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Original Paper

Medication adherence is protective of decompensation and mortality in HBV-related cirrhosis patients

Running title: Drug adherence in hepatitis B related cirrhosis

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Abstract

Objectives

To evaluate the medication adherence among CHB-related cirrhosis patients with decompensation and mortality, and to analyze the effect of medication adherence on the patients' prognosis.

Participants

Two prognosis end points (decompensation and mortality) were used respectively to classify study subjects into two different case-control sets in this retrospective case-control study.

Outcome measures

Decompensation and mortality were defined from 2007 to 2016 using a population-based medical claims database. Medication possession ratio (MPR) was used as a measure of treatment adherence.

Results and conclusion

Between decompensated and compensated patients, longer term treatment adherence is seen higher in the compensated group versus the decompensated group: 1-year MPR (0.65±0.43 vs. 0.57±0.53), and 6-month MPR (0.79±0.52 vs. 0.76±0.79). On the contrary, 3-month adherence is higher in the decompensated group (1.00±1.15 vs. 0.96±0.79). For patients with and without mortality, drug adherence is ubiquitously higher in the alive group regardless of follow-up length: 1-year MPR (0.62±0.44 vs. 0.50±0.51), 6-month MPR (0.78±0.62 vs. 0.69±0.72) and 3-month MPR (0.97±0.91 vs. 0.96±1.12). After accounting for confounding variables, we find that the likelihood of complicated cirrhosis is significantly lower in more adherent patient and the benefit increases with more persistent adherence (log 1-year MPR OR: 0.75, 95% CI: 0.73-0.77. Similar results are observed for the adjusted likelihood of mortality. Adherence to antiviral therapy lowers risk for decompensation compared with those

with nonadherence, and also reduces overall risk for death in cirrhotic patients.

Keywords: cirrhosis; hepatitis B; medication adherence; prognosis

Strengths and Limitations of this study:

- No study has yet provided empirical evidence on the adherence rate of cirrhosis patients on antiviral therapy and quantified the level of adherence required to avert adverse outcomes.
- Medication possession ratio (MPR) can be a robust estimate of treatment adherence over time as it takes into account the period when patient stops and resumes medication.
- This is a population-based case-control study using nationwide claims data, and the distribution of general characteristics of our study subjects appears to be similar to the general demographics of HBV-related cirrhosis patients.
- We had no imaging data or laboratory test results to confirm the severity or the diagnosis of cirrhosis in each of our subjects.
- Adherent level estimated using MPR may not represent the actual medication adherence exhibited by the study subjects as it was calculated based on prescription history and not the actual uptake of medication by the patients.

Introduction

With the growing prevalence of chronic diseases globally, medication adherence to therapy has become one of the highly concerned issues in recent years. Patient adherence refers to the extent to which a patient complies with the doctor's orders or recommendations given by a healthcare provider. Unfortunately, patient adherence is generally not high. Statistics indicate that only about 50% of chronic disease patients worldwide taking medications in accordance with doctors' orders. This result not only leads to poor clinical treatment results, but also increases mortality and generates substantial economic burden (Celio et al, 2018).

Cirrhosis is an irreversible liver disease characterized by poor liver function due to long-term damage like alcohol use or viral infections such as chronic hepatitis B (CHB) and chronic hepatitis C (CHC). In southeast Asian nations, CHB- and CHC-related cirrhosis is particularly prevalent (GBD 2017 Cirrhosis Collaborators, 2020). According to its natural clinical course and symptoms, cirrhosis can be divided into two stages of compensated (CC) and decompensated cirrhosis (DC). The former stage is characterized by an absence of complications, whereas the latter is an advanced condition with life-threatening conditions develop from elevated portal hypertension. DC is associated with complications such as varicose bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy (EASL, 2018). Previous findings suggest that the median survival time for patients with CC is 12 years and the treatment rate is about 70-80%, while the median survival time for patients with DC is less than two years and the treatment rate is about 50-60% (D'Amico et al, 2006; Shah and Amarapurkar, 2018). Other related literature also showed that the death rate of patients with DC is 4 times that of healthy individuals, 30% of patients die within one month, and 63% of patients die within one year (Arvaniti et al., 2010).

For the treatment of cirrhosis, antiviral therapy has shown positive effect on the improvement of cirrhosis and its complications (Peng et al, 2012; Piotrowski and Boron-Kaczmarska, 2017). However, treatment adherence in chronic patients is usually not high, as they may have low perception of the effectiveness or necessity of prescribed medications (Horne et al, 2013; Hayward et al, 2017). There is a scarcity of studies illustrating the benefits of maintaining adherence with viral hepatitis-related cirrhosis patients. Moreover, as many studies have discussed the advantages of good treatment adherence, no study has yet provided empirical evidence on the pragmatic adherence rate of cirrhosis patients on antiviral therapy and quantified the level of adherence required to avert adverse outcomes, e.g., how adherent are cirrhotic patients to their treatment regimens and how adherent is sufficient to prevent disease progression reduce complication risks among these patients.

The objective of present study was to first compare the medication adherence between CHB-related cirrhosis patients with and without decompensation, and to subsequently analyze the effect of medication adherence on the patients' prognosis (decompensation and mortality). To ensure that both short- and long-term adherence is considered, medication possession ratio was calculated for three-month, six-month and one-year periods.

Materials and Methods

Study design and subject selection

This is a retrospective case-control study using secondary data from administrative claims-based database released by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW), Taiwan. Patients who were aged over 20 years old and diagnosed with chronic hepatitis B (ICD-9-CM:

070.32, 070.33, V02.61) and cirrhosis (571.4, 571.5, 571.8) were first identified from the database. To ensure that the cirrhosis of our study sample is derived from hepatitis B, patients diagnosed with the following conditions were excluded: alcoholic fatty liver cirrhosis (571.0), alcoholic cirrhosis (57.11, 571.2, 571.3), biliary cirrhosis (571.6), congenital cirrhosis (777.8), hemochromatosis (275.0), or the syphilitic cirrhosis (095.3). Observation period starts from 2007 and ends in 2016 for a total of 10 years.

Two prognosis end points were used respectively to classify study subjects into two different case-control sets: 1) presence of complications (case: decompensated cirrhosis, control: compensated cirrhosis), 2) mortality (case: dead, control: alive). Decompensation was defined when the subject had been diagnosed with at least one of the following conditions: esophageal variceal bleeding (456.0), ascites (789.5), spontaneous bacterial peritonitis (567.23), hepatorenal syndrome (572.4), and hepatic encephalopathy (572.2), while compensation was considered in the absence of any of the above complications. Mortality was ascertained if death was recorded after the date of diagnosis for cirrhosis. Each case-control set was matched 1:1 using propensity score matching according to gender, age, and post-onset medication interval. Post-onset medication interval was to ensure that the case and control patients were not too far apart in terms of their medical history (i.e., how long since they have been diagnosed with hepatitis B).

Medication and adherence measurements

Five antiviral drugs have been approved for the treatment of HBV infection in patients with relevant indications. In this study, HBV patients treated with nucleos(t)ide analogues (NUCs) were identified: lamivudine (LAM), adefovir dipivoxil (ADV), telbivudine (LdT), entecavir (ETV) and tenofovir disoproxil

fumarate (TDF). Medication possession ratio (MPR) was calculated for 3, 6, and 12 months prior to the date of prognosis in patients that were being prescribed with the antiviral medication(s). For controls, MPR was estimated for 3, 6, and 12 months prior to the end of the observation period. MPR is a commonly-used indirect measure of drug adherence and refers to the proportion of days a patient has a supply of drugs during the observation period. When there are multiple medications, the amount of prescription drugs is taken into account in the denominator. Good adherence is when the MPR is greater than 0.75 or 0.80. However, if the MPR is higher than 1, there is the possibility of overdose and overlap-use of the patient. Most studies use 0.80 as a cut-off point for determining good or poor adherence.

Statistical analyses

SAS version 9.4 statistical software package was used to perform statistical analyses in this study. Patient characteristics and treatment methods were descriptively analyzed, and the results were presented in the form of means, standard deviations, frequencies, percentage, etc. For the distribution statistics and continuous data comparison between the groups, Wilcoxon's rank-sum test was used. For categorical variables such as patient traits and treatment modalities, Chi-square test or Fisher's exact test was used to test the differences between study groups. Collinearity test was conducted to exclude any variables with collinearity problems. Natural logarithm (log) of MPR was also taken to standardize its distribution. Finally, for inferential statistics, conditional logistic regression models were used to estimate the odds of prognosis (decompensation or mortality) after accounting for MPR and other covariates. Odds ratio (OR) and 95% confidence interval for poor prognosis are presented as results in the included tables.

Ethics approval

This study was approved by China Medical University and Hospital ethics committee (CMUH107-REC2-105) and was supported by the following grants: MOST 107-2314-B-039 -065 -MY3 and CMU107-Z-04.

Results

From the population-based database, a total of 10,180 decompensated cirrhosis and 10,180 compensated cirrhosis patients are matched. Similarly, 9,724 patients who died from cirrhosis and 9,724 cirrhosis patients who are alive during the study period are identified and matched. In general, regardless of the prognosis (decompensation or death), medication adherence increases as time approaches closer to the time of adverse outcome (Table 1). For example, 1-year, 6-month, and 3-month MPRs in decompensated and compensated cirrhotic subjects are 0.61±0.48, 0.77±0.67, and 0.98±0.99, respectively. A slightly lower MPR but similar pattern is found when we examined MPR in cirrhosis patients with and without mortality: 1-year, 6-month, and 3-month MPRs are 0.56±0.48, 0.74±0.67, and 0.97±1.02. It is worthy to note that long term (>3-month) MPRs are all shown to be under 0.80.

Table 2 shows the post-matching characteristics of study subject groups divided by prognosis. In decompensated group, 34.8% (n=3,542) of patients experienced 2 or more complications, 33.6% (n=3,424) had ascites, while the compensated control group had no complications as expected. The pattern of NUC uptake differs significantly between the two groups: the top three most commonly used NUCs in decompensated patients are ETV (61.1%), LAM (14.2%), and TDF (10.4%), and ETV (59.6%), TDF (19.8%), LAM (9.58%) in compensated patients. The proportion of patients undergoing more than two NUC treatments is relatively higher in

complicated cirrhosis patients (7.11% vs. 4.93%; p<0.001). Longer term treatment adherence seems higher on average in the compensated group versus decompensated group: 1-year MPR (0.65±0.43 vs. 0.57±0.53), and 6-month MPR (0.79±0.52 vs. 0.76±0.79). On the contrary, 3-month adherence is higher in the decompensated group (1.00±1.15 vs. 0.96±0.79).

In the set of analysis examining mortality as outcome, the occurrence of every complication is significantly higher in cirrhosis patients who died (cases) than in those who are still alive (controls) (Table 2). Most pronounced difference is seen in two or more concurrent complications (23.5% vs. 2.93%) and ascites (15.4% vs. 4.65%). Most of the control patients do not experience any complication (88.6%) unlike the case patients with just 45.5%. Drug adherence is ubiquitously higher in the alive group regardless of length of follow-up (p<0.001): 1-year MPR (0.62±0.44 vs. 0.50±0.51), 6-month MPR (0.78±0.62 vs. 0.69±0.72) and 3-month MPR (0.97±0.91 vs. 0.96±1.12).

After accounting for confounding variables, we find that the likelihood of complicated cirrhosis is significantly lower in more adherent patients. In the results from multivariate analysis presented in Table 3, longer persistent adherence (log 1-year MPR) is associated with most apparent decreased odds of decompensation (OR: 0.75, 95% CI: 0.73-0.77, p<0.001). Likelihood for the poor prognosis slightly elevates when adherence continues for shorter span: log 6-month MPR (OR: 0.79, 95% CI: 0.76-0.81, p<0.001), and log 3-month MPR (OR: 0.85, 95% CI: 0.83-0.88, p<0.001). Older age is also found to be related to slightly increased odds of decompensation (p<0.001).

Similar results are observed for the adjusted likelihood of mortality: better adherence is also associated with lower chance of mortality particularly with longer adherence: log 1-year MPR (OR: 0.70, 95% CI: 0.68-0.72, p<0.001), log 6-month

MPR (OR: 0.72, 95% CI: 0.69-0.75, p<0.001), and log 3-month MPR (OR: 0.78, 95% CI: 0.75-0.81, p<0.001) (Table 4). In addition, having two or more complications considerably increases the odds of mortality by 16-fold which is much higher than the other complication categories. Contrary to the increased risk of mortality imposed by older age, the use of NUCs generally averts patients from the adverse event.

Discussion

The present study provides information from a nationwide retrospective study of cirrhosis patients 20 years and older induced by viral hepatitis B. Unfortunately, despite Taiwan's readily accessible universal coverage health care system, patient adherence to therapy of cirrhosis remains inadequate, particularly in the long run (i.e., 1-year MPR: 0.56-0.61). This finding is consistent with previous studies examining adherent behavior in CHB patients from other countries (Allard et al, 2017; Xu et al, 2018). More importantly, we demonstrated that adherent behavior generally reduces the likelihood of poor prognosis, and the benefits of long-term adherence is evidently more pronounced than that of the short-term. The fact that patient adherence greatly escalates during the short time leading up to adverse outcomes indicates that patients' healthcare seeking behaviors are still very reactive rather than proactive (i.e., proactive behavior should indicate a consistent pattern of medication use since the point of diagnosis, and not particularly prior to the occurrence of complications). Furthermore, the occurrence of complications, such as HRS and HE, exacerbates the likelihood of mortality, especially if two or more are collectively observed.

Treatment adherence has been widely proven to be associated with better virology response and patient-reported outcomes in patients with CHB infection prior to the development of cirrhosis (Allard et al, 2020; Grossi et al, 2017; Lieveld et al,

2013; Younossi et al, 2019). Results of this study, however, showed that adherence to antiviral therapy effectively prevents the development of subsequent complications and death among HBV-related cirrhosis patients. After accounting for other confounding characteristics such as gender, age, type of complications, and treatment methods, this association still remained statistically significant. Therefore, we confirm that the better the patient's medication adherence, the lower their risk of subsequent poor prognosis. This is similar to a Taiwanese cohort study of 1315 treatment-naïve CHB-related cirrhosis patients; it is found that 4-year ETV therapy significantly decreases patients' risk of cirrhotic complications and all-cause mortality (Su et al, 2016). Another study conducted in Korean CHB patients revealed that poor adherence to ETV therapy was associated with increased risk of cirrhotic complications and all-cause mortality (Shin et al, 2018). As Taiwan offers universal coverage to healthcare and financial support to low-income households, affordability of medication should not be a chief barrier to nonadherence as past studies have suggested (Hayward et al, 2017; Xu et al, 2018). It is possible that, under our context of study, poor adherence may be due to patients' low perception of treatment benefit or their reluctance to comply without experiencing obvious symptoms (Hayward et al, 2017). Nevertheless, there have also been studies that reported very good medication adherence to NUCs among patients with CHB. A US study using self-reported survey found an adherence rate of 100% in 74.1% of its subjects (Chotiyaputta et al, 2012). Another study from the Netherlands reported 70% of CHB patients presented an adherence rate of over 80% towards entecavir (van Vlerken et al, 2015). It is possible that the factors and the barriers associated with adherence to antiviral treatment among CHB patients are context- and/or culture-specific (Kidd and Altman, 2000).

The distribution of general characteristics of our study subjects appears to be similar to the general demographics of HBV-related cirrhosis patients; here we find

that these patients are mostly male with a mean age of approximately 60 years, which is similar to the demographics found in past studies (Hung et al., 2019; Rubin et al., 2020). Among the used NUCs, patients have been predominantly prescribed entecavir as it is still considered a first-line treatment for patients with CHB (Chien et al., 2019). The use of MPR as a measure of drug adherence has also been adopted in many previous studies (Friedman et al, 2007; Allard et al, 2020; Zhang et al, 2014). It is believed that MPR can be a robust estimate of treatment adherence over time as it takes into account the period when patient stops and resumes medication (Friedman et al, 2007).

Nevertheless, our study is not without limitations. First, the primary source of data for this study was a medical claims-based database, hence, MPR was calculated based on prescription history and not the actual uptake of medication by the patients. Hence, the adherent level estimated using MPR may not represent the actual medication adherence exhibited by the study subjects. Second, although population-based claims database provided us with an opportunity to study patient adherence in a large scale, we had no imaging data or laboratory test results to confirm the severity or the diagnosis of cirrhosis in each of our subjects. Therefore, the variability in patients' conditions and their consequent probability of disease progression could not be considered. Other important factors leading up to adverse prognosis may not be explored, including time since diagnosis and lifestyle factors. Nonetheless, with the high prevalence of HBV in the context under study, we had obtained a sufficient sample size for analyses and estimates for robust results.

In conclusion, findings of this study demonstrate that prompt follow-up and strict adherence to prescribed antiviral therapy should be highly endorsed in patients with HBV-related cirrhosis particularly by doctors, while a lack of adherence or non-adherence would lead to pervasive threat to patients' health, including transition to

decompensation state and possible death. We hope that findings of this study would shed some light for future studies which may aim to investigate the rolling out of policies targeting the context-specific factors associated with poor adherence in cirrhosis patients, possibly including enhanced adherence counselling in clinical setting.

Summary of Study

The objective of present study was to first compare the medication adherence between CHB-related cirrhosis patients with and without decompensation, and subsequently to analyze the effect of medication adherence on the patients' prognosis (decompensation and mortality). Using medication-possession ratio as a measure for adherence, we find that patient adherence to therapy of cirrhosis remains inadequate compared with other countries. The lack of adherent behavior, particularly in the long run, may significantly diminish the potential benefits of treatment intervention.

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Conflicts of interests

The authors disclose no potential financial or nonfinancial conflict of interests.

Author Statement

VCR Hsieh is guarantor of the article.

KY Fu, JA Chen, and VCR Hsieh were involved in design, data collection, interpretation and preparation of the initial manuscript.

ML Hsieh and VCR Hsieh were involved in critically appraising and revising the manuscript prior to approving the final version.

All authors approved the final version of the manuscript and the authorship list.

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Table 1. Descriptive statistics of medication adherence and prognosis among chronic hepatitis B virus-related cirrhosis patients.

Dependent variable	Medication Adherence (MPR)	Mean	Standard deviation	Median
Decompensation	3-month	**0.98**	0.99	0.93
	6-month	**0.77**	0.67	0.74
	1-year	**0.61**	0.48	0.54
Death	3-month	**0.97**	1.02	0.92
	6-month	**0.74**	0.67	0.67
	1-year	**0.56**	0.48	0.46

Table 2. Post-matching characteristic profile of cirrhosis subjects by prognosis (decompensation/compensation; and death/alive).

Variable	Decompensated		Compensated		P-value	Death		Alive		P-value
	n	%	n	%		n	%	n	%	
Total	10,180	50.0	10,180	50.0		9,724	50.0	9,724	50.0	
Sex					1.00					1.00
Male	7,453	73.2	7,453	73.2		7,780	80.0	7,780	80.0	
Female	2,727	26.8	2,727	26.8		1,944	20.0	1,944	20.0	
Age (mean, SD)	60.1	12.0	59.7	12.0	0.06	60.4	12.0	60.0	12.0	0.06
Complications					<0.001					<0.001
Varicose vein bleeding	526	5.2	0	0		156	1.60	46	0.47	
Ascites	3,424	33.6	0	0		1,498	15.4	452	4.65	
SBP	414	4.07	0	0		187	1.92	57	0.59	
HRS	153	1.50	0	0		101	1.04	18	0.19	
HE	2,121	20.8	0	0		1,078	11.1	247	2.54	
Two or more	3,542	34.8	0	0		2,281	23.5	285	2.93	
None	0	0	10,180	100.0		4,423	45.5	8,619	88.6	
NUCs					<0.001					<0.001
LAM	1,448	14.2	975	9.58		1,352	13.9	1,117	11.5	
ADV	74	0.73	85	0.83		77	0.79	83	0.85	
LdT	656	6.44	533	5.24		759	7.81	533	5.48	
ETV	6,216	61.1	6,065	59.6		5,912	60.8	5,693	58.6	
TDF	1,062	10.4	2,020	19.8		917	9.43	1,881	19.3	
Two or more combined treatments	724	7.11	502	4.93		707	7.27	417	4.29	
MPR (mean, SD)										
3-month	1.00	1.15	0.96	0.79	<0.001	0.96	1.12	0.97	0.91	<0.001
6-month	0.76	0.79	0.79	0.52	<0.001	0.69	0.72	0.78	0.62	<0.001
1-year	0.57	0.53	0.65	0.43	<0.001	0.50	0.51	0.62	0.44	<0.001

Abbreviations: SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome; HE, hepatic encephalopathy. NUCs, nucleos(t)ide analogues; LAM, lamivudine only; ADV, adefovir dipivoxil only; LdT, telbivudine only; ETV, entecavir only; TDF, tenofovir disoproxil fumarate only; MPR, medication possession ratio.

Table 3. Conditional logistic regression analysis of decompensation in cirrhosis patients.

Variable	Crude			After adjusting -log Three-months MPR			After adjusting -log Six-months MPR			After adjusting -log One-year MPR		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Medication adherence												
log 3-month MPR	**0.85**	0.82 0.88	<0.001	**0.85**	0.83 0.88	<0.001						
log 6-month MPR	**0.78**	0.76 0.81	<0.001				**0.79**	0.76 0.81	<0.001			
log 1-yr MPR	**0.75**	0.73 0.77	<0.001							**0.75**	0.73 0.77	<0.001
Age	**1.04**	1.03 1.04	<0.001	**1.04**	1.03 1.04	<0.001	**1.03**	1.03 1.04	<0.001	**1.03**	1.03 1.04	<0.001
NUCs												
LAM	**1.08**	0.94 1.25	0.27	**1.09**	0.95 1.27	0.22	**1.12**	0.97 1.29	0.14	**1.16**	1.00 1.35	0.04
ADV	**0.63**	0.45 0.88	0.007	**0.63**	0.45 0.88	0.007	**0.64**	0.45 0.90	0.01	**0.68**	0.48 0.96	0.03
LdT	**0.88**	0.75 1.04	0.14	**0.89**	0.76 1.05	0.18	**0.92**	0.78 1.08	0.30	**0.95**	0.81 1.13	0.58
ETV	**0.73**	0.65 0.83	<0.001	**0.73**	0.65 0.83	<0.001	**0.75**	0.67 0.85	<0.001	**0.79**	0.70 0.89	<0.001
TDF	**0.38**	0.33 0.43	<0.001	**0.38**	0.33 0.44	<0.001	**0.39**	0.34 0.45	<0.001	**0.41**	0.36 0.48	<0.001
Two or more combined treatments	**1**			**1**			**1**			**1**		

NUCs, nucleos(t)ide analogues; LAM, lamivudine only; ADV, adefovir dipivoxil only; LdT, telbivudine only; ETV, entecavir only; TDF, tenofovir disoproxil fumarate only; MPR, medication possession ratio.

Table 4. Conditional Logistic regression analysis of mortality in cirrhosis patients.

Variable	Crude			After adjusting -log Three-months MPR			After adjusting -log Six-months MPR			After adjusting -log One-year MPR		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Medication adherence												
log 3-month MPR	**0.80**	0.78 0.83	<0.001	**0.78**	0.75 0.81	<0.001						
log 6-month MPR	**0.72**	0.70 0.74	<0.001				**0.72**	0.69 0.75	<0.001			
log 1-yr MPR	**0.69**	0.67 0.71	<0.001							**0.70**	0.68 0.72	<0.001
Age	**1.04**	1.03 1.05	<0.001	**1.03**	1.02 1.04	<0.001	**1.03**	1.02 1.04	<0.001	**1.03**	1.02 1.04	<0.001
Complications												
Varicose vein bleeding	**6.0**	4.20 8.83	<0.001	**6.57**	4.53 9.52	<0.001	**6.71**	4.62 9.76	<0.001	**6.65**	4.57 9.68	<0.001
Ascites	**6.73**	5.90 7.67	<0.001	**6.58**	5.76 7.50	<0.001	**6.55**	5.74 7.48	<0.001	**6.47**	5.66 7.40	<0.001
SBP	**7.41**	5.28 10.4	<0.001	**7.22**	5.12 10.2	<0.001	**6.93**	4.89 9.81	<0.001	**6.71**	4.73 9.54	<0.001
HRS	**12.5**	7.17 21.9	<0.001	**12.7**	7.18 22.5	<0.001	**12.0**	6.71 21.4	<0.001	**11.3**	6.30 20.4	<0.001
HE	**9.18**	7.76 10.9	<0.001	**8.98**	7.58 10.6	<0.001	**8.71**	7.34 10.3	<0.001	**8.45**	7.11 10.0	<0.001
Two or more	**15.7**	13.5 18.2	<0.001	**16.1**	13.8 18.7	<0.001	**16.2**	13.9 18.8	<0.001	**16.0**	13.7 18.6	<0.001
None	**1**			**1**			**1**			**1**		
NUCs												
LAM	**0.71**	0.61 0.82	<0.001	**0.71**	0.59 0.85	<0.001	**0.71**	0.59 0.86	<0.001	**0.74**	0.61 0.89	<0.001
ADV	**0.55**	0.39 0.77	<0.001	**0.65**	0.43 0.97	0.04	**0.68**	0.45 1.03	0.07	**0.75**	0.49 1.15	0.18
LdT	**0.84**	0.71 1.00	0.04	**1.00**	0.82 1.23	0.99	**1.03**	0.84 1.27	0.75	**1.08**	0.88 1.33	0.46
ETV	**0.62**	0.54 0.70	<0.001	**0.72**	0.62 0.84	<0.001	**0.74**	0.63 0.86	<0.001	**0.77**	0.66 0.91	<0.001
TDF	**0.29**	0.25 0.34	<0.001	**0.41**	0.34 0.49	<0.001	**0.43**	0.36 0.51	<0.001	**0.45**	0.37 0.54	<0.001
Two or more combined treatments	**1**			**1**			**1**			**1**		

SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome; HE, hepatic encephalopathy. NUCs, nucleos(t)ide analogues; LAM, lamivudine only; ADV, adefovir dipivoxil only; LdT, telbivudine only; ETV, entecavir only; TDF, tenofovir disoproxil fumarate only; MPR, medication possession ratio.

Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	p.1
Abstract	#1b	Provide in the abstract an informative and balanced summary	p.2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	p.4
Objectives	#3	State specific objectives, including any prespecified hypotheses	p.5
Methods			
Study design	#4	Present key elements of study design early in the paper	p.5-6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p.5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	p.5-6
Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	p.6
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p.6-7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	p.5-6

		group. Give information separately for cases and controls.	
Bias	#9	Describe any efforts to address potential sources of bias	NA
Study size	#10	Explain how the study size was arrived at	p.5-6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	p.12
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	p.7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	NA
Statistical methods	#12c	Explain how missing data were addressed	NA
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	p.6
Statistical methods	#12e	Describe any sensitivity analyses	NA
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	p.8
Participants	#13b	Give reasons for non-participation at each stage	NA

Participants	#13c	Consider use of a flow diagram	NA
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	p.8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	NA
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	p.8
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p.8-9
Main results	#16b	Report category boundaries when continuous variables were categorized	p.8-9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	#18	Summarise key results with reference to study objectives	p.10-11

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	p.12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	p.12-13
Generalisability	#21	Discuss the generalisability (external validity) of the study results	p.12-13
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p.14

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Association between medication adherence and disease outcomes in hepatitis B-related cirrhosis patients: a population-based case-control study

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Original Paper

Association between medication adherence and disease outcomes in hepatitis B-related cirrhosis patients: a population-based case-control study

Running title: Drug adherence in hepatitis B related cirrhosis

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Figures: 0

Abstract

Objective

To evaluate medication adherence among hepatitis B-related cirrhosis patients who developed decompensation and mortality and to examine the association between medication adherence and patients' disease outcomes.

Design

In this retrospective case-control study, patients aged over 20 years old and diagnosed with both chronic hepatitis B and cirrhosis from 2007 to 2016 are identified using a population-based medical claims database. Two prognosis end points (decompensation and mortality) are used respectively to classify subjects into two different case-control sets. Study groups are propensity-score matched. Medication possession ratio (MPR) is used as a measure of treatment adherence for oral antiviral drugs, and conditional logistic regression models are used to estimate the odds of decompensation and mortality after accounting for MPR and other covariates.

Results

Between decompensated and compensated patients, longer term treatment adherence is seen higher in the compensated group versus the decompensated group: 1-year MPR (0.65±0.43 vs. 0.57±0.53), and 6-month MPR (0.79±0.52 vs. 0.76±0.79). On the contrary, 3-month adherence is higher in the decompensated group (1.00±1.15 vs. 0.96±0.79). For patients with and without mortality, drug adherence is ubiquitously higher in the alive group regardless of follow-up length: 1-year MPR (0.62±0.44 vs. 0.50±0.51), 6-month MPR (0.78±0.62 vs. 0.69±0.72) and 3-month MPR (0.97±0.91 vs. 0.96±1.12). After accounting for confounding variables, we find that the likelihood of complicated cirrhosis is significantly lower in more adherent patients and the benefit increases with more persistent adherence (log 1-year MPR OR: 0.75, 95% CI: 0.73-0.77). Similar results are observed for the adjusted likelihood of

mortality (log 1-year MPR OR: 0.70, 95% CI: 0.68-0.72).

Conclusions

Long term patient adherence to antiviral therapy remains inadequate in HBV-related cirrhosis patients. Their adherence to oral antiviral therapy appears to be inversely associated with decompensation and mortality.

Keywords: cirrhosis; hepatitis B; medication adherence; prognosis; decompensation; mortality

Strengths and Limitations of this study:

- No study has yet provided empirical evidence on the adherence rate of HBV-related cirrhosis patients on oral antiviral therapy and quantified the level of adherence required to avert adverse outcomes.
- Medication possession ratio (MPR) can be a robust estimate of treatment adherence over time as it takes into account the period when patient stops and resumes medication.
- This is a population-based case-control study using nationwide medical claims data, and the distribution of general characteristics of our study subjects appears to be similar to the general demographics of HBV-related cirrhosis patients.
- We have no imaging data or laboratory test results to confirm the severity or the diagnosis of cirrhosis in each of our subjects.
- Adherent level estimated using MPR may not represent the actual medication adherence exhibited by the study subjects as it is calculated based on prescription history and not the actual uptake of medication by the patients.

Introduction

With the growing prevalence of chronic diseases globally, medication adherence to therapy has become one of the highly concerned issues in recent years. Patient adherence refers to the extent to which a patient complies with the doctor's orders or recommendations given by a healthcare provider. Unfortunately, patient adherence is generally not high. Statistics indicate that only about 50% of chronic disease patients worldwide taking medications in accordance with doctors' orders. This result not only leads to poor clinical treatment results, but also increases mortality and generates substantial economic burden.[1]

Cirrhosis is an irreversible liver disease characterised by poor liver function due to long-term damage like alcohol use or viral infections such as chronic hepatitis B (CHB) and chronic hepatitis C (CHC). In southeast Asian nations, CHB- and CHC-related cirrhosis is particularly prevalent.[2] According to its natural clinical course and symptoms, cirrhosis can be divided into two stages of compensated (CC) and decompensated cirrhosis (DC). The former stage is characterised by an absence of complications, whereas the latter is an advanced condition with life-threatening conditions developed from elevated portal hypertension. DC is associated with complications such as varicose bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy.[3] Previous findings suggest that the median survival time for patients with CC is 12 years and the treatment rate is about 70-80%, while the median survival time for patients with DC is less than two years and the treatment rate is about 50-60%.[4 5] Other related literature also showed that the death rate of patients with DC is 4 times that of healthy individuals, 30% of patients die within one month, and 63% of patients die within one year.[6]

For the treatment of cirrhosis, antiviral therapy has shown positive effect on the

improvement of cirrhosis and its complications.[7 8] However, treatment adherence in chronic patients is usually not high, as they may have low perception of the effectiveness or necessity of prescribed medications.[9 10] Under Taiwan's single payer system, the National Health Insurance (NHI), hepatitis B virus (HBV) treatment is placed under a pay-for-performance scheme. Oral antiviral drugs that have been approved for the treatment of HBV infection are entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide, lamivudine, telbivudine, and adefovir dipivoxil. Tenofovir alafenamide, however, was not reimbursed until 2017. These antiviral drugs can be prescribed primarily based on clinician's evaluation of patient's HBsAg, HBeAg, alanine aminotransferase (ALT), and HBV DNA status under the NHI Drug Dispensing Items and Fee Schedule guidelines. There is a scarcity of studies illustrating the benefits of maintaining adherence with viral hepatitis-related cirrhosis patients. Moreover, as many studies have discussed the advantages of good treatment adherence, no study has yet provided empirical evidence on the pragmatic adherence rate of cirrhosis patients on antiviral therapy and quantified the level of adherence required to avert adverse outcomes, e.g., how adherent are cirrhotic patients to their treatment regimens and how adherent is sufficient to prevent disease progression reduce complication risks among these patients.

The objective of the present study is to first compare the medication adherence between HBV-related cirrhosis patients with and without decompensation, and to subsequently analyse the association between medication adherence and the patients' prognosis (decompensation and mortality). To ensure that both short- and long-term adherence is considered, medication possession ratio was calculated for three-month, six-month and one-year periods.

Materials and Methods

Study design and subject selection

This is a retrospective case-control study using secondary data from an administrative claims-based database released by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW), Taiwan. Patients who were aged over 20 years old and diagnosed with chronic hepatitis B (ICD-9-CM: 070.32, 070.33, V02.61) and cirrhosis (571.4, 571.5, 571.8) between 2007 and 2016 were first identified from the database. To ensure that the cirrhosis of our study subjects is derived from hepatitis B, patients diagnosed with the following conditions were excluded: alcoholic fatty liver cirrhosis (571.0), alcoholic cirrhosis (571.1, 571.2, 571.3), biliary cirrhosis (571.6), congenital cirrhosis (777.8), hemochromatosis (275.0), or the syphilitic cirrhosis (095.3).

Two prognosis endpoints were used respectively to classify study subjects into two different case-control sets: 1) presence of complications (case: decompensated cirrhosis, control: compensated cirrhosis), 2) mortality (case: dead, control: alive). These endpoints must occur following the diagnoses of chronic hepatitis B and cirrhosis. Decompensation was defined when the subject had been diagnosed with at least one of the following conditions: esophageal variceal bleeding (456.0), ascites (789.5), spontaneous bacterial peritonitis (567.23), hepatorenal syndrome (572.4), and hepatic encephalopathy (572.2), while compensation was considered in the absence of any of the above complications. Mortality was ascertained if death was recorded after the date of diagnosis for cirrhosis. Each case-control set was matched 1:1 using propensity score matching according to gender, age, and post-onset medication interval. Post-onset medication interval was to ensure that the case and control patients were not too far apart in terms of their medical history (i.e., how long since they have been diagnosed with hepatitis B).

Medication and adherence measurements

Five oral antiviral drugs have been approved for the treatment of HBV infection in patients with relevant indications. In this study, HBV patients treated with nucleos(t)ide analogues (NUCs) were identified: lamivudine (LAM), adefovir dipivoxil (ADV), telbivudine (LdT), entecavir (ETV) and tenofovir disoproxil fumarate (TDF). Medication possession ratio (MPR) was calculated for 3, 6, and 12 months prior to the date of decompensation and mortality in subjects that were being prescribed with the antiviral medication(s). Thus, there should be no concern that MPR for cirrhotic patients included in this study would be lower due to complications. For controls, MPR was estimated for 3, 6, and 12 months prior to the end of the observation period. MPR is a commonly-used indirect measure of drug adherence and refers to the proportion of days a patient has a supply of drugs during the observation period. For the objective of this study, we solely consider medications associated with HBV-related cirrhosis, and not others. Under Taiwan's national health insurance pay-for-performance payment scheme for chronic HBV therapy, antiviral medications should not overlap, as no multiple antiviral drugs should be prescribed concomitantly. Under this circumstance, patients would not be given more drugs prior to the date of next prescription. For this reason, we used MPR to estimate patient adherence, believing that the chance for multiple and overlapping drugs is unlikely (proportion-of-days-covered would be a better adherence measure if the chance of overlapping medication is high). Good adherence is when the MPR is greater than 0.75 or 0.80. Most studies use 0.80 as a cut-off point for determining good or poor adherence.

Statistical analyses

SAS version 9.4 statistical software package was used to perform statistical analyses in this study. Patient characteristics and treatment methods were descriptively analysed, and the results were presented in the form of means, standard deviations, frequencies, percentage, etc. For the distribution statistics and continuous data comparison between the groups, Wilcoxon's rank-sum test was used. For categorical variables such as patient traits and treatment modalities, Chi-square test or Fisher's exact test was used to test the differences between study groups. Collinearity test was conducted to exclude any variables with collinearity problems. Natural logarithm (log) of MPR was also taken to standardise its distribution. Finally, for inferential statistics, conditional logistic regression models were used to estimate the odds of prognosis (decompensation or mortality) after accounting for MPR and other covariates. Odds ratio (OR) and 95% confidence interval for poor prognosis are presented as results in the included tables.

Ethics approval

This study was approved by China Medical University and Hospital ethics committee (CMUH107-REC2-105) and was supported by the following grants: MOST 107-2314-B-039-065-MY3 and CMU107-Z-04.

Results

From the population-based database, a total of 10,180 decompensated cirrhosis and 10,180 compensated cirrhosis patients are matched. Similarly, 9,724 patients who died from cirrhosis and 9,724 cirrhosis patients who were alive during the study period are identified and matched. In general, regardless of the prognosis (decompensation or death), medication adherence increases as time approaches closer

to the time of adverse outcome (Table 1). For example, 1-year, 6-month, and 3-month MPRs in decompensated and compensated cirrhotic subjects are 0.61±0.48, 0.77±0.67, and 0.98±0.99, respectively. A slightly lower MPR but similar pattern is found when we examine MPR in cirrhosis patients with and without mortality: 1-year, 6-month, and 3-month MPRs are 0.56±0.48, 0.74±0.67, and 0.97±1.02. It is worthy to note that long term (>3-month) MPRs are all shown to be under 0.80.

Table 2 shows the post-matching characteristics of study subject groups divided by prognosis. In the decompensated group, 34.8% (n=3,542) of patients experienced 2 or more complications, 33.6% (n=3,424) had ascites, while the compensated control group had no complications as expected. The pattern of NUC uptake differs significantly between the two groups: the top three most commonly used NUCs in decompensated patients are ETV (61.1%), LAM (14.2%), and TDF (10.4%), and ETV (59.6%), TDF (19.8%), LAM (9.58%) in compensated patients. The proportion of patients undergoing more than two NUC treatments is relatively higher in complicated cirrhosis patients (7.11% vs. 4.93%; $p<0.001$). Longer term treatment adherence seems higher on average in the compensated group versus decompensated group: 1-year MPR (0.65±0.43 vs. 0.57±0.53), and 6-month MPR (0.79±0.52 vs. 0.76±0.79). On the contrary, 3-month adherence is higher in the decompensated group (1.00±1.15 vs. 0.96±0.79).

In the set of analysis examining mortality as outcome, the occurrence of every complication is significantly higher in cirrhosis patients who died (cases) than in those who are still alive (controls) (Table 2). Most pronounced difference is seen in two or more concurrent complications (23.5% vs. 2.93%) and ascites (15.4% vs. 4.65%). Most of the control patients do not experience any complication (88.6%) unlike the case patients with just 45.5%. Drug adherence is ubiquitously higher in the alive group regardless of length of follow-up ($p<0.001$): 1-year MPR (0.62±0.44 vs.

0.50±0.51), 6-month MPR (0.78±0.62 vs. 0.69±0.72) and 3-month MPR (0.97±0.91 vs. 0.96±1.12).

After accounting for confounding variables, we find that the likelihood of complicated cirrhosis is significantly lower in more adherent patients. In the results from multivariate analysis presented in Table 3, longer persistent adherence (log 1-year MPR) is associated with most apparent decreased odds of decompensation (OR: 0.75, 95% CI: 0.73-0.77, p<0.001). Likelihood for the poor prognosis is slightly elevated when adherence continues for shorter span: log 6-month MPR (OR: 0.79, 95% CI: 0.76-0.81, p<0.001), and log 3-month MPR (OR: 0.85, 95% CI: 0.83-0.88, p<0.001). Older age is also found to be related to slightly increased odds of decompensation (p<0.001).

Similar results are observed for the adjusted likelihood of mortality: better adherence is also associated with lower chance of mortality particularly with longer adherence: log 1-year MPR (OR: 0.70, 95% CI: 0.68-0.72, p<0.001), log 6-month MPR (OR: 0.72, 95% CI: 0.69-0.75, p<0.001), and log 3-month MPR (OR: 0.78, 95% CI: 0.75-0.81, p<0.001) (Table 4). In addition, having two or more complications considerably increases the odds of mortality by 16-fold which is much higher than the other complication categories. Contrary to the increased risk of mortality imposed by older age, the use of NUCs generally averts patients from the adverse event.

Discussion

The present study provides useful information from a nationwide retrospective study of cirrhosis patients induced by viral hepatitis B. As we have observed, despite Taiwan's readily accessible universal coverage health care system, patient adherence to antiviral therapy remains inadequate, particularly in the long run (i.e., 1-year MPR:

0.56-0.61). This finding is consistent with previous studies from other countries examining adherent behaviour in CHB patients.[11 12] More importantly, we demonstrate that the likelihood of poor prognosis is negatively associated with adherent behaviour, and the benefits of long-term adherence are evidently more pronounced than that of the short-term. The fact that patient adherence greatly escalates during the short time leading up to adverse outcomes indicates that patients' healthcare seeking behaviours are still very reactive rather than proactive (i.e., proactive behaviour should indicate a consistent pattern of medication use since the point of diagnosis, and not particularly prior to the occurrence of complications). Furthermore, the occurrence of complications, such as HRS and HE, exacerbates the likelihood of mortality, especially if two or more are collectively observed.

Treatment adherence has been widely proven to be associated with better virology response and patient-reported outcomes in patients with CHB infection before progression to cirrhosis.[13-16] Results of this study, however, show that adherence to antiviral therapy is inversely associated with the development of subsequent complications and death among HBV-related cirrhosis patients. After accounting for other confounding characteristics such as gender, age, type of complications, and treatment methods, this association still remains statistically significant. Therefore, we confirm that odds of subsequent poor prognosis are inversely linked to patients' medication adherence. This is similar to a Taiwanese cohort study of 1315 treatment-naïve CHB-related cirrhosis patients; it is found that 4-year ETV therapy significantly decreases patients' risk of cirrhotic complications and all-cause mortality.[17] Another study conducted in Korean CHB patients reveal that poor adherence to ETV therapy is associated with increased risk of cirrhotic complications and all-cause mortality.[18] As Taiwan offers universal coverage to healthcare and financial support to low-income households, affordability of

medication should not be a chief barrier to nonadherence, just as past studies have suggested.[10 12] It is possible that, under our context of study, poor adherence may be due to patients' low perception of treatment benefit or their reluctance to comply without experiencing obvious symptoms.[10] Nevertheless, there also have been studies that report very good medication adherence to NUCs among patients with CHB. A US study using self-reported survey found an adherence rate of 100% in 74.1% of its subjects.[19] Another study from the Netherlands reported 70% of CHB patients presented an adherence rate of over 80% towards entecavir.[20] It is possible that the factors and the barriers associated with adherence to antiviral treatment among CHB patients are context- and/or culture-specific.[21]

The distribution of general characteristics of our study subjects appears to be similar to the general demographics of HBV-related cirrhosis patients; here we find that these patients are mostly male with a mean age of approximately 60 years, which is similar to the demographics found in past studies.[22 23] Among the used NUCs, patients have been predominantly prescribed entecavir, since it is still considered the first-line treatment for patients with CHB.[24] The use of MPR as a measure of drug adherence has also been adopted in many previous studies.[13 25 26] It is believed that MPR can be a robust estimate of treatment adherence over time as it takes into account the period when patient stops and resumes medication.[25]

Nevertheless, our study is not without limitations. First, the primary source of data for this study is a medical claims-based database, hence, MPR is calculated based on prescription history and not the actual uptake of medication by the patients. Hence, the adherent level estimated using MPR may not represent the actual medication adherence exhibited by the study subjects. Second, although the population-based claims database provided us with an opportunity to study patient adherence on a large scale, we have no imaging data or laboratory test results to confirm the severity or the

diagnosis of cirrhosis in each of our subjects. Therefore, the variability in patients' conditions and their consequent probability of disease progression cannot be considered. Since hepatocellular carcinoma (HCC) may also cause decompensation and mortality independent of cirrhosis, we cannot account for HCC developed before the study period without available data. Thus, it is possible that we may have under-estimated the effect of medication adherence (i.e., even lower odds of decompensation and death for adherent behaviour after removing HCC-induced decompensation and mortality). Other important factors leading up to adverse prognosis may not be explored, including time since diagnosis and lifestyle factors. Nonetheless, with the high prevalence of HBV in the context under study, we have obtained a sufficient sample size for analyses and estimates for robust results.

In conclusion, findings of this study demonstrate that prompt follow-up and strict adherence to prescribed antiviral therapy should be highly endorsed in patients with HBV-related cirrhosis particularly by doctors, while a lack of adherence or non-adherence can be associated with pervasive threat to patients' health, including transition to decompensation state and possible death. We hope that findings of this study would shed some light for future studies which may aim to investigate the rolling out of policies targeting the context-specific factors associated with poor adherence in cirrhosis patients, possibly including enhanced adherence counselling in clinical settings.

Summary of Study

The objective of the present study is to first compare the medication adherence between HBV-related cirrhosis patients with and without decompensation, and subsequently to analyse the association between medication adherence and the

patients' prognosis (decompensation and mortality). Using medication-possession ratio as a measure for adherence, we find that patient adherence to therapy of cirrhosis remains inadequate compared with other countries. Patients lacking adherent behaviour, particularly in the long run, appear to have lower potential benefits of treatment intervention.

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Contributors

KY Fu, JA Chen, and VCR Hsieh were involved in design, data collection, data analysis, interpretation of results, and preparation of the initial manuscript.

ML Hsieh and VCR Hsieh were involved in critically appraising and revising the manuscript prior to approving the final version.

All authors approved the final version of the manuscript and the authorship list.

VCR Hsieh is guarantor of the article.

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Competing interests

None declared.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data availability statement

No additional data available.

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Table 1. Descriptive statistics of medication adherence and prognosis among chronic hepatitis B virus-related cirrhosis patients.

Dependent variable	Medication Adherence (MPR)	Mean	Standard deviation	Median
Decompensation	3-month	**0.98**	0.99	0.93
	6-month	**0.77**	0.67	0.74
	1-year	**0.61**	0.48	0.54
Death	3-month	**0.97**	1.02	0.92
	6-month	**0.74**	0.67	0.67
	1-year	**0.56**	0.48	0.46

Table 2. Post-matching characteristic profile of cirrhosis subjects by prognosis (decompensation/compensation; and death/alive).

Variable	Decompensated		Compensated		P-value	Death		Alive		P-value
	n	%	n	%		n	%	n	%	
Total	10,180	50.0	10,180	50.0		9,724	50.0	9,724	50.0	
Sex					1.00					1.00
Male	7,453	73.2	7,453	73.2		7,780	80.0	7,780	80.0	
Female	2,727	26.8	2,727	26.8		1,944	20.0	1,944	20.0	
Age (mean, SD)	60.1	12.0	59.7	12.0	0.06	60.4	12.0	60.0	12.0	0.06
Complications					<0.001					<0.001
Varicose vein bleeding	526	5.2	0	0		156	1.60	46	0.47	
Ascites	3,424	33.6	0	0		1,498	15.4	452	4.65	
SBP	414	4.07	0	0		187	1.92	57	0.59	
HRS	153	1.50	0	0		101	1.04	18	0.19	
HE	2,121	20.8	0	0		1,078	11.1	247	2.54	
Two or more	3,542	34.8	0	0		2,281	23.5	285	2.93	
None	0	0	10,180	100.0		4,423	45.5	8,619	88.6	
NUCs					<0.001					<0.001
LAM	1,448	14.2	975	9.58		1,352	13.9	1,117	11.5	
ADV	74	0.73	85	0.83		77	0.79	83	0.85	
LdT	656	6.44	533	5.24		759	7.81	533	5.48	
ETV	6,216	61.1	6,065	59.6		5,912	60.8	5,693	58.6	
TDF	1,062	10.4	2,020	19.8		917	9.43	1,881	19.3	
Two or more combined treatments	724	7.11	502	4.93		707	7.27	417	4.29	
MPR (mean, SD)										
3-month	1.00	1.15	0.96	0.79	<0.001	0.96	1.12	0.97	0.91	<0.001
6-month	0.76	0.79	0.79	0.52	<0.001	0.69	0.72	0.78	0.62	<0.001
1-year	0.57	0.53	0.65	0.43	<0.001	0.50	0.51	0.62	0.44	<0.001

Abbreviations: SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome; HE, hepatic encephalopathy. NUCs, nucleos(t)ide analogues; LAM, lamivudine only; ADV, adefovir dipivoxil only; LdT, telbivudine only; ETV, entecavir only; TDF, tenofovir disoproxil fumarate only; MPR, medication possession ratio.

Table 3. Conditional logistic regression analysis of decompensation in cirrhosis patients.

Variable	Crude			Adjusted log 3-month MPR			Adjusted log 6-month MPR			Adjusted log 1-year MPR		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Medication adherence												
log 3-month MPR	**0.85**	0.82 0.88	<0.001	**0.85**	0.83 0.88	<0.001						
log 6-month MPR	**0.78**	0.76 0.81	<0.001				**0.79**	0.76 0.81	<0.001			
log 1-yr MPR	**0.75**	0.73 0.77	<0.001							**0.75**	0.73 0.77	<0.001
Age	**1.04**	1.03 1.04	<0.001	**1.04**	1.03 1.04	<0.001	**1.03**	1.03 1.04	<0.001	**1.03**	1.03 1.04	<0.001
NUCs												
LAM	**1.08**	0.94 1.25	0.27	**1.09**	0.95 1.27	0.22	**1.12**	0.97 1.29	0.14	**1.16**	1.00 1.35	0.04
ADV	**0.63**	0.45 0.88	0.007	**0.63**	0.45 0.88	0.007	**0.64**	0.45 0.90	0.01	**0.68**	0.48 0.96	0.03
LdT	**0.88**	0.75 1.04	0.14	**0.89**	0.76 1.05	0.18	**0.92**	0.78 1.08	0.30	**0.95**	0.81 1.13	0.58
ETV	**0.73**	0.65 0.83	<0.001	**0.73**	0.65 0.83	<0.001	**0.75**	0.67 0.85	<0.001	**0.79**	0.70 0.89	<0.001
TDF	**0.38**	0.33 0.43	<0.001	**0.38**	0.33 0.44	<0.001	**0.39**	0.34 0.45	<0.001	**0.41**	0.36 0.48	<0.001
Two or more combined treatments	**1**			**1**			**1**			**1**		

NUCs, nucleos(t)ide analogues; LAM, lamivudine only; ADV, adefovir dipivoxil only; LdT, telbivudine only; ETV, entecavir only; TDF, tenofovir disoproxil fumarate only; MPR, medication possession ratio.

Table 4. Conditional Logistic regression analysis of mortality in cirrhosis patients.

Variable	Crude			Adjusted log 3-month MPR			Adjusted log 6-month MPR			Adjusted log 1-year MPR		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Medication adherence												
log 3-month MPR	**0.80**	0.78 0.83	<0.001	**0.78**	0.75 0.81	<0.001						
log 6-month MPR	**0.72**	0.70 0.74	<0.001				**0.72**	0.69 0.75	<0.001			
log 1-yr MPR	**0.69**	0.67 0.71	<0.001							**0.70**	0.68 0.72	<0.001
Age	**1.04**	1.03 1.05	<0.001	**1.03**	1.02 1.04	<0.001	**1.03**	1.02 1.04	<0.001	**1.03**	1.02 1.04	<0.001
Complications												
Varicose vein bleeding	**6.00**	4.20 8.83	<0.001	**6.57**	4.53 9.52	<0.001	**6.71**	4.62 9.76	<0.001	**6.65**	4.57 9.68	<0.001
Ascites	**6.73**	5.90 7.67	<0.001	**6.58**	5.76 7.50	<0.001	**6.55**	5.74 7.48	<0.001	**6.47**	5.66 7.40	<0.001
SBP	**7.41**	5.28 10.4	<0.001	**7.22**	5.12 10.2	<0.001	**6.93**	4.89 9.81	<0.001	**6.71**	4.73 9.54	<0.001
HRS	**12.5**	7.17 21.9	<0.001	**12.7**	7.18 22.5	<0.001	**12.0**	6.71 21.4	<0.001	**11.3**	6.30 20.4	<0.001
HE	**9.18**	7.76 10.9	<0.001	**8.98**	7.58 10.6	<0.001	**8.71**	7.34 10.3	<0.001	**8.45**	7.11 10.0	<0.001
Two or more	**15.7**	13.5 18.2	<0.001	**16.1**	13.8 18.7	<0.001	**16.2**	13.9 18.8	<0.001	**16.0**	13.7 18.6	<0.001
None	**1**			**1**			**1**			**1**		
NUCs												
LAM	**0.71**	0.61 0.82	<0.001	**0.71**	0.59 0.85	<0.001	**0.71**	0.59 0.86	<0.001	**0.74**	0.61 0.89	<0.001
ADV	**0.55**	0.39 0.77	<0.001	**0.65**	0.43 0.97	0.04	**0.68**	0.45 1.03	0.07	**0.75**	0.49 1.15	0.18
LdT	**0.84**	0.71 1.00	0.04	**1.00**	0.82 1.23	0.99	**1.03**	0.84 1.27	0.75	**1.08**	0.88 1.33	0.46
ETV	**0.62**	0.54 0.70	<0.001	**0.72**	0.62 0.84	<0.001	**0.74**	0.63 0.86	<0.001	**0.77**	0.66 0.91	<0.001
TDF	**0.29**	0.25 0.34	<0.001	**0.41**	0.34 0.49	<0.001	**0.43**	0.36 0.51	<0.001	**0.45**	0.37 0.54	<0.001
Two or more combined treatments	**1**			**1**			**1**			**1**		

SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome; HE, hepatic encephalopathy. NUCs, nucleos(t)ide analogues; LAM, lamivudine only; ADV, adefovir dipivoxil only; LdT, telbivudine only; ETV, entecavir only; TDF, tenofovir disoproxil fumarate only; MPR, medication possession ratio.

Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	p.1
Abstract	#1b	Provide in the abstract an informative and balanced summary	p.2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	p.4
Objectives	#3	State specific objectives, including any prespecified hypotheses	p.5
Methods			
Study design	#4	Present key elements of study design early in the paper	p.5-6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p.5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	p.5-6
Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	p.6
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p.6-7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	p.5-6

		group. Give information separately for cases and controls.	
Bias	#9	Describe any efforts to address potential sources of bias	NA
Study size	#10	Explain how the study size was arrived at	p.5-6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	p.12
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	p.7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	NA
Statistical methods	#12c	Explain how missing data were addressed	NA
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	p.6
Statistical methods	#12e	Describe any sensitivity analyses	NA
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	p.8
Participants	#13b	Give reasons for non-participation at each stage	NA

Participants	#13c	Consider use of a flow diagram	NA
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	p.8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	NA
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	p.8
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p.8-9
Main results	#16b	Report category boundaries when continuous variables were categorized	p.8-9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	#18	Summarise key results with reference to study objectives	p.10-11

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	p.12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	p.12-13
Generalisability	#21	Discuss the generalisability (external validity) of the study results	p.12-13
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p.14