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

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ABSTRACT

Objective To evaluate medication adherence among patients with hepatitis B-related cirrhosis 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 endpoints (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 to 0.77). Similar results are observed for the adjusted likelihood of mortality (log 1-year MPR OR: 0.70, 95% CI: 0.68 to 0.72).

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ No study has yet provided empirical evidence on the adherence rate of patients with hepatitis B virus (HBV)-related cirrhosis 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 a 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 patients with HBV-related cirrhosis.
⇒ We have no imaging data or laboratory test results to confirm the severity or the diagnosis of cirrhosis in each of our study subjects.
⇒ Adherence level estimated using MPR may not represent the actual medication adherence exhibited by the study subjects since 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 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 patients with chronic disease worldwide are taking medications in accordance with doctors' orders. This result not only leads to poor clinical treatment results, but it 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)

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and chronic hepatitis C (CHC). In Southeast Asian nations, CHB-related 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 (HRS) and hepatic encephalopathy (HE).[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 2 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 four times that of healthy individuals, with 30% of patients die within 1 month and 63% of patients die within 1 year.[6]

For the treatment of cirrhosis, antiviral therapy has shown beneficial effect on the prognosis of cirrhosis and its complications.[7 8] However, treatment adherence in chronic patients is usually not high, as patients 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 (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide, lamivudine (LAM), telbivudine (LdT) and adefovir dipivoxil (ADV). Tenofovir alafenamide, however, was not reimbursed until 2017. These antiviral drugs can be prescribed primarily based on clinicians' evaluation of patients' hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), alanine aminotransferase, 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 in patients with viral hepatitis-related cirrhosis. 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 patients with cirrhosis on oral antiviral therapy and quantified the level of adherence required to avert adverse outcomes (eg, how adherent are patients with cirrhosis to their treatment regimens and how much adherence is sufficient to prevent disease progression and reduce complication risks among these patients).

The objective of the present study is to first compare the medication adherence between patients with HBV-related cirrhosis 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-term and long-term adherence are considered, medication possession ratio (MPR) is calculated for 3-month, 6-month and 1-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, Taiwan. Patients who were aged over 20 years old and diagnosed with CHB (International Classification of Diseases, Ninth Revision, Clinical Modification (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 was 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), haemochromatosis (275.0) or 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: DC, control: CC), (2) mortality (case: dead, control: alive). These endpoints must occur following the diagnoses of CHB and cirrhosis. Decompensation was defined when the subject had been diagnosed with at least one of the following conditions: oesophageal variceal bleeding (456.0), ascites (789.5), spontaneous bacterial peritonitis (567.23), HRS (572.4) and HE (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 (ie, 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, patients with HBV treated with nucleos(t)ide analogues (NUCs) were identified: LAM, ADV, LdT, ETV and TDF. MPR was calculated for 3, 6, and 12 months prior to the date of decompensation and mortality in subjects who were being prescribed with the antiviral medication(s). Thus, there should be no concern that MPR for patients with cirrhosis 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 study 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 study period. For the objective of this study, we solely consider medications associated with HBV-related cirrhosis, and

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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 sometimes 0.80. Most studies use 0.80 as a cut-off point for determining good adherence.

Statistical analyses

SAS V.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, SDs, 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, X^2 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. OR and 95% CI for poor prognosis are presented as results in the included tables.

RESULTS

From the population-based database, a total of 10 180 patients with DC and 10 180 patients with CC are matched. Similarly, 9724 patients who died from cirrhosis and 9724 patients with cirrhosis 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 subjects with DC and CC 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 patients with cirrhosis 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 by prognosis. In the decompensated group, 34.8% (n=3542) of patients experienced two or more complications, 33.6% (n=3424) 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 in compensated patients are ETV (59.6%), TDF (19.8%) and LAM (9.58%). The proportion of patients that had undergone more than two NUC treatments is relatively higher in patients with complicated cirrhosis (7.11% vs 4.93%; p<0.001). Overall, longer term treatment adherence seems to be 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; p<0.001).

In the set of analyses examining mortality as outcome, the occurrence of every complication is significantly higher in patients with cirrhosis 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

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

Dependent variable	Medication adherence (MPR)	Mean	SD	Median
Decompensation	3 months	0.98	0.99	0.93
	6 months	0.77	0.67	0.74
	1 year	0.61	0.48	0.54
Death	3 months	0.97	1.02	0.92
	6 months	0.74	0.67	0.67
	1 year	0.56	0.48	0.46

MPR, medication possession ratio.

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

	Decompensated		Compensated			Dead		Alive		
Variable	**n**	**%**	**n**	**%**	**P value**	**n**	**%**	**n**	**%**	**P value**
Total	10180	50.0	10180	50.0		9724	50.0	9724	50.0	
Sex					1.00					1.00
Male	7453	73.2	7453	73.2		7780	80.0	7780	80.0	
Female	2727	26.8	2727	26.8		1944	20.0	1944	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	3424	33.6	0	0		1498	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	2121	20.8	0	0		1078	11.1	247	2.54	
Two or more	3542	34.8	0	0		2281	23.5	285	2.93	
None	0	0	10180	100.0		4423	45.5	8619	88.6	
NUCs					<0.001					<0.001
LAM	1448	14.2	975	9.58		1352	13.9	1117	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	6216	61.1	6065	59.6		5912	60.8	5693	58.6	
TDF	1062	10.4	2020	19.8		917	9.43	1881	19.3	
Two or more treatments	724	7.11	502	4.93		707	7.27	417	4.29	
MPR (mean, SD)										
3 months	1.00	1.15	0.96	0.79	<0.001	0.96	1.12	0.97	0.91	<0.001
6 months	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

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

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 to 0.77, p<0.001). Likelihood of the poor prognosis is slightly elevated when adherence continues for shorter spans: log 6-month MPR (OR: 0.79, 95% CI: 0.76 to 0.81, p<0.001) and log 3-month MPR (OR: 0.85, 95% CI: 0.83 to 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 to 0.72, p<0.001), log 6-month MPR (OR: 0.72, 95% CI: 0.69 to 0.75, p<0.001) and log 3-month MPR (OR: 0.78, 95% CI: 0.75 to 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 (i.e., single complication). Contrary to the increased risk of mortality imposed by older age, the use of NUCs is generally associated with averting patients from the adverse event.

DISCUSSION

The present study provides useful information from a nationwide retrospective study of patients with cirrhosis induced by viral hepatitis B. As we have observed, despite Taiwan's readily accessible universal coverage healthcare system, patient adherence to antiviral therapy remains inadequate, particularly in the long run (ie, 1-year MPR: 0.56–0.61). This finding is consistent with previous studies from other countries examining adherence behaviour in patients with CHB.[11 12] More importantly, we demonstrate that the likelihood of poor prognosis is negatively associated with adherence behaviour, and the benefits of long-term adherence are evidently more pronounced than that of the short-term. The fact that

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Table 3 Conditional logistic regression analysis for decompensation in patients with HBV-related cirrhosis

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 to 0.88	<0.001	0.85	0.83 to 0.88	<0.001						
log 6-month MPR	0.78	0.76 to 0.81	<0.001				0.79	0.76 to 0.81	<0.001			
log 1-year MPR	0.75	0.73 to 0.77	<0.001							0.75	0.73 to 0.77	<0.001
Age	1.04	1.03 to 1.04	<0.001	1.04	1.03 to 1.04	<0.001	1.03	1.03 to 1.04	<0.001	1.03	1.03 to 1.04	<0.001
NUCs												
LAM	1.08	0.94 to 1.25	0.27	1.09	0.95 to 1.27	0.22	1.12	0.97 to 1.29	0.14	1.16	1 to 1.35	0.04
ADV	0.63	0.45 to 0.88	0.007	0.63	0.45 to 0.88	0.007	0.64	0.45 to 0.9	0.01	0.68	0.48 to 0.96	0.03
LdT	0.88	0.75 to 1.04	0.14	0.89	0.76 to 1.05	0.18	0.92	0.78 to 1.08	0.3	0.95	0.81 to 1.13	0.58
ETV	0.73	0.65 to 0.83	<0.001	0.73	0.65 to 0.83	<0.001	0.75	0.67 to 0.85	<0.001	0.79	0.7 to 0.89	<0.001
TDF	0.38	0.33 to 0.43	<0.001	0.38	0.33 to 0.44	<0.001	0.39	0.34 to 0.45	<0.001	0.41	0.36 to 0.48	<0.001
Two or more treatments	1			1			1			1		

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

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 (ie, 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, nevertheless, show that adherence to antiviral therapy is inversely associated with the development of subsequent complications and death among patients with HBV-related cirrhosis. 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 patients with CHB-related cirrhosis; 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 patients with CHB reveals 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 non-adherence, 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 patients with CHB presented an adherence rate of over 80% towards ETV.[20] It is possible that the factors and the barriers associated with adherence to oral antiviral treatment among patients with CHB 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 patients with HBV-related cirrhosis; 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 ETV, 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

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Table 4 Conditional logistic regression analysis for mortality in patients with HBV-related cirrhosis

	Crude			Adjusted log 3-month MPR			Adjusted log 6-month MPR			Adjusted log 1-year MPR		
Variable	**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	0.8	0.78 to 0.83	<0.001	0.78	0.75 to 0.81	<0.001						
log 6-month MPR	0.72	0.7 to 0.74	<0.001				0.72	0.69 to 0.75	<0.001			
log 1-year MPR	0.69	0.67 to 0.71	<0.001							0.7	0.68 to 0.72	<0.001
Age	1.04	1.03 to 1.05	<0.001	1.03	1.02 to 1.04	<0.001	1.03	1.02 to 1.04	<0.001	1.03	1.02 to 1.04	<0.001
Complications												
Varicose vein bleeding	6	4.2 to 8.83	<0.001	6.57	4.53 to 9.52	<0.001	6.71	4.62 to 9.76	<0.001	6.65	4.57 to 9.68	<0.001
Ascites	6.73	5.9 to 7.67	<0.001	6.58	5.76 to 7.5	<0.001	6.55	5.74 to 7.48	<0.001	6.47	5.66 to 7.4	<0.001
SBP	7.41	5.28 to 10.4	<0.001	7.22	5.12 to 10.2	<0.001	6.93	4.89 to 9.81	<0.001	6.71	4.73 to 9.54	<0.001
HRS	12.5	7.17 to 21.9	<0.001	12.7	7.18 to 22.5	<0.001	12	6.71 to 21.4	<0.001	11.3	6.3 to 20.4	<0.001
HE	9.18	7.76 to 10.9	<0.001	8.98	7.58 to 10.6	<0.001	8.71	7.34 to 10.3	<0.001	8.45	7.11 to 10	<0.001
Two or more	15.7	13.5 to 18.2	<0.001	16.1	13.8 to 18.7	<0.001	16.2	13.9 to 18.8	<0.001	16	13.7 to 18.6	<0.001
None	1			1			1			1		
NUCs												
LAM	0.71	0.61 to 0.82	<0.001	0.71	0.59 to 0.85	<0.001	0.71	0.59 to 0.86	<0.001	0.74	0.61 to 0.89	<0.001
ADV	0.55	0.39 to 0.77	<0.001	0.65	0.43 to 0.97	0.04	0.68	0.45 to 1.03	0.07	0.75	0.49 to 1.15	0.18
LdT	0.84	0.71 to 1	0.04	1	0.82 to 1.23	0.99	1.03	0.84 to 1.27	0.75	1.08	0.88 to 1.33	0.46
ETV	0.62	0.54 to 0.7	<0.001	0.72	0.62 to 0.84	<0.001	0.74	0.63 to 0.86	<0.001	0.77	0.66 to 0.91	<0.001
TDF	0.29	0.25 to 0.34	<0.001	0.41	0.34 to 0.49	<0.001	0.43	0.36 to 0.51	<0.001	0.45	0.37 to 0.54	<0.001
Two or more treatments	1			1			1			1		

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

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adherence over time as it takes into account the period when a patient stops and resumes medication.[25]

However, 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. Thus, the adherence level estimated using MPR may not represent the actual medication adherence exhibited by 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. As a result, the variability in patients' clinical conditions and their consequent chance 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 underestimated the effect of medication adherence (ie, even lower odds of decompensation and death for adherence behaviour after removing HCC-induced decompensation and mortality). Other important factors leading up to adverse prognosis cannot 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 population-based analyses and estimates.

In conclusion, findings of this study demonstrate that prompt follow-up and strict adherence to prescribed oral 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 will shed some light for future studies which may aim to investigate the rolling out of policies targeting context-specific factors associated with poor adherence in patients with cirrhosis, 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 patients with HBV-related cirrhosis with and without decompensation, and to subsequently analyse the association between medication adherence and the patients' prognosis (decompensation and mortality). Using MPR as a measure for medication adherence, we find that patients' adherence to therapy of cirrhosis remains inadequate compared with other countries. Furthermore, patients with adherent behaviour, particularly in the long run, appear to have higher potential benefits of treatment intervention.

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Patient consent for publication Not required.

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