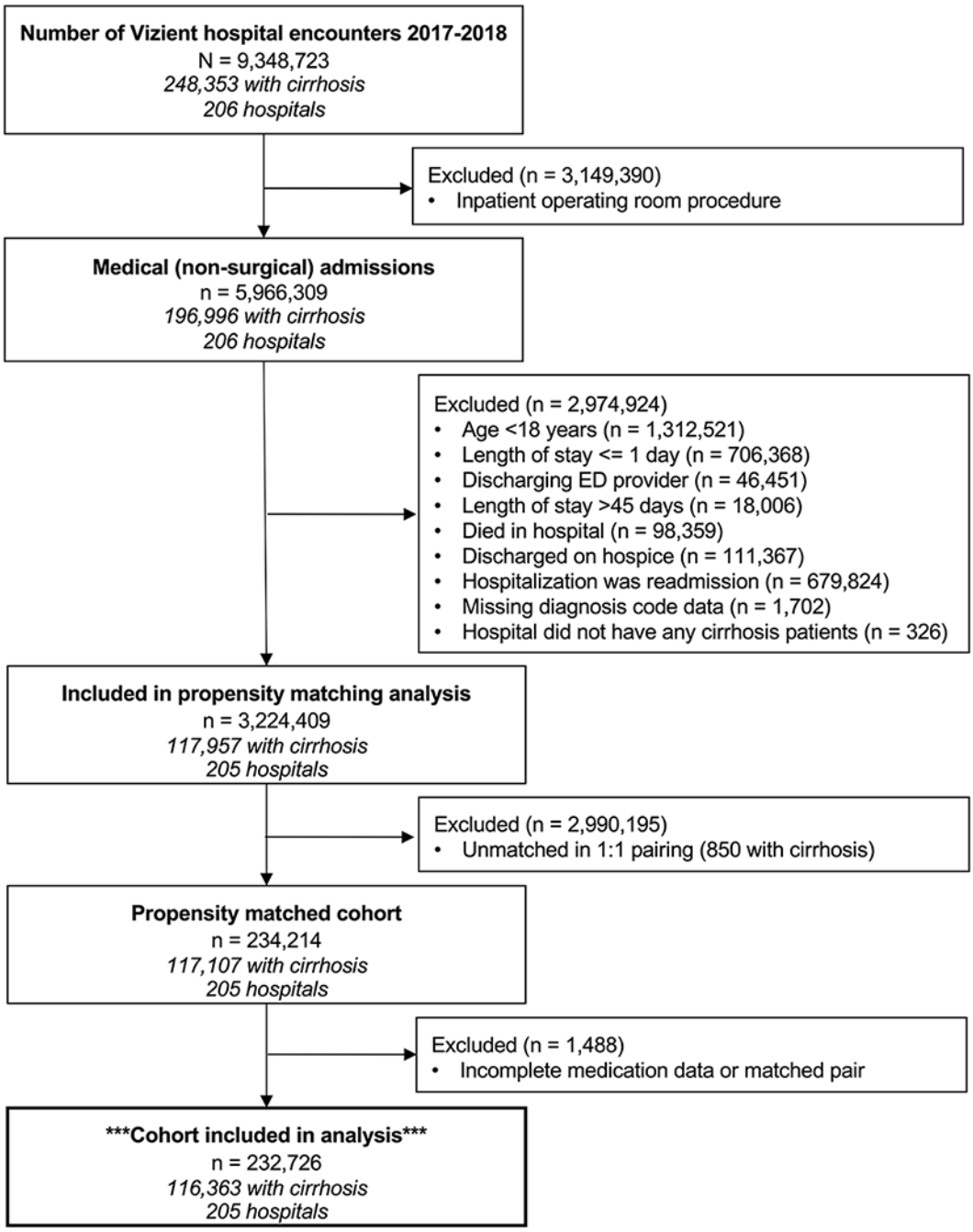


Figure 1.
Flow diagram of Vizient patients included in analysis

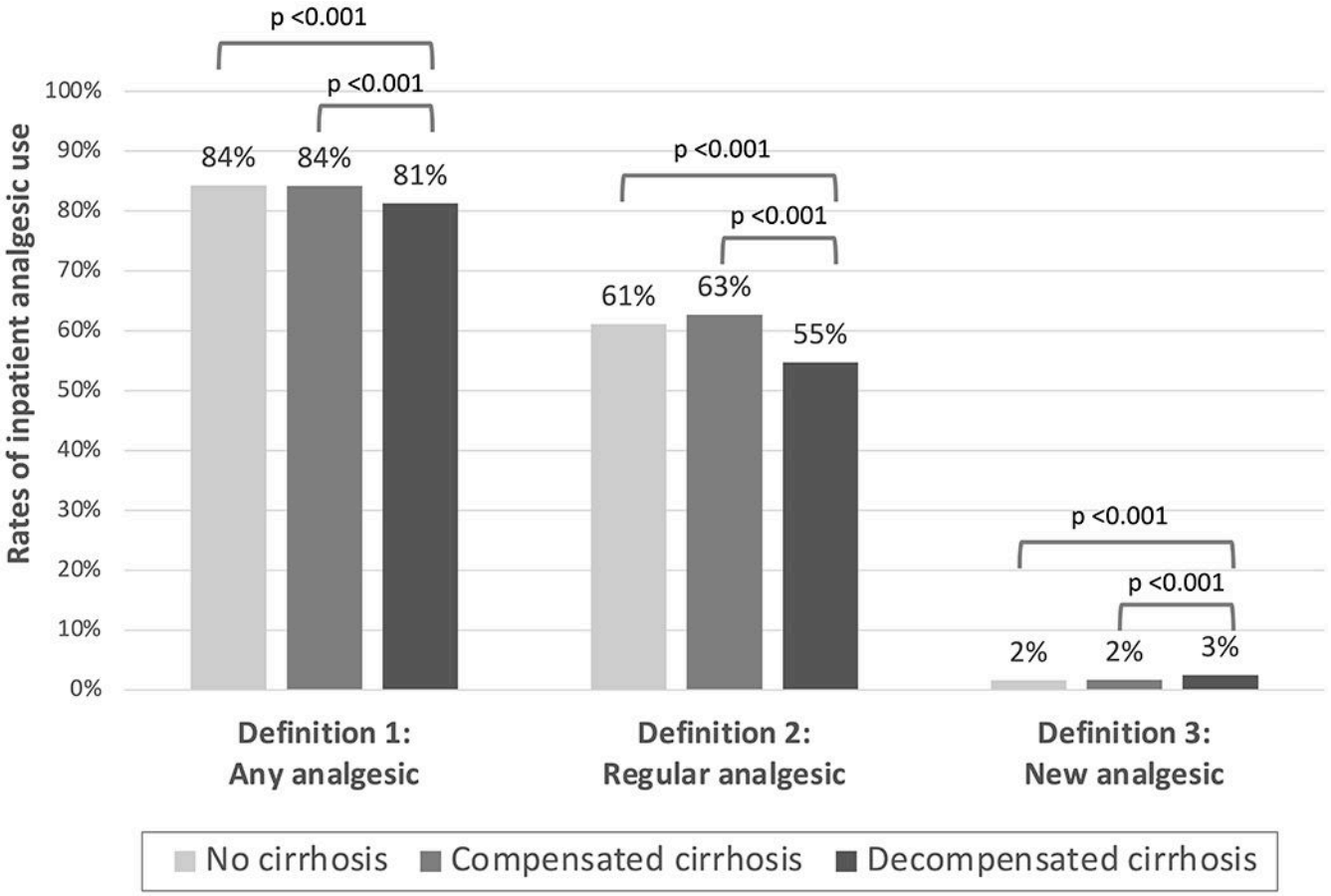
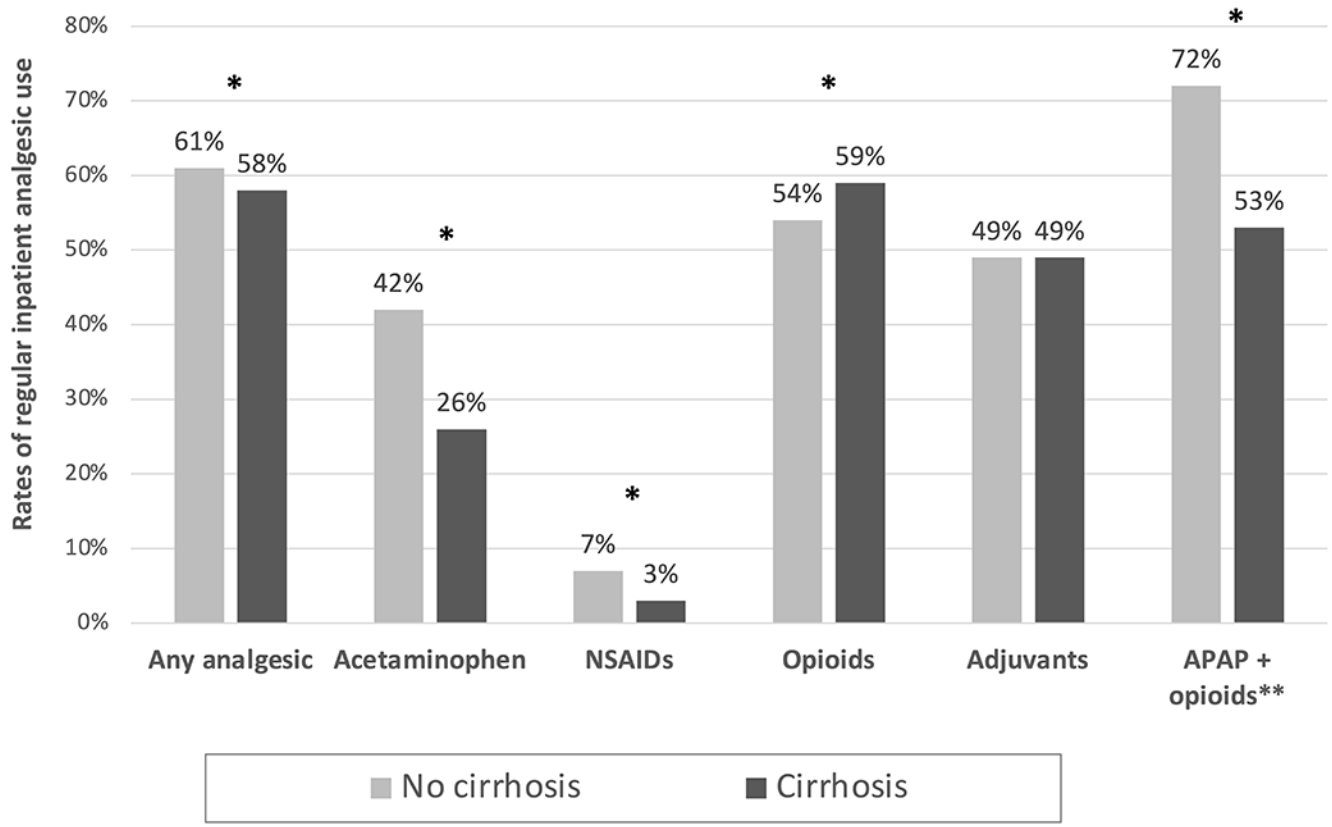


Figure 2.
Rates of inpatient analgesic use by cirrhosis and decompensation status



* p<0.001 on conditional logistic regression
** Any APAP use among patients with regular opioid use

Figure 3.
Rates of regular analgesic use by time in hospitalized patients with and without cirrhosis

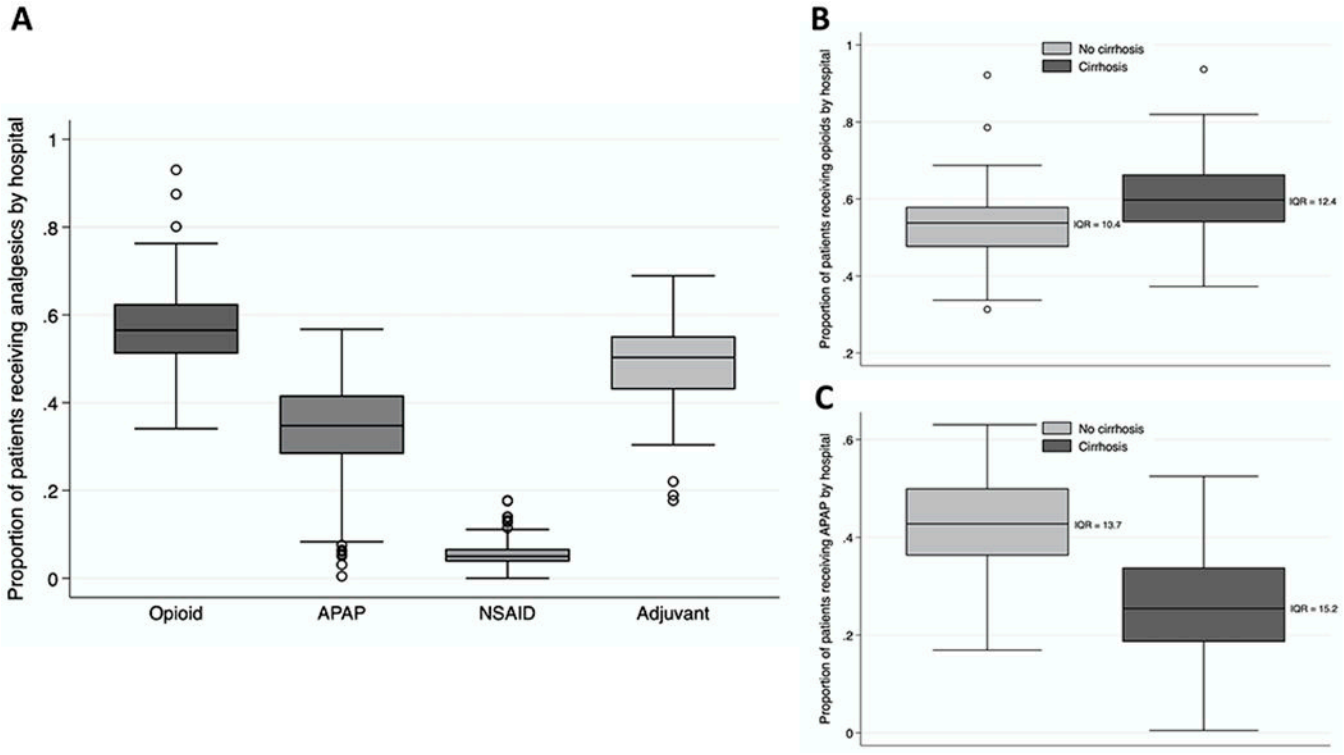


Figure 4.

Hospital-level variation in analgesic use by analgesic type (A) in patients with and without cirrhosis, and in patients receiving opioids (B) and APAP (C) by cirrhosis status.

Table 1.

Baseline characteristics of matched cohort

	Total N = 232,726	No cirrhosis n = 116,363 (*50%*)	Cirrhosis n = 116,363 (*50%*)	P-value
Matching covariates, *percent or median (IQR)*				
Female gender	40.2%	40.3%	40.2%	0.60
Age group				
18-30	2.3%	2.3%	2.3%	
31-50	21.2%	21.2%	21.1%	0.33
51-64	44.6%	44.5%	44.6%	
65+	32.0%	31.9%	32.0%	
Race				
White	70.7%	71.0%	70.5%	
Black	14.8%	14.8%	14.8%	<0.001
Hispanic	11.1%	10.9%	11.2%	
Other	3.4%	3.3%	3.6%	
Primary Payer				
Private/Commercial	19.4%	19.4%	19.3%	
Medicaid	26.8%	26.8%	26.8%	0.69
Medicare	45.4%	45.4%	45.4%	
Other	8.4%	8.4%	8.5%	
Charlson Comorbidity Index	2.0 (1.0-4.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	<0.001
Chronic pain ICD-10 code	10.5%	10.2%	10.7%	<0.001
Service				
Medical	89.90%	90.0%	89.8%	
Surgical	2.80%	2.8%	2.9%	0.08
Other	7.30%	7.2%	7.4%	
Region *				
Northeast	26.9%			
Midwest	32.1%			
West	14.6%			
South	26.4%			
Teaching Hospital *	80.9%			
Liver Transplant Center *	63.1%			
Other covariates, *percent*				
Admission Status				
Emergency	77.1%	76.8%	77.5%	
Urgent	17.4%	16.7%	18.2%	<0.001
Elective	4.3%	5.4%	3.2%	
Other	1.1%	1.2%	1.1%	
Transfer	17.4%	15.7%	19.1%	<0.001

	Total N = 232,726	No cirrhosis n = 116,363 (*50%*)	Cirrhosis n = 116,363 (*50%*)	P-value
Cirrhosis etiology				
Alcohol		-	39.1%	
Hepatitis C		-	12.9%	
NASH/other		-	48.0%	
Hepatocellular carcinoma		-	5.6%	
Cirrhosis complications				
Decompensated cirrhosis		-	54.6%	
Ascites		-	43.2%	
Hepatic encephalopathy		-	23.1%	
Varices		-	25.9%	
Variceal Bleed		-	5.4%	
Spontaneous bacterial peritonitis		-	3.9%	
Hepatorenal syndrome		-	3.7%	

* Propensity matching model stratified by hospital, so all hospital characteristics (including region) are identical between groups

IQR, interquartile range; ICD-10, International Classification of Diseases, 10th revision; NASH, nonalcoholic steatohepatitis

Table 2.

Risk factors for regular inpatient opioid use among cirrhosis inpatients with persistent pain (n = 67,898)*

	Unadjusted			Adjusted		
	OR	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**
DEMOGRAPHIC						
Female gender	0.91	0.88-0.94	<0.001	0.96	0.93-0.99	<0.001
Age group						
18-30	REF			REF		
31-50	0.86	0.74-0.99	0.04	0.83	0.71-0.96	0.01
51-64	0.70	0.61-0.82	<0.001	0.62	0.54-0.72	<0.001
65 and over	0.40	0.34-0.46	<0.001	0.34	0.29-0.39	<0.001
Race						
White	REF			REF		
Black	1.19	1.11-1.28	<0.001	1.17	1.09-1.26	<0.001
Hispanic	0.93	0.84-1.02	0.1	0.89	0.82-0.97	0.007
Other	0.75	0.65-0.85	<0.001	0.82	0.73-0.91	<0.001
Region						
Northeast	REF			REF		
Midwest	1.15	0.99-1.33	0.07	1.08	0.94-1.23	0.27
South	1.37	1.12-1.67	0.002	1.28	1.04-1.59	0.02
West	1.39	1.18-1.62	<0.001	1.31	1.12-1.54	0.001
Primary payer						
Private	REF			REF		
Medicaid	1.28	1.18-1.39	<0.001	1.13	1.04-1.23	0.003
Medicare	0.89	0.84-0.95	0.001	1.14	1.06-1.21	<0.001
Other	1.17	1.02-1.34	0.02	1.06	0.91-1.24	0.46
CLINICAL						
Charlson Comorbidity Index	0.99	0.98-0.99	0.001	1.02	1.02-1.03	<0.001
Chronic pain diagnosis	2.18	2.05-2.33	<0.001	2.20	2.06-2.35	<0.001
Cirrhosis etiology						
Alcohol	REF			REF		
Hepatitis C	1.60	1.50-1.71	<0.001	1.47	1.39-1.56	<0.001
NASH/other	0.97	0.93-1.02	0.25	1.14	1.08-1.20	<0.001
Decompensated cirrhosis	1.06	1.01-1.11	0.02			
Ascites	1.21	1.14-1.28	<0.001	1.31	1.23-1.38	<0.001
Hepatic encephalopathy	0.81	0.75-0.87	<0.001	0.76	0.70-0.81	<0.001

	Unadjusted			Adjusted		
	OR	**95% CI**	**p-value**	**AOR**	**95% CI**	**p-value**
HOSPITALIZATION						
Surgical service**	2.37	2.08-2.69	<0.001	2.85	2.47-3.28	<0.001
Outside hospital transfer	1.13	1.06-1.20	<0.001	1.14	1.06-1.22	<0.001
Transplant center	0.93	0.82-1.05	0.24			
Teaching hospital	0.87	0.76-0.98	0.02	0.73	0.65-0.82	<0.001

* All analyses clustered by hospital; persistent pain defined as use of any analgesic on >50% of hospital days

** Patients with operating room procedures performed during this hospitalization have been excluded

OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio; NASH, nonalcoholic steatohepatitis