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ORIGINAL ARTICLE

Population-based study of Entecavir and long-term mortality in chronic hepatitis B–related decompensated liver cirrhosis



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KEYWORDS

Decompensated liver cirrhosis;
Chronic hepatitis B;
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Summary

Background and aims: We lack population-based studies that identify the role of entecavir (ETV) in extending long-term survival in chronic hepatitis B (CHB)-related decompensated liver cirrhotic patients. Since 2010, National Health Insurance in Taiwan has covered long-term medical payment for antiviral therapy in CHB-related cirrhotic patients whose HBV DNA is ≥ 2000 IU/mL. We studied the effect of ETV on the mortality of CHB-related decompensated cirrhosis patients compared with patients who did not receive antiviral agents at baseline.

Methods: From the Taiwan National Health Insurance Database, we collected 758 CHB-related decompensated cirrhosis patients with elevated viral loads (HBV DNA ≥ 2000 IU/mL) using ETV and discharged between January 1, 2010, and December 31, 2013. The comparison group consisted of 1516 selected CHB-related decompensated cirrhotic patients without antiviral therapy at baseline using propensity score matching analysis.

Results: The 1-, 2-, and 3-year mortality probabilities were 34.7%, 42.5%, and 48.5% in the ETV group and 21.1%, 37.8% and 51.3% in the non-ETV group, respectively. Based on a Cox proportional hazards regression model adjusted by patients' sex, age, and comorbid disorders, the hazard ratios (HR) in the ETV group for 1-year, 1–2-year, and 2–3-year mortalities were 1.22 (95% confidence interval [CI] 1.05–1.43, $P = .010$), 1.02 (0.86–1.20, $P = .866$), and 0.59 (0.38–0.90, $P = .016$), compared with the non-ETV group.

Abbreviations: CHB, chronic hepatitis B; CI, confidence interval; ETV, entecavir; EVB, esophageal variceal bleeding; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HE, hepatic encephalopathy; HR, hazard ratio; ICD-9-CM, international classification of diseases, ninth revision, clinical modification; NHIRD, Taiwan national health insurance research database; PSM, propensity score matching; RFI, renal function impairment.

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Conclusions: Even in CHB-related decompensated cirrhotic patients, higher initial viral loads were correlated with poor outcomes. However, the long-term usage of ETV can decrease long-term mortality in these patients.

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Introduction

Patients who have cirrhosis with ascites, hepatic encephalopathy (HE), or esophageal variceal bleeding (EVB) are in the decompensated status of liver cirrhosis and typically have a poor prognosis. In compensated cirrhosis patients, survival is relatively good at about 85% at 5 years; however, patients with decompensated cirrhosis have a poor prognosis of about 14%–35% survival at 5 years [1–3]. Overall, chronic hepatitis B (CHB) patients' viral load of hepatitis B virus (HBV) correlates with their outcomes [3]. The efficacy of potent viral suppression with more efficient antiviral therapy in CHB is well established, [4,5] and entecavir (ETV) can improve the long-term liver function in CHB patients. In a recent study, antiviral therapy significantly improved the natural history of patients with decompensated cirrhosis and also increased survival [6]. Although the survival benefit of ETV in decompensated CHB-related cirrhotic patients was established in this study, we still would like to know the real efficacy of ETV in real-world patients. Using the national healthcare database in Taiwan, we designed this population-based study to identify the role of ETV in these patients.

Beginning in 2010, the National Health Insurance in Taiwan has covered long-term antiviral therapy in CHB-related cirrhotic patients whose HBV DNA levels were > 2000 IU/mL. The study aimed to identify the effect of ETV on mortality in CHB-related decompensated cirrhotic patients compared with patients who did not receive antiviral agents, probably because of the latter's generally lower viral load at baseline. Furthermore, via subgroup analysis this study also aimed to identify the efficacy of ETV on survival among less-complicated and more-complicated decompensated cirrhotic patients.

Patients and methods

Database

The National Health Insurance program was established in Taiwan in 1995. Currently, the National Health Insurance Administration in Taiwan covers $> 99\%$ of the population of Taiwan. For medical payments, medical records from the treating medical institutions must be provided to the National Health Insurance Administration. These medical records comprise a database, the Taiwan National Health Insurance Research Database (NHIRD), which includes all diagnostic coding information for hospitalized patients in

Taiwan. Many studies have used the database to evaluate medical diseases [7–9].

Since 2010, costs for long-term use of antiviral agents for CHB-related cirrhosis have been covered by the Taiwan National Health Insurance program. In order to ensure the best use of antiviral agents and to monitor treatment effects or patient compliance, all these patients must be registered in the specific program for CHB care. Patients in this special program for CHB care, including the long-term use of antiviral agents for CHB-related cirrhosis, must meet all 3 admissions requirements:

- positive for hepatitis B surface antigen (HBsAg);
- HBV DNA ≥ 2000 IU/mL;
- the diagnosis of liver cirrhosis should be based on either liver biopsy or imaging, possibly also combined with the presence of splenomegaly or the presence of esophageal or gastric varices.

This study was approved by the National Health Research Institute in Taiwan (application and agreement number 104359). The privacy of the healthcare providers and patients reported in this study was protected by using a secondary de-identified NHIRD dataset. This study was approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital, Chiayi, Taiwan (IRB B10403026). Because all identifying personal information was removed from the secondary files, the review board waived the requirement for written informed consent from all patients in the present study.

Study Sample

Taiwanese patients who were discharged with the diagnosis of cirrhosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 571.2 or 571.5) between January 1, 2010, and December 31, 2013, were screened. All the patients were followed up to December 31, 2013. The ETV group was defined as patients who received ETV during hospitalization. According to the medical payment criteria of the Taiwan National Health Insurance program, all of the patients in the ETV treatment group were required to have HBV DNA levels that were ≥ 2000 IU/mL. Decompensated liver cirrhosis in our study was defined as HE (ICD-9-CM code 572.2), EVB (ICD-9-CM codes 456.0 or 456.20), or ascites (ICD-9-CM code 789.5, patients with spontaneous bacterial peritonitis, or procedure code 54.91). In cases of multiple hospitalizations of one patient, only the first episode was enrolled. The comparison group (the non-ETV group) included decompensated cirrhotic patients who

Table 1 Demographic characteristics of chronic Hepatitis B-related decompensated cirrhotic Patients treated with or without Entecavir.

	ETV group (n = 758)	Non-ETV group (n = 1516)	P-value
Male sex, n (%)	582 (76.8)	1169 (77.1)	.860
Age, yrs	54.2 ± 12.1	53.9 ± 12.7	.647
HE, n (%)	299 (39.4)	579 (38.2)	.563
EVB, n (%)	155 (20.4)	305 (20.1)	.854
Ascites, n (%)	452 (59.6)	901 (59.4)	.928
RFI, n (%)	45 (5.9)	79 (5.2)	.473
HCV, n (%)	40 (5.3)	75 (4.9)	.735
Alcoholism, n (%)	182 (24.0)	372 (24.5)	.782

EVB: esophageal variceal bleeding; HCV: co-infected with hepatitis C virus; HE: hepatic encephalopathy; RFI: renal function impairment.

did not receive ETV or any other antiviral drugs for CHB approved for payment by the Taiwan National Health Insurance program at baseline. The exclusion criteria included patients who had hepatocellular carcinoma at the index date.

To avoid interference from measured confounding factors, a one-to-two case–control match was established using propensity score matching (PSM) with respect to age, sex, alcoholism, renal function impairment (ICD-9-CM codes 584, 585, 586, 572.4, or other procedure codes related to renal failure), and hepatitis C virus (HCV) coinfection.

Statistical analyses

We used SPSS for Windows, version 22.0 (IBM, Chicago, IL, USA) to perform the analyses in our study. The chi-square test was used to compare categorical variables, and Student's *t* test was used to compare continuous variables. In order to identify risk factors for mortality, the Cox hazards regression model was used to control for the effects of confounding factors. We used hazard ratios (HR) along with 95% confidence intervals (CI) using a significance level of 0.05. Hazard ratios for 3-year mortality were calculated for comparisons between the ETV group and non-ETV group. We also calculated the 2-year mortality of patients who survived > 1 year, as well as the 3-year mortality of patients who survived > 2 years.

Results

From the Taiwan National Health Insurance Database, we collected 758 CHB-related decompensated cirrhotic patients who received ETV and whose HBV DNA levels were ≥ 2000 IU/mL. After PSM, another 1516 CHB-related decompensated liver cirrhotic patients were identified as the non-ETV group. In the ETV group, the mean age was 54.2 ± 12.9 years; 582 (76.8 %) patients were males. [Table 1](#) shows the demographic characteristics of enrolled patients in the ETV and non-ETV groups after PSM. The basic characteristics of both groups were similar, except, by definition, the baseline viral burden in each group.

Table 2 Adjusted hazard ratios for 3-year mortality in decompensated chronic Hepatitis B-related decompensated liver cirrhosis patients.

Variable	Hazard ratio	95% Confidence interval	P-value
Age	1.02	1.02–1.03	< .001
Male sex	1.07	0.92–1.25	.364
EVB	0.74	0.59–0.92	.006
HE	1.77	1.51–2.08	< .001
Ascites	1.73	1.46–2.05	< .001
ETV	0.99	0.87–1.13	.842
RFI	2.28	1.83–2.84	< .001
HCV	1.38	1.08–1.77	.009
Alcoholism	1.14	0.97–1.34	.102

ETV: entecavir; EVB: esophageal variceal bleeding; HCV: co-infected with hepatitis C virus; HE: hepatic encephalopathy; RFI: renal function impairment.

The 1-, 2-, and 3-year mortality probabilities were 34.7%, 42.5%, and 48.5% in the ETV group and 21.1%, 37.8%, and 51.3% in the non-ETV group. After adjusting for sex, age, and other underlying comorbidities, the 3-year mortality HR associated with the use of ETV was 0.99 (95% CI = 0.87–1.13, $P = .842$, compared with the non-ETV group). The other statistically different prognostic factors were as follows: renal function impairment (RFI) (HR = 2.28, 95% CI = 1.83–2.84, $P < .001$), age (HR = 1.02, 95% CI = 1.02–1.03, $P < .001$), EVB (HR = 0.74, 95% CI = 0.59–0.92, $P = .006$), ascites (HR = 1.73, 95% CI = 1.46–2.05, $P < .001$), HCV coinfection (HR = 1.08, 95% CI = 1.02–1.03, $P = .009$), and HE (HR = 1.77, 95% CI = 1.51–2.08, $P < .001$). The results are shown in [Table 2](#).

In order to evaluate the effects of ETV on mortality in greater detail, we also calculated the 2-year mortality of patients who survived > 1 year, as well as the 3-year mortality of patients who survived > 2 years. After Cox proportional hazards regression adjustment for the patients' sex, age, and comorbid disorders, the HR in ETV group for 1-year, 1–2-year, and 2–3-year mortalities were 1.22 (95% CI 1.05–1.43, $P = .010$), 1.02 (95% CI 0.86–1.20, $P = .866$), and 0.59 (95% CI

Table 3 Crude and adjusted hazard ratios for entecavir (0–1 year, 1–2 year, and 2–3 year mortalities) in chronic Hepatitis B-related decompensated cirrhotic patients.

Period	Hazard ratio	95% Confidence interval	P-value
0–1 year			
Crude HR	1.24	1.06–1.45	.007
Adjusted	1.22	1.05–1.43	.010
HR			
1–2 year			
Crude HR	1.01	0.85–1.19	.958
Adjusted HR	1.02	0.86–1.20	.866
2–3 year			
Crude HR	0.62	0.40–0.94	.026
Adjusted HR	0.59	0.38–0.90	.016

HR: hazard ratio.

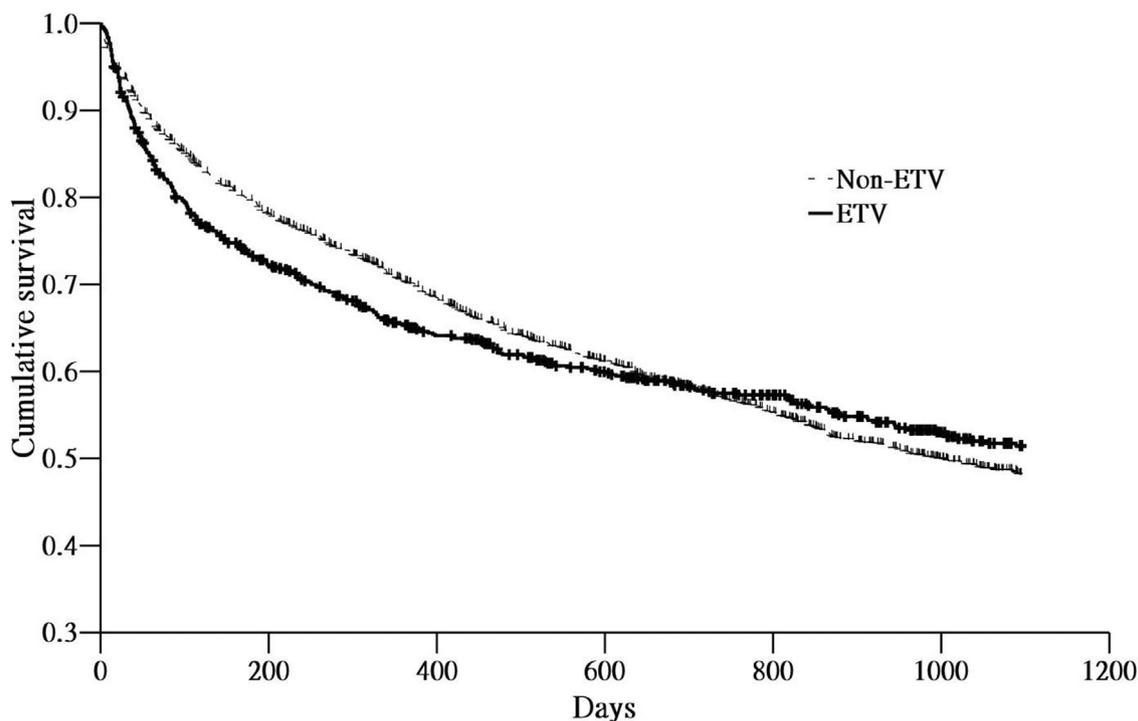


Figure 1 Kaplan–Meier survival analysis for chronic hepatitis B-related decompensated cirrhotic patients with or without entecavir (ETV).

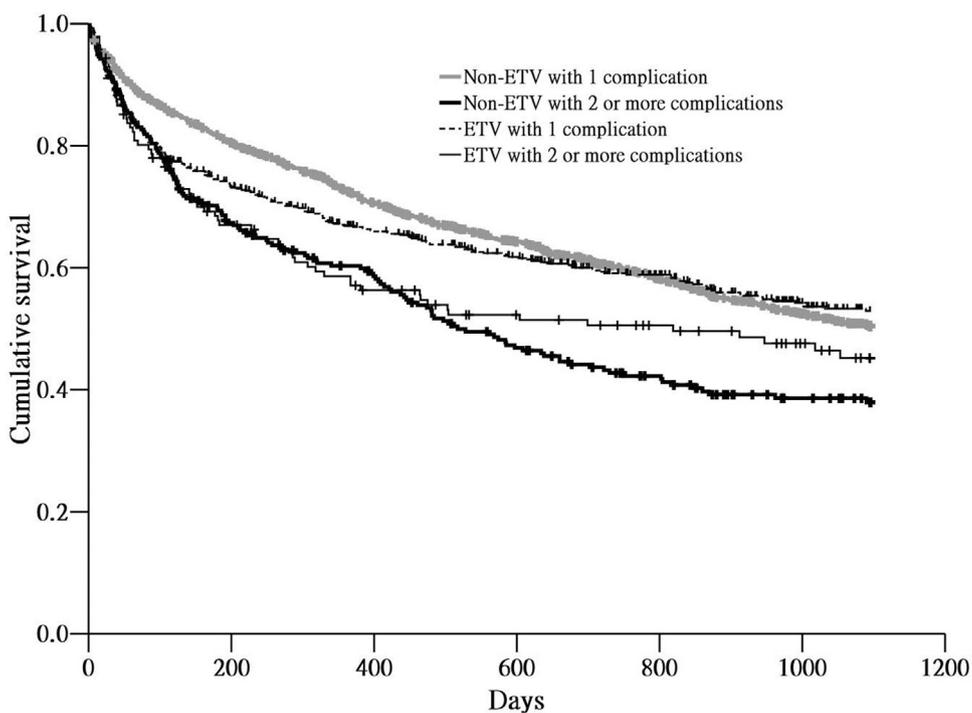


Figure 2 Kaplan–Meier survival analysis for chronic hepatitis B-related decompensated cirrhotic patients with or without entecavir (ETV), by number of complications.

0.38–0.90, $P = .016$) compared with the non-ETV group. The results are shown in [Table 3](#).

[Fig. 1](#) demonstrates the Kaplan–Meier 3-year survival curve in CHB-related decompensated cirrhotic patients with and without ETV treatment at baseline; the log-rank test

did not reveal a statistically significant difference ($P = .885$). However, the 2- to 3-year log-rank test for patients who survived > 2 years revealed a statistically significant difference ($P = .025$). In a subgroup analysis, we compared the less complicated (1 complication) and more complicated (2–3

complications) subgroups in both the ETV and the non-ETV groups. Fig. 2 demonstrates the long-term mortality in these 4 groups. The beneficial efficacy of ETV in long-term survival is significant, whether in the less-complicated group or the more-complicated group (ie, among the subgroups in the ETV and non-ETV groups).

Discussion

Although the beneficial effects of antiviral therapy on CHB-related decompensated liver cirrhosis was established by a previous study, [6] we still need to know the real-world drug efficacy in these patients. The major strength of the present study is that it is the first nationwide population-based study that enrolled large case numbers of HBV-related decompensated cirrhosis patients. Using such population-based data can provide a broad view of these patients and can also indicate the real efficacy of treatments used in clinical practice. The findings of our study provide strong evidence for the long-term benefits of ETV for HBV-related decompensated cirrhosis, and the results are compatible with findings from a previous study [6]. Furthermore, in the subgroup analysis, we also found significant efficacy of ETV in terms of long-term survival even in decompensated cirrhotic patients with a greater number of cirrhosis-related complications.

In our study, although we used PSM for the ETV and non-ETV groups in order to avoid the interference of these factors on mortality measurements, some basic difference between the groups could not be avoided. In the ETV group, the HBV DNA level should be ≥ 2000 IU/mL because of the Taiwan Health Insurance Program covers ETV treatment only when the viral level is at or above this level in cirrhotic patients. This also means that in the non-ETV group, the viral load is < 2000 IU/mL. In other words, the survival is lower during the initial period in the ETV group (relatively higher viral load) than in the non-ETV group (relatively lower viral load). This result is consistent with the findings of previous studies that revealed that high viral loads are correlated with a poor prognosis in CHB-related liver disease [10–12]. However, with the increasing duration of ETV usage, the beneficial effects on survival were also increasing, which also is compatible with current knowledge and supports the use of these kinds of antiviral drugs during the earliest stage possible of liver disease [13–15].

In this study, the statistically different prognostic factors of 3-year mortality in patients who had CHB-related decompensated liver cirrhosis were RFI (HR=2.28, 95% CI=1.83–2.84, $P < .001$), age (HR=1.02, 95% CI=1.02–1.03, $P < .001$), EVB (HR=0.74, 95% CI=0.59–0.92, $P = .006$), ascites (HR=1.73, 95% CI=1.46–2.05, $P < .001$), HCV coinfection (HR=1.08, 95% CI=1.02–1.03, $P = .009$), and HE (HR=1.77, 95% CI=1.51–2.08, $P < .001$). These findings are compatible with our current knowledge and the results of previous studies [16–20]. Not surprisingly, EVB seemed to be a “favorable” factor in these patients because all the patients in this study were in decompensated status, whether EVB, HE, or ascites, and, compared with the other 2 complications (HE or ascites), EVB was considered a favorable outcome factor. In all of the cirrhosis-related complications, EVB is a relatively less severe complication.

In a previous study and during the first month after bleeding onset, the EBV group had higher mortality rates than did patients without complications (10% versus 4%), but long-term mortality in both groups was similar [21]. Our study also showed comparable results.

To better understand the effect of ETV on CHB-related decompensated cirrhosis, we conducted subgroup analyses. We compared the mortality of ETV in patients with fewer complications (1 complication), ETV in patients with more complications (≥ 2 complications), non-ETV treatment in patients with fewer complications (1 complication), and ETV in patients with more complications (≥ 2 complications). Independently of the number of complications or liver preservation status, ETV is associated with positive long-term survival.

Our study provides strong evidence of the positive effect of ETV on the long-term mortality of CHB-related decompensated cirrhotic patients. The survival benefit seems to increase after long-term use. However, there were several limitations to our study. First, although the severity of liver cirrhosis is commonly evaluated by the Mayo Clinic model for end-stage liver disease (MELD) score or the Child–Pugh Score, we could not identify laboratory data such as bilirubin, albumin, or prothrombin time by ICD-9 coding numbers in this database. However, all the patients in our study were in decompensated cirrhosis, and cirrhosis-related complications such as HE, EVB, or ascites were taken into consideration and help ensure that the results of our study are reliable. Second, the duration of patients' exposure to ETV before admission could not be determined, and we also could not assess patients' compliance with prescriptions of ETV after discharge. However, since 2010 the Taiwan National Health Insurance program has covered the long-term fees for ETV in patients who have CHB-related cirrhosis. In order to verify the treatment indications and effects of antiviral agents, all patients who use antiviral agents for CHB must be registered and followed in this program. These data also make the results of our study more reliable. Third, the elastometry or HBV genotype was not provided by the National Health Insurance program in Taiwan. We could not know the real elastometry or HBV genotype in each patient.

Despite these limitations, this nationwide population-based study found that even in CHB-related decompensated cirrhotic patients, initial higher viral loads were correlated with poor outcomes. The long-term use of ETV can decrease mortality in decompensated CHB-related cirrhotic patients. No matter the liver preservation status in decompensated liver cirrhosis patients, the long-term beneficial effect on survival of ETV is clear.

Authors' contributions

Tsung-Hsing Hung, Hsing-Feng Lee, and Chen-Chi Tsai: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript.

Chih-Chun Tsai and Tsung-Hsing Hung: statistical analysis.

Disclosure of interest

The authors declare that they have no conflict of interest.

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