



Opioid prescriptions are associated with hepatic encephalopathy in a national cohort of patients with compensated cirrhosis

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Summary

Background: Opioids are often prescribed for pain in cirrhosis and may increase the risk of hepatic encephalopathy (HE).

Aim: To assess the association between opioids and HE in patients with well-compensated cirrhosis.

Methods: We used the IQVIA PharMetrics (Durham, NC) database to identify patients aged 18-64 years with cirrhosis. We excluded patients with any decompensation event from 1 year before cirrhosis diagnosis to 6 months after cirrhosis diagnosis. Over the 6 months after cirrhosis diagnosis, we determined the duration of continuous opioid use and classified use into short term (1-89 days) and chronic (90-180 days). We assessed whether patients developed HE over the subsequent year (ie 6-18 months after cirrhosis diagnosis). We used a landmark analysis and performed multivariable Cox proportional hazards regression to assess associations between opioid use and HE, adjusting for relevant confounders.

Results: The cohort included 6451 patients with compensated cirrhosis, of whom 23.3% and 4.7% had short-term and chronic opioid prescriptions respectively. Over the subsequent year, HE occurred in 6.3% patients with chronic opioid prescriptions, 5.0% with short-term opioid prescriptions and 3.3% with no opioid prescriptions. In the multivariable model, an increased risk of HE was observed with short-term (adjusted hazard ratio, HR 1.44, 95% CI 1.07-1.94) and chronic opioid prescriptions (adjusted HR 1.83, 95% CI 1.07-3.12) compared to no opioid prescriptions.

Conclusion: In this national cohort of privately insured patients with cirrhosis, opioid prescriptions were associated with the risk of incident HE. Opioid use should be minimised in those with cirrhosis and, when required, limited to short duration.

1 | INTRODUCTION

Hepatic encephalopathy (HE) is a debilitating and common complication of cirrhosis.¹ HE is independently associated with decreased health-related quality of life and reduced survival.^{2,3} Sedating and psychoactive medications such as opioids may contribute to the risk of HE through multiple mechanisms. For example, opioids could lead to altered gut microbiota, upregulation in central mu-opioid receptors and slowed intestinal motility, which could increase intestinal absorption of ammonia and inflammatory mediators.⁴⁻⁷ Despite their potential harms, opioid use is frequent and increasing over time in patients with cirrhosis, possibly due to the avoidance of nonsteroidal anti-inflammatory drugs and acetaminophen in these patients.⁸⁻¹³ In an era of increasing opioid use, the relative risk of HE among patients taking opioids remains unclear.⁸

Studies examining the association between opioids and HE have been conflicting and there have been no studies demonstrating an association between opioids and HE in younger patients with well-compensated cirrhosis. A study within the United States Medicare population demonstrated that opioid prescriptions were associated with increased incidence of HE.¹⁴ However, given the data source, this population was older and may have been more susceptible to centrally acting medications due to decreased baseline cognitive reserve. It may be that younger patients with cirrhosis are able to safely tolerate opioids. In fact, one single-centre study reported that an opioid prescription at discharge increased overall readmissions, but not hepatic encephalopathy-related readmissions over 6 months.⁶ Furthermore, in a longitudinal cohort of United States veterans, baseline opioid use was not found to be an independent predictor of hepatic encephalopathy.¹⁵

Therefore, given the uncertain association between opioids and HE, we aimed to assess the association between opioid use and incident hepatic encephalopathy among a nationally representative cohort of younger, privately insured patients with no prior decompensation events. We also aimed to assess whether duration of opioid prescription influences the risk of HE. We hypothesised that opioid prescriptions and particularly chronic use would be associated with incident HE.

2 | MATERIALS AND METHODS

2.1 | Data source

Our data source was the IQVIA Pharmedics (Durham, NC) database from 1 January 2007 to 30 September 2015. This database includes claims data on pharmacy and medical coverage for more than 27 million Americans with private health insurance. This data source has been used by others and has been demonstrated to be demographically representative of commercially insured US patients.¹⁶

Given that data were obtained from a de-identified database, the University of North Carolina Institutional Review Board deemed this project to be exempt from full review.

2.2 | Patient population

We identified all patients aged 18-64 years with cirrhosis, defined as the presence of two or more International Classification of Diseases, Ninth Revision (ICD-9) codes for cirrhosis (571.5 or 571.2) on separate dates. Previous validation studies have demonstrated that the presence of two outpatient ICD-9 codes improves the positive predictive value of correctly identifying cirrhosis based on a gold standard of medical record review.^{17,18} The 'diagnosis date' of cirrhosis was defined as the first ICD-9 code present in the database.

We limited our analysis to patients without prior decompensation events, allowing us to capture truly incident HE events in a population with newly identified cirrhosis. In order to define this well-compensated population, we excluded patients with any ICD-9 codes, Current Procedural Terminology codes or pharmacy claims for HE, varices/variceal haemorrhage, spontaneous bacterial peritonitis, ascites, hepatorenal syndrome/end-stage renal disease, hepatocellular carcinoma, transjugular intrahepatic portosystemic shunt procedure or jaundice (Table S1). We also excluded patients who underwent prior liver transplantation.

We required at least 12 months of continuous health plan enrolment with pharmacy benefits before the diagnosis of cirrhosis. This run-in period was used to determine patient demographics, comorbidities, aetiology of cirrhosis (alcohol-related liver disease [ALD], viral hepatitis, other), complications of liver disease and other medications (Tables S1 and S2). Additionally, we required 18 months of continuous health plan enrolment with pharmacy benefits after the diagnosis of cirrhosis. We limited enrolment to those ≤ 64 years old to avoid patients with dual Medicare enrolment whose claims may not be captured accurately in this database.

2.3 | Exposure assessment

Our exposure was defined as a claim for a prescription opioid in the outpatient setting over the 6 months after cirrhosis diagnosis. The 6-month exposure period was chosen a priori to provide sufficient power to assess the association between opioid prescriptions and HE and to reduce the risk of confounding by indication and misclassification of opioid use. We performed sensitivity analyses using exposure periods of 3 and 9 months.

The primary analysis included all opioids listed in Table S2 and a sensitivity analysis excluded tramadol and propoxyphene. We categorised opioid prescriptions as short term (1-89 days) and chronic (≥ 90 days) based on the longest continuous opioid prescription recorded, allowing gaps of up to 7 days. Additional information on the assessment of exposures is shown in Figure 1.

2.4 | Outcome assessment

Our primary outcome was time to incident hepatic encephalopathy occurring from 6 to 18 months after cirrhosis diagnosis. We defined HE as the presence of at least one ICD-9 code (572.2) and/or prescription for lactulose or rifaximin. We used a combination of ICD codes and medications given the low negative predictive value of ICD codes alone for identifying HE episodes.^{19,20}

We performed a secondary analysis examining the association between opioid prescriptions and any episode of non-HE decompensation event (composite outcome): variceal haemorrhage, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome or placement of transjugular intrahepatic portosystemic shunt (presumably for variceal haemorrhage or ascites) (Table S1).

2.5 | Sensitivity analyses

We performed several sensitivity analyses to assess internal validity of the database. We first assessed the association between positive and negative control medications and HE. Positive controls (ie active comparators) are medications that may be used to treat pain and thus evaluate for unmeasured confounders common among those with pain.^{21,22} Our positive controls were tricyclic antidepressants and gabapentin. Negative controls are medications that are not prescribed for pain and unlikely to cause the outcome of interest. Our negative controls, which included statins and levothyroxine, can assess for healthy user bias or confounding by selective prescribing.

These biases result due to preferential prescribing of medications for patients who are healthier at baseline and avoidance of prescribing among those who are frail or particularly ill. Lastly, we assessed benzodiazepine use given that these medications are often used in combination with opioids and may confound the relationship between opioids and HE. In these analyses, we examined the adjusted hazard ratios (HRs) for models where an additional category of 'control drug only' (eg gabapentin, tricyclic antidepressants, levothyroxine, statins, benzodiazepines) was added to the exposure definition.

Additionally, we performed a sensitivity analysis employing a true new user design, in which we excluded patients with an opioid prescription within the 6 months prior to cirrhosis diagnosis.

2.6 | Statistical analysis

We assessed baseline characteristics among those with no opioid prescriptions, short-term prescriptions and chronic opioids prescriptions. For continuous variables, we reported medians with interquartile ranges and reported proportions for categorical variables. We performed bivariate comparisons by opioid exposure using Kruskal-Wallis for continuous variables and chi-squared for categorical variables. Statistical analyses were carried out using R version 3.4.2.

We used a landmark analysis that aims to estimate the time-to-event probabilities in each exposure category, conditional on the exposure status of patients at the landmark time (Figure 1).²³ In a landmark analysis, the point at which we evaluate the exposure status of patients is fixed and the analysis is limited to patients who have

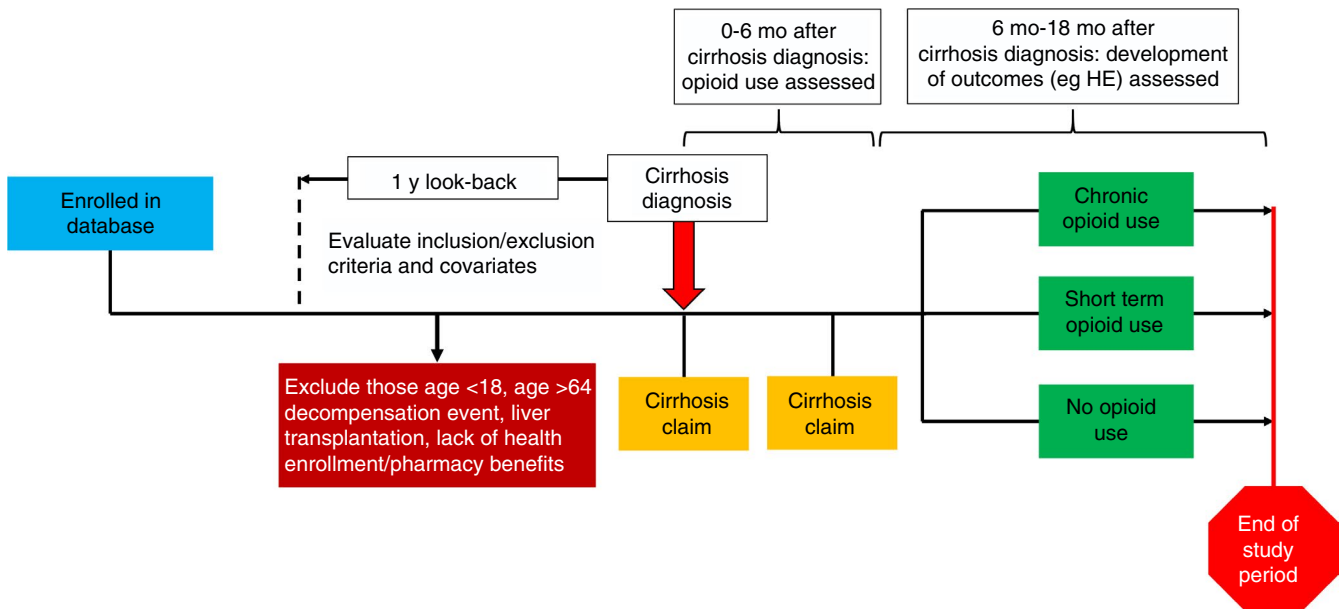


FIGURE 1 Overview of assessment of exposure to opioids and outcomes including HE and non-HE decompensation events. All patients enrolled in the IQVIA Pharmetrics database with at least two ICD-9 codes for cirrhosis were included in the cohort. There was a 1-y look-back period prior to cirrhosis diagnosis during which covariates and exclusion criteria were assessed. Patients aged 18-64 y with continuous health enrolment/pharmacy benefits and no decompensation events were included. Exposure to opioids was assessed in the 6 mo after cirrhosis diagnosis. In the year after the exposure assessment period (ie 6 mo-1 y after cirrhosis diagnosis), patients were assessed for the presence of HE or non-HE decompensation events

not yet experienced our outcome of interest (HE) by the landmark time, which was set at 6 months after cirrhosis diagnosis. We thus exclude all patients who experience HE before the landmark time and ignore all opioid claims after the landmark time. As a result, this analysis reduces the risk of bias resulting from a patient's opioid classification changing through the course of the follow-up time and ensures a uniform exposure assessment for patients who do and do not develop HE. In addition, this approach limits confounding by indication that may occur if patients receive opioids for an event that increases their likelihood of HE, such as a surgical procedure. Furthermore, this approach limits inclusion of patients prescribed lactulose for opioid-induced constipation or prescribed opioids and, as a result, given lactulose or rifaximin for primary prophylaxis against HE. Lastly, we chose to censor follow-up data at 1-year after the landmark time, since HE events that occur >1 year after an opioid prescription are unlikely to be related to this prescription.

We used multivariable Cox proportional hazards regression to assess associations between opioid use and development of HE, adjusting for age, sex, region, cirrhosis aetiology, depression, Charlson comorbidity index (CCI) and prior opioid use. We also performed multivariable Cox proportional hazards regression to assess the association between opioid use and non-HE decompensation events. These covariates were chosen a priori based on their potential association with both opioid use and development of HE.

3 | RESULTS

3.1 | Baseline characteristics and opioid use

The cohort included 6451 patients without any decompensation events within 1 year prior to cirrhosis diagnosis (Figure 2). The median age at cirrhosis diagnosis was 54 years (p_{25} - p_{75} 49-58) and 57.9% were male. Other baseline patient characteristics can be found in Table 1.

Overall, 1806 patients (28.0%) were prescribed opioids during the 6 months after cirrhosis diagnosis. Among this group, the median cumulative days of opioids prescribed was 8 days (p_{25} - p_{75} 2-40). Short-term opioids were used by 1505 patients (23.3%) and chronic opioids were used by 301 patients (4.7%). The median duration of use was 5 and 153 days among short-term and chronic opioid prescriptions respectively. The most common opioids used were oxycodone, tramadol and fentanyl. Those with short-term and chronic opioid prescriptions had a higher proportion of female patients, non-ALD aetiology, CCI >2, diabetes mellitus and depression (Table 1).

3.2 | Development of hepatic encephalopathy

Over a 1-year follow-up period, 250 (3.9%) of the cohort developed HE (Table 2). HE incidence was highest among those with chronic opioid prescriptions (6.3%) compared to short-term opioids (5.0%) and no opioids (3.3%) (Figure 3). In the multivariable Cox proportional hazards model, both short-term opioid prescriptions (adjusted

HR 1.44, 95% CI 1.07-1.94) and chronic opioid prescriptions (adjusted HR 1.83, 95% CI 1.07-3.12) were significantly associated with the risk of hepatic encephalopathy.

For our sensitivity analysis using a 3-month exposure period, the rates of HE between 3 and 18 months after index remained higher among opioid users (5.3%) compared to non-opioid users (4.9%) but this difference was not statistically significant in the multivariable model (adjusted HR 1.17, 95% CI 0.96-1.44). When using a 9-month exposure period, HE rates from 9 to 21 months after index were lowest among those without opioid prescriptions ($n = 120$, 3.0%) compared to those with short-term ($n = 66$, 5.2%) and chronic prescriptions ($n = 16$, 5.1%). In the multivariable Cox proportional hazards models, opioid use was significantly associated with HE among short-term users (AHR 1.73, 95% CI 1.26-2.33) but not significantly associated among chronic users (AHR 1.54, 95% CI 0.91-2.62), although the direction of the association remained. Lastly, in the sensitivity analysis excluding tramadol and propoxyphene from the exposure definition there remained a statistically significant association between opioid use and HE among patients with both short-term opioids (adjusted HR 1.88, 95% CI 1.43-2.46) and chronic opioids (adjusted HR 2.34, 95% CI 1.59-3.44).

In all sensitivity analyses of positive and negative controls, both levels of opioid use remained significantly associated with HE, while prescriptions for gabapentin only (adjusted HR 1.68, 95% CI 0.62-4.59), tricyclic antidepressants only (adjusted HR 0.90, 95% CI 0.44-1.86), levothyroxine only (adjusted HR 1.34, 95% CI 0.49-3.64) and statins only (adjusted HR 0.74, 95% CI 0.39-1.41) were not significantly associated with the development of HE. Benzodiazepines only were associated with a significantly increased risk of HE in the unadjusted analysis (HR 1.77, 95% CI 1.17-2.68) but the association was not statistically significant in the multivariable model (adjusted HR 1.51, 95% CI 0.98-2.31).

When excluding all patients with an opioid prescription within 6 months prior to cirrhosis diagnosis, the associations remained directionally similar and significant for short-term opioid use (adjusted HR 1.47, 95% CI 1.03-2.09) but was no longer statistically significant for chronic opioid use (adjusted HR 1.55, 95% CI 0.38-6.30).

There were no missing data for the unadjusted models examining the association between opioid prescriptions and HE. For adjusted models, there were 306 missing observations (4.7%) for our primary analysis and all subgroup analyses. Individuals with missing data were excluded from these models.

3.3 | Other decompensation events

Overall, 771 patients (12.0%) also developed non-HE decompensation events over 1 year, with similar rates among those with no opioid prescriptions (12.0%), short-term opioids (12.0%) and chronic opioids (11.6%) (Figure 4). These non-HE decompensation events included 718 with ascites, 385 with variceal haemorrhage, 13 with spontaneous bacterial peritonitis and eight with hepatorenal syndrome. In the multivariable Cox proportional hazards models, neither

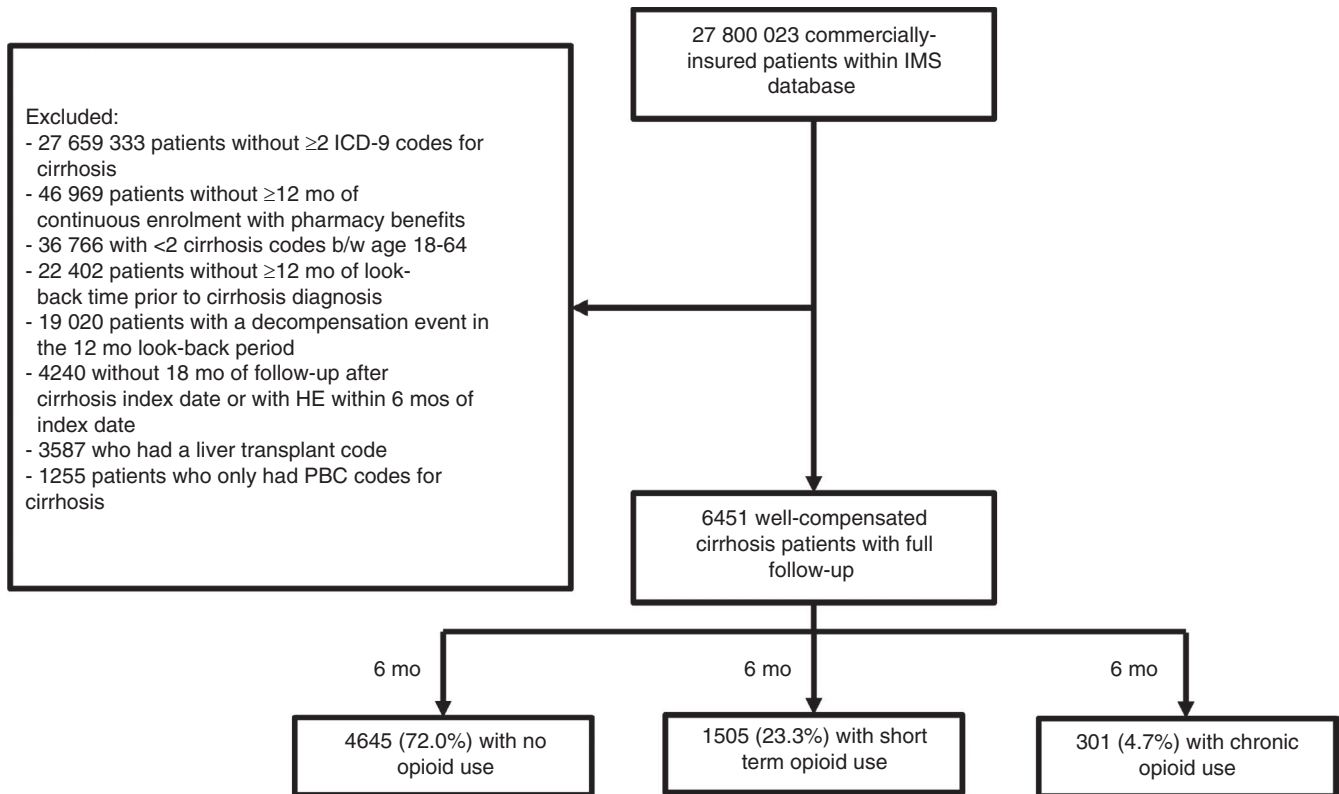


FIGURE 2 Flow diagram of cirrhosis patients including in our analysis cohort. The cohort included patients with at least two ICD-9 codes for cirrhosis with sufficient insurance/pharmacy coverage, a 12-mo look-back, no decompensation events during the look-back and no episodes of HE during the 6 mo after cirrhosis index date. Our final cohort included 6451 well-compensated cirrhosis patients who were followed for 6 mo to assess their exposure to opioids and then for a further 1 yr to assess for the development of incident HE

short-term opioids (adjusted HR 0.96, 95% CI 0.80-1.16) nor chronic opioids (adjusted HR 0.93, 95% CI 0.64-1.35) were associated with a statistically significantly increased risk of non-HE decompensation events.

4 | DISCUSSION

In this nationwide cohort of privately insured patients with cirrhosis, both short-term and chronic opioid prescriptions were independently associated with an increased risk of HE. Our study provides several novel findings. First, 28% of cirrhosis patients received opioids and that the annual incidence of HE development was 1.9-fold higher among patients with chronic opioid prescriptions compared to those with no opioid prescriptions. Second, the liver-specific morbidity of opioids was limited to HE, and not other decompensation events. These findings suggest that opioids, particularly when used chronically, may not be safe even in younger patients with well-compensated cirrhosis.

4.1 | Opioids are uniquely unsafe in cirrhosis

These data expand the literature on the risks of opioids in cirrhosis in multiple ways. First, using positive and negative controls, we showed that the risk of HE was specific to opioid exposure, decreasing

concern for confounding by indication. Second, there was no association between opioid prescriptions and other decompensation events, suggesting that our results were not confounded by the severity of liver disease. In other words, if opioid use was more frequent in patients with more advanced cirrhosis, we would expect all decompensation events to be associated with opioid prescriptions. Third, we found that these associations are present even among younger patients with well-compensated cirrhosis.

Our findings add to the data from Medicare demonstrating that opioids are associated with an increased risk of HE.¹⁴ This Medicare study included a much older population than our current study and did not limit their population to those with well-compensated cirrhosis. Our findings demonstrate that this potential harm of opioids extends to younger patients with well-compensated cirrhosis.

4.2 | Implications of these findings

In light of the association between opioids and HE, providers should explore nonpharmacologic and non-opioid options for pain control. Exercise, including resistance training, might be a particularly attractive nonpharmacologic strategy for pain control given that it improves muscle mass and combats sarcopenia, which is associated with the development of HE and poor outcomes in those with cirrhosis.^{4,24-28} Topical therapies like capsaicin and low-dose acetaminophen (≤ 2 g/

TABLE 1 Baseline patient characteristics by opioid use status

	No opioids (n = 4645)	Short-term opioids (n = 1505)	Chronic opioids (n = 301)	P-value ^a
Age, y (median, P ₂₅ -P ₇₅)	54 (49-58)	53 (48-58)	53 (50-58)	0.092
Male Sex	2786 (60.0)	774 (51.4)	175 (58.1)	<0.001
Region				
East	912 (19.6)	244 (16.2)	49 (16.3)	0.024
Midwest	1388 (29.9)	455 (30.2)	68 (22.6)	
South	1372 (29.5)	377 (25.0)	60 (19.9)	
West	973 (20.9)	429 (28.5)	124 (41.2)	
CCI (%)				
1	2244 (48.3)	540 (35.9)	95 (31.6)	<0.001
2	1303 (28.1)	465 (30.9)	87 (28.9)	
>2	1098 (23.6)	500 (33.2)	119 (39.5)	
Depression	508 (10.9)	254 (16.9)	74 (24.6)	<0.001
Diabetes mellitus	1154 (24.8)	462 (30.7)	94 (31.2)	<0.001
Cirrhosis aetiology				
ALD	747 (16.1)	222 (14.8)	27 (9.0)	<0.001
Viral hepatitis	1660 (35.7)	509 (33.8)	139 (46.2)	
Other	2238 (48.2)	774 (51.4)	135 (44.9)	
TCA use	224 (4.8)	158 (10.5)	47 (15.6)	<0.001
Statin use	392 (8.4)	194 (12.9)	32 (10.6)	<0.001
Levothyroxine use	92 (2.0)	40 (2.7)	9 (3.0)	0.183
Gabapentinoid use	59 (1.3)	50 (3.3)	37 (12.3)	<0.001
Benzodiazepine use	498 (10.7)	283 (18.8)	111 (36.9)	<0.001
Prior opioids ^b	701 (15.1)	607 (40.3)	261 (86.7)	<0.001

Note: Values within parenthesis are expressed in % and/or p25-p75.

Abbreviations: ALD, alcohol-related liver disease; CCI, Charlson Comorbidity Index; TCA, tricyclic antidepressant.

^aBivariate comparison via Kruskal-Wallis test for continuous variables and chi-squared for categorical variables.

^bOpioid prescription in the year prior to cirrhosis diagnosis.

day) should be considered the first-line analgesic options for patients with cirrhosis given their low risk of harms. Additional studies are needed of other analgesics, including gabapentin, which has uncertain efficacy and potential harms, especially in patients with cirrhosis.¹³

The high incidence of HE among chronic opioid users in our cohort reinforces the importance of minimising the duration of opioid use when they are needed. This is particularly important given the uncertain effectiveness of chronic opioids for treating pain.²⁹ When opioids are required in patients with cirrhosis, providers should maintain a high vigilance for identifying HE. Despite recommendations to screen patients with cirrhosis for covert HE (a precursor to overt HE that can be treated with lactulose or rifaximin) most patients do not receive this screening.^{30,31} Given our findings, providers could consider screening well-compensated cirrhosis patients on opioids for overt hepatic encephalopathy with point of care applications like the EncephalApp Stroop smartphone App or the four validated questions of the Sickness Index Profile followed by formal psychometric testing.³²⁻³⁴

4.3 | Study strengths and limitations

This study has many strengths including its large, nationwide cohort of privately insured individuals. Moreover, we provided a novel examination of the potential risks of opioids among younger patients with no recent decompensation events. However, our findings must be interpreted in the context of this study's potential limitations.

First, given the lack of laboratory values in our data set, we were unable to compute model for end-stage liver disease or Child-Pugh Turcotte scores in order to account for the severity of liver disease. To mitigate this limitation, we restricted the cohort to those with well-compensated cirrhosis. Relatedly, there is the potential for confounding introduced as a result of increased opioid use among patients with more severe liver disease or other unmeasured confounders common to patients with pain. However, the use of landmark analysis, the lack of association between positive/negative exposure controls on HE events and the similar rates of non-HE

TABLE 2 Association between opioids and positive/negative controls on hepatic encephalopathy

	Number of patients (%)	Number who developed HE/1 y (%)	Crude HR (95% CI)	Adjusted HR ^a (95% CI)
Opioids				
No opioids	4645 (72.0)	155 (3.3)	Ref.	Ref.
Short-term opioids	1505 (23.3)	76 (5.0)	1.53 (1.16-2.01)	1.44 (1.07-1.94)
Chronic opioids	301 (4.7)	19 (6.3)	1.94 (1.20-3.12)	1.83 (1.07-3.12)
Gabapentin				
No opioids or gabapentin	4586 (71.1)	151(3.3)	Ref.	Ref.
Short-term opioids	1505 (23.3)	76 (5.0)	1.55 (1.17-2.04)	1.46 (1.08-1.97)
Chronic opioids	301 (4.7)	19 (6.3)	1.96 (1.22-3.16)	1.86 (1.09-3.19)
Gabapentin only	59 (0.9)	4 (6.8)	2.10 (0.78-5.68)	1.68 (0.62-4.59)
Tricyclic antidepressants				
No opioids or tricyclic antidepressants	4421 (68.5)	147 (3.3)	Ref.	Ref.
Short-term opioids	1505 (23.3)	76 (5.0)	1.53 (1.16-2.02)	1.43 (1.06-1.94)
Chronic opioids	301 (4.7)	19 (6.3)	1.94 (1.21-3.13)	1.81 (1.06-3.11)
Tricyclic antidepressants only	224 (3.5)	8 (3.6)	1.08 (0.53-2.20)	0.90 (0.44-1.86)
Levothyroxine				
No opioids or levothyroxine	4553 (70.6)	151 (3.3)	Ref.	Ref.
Short-term opioids	1505 (23.3)	76 (5.0)	1.53 (1.17-2.03)	1.45 (1.08-1.96)
Chronic opioids	301 (4.7)	19 (6.3)	1.95 (1.21-3.14)	1.84 (1.08-3.14)
Levothyroxine only	92 (1.4)	4 (4.3)	1.34 (0.50-3.62)	1.34 (0.49-3.64)
Statins				
No opioids or statins	4253 (65.9)	145 (3.4)	Ref.	Ref.
Short-term opioids	1505 (23.3)	76 (5.0)	1.49 (1.13-1.97)	1.40 (1.04-1.90)
Chronic opioids	301 (4.7)	19 (6.3)	1.89 (1.17-3.06)	1.78 (1.04-3.05)
Statins only	392 (6.1)	10 (2.6)	0.75 (0.39-1.41)	0.74 (0.39-1.41)
Benzodiazepines				
No opioids or benzodiazepines	4147 (64.3)	128 (3.1)	Ref.	Ref.
Short-term opioids	1505 (23.3)	76 (5.0)	1.65 (1.24-2.19)	1.54 (1.13-2.09)
Chronic opioids	301 (4.7)	19 (6.3)	2.09 (1.29-3.39)	1.95 (1.14-3.35)
Benzodiazepines only	498 (7.7)	27 (5.4)	1.77 (1.17-2.68)	1.51 (0.98-2.31)

^aAdjusted for age, sex, region, cirrhosis aetiology, depression, Charlson comorbidity index (CCI) and prior opioid use.

decompensation events within opioid groups all provide reassurance against confounding.

Given that our outcome definitions relied on ICD codes and medication prescription data, there is a possibility of misclassification of HE cases and other decompensation events. For instance, it may be that opioid-induced altered mental status is being misdiagnosed as HE. However, the annual incidence of HE and other decompensation events are comparable to what has been published in the literature, providing external validity to our results.^{15,35-38} In addition, any event prompting a billing code for HE or the initiation of lactulose/rifaximin is likely to be clinically important. Furthermore, the separation of exposure and outcome assessment through the landmark analysis limits the inclusion of episodes of altered mental status occurring immediately after opioid initiation, patients who were treated with lactulose for

opioid-induced constipation or put on lactulose or rifaximin as HE prophylaxis after being started on opioids. Lastly, a 6-month exposure period was chosen a priori to reduce the risk of a type II error, confounding by indication and misclassification of opioid use. While the sensitivity analyses using exposure periods of 3 and 9 months had some nonsignificant results, the direction of these associations remained and we suspect these were due to misclassification of opioid use and type II error respectively.

5 | CONCLUSION

In this national study of younger, privately insured patients with cirrhosis and no recent decompensation events, prescriptions for opioids were associated with HE. In light of this potential harm of opioid

Cumulative Incidence of Hepatic Encephalopathy by Opioid Status

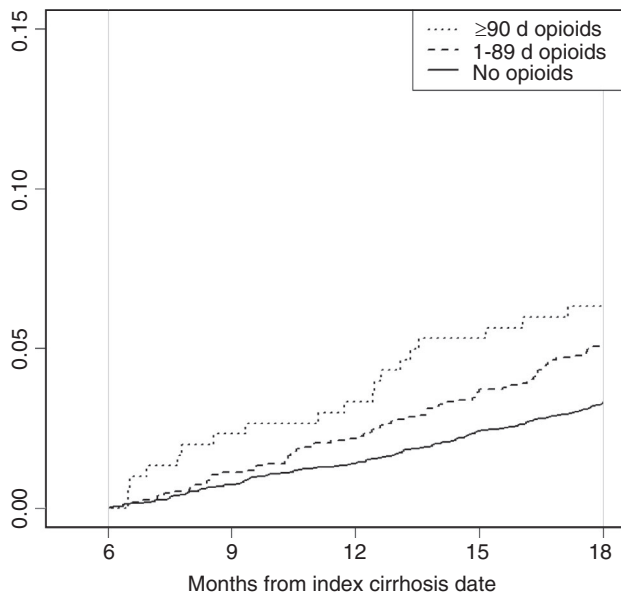


FIGURE 3 Cumulative incidence of hepatic encephalopathy among patients with previously compensated cirrhosis by opioid use. The cumulative incidence of hepatic encephalopathy over a year among patients with no opioid prescriptions, short-term opioids and chronic opioid prescriptions during our exposure assessment period (0-6 mo after cirrhosis diagnosis)

prescriptions, these medications should be avoided when possible

Cumulative Incidence of Other Events by Opioid Status

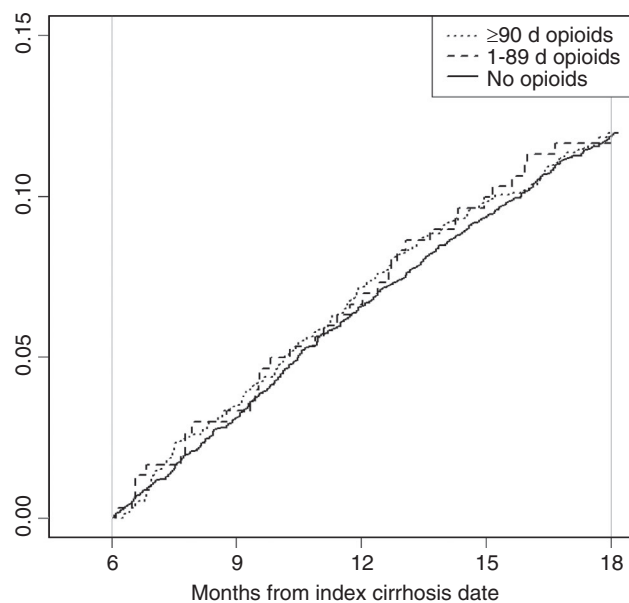


FIGURE 4 Cumulative incidence of non-HE decompensation events among patients with previously compensated cirrhosis by opioid use. The cumulative incidence of nonhepatic encephalopathy decompensation events over a year among patients with no opioids, short-term opioid prescriptions and chronic opioid prescriptions during our exposure assessment period (0-6 months after cirrhosis diagnosis)

even in patients with well-compensated cirrhosis. When opioid use is required, it should be short duration and clinicians should maintain a high vigilance for detecting HE. These associations could also be further explored with prospective studies of the safety of opioids in patients with cirrhosis and additional study investigating the mechanisms linking opioids and HE.

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AUTHORSHIP

Guarantor of the article: Andrew M. Moon.

Author contributions: Andrew M. Moon: Study concept and design, interpretation of data, drafting and critical revision of manuscript. Yue Jiang: Study concept and design, data extraction, statistical analysis, critical revision of manuscript. Shari S. Rogal, Elliot B. Tapper, Sarah R. Lieber and A. Sidney Barritt: Study concept and design, interpretation of data and critical revision of manuscript. All authors approved the final version of this manuscript.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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