



Prevalence and clinical significance of serum sodium variability in patients with acute-on-chronic liver diseases: a prospective multicenter study in China

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Abstract

Background No reports exist regarding the prevalence of different Na levels and their relationship with 90-day prognosis in hospitalized patients with acute-on-chronic liver disease (AoCLD) in China. Therefore, the benefit of hyponatremia correction in AoCLD patients remains unclear.

Methods We prospectively collected the data of 3970 patients with AoCLD from the CATCH-LIFE cohort in China. The prevalence of different Na levels (≤ 120 ; 120–135; 135–145; > 145) and their relationship with 90-day prognosis were analyzed. For hyponatremic patients, we measured Na levels on days 4 and 7 and compared their characteristics, based on whether hyponatremia was corrected.

Results A total of 3880 patients were involved; 712 of those developed adverse outcomes within 90 days. There were 80 (2.06%) hypernatremic, 28 (0.72%) severe hyponatremic, and 813 (20.95%) mild hyponatremic patients at admission. After adjusting for all confounding factors, the risk of 90-day adverse outcomes decreased by 5% (odds ratio [OR] 0.95; 95% confidence interval [CI] 0.93–0.97; $p < 0.001$), 24% (OR 0.76; 95% CI 0.70–0.84; $p < 0.001$), and 42% (OR 0.58; 95% CI 0.49–0.70; $p < 0.001$) as Na level increased by 1, 5, and 10 mmol/L, respectively. Noncorrection of hyponatremia on days 4 and 7 was associated with 2.05-fold (hazard ratio [HR], 2.05; 95% CI, 1.50–2.79; $p < 0.001$) and 1.46-fold (HR 1.46; 95% CI 1.05–2.02; $p = 0.028$) higher risk of adverse outcomes.

Conclusions Hyponatremia was an independent risk factor for a poor 90-day prognosis in patients with AoCLD. Failure to correct hyponatremia in a week after admission was often associated with increased mortality. (ClinicalTrials.gov number: NCT02457637, NCT03641872).

Clinical Trial Numbers This study is registered at Shanghai www.clinicaltrials.org (NCT02457637 and NCT03641872).

Keywords Prevalence · Significance · Serum sodium · Na · Hyponatremia · Adverse outcome · 90-day · Prognosis · Acute-on-chronic liver disease · AoCLD

Introduction

With the development of the global economy and the popularization of antiviral drugs, chronic hepatitis B and C have been gradually controlled; however, the incidence of fatty liver disease and drug-induced liver injury is increasing annually [1]. Chronic liver disease (CLD) remains a frequent cause of death. In 2017, 1.32 million people died directly because of liver cirrhosis, which accounts for 2–4% of

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deaths annually [2, 3]. During the coronavirus disease 2019 (COVID-19) pandemic, mortality was also significantly higher in patients with CLD than in those without CLD [4]. To improve the prognosis of cirrhotic patients, the model for end-stage liver disease (MELD) score has been used since 2002 to rank and prioritize liver transplantation (LT) candidates [5, 6]. Since then, some researchers have found that hyponatremia was an independent prognostic factor in cirrhotic patients [7–9]. Therefore, more optimized prediction tools, such as the Model for end-stage liver disease-sodium (MELD-Na) and United Kingdom Model for end-stage liver disease (UKELD) scores, have been developed [9–11]. Most previous studies confirm that serum sodium (Na) is closely associated with the severity and complications of liver cirrhosis and affects a patient's health-related quality of life (HRQOL) and perioperative mortality after transplantation [12, 13]. Hyponatremic patients have longer hospital stays and higher hospitalization rates [14]. The subsequent mortality of patients with hyponatremia is also significantly increased, regardless of accompanying diseases [15].

An abnormal Na level seems to be a common electrolyte disorder in clinical practice, but it often indicates a risk of other complications. However, there was insufficient information regarding the prevalence of different Na levels and their relationship with 90-day prognosis in hospitalized patients with acute-on-chronic liver disease (AoCLD) in areas with a high prevalence of hepatitis B virus (HBV) in China [16]. The benefit of hyponatremia correction at 4–7 days after admission in patients with AoCLD remains unclear. Therefore, this study aimed to describe the prevalence and clinical significance of Na variability in this population.

Methods

Patients

In total, 3970 patients with AoCLD were included in this study from the CATCH-LIFE cohort [16–18], which was a multicenter prospective cohort study conducted by the Chinese Chronic Liver Failure (CLIF) Federation (comprising 15 tertiary hospitals in a high HBV epidemic area) conducted from 2015 to 2016 and from 2018 to 2019. The ethics committee of Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University (Shanghai, China) approved the study and registered it at Shanghai www.clinicaltrials.org (NCT02457637, NCT03641872). The study was performed in accordance with the standards of the Declaration of Helsinki. Written informed consent was obtained from all patients. All authors have access to the study data and reviewed and approved the final manuscript.

Related event definitions

AoCLD is a nonmalignant CLD with acute decompensation (AD) or acute liver injury (ALI). CLD is considered cirrhotic or noncirrhotic liver disease with a history of liver dysfunction lasting > 6 months. Cirrhosis was diagnosed based on findings of computed tomography/magnetic resonance imaging (CT/MRI) scans and laboratory tests, clinical symptoms, and history of liver disease. A diagnosis of AD requires individuals to have at least one acute decompensation event, which includes gastrointestinal hemorrhage, hepatic encephalopathy, overt ascites, bacterial infection (e.g., spontaneous peritonitis and pneumonia), or jaundice [i.e., total bilirubin (TBIL) > 5 mg/dL] within 1 month before enrollment. ALI was defined as alanine aminotransferase or aspartate aminotransferase levels three times more than the upper limit of the normal range (ULN) (but < 40 IU/L) or a total bilirubin level two times more than the ULN (but < 1 mg/dL) within a week. The definition of 90-day adverse outcomes or poor prognosis was death or LT.

Based on the definition of hyponatremia [19–21], all patients were classified into four groups as follows: severe hyponatremia (Na level, ≤ 120 mmol/L), mild hyponatremia (Na level, > 120 and < 135 mmol/L), normal serum sodium (Na level, ≥ 135 and ≤ 145 mmol/L), and hypernatremia (Na level > 145 mmol/L) groups. The exclusion criteria were as follows: (1) age < 15 years or > 80 years, (2) pregnancy, (3) severe chronic extrahepatic disease, and (4) hepatocellular carcinoma or other liver malignancies before or during admission, and extrahepatic malignancies.

Data collection

Data pertaining to demographics, medical history, biochemical indicators, and imaging data were prospectively recorded at each center. After admission, all patients were followed up for 90 days, and the outcomes were recorded (endpoint events included LT or death).

Statistical analysis

Data were summarized using the appropriate descriptive statistics (i.e., median and interquartile range for continuous variables and frequency and percentage for categorical parameters). The Mann–Whitney *U* test was used for non-parametric pairwise comparisons, and the Chi-square test or Fisher's exact test was used for categorical variables. For more than three variables, non-normal continuous variables were analyzed using the Kruskal–Wallis test.

We estimated the potential confounding factors that impact the prognosis of AoCLD patients by univariate and

subgroup analyses, which showed a statistically significant interaction ($p < 0.05$). When Na level was used as a continuous variable and a categorical variable, multiple covariates (i.e., potential confounding factors) were gradually introduced to analyze the influence of unadjusted and multivariate-adjusted Na level on 90-day adverse outcomes using the backward stepwise (likelihood ratio) method of binary logistic regression. Furthermore, a generalized additive model and smooth curve fitting were used to describe the relationship between Na level and 90-day adverse outcomes. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. The main objective of this study was to assess the effect of Na level on the risk of 90-day adverse outcomes.

All statistical tests were two-tailed, and bilateral α of < 0.05 was statistically significant. SPSS 25 (IBM, Seattle, WA, USA) and R version 4.0.4 software (<http://www.r-project.org>) were used for statistical analysis and plots.

Results

Characteristics of the study population

Finally, 3880 patients were analyzed in this study according to the inclusion and exclusion criteria (Fig. 1). We determined not more than 5% missing data for each variable used on admission (Supplementary Fig. 1). The prevalence of different Na levels (i.e., hyponatremia, normonatremia, hypernatremia) in patients with AoCLD and their characteristics are summarized in Table 1. The incidence of alcoholic liver disease and chronic hepatitis B were significantly different between the Na level groups ($p < 0.05$).

The lower the Na level, the higher the proportion of liver cirrhosis and the worse the liver function score, including MELD, sequential organ failure assessment (SOFA), Child–Pugh, and other related scores ($p < 0.05$). At admission, patients in the hyponatremic groups had a higher frequency of AD events (e.g., ascites, hepatic encephalopathy, infection, and jaundice, but not gastrointestinal bleeding; $p < 0.05$). Moreover, TBIL, international normalized ratio (INR), serum creatinine (CR) level, blood urea nitrogen, and white blood cell (WBC) counts were also higher in the hyponatremic groups ($p < 0.05$) (Table 1; Supplementary Fig. 2).

Ninety-day adverse outcomes

Among the 3880 patients, 712 (18.35%) had 90-day adverse outcomes (498 deaths and 214 LT). The severe hyponatremia group had the highest incidence of adverse outcomes

(50.0%, $p < 0.05$) and LT-free mortality (48.2%, $p < 0.05$) (Table 1; Supplementary Fig. 3a).

Relationship between hyponatremia and 90-day adverse outcomes

Interactions between Na level and 90-day adverse outcomes were observed in subgroups with different TBIL levels, INR, CR levels, age, and incidence of cirrhosis, ascites, infection, and hepatic encephalopathy ($p < 0.05$), but not for sex and etiology (Supplementary Fig. 3b). Among patients with hepatitis B, regardless of receiving nucleotide/nucleoside analogs (NUCs) before admission, Na level remained an independent risk factor for 90-day adverse outcomes. We constructed four models (i.e., 1 unadjusted and 3 adjusted) to evaluate the relationship between Na level and 90-day adverse outcomes. Univariate and multivariate analyses showed that Na levels were inversely associated with the incidence of 90-day adverse outcomes (for trend, $p < 0.001$) (Table 2). After adjusting for all confounding factors that may affect the outcomes, the severe hyponatremia group had the highest risk of 90-day adverse outcomes (odds ratio [OR] 2.36; 95% confidence interval [CI] 0.98–5.67; $p = 0.056$). Therefore, hyponatremia was an independent risk factor for 90-day adverse outcomes in patients with AoCLD. When Na level was analyzed as a continuous variable, the risk of 90-day adverse outcomes decreased by 5% (OR 0.95; 95% CI 0.93–0.97; $p < 0.001$), 24% (OR, 0.76; 95% CI 0.70–0.84; $p < 0.001$), and 42% (OR 0.58; 95% CI 0.49–0.70; $p < 0.001$) for Na level increasing by 1, 5, and 10 mmol/L, respectively, after adjusting for all confounding factors. Similar results were obtained for the cirrhosis subgroup (Table 3). In the noncirrhotic population, hyponatremia increased the risk of 90-day adverse outcomes; however, no significant difference existed after adjusting for all confounding factors (Table 4). Finally, we found that the results were consistent with the original data, based on sensitivity analysis of multiple imputation missing values (Supplementary Tables 1–3).

The generalized additive model showed that, when the Na level was < 135 mmol/L, the relationship between the Na level and the incidence of 90-day adverse outcomes was approximately linear and negatively correlated, regardless of the correction of the confounding factors (Fig. 2a,b). However, when the Na level was > 135 mmol/L, the risk of 90-day adverse outcomes did not significantly increase. Therefore, a Na level of 135 mmol/L could be used as the cut-off value. The risk of 90-day adverse outcomes in patients with hyponatremia (Na level < 135 mmol/L) was significantly higher than that in patients without hyponatremia (Na level ≥ 135 mmol/L) (hazard ratio [HR], 3.01;

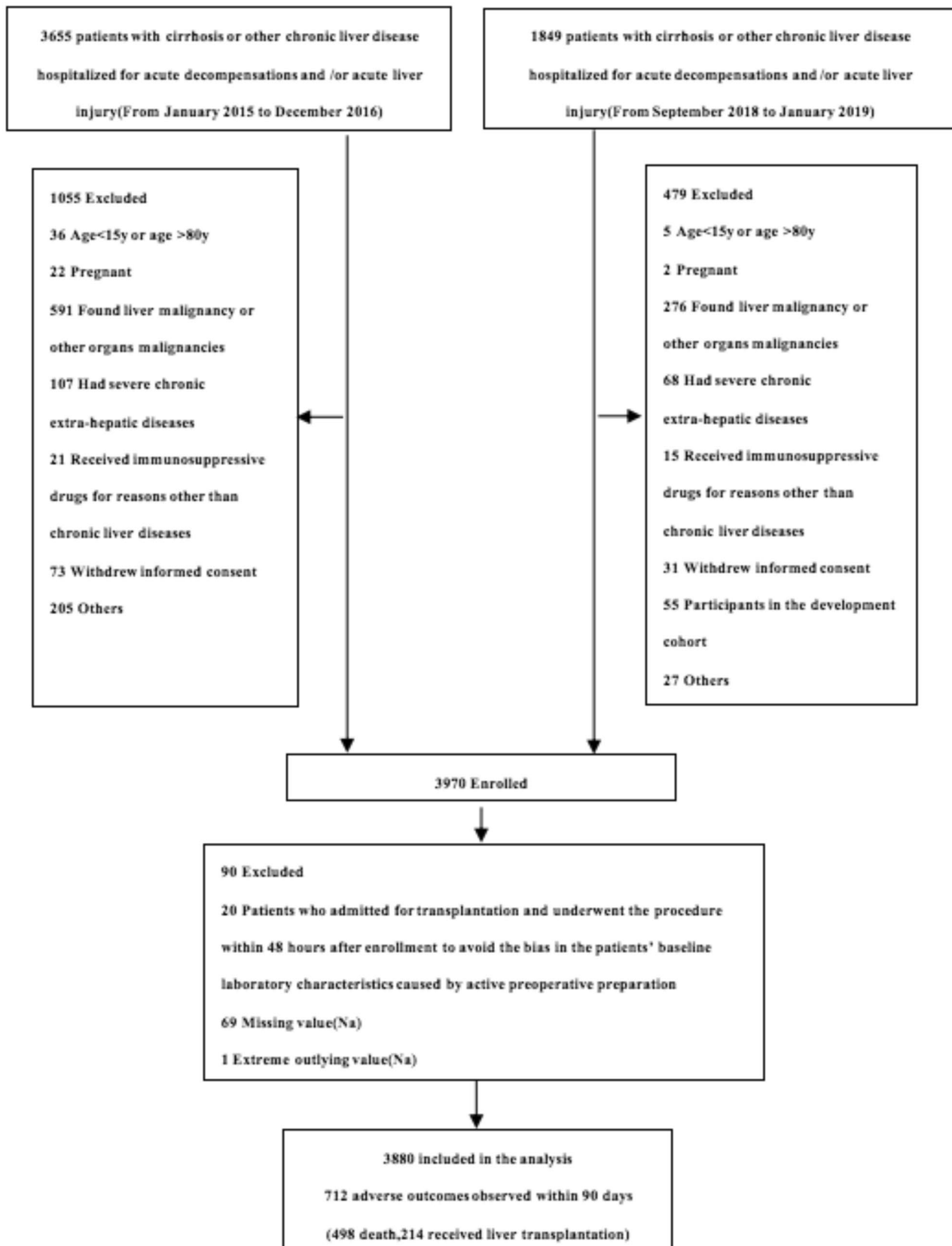


Fig. 1 Flow chart of all enrolled patients after applying the inclusion and exclusion criteria

Table 1 Baseline characteristics of patients with AoCLD among different Na level groups

Characteristics	Na ≤ 120 mmol/L (n = 28)	120 < Na < 135 mmol/L (n = 813)	135 ≤ Na ≤ 145 mmol/L (n = 2959)	Na > 145 mmol/L (n = 80)	p value
<i>Demographics</i>					
Age (years)	51.57 [43.14–59.28]	50.86 [43–58.85]	47.96 [39.15–57.13]	55 [43.38–62]	0.000
Sex (male)	16 (57.1)	621 (76.4)	2170 (73.3)	51 (63.7)	0.010
<i>Etiology</i>					
Alcoholic	7 (25)	95 (11.7)	229 (7.7)	8 (10)	0.000
HBV	11 (39.3)	429 (52.8)	1705 (57.6)	41 (51.2)	0.016
AIH	2 (7.1)	62 (7.6)	275 (9.3)	11 (13.8)	0.228
HCV	1 (3.6)	20 (2.5)	82 (2.8)	4 (5)	0.669
NAFLD	0 (0)	1 (0.1)	38 (1.3)	0 (0)	0.021
Schistosomiasis	0 (0)	7 (0.9)	16 (0.5)	2 (2.5)	0.134
HBV + Alcoholic	4 (14.3)	102 (12.5)	241 (8.1)	4 (5)	0.001
HBV + AIH	0 (0)	4 (0.5)	9 (0.3)	0 (0)	0.790
HBV + HCV	0 (0)	5 (0.6)	10 (0.3)	1 (1.3)	0.441
HBV + NAFLD	0 (0)	12 (1.5)	87 (2.9)	1 (1.3)	0.079
HBV + HEV	1 (3.6)	11 (1.4)	58 (2)	3 (3.8)	0.351
HBV + Schistosomiasis	1 (3.6)	5 (0.6)	17 (0.6)	0 (0)	0.194
<i>Cirrhosis status</i>					
non-cirrhosis	1 (3.6)	114 (14)	969 (32.7)	22 (27.5)	0.000
compensated cirrhosis	8 (28.6)	370 (45.5)	1221 (41.3)	26 (32.5)	0.000
decompensated cirrhosis	19 (67.9)	329 (40.5)	769 (26)	32 (40)	0.000
<i>Acute decompensation</i>					
HE					
Grade 0	22 (78.6)	709 (87.2)	2758 (93.2)	56 (30)	0.000
Grade 1	2 (7.1)	27 (3.3)	92 (3.1)	5 (6.3)	
Grade 2	4 (14.3)	50 (6.2)	72 (2.4)	10 (12.5)	
Grade 3	0 (0)	23 (2.8)	26 (0.9)	5 (6.3)	
Grade 4	0 (0)	4 (0.5)	11 (0.4)	4 (5)	
Infection	10 (35.7)	306 (37.6)	511 (17.3)	12 (15)	0.000
Ascites	17 (60.7)	546 (67.2)	1236 (41.8)	32 (40)	0.000
Gastrointestinal bleeding	4 (14.3)	113 (13.9)	436 (14.7)	15 (18.8)	0.707
Jaundice	20 (71.4)	543 (66.8)	1250 (42.2)	22 (27.5)	0.000
<i>Laboratory tests</i>					
ALT (U/L)	73.3 [39.23–135.63]	60.2 [29.8–192]	106 [33.1–472]	53 [26–241]	0.000
AST (U/L)	113.75 [41.28–172.9]	96 [49.5–208.05]	112 [47–299.35]	84.9 [35.6–161]	0.000
ALB (g/L)	30.4 [26.4–35.08]	29.6 [25.7–33.25]	32.9 [28.8–37.4]	32.9 [28.25–37.6]	0.000
TBIL (mg/dL)	12.21 [3.37–26.84]	11.11 [3.19–22.96]	3.42 [1.44–12.14]	2.04 [1.25–6.57]	0.000
INR	2.04 [1.37–2.69]	1.68 [1.36–2.23]	1.37 [1.16–1.7]	1.31 [1.16–1.62]	0.000
CR (mg/dL)	0.84 [0.58–1.35]	0.81 [0.67–1.08]	0.76 [0.63–0.91]	0.8 [0.6–0.96]	0.000
BUN (mmol/L)	9.53 [4.57–14.95]	5.81 [4.04–8.6]	4.3 [3.3–5.89]	5.3 [3.83–9.23]	0.000
WBC (× 10 ⁹ /L)	7.38 [3.6–11.67]	6.2 [4.17–9.21]	4.8 [3.5–6.54]	4.38 [3.15–5.82]	0.000
PLT (× 10 ⁹ /L)	67 [45.5–122]	79 [52–121]	98 [60–150.2]	74 [51–131]	0.000
HB (g/L)	106.5 [81.5–128.3]	108 [86–127]	120 [99–137]	117 [92–130]	0.000
K (mmol/L)	4.47 [3.52–5.05]	3.9 [3.5–4.3]	3.85 [3.54–4.17]	3.8 [3.3–4.1]	0.093
PaO ₂ /FiO ₂	476.19 [466.67–476.19]	471.43 [466.67–476.19]	476.19 [466.67–476.19]	476.19 [466.67–476.19]	0.000
MAP (mmHg)	86.67 [80.5–93.33]	88 [80.67–93.33]	89 [83.33–95]	93.33 [86.67–98]	0.000
<i>Scores</i>					
MELD	23 [17.5–31]	21 [15–27]	15 [10–21]	12 [10–17]	0.000
MELD_Na	33 [30.25–37]	25 [20–30]	15 [10–22]	7 [5–13]	0.000
iMELD	55 [51–64.5]	44 [38–50]	32 [26–38]	26 [23–33]	0.000

Table 1 (continued)

Characteristics	Na ≤ 120 mmol/L (n = 28)	120 < Na < 135 mmol/L (n = 813)	135 ≤ Na ≤ 145 mmol/L (n = 2959)	Na > 145 mmol/L (n = 80)	p value
CLIF_SOFA	6 [5.25–8]	7 [5–7]	4 [2–6]	4 [2–7]	0.000
SOFA	10 [9–11]	9 [8–10]	8 [6–9]	7 [7–9]	0.000
CHILD_PUGH	10.5 [9–11.75]	10 [9–11]	8 [7–10]	8 [7–10]	0.000
<i>Outcomes</i>					
90-day adverse outcomes	14 (50)	286 (35.2)	398 (13.5)	14 (17.5)	0.000
90-day death	13 (46.4)	212 (26.1)	261 (8.8)	12 (15)	0.000
90-day LT	1 (3.6)	74 (9.1)	137 (4.6)	2 (2.5)	0.000

Na serum sodium, HBV hepatitis B virus, AIH autoimmune hepatitis, HCV hepatitis C virus, HE hepatic encephalopathy, ALT aspartate aminotransferase, AST alanine aminotransferase, ALB albumin, TBIL total bilirubin, INR international normalized ratio, CR serum creatinine, BUN blood urea nitrogen, WBC white blood cell, HB hemoglobin, PLT platelet, K serum potassium, PaO₂ arterial partial pressure of oxygen, FiO₂ fraction of inspired O₂, MAP mean arterial pressure, MELD model for end-stage liver disease, iMELD integrated MELD, SOFA Sequential Organ Failure Assessment, CLIF-SOFA Chronic Liver Failure Assessment, Child–Pugh Child–Turcotte–Pugh, LT liver transplantation

*Continuous variables are presented as median (interquartile range); categorical variables are presented as n(percentage)

Table 2 Adjusted effects of Na level on 90-day adverse outcomes (death or LT) in all patients (n = 3880)

	Number of 90-day adverse outcomes (percentage)	OR, 95% CI, p value Model I	OR, 95% CI, p value Model II	OR, 95% CI, p value Model III	OR, 95% CI, p value Model IV
Na (continuous)	712 (18.35)	0.88 (0.87,0.90) < 0.001	0.90 (0.88,0.91) < 0.001	0.91 (0.89,0.92) < 0.001	0.95 (0.93,0.97) < 0.001
<i>Na-categorical</i>					
(Na 135–145 mmol/L)	398 (13.5)	1	1	1	1
(Na > 145 mmol/L)	14 (17.5)	1.37 (1.02,1.83) 0.039	1.30 (0.72,2.36) 0.386	0.91 (0.89,1.85) 0.991	1.21 (0.63,2.34) 0.565
(Na 120–135 mmol/L)	286 (35.2)	3.49 (2.92,4.18) < 0.001	3.02 (2.52,3.63) < 0.001	2.56 (2.12,3.09) < 0.001	1.72 (1.39,2.13) < 0.001
(Na ≤ 120 mmol/L)	14 (50)	6.44 (3.05,13.60) < 0.001	5.19 (2.45,11.03) < 0.001	4.41 (2.03,9.58) < 0.001	2.36 (0.98,5.67) 0.056
p value for trend*		< 0.001	< 0.001	< 0.001	< 0.001
Na (continuous 5 mmol/L decrease)		0.54 (0.50,0.59) < 0.001	0.58, (0.53,0.63) < 0.001	0.62, (0.57,0.67) < 0.001	0.76 (0.70,0.84) < 0.001
Na (continu- ous 10 mmol/L decrease)		0.29 (0.25,0.34) < 0.001	0.33 (0.28,0.39) < 0.001	0.38 (0.32,0.45) < 0.001	0.58 (0.49,0.70) < 0.001

Model I Un-adjusted;

Model II Adjusted for age, sex, cirrhosis;

Model III Adjusted for age, sex, cirrhosis, HE, ascites, infection;

Model IV Adjusted for age, sex, cirrhosis, HE, ascites, infection, TBIL, INR, CR;

CI confidence interval

*Test for trend based on variables containing median value for each group

95% CI 2.50–3.62; $p < 0.001$) (Fig. 2c), regardless of cirrhosis (Supplementary Fig. 4a, b).

Dynamic changes in Na level on days 4 and 7 related to 90-day adverse outcomes

If the Na level of patients increased to > 135 mmol/L, hyponatremia was corrected. The 90-day survival rate was

significantly higher in the corrected group than in the uncorrected group, regardless of the correction of hyponatremia on days 4 or 7 after admission (75.2% vs. 56.1% and 75.4% vs. 66.4%; $p < 0.05$) (Fig. 2d, e).

On day 4, the MELD, SOFA, and Child–Pugh scores, baseline WBC, and baseline TBIL, INR, and CR levels in the uncorrected group were significantly higher than those in the corrected group. The corrected group had a lower

Table 3 Adjusted effects of Na level on 90-day adverse outcomes (death or LT) in cirrhosis patients ($n = 2774$)

	Number of 90-day adverse outcomes (percentage)	OR, 95% CI, p value Model I	OR, 95% CI, p value Model II	OR, 95% CI, p value Model III	OR, 95% CI, p value Model IV
Na (continuous)	626 (22.57)	0.90 (0.88,0.91) <0.001	0.90 (0.88,0.91) <0.001	0.91 (0.89,0.92) <0.001	0.95 (0.93,0.96) <0.001
<i>Na-categorical</i>					
(Na 135–145 mmol/L)	336 (16.9)	1	1	1	1
(Na > 145 mmol/L)	11 (19)	1.15 (0.59,2.24)0.677	1.17 (0.60,2.29)0.641	0.92 (0.47,1.83)0.822	1.20 (0.58,2.50)0.623
(Na 120–135 mmol/L)	266 (38.1)	3.02 (2.50,3.67) <0.001	3.02 (2.49,3.66) <0.001	2.64 (2.16,3.23) <0.001	1.78 (1.42,2.23) <0.001
(Na ≤ 120 mmol/L)	13 (48.1)	4.57 (2.13,9.81) <0.001	4.64 (2.16,9.96) <0.001	4.01 (1.84,8.74) <0.001	2.13 (0.86,5.24)0.100
p value for trend*		<0.001	<0.001	<0.001	<0.001
Na (continuous 5 mmol/L decrease)		0.58 (0.53,0.63) <0.001	0.58 (0.53,0.63) <0.001	0.6 (0.56,0.67) <0.001	0.75 (0.68,0.83) <0.001
Na (continuous 10 mmol/L decrease)		0.34 (0.28,0.40) <0.001	0.34 (0.28,0.40) <0.001	0.3 (0.31,0.45) <0.001	0.57 (0.47,0.69) <0.001

Model I Un-adjusted;

Model II Adjusted for age, sex;

Model III Adjusted for age, sex, HE, ascites, infection;

Model IV Adjusted for age, sex, HE, ascites, infection, TBIL, INR, CR;

CI confidence interval

*Test for trend based on variables containing median value for each group

Table 4 Adjusted effects of Na level on 90-day adverse outcomes (death or LT) in the non-cirrhotic patients ($n = 1106$)

	Number of 90-day adverse outcomes (percentage)	OR,95% CI, p value Model I	OR, 95% CI, p value Model II	OR, 95% CI, p value Model III	OR, 95% CI, p value Model IV
Na (continuous)	86 (7.78)	0.88 (0.84,0.94) <0.001	0.89 (0.84,0.94) <0.001	0.93 (0.88,0.99)0.023	0.99 (0.93,1.05)0.659
<i>Na (categorical)</i>					
(Na level 135–145 mmol/L)	62 (6.4)	1	1	1	1
(Na level > 145 mmol/L)	3 (13.6)	2.31 (0.67,8.02)0.187	2.22 (0.63,7.84)0.215	1.98 (0.44,8.89)0.371	1.69 (0.36,7.98)0.505
(Na level 120–135 mmol/L)	21 (18.2)	3.27 (1.91,5.60) <0.001	2.9 (1.69,5.04) <0.001	2.06 (1.10,3.83)0.024	1.47 (0.76,2.81)0.250
p value for trend*		<0.001	<0.001	0.023	0.207
Na (Continuous 5 mmol/L decrease)		0.54 (0.41,0.72) <0.001	0.56 (0.43,0.74) <0.001	0.71 (0.53,0.96)0.023	0.93 (0.68,1.28)0.659
Na (Continuous 10 mmol/L decrease)		0.29 (0.17,0.51) <0.001	0.32 (0.18,0.55) <0.001	0.51 (0.28,0.91)0.023	0.87 (0.46,1.63)0.659

Model I Un-adjusted;

Model II Adjusted for age, sex;

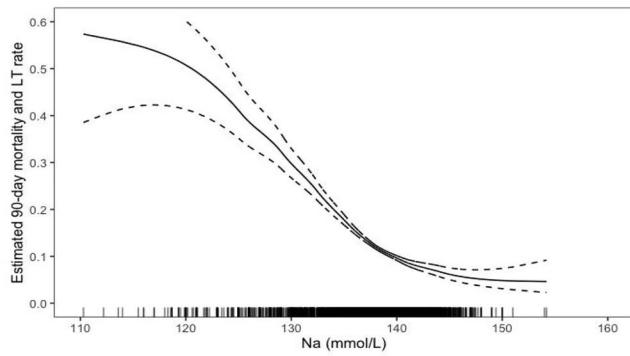
Model III Adjusted for age, sex, HE, ascites, infection;

Model IV Adjusted for age, sex, HE, ascites, infection, TBIL, INR, CR;

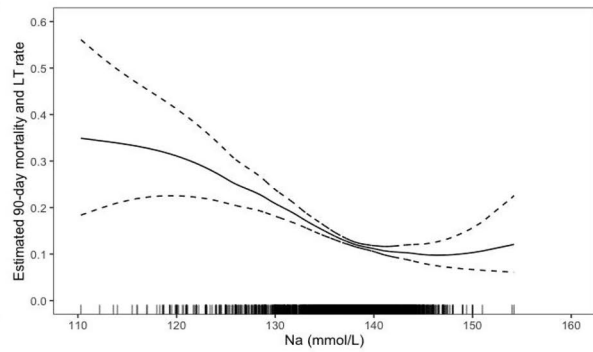
CI confidence interval

*Test for trend based on variables containing median value for each group

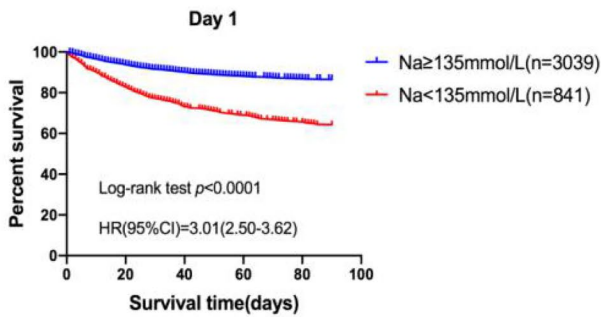
a



b

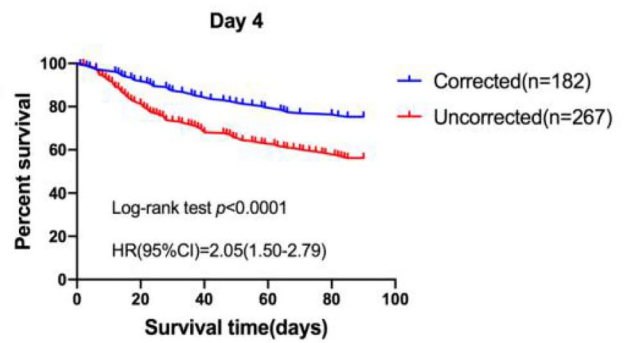


c



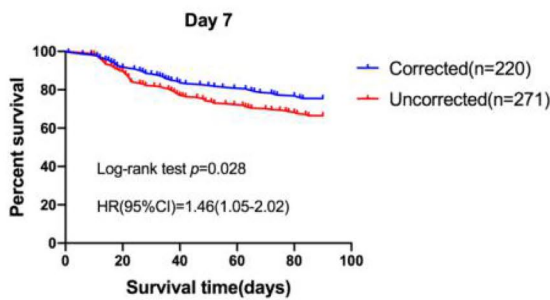
Sodium_cutoff	Total number	Adverse outcome	After adjusted	
			Number	Percentage survival
<135	841	300	541	64.3%
≥135	3039	412	2627	86.4%
All	3880	712	3168	81.6%

d



Sodium_cutoff	Total number	Adverse outcome	After adjusted	
			Number	Percentage survival
<135	267	117	150	56.1%
≥135	182	45	137	75.2%
All	449	162	287	63.9%

e



Sodium_cutoff	Total number	Adverse outcome	After adjusted	
			Number	Percentage survival
<135	271	91	180	66.4%
≥135	220	54	166	75.4%
All	491	145	346	70.4%

f

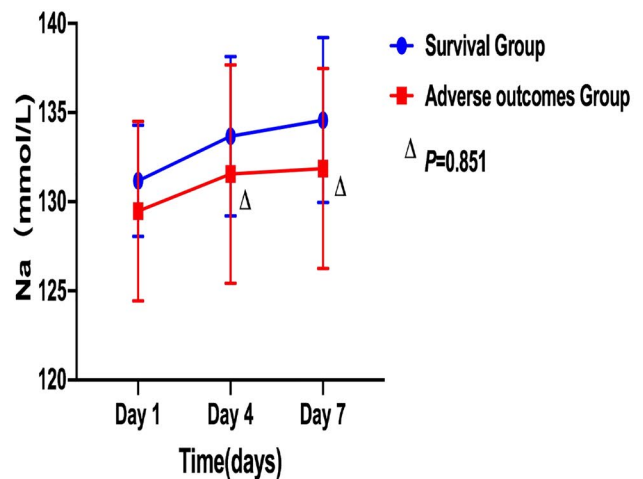


Fig. 2 **a** The association between Na level and 90-day adverse outcomes in patients with AoCLD (unadjusted). **b** The association between Na level and 90-day adverse outcomes in patients with AoCLD (adjusted). **c** Survival analysis, based on the Na cut-off value, using the Kaplan–Meier method. **d** Kaplan–Meier curves of patients with corrected or uncorrected hyponatremia on day 4 after admission. **e** Kaplan–Meier curves of patients with corrected or uncorrected hyponatremia on day 7 after admission. **f** Dynamic changes in Na level between the survival group and adverse outcome group 7 days after admission

incidence of cirrhosis, ascites, and infection than the uncorrected group ($p < 0.05$) (Supplementary Table 4). Dynamic observation revealed that the Na levels on days 4 and 7 were significantly lower in patients with 90-day adverse outcomes after admission than in patients in the survival group ($p < 0.05$). However, in the 90-day adverse outcomes group, changes in Na level were not significantly different between days 4 and 7 ($p = 0.851$) (Fig. 2f).

Discussion

Our study population represents most inpatients with liver disease in areas with a high prevalence of HBV in China. Therefore, despite the fact that hyponatremia is a well-recognized complication of cirrhotic patients, a specific analysis of hyponatremia in patients with AoCLD had so far not been reported. The investigation of this relationship is clinically relevant, given the important physiological effects of low serum Na levels and the well-demonstrated relationship between hyponatremia and survival in a Chinese population with CLD. To the best of our knowledge, this study is the first to describe the prevalence of hyponatremia, normonatremia, and hypernatremia and their relationship with 90-day prognosis in hospitalized patients with AoCLD. We confirmed that hyponatremia is an independent risk factor for 90-day adverse outcomes in this population, which is independent of other indicators reflecting liver dysfunction, regardless of the etiology of chronic liver disease and whether patients with hepatitis B have received NUCs before admission. The risk of 90-day adverse outcomes decreased by 5%, 24%, and 42% for Na levels increased by 1, 5, and 10 mmol/L, respectively. These patients whose hyponatremia could be corrected on days 4 or 7 had a better prognosis than those whose hyponatremia could not be corrected.

In the past few decades, major studies [7, 9–12] have confirmed that hyponatremia is an independent risk factor for poor prognosis in cirrhotic patients. The European CANONIC cohort study in 2014 indicated that hyponatremia was also an independent risk factor for 90-day poor prognosis in patients with acute-on-chronic liver failure [22]. As expected, our study showed similar results in hospitalized patients with AoCLD. The LT-free mortality of patients with

severe hyponatremia in our study (48%) was higher than that reported in a previous study [23]. In advanced cirrhosis, renal free water clearance function is impaired, serum Na balance is not maintained, and diluted hyponatremia occurs and is reasonably considered present; however, due to its unique human physiopathological mechanisms of systemic vasodilatation, clinicians often ignore it in daily practice [12]. Previous research showed that hyponatremia is usually accompanied by various complications in cirrhotic patients, which somewhat reflect the severity of portal hypertension [19, 24]. In our study, the incidence of liver cirrhosis, ascites, infection, hepatic encephalopathy, and jaundice in hyponatremic patients was also significantly higher, especially in patients with severe hyponatremia. Patients with severe hyponatremia tended to have a poorer liver function and higher 90-day mortality. Thus, LT should be actively considered for this population. Moreover, it is worth mentioning that 18.2% of noncirrhotic patients in our cohort still had hyponatremia and a risk of 90-day adverse outcomes. This number was only slightly lower than that in cirrhotic patients. Interestingly, after adjusting for acute decompensated events in noncirrhotic patients, the risk of 90-day adverse outcomes was statistically significant. However, the risk disappeared after the MELD score was adjusted, which suggested that Na level was not a predictor of 90-day prognosis in noncirrhotic patients. This finding was different from that in cirrhotic patients as the mechanisms of hyponatremia differ.

The European Association for the Study of the Liver guidelines (Clinical Practice Guidelines for the Management of Patients with Decompensated Cirrhosis) recommends that cirrhotic patients limit fluid intake and increase the dose of diuretics or use vaptans to increase the excretion of renal solute free water and other measures to improve hyponatremia when Na level is < 130 mmol/L [25]. In fact, high-level hyponatremia (Na level, 130–135 mmol/L) is deemed unsuitable for treatment because it is always considered a frequent and harmless feature of severe liver disease [26]. In our study, there were 86 patients with Na level of 125 mmol/L and 755 patients with Na level between > 125 mmol/L and < 135 mmol/L. However, when Na level was < 135 mmol/L, the risk of 90-day adverse outcomes increased, which was stricter than the 130 mmol/L recommended by the guidelines [25]. This finding suggests the necessity of hyponatremia correction in patients with AoCLD. Na level of < 135 mmol/L should be considered for management by clinicians. Ahluwalia et al. [27] found that cirrhotic patients can benefit from hyponatremia correction, which improves cognitive function and HRQOL. Dedicated specialist input and active treatment of severe hyponatremia can effectively reduce mortality [28]. Based on experience from the European CANONIC cohort study, most of the patients will have a clear prognosis between days 3 and 7

of hospital admission, and clinical decisions, such as evaluation for liver transplant or discussion over goals of care, could be tailored using clinical scores [29]. However, there is limited information regarding whether hyponatremia correction in 1 week could improve the 90-day prognosis. Our study suggests that hyponatremia correction was associated with improvement in clinically relevant outcomes, regardless of day 4 or 7. The Na level increased continuously from day 4 to 7 in hyponatremic patients who survived; therefore, focusing on dynamic changes in Na level and managing hyponatremia in AoCLD in the first week after admission are crucial. Persistent abnormal Na level is often associated with an increased risk of death. This finding is supported by the fact that hyponatremia could not be corrected on day 4, and hyponatremic patients had a higher mortality rate, MELD score, and incidence of cirrhosis, infection, and ascites than those without hyponatremia. Therefore, managing complications associated with hyponatremia is essential. However, this needs to be further studied in patients with AoCLD and those with hyponatremia.

This was a large multicenter, prospective cohort study focused on areas with a high prevalence of HBV in China. All patients were followed up for 90 days, and most data were collected to ensure authenticity and integrity. In addition to the baseline material, we similarly analyzed the dynamic Na levels on days 4 and 7 after admission.

This study has some limitations. First, there were some missing values for the dynamic Na level. Second, owing to the nature of observational studies and various patient conditions, therapy measures of hyponatremia were not unified among the centers; however, we employed a unified standard of diagnosis and treatment for hyponatremia [30].

In conclusion, our study showed that hyponatremia is an independent risk factor for 90-day adverse outcomes in hospitalized patients with AoCLD. Elevated Na levels reduced the risk of 90-day adverse outcomes, and failure to correct hyponatremia in a week after admission was often associated with increased mortality. Therefore, clinicians should focus on hyponatremia in patients with AoCLD and actively manage its related complications in daily clinical practice for hyponatremia correction.

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Author contributions XM, HL, XW, GD, and YH contributed equally and share first authorship. HL, GD, XW, XZ, YH, JC, ZM, YG, FL, XL, YS, YZ, HY, and ZQ obtained the funding. ZQ and WY designed the study. LQ, WG, YZ, XX, YZ, SS, YH, QZ, YX, CZ, JC, ZH, BL, XJ, GZ, HW, YC, SL, NG, CL, JL, TL, RZ, XZ, and HR collected the data. WZ directed statistical analysis. XM drafted the manuscript. ZQ and WY contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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Data and material availability All data included in this study are available upon request by contact with the corresponding author.

Code availability All codes used in this study followed the manuals of each R package, which are fully open accessed.

Declarations

Conflict of interest Xue Mei, Hai Li, Guohong Deng, Xianbo Wang, Xin Zheng, Yan Huang, Jinjun Chen, Zhongji Meng, Yanhang Gao, Feng Liu, Xiaobo Lu, Yu Shi, Yubao Zheng, Huadong Yan, Weituo Zhang, Liang Qiao, Wenyi Gu, Yan Zhang, Xiaomei Xiang, Yi Zhou, Shuning Sun, Yixin Hou, Qun Zhang, Yan Xiong, Congcong Zou, Jun Chen, Zebing Huang, Beiling Li, Xiuhua Jiang, Guotao Zhong, Haiyu Wang, Yuanyuan Chen, Sen Luo, Na Gao, Chunyan Liu, Jing Li, Tao Li, Rongjiong Zheng, Xinyi Zhou, Haotang Ren, Wei Yuan, Zhiping Qian declare that they have no conflict of interest.

Ethics approval The ethics committee of Ren Ji Hospital (the lead center of the CATCH-LIFE study), School of Medicine, Shanghai Jiaotong University (Shanghai, China) approved the study [ethics code: (2014)148k and (2016)142k].

Consent to participate Written informed consent was obtained from all patients.

Consent for publication All authors of this manuscript have read and approved the final submitted version and are aware that they are listed as an author on this paper.

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