Original Article
Serum sodium, potassium, calcium, and chlorine for predicting the in-hospital mortality in cirrhotic patients with acute upper gastrointestinal bleeding: a retrospective observational study

Zheng Ning[1,2*], Xingshun Qi[1*], Feifei Hou[1,3], Jiancheng Zhao[1,3], Ying Peng[1,2], Hongyu Li[1], Jing Li[1,2], Han Deng[1,2], Xintong Zhang[1,4], Xiaozhong Guo[1]

[1]Liver Cirrhosis Study Group, Department of Gastroenterology, General Hospital of Shenyang Military Area, Shenyang, China; [2]Postgraduate College, Dalian Medical University, Dalian, China; [3]Postgraduate College, Liaoning University of Traditional Chinese Medicine, Shenyang, China; [4]Postgraduate College, Fourth Military Medical University, Xi'an, China. *Equal contributors.

Abstract: Background and aims: The association of electrolytes with the outcomes of acute upper gastrointestinal bleeding (AUGIB) in liver cirrhosis remains unclear. A retrospective observational study aimed to explore whether or not serum sodium, potassium, calcium, and chlorine could predict the in-hospital mortality in such patients. Methods: All consecutive patients with liver cirrhosis and AUGIB admitting to our hospital between January 2011 and June 2014 were retrospectively included in this study. Serum sodium, potassium, calcium, and chlorine concentrations were collected. Their prognostic values were evaluated by receiver operating characteristic (ROC) curve analyses. Areas under curve (AUCs) with 95% confidence intervals (CIs), sensitivity, and specificity were reported. Results: Overall, 713 cirrhotic patients with AUGIB were included. ROC curve analyses demonstrated that serum sodium, potassium, and chlorine, rather than calcium, could significantly predict the in-hospital death (AUC=0.619, 95% CI: 0.508-0.729, P=0.023; AUC=0.615, 95% CI: 0.502-0.728, P=0.028; AUC=0.605, 95% CI: 0.475-0.735, P=0.045; AUC=0.423, 95% CI: 0.248-0.597, P=0.296, respectively). The best cut-off value of serum sodium, potassium, and chlorine was 140.5 mmol/L (sensitivity: 56%; specificity: 71%), 4.34 mmol/L (sensitivity: 53.1%; specificity: 74.4%) and 112.9 mmol/L (sensitivity: 37.5%; specificity: 92.9%), respectively. The in-hospital mortality was significantly different between patients with sodium >140.5 mmol/L and ≤140.5 mmol/L (8.7% *vs.* 2.1%, P<0.001), between patients with potassium >4.34 and ≤4.34 mmol/L (8.5% *vs.* 3.4%, P=0.005), and between patients with chlorine >112.9 and ≤112.9 mmol/L (20.7% *vs.* 3.2%, P<0.001). Conclusion: Higher serum sodium, potassium, and chlorine concentrations were positively associated with increased in-hospital mortality of cirrhotic patients with AUGIB.

Keywords: Electrolyte, liver cirrhosis, hepatic, prognosis, death

Introduction

Liver cirrhosis is the end stage of chronic liver diseases [1], which can lead to portal hypertension-related complications and liver failure. Acute upper gastrointestinal bleeding (AUGIB) is one of the most lethal complications of liver cirrhosis. Most of AUGIB events originate from the rupture of gastroesophageal varices [2]. It is clinically important to predict the early mortality (e.g. in-hospital mortality) of cirrhotic patients with AUGIB. The knowledge is useful to alert the physicians, patients, and patients' family members about who is at a high risk of early death. Although this issue has been explored by numerous studies [3], few studies have focused on the role of electrolyte balance in predicting the outcomes of AUGIB in liver cirrhosis. By comparison, the impact of serum sodium on the outcome of cirrhotic patients with ascites has been widely identified [4, 5]. Additionally, as we have known, model for end stage liver disease (MELD) score is an important index for assessing the prognosis of liver cirrhosis [6]. Notably, the incorporation of serum sodium into the MELD score (i.e., MELD-

Table 1. Patient characteristics

Variables	No. Pts available	Results
Age-years	713	56.17 ± 12.00
Sex (Male/Female), n (%)	713	479 (67.2)/234 (32.8)
Causes of liver diseases, n (%)	713	
HBV		204 (28.6)
HCV		46 (6.5)
HBV+HCV		4 (0.6)
Alcohol		185 (25.9)
HBV+Alcohol		37 (5.2)
HCV+Alcohol		9 (1.3)
HBV+HCV+Alcohol		3 (0.4)
Autoimmune		46 (6.5)
Drug		20 (2.8)
Cholestatic		13 (1.8)
Others		5 (0.7)
Unknown		141 (19.8)
Ascites, n (%)	711	
No		378 (53.2)
Mild		79 (11.1)
Moderate and severe		254 (35.7)
HE, n (%)	711	
No		666 (93.7)
Grade I-II		37 (5.2)
Grade III-IV		8 (1.1)
RBC (10^{12}/L)	709	2.69 ± 1.51
Hb (g/L)	709	74.35 ± 22.17
WBC (10^9/L)	709	6.27 ± 5.42
PLT (10^9/L)	709	98.36 ± 88.58
TBIL (μmol/L)	686	28.23 ± 35.20
DBIL (μmol/L)	686	13.95 ± 23.89
IBIL (μmol/L)	686	14.31 ± 13.88
ALB (g/L)	683	30.27 ± 6.51
ALT (U/L)	686	32.71 ± 50.22
AST (U/L)	686	50.31 ± 102.64
ALP (U/L)	685	92.08 ± 81.19
GGT (U/L)	685	81.03 ± 131.22
BUN (mmol/L)	662	9.02 ± 5.87
Cr (μmol/L)	662	71.13 ± 63.96
Potassium (mmol/L)	684	4.11 ± 0.55
Sodium (mmol/L)	684	138.48 ± 4.53
Calcium (mmol/L)	360	2.04 ± 0.22
Chlorine (mmol/L)	683	106.84 ± 5.85
PT (second)	652	17.19 ± 5.30
APTT (second)	647	41.65 ± 10.20
INR	647	1.44 ± 0.66
Child-Pugh score	618	7.54 ± 1.88
Child-Pugh class, n (%)		

Na score) has further improved the prognostic significance [7]. Thus, we hypothesized that serum sodium and other electrolytes might be also associated with the prognosis of AUGIB in liver cirrhosis. The aim of our study was to explore whether or not serum sodium, potassium, calcium, and chlorine could predict the in-hospital mortality of cirrhotic patients with AUGIB.

Patients and methods

Patient selection

In this retrospective observational study, all patients who were consecutively admitted to our hospital between January 2011 and June 2014 were eligible. Inclusion criteria should be as follows: 1) a diagnosis of liver cirrhosis; and 2) AUGIB, regardless of variceal and non-variceal bleeding. AUGIB was defined as a new episode of upper gastrointestinal bleeding within 5 days before our admission. Malignancy was excluded. Because only the in-hospital death was observed, repeated admission was not excluded. Some patients had been included in our previous studies [8-11]. This study protocol was approved by the Ethic Committee of our hospital (number k [2015] 18). Due to the study objective and design, the patients' informed consent was waived.

Data collection

All patients' medical charts were retrospectively reviewed to collect the following baseline data: age, sex, cause of liver cirrhosis, AUGIB, ascites, hepatic encephalopathy, and routine laboratory data. AUGIB was independently evaluated by two investigators, and finally validated by another investigator. The discrepancy was resolved after their discussions. Grade of ascites and hepatic encephalopathy were established according to the relevant criteria [12, 13]. The laboratory data primarily

A		213 (34.5)
B		309 (50.0)
C		96 (15.5)
MELD score	620	7.09 ± 6.57

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; RBC, red blood cell; Hb, hemoglobin; WBC, white blood cell; PLT, platelet; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio; MELD, model for end stage liver disease.

Table 2. Treatment options for AUGIB

Treatment options	No. Pts available	Results
Endoscopic treatment, n (%)	713	427 (59.9)
Sengstaken-Blackmore tube, n (%)	713	19 (2.7)
Somatostatin, n (%)	713	656 (92.0)
Blood transfusion, n (%)	713	451 (63.3)
Hemostatics, n (%)	713	593 (83.2)
Proton pump inhibitor, n (%)	713	698 (97.9)
Splenectomy, n (%)	704	4 (0.6)

included red blood cell count, hemoglobin, white blood cell count, platelet count, total bilirubin, direct bilirubin, indirect bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, blood urea nitrogen, creatinine, prothrombin time, activated partial thromboplastin time, international normalized ratio, sodium, potassium, calcium, and chlorine. In our hospital, the reference range of serum sodium, potassium, calcium, and chlorine was 135-145 mmol/L, 3.5-4.5 mmol/L, 2.2-2.5 mmol/L, and 99-110 mmol/L, respectively. Child-Pugh and MELD scores were calculated according to the relevant formulas [6, 14]. The treatment options for AUGIB were also collected, including endoscopic treatment, Sengstaken-Blackmore tube, somatostatin, blood transfusion, hemostatics, proton pump inhibitor, and surgery. The in-hospital death and cause of death were clearly recorded.

Statistical analysis

Continuous and categorical data were expressed as mean ± standard deviation and frequency (percentage), respectively. The patients were divided into hyper-electrolyte, normal electrolyte, and hypo-electrolyte groups according to the reference range of serum sodium, potassium, calcium, and chlorine levels. The in-hospital mortality was compared among groups by Chi-square tests. Receiver operating characteristic (ROC) curve analysis was employed to identify the best cut-off value of serum sodium, potassium, calcium, and chlorine concentrations for predicting the in-hospital death. Areas under curve (AUCs) with 95% confidence intervals (CIs) were calculated. Sensitivity and specificity were also reported. Two-sided *P* value <0.05 was considered statistically significant. All statistical analyses were performed by using SPSS Statistics version 17.0.0.

Results

During the enrollment period, a total of 713 cirrhotic patients with AUGIB were included in the study. Patient characteristics were shown in **Table 1**. A majority of patients had HBV and alcohol abuse related liver cirrhosis. Among them, Child-Pugh scores were available in 618 patients; 213, 309, and 96 patients had Child-Pugh class A, B, and C, respectively. Treatment options for AUGIB were shown in **Table 2**. In-hospital mortality was 4.6% (33/713). Distribution of serum sodium, potassium, calcium, and chlorine concentrations were shown in **Figure 1A-D**.
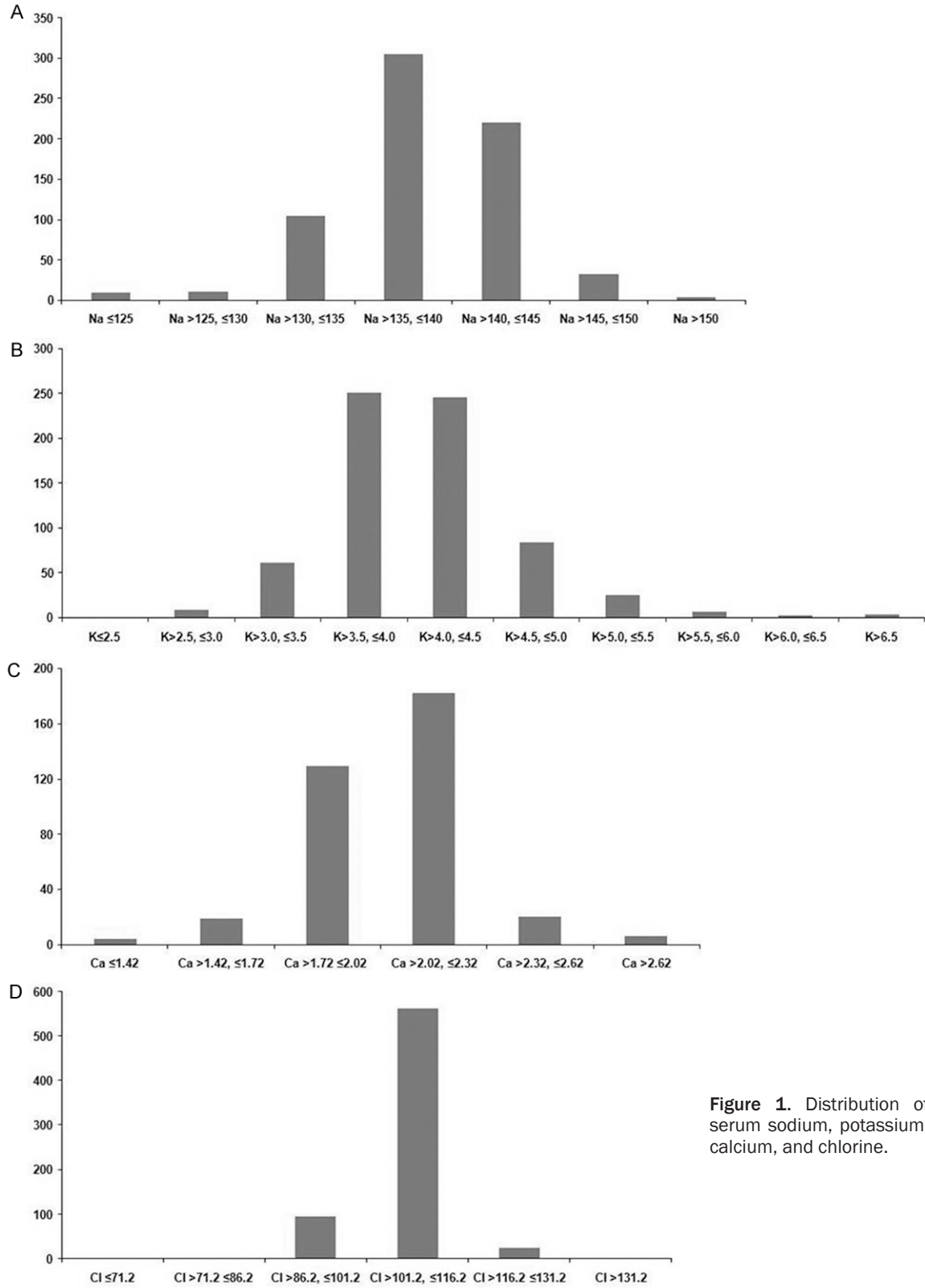
Serum sodium

Serum sodium was available in 684 patients. Among them, 120, 528, and 36 patients had serum sodium concentration of <135 mmol/L, 135-145 mmol/L, and >145 mmol/L, respectively (Supplementary Figure 1A). The in-hospital mortality was 3.3% (4/120), 4.7% (25/528), and 8.3% (3/36), respectively (P=0.456) (Supplementary Figure 1B).

Serum potassium

Serum potassium was available in 684 patients. Among them, 51, 622, and 11 patients had a serum potassium concentration of <3.5 mmol/L, 3.5-4.5 mmol/L, and >4.5 mmol/L,
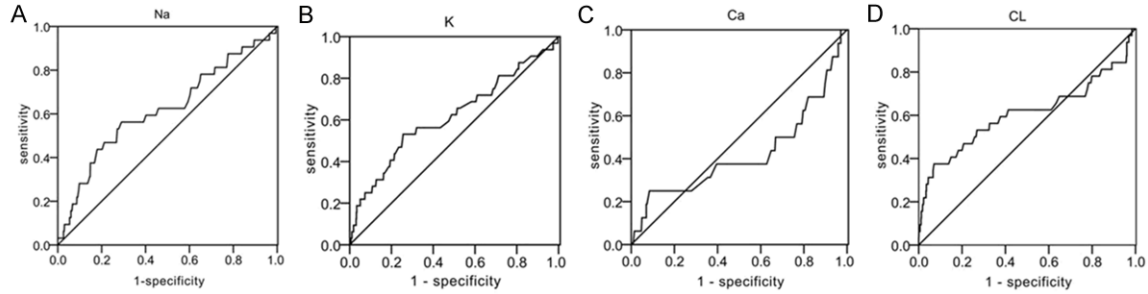
Figure 1. Distribution of serum sodium, potassium, calcium, and chlorine.

respectively (Supplementary Figure 2A). The in-hospital mortality was 3.9% (2/51), 4.5% (28/622), and 18.2% (2/11), respectively (P= 0.100) (Supplementary Figure 2B).

Figure 2. ROC results of serum sodium, potassium, calcium, and chlorine for predicting the in-hospital mortality in cirrhotic patients with AUGIB.

Serum calcium

Serum calcium was available in 360 patients. Among them, 294, 55, and 11 patients had a serum potassium concentration of <2.2 mmol/L, 2.2-2.5 mmol/L, and >2.5 mmol/L, respectively (Supplementary Figure 3A). The in-hospital mortality was 4.1% (12/294), 5.5% (3/55), and 9.1% (1/11), respectively (P=0.676) (Supplementary Figure 3B).

Serum chlorine

Serum chlorine was available in 683 patients. Among them, 51, 444, and 188 patients had a serum potassium concentration of <99 mmol/L, 99-110 mmol/L, and >110 mmol/L, respectively (Supplementary Figure 4A). The in-hospital mortality was 9.8% (5/51), 2.5% (11/444), and 8.5% (16/188), respectively (P=0.001) (Supplementary Figure 4B).

ROC curve analysis

AUC of serum sodium concentration for predicting the in-hospital death was 0.619±0.056 (95% CI: 0.508-0.729, P=0.023) (**Figure 2A**). The best cut-off value of serum sodium was 140.5 mmol/L with a sensitivity of 56% and a specificity of 71%.

AUC of serum potassium concentration for predicting the in-hospital death was 0.615±0.058 (95% CI: 0.502-0.728, P=0.028) (**Figure 2B**). The best cut-off value of serum potassium was 4.34 mmol/L with a sensitivity of 53.1% and a specificity of 74.4%.

AUC of serum calcium concentration for predicting the in-hospital death was 0.423±0.089 (95% CI: 0.248-0.597, P=0.296) (**Figure 2C**). The best cut-off value of serum calcium was 2.30 mmol/L with a sensitivity of 25.0% and a specificity of 91.6%.

AUC of serum chlorine concentration for predicting the in-hospital death was 0.605±0.066 (95% CI: 0.475-0.735, P=0.045) (**Figure 2D**). The best cut-off value of serum chlorine was 112.9 mmol/L with a sensitivity of 37.5% and a specificity of 92.9%.

In-hospital mortality according to the cut-off value

Serum sodium concentration was > and ≤140.5 mmol/L in 207 and 477 patients, respectively. The in-hospital mortality was 8.7% (18/207) and 2.1% (14/477), respectively (P<0.001).

Serum potassium concentration was > and ≤4.34 mmol/L in 177 and 507 patients, respectively. The in-hospital mortality was 8.5% (15/177) and 3.4% (17/507), respectively (P=0.005).

Serum chlorine concentration was > and ≤112.9 mmol/L in 58 and 625 patients, respectively. The in-hospital mortality was 20.7% (12/58) and 3.2% (20/625), respectively (P<0.001).

Discussion

This was a large retrospective observational study, which aimed at evaluating the role of serum sodium, potassium, calcium, and chlorine in predicting the in-hospital mortality of cirrhotic patients with AUGIB. Their respective cut-off values were also identified by the ROC curve analyses. We found that higher serum sodium, potassium, and chlorine concentrations were significantly associated with the in-hospital mortality of cirrhotic patients with

AUGIB. This phenomenon was almost opposite to previous findings that lower serum sodium concentration was associated with worse outcomes of cirrhotic patients with ascites [4, 15]. It might be explained by a situation that acute bleeding events might cause pachyemia conditions, thereby potentially elevating the electrolyte concentrations. If so, the elevation of electrolyte concentrations might be positively associated with the severity of AUGIB.

Lots of studies have confirmed that hyponatremia is significantly associated with poor prognosis of cirrhotic patients. Angeli et al. prospectively enrolled 997 consecutive patients with liver cirrhosis and ascites between March 2003 and August 2003 from 28 centers in Europe, North and South America, and Asia [15]. Low serum sodium concentrations were associated with higher frequency of severe ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. Recently, Umemura et al. also found that patients with serum sodium concentration <139 mEq/L had a significantly lower cumulative survival rate than those with serum sodium concentration >139 mEq/L [16]. On the other hand, in the ambulatory setting, hyponatremia is significantly associated with an increased risk of all-cause mortality [17]. To the best of our knowledge, our study have for the first time identified the role of hypernatremia in predicting the in-hospital mortality of cirrhotic patients with AUGIB. By comparison, we found that serum sodium >140.5 mmol/L was significantly associated with higher in-hospital mortality. Notably, cirrhotic patients with AUGIB should be regarded as our study population, rather than those with ascites. It is reasonable to speculate that the predictive value of serum sodium should be variable among the study population. Indeed, in one early study, Rodes et al. reported 3 cases with liver cirrhosis and ascites, suggesting that the occurrence of gastrointestinal bleeding led to an increase in blood urea nitrogen and plasma osmolality, thereby producing osmotic diuresis and hypernatremia [18]. Presumably, the severity of AUGIB might be reflected by serum sodium levels in liver cirrhosis.

In a Swedish prospective multicenter study, serum potassium had the strongest correlation with mortality. Hyperkalemia had a significantly higher risk of death than hypokalemia in cir-

rhotic patients with ascites [19]. It should be noticed that all 22 patients with serum potassium concentration ≥4.8 mmol/L died within 1 year. Similarly, our study also found that serum potassium concentration >4.34 mmol/L was significantly associated with a higher in-hospital mortality of cirrhotic patients with AUGIB.

Although calcium metabolism was often influenced by chronic liver diseases [20], especially primary biliary cirrhosis, few studies assessed the role of calcium levels in predicting the outcomes of liver cirrhosis [21]. A nested case-control study by Yin et al. demonstrated a positive correlation of serum calcium level with risk of liver cirrhosis. Genovesi et al. also found that lower plasma calcium levels were significantly associated with longer QTc intervals, which might induce potentially lethal complications [22]. However, our study did not find any significant associations between calcium levels and risk of in-hospital death.

Until now, few studies have explored the association of serum chlorine concentration with the prognosis of liver cirrhosis. However, the role of chlorine in other patients has been analyzed. Some studies favored a positive association of chlorine concentration with poor outcome. Zhao et al. found that an increased chlorine concentration was independently associated with the presence of coronary heart disease in Han Chinese population [23]. Others suggested an inverse association of chlorine concentration with poor outcome. Kimura et al. compared the chlorine concentration after thoracic or abdominal surgery between hospital survivors and non-survivors. Hypochloremia was independently associated with in-hospital death (odds ratio=5.8, 95% CI=1.1-30.2) [24]. Notably, the in-hospital mortality was significantly higher in patients with hypochloremia than in those with normal chlorine concentration (28.6% versus 6.0%, P=0.007). McCallum et al. found that serum chlorine concentration <100 mEq/L at baseline was independently associated with an increased mortality in hypertensive patients during a long-term follow-up [25]. Grodin et al. also found that admission serum chloride level <99 mEq/L had a significantly higher mortality than serum chloride level ≥99 mEq/L in patients with acute decompensated heart failure [26]. In our study, the ROC curve analysis demonstrated that an ele-

vated serum chlorine concentration might be associated with the in-hospital mortality of AUGIB in liver cirrhosis. Notably, the specificity of serum chlorine for predicting the in-hospital mortality was very high. In other words, serum chlorine <112.9 mmol/L could accurately predict the probability of being alive during hospitalization.

Our study had several limitations. First, due to the retrospective nature, the potential bias of patient selection should never be neglected. Not all included patients underwent the laboratory tests for electrolyte levels. Calcium levels were available in less than 50% of patients. Second, not all included patients underwent endoscopic examinations. Thus, we did not separate patients with acute variceal bleeding into an individual group. Third, the endpoint was in-hospital death, but the long-term follow-up outcomes were not available.

In conclusion, serum sodium, potassium, and chlorine concentrations should be incorporated into the model for predicting the in-hospital mortality of cirrhotic patients with AUGIB. Considering that their prognostic accuracy might be relatively modest, further studies should validate the clinical usefulness of serum sodium, potassium, and chlorine concentrations.

Disclosure of conflict of interest

None.

Authors' contribution

Zheng Ning: reviewed the literature, wrote the protocol, collected the data, and performed the statistical analysis. Xingshun Qi: designed the study, wrote the protocol, performed the statistical analysis, interpreted the data, and drafted the manuscript. Feifei Hou, Jiancheng Zhao, Ying Peng, Jing Li, Han Deng, Xintong Zhang collected the data. Xiaozhong Guo and Hongyu Li gave critical comments and revised the manuscript. All authors have made an intellectual contribution to the manuscript and approved the submission.

Address correspondence to: Drs. Hongyu Li, Xiaozhong Guo and Xingshun Qi, Liver Cirrhosis Study Group, Department of Gastroenterology, General Hospital of Shenyang Military Area, 83 Wenhua Road, Shenyang 110840, China. Tel: 86-24-2889-7603; Fax: 86-24-28851113; E-mail: 13309887-041@163.com (HYL); guo_xiao_zhong@126.com (XZG); xingshunqi@126.com (XSQ)

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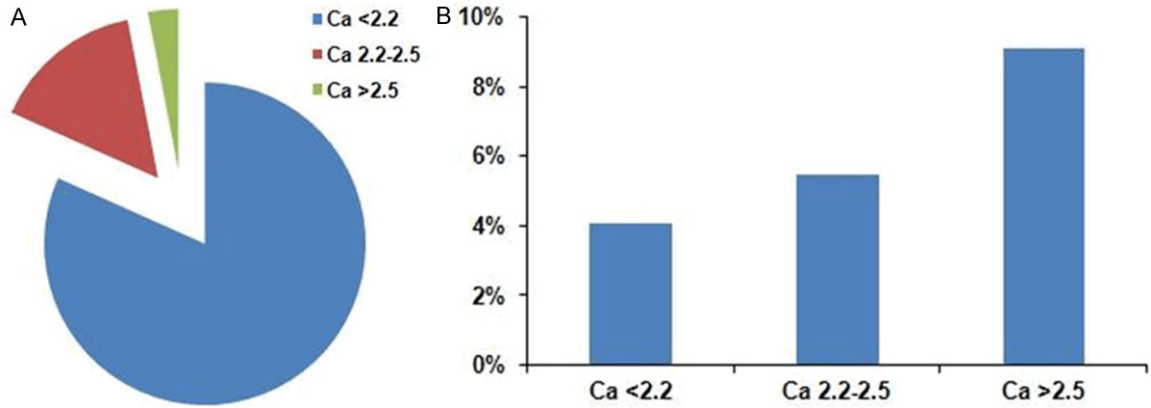
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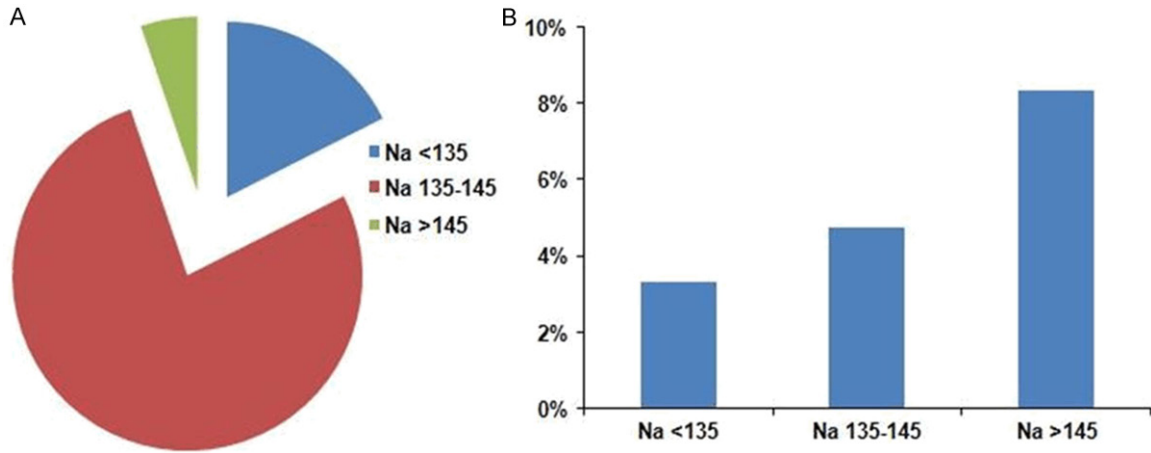
Supplementary Figure 1. In-hospital mortality according to the normal range of serum sodium. A. Proportion of serum sodium. B. In-hospital mortality.
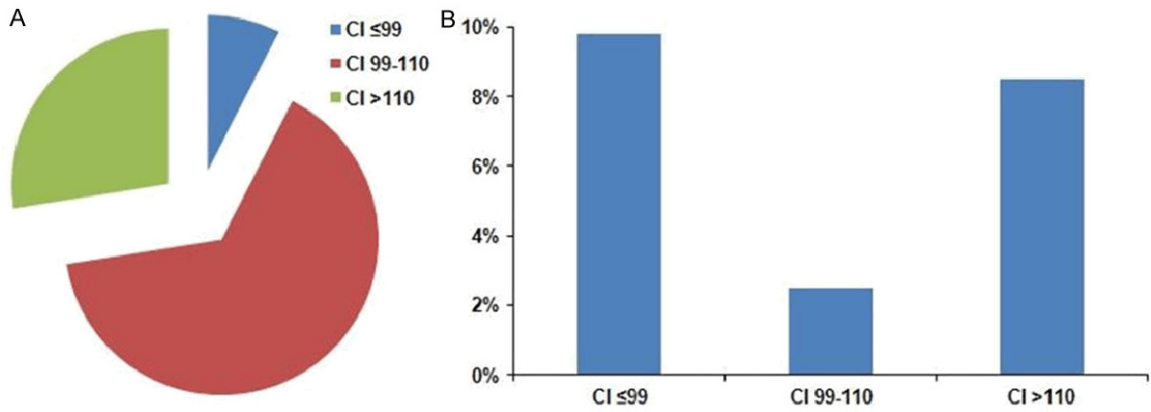
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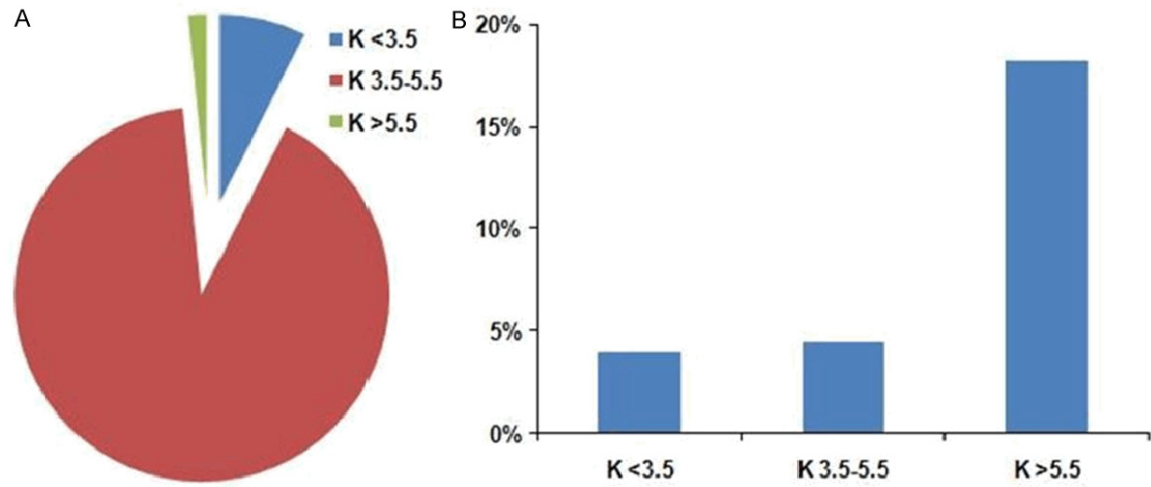
Supplementary Figure 2. In-hospital mortality according to the normal range of serum potassium. A. Proportion of serum potassium. B. In-hospital mortality.

Supplementary Figure 3. In-hospital mortality according to the normal range of serum calcium. A. Proportion of serum calcium. B. In-hospital mortality.

Supplementary Figure 4. In-hospital mortality according to the normal range of serum chlorine. A. Proportion of serum chlorine. B. In-hospital mortality.