Original Article

Association of hepatitis B e antigen and DNA viral load with severity of liver dysfunction and in-hospital outcomes in hepatitis B-related liver cirrhosis

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Background: Hepatitis B virus (HBV) infection is a common cause of liver cirrhosis. Our study aimed to evaluate the clinical relevance of hepatitis B e antigen (HBeAg) and HBV DNA viral load in HBV-related liver cirrhosis.

Methods: All HBV-related cirrhosis patients consecutively admitted to our hospital between January 2012 and June 2014 were retrospectively reviewed. Clinical profiles were collected. HBV DNA viral load would be detectable, if HBV DNA viral load was >200 IU/mL.

Results: Overall, 428 patients were included. The prevalence of positive HBeAg was 11.9% (40/335). HBeAg-positive patients had significantly higher proportions of moderate-large ascites and Child-Pugh class B/C than HBeAg-negative patients. The in-hospital mortality was not significantly different between them. The prevalence of detectable HBV DNA viral load was 38.25% (109/285). Patients with detectable HBV DNA viral load had a significantly higher proportion of moderate-large ascites and higher Child-Pugh and model for end-stage liver disease (MELD) scores than patients with undetectable HBV DNA viral load. The in-hospital mortality was not significantly different between them. The prevalence of HBV DNA viral load >2,000 IU/mL was 31.9% (91/285). Patients with HBV DNA viral load >2,000 IU/mL had significantly higher proportions of moderate-large ascites and in-hospital death and higher Child-Pugh and MELD scores than patients with HBV DNA viral load <2,000 IU/mL. After adjusting Child-Pugh score, HBV DNA viral load >2,000 IU/mL was not significantly associated with in-hospital death (odds ratio =2.154, P=0.272).

Conclusions: In HBV-related cirrhosis, HBeAg and HBV DNA viral load were significantly associated with the severity of liver dysfunction, but not independently associated with in-hospital death.

Keywords: Liver cirrhosis; hepatitis B virus (HBV); survival; mortality; Child-Pugh

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Introduction

About 240 million people are infected with hepatitis B virus (HBV) worldwide (1). In patients with untreated chronic hepatitis B, the 5-year cumulative incidence of cirrhosis ranges from 8% to 20% (2). The 5-year mortality in patients with cirrhosis is 14–35% (3-7). Notably, 60% of cases with liver cirrhosis result from HBV infection in China (8).

Chronic HBV patients usually present either as positive or negative hepatitis B e antigen (HBeAg). Traditionally, the natural history of chronic HBV infection is usually divided into the immune tolerant phase, immune reactive HBeAg-positive phase, inactive HBV carrier state, HBeAg-negative chronic HBV infection phase, and HBsAg-negative phase (9-11). According to the updated guidelines, the natural history is defined as follows: HBeAg-positive chronic HBV infection, HBeAg-positive chronic hepatitis B, HBeAg-negative chronic HBV infection, HBeAg-negative chronic hepatitis B, and HBsAg-negative phase (2). HBV DNA viral load also plays an important role in the diagnosis and treatment of chronic HBV infection. As HBV continues to infect the liver, repeated inflammatory necrosis results in the regeneration and repair and activation of hepatic stellate cells. The abnormal deposition of extracellular matrix induces liver fibrosis and ultimately leads to liver cirrhosis (9,12). While the role of HBeAg status and HBV DNA viral levels for estimating the risk of individuals to progress to liver cirrhosis or hepatocellular carcinoma is well established in Asian and Caucasian cohorts (2), their clinical relevance as biomarkers in patients with HBV-related liver cirrhosis for complications and short-term mortality is unclear.

Herein, we conducted a retrospective monocentric study to evaluate the impact of HBeAg status and HBV DNA viral load on the clinical profiles and in-hospital mortality of patients with HBV-related liver cirrhosis.

Methods

Study design

All liver cirrhosis patients with chronic HBV infection who were consecutively admitted to our hospital between January 2012 and June 2014 were considered eligible for the study. All eligible patients were positive for HBsAg. The exclusion criteria were as follows: liver cancer or co-diagnosed with other malignant tumors; co-infection with hepatitis C virus or other chronic liver diseases; and a history of alcohol abuse. As our study endpoint was the in-hospital death, repeated admissions were included. The study protocol was approved by the Medical Ethical Committee of our hospital. The approval number was No. k[2015]39.

Laboratory tests

The following data were collected at the moment of the subjects' admissions: age, sex, red blood cell count (RBC), hemoglobin (Hb), white blood cell count (WBC), platelet count (PLT), total bilirubin (TBIL), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), sodium (Na), kalium (K), international normalized ratio (INR), acute upper gastrointestinal bleeding (AUGIB), HBsAg, hepatitis B surface antibody (HBsAb), HBeAg, hepatitis B e antibody (HBeAb), hepatitis B core antibody (HBcAb), and HBV DNA viral load. Child-Pugh and model for end-stage liver disease (MELD) scores were calculated according to the results of laboratory tests and grades of ascites and hepatic encephalopathy (HE) (13,14). In-hospital death was recorded.

The serum HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb expression and quantification of HBV DNA viral load were detected by the electrochemiluminescence immunoassay with relevant reagents (Huake Co. Ltd., Shanghai, China) at the Department of Laboratory Medicine of our hospital. Detectable HBV DNA viral load was defined as HBV DNA viral load was more than 200 IU/mL (1 IU/mL=5 copies/mL) (15).

Definition and diagnosis

Chronic HBV infection is defined as hepatitis B surface antigen (HBsAg) positivity for more than 6 months. The

clinical diagnosis of liver cirrhosis is made on the basis of clinical presentations, medical imaging examination, and laboratory abnormalities (16,17). Ascites is classified as three grades: (I) mild ascites only detectable by ultrasound; (II) moderate ascites with symmetrical distension of the abdomen; and (III) tense ascites (18,19). Hepatic encephalopathy (HE) manifests as impaired disturbance of consciousness, abnormal behavior, or coma (20).

Statistical analysis

Statistical analysis was performed using the SPSS statistics 17.0.0 software. Continuous data were expressed as mean ± standard deviation or median (range), and were compared by the non-parametric tests. Categorical data were expressed as frequency (percentage), and were compared by the Chi-square tests. The correlation analyses were performed by the Spearman rank test. Logistic regression analyses were performed to check the independent risk factor for in-hospital death. A two-sided P<0.05 was considered to be statistically significant.

Results

A total of 428 HBsAg-positive patients with liver cirrhosis were enrolled in this study. Among them, 284 (284/428, 66.4%) patients were male, and the median age was 53.91 years (range, 25.62–86.93 years). The proportion of positive HBsAg, positive HBeAb, and detectable HBV DNA viral load was 11.9% (40/335), 50.7% (170/335), and 38.25% (109/285), respectively. None (0/428) had positive HBsAb. The median HBV DNA viral load in 109 patients with detectable HBV DNA viral load was 94,000 IU/mL (range, 220–48,000,000 IU/mL). The in-hospital mortality was 3.7% (16/428). The patient characteristics were shown in *Table 1*. The causes of death were as follows: gastrointestinal bleeding (n=5), sudden death and pulmonary embolism (n=1), and liver failure with multiple organ failure (n=10).

Comparison between HBeAg-negative and HBeAg-positive patients

Compared with HBeAg-negative patients, HBeAg-positive patients had significantly higher HBV DNA viral load, ALT, AST, ALP, GGT, and Child-Pugh score, higher proportions of moderate-large ascites and Child-Pugh class B-C, and lower ALB (*Table 2*). The in-hospital mortality was not significantly different between HBeAg-negative and HBeAg-positive patients (3.7% *vs.* 2.5%, P=0.695). After adjusting the Child-Pugh score, the HBeAg status remained not associated with in-hospital death in a multivariate logistic regression analysis (odds ratio =0.494; 95% CI, 0.057–4.274; P=0.522).

Comparison between patients with undetectable and detectable HBV DNA viral load

Compared with patients with undetectable HBV DNA viral load, patients with detectable HBV DNA viral load were significantly older and had significantly higher Hb, TBIL, ALT, AST, ALP, GGT, Cr, INR, Child-Pugh score, and MELD score, higher proportions of moderate-large ascites and Child-Pugh class B-C, lower ALB and Ca, and a lower proportion of AUGIB (*Table 3*). The in-hospital mortality was not significantly different between patients with undetectable and detectable HBV DNA viral load (2.3% *vs.* 6.4%, P=0.077). After adjusting the Child-Pugh score, detectable HBV DNA viral load remained not associated with in-hospital death in a multivariate logistic regression analysis (odds ratio =1.919; 95% CI, 0.486–7.578; P=0.353).

Comparison between patients with HBV DNA viral load <2,000 and >2,000 IU/Ml

Compared with patients with HBV DNA viral load <2,000 IU/mL, patients with HBV DNA viral load >2,000 IU/mL were significantly older and had significantly higher Hb, TBIL, ALT, AST, ALP, GGT, Cr, INR, Child-Pugh score, and MELD score, higher proportions of moderate-large ascites and Child-Pugh class B-C, lower ALB, Ca, and Na, and a lower proportion of AUGIB (*Table 4*). The in-hospital mortality was higher in patients with HBV DNA viral load >2,000 IU/mL than in those with HBV DNA viral load <2,000 IU/mL (7.7% *vs.* 2.1%, P=0.021). After adjusting the Child-Pugh score, HBV DNA viral load >2,000 IU/mL was not an independent risk factor for in-hospital death in a multivariate logistic regression analysis (odds ratio =2.154; 95% CI, 0.548–8.468; P=0.272).

Correlation analysis of HBV DNA viral load

In 109 patients with detectable HBV DNA, the HBV DNA viral load positively correlated with ALT, AST, ALP, BUN, INR, Child-Pugh score, and MELD score, and negatively correlated with RBC, Hb, ALB, and Ca (*Table 5*).

Table 1 Patient characteristics

Variables	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)
Age (years)	428	53.54±10.95	53.91 (25.62–86.93)
Sex (male/female)	428	284 (66.4)/144 (33.6)	
HBsAg (negative/positive)	428	0 (0)/428 (100.0)	
HBsAb (negative/positive)	335	335 (100.0)/0 (0)	
HBeAg (negative/positive)	335	295 (88.1)/40 (11.9)	
HBeAb (negative/positive)	335	165 (49.3)/170 (50.7)	
HBcAb-IgG (negative/positive)	335	22 (6.6)/313 (93.4)	
HBcAb-IgM (negative/positive)	335	333 (99.4)/2 (0.6)	
HBV DNA load (undetectable/detectable)	285	176 (61.8)/109 (38.2)	
HBV DNA vial load in patients with detectable HBV DNA load (>200 IU/mL)	109	1,237,000±5,290,716	94,000 [220–48,000,000]
Ascites	427		
No		244 (57.1)	
Mild		51 (11.9)	
Moderate and large		132 (30.9)	
HE	427		
No		409 (95.8)	
Grade I–II		15 (3.5)	
Grade III–IV		3 (0.7)	
AUGIB	427	128 (30.0)	
RBC (10^{12}/L)	426	3.27±0.90	3.18 (0.98–5.45)
Hb (g/L)	426	97.52±31.57	94.50 (23.00–170.00)
WBC (10^9/L)	426	4.59±3.64	3.70 (0.30–29.10)
PLT (10^9/L)	426	89.40±83.77	70.50 (13.00–1,278.00)
TBIL (μmol/L)	423	33.15±64.11	19.60 (1.90–809.80)
ALB (g/L)	411	32.68±7.03	33.20 (14.20–52.80)
ALT (U/L)	424	52.46±185.14	28.00 (6.00–3,471.00)
AST (U/L)	424	89.34±603.01	34.00 (10.00–12,148.00)
ALP (U/L)	424	89.20±54.08	77.00 (29.00–586.00)
GGT (U/L)	424	54.04±64.76	32.00 (5.00–542.00)
BUN (mmol/L)	414	7.25±5.87	5.72 (2.03–61.88)
Cr (μmol/L)	414	76.31±92.80	58.00 (21.00–977.00)
K (mmol/L)	416	4.07±0.50	4.07 (2.56–7.87)
Na (mmol/L)	416	138.80±4.23	139.75 (116.40–148.50)

Table 1 *(continued)*

Table 1 *(continued)*

Variables	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)
Ca (mmol/L)	216	2.08±0.20	2.07 (1.61–2.89)
Blood ammonia (μmol/L)	192	50.89±51.42	40.50 (9.00–480.00)
INR	414	1.41±0.84	1.24 (0.83–13.40)
Child-Pugh score	398	7.16±2.01	7.00 (5.00–4.00)
Child-Pugh class	398		
A		185 (46.5)	
B		163 (41.0)	
C		50 (12.5)	
MELD score	402	6.74±7.53	4.93 (–6.91–51.64)
In-hospital death	428	16 (3.7)	

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; HBcAb, hepatitis B core antibody; HE, hepatic encephalopathy; AUGIB, acute upper gastrointestinal bleeding; RBC, red blood cell count; Hb, hemoglobin; WBC, white blood cell count; PLT, platelet count; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; K, kalium; Na, sodium; Ca, calcium; INR, international normalized ratio; MELD, model for end-stage liver disease.

Table 2 Comparison between HBeAg-negative and HBeAg-positive hepatitis B virus liver cirrhosis patients

Variables	HBeAg-negative			HBeAg-positive			P value
	No. of patients available	Mean±SD or frequency (percentage)	Median (range)	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	
Age (years)	295	54.21±10.70	54.31 (27.42–86.93)	40	55.77±12.64	57.43 (25.62–79.88)	0.247
Sex (male/female)	295	199 (67.5)/96 (32.5)		40	21 (52.5)/19 (47.5)		0.062
HBsAg (negative/positive)	295	0 (0)/295 (100.0)		40	0 (0)/40 (100.0)		–
HBsAb (negative/positive)	295	295 (100.0)/0 (0)		40	40 (100.0)/0 (0)		–
HBeAg (negative/positive)	295	295 (100.0)/0 (0)		40	0 (0) /40 (100.0)		<0.001
HBeAb (negative/positive)	295	126 (42.7)/169 (57.3)		40	39 (97.5)/1 (2.5)		<0.001
HBcAb-IgG (negative/positive)	295	18 (6.1)/277 (93.9)		40	4 (10.0)/36 (90.0)		0.379
HBcAb-IgM (negative/positive)	295	295 (100.0)/0 (0)		40	38 (99.4)/2 (0.6)		0.003
HBV DNA (undetectable/detectable)	248	168 (67.7)/80 (32.3)		32	4 (12.5)/28 (87.5)		<0.001
HBV DNA viral load in patients with detectable HBV DNA load (>200 IU/mL)	80	1,227,538±6,053,034	54,000 [220–48,000,000]	28	1,241,072±2,178,868	250,000 [600–48,000,000]	0.001

Table 2 *(continued)*

Table 2 *(continued)*

Variables	HBeAg-negative			HBeAg-positive			P value
	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	
Ascites	295			40			0.002
No		180 (61.0)			15 (37.5)		
Mild		39 (13.2)			4 (10.0)		
Moderate and large		76 (25.8)			21 (52.5)		
HE	295			40			0.623
No		281 (95.3)			39 (97.5)		
Grade I–II		11 (3.7)			1 (2.5)		
Grade III–IV		3 (1.0)			0 (0)		
AUGIB	295	83 (28.1)		40	8 (20.0)		0.278
RBC (10^{12}/L)	293	3.33±0.91	3.28 (0.98–5.45)	40	3.33±0.76	3.16 (1.87–5.33)	0.994
Hb (g/L)	293	98.58±32.27	97.00 (23.00–170.00)	40	104.55±29.38	104.50 (41.00–157.00)	0.220
WBC (10^9/L)	293	4.67±3.79	3.80 (0.30–29.10)	40	4.40±2.22	3.75 (1.50–11.20)	0.628
PLT (10^9/L)	293	85.91±56.02	71.00 (14.00–384.00)	40	103.60±80.07	66.50 (20.00–344.00)	0.483
TBIL (μmol/L)	293	33.20±63.98	19.80 (1.90–809.80)	40	46.61±101.21	20.90 (6.00–607.80)	0.445
ALB (g/L)	283	33.26±6.84	34.00 (14.20–52.80)	37	30.74±6.78	30.70 (17.90–48.80)	0.020
ALT (U/L)	294	56.55±220.17	28.00 (6.00–3,471.00)	40	61.93±57.05	38.50 (10.00–278.00)	0.002
AST (U/L)	294	101.13±718.90	33.50 (10.00–12148.00)	40	81.05±69.43	52.50 (15.00–304.00)	<0.001
ALP (U/L)	294	86.98±50.73	76.50 (29.00–586.00)	40	101.37±41.18	100.50 (41.00–226.50)	0.007
GGT (U/L)	294	53.07±62.75	32.00 (5.00–542.00)	40	70.00±81.45	50.00 (12.00–504.00)	0.024
BUN (mmol/L)	285	6.96±4.67	5.66 (2.03–46.54)	38	7.14±3.98	6.21 (2.43–20.66)	0.605
Cr (μmol/L)	285	76.00±99.58	58.40 (21.00–988.00)	38	75.41±53.25	59.50 (37.00–309.00)	0.806
K (mmol/L)	287	4.05±0.45	4.06 (2.56–5.81)	37	4.16±0.49	4.07 (3.34–5.80)	0.425

Table 2 *(continued)*

Table 2 *(continued)*

Variables	HBeAg-negative			HBeAg-positive			P value
	No. of patients available	Mean±SD or frequency (percentage)	Median (range)	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	
Na (mmol/L)	287	138.96±4.11	139.90 (122.90–148.50)	37	138.19±3.96	137.90 (130.80–145.40)	0.251
Ca (mmol/L)	155	2.08±0.19	2.10 (1.61–2.82)	17	2.11±0.16	2.10 (1.82–2.45)	0.630
Blood ammonia (μmol/L)	130	51.20±54.85	42.00 (9.00–480.00)	18	57.78±55.96	37.00 (9.00–227.00)	0.552
INR	284	1.39±0.92	1.22 (0.83–13.40)	38	1.49±0.75	1.35 (0.87–5.21)	0.141
Child-Pugh score	274	7.02±1.97	7.00 (5.00–14.00)	36	7.86±1.88	8.00 (5.00–12.00)	0.007
Child-Pugh class	274			36			0.052
A		135 (49.3)			10 (27.8)		
B		106 (38.7)			20 (55.6)		
C		33 (12.0)			6 (16.7)		
MELD score	276	6.51±7.50	4.94 (–6.91–51.64)	37	8.39±8.28	5.51 (–2.39–42.68)	0.116
In-hospital death	295	11 (3.7)		40	1 (2.5)		0.695

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; HBcAb, hepatitis B core antibody; HE, hepatic encephalopathy; AUGIB, acute upper gastrointestinal bleeding; RBC, red blood cell count; Hb, hemoglobin; WBC, white blood cell count; PLT, platelet count; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; K, kalium; Na, sodium; Ca, calcium; INR, international normalized ratio; MELD, model for end-stage liver disease.

Table 3 Comparison between patients with undetectable and detectable HBV DNA load

Variables	Undetectable HBV DNA load			Detectable HBV DNA load			P value
	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	
Age (years)	176	53.48±10.75	53.86 (27.42–84.90)	109	56.14±11.68	57.15 (25.62–86.93)	0.039
Sex (male/female)	176	116 (65.9)/60 (34.1)		109	67 (61.5)/42 (38.5)		0.447
HBsAg (negative/positive)	176	0 (0)/176 (100.0)		109	0 (0)/109 (100.0)		–
HBsAb (negative/positive)	172	172 (100.0)/0 (0)		108	108 (100)/0 (0)		–

Table 3 *(continued)*

Table 3 *(continued)*

Variables	Undetectable HBV DNA load			Detectable HBV DNA load			P value
	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	
HBeAg (negative/positive)	172	168 (97.7)/4 (2.3)		108	80 (74.1)/28 (25.9)		<0.001
HBeAb (negative/positive)	172	77 (44.8)/95 (55.2)		108	59 (54.6)/49 (45.4)		0.108
HBcAb-IgG (negative/positive)	172	15 (8.7)/157 (91.3)		108	5 (4.6)/103 (95.4)		0.196
HBcAb-IgM (negative/positive)	172	172 (100.0)/0 (0)		108	106 (98.1)/2(1.9)		0.073
HBV DNA viral load in patients with detectable HBV DNA load (>200 IU/mL)	176	NA		109	1,237,000±5,290,716	94,000 [220–48,000,000]	–
Ascites	176			109			<0.001
No		118 (67.0)			47 (43.1)		
Mild		22 (12.5)			12 (11.0)		
Moderate and large		36 (20.5)			50 (45.9)		
HE	176			109			0.197
No		165 (93.8)			107 (98.2)		
Grade I–II		9 (5.1)			2 (1.8)		
Grade III–IV		2 (1.1)			0 (0)		
AUGIB	176	63 (35.8)		109	18 (16.5)		<0.001
RBC (10^{12}/L)	174	3.28±0.91	3.22 (0.98–5.45)	109	2.36±0.85	3.24 (1.72–5.38)	0.536
Hb (g/L)	174	95.12±32.49	89.50 (23.00–157.00)	109	104.68±29.49	104.33 (41.00–170.00)	0.013
WBC (10^9/L)	174	4.62±3.73	3.65 (1.00–26.30)	109	4.56±3.27	3.90 (0.30–29.10)	0.389
PLT (10^9/L)	174	84.28±57.47	64.50 (16.00–384.00)	109	89.95±63.87	64.00 (23.00–344.00)	0.622
TBIL (μmol/L)	175	25.92±36.64	17.70 (1.90–359.40)	109	39.71±74.88	22.00 (3.90–607.80)	0.016
ALB (g/L)	171	34.41±6.85	34.80 (14.20–52.80)	105	30.61±6.28	30.90 (17.40–48.80)	<0.001
ALT (U/L)	175	51.36±261.73	24.00 (6.00–3471.00)	109	68.28±139.29	38.00 (8.00–1335.00)	<0.001
AST (U/L)	175	113.34±920.48	29.00 (10.00–12148.00)	109	90.47±170.82	45.00 (16.00–1,366.00)	<0.001
ALP (U/L)	175	82.51±52.23	75.00 (29.00–586.00)	109	98.45±42.19	89.00 (39.00–288.00)	<0.001

Table 3 *(continued)*

Table 3 *(continued)*

Variables	Undetectable HBV DNA load			Detectable HBV DNA load			P value
	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	
GGT (U/L)	175	45.76±58.20	27.00 (5.00–542.00)	109	61.76±47.71	51.00 (12.00–308.00)	<0.001
BUN (mmol/L)	174	7.02±4.73	5.69 (2.03–46.54)	104	7.43±5.02	6.05 (2.56–37.54)	0.371
Cr (μmol/L)	174	74.00±94.65	56.00 (21.00–816.00)	104	85.63±114.21	61.25 (35.00–998.00)	0.014
K (mmol/L)	173	4.07±0.41	4.08 (3.10–5.81)	104	4.03±0.49	4.09 (2.56–5.11)	0.817
Na (mmol/L)	173	139.28±3.89	139.50 (124.60–148.50)	104	138.43±4.11	139.50 (128.00–147.10)	0.100
Ca (mmol/L)	90	2.11±0.21	2.13 (1.61–2.82)	59	2.04±0.15	2.05 (1.69–2.40)	0.032
Blood ammonia (μmol/L)	67	49.30±40.30	44.00 (9.00–174.00)	50	54.12±50.46	39.00 (9.00–227.00)	0.806
INR	172	1.41±1.14	1.20 (0.83–13.40)	103	1.42±0.57	1.27 (0.83–5.21)	0.045
Child-Pugh score	167	6.71±1.81	6.00 (5.00–14.00)	100	7.75±2.02	8.00 (5.00–12.00)	<0.001
Child-Pugh class	167			100			0.002
A		90 (53.9)			35 (35.0)		
B		64 (38.3)			45 (45.0)		
C		13 (7.8)			20 (20.0)		
MELD score	170	5.68±7.58	4.22 (–6.91–51.64)	100	8.51±8.12	6.70 (–4.19–42.68)	0.001
In-hospital death	176	4 (2.3)		109	7 (6.4)		0.077

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; HBcAb, hepatitis B core antibody; HE, hepatic encephalopathy; AUGIB, acute upper gastrointestinal bleeding; RBC, red blood cell count; Hb, hemoglobin; WBC, white blood cell count; PLT, platelet count; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; K, kalium; Na, sodium; Ca, calcium; INR, international normalized ratio; MELD, model for end-stage liver disease.

Table 4 Comparison between patients with serum HBV DNA load <2,000 and >2,000 IU/mL

Variables	HBV DNA load <2,000 IU/mL			HBV DNA load >2,000 IU/mL			P value
	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	
Age (years)	194	53.38±10.52	53.86 (27.42–84.90)	91	56.88±12.17	57.75 (25.62–86.93)	0.011
Sex (male/female)	194	128 (66.0)/66 (34.0)		91	55 (60.4)/36 (39.6)		0.363

Table 4 *(continued)*

Table 4 *(continued)*

Variables	HBV DNA load <2,000 IU/mL			HBV DNA load >2,000 IU/mL			P value
	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	
HBsAb (negative/positive)	190	190 (100.0)/0 (0)		90	90 (100.0)/0 (0)		–
HBeAg (negative/positive)	190	185 (97.4)/5 (2.6)		90	63 (70.0)/27 (30.0)		<0.001
HBeAb (negative/Positive)	190	84 (44.2)/106 (55.8)		90	52 (57.8)/38 (42.2)		0.034
HBcAb-IgG (negative/positive)	190	16 (8.4)/174 (91.6)		90	4 (4.4)/86 (95.6)		0.228
HBcAb-IgM (negative/positive)	190	190 (100.0)/0 (0)		90	88 (97.8)/2 (2.2)		0.039
HBV DNA viral load in patients with detectable HBV DNA load (>200 IU/mL)	194	782±1,140	640 [220–1,880]	91	1,481,528±5,764,018	148,000 [220–48,000,000]	<0.001
Ascites	194			91			<0.001
No		131 (67.5)			34 (37.4)		
Mild		24 (12.4)			10 (11.0)		
Moderate and large		39 (20.1)			51 (51.6)		
HE	194			91			0.262
No		183 (94.3)			89 (97.8)		
Grade I–II		9 (4.6)			2 (2.2)		
Grade III–IV		2 (1.1)			0 (0)		
AUGIB, n (%)	194	65 (33.5)		91	16 (17.6)		0.005
RBC (10^{12}/L)	192	3.32±0.94	3.25 (0.98–5.45)	91	3.29±0.77	3.16 (1.72–5.38)	0.802
Hb (g/L)	192	97.05±33.32	91.50 (23.00–169.00)	91	102.49±27.64	104.00 (41.00–170.00)	0.121
WBC (10^9/L)	192	4.65±3.65	3.70 (1.00–26.30)	91	4.48±3.37	3.80 (0.30–29.10)	0.724
PLT (10^9/L)	192	85.49±57.80	65.50 (16.00–384.00)	91	88.52±64.57	63.00 (23.00–344.00)	0.953
TBIL (μmol/L)	193	25.24±35.26	16.90 (1.90–359.40)	91	43.89±81.08	24.30 (3.90–607.80)	0.001
ALB (g/L)	189	34.61±6.68	34.90 (14.20–52.80)	87	29.39±5.89	28.90 (17.40–48.80)	<0.001
ALT (U/L)	193	49.40±249.30	24.00 (6.00–3,471.00)	91	75.78±151.22	41.00 (10.00–1,335.00)	<0.001
AST (U/L)	193	105.98±876.61	29.00 (10.00–12,148.00)	91	101.54±184.78	52.00 (24.00–1,366.00)	<0.001

Table 4 *(continued)*

Table 4 *(continued)*

Variables	HBV DNA load <2,000 IU/mL			HBV DNA load >2,000 IU/mL			P value
	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	No. of patients available	Mean ± SD or frequency (percentage)	Median (range)	
GGT (U/L)	193	46.31±57.01	27.00 (5.00–542.00)	91	63.75±48.26	53.00 (16.00–308.00)	<0.001
BUN (mmol/L)	191	6.92±4.62	5.59 (2.03–46.54)	87	7.72±5.26	6.47 (2.56–37.54)	0.072
Cr (μmol/L)	191	73.21±90.49	56.00 (21.00–816.00)	87	89.64±124.37	61.50 (35.00–998.00)	0.041
K (mmol/L)	191	4.06±0.40	4.08 (3.10–5.81)	86	4.04±0.52	4.10 (2.56–5.11)	0.847
Na (mmol/L)	191	139.35±3.80	140.10 (124.60–148.50)	86	138.11±4.27	139.20 (128.00–147.10)	0.022
Ca (mmol/L)	101	2.11±0.21	2.10 (1.61–2.82)	48	2.03±0.16	2.03 (1.69–2.40)	0.024
Blood ammonia (μmol/L)	72	47.58±39.89	42.50 (9.00–174.00)	45	57.40±51.55	42.00 (9.00–227.00)	0.384
INR	189	1.39±1.09	1.19 (0.83–13.40)	86	1.49±0.60	1.33 (0.83–5.21)	<0.001
Child-Pugh score	184	6.65±1.79	6.00 (5.00–14.00)	83	8.10±1.95	8.00 (5.00–12.00)	<0.001
Child-Pugh class	184			83			<0.001
A		102 (55.4)			23 (27.7)		
B		68 (37.0)			41 (49.4)		
C		14 (7.6)			19 (22.9)		
MELD score	186	5.52±7.32	4.20 (−6.91–51.64)	84	9.41±8.46	8.08 (−4.19–42.68)	<0.001
In-hospital death	194	4 (2.1)		91	7 (7.7)		0.021

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBeAb, hepatitis B e antibody; HBcAb, hepatitis B core antibody; HE, hepatic encephalopathy; AUGIB, acute upper gastrointestinal bleeding; RBC, red blood cell count; Hb, hemoglobin; WBC, white blood cell count; PLT, platelet count; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; K, kalium; Na, sodium; Ca, calcium; INR, international normalized ratio; MELD, model for end-stage liver disease.

Discussion

Major findings of our study were as follows: (I) the in-hospital mortality of cirrhotic patients with HBV DNA viral load >2,000 IU/mL was significantly elevated, but this association was compromised after adjusting the Child-Pugh score; (II) positive HBeAg, detectable HBV DNA viral load, and HBV DNA viral load >2,000 IU/mL were all related to the degree of liver and renal dysfunction, as indicated by biomarkers, such as TBIL, ALT, AST, ALP, GGT, Cr, and Child-Pugh and MELD scores; and (III) there was a significant correlation of HBV DNA viral load with worsening liver function laboratory/features.

Clinical practice guidelines on the management of chronic hepatitis B published by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) indicated that age was an important predictive factor for the progression of liver cirrhosis in chronic HBV infection patients (2,21-24). Chinese clinical practice guideline also suggested that the risk of liver cirrhosis in HBV patients would be increased with age and high serum HBV DNA viral load, especially in patients with age above 40 years. Additional studies reported that liver injury was more significant in chronic HBV patients

Table 5 Correlation analysis of HBV DNA load in 109 patients with detectable HBV DNA load

Variables	Correlation coefficient	P value
Age (years)	0.137	0.157
RBC (10^{12}/L)	−0.195	0.042
Hb (g/L)	−0.199	0.038
WBC (10^9/L)	0.088	0.365
PLT (10^9/L)	−0.164	0.088
TBIL (μmol/L)	0.184	0.055
ALB (g/L)	−0.369	<0.001
ALT (U/L)	0.381	<0.001
AST (U/L)	0.505	<0.001
ALP (U/L)	0.232	0.015
GGT (U/L)	0.104	0.280
BUN (mmol/L)	0.289	0.003
Cr (μmol/L)	0.099	0.317
K (mmol/L)	0.171	0.083
Na (mmol/L)	−0.163	0.098
Ca (mmol/L)	−0.293	0.024
Blood ammonia (μmol/L)	0.118	0.413
INR	0.323	0.001
Child-Pugh score	0.427	<0.001
MELD score	0.322	0.001

HBV, hepatitis B virus; HE, hepatic encephalopathy; AUGIB, acute upper gastrointestinal bleeding; RBC, red blood cell count; Hb, hemoglobin; WBC, white blood cell count; PLT, platelet count; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; K, kalium; Na, sodium; Ca, calcium; INR, international normalized ratio; MELD, model for end stage liver disease.

with age above 46 years (25-27). Consistent with these findings, our patients with HBV-related liver cirrhosis had a median age of 53.91 years (range, 25.62–86.93 years).

HBeAg status, liver function, serum HBV DNA viral load, and liver histology are important factors in determining the severity of liver diseases (2,21,23,24). HBeAg is a significant marker of viral infectivity and persistence, and plays an important role in the natural history of chronic HBV (28). Traditionally, HBeAg seroconversion is defined as negative HBeAg and positive HBeAb with an associated reduction in HBV viral replication and a lower infectivity in the natural history of infection. In our study, the prevalence of HBeAg-negative patients was 88.1% (295/335) and the prevalence of HBeAb-positive patients was 57.3% (169/295) in HBeAg-negative patients. The data suggested that most of HBV-related cirrhotic patients had experienced HBeAg seroconversion. Our study found that HBeAg-negative patients with cirrhosis had significantly better liver function than HBeAg-positive patients, indicating that lack of HBeAg seroconversion (and subsequent high viremia) posed a particular risk for cirrhotic patients. However, some studies reported that HBeAg-negative patients with or without cirrhosis still could have experienced a high viral replication and/or risk of viral hepatitis exacerbation (25,29,30). Similarly, HBeAg-negative HBV patients with elevated ALT and active histological changes could experience faster progression to liver cirrhosis than HBeAg-positive HBV patients (31). The potential reasons included: (I) a longer duration of infection in HBeAg-negative patients than in HBeAg-positive patients; and (II) core promoter mutations that might increase the replication efficacy of HBV (32-35).

Some studies had reported that long-term antiviral therapy could improve the survival of patients with HBV-related liver cirrhosis (36-38), but few studies explored the impact of HBeAg status and HBV DNA viral load on the severity of liver dysfunction and in-hospital outcomes in HBV-related liver cirrhosis patients. Our study revealed higher likelihood of adverse outcomes in cirrhotic patients with HBV DNA viral load, thereby suggesting that antiviral treatment is urgently required in such patients. This is consistent with the recommendations from EASL guideline regarding management of HBV (2,22). Unfortunately, information regarding use of antiviral therapy was unavailable in our study. Accordingly, future studies should explore whether the initiation of antiviral therapy could improve the outcomes of HBV-related liver cirrhosis patients with HBV DNA viral load >2,000 IU/mL.

A lower proportion of AUGIB and higher Hb levels were observed in patients with HBV DNA viral load >2,000 IU/mL. Similarly, HBV DNA viral load negatively correlated with RBC and Hb. These findings suggested that patients with higher HBV DNA viral load might suffer from less bleeding events but had worse liver function. Indeed, the major cause of hospital admission in patients with HBV DNA viral load >2,000 IU/mL might be liver dysfunction; by contrast, the major cause of hospital admission in patients with HBV DNA viral load

<2,000 IU/mL might be acute gastrointestinal bleeding.

Our study had some limitations. First, not all HBV patients had data available for HBeAg, HBeAb, and HBV DNA viral load. Second, the diagnosis of cirrhosis was not confirmed by liver histology. Third, this was a single-center observational study and we did not collect the long-term follow-up data. Fourth, we are unable to dissect a potential role of antiviral therapy. Some of patients with undetectable HBV DNA viral load might have been on nucleoside/nucleotide analogues.

In conclusion, HBeAg and HBV DNA viral load are factors associated with the severity of liver dysfunction in HBV-related liver cirrhosis patients. More importantly, the in-hospital mortality was significantly higher in such patients with HBV DNA viral load >2,000 IU/mL, but it was not an independent risk factor for death, after adjusting the Child-Pugh score.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.09.10). Xingshun Qi serves as an Editor-in-Chief of *AME Medical Journal*. Eric M. Yoshida serves as an unpaid Associate Editor-in-Chief of *AME Medical Journal* from Jun 2017 to Jun 2019. Nahum Mendez-Sanchez serves as an unpaid editorial board member of *AME Medical Journal* from Mar 2017 to Mar 2019. Fernando Gomes Romeiro serves as an unpaid editorial board member of *AME Medical Journal* from Apr 2017 to Apr 2019. Andrea Mancuso serves as an unpaid editorial board member of *AME Medical Journal* from Mar 2017 to Mar 2019. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Medical Ethical Committee of our hospital. The approval number was No. k[2015]39. Informed consent was waived due to the retrospective nature of the study.

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