Research Article

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Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis

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Background & Aims: Taiwan has a high prevalence of hepatitis B viral (HBV) infection and hepatocellular carcinoma (HCC) with increasing consumption of alcohol. We investigated the impact of heavy alcohol consumption and HBV infection on HCC in cirrhotic patients.

Methods: 966 cirrhotic patients (132 with HBV infection and alcoholism, 632 with HBV infection, and patients with alcoholism) were enrolled between 2000 and 2009 and followed until 2011. The primary end point was newly developed HCC.

Results: Within the three patient groups (cirrhotic patients with HBV infection and alcoholism, HBV infection alone, and alcoholism alone) 38 (28.8%), 100 (15.8%), and 21 (10.4%) showed newly developed HCC, respectively. The 10-year cumulative (52.8% *vs.* 39.8% *vs.* 25.6%, p <0.001) and annual incidences (9.9%, 4.1%, and 2.1%) of HCC were significantly higher in cirrhotic patients with HBV infection and alcoholism than those in patients with HBV infection or alcoholism alone. For patients with HBV infection and alcoholism, baseline serum HBV DNA (OR = 16.8, p = 0.025), antiviral nucleos(t)ides analogues (NUCs) therapy (OR = 0.01, p = 0.035), and serum α-fetoprotein (OR = 1.18, p = 0.045) were risk predictors of HCC by multivariate logistic regression models. The cumulative incidence of HCC was higher in patients with higher baseline serum HBV DNA. Antiviral NUCs therapy reduced the incidence of HCC.

Conclusions: Heavy alcohol consumption significantly increased the risk of HCC in HBV-related cirrhotic patients. Elevated baseline serum HBV DNA was a strong risk predictor of HCC and antiviral NUCs therapy reduced the incidence of HCC in cirrhotic patients with HBV infection and alcoholism.

Keywords: Alcoholism; Chronic hepatitis B; Hepatitis B virus DNA; Nucleos(t)ides analogues; Liver cirrhosis; Hepatocellular carcinoma.

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Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HBV DNA, Hepatitis B virus DNA; NUCs, nucleos(t)ides analogues; HbsAg, hepatitis B surface antigen; HbeAg, hepatitis B e antigen; CHB, chronic hepatitis B; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; CI, confidence interval.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most commonly occurring cancer and the third most common cause of cancer-related death worldwide [1–3]. In Western countries, chronic alcohol use of greater than 80 g per day for more than 5 years increases the risk of HCC, and alcoholic cirrhosis is also a definite risk factor for HCC [4–7]. Taiwan is a region of high prevalence of chronic hepatitis B (CHB) with increasing alcoholic liver disease [8–10]. Hepatitis B virus (HBV) infection has also been recognized as a major risk factor for cirrhosis and HCC [11,12]. Serum HBV DNA level is a marker of viral replication and elevated serum HBV DNA level is a strong risk predictor of HCC in CHB patients [13–17]. Antiviral nucleos(t)ide analogues (NUCs) have been widely used to reduce the development of HCC in CHB patients with fibrosis or cirrhosis [18–20].

The synergism and interaction between HBV infection and alcohol consumption, in the pathogenesis of chronic liver disease and clinical outcomes, have been reported [4–6,21]. However, the role of heavy alcohol consumption and HBV infection on the development of HCC remains uncertain and needs to be explored. We investigated the impact of heavy alcohol consumption and HBV infection on the development of HCC in cirrhotic patients.

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Table 1. Demographic data of all cirrhotic patients.

Characteristics	HBV + alcoholism (n = 132)	HBV (n = 632)	Alcoholism (n = 202)
Sex (male)	112 (85%)	521 (82%)	165 (82%)
Age (yr)	43.9 (21-65)[a,b]	47.8 (23-86)[c]	49.3 (27-76)
Alcohol intake (g/d)	190 (80-350)[a]	5 (0-20)[c]	186 (80-600)
Alcohol intake duration (yr)	20 (5-30)	n.a.	18 (5-30)
AST (IU/L)	110 (34-1133)[a,b]	66 (23-753)[c]	136 (29-491)
ALT (IU/L)	45 (14-278)[b]	55 (20-827)[c]	43 (10-252)
Total bilirubin (mg/dl)	2.9 (0.3-11.4)[b]	1.6 (0.3-26.5)[c]	2.5 (0.5-37.9)
Alkaline phosphatase (IU/L)	305 (161-1484)	237 (75-659)[c]	290 (85-889)
γ-glutamyltransferase (IU/L)	173 (33-1148)[a,b]	152 (22-784)[c]	269 (11-1240)
Albumin (g/dl)	3.0 (2.0-4.8)[a,b]	3.4 (2.2-4.8)	3.3 (1.8-4.6)
Platelet count (x10^3/ml)	93 (23-286)[a,b]	142 (25-386)	136 (13-333)
INR	1.4 (0.9-2.3)	1.2 (0.9-3.1)	1.3 (0.9-2.9)
α-fetoprotein (ng/ml)	8 (1-686)	8 (1-567)	6 (1-260)
HBsAg-positive	132 (100%)[b]	632 (100%)[c]	0 (0%)
HBeAg-positive	48 (36%)	221 (35%)	n.a.
Baseline HBV DNA (log_{10} copies/ml)	4.1 (0-9.1)[a]	5.3 (0-9.1)	n.a.
Baseline HBV DNA (>5 log_{10} copies/ml)	71 (54%)[a]	240 (47%)	n.a.
HBV genotypes B *vs.* C	45/56	131/163	n.a.
Antiviral NUCs therapy - yes	71 (54%)[a]	385 (61%)	n.a.
Child-Pugh class			
A	62 (46%)[a,b]	362 (57%)	110 (54%)
B	35 (27%)	179 (29%)	60 (30%)
C	35 (27%)[a,b]	91 (14%)	32 (16%)
HCC development	38 (28.8%)[a,b]	100 (15.8%)[c]	21 (10.4%)
Annual HCC incidence (%/yr)	9.9	4.1	2.1

Data shown as median (range) or number (%).
AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; n.a., data not available; NUCs, nucleos(t)ides; HCC, hepatocellular carcinoma.
[a]*p* value <0.05, HBV and alcoholism *vs.* HBV.
[b]*p* value <0.05, HBV and alcoholism *vs.* alcoholism.
[c]*p* value <0.05, HBV *vs.* alcoholism.

Cancer

Patients and methods

Patients

We retrospectively reviewed 966 consecutive, documented cirrhotic patients (132 with heavy alcoholism and HBV infection, 632 with HBV infection, and 202 with heavy alcoholism) at the Cathay General Hospital, Taipei, North Taiwan, and E-DA Hospital/I-SHOU University, Kaohsiung, South Taiwan, between 2000 and 2009. We followed these patients until December 2011. All patients were followed-up for more than 6 months. The alcohol consumption behavior of each patient was routinely evaluated by interviewing patients and family members. Each patient completed a questionnaire on drinking habits, including the age when the patient started or stopped drinking, duration of drinking, types of alcohol, and amount of alcohol per day.

All participants were assured that their anonymity would be preserved and that each participant in the study would be identified only by a number. The evaluations commenced after approval of the study protocols by the Institutional Review Board of Cathay General Hospital and E-DA hospital.

For the study, heavy alcoholism was defined as consuming more than 80 g of ethanol each day for at least 5 years. CHB was defined as the patient being serum hepatitis B surface antigen (HBsAg)-positive for more than 6 months. Liver cirrhosis was clinically defined based on ultrasound, acoustic radiation force impulse (ARFI), computer tomography (CT), magnetic resonance imaging (MRI), upper gastrointestinal endoscopy, and laboratory tests. The cirrhosis diagnoses included (1) histological presence of cirrhosis (55%), or (2) finding of definite cirrhosis by imaging (9%), or (3) a chronic liver disease pattern plus esophageal varices or thrombocytopenia (<150 K/mm^3) (36%) [22]. Patients with other causes of cirrhosis, chronic hepatitis C, HCC, and liver transplantation were excluded. The primary end point was considered to be newly developed HCC after a six-month follow-up. Newly developed HCC cases were ascertained by follow-up examinations, medical records, or National Cancer Registry profiles.

Surveillance

All patients underwent blood chemistry and α-fetoprotein (AFP) tests every 3 months; and imaging examinations including ultrasonography, CT, or MRI every 3–6 months, or when necessary. HCC was diagnosed on the basis of the results of histological examination (62%) or typical findings of multi-dynamic CT or dynamic contrast enhancement MRI (38%), according to the American Association for the Study of Liver Diseases HCC guidelines [23], including early enhancement during the arterial phase, early washout during the venous phase, and washout persistence in the delayed phase. All patients were assessed for the occurrence of ascites and hepatic encephalopathy to define the Child-Pugh score and Child-Pugh class.

HBV marker assay

All patients were tested for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and anti-HBe antibody (Abbott Laboratories, Chicago, IL, USA), and serum HBV DNA (Cobas Amplicor, Hepatitis B Virus Test; Roche Diagnostics, Branchburg, NJ, USA) with a lower detection limit of 300 copies/ml. HBV genotypes were determined by using the polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) of the surface gene of HBV.

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Treatments

Alcoholic patients were encouraged to abstain from alcohol. Ninety-two cirrhotic patients had detectable HBV DNA $\geqslant 10^4$ copies/ml. Seventy-one of them were administered antiviral nucleos(t)ides analogues (NUCs) therapy (29 lamivudine, 32 entecavir, and 10 telbivudine) and the remaining 21 patients refused antiviral NUCs therapy. Forty patients with low HBV DNA load $<10^4$ copies/ml were not administered antiviral NUCs therapy.

Statistical analyses

Data were expressed either as median (range) or percentage (%). Continuous variables were analyzed using Student's *t*-test. Categorical variables were analyzed using Pearson's Chi-square test or Fisher's exact test, as appropriate. The annual rate of HCC was calculated by dividing the number of newly developed HCC cases by the person-years of follow-up. The cumulative rate of HCC was calculated using the Kaplan–Meier analysis and differences were evaluated by the log-rank test. The risk predictors of HCC were evaluated by univariate and multivariate logistic regression. Four logistic regression models were generated: gender plus age only (Model 1); gender, age, viral factors, plus alcohol use (Model 2); gender, age, viral factors, alcohol use, plus disease severity (Model 3); and gender, age, viral factors, alcohol use, disease severity, plus blood tests (Model 4). Factors with *p* values of <0.05 were tested by multivariate logistic analysis. A *p* value of <0.05 was considered significant. All analyses were performed using the Statistical Package for Social Sciences (SPSS, version 15.0; Chicago, IL, USA).

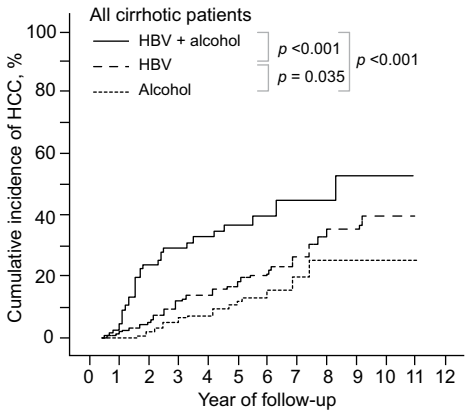
Results

Baseline characteristics

The baseline characteristics of cirrhotic patients with concomitant HBV infection and alcoholism, HBV infection alone, and alcoholism alone are presented in Table 1. The rate was 13.7%, 65.4%, and 20.9% in cirrhotic patients with concomitant HBV infection and alcoholism, HBV infection alone, and alcoholism alone, respectively. The cirrhotic patients were found to be predominantly male. The mean age of patients with concomitant HBV infection and alcoholism was significantly younger than that in patients with HBV infection alone or alcoholism alone (43.9 *vs.* 47.8 *vs.* 49.3 years, $p = 0.03$). The rate of Child-Pugh class A with concomitant HBV infection and alcoholism was significantly less than that in patients with HBV infection alone or alcoholism alone (46% *vs.* 57% *vs.* 54%, $p = 0.04$).

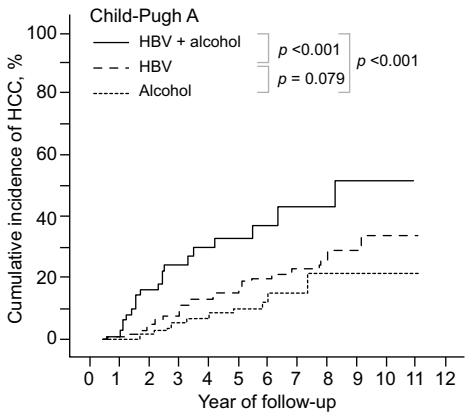
Newly developed HCC in all cirrhotic patients

Thirty-eight (28.8%), 100 (15.8%), and 21 (10.4%) patients with concomitant HBV infection and alcoholism, HBV infection alone, and alcoholism alone, respectively, were found to have newly developed HCC after 6 months of follow-up (Table 1). Three, 8, and 2 patients in the each group, respectively, had newly developed HCC within six months. The 1-, 3-, 5-, and 10-year cumulative incidence of HCC was 3.1%, 28.7%, 36.8%, and 52.8%, respectively, for the patients with concomitant HBV infection and alcoholism; 1.2%, 9.4%, 18.4% and 39.8%, respectively, for the patients with HBV infection alone; and 1.1%, 6.1%, 10.7% and 25.6%, respectively, for the patients with alcoholism alone (Fig. 1). The 10-year cumulative incidence of HCC was higher in patients with concomitant HBV infection and alcoholism than in those with HBV infection alone or alcoholism alone (52.8% *vs.* 39.8% *vs.* 25.6%, $p < 0.001$). The mean follow-up period was 2.9, 3.9, and 5.2 years for the patients with concomitant HBV infection and alcoholism, HBV infection alone, and alcoholism alone, respectively. The annual incidence of HCC was 9.9%, 4.1%,



	Year of follow-up											
Patients at risk	0	1	2	3	4	5	6	7	8	9	10	11
HBV + alcohol	132	119	63	44	36	28	15	10	8	5	3	0
HBV	632	542	484	436	318	290	90	40	26	19	2	2
Alcohol	202	176	159	145	116	107	36	17	11	9	2	1

Fig. 1. The cumulative incidence of HCC was higher in all cirrhotic patients with concomitant HBV infection and alcoholism than in those with HBV infection alone or alcoholism alone.



	Year of follow-up											
Patients at risk	0	1	2	3	4	5	6	7	8	9	10	11
HBV + alcohol	62	60	47	32	25	20	12	8	7	5	3	0
HBV	362	346	314	295	226	202	69	35	22	18	1	1
Alcohol	110	108	105	102	96	79	31	16	11	10	2	1

Fig. 2. The cumulative incidence of HCC was higher in compensated cirrhotic patients with concomitant HBV infection and alcoholism than in those with HBV infection alone or alcoholism alone.

and 2.1% for the patients with concomitant HBV infection and alcoholism, HBV infection alone, and alcoholism alone, respectively (Table 1).

Newly developed HCC in cirrhotic patients by Child-Pugh class

Among compensated cirrhotic patients, 20 (32.3%), 62 (17.2%), and 13 (11.8%) patients with concomitant HBV infection and

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Table 2. Multivariate regression models predicting hepatocellular carcinoma in cirrhotic patients with HBV infection and heavy alcoholism.

	Univariate		Multivariate							
			Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
General data										
Male	0.93 (0.33-2.64)	0.897	1.02 (0.36-2.91)	0.974	0.32 (0.14-7.26)	0.475	0.28 (0.01-9.90)	0.486	0.09 (0.01-72.7)	0.484
Age (yr)	0.96 (0.92-1.01)	0.074	0.96 (0.92-1.11)	0.074	0.98 (0.90-1.06)	0.562	0.98 (0.90-1.07)	0.683	1.10 (0.85-1.43)	0.468
Viral factors										
HBeAg positive	0.83 (0.56-6.62)	0.637			1.95 (0.35-10.9)	0.447	2.03 (0.36-11.7)	0.428	5.28 (0.50-62.3)	0.108
Baseline HBV DNA (per $\log_{10}$ copies/ml)	1.99 (1.46-3.66)	<0.001			11.6 (3.42-39.6)	<0.001	12.7 (3.38-47.8)	<0.001	16.8 (1.94-104)	0.025
HBV genotype B *vs.* C	2.19 (0.95-5.04)	0.066			0.85 (0.18-4.03)	0.834	1.08 (0.21-5.45)	0.927	1.26 (0.52-5.28)	0.523
Antiviral NUCs therapy	0.38 (0.17-0.83)	0.014			0.15 (0.01-0.15)	<0.001	0.14 (0.21-0.71)	0.001	0.01 (0.01-0.62)	0.035
Alcohol use										
Intake (g/day)	1.01 (1.00-1.01)	0.023			1.01 (0.99-1.01)	0.246	1.01 (1.00-1.02)	0.134	1.01 (0.98-1.03)	0.310
Intake duration (yr)	0.92 (0.86-0.99)	0.020			1.04 (1.01-1.12)	0.043	1.03 (1.01-1.09)	0.049	1.02 (0.96-1.16)	0.148
Disease severity										
Child-Pugh class										
B *vs.* A	1.02 (0.46-2.63)	0.842					0.45 (0.07-3.12)	0.420	0.28 (0.05-6.35)	0.281
C *vs.* A	0.43 (0.16-1.21)	0.112					0.16 (0.16-1.59)	0.118	1.78 (0.01-52.4)	0.687
Blood tests										
AST (IU/L)	1.02 (0.99-1.04)	0.214							1.01 (0.99-1.03)	0.404
ALT (IU/L)	1.00 (0.99-1.01)	0.761							0.98 (0.89-1.06)	0.543
Total bilirubin (mg/dl)	1.28 (0.98-2.69)	0.164							1.84 (0.86-3.93)	0.119
Alkaline phosphatase (IU/L)	1.06 (0.99-1.38)	0.153							0.99 (0.98-1.01)	0.711
Albumin (g/dl)	2.73 (0.96-6.23)	0.083							3.69 (0.11-28.9)	0.471
α-fetoprotein (ng/ml)	1.09 (1.04-1.11)	0.001							1.18 (1.01-1.38)	0.045

Multivariate regression models were generated sequentially with gender plus age (Model 1), gender, age, viral factors, plus alcohol use (Model 2), gender, age, viral factors, alcohol use, plus disease severity (Model 3), and gender, age, viral factors, alcohol use, disease severity, plus blood tests (Model 4), respectively.
OR, odds ratio; CI, confidence interval; NUCs, nucleos(t)ides; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

alcoholism, HBV infection alone, and alcoholism alone, respectively, were found to have newly developed HCC after 6 months of follow-up. The 1-, 3-, 5-, and 10-year cumulative incidence of HCC was 3.2%, 24.5%, 32.9% and 51.5%, respectively, for the patients with concomitant HBV infection and alcoholism; 0.6%, 7.8%, 15.3% and 33.8%, respectively, for the patients with HBV infection alone; and 0%, 4.8%, 8.9% and 21.4%, respectively, for the patients with alcoholism alone (Fig. 2). The 10-year cumulative incidence of HCC was higher in the patients with concomitant HBV infection and alcoholism than those with HBV infection alone or alcoholism alone (51.5% *vs.* 33.8% *vs.* 21.4%, p <0.001). The annual incidence of HCC was 7.8%, 3.7%, and 1.9% for the patients with concomitant HBV infection and alcoholism, HBV infection alone, and alcoholism alone, respectively. For cirrhotic patients with Child-Pugh class B and C, the cumulative incidence of HCC did not show a statistical significance.

Risk predictors of HCC

In cirrhotic patients with concomitant HBV infection and alcoholism, baseline serum HBV DNA level, antiviral NUCs therapy, serum α-fetoprotein, daily amount of alcohol intake, and years of alcohol intake were significantly associated with the incidence of HCC by univariate analyses (Table 2). Furthermore, in a series of multivariate logistic regression models (Table 2), there was not a significant association between gender, age, and incidence of HCC in Model 1. In Model 2, baseline serum HBV DNA levels [odds ratio (OR) = 11.6; 95% confidence interval (CI): 3.42–39.6, p <0.001], antiviral NUCs therapy (OR = 0.15; 95% CI: 0.01–0.15, p <0.001), and years of alcohol intake (OR = 1.04; 95% CI: 1.01–1.12, p = 0.043) were significantly associated with the incidence of HCC. The influence of daily amount of alcohol intake on the incidence of HCC was attenuated when age, gender, HBeAg positive, baseline serum HBV DNA, HBV genotype B *vs.* C, antiviral NUCs therapy, and years of alcohol intake were included in Model 2. In Model 3, baseline serum HBV DNA levels (OR = 12.7; 95% CI: 3.38–47.8, p <0.001), antiviral NUCs therapy (OR = 0.14; 95% CI: 0.21–0.71, p = 0.001), and years of alcohol intake (OR = 1.03; 95% CI: 1.01–1.09, p = 0.049) remained significantly associated with the incidence of HCC. The influence of daily amount of alcohol intake on the incidence of HCC was attenuated when age, gender, HBeAg positive, baseline serum HBV DNA, HBV genotype B *vs.* C, antiviral NUCs therapy, years of alcohol intake, Child-Pugh class B *vs.* A, and Child-Pugh C *vs.* A were included in Model 3. In Model 4, baseline serum HBV DNA levels (OR = 16.8; 95% CI: 1.94–104, p = 0.025), and antiviral NUCs therapy (OR = 0.01; 95% CI: 0.01–0.62, p = 0.035) were still significantly associated with the incidence of HCC. Moreover, serum α-fetoprotein

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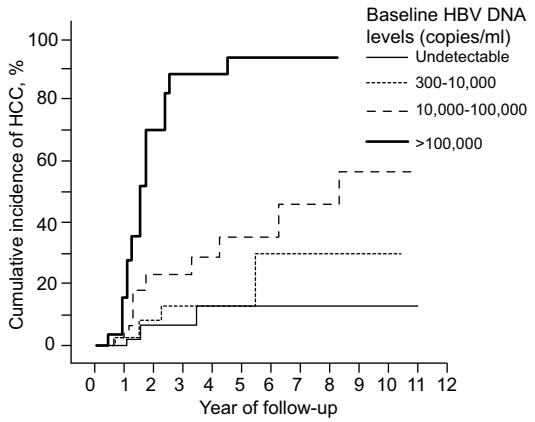
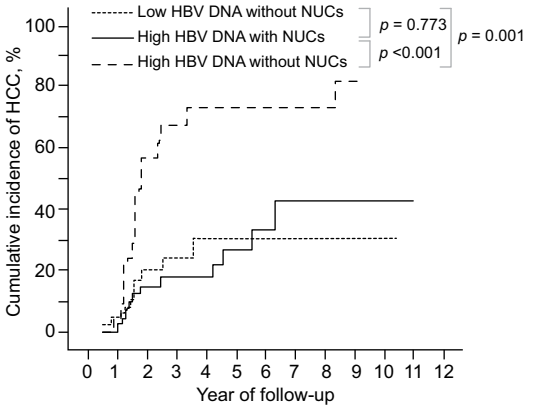


	Year of follow-up											
Patients at risk	0	1	2	3	4	5	6	7	8	9	10	11
>100,000	25	23	5	2	2	1	1	1	1	0	0	
10,000-100,000	31	27	13	13	12	8	7	5	5	3	1	
300-10,000	44	39	23	13	7	7	3	2	1	1	1	
Undetectable	32	29	22	16	15	12	4	2	1	1	1	

Fig. 3. Alcoholic cirrhotic patients with higher HBV DNA load had a significantly increased incidence of hepatocellular carcinoma.



	Year of follow-up											
Patients at risk	0	1	2	3	4	5	6	7	8	9	10	11
High HBV DNA without NUCs	21	20	8	6	5	5	4	3	3	1	0	0
High HBV DNA with NUCs	71	65	32	22	20	12	8	5	4	3	2	0
Low HBV DNA without NUCs	40	34	23	16	11	11	3	2	1	1	1	0

Fig. 4. Antiviral nucleos(t)ides reduced the cumulative incidence of hepatocellular carcinoma in cirrhotic patients with concomitant HBV infection and alcoholism.

(OR = 1.18; 95% CI: 1.01–1.38, $p = 0.045$) was significantly associated with the incidence of HCC. The influence of daily amount of alcohol intake and years of alcohol intake on the incidence of HCC was attenuated when age, gender, HBeAg positive, baseline serum HBV DNA, HBV genotype B *vs.* C, antiviral NUCs therapy, Child-Pugh class B *vs.* A, Child-Pugh C *vs.* A, serum AST, serum ALT, serum total bilirubin, serum alkaline phosphatase, serum albumin, and serum α-fetoprotein were included in Model 4. In addition, the cumulative incidence of HCC during the follow-up period was significantly higher in those patients with higher baseline serum HBV DNA levels than those with lower baseline serum HBV DNA levels (Fig. 3). For patients with HBV viremia, the cumulative incidence of HCC was reduced by antiviral NUCs therapy (Fig. 4).

Discussion

Our data showed that the 5-year cumulative incidence of HCC is 10.7% in alcoholic cirrhotic patients. Our data also showed that alcoholic cirrhotic patients with concomitant HBV infection have significantly higher incidence of HCC than those with HBV infection alone or alcoholism alone. The 5-year cumulative incidence of HCC was up to 36.8% in the patients with concomitant HBV infection and alcoholism. Our findings are consistent with earlier studies that found the synergism between severe alcohol abuse and viral hepatitis infection increases the incidence of HCC [4–7,24,25].

Our data also confirmed that HCC occurred at younger age in patients with concomitant HBV infection and alcoholism than those with HBV infection alone or alcoholism alone (43.9 *vs.* 47.8 *vs.* 49.3 years, $p = 0.03$). Moreover, the rate of Child-Pugh class A with concomitant HBV infection and alcoholism was significantly less than that with HBV infection alone or alcoholism alone (46% *vs.* 57% *vs.* 54%, $p = 0.04$). The synergism between alcoholism and HBV infection leads to more severe liver disease and earlier occurrence of HCC. Therefore, alcoholic cirrhotic patients with concomitant HBV infection should be closely screened for HCC.

Our data showed that alcoholic cirrhotic patients with higher serum HBV DNA levels had higher incidence of HCC than those with lower serum HBV DNA levels at the study entry. Our findings confirm that increasing HBV DNA levels precipitate the progression of liver cirrhosis to HCC. Our data are compatible with the large nationwide REVEAL-HBV study in Taiwan [13–15] for CHB without alcoholism, which showed serum HBV DNA at study entry is a significant risk predictor of HCC. Therefore, baseline serum HBV DNA level is a risk predictor of HCC in cirrhosis with concomitant HBV infection and alcoholism. To the best of our knowledge, this finding has not previously been reported in the literature.

Antiviral NUCs therapy has been widely used for the treatment of HBV-related cirrhosis [19,20]. Our study showed that antiviral NUCs therapy significantly reduces the incidence of HCC in alcoholic cirrhotic patients with concomitant HBV infection. Our findings are consistent with recent large-population, international studies, which showed antiviral NUCs therapy reduced the incidence of HCC in CHB patients without alcoholism [18,26–29]. Therefore, aggressive antiviral NUCs therapy should be considered in alcoholic cirrhosis with detectable serum HBV DNA, in order to reduce the incidence of HCC. To the best of our knowledge, the use of antiviral NUCs therapy to reduce the incidence of HCC in alcoholic cirrhosis with concomitant HBV infection has not been previously reported.

The limitations of the study include the following: the retrospective study might have resulted in unintended bias; in addition, 45% of patients did not have a liver biopsy to confirm the diagnosis of cirrhosis because of hepatic failure with coagulopathy, and massive ascites. Although these patients had upper

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endoscopies to confirm the presentation of esophageal varices, the lack of a biopsy might lead to an underestimation of cirrhosis in the patient population.

In conclusion, alcoholic cirrhotic patients with concomitant HBV infection have significantly higher incidence of HCC than those with HBV infection alone or alcoholism alone. The occurrence of HCC was at younger ages in patients with concomitant HBV infection and alcoholism than those with HBV infection alone or alcoholism alone. Elevated HBV DNA levels were a strong risk predictor of HCC in alcoholic cirrhotic patients with concomitant HBV infection. Antiviral NUCs therapy significantly reduces the incidence of HCC in alcoholic cirrhotic patients with concomitant HBV infection. Aggressive antiviral NUCs therapy should be considered in alcoholic cirrhosis with detectable serum HBV DNA in order to reduce the incidence of HCC.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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