探討大量飲酒、ALDH2 rs671基因多型性和B型肝炎感染在肝硬化患者的肝癌發生率及整體死亡率的相關性

Association of Heavy Alcohol Intake and *ALDH2* rs671 Polymorphism With Hepatocellular Carcinoma and Mortality in Patients With Hepatitis B Virus-Related Cirrhosis

Pojen Hsiao MD [1,5] , Pei-Min Hsieh, MD [3,4] , Yu-Chan Li [1,5] , Yaw-Sen Chen MD [3,5] , Chih-Wen Lin, MD, PhD [1,2,5]

[1]Division of Gastroenterology and Hepatology, E-Da Dachang Hospital, I-Shou University, Kaohsiung; [2]Division of Gastroenterology and Hepatology, Department of Medicine, E-Da Hospital, I-Shou University, Kaohsiung; [3]Department of Surgery, E-Da Hospital, I-Shou University, Kaohsiung; [4]Department of Surgery, E-Da Cancer Hospital, I-Shou University, Kaohsiung; [5]School of Medicine, College of Medicine, I-Shou University, Kaohsiung; Taiwan.

INTRODUCTION

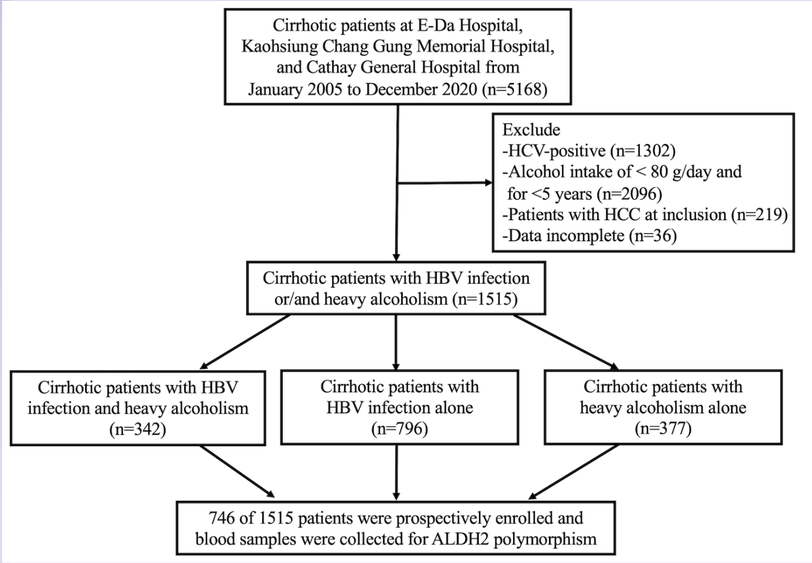
- Hepatitis B virus (HBV) infection and alcoholism are risk factors for hepatocellular carcinoma (HCC) and mortality.
- The synergistic effect of alcohol intake and HBV infection on clinical prognosis has been reported.
- Our previous study demonstrated that heavy alcohol consumption promoted the incidence of HCC in HBV-related cirrhosis and that antiviral therapy reduced the risk of HCC in cirrhotic patients with HBV infection and alcoholism.
- About 45% of Han Chinese (East Asians) carry a single point mutation in aldehyde dehydrogenase 2*2 (ALDH2).
- The ALDH2 polymorphism is an effect of the development of HCC in alcoholic liver disease.

AIMS

This study aims to investigate the impact of heavy alcohol intake, ALDH2 polymorphism and HBV infection on the clinical prognosis of cirrhotic patients

METHOD

Study flowchart for the inclusion of participants

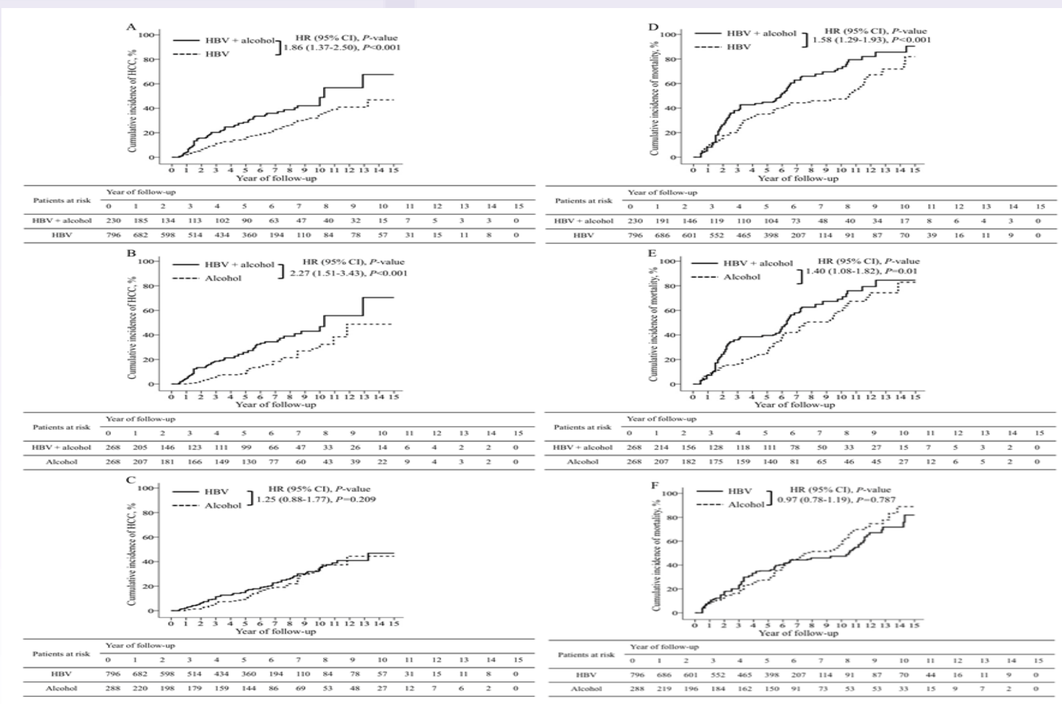


- We followed these patients until June 2021.
- All patients were followed up for more than 6 months.
- Heavy alcohol intake was defined as consuming more than 80g of ethanol each day for at least 5 years.
- The primary endpoint was newly developed HCC and the secondary endpoint was overall mortality after more than six months of follow-up.

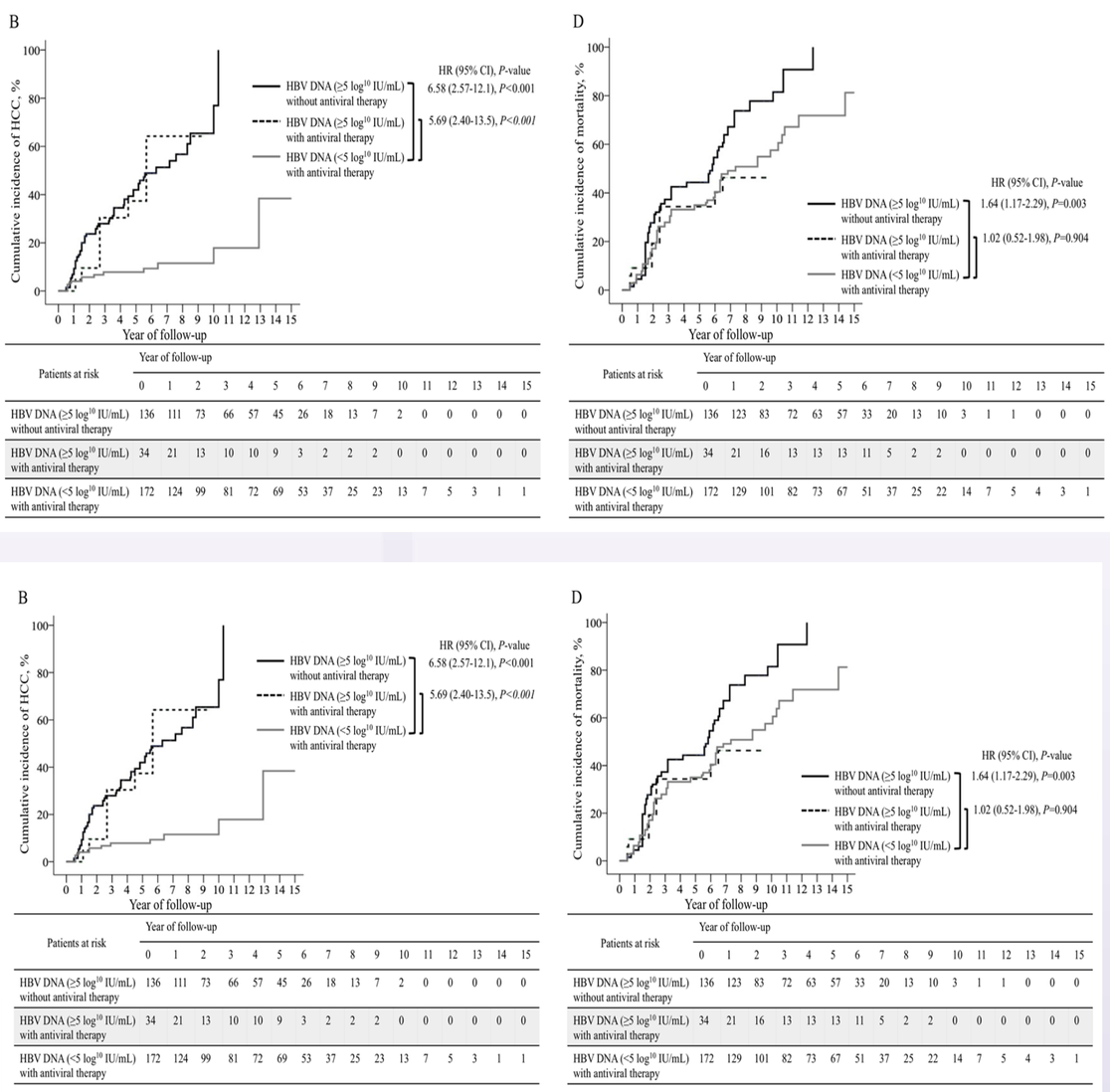
RESULTS

Table 1. Demographic data of all cirrhotic patients

Characteristics	Total cohort (n=1515)	HBV + alcoholism (n =342)	HBV (n =796)	Alcoholism (n = 377)	*P*-value*
Gender (male)	1277 (84.3)	314 (91.8)a	647 (81.3)	316 (83.8)c	<0.001
Age (years)	49 (21-77)	44 (21-72)a	49 (30-77)	49 (30-75)c	<0.001
BMI (kg/m^2)	23.6 (16.8-41.9)	25.1 (18.5-41.9)a	23.3 (16.8-37.3)	23.3 (16.8-40.8)c	<0.001
Alcohol intake (g/day)	12 (0-600)	160 (80-350)a	0 (0-20)b	150 (80-600)c	<0.001
Alcohol intake duration (years)	0 (0-30)	20 (5-30)a	0 (0-5)b	16 (5-30)	<0.001
Abstinence	408 (56.7)	171 (50)	N/A	237 (62.9)c	<0.001
ALDH2 polymorphisms					
GG	329 (44.1)	157 (55.4)a	81 (33.1)b	81 (44.0)c	<0.001
GA/AA	417 (55.9)	137 (44.6)	164 (66.9)	116 (56.0)	
AST (IU/L)	110 (18-1133)	86 (18-1133)a	114 (18-491)	113 (24-491)c	<0.001
ALT (IU/L)	43 (10-488)	45 (13-278)	43 (10-488)	41 (10-252)	0.706
Total bilirubin (mg/dL)	2.1 (0.3-37.9)	1.7 (0.3-19.9)a	2.1 (0.4-37.9)	2.1 (0.5-37.9)c	<0.001
Alkaline phosphatase (IU/L)	298 (33-1484)	311 (88-1484)a	275 (60-889)b	324 (33-1092)c	<0.001
γ-GT (IU/L)	214 (11-1992)	179 (14-1992)	213 (11-1240)	287 (11-1240)c	0.71
Albumin (g/dL)	3.2 (1.8-4.8)	3.2 (2.0-4.8)	3.2 (1.8-4.8)	3.3 (1.8-4.6)	0.58
Platelet count (x10^3/mL)	92 (33-633)	76 (17-286)a	99 (33-633)	94 (33-633)c	<0.001
INR	1.2 (0.88-2.9)	1.1 (0.9-2.3)a	1.2 (0.9-2.9)	1.2 (0.9-2.9)	0.043
α-fetoprotein (ng/mL)	5 (1-866)	6.5 (1-886)a	5 (1-660)	5 (1-660)	0.088
HBsAg-positive	1138 (75.1)	342 (100)	796 (100)b	0 (0)c	<0.001
HBeAg-positive	360 (23.8)	90 (26.3)a	270 (33.9)b	0 (0)c	<0.001
Baseline HBV DNA (log^{10} IU/mL)	3.8 (0-9.0)	4.1 (0-9.0)	5.3 (0-9.0)b	0 (0)c	<0.001
Baseline HBV DNA (≥5 log^{10} IU/mL)	449 (29.6)	136 (39.8)	313 (39.3)b	0 (0)c	<0.001
Antiviral NUCs therapy - positive	975 (64.5)	308 (90.1)a	667 (83.8)b	0 (0)c	<0.001
Child-Pugh class					
A	644 (42.5)	172 (50.3)a	317 (39.8)	155 (41.1)c	<0.001
B	553 (36.5)	85 (24.9)a	316 (39.7)	152 (40.3)c	<0.001
C	318 (21)	85 (24.7)a	163 (20.5)	70 (18.6)c	<0.001
Follow up time (year)	5.0 (0.5-15)	2.8 (0.5-15)a	5.0 (0.5-15)	5.1 (0.5-15)	<0.001
HCC development	270 (17.8)	81 (23.7)a	134 (16.8)	55 (14.6)c	0.004
Annual HCC incidence (%/year)	3.5	5.9a	3.6	2.9c	<0.001
Mortality	627 (41.4)	155 (45.3)	322 (40.5)	150 (39.8)	0.238
Annual mortality incidence (%/year)	8.3	11.3a	8.6	7.9c	<0.001



The cumulative incidences of HCC (A) and mortality (B) were significantly higher in cirrhotic patients with concomitant HBV infection and alcoholism than in those with HBV infection alone or alcoholism alone after after propensity score matching.



Patients at risk	Year of follow-up															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HBV DNA (≥5 log10 IU/mL) without antiviral therapy	136	111	73	66	57	45	26	18	13	7	2	0	0	0	0	0
HBV DNA (≥5 log10 IU/mL) with antiviral therapy	34	21	13	10	10	9	3	2	2	2	0	0	0	0	0	0
HBV DNA (<5 log10 IU/mL) with antiviral therapy	172	124	99	81	72	69	53	37	25	23	13	7	5	3	1	1

Patients at risk	Year of follow-up															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HBV DNA (≥5 log10 IU/mL) without antiviral therapy	136	123	83	72	63	57	33	20	13	10	3	1	1	0	0	0
HBV DNA (≥5 log10 IU/mL) with antiviral therapy	34	21	16	13	13	13	11	5	2	2	0	0	0	0	0	0
HBV DNA (<5 log10 IU/mL) with antiviral therapy	172	129	101	82	73	67	51	37	25	22	14	7	5	4	3	1

The cumulative incidences of HCC and mortality according to alcohol intake with the ALDH2 polymorphism and serum HBV DNA levels with antiviral NUC therapy.

Patients with the GA/AA allele with alcohol intake >160 g/day were remarkably correlated with increased incidences of HCC and mortality compared with patients with the GG allele with alcohol intake 80-160 g/day (A and C).

Table 2. ALDH2 rs671 polymorphism is significantly associated with a higher risk of HCC development and related mortality

Characteristics	ALDH2 polymorphisms	Total cohort (n=746)	HBV + alcoholism (n =294)	HBV (n =245)	Alcoholism (n = 207)	P-value*
Genotypes	GG	329 (44.1)	157 (55.4)a	81 (33.1)b	81 (44.0)c	<0.001
	GA/AA	417 (55.9)	137 (44.6)	164 (66.9)	116 (56.0)	
HCC development	GG	36 (10.9)	7/157 (4.5)a	23/81 (28.4)b	6/91 (6.6)c	<0.001
	GA/AA	147 (35.3)	66/137 (48.2)	50/164 (30.5)	31/116 (26.7)	
	HR (95% CI)	12.6 (5.80-27.6)	10.5 (4.80-22.8)	1.13 (0.68-1.91)	4.68 (1.94-11.2)	
	P-value#	<0.001	<0.001	0.62	0.001	
Mortality	GG	109 (33.1)	51/157 (42.5)a	36/81 (44.4)b	22/91 (24.2)c	<0.001
	GA/AA	250/417 (60.0)	91/137 (66.4)	82/164 (50.0)	77/116 (66.4)	
	HR (95% CI)	1.46 (1.04-2.05)	1.55 (1.09-2.19)	0.99 (0.67-1.47)	3.01 (1.87-4.86)	
	P-value#	0.027	0.012	0.969	<0.001	

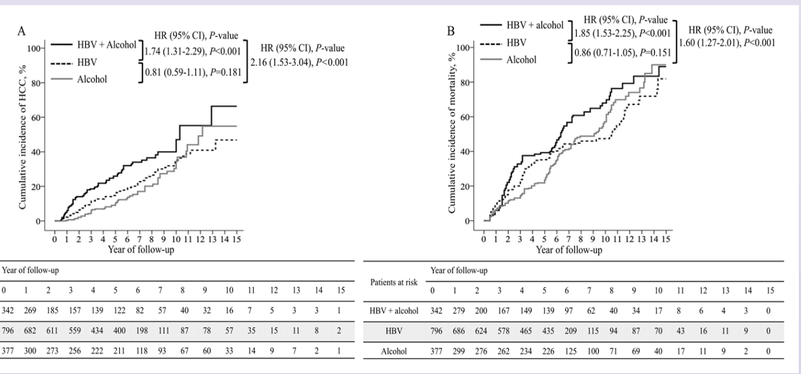
a: *P*-value < 0.05, HBV and alcoholism *vs.* HBV; b: *P*-value < 0.05, HBV and alcoholism *vs.* alcoholism; c: *P*-value < 0.05, HBV *vs.* alcoholism; *P*-value is used by Chi-squared tests.
*: *P*-value is used by one-way ANOVA test among three groups.
#: *P*-value is used by Cox regression analyses.

Patients at risk	Year of follow-up															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HBV DNA (≥5 log10 IU/mL) without antiviral therapy	136	111	73	66	57	45	26	18	13	7	2	0	0	0	0	0
HBV DNA (≥5 log10 IU/mL) with antiviral therapy	34	21	13	10	10	9	3	2	2	2	0	0	0	0	0	0
HBV DNA (<5 log10 IU/mL) with antiviral therapy	172	124	99	81	72	69	53	37	25	23	13	7	5	3	1	1

Patients at risk	Year of follow-up															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HBV DNA (≥5 log10 IU/mL) without antiviral therapy	136	123	83	72	63	57	33	20	13	10	3	1	1	0	0	0
HBV DNA (≥5 log10 IU/mL) with antiviral therapy	34	21	16	13	13	13	11	5	2	2	0	0	0	0	0	0
HBV DNA (<5 log10 IU/mL) with antiviral therapy	172	129	101	82	73	67	51	37	25	22	14	7	5	4	3	1

Patients with high serum HBV DNA without antiviral NUC therapy were remarkably correlated with increased incidences of HCC and mortality compared with patients with low serum HBV DNA with antiviral NUC therapy (B and D).

The cumulative incidences of HCC (A) and mortality (B) were higher in cirrhotic patients with concomitant HBV infection and alcoholism than those with HBV infection alone or alcoholism alone.



Patients at risk	Year of follow-up															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HBV + alcohol	342	269	185	157	139	122	82	57	40	32	16	7	5	3	3	1
HBV	796	682	611	559	434	400	198	111	87	78	57	35	15	11	8	2
Alcohol	377	300	273	256	222	211	118	93	67	60	33	14	9	7	2	1

Patients at risk	Year of follow-up															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
HBV + alcohol	342	279	200	167	149	139	97	62	40	34	17	8	6	4	3	0
HBV	796	686	624	578	465	435	209	115	94	87	70	43	16	11	9	0
Alcohol	377	299	276	262	234	226	125	100	71	69	40	17	11	9	2	0

CONCLUSION

- **Cirrhotic patients with concomitant HBV infection and heavy alcoholism had significantly higher incidences of HCC development and mortality than those with HBV infection alone or alcoholism before and after PSM.**
- **Heavy alcohol intake and ALDH2 rs671 polymorphism significantly increased the incidence and risk of HCC and mortality in HBV-related cirrhotic patients.**

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