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Original Article

Hyponatremia is an independent risk factor for mortality from hepatitis B virus-associated acute-on-chronic liver failure

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Abstract: Introduction: Hepatitis B virus-associated acute-on-chronic liver failure (HBV-ACLF) has a poor prognosis. This analysis aimed to assess whether hyponatremia has any prognostic value for patients with HBV-ACLF. Methods: We performed an analysis of the "Study on HBV-ACLF treated with integrated traditional Chinese and Western Medicine" (2012ZX10005-005) database. From 1059 patients admitted to 17 Chinese centers with suspected HBV-ACLF, we identified 567 who fulfilled the criteria of HBV-ACLF established by the Asia Pacific Association for the Study of the Liver in 2014. Results: Of 567 patients, 45.5% had hyponatremia at inclusion. These patients exhibited significantly greater liver impairment (as indicated by higher levels of serum bilirubin, international normalized ratio, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase and lactate dehydrogenase, and a lower level of cholinesterase), higher serum creatinine, and lower serum lipid levels compared to the HBV-ACLF patients without hyponatremia. After adjusting for potential confounders, hyponatremia at inclusion was an independent risk factor for mortality, nearly doubling the risk of death by 48 weeks (hazard ratio [95% CI], 1.827 [1.036-3.221]; P = 0.037). Only 51.4% of the HBV-ACLF patients with hyponatremia achieved 48-week transplant-free survival compared to 65.9% without hyponatremia (P < 0.001). Conclusion: Hyponatremia is an independent risk factor for mortality in patients with HBV-ACLF.

Keywords: Hyponatremia, hepatitis B virus-associated acute-on-chronic liver failure, prognosis

Introduction

Hyponatremia is a marker for poor prognosis in patients with decompensated cirrhosis [1-3] and an important marker of prognosis in patients with cirrhosis awaiting liver transplantation [2, 4-6]. Hyponatremia is closely associated with the impairment of renal function, advanced portal hypertension, and fluid loss [7]. In patients with cirrhosis and ascites, the five-year probability of developing hyponatremia is 37.1%, and patients with hyponatremia show only a 25.6% probability of one-year survival. Despite ample data on the prognostic value of hyponatremia for cirrhosis patients, there is no specific information on the clinical impact of hyponatremia in patients with hepatitis B virus-associated acute-on-chronic liver failure (HBV-ACLF). HBV-ACLF is an increasingly recognized potentially fatal liver disease involving the severe, acute exacerbation of liver dysfunction in patients with previously diagnosed or undiagnosed chronic liver disease due to the hepatitis B virus [8], and HBV-ACLF is the major form of ACLF in China [9]. Studies have found a greater severity and mortality for HBV-ACLF than for alcohol-related ACLF [10]. The reported prognosis of HBV-ACLF is very poor, with 3-month mortality rate over 50% without liver transplantation [11]. The identification of prognostic factors is critical for the improved management of HBV-ACLF. Previous studies have identified factors related to HBV-ACLF prognosis [12], such as the aggravation of hepatic encephalopathy (≥ grade III), the development of infection, and the presence of moderate to severe ascites, but it is still unclear whether hyponatremia influences HBV-ACLF prognosis. Therefore, the aim of this analysis was to deter-

mine the specific effects of hyponatremia on the outcome of HBV-ACLF.

Methods

Patients

We analyzed HBV-ACLF cases from the twelfth Five-years Great Science and Technology Project "Study on HBV-ACLF Treated with Integrated Traditional Chinese Medicine and Western Medicine" (2012ZX10005-005), a prospective multicenter randomized control study. All the cases from seventeen clinical institutions from November 31, 2012 to December 31, 2014 were enrolled: 302 Military Hospital, Beijing Ditan Hospital, Beijing Youan Hospital, Shanghai Public Health Clinical Center, Tongji Hospital, Tianjin Infectious Disease Hospital, Fuzhou Infectious Disease Hospital, Hubei Provincial Hospital of Traditional Chinese Medicine, Jilin Hepatobiliary Hospital, The First Affiliated Hospital of Guangxi University of Traditional Chinese Medicine, The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine, The Third Affiliated Hospital of Zhongshan University, The Sixth People's Hospital of Shenyang, Xixi Hospital of Hangzhou, Shenzhen Traditional Chinese Medicine Hospital, The Third People's Hospital of Shenzhen, and Chengdu Public Health Clinical Center. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice. All patients volunteered to join the study and provided written informed consent before participating. Approvals were obtained from the Ethics Committee of 302 Military Hospital of China (2011 No. 16).

The diagnosis of ACLF complied with the diagnostic and therapeutic guidelines for liver failure established in 2014 [8]. Acute-on-chronic liver failure is the main clinical manifestation of short-term acute hepatic decompensation (usually occurring within 4 weeks) on the basis of an underlying chronic liver disease.

The diagnostic criteria were (1) jaundice (serum bilirubin ≥ 5 mg/dL [≥ 85 μmol/l]), (2) coagulopathy (INR ≥ 1.5 or prothrombin activity ≤ 40%), and (3) ascites and/or encephalopathy as determined by physical examination.

The inclusion criteria were (1) patients with chronic liver disease due to hepatitis B virus infection, (2) patients with acute deteriorated liver function within 4 weeks, (3) patients with progressive jaundice (serum bilirubin ≥ 5 mg/dL), (4) patients with a risk of bleeding (prothrombin activity ≤ 40%) or international normalized ratio (INR ≥ 1.5), (5) ascites and/or encephalopathy as determined by physical examination. The exclusion criteria were (1) participation in other clinical trials within the last 3 months, (2) pregnancy or breastfeeding, (3) acute or sub-acute hepatic failure or chronic hepatic failure, (4) other etiologies such as autoimmunity, drugs, alcohol, toxins, or parasites that may contribute to ACLF, (5) hepatocellular carcinoma, (6) other serious general or psychological diseases, (7) human immunodeficiency virus infection, (8) brain edema and/or infection at the time of enrollment (including septic shock and fungal infection), and (9) type 1 hepatorenal syndrome (characterized by clinical features including severe progressive renal failure, oliguria for several days less than 2 weeks, and serum creatinine > 221 μmol/L).

A flow diagram of patient selection is shown in **Figure 1**. A total of 1059 patients with HBV-ACLF were identified from November 31, 2012 to December 31, 2014, of which 416 patients who did not fulfill the criteria and 76 patients without consecutive records were excluded. Ultimately, 567 patients were included in the analysis.

Statistics

Continuous variables are expressed as the mean ± standard deviation (SD) while categorical variables are expressed as frequencies and percentages. Univariable analyses included Student's t test for pair-wise comparison of parametric data distributions, the Mann-Whitney U test for pair-wise comparison of nonparametric distributions, and chi-square tests for comparison of categorical variables. Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test. A proportional hazards model was constructed to assess the effect of hyponatremia on the outcome, adjusting for potential confounders and considering liver transplantation and traditional Chinese medicine (TCM) as competing risks. The choice of variables for the multivariable

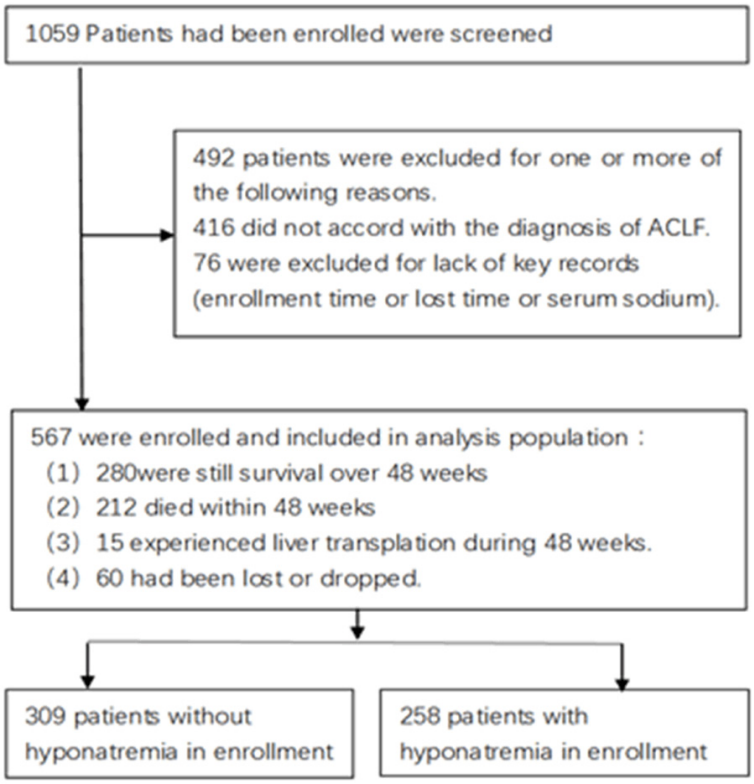

Figure 1. Study flow diagram.

analysis was based on the results of univariable analysis and clinical correlation. $P < 0.05$ was considered statistically significant for all tests. All statistical analyses were performed using Statistical Package for the Social Sciences version 17.0.

Results

Clinical characteristics

The prevalence of hyponatremia in patients with HBV-ACLF is summarized in **Figure 1**. Patients with hyponatremia exhibited a higher frequency of upper gastrointestinal bleeding at admission. Moreover, patients with hyponatremia showed greater impairment in indices of liver function (higher levels of serum bilirubin, international normalized ratio, aspartate transaminase levels, alanine transaminase, gamma-glutamyl transferase levels and lactate dehydrogenase, and a lower level of cholinesterase), higher serum creatinine, and lower serum lipid levels compared to patients without hyponatremia. In addition, the leukocyte, erythrocyte, and platelet counts were higher in the patients with hyponatremia (**Table 1**).

Effects of hyponatremia on HBV-ACLF-associated mortality

By 48 weeks post-enrollment, 212 of the 567 patients had died (37.4%) and 15 patients (2.6%) had received a liver transplant. The mortality rate was significantly greater in patients with hyponatremia at enrollment compared to those without (43.8% vs. 32.0%, $P = 0.004$). Alternatively, there were no significant differences in the liver transplant rate (1.9% vs. 3.2%, $P = 0.337$), antiviral treatment (100% vs. 99.4%, $P = 0.195$), artificial liver support (39.5% vs. 42.1%, $P = 0.541$), and traditional Chinese medicine (TCM) treatment rate (68.2% vs. 62.5%, $P = 0.152$) between the patient groups. Several factors measured at study enrollment were associated with hyponatremia (**Table 1**), and the following variables were found to be predictors of 48-week mortality by univariable analysis: age, presence of hepatic encephalopathy (HE), hepatorenal syndrome (HRS), upper gastrointestinal bleeding (UGB) and cirrhosis, serum bilirubin, serum creatinine, prothrombin activity, hemoglobin, and platelet count. All these variables were included as potential confounders for the adjusted estimates of hyponatremia effects on mortality. The following major interventions were also considered: TMC treatment, liver transplant, antiviral medication, and artificial liver support. The competing-risks proportional hazards model was first fitted by including all potential confounders selected by univariable analyses (**Table 2**). After adjusting for confounding variables, hyponatremia was found to nearly double the risk of dying from HBV-ACLF at 48 weeks (**Table 2**). The survival curves of patients with and without hyponatremia at inclusion are shown in **Figure 2**. Hyponatremia was associated with a significantly poorer prognosis. Patients without hyponatremia had a 48-week survival probability of 65.9% compared to only 51.4% for patients with hyponatremia (log-rank test, $X^2 = 10.905$, $P = 0.001$). Similar differences in survival prob-

Table 1. Characteristics of HBV-ACLF patients according to the presence of hyponatremia at study inclusion

Patient characteristics	Patients without hyponatremia (n = 309)	Patients with hyponatremia (n = 258)	*P* value
Age (years)	44.4 ± 10.9	45.6 ± 10.4	0.183
Sex (male)	267 (86.4%)	211 (81.8%)	0.132
Albumin (g/L)	30.57 ± 4.72	31.02 ± 5.23	0.649
Serum bilirubin (mg/dL)	19.34 ± 7.61	20.99 ± 8.47	0.015
ALT (U/L)	383.59 ± 450.86	193.52 ± 300.16	< 0.001
AST (U/L)	306.27 ± 343.68	200.25 ± 256.15	< 0.001
GGT (U/L)	83.42 ± 50.12	66.45 ± 49.20	< 0.001
ALP (U/L)	154.86 ± 64.10	145.49 ± 61.15	0.080
TBA (μmol/L)	254.77 ± 590.47	236.49 ± 465.55	0.695
CHE (U/L)	3218.44 ± 1550.19	2669.82 ± 1653.49	< 0.001
LDH (U/L)	263.72 ± 122.99	240.55 ± 79.13	0.041
Serum creatinine (μmol/L)	73.10 ± 28.69	82.72 ± 34.73	< 0.001
PTA (%)	31.38 ± 6.82	30.00 ± 7.98	0.028
INR	2.98 ± 10.84	3.48 ± 13.62	0.641
WBC ($\times 10^3/mm^3$)	7.72 ± 3.99	7.07 ± 3.04	0.030
RBC ($\times 10^4/mm^3$)	3.81 ± 0.76	3.36 ± 0.86	< 0.001
Hemoglobin (g/L)	121.46 ± 20.23	106.79 ± 24.10	< 0.001
PLT ($\times 10^3/mm^3$)	96.13 ± 47.80	81.71 ± 42.94	< 0.001
TC	2.21 ± 0.87	1.97 ± 0.95	0.004
TG	1.11 ± 0.92	0.93 ± 0.79	0.034
AFP	131.01 ± 287.04	114.13 ± 213.39	0.455
BLA (μmol/L)	63.02 ± 45.27	59.96 ± 38.50	0.432
Cirrhosis	79 (25.6%)	69 (26.7%)	0.750
HE	47 (15.3%)	37 (14.5%)	0.791
UGB	2 (0.6%)	12 (4.7%)	0.002
SBP	111 (36.2%)	106 (41.6%)	0.190
HRS	11 (3.6%)	13 (5.1%)	0.377

Data expressed as the mean ± standard deviation or the number of patients (%). HBV-ACLF: Hepatitis B virus-associated acute-on-chronic liver failure, ALT: alanine transaminase, AST: aspartate transaminase, GGT: γ-glutamyl transferase, ALP: alkaline phosphatase, TBA: total bile acid, CHE: cholinesterase, LDH: lactate dehydrogenase, PTA: prothrombin activity, INR: International normalized ratio, WBC: white blood cell count, RBC: red blood cell count, PLT: platelet count, TC: total cholesterol, TG: triglyceride, AFP: α-fetoprotein, BLA: blood ammonia, HE: hepatic encephalopathy, UGB: upper gastrointestinal bleeding, SBP: spontaneous bacterial peritonitis, HRS: hepatorenal syndrome.

ability were observed at 28-days and 8-weeks between the two groups (log-rank test. at 28-days: 83.7% vs. 76.5%, $X^2 = 4.291$, P = 0.038. at 8-weeks: 75.3% vs. 63.6%, $X^2 = 7.440$, P = 0.006).

Discussion

Our analysis indicates that hyponatremia is an independent risk factor for earlier mortality from Hepatitis B virus-associated acute-on-chronic liver failure (HBV-ACLF). Patients with hyponatremia at enrollment demonstrated a significantly higher 48-week mortality rate than HBV-ACLF patients without hyponatremia (65.9% vs. 51.4%, HR = 1.827). This result is in accord with the CANONIC study, which found that hyponatremia increased the risk of 90-day mortality from ACLF patients in the Western and alcohol-related ACLF as a dominant position [13], although hyponatremia in that study was defined as serum sodium ≤ 130 mmol/L as opposed to ≤ 135 mmol/L in the current study. While sodium concentration ≤ 130 mmol/L has been used to define hyponatremia for patients with cirrhosis [14, 15], it is unclear whether this threshold is appropriate for patients with non-cirrhotic liver disease. As non-cirrhotic patients were included in our study, we diagnosed the hyponatremia as serum sodium below 135 mmol/L. Older age, higher level of prothrombin activity, elevated serum bilirubin, and the presence of hepatic encephalopathy were also independent prognostic factors associated with the increased risk of HBV-ACLF mortality, consistent with a previous study that age, hepatic encephalopathy, and total bilirubin appeared to be prognostic indicators for all-cause ACLF with a poor outcome [16].

It was once widely believed that hyponatremia is a complication of advanced cirrhosis, but in this analysis, hyponatremia was also frequent in HBV-ACLF patients without preexisting cirrhosis. The prevalence of hyponatremia in this study cohort was higher than that of preexist-

Table 2. Factors associated with death

Parameter	Univariate analyses			Multivariate analyses		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Hyponatremia (yes vs. no[+])	1.552	1.185-2.033	0.001	1.827	1.036-3.221	0.037
Age (per 10 years increase)	1.028	1.015-1.041	0.000	1.027	1.000-1.054	0.049
Sex (male or female[+])	1.106	0.779-1.570	0.574	-		
Albumin (< 30 g/L or ≥ 30 g/L[+])	1.004	0.989-1.019	0.631	-		
Serum bilirubin (per 1 mg/dL)	1.051	1.035-1.068	0.000	1.050	1.014-1.087	0.007
Serum creatinine (mg/dL) (< 1 or ≥ 1[+])	1.010	1.006-1.013	0.000	1.002	0.992-1.012	0.706
PTA (per 10% increase)	0.928	0.911-0.945	0.000	0.915	0.880-0.952	< 0.001
WBC ($\times 10^3/mm^3$) (< 4 or ≥ 4[+])	1.057	1.019-1.096	0.003	1.071	0.988-1.161	0.094
Hemoglobin (g/L) (< 12 or ≥ 12[+])	0.992	0.986-0.998	0.005	0.988	0.966-1.011	0.313
PLT ($\times 10^3/mm^3$) (< 100 or ≥ 100[+])	0.995	0.992-0.999	0.005	0.997	0.990-1.004	0.477
Cirrhosis (yes vs. no[+])	1.615	1.216-2.146	0.001	1.356	0.795-2.313	0.264
HE (yes vs. no[+])	2.232	1.613-3.089	0.000	1.931	1.039-3.589	0.037
UGB (yes vs. no[+])	3.004	1.589-5.679	0.001	1.440	0.146-14.179	0.755
SBP (yes vs. no[+])	1.237	0.940-1.628	0.129	-		
HRS (yes vs. no[+])	4.582	2.913-7.208	0.000	0.913	0.232-3.591	0.896
Interventions						
TCM (yes vs. no[+])	1.335	1.015-1.756	0.039	0.772	0.456-1.309	0.337
Liver transplant (yes[+] vs. no)	4.332	2.596-7.230	0.000	3.286	1.155-9.344	0.026
Antiviral (yes vs. no[+])	0.531	0.074-3.787	0.528	-		
Artificial liver (yes vs. no[+])	0.847	0.643-1.116	0.238	-		

[+]: reference value, TCM: Traditional Chinese medicine, HR: Hazard ratio, CI: confidence interval. -: variables were not taken into.

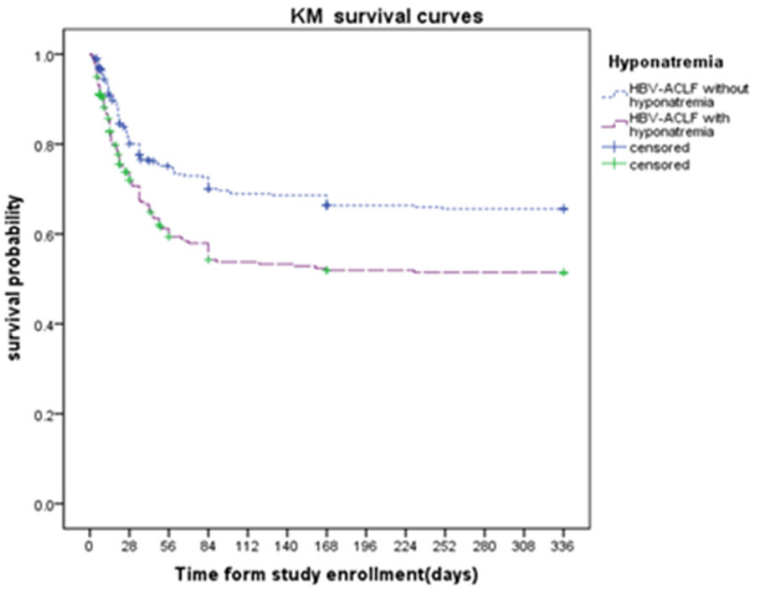

Figure 2. Survival curves in patients with HBV-ACLF according to the presence of hyponatremia at inclusion.

ing cirrhosis (45.5% vs. 26.1%, P < 0.001), and the prevalence of hyponatremia was similar between patients with and without preexisting cirrhosis (45.1% vs. 46.6%, P = 0.750). Moreover, the presence of hyponatremia was also associated with a greater mortality rate at 48 weeks in HBV-ACLF patients without preexisting cirrhosis than it was in patients with preexisting cirrhosis (39.7% vs. 28.7%, P = 0.018, HR = 1.635, 95% CI: 1.087-2.459). The development of hyponatremia has been linked to severe inflammation in patients without cirrhosis [17, 18]. However, the pathophysiology of hyponatremia in HBV-ACLF patients without preexisting cirrhosis requires further study.

In conclusion, this study identifies hyponatremia as an independent risk factor for 48-week mortality from HBV-ACLF. We suggest that HBV-ACLF patients be closely monitored for hyponatremia (serum sodium ≤ 135 mmol/L rather than the ≤ 130 mmol/L definition for cir-

rhosis), especially those without preexisting cirrhosis.

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Disclosure of conflict of interest

None.

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