Received: 29 June 2020 | Revised: 30 July 2020 | Accepted: 8 August 2020

DOI: 10.1002/jcla.23553

RESEARCH ARTICLE

WILEY

# Ammonia predicts poor outcomes in patients with hepatitis B virus-related acute-on-chronic liver failure

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## Abstract

**Background:** Hepatic encephalopathy (HE) is a common feature of acute liver failure and has been reported to be associated with poor outcomes. Ammonia is thought to be central to the pathogenesis of HE, but its role in hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is unclear. The present study aimed to assess the prognostic role of ammonia level for patients with HBV-ACLF.

**Methods:** We retrospectively recruited 127 patients diagnosed with HBV-ACLF for the present study.

**Results:** Ammonia levels at the time of admission were higher among non-surviving participants than in survivors. Increased ammonia level was found to be associated with severe liver disease and was identified as an independent predictor for mortality in patients with HBV-ACLF.

**Conclusions:** Our results suggest that high ammonia level at admission is an independent factor for predicting short-term mortality in patients with HBV-ACLF. Therefore, ammonia levels may represent a therapeutic target for this condition.

KEYWORDS

acute-on-chronic liver failure, ammonia, Hepatitis B virus, mortality

## 1 | INTRODUCTION

Acute-on-chronic liver failure (ACLF) is the rapid deterioration of liver function in chronic liver disease often associated with the development of serious complications such as hepatorenal syndrome and hepatic encephalopathy (HE) within a short period of time.[1,2] The condition has a high rate of short-term mortality, with previous studies reporting that around 50%–90% ACLF patients will die within 1 month of diagnosis.[3,4] While the definition and etiology of ACLF differ between Eastern and Western countries, the condition is generally described as acute deterioration of pre-existing chronic liver disease, and guidelines identify patients with cirrhosis at a high risk of short-term mortality in cases that develop ACLF. Alcoholic liver disease is the most common etiology of ACLF in patients from Europe and North America; however, hepatitis B virus (HBV) infection represents the major etiology among patients from the Asia-Pacific region. Based on the results of the European Association for the Study of the Liver definition of ACLF, the Chinese Group on the Study of Severe Hepatitis B (COSSH) recently developed new criteria for HBV-ACLF and established a prognostic score based on characteristics of Chinese patients with HBV and chronic liver disease.[5] Regardless of the presence of cirrhosis, patients with chronic hepatitis B with total bilirubin (TBIL) of ≥205 μmol/L and international normalized ratio (INR) of ≥1.5 are defined as HBV-ACLF according to the new criteria for HBV-ACLF. These criteria bridge the

**Abbreviations:** ACLF, acute-on-chronic liver failure; AUCs, Areas under the curve; CI, Confidence interval; CLD, Chronic liver diseases; COSSH-ACLFs, COSSH-ACLF score; HBV, Hepatitis B virus; HE, Hepatic encephalopathy; INR, International normalized ratio; MELD score, Model for End-stage liver disease score; TBIL, Total bilirubin.

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gap in the diagnostic criteria of the European Association for the Study of the Liver for HBV-ACLF. The new criteria lead to a 20% increase in the number of patients diagnosed with HBV-ACLF, meaning that more patients will receive appropriate intensive management.[5]

Hepatic encephalopathy is a common feature of acute liver failure and is associated with mortality.[6] Hyperammonemia is thought to be central to the pathogenesis of HE [7] as well as being associated with intracranial hypertension leading to death in acute liver failure.[8] Sawhney et al reported that failure to decrease ammonia levels in patients with ACLF increases the risk of death. Decreased ammonia levels have been observed in surviving patients with ACLF without HE, indicating that ammonia level influences the outcome of ACLF beyond contributing to HE.[9] Together, these results suggest that ammonia level is a new prognostic biomarker and therapeutic target. Additionally, ammonia levels reportedly predict mortality in patients with alcoholic hepatitis[10] and transplant-free survival in patients with acutely decompensated cirrhosis,[11] and have been demonstrated to be higher in non-surviving patients with ACLF compared with survivors.[12] Despite these known correlations, the role of ammonia level in the COSSH definition of ACLF remains poorly understood. Therefore, we aimed to investigate ammonia levels in patients with HBV-ACLF diagnosed according to the COSSH-ACLF definition and evaluate the prognostic value of ammonia level in such patients.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

We recruited all patients with HBV-ACLF (defined as TBIL ≥ 205 μmol/L and INR ≥ 1.5 according to COSSH-ACLF criteria) who were treated at our institution between July 2018 and February 2020 for this retrospective study. Exclusion criteria were as follows: (a) acute hepatitis, (b) viral infection other than HBV, (c) drug-induced liver injury, (d) blood-system disease, (e) malignancies, (f) incomplete data, (g) alcoholic liver disease, and (h) autoimmune hepatitis. All patients were given standard medical treatments including energy supplements, intravenous infusion of albumin and plasma, preventive treatment for complications, and antiviral therapy after admission. The 28-day survival rate was determined.

This study and all its protocols conformed to the principles of the Declaration of Helsinki and were approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University College of Medicine.

### 2.2 | Data collection

Demographic data and laboratory parameters for all patients were extracted by retrospective review of medical records. Laboratory parameters included total protein, albumin, alanine aminotransferase, aspartate aminotransferase, creatinine, TBIL, arterial ammonia, INR, white blood cell count, platelet count, and blood urea nitrogen. Arterial ammonia was estimated within 24 hours of admission using a dry chemistry system (Vitros 350; Ortho Clinical Diagnostic, Rochester, NY, USA) in heparinized plasma. The normal range for ammonia is 10-47 μmol/L. Prognostic scores (including Model for End-stage Liver Disease [MELD] and COSSH-ACLF [COSSH-ACLF] scores) were calculated using baseline values of the relevant parameters (measured at the time of admission).

### 2.3 | Calculation of scores

The MELD score was calculated using the following formula: $3.78 \times \ln(\text{TBIL, mg/dL}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{Cr, mg/dL}) + 6.43$.[13] The COSSH-ACLF score was calculated using the following formula: $0.741 \times \text{INR} + 0.523 \times \text{HBV-SOFA} + 0.026 \times \text{age} + 0.003 \times \text{TBIL}$, where HBV-SOFA refers to the Sequential Organ Failure Score based on the severity of kidney injury, hepatic encephalopathy, circulation, and respiratory function according to COSSH-ACLF criteria.[5]

### 2.4 | Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (25th centile; 75th centile) and were analyzed using the Student's t test or the Mann-Whitney U test, as appropriate. Categorical data are expressed as number (percentage) and were compared using the $\chi^2$ test. Correlations between variables were examined using Spearman's correlation. Logistic regression and receiver operating characteristic curve analyses were used to identify independent factors for mortality in patients with HBV-ACLF. All statistical analyses were carried out using SPSS 14.2 (Chicago, IL, USA) and MedCalc 11.6.1 (Ostend, Belgium). Statistical significance was set at $P < .05$.

## 3 | RESULTS

### 3.1 | Patient characteristics

Of 180 patients that were recruited for the present study, 53 were excluded: five due to hepatocellular carcinoma, four due to autoimmune liver disease, three due to HIV infection, twenty-four due to superinfection with hepatitis A or C virus, eleven due to alcoholic liver disease, two due to incomplete data and two due to blood-system diseases. Finally, 127 patients with HBV-ACLF were enrolled for analysis. Baseline characteristics and biochemical data of participants are listed in Table 1. The median ammonia level at enrollment was 55.0 (interquartile range, 36.0-76.0) and 77 patients (60.6%) had high ammonia at the time of admission. Ammonia level was found to be positively correlated to MELD score ($r = 0.334$, $P < .001$) and COSSH-ACLF score ($r = 0.311$, $P < .001$) (Figure 1). In the study population, there were 61 patients with cirrhosis and 66 patients without cirrhosis. No significant difference between the two groups

**TABLE 1** Comparison of baseline characteristics of survivors and non-survivors

| | All patients (n = 127) | Surviving patients (n = 87) | Non-surviving patients (n = 40) | *P* |
|---|---|---|---|---|
| Gender (female/male) | 10/117 | 7/80 | 3/37 | .804 |
| Age (years) | 46.3 ± 12.7 | 45.7 ± 12.8 | 47.5 ± 12.6 | .455 |
| Total protein (g/L) | 57.4 ± 6.7 | 58.0 ± 6.6 | 56.2 ± 6.7 | .175 |
| Albumin (g/L) | 31.6 ± 3.8 | 31.6 ± 4.0 | 31.6 ± 3.5 | .993 |
| Alanine aminotransferase (U/L) | 230.0 (110.0-366.0) | 205.0 (103.3-357.0) | 284.0 (140.0-388.5) | .205 |
| Aspartate aminotransferase (U/L) | 126.0 (88.0-205.0) | 125.0 (81.0-200.0) | 136.0 (100.0-205.5) | .329 |
| Serum creatinine (μmol/L) | 60.0 (53.0-72.0) | 61.0 (53.0-71.8) | 58.5 (55.0-75.5) | .586 |
| TBIL (μmol/L) | 366.6 (292.5-433.3) | 349.2 (283.1-416.4) | 388.3(325.9-510.8) | .004 |
| Blood urea nitrogen (μmol/L) | 3.9 (2.9-5.3) | 3.9 (2.7-4.9) | 3.9(3.0-6.5) | .259 |
| INR | 2.0 ± 0.6 | 1.8 ± 0.5 | 2.4 ± 0.7 | <.001 |
| White blood cell count ($\times 10^9$/L) | 6.9 (4.9-9.3) | 6.4 (4.7-8.3) | 8.4 (6.5-10.2) | .002 |
| Platelet count ($\times 10^9$/L) | 109.7 ± 57.4 | 113.5 ± 58.3 | 101.5 ± 55.2 | .275 |
| Ammonia (μmol/L) | 55.0 (36.0-76.0) | 48.0 (34.3-65.0) | 77.0 (55.0-100.5) | <.001 |
| COSSH-ACLFs | 6.46 (5.83-7.22) | 6.24 (5.71-6.69) | 7.43 (6.77-8.11) | <.001 |
| MELD score | 30.8 (28.0-34.4) | 30.2 (27.4-32.0) | 34.6 (31.8-38.5) | <.001 |

*Note:* Data are expressed as number, mean ± standard deviation or median (interquartile range).

Abbreviations: COSSH-ACLFs, Chinese Group on the Study of Severe Hepatitis B Acute-on-Chronic Liver Failure score; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; TBIL, total bilirubin.

except that the age of the cirrhosis group was higher than that of the non-cirrhosis group (Table S1).

Among the 127 participants, 87 survived and 40 died, representing a 28-day mortality rate of 31.5%. Demographic and laboratory data of non-survivors and survivors are detailed in Table 2. The mean MELD score, TBIL, INR, white blood cell count, ammonia, and COSSH-ACLF score were higher among non-surviving participants; however, the mean age, gender ratio, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, creatinine, blood urea nitrogen, and platelet count were not significantly different between survivors and non-survivors.

## 3.2 | Factors associated with mortality

Univariate analysis revealed ammonia level, MELD score, white blood cell count, and COSSH-ACLF score to be associated with 28-day mortality in patients with HBV-ACLF; however, multivariate analysis identified only COSSH-ACLF score and ammonia level as independent predictors of mortality (Table 2). The prognostic values of COSSH-ACLF score and ammonia for predicting outcomes were assessed by analyzing the area under the receiver operating characteristic curve. The cut-off values, sensitivity, and specificity were 73 μmol/L, 60.0%, and 87.4% for ammonia level and 6.7, 80.0%, and 79.3% for COSSH-ACLF score, respectively. The powers of COSSH-ACLF score and ammonia for predicting outcome were not significantly different, indicated by their similar area under curve values (0.842 and 0.758, respectively, $P = .170$). When the COSSH-ACLF score and ammonia level were combined, the area under the curve for predicting mortality was 0.877 ± 0.037, which was higher than that of either parameter alone (both $P < .05$) (Figure 2).

## 3.3 | Baseline characteristics and factors related to ammonia level

Dividing patients according to the ammonia cut-off value of 73 μmol/L revealed higher ammonia level to be associated with

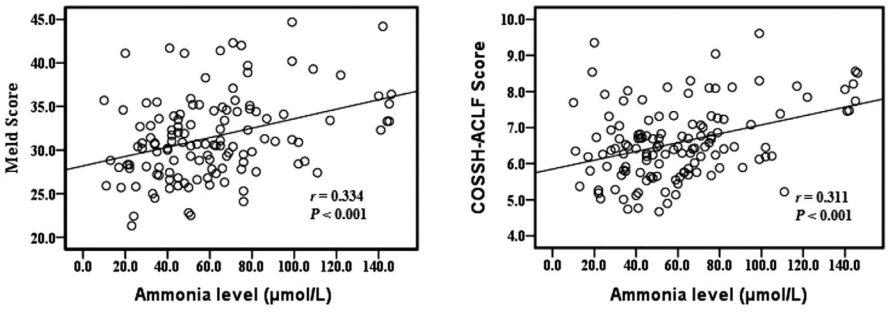


**FIGURE 1** Scatter graphs illustrating the correlations between ammonia level and Model for End-stage Liver Disease score and Chinese Group on the Study of Severe Hepatitis B Acute-on-Chronic Liver Failure score among patients with hepatitis B virus-related acute-on-chronic liver failure

**TABLE 2** Results of univariate and multivariate logistic regression analysis of independent factors associated with outcomes of hepatitis B virus-related acute-on-chronic liver failure

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | *P* | Odds ratio | 95% CI | *P* |
| Age (years) | 1.011 | 0.982-1.042 | .452 | | | |
| MELD score | 1.254 | 1.143-1.388 | <.001 | | | |
| Ammonia(μmol/L) | 1.034 | 1.018-1.050 | <.001 | 1.028 | 1.009-1.0.48 | 0.004 |
| White blood cell count ($\times 10^9$/L) | 1.204 | 1.064-1.364 | .001 | | | |
| Albumin (g/L) | 0.999 | 0.906-1.103 | .993 | | | |
| COSSH-ACLFs | 5.032 | 2.764-9.164 | <.001 | 4.330 | 2.320-8.081 | <.001 |

Abbreviations: CI, confidence interval; COSSH-ACLFs, Chinese Group on the Study of Severe Hepatitis B Acute-on-Chronic Liver Failure score; MELD, Model for End-stage Liver Disease.

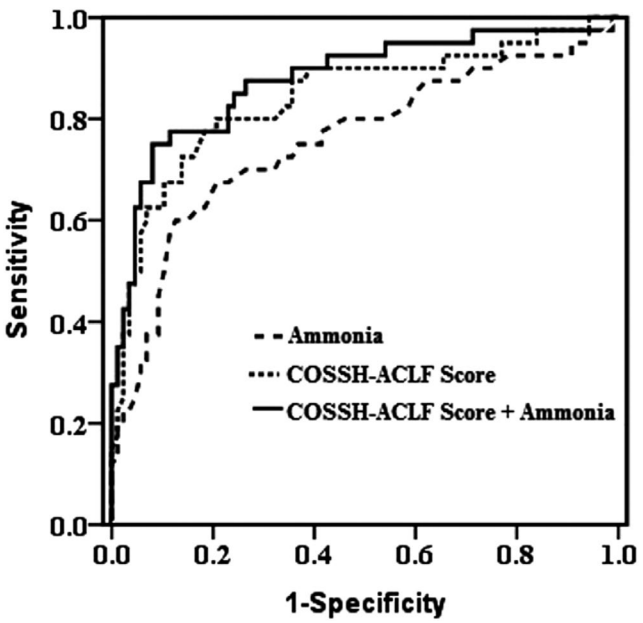


**FIGURE 2** Receiver operating characteristic curves indicating the relative efficiencies of Chinese Group on the Study of Severe Hepatitis B Acute-on-Chronic Liver Failure score, ammonia level and the combination of both for predicting 28-day mortality in patients with hepatitis B virus-related acute-on-chronic liver failure

higher alanine aminotransferase, INR, mortality rate, COSSH-ACLF score and MELD score (all $P < .05$). Data stratified by ammonia cut-off level are summarized in Table 3.

## 4 | DISCUSSION

The differences between the Eastern and Western diagnostic criteria for ACLF have resulted in considerable discrepancies in the identification, rescue regimen, and eventual prognosis of the condition.[14-16] For the present study, we used the COSSH-ACLF criteria for HBV-ACLF; this system has been validated for early diagnosis of HBV-ACLF.[5] Our study is the first to evaluate the prognostic value of ammonia level in patients with HBV-ACLF defined by COSSH criteria. We demonstrate that increased ammonia levels are associated with increased risk of mortality. Furthermore, our findings indicate that ammonia level may serve as an independent biomarker of mortality.

The MELD score is the most commonly used model to predict prognosis of liver disease and incorporates three laboratory variables: TBIL, INR, and creatinine.[17,18] Although the MELD score considers liver dysfunction and renal insufficiency, it fails to incorporate other crucial factors such as HE, organ failures, or infection, which can affect the prognosis.[19] Our analyses did not identify MELD score as an independent predictor of death; however, the association of COSSH-ACLF score with mortality was identified in univariate and multivariate analysis. This result is consistent with previous studies, which have reported COSSH-ACLF score to be superior or comparable with other scores for the evaluation of severity and prediction of poor outcomes of HBV-ACLF.[5,20] We believe this is partly because the COSSH-ACLF score considers organ failures (such as cerebral or respiratory function failure), which MELD score does not include. Previous studies have identified several factors including mean platelet volume,[21] plasma fibrinogen level,[22] serum homocysteine,[23] and serum ferritin [24] to be associated with poor outcomes of HBV-ACLF. The present study complements these studies, adding high ammonia level as a predictor of prognosis in patients with HBV-ACLF. Moreover, combining COSSH-ACLF score with ammonia level adds to the power of the score for predicting mortality.

The relationship between ammonia level and unfavorable outcome of HBV-ACLF is complex and is yet to be fully elucidated. Because ACLF itself is associated with mortality, systemic inflammation, and organ failure, it is unclear which factors associated with ammonia level are relevant to patients with ACLF. The present study demonstrates the significant positive correlation of ammonia level with MELD and COSSH-ACLF scores, as patients presenting with higher ammonia levels had higher risk of in-hospital mortality than those with lower ammonia levels. Moreover, the association of hyperammonemia with parameters that reflect the severity of liver disease indicates higher ammonia levels to be predictive of the severity and progression of liver injury among patients with HBV-ACLF. Our conclusions are consistent with those of Ye and

**TABLE 3** Clinical data according to ammonia level

| | Low group (Ammonia < 73μmol/L, n = 91) | High group (Ammonia ≥ 73μmol/L, n = 36) | *P* |
|---|---|---|---|
| Gender (male/female) | 84/7 | 33/3 | .807 |
| Age (years) | 45.5 ± 12.7 | 48.2 ± 122. | .293 |
| Total protein (g/L) | 57.8 ± 6.9 | 56.5 ± 6.1 | .310 |
| Albumin (g/L) | 31.2 ± 3.5 | 31.7 ± 4.0 | .534 |
| Alanine aminotransferase (U/L) | 169.0 (94.0-375.8) | 280.0 (195.5-364.0) | .020 |
| Aspartate aminotransferase (U/L) | 126.0(82.3-182.8) | 142.5 (94.5-257.0) | .208 |
| TBIL (μmol/L) | 373.7 (290.4-423.6) | 438.0 (300.9-468.2) | .879 |
| Blood urea nitrogen (μmol/L) | 4.0(2.7-4.9) | 3.8 (3.0-6.1) | .410 |
| INR | 1.86 ± 0.58 | 2.36 ± 0.56 | <.001 |
| Serum creatinine (μmol/L) | 61.0 (53.0-72.0) | 58.5 (52.5-71.0) | .806 |
| White blood cell count ($\times 10^9$/L) | 6.8(4.8-9.0) | 7.4(5.6-9.7) | .079 |
| Platelet count ($\times 10^9$/L) | 113.7 ± 59.4 | 99.6 ± 51.4 | .215 |
| MELD score | 30.5 (27.5-33.3) | 33.4 (29.7-36.3) | .003 |
| COSSH-ACLFs | 6.3 (5.7-6.8) | 7.2 (6.4-8.1) | <.001 |
| 28-day mortality (yes/no) | 16/75 | 24/12 | <.001 |

*Note:* Data are expressed as n, mean ± standard deviation or median (interquartile range).

Abbreviations: COSSH-ACLFs, Chinese Group on the Study of Severe Hepatitis B Acute-on-Chronic Liver Failure score; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; TBIL, total bilirubin.

colleagues,[25] who determined hyperammonemia to play a key role in the pathogenesis of HBV-ACLF and demonstrated that decreasing ammonia level through plasma exchange resulted in improved survival. Shalimar *et al* reported ammonia to be a prognostic indicator for short-term outcomes in patients with cirrhosis, indicating ammonia to be a potential therapeutic target.[26] The metabolism of ammonia is a complex, multiorgan process involving the liver, kidneys, muscles, and brain.[27-30] While most patients of the present study had high ammonia at the time of admission, there were no differences in creatinine or blood urea nitrogen levels between patients with high and low ammonia. We hypothesized that impaired liver clearance is an essential contributor to hyperammonemia in patients with HBV-ACLF. Reciprocally, hyperammonemia has been shown to lead to liver-cell injury and, consequently, worse outcomes.[31]

Our study has some limitations which should be acknowledged. First, the study was retrospective in nature and the sample size was small. Second, ammonia levels were not measured dynamically; thus, it remains unclear whether stepwise changes in ammonia levels occur when the patient's condition deteriorates. Third, the mechanism underlying the contribution of ammonia level to the progression of HBV-ACLF remains unclear. Further prospective multi-center studies are needed to clarify these uncertainties and confirm our conclusions.

In summary, the current study indicated that the ammonia was a simple and objective biomarker that could predict the short-term mortality rate of patients with HBV-ACLF. ammonia may provide valuable information to supplement conventional approaches of assessing disease condition in these patients. It represents a useful tool in clinical practice, to assess patient prognosis and help clinicians identify individuals in need of greater care. Prospective clinical studies are necessary to validate these findings and additionally investigations into diagnostic workup and appropriate treatment strategies for patients with HBV-ACLF with regard to ammonia level are warranted.

## ACKNOWLEDGMENTS

We thank Amy Phillips, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Zhang J, Liu X, Ye B, Chen H. Ammonia predicts poor outcomes in patients with hepatitis B virus-related acute-on-chronic liver failure. *J Clin Lab Anal*. 2020;34:e23553. https://doi.org/10.1002/jcla.23553