ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2021 January 26; 9(3): 521-763

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 9 Number 3 January 26, 2021

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

Observational Study

SYSTEMATIC REVIEWS

CASE REPORT

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 3 January 26, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 3 January 26, 2021

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 3 January 26, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Dr. Marcelo A F Ribeiro Jr. is Full Professor of Surgery at Pontifical Catholic University – PUC Sorocaba – General and Trauma Surgery, and Professor of the Post-Graduation Program in Surgery, IAMSPE São Paulo (Brazil). He serves as Member and Fellow of the Brazilian College of Surgeons, Brazilian College of Digestive Surgery, Brazilian Trauma Society (General Secretary), American College of Surgeons, American Association for the Surgery of Trauma, Eastern Association for the Surgery of Trauma, and Pan-American Trauma Society (being Chairman of the Education Committee and Member of the Board). (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJCC* as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2019 is 0.3 and Scopus CiteScore rank 2019: General Medicine is 394/529.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Dennis A Bloomfield, Sandro Vento, Bao-gan Peng

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
January 26, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2021 January 26; 9(3): 552-564

DOI: 10.12998/wjcc.v9.i3.552

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

Role of ammonia in predicting the outcome of patients with acute-on-chronic liver failure

Stefan Chiriac, Carol Stanciu, Camelia Cojocariu, Ana-Maria Singeap, Catalin Sfarti, Tudor Cuciureanu, Irina Girleanu, Razvan Alexandru Igna, Anca Trifan

ORCID number: Stefan Chiriac 0000-0003-2497-9236; Carol Stanciu 0000-0002-6427-4049; Camelia Cojocariu 0000-0001-6395-335X; Ana-Maria Singeap 0000-0001-5621-548X; Catalin Sfarti 0000-0001-7074-5938; Tudor Cuciureanu 0000-0003-1550-8870; Irina Girleanu 0000-0001-5925-1232; Razvan Alexandru Igna 0000-0003-2182-7130; Anca Trifan 0000-0001-9144-5520.

Author contributions: Chiriac S wrote the original draft of the manuscript and performed the statistical analysis; Stanciu C coordinated the manuscript drafting and revised it critically; Cojocariu C designed the methodology and edited the manuscript; Singeap A, Cuciureanu T, Girleanu I and Sfarti C participated in the writing of the manuscript and performed the acquisition of data; Igna RA participated in the analysis and interpretation of data; Trifan A, conceptualized and critically revised the manuscript for important intellectual content; all authors read and approved the final version of the manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of the "Grigore T. Popa" University of Medicine and

Stefan Chiriac, Camelia Cojocariu, Ana-Maria Singeap, Catalin Sfarti, Tudor Cuciureanu, Irina Girleanu, Anca Trifan, Department of Gastroenterology, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi 700115, Romania

Stefan Chiriac, Carol Stanciu, Camelia Cojocariu, Ana-Maria Singeap, Catalin Sfarti, Irina Girleanu, Anca Trifan, Institute of Gastroenterology and Hepatology, "St. Spiridon" Emergency Hospital, Iasi 700111, Romania

Razvan Alexandru Igna, Intensive Care, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi 700115, Romania

Corresponding author: Camelia Cojocariu, MD, PhD, Assistant Professor, Doctor, Department of Gastroenterology, "Grigore T. Popa" University of Medicine and Pharmacy, 16 Universitatii Street, Iasi 700115, Iasi, Romania. cameliacojocariu@yahoo.com

Abstract

BACKGROUND

High venous ammonia (VA) values have been proven to be a part of the mechanism of hepatic encephalopathy in patients with liver cirrhosis (LC) as well as acute hepatitis. Moreover, VA has been associated with poor prognosis and high mortality in these clinical settings. However, the role of ammonia in acute-on-chronic liver failure (ACLF) has not yet been clearly established.

AIM

To assess the role of VA in predicting the outcome of cirrhotic patients with ACLF in a tertiary care center.

METHODS

We performed a retrospective observational study including consecutive patients with LC hospitalized for acute non-elective indications such as ascites, hepatic encephalopathy (HE), upper gastrointestinal bleeding, or bacterial infections that fulfilled the Asian Pacific Association for the Study of the Liver (APASL) criteria for ACLF. The study was conducted in "St. Spiridon" University Hospital, Iasi, Romania, a tertiary care center, between January 2017 and January 2019. The APASL ACLF Research Consortium (AARC) score was calculated and ACLF grade was established accordingly. West-haven classification was used for HE. Statistical analysis was performed using IBM SPSS version 22.0.

Pharmacy Iasi, Romania.

Informed consent statement: There was no requirement for the informed written consent because of the retrospective nature of the study; all of the patients signed an informed consent upon hospitalization agreeing to receive treatment.

Conflict-of-interest statement: The authors declare no conflict of interest in relation to this study.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: Romania

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: October 3, 2020
Peer-review started: October 3, 2020
First decision: November 23, 2020
Revised: December 2, 2020
Accepted: December 16, 2020
Article in press: December 16, 2020
Published online: January 26, 2021

P-Reviewer: Meng Q

RESULTS

Four hundred and forty-six patients were included, aged 59 (50-65) years, 57.4% men. Child-Pugh, model for end-stage liver disease (MELD) and AARC scores were 11 (10-12), 19.13 ± 6.79, and 7 (6-8), respectively. 66.4% had ACLF grade I, 31.2% ACLF grade II, and 2.5% ACLF grade III. HE was diagnosed in 83.9%, 34% grade I, 37.2% grade II, 23.5% grade III, and 5.3% grade IV. Overall mortality was 7.8%. VA was 103 (78-148) μmol/L. Receiver operating characteristic analysis showed good accuracy for the prediction of in-hospital mortality for the AARC score [Area under the curve (AUC) = 0.886], MELD score (AUC = 0.816), VA (AUC = 0.812) and a fair accuracy for the Child-Pugh score (AUC = 0.799). Subsequently, a cut-off value for the prediction of mortality was identified for VA (152.5 μmol/L, sensitivity = 0.706, 1-specificity = 0.190). Univariate analysis found acute kidney injury, severe HE (grade III or IV), VA ≥ 152.5 μmol/L, MELD score ≥ 22.5, Child-Pugh score ≥ 12.5, and AARC score ≥ 8.5 to be associated with in-hospital mortality. Multivariate analysis identified AARC score ≥ 8.5 and venous ammonia ≥ 152 μmol/L to be independent predictors of in-hospital mortality.

CONCLUSION

VA could be used as an inexpensive predictor of in-hospital mortality in patients with ACLF. Patients with both ACLF and VA > 152.5 μmol/L have a high risk for a poor outcome.

Key Words: Venous ammonia; Hepatic encephalopathy; Acute-on-chronic liver failure; Asian Pacific Association for the Study of the Liver Acute-on-chronic Liver Failure Research Consortium score; Cirrhosis; Mortality

Core Tip: Hyperammonemia has been associated with hepatic encephalopathy and high mortality in patients with liver cirrhosis. Acute-on-chronic liver failure is a relatively new defined syndrome presenting high 28-d mortality. The role of hyperammonemia in acute-on-chronic liver failure has not yet been clearly established. Venous ammonia presents a good predictive value for in-hospital mortality in patients with acute-on-chronic liver failure (ACLF), with a cut-off value of 152.5 μmol/L, sensitivity = 0.706, 1-specificity = 0.190 and is associated with severe hepatic encephalopathy in patients with ACLF. Thus, venous ammonia has the potential to be used as a prognostic marker in the evaluation of patients with ACLF.

Citation: Chiriac S, Stanciu C, Cojocariu C, Singeap AM, Sfarti C, Cuciureanu T, Girleanu I, Igna RA, Trifan A. Role of ammonia in predicting the outcome of patients with acute-on-chronic liver failure. *World J Clin Cases* 2021; 9(3): 552-564
URL: https://www.wjgnet.com/2307-8960/full/v9/i3/552.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i3.552

INTRODUCTION

Hyperammonemia has been traditionally associated with hepatic encephalopathy (HE) and with liver cirrhosis (LC). Hyperammonemia has occured as a consequence of the reduction in the detoxification capabilities of the liver in the setting of liver failure as well as with increased intestinal production of ammonia[1]. However, several other conditions that determine an imbalance between the production and the clearance of ammonia such as infections with urease-producing bacteria, high-protein diet, malignancy, sarcopenia, renal failure, gastrointestinal (GI) bleeding, gastric bypass, and organ transplantation can also determine high ammonia levels[2] and sometimes lead to non-cirrhotic encephalopathy[3].

Both LC and acute liver failure are known factors for hyperammonemia, but the relation between hyperammonemia and HE is still being debated. Acute-on-chronic liver failure (ACLF) is a relatively recently recognized syndrome that is different from

S-Editor: Gao CC
L-Editor: A
P-Editor: Liu JH

LC and acute liver failure in terms of outcome. Several international societies and consortia have attempted to characterize this syndrome however, a universally accepted definition has not yet been found. The latest definition was enunciated by The Asian Pacific Association for the Study of the Liver (APASL), defining ACLF as jaundice and coagulopathy complicated within four weeks by clinical ascites and/or encephalopathy in a patient with a previously diagnosed or undiagnosed chronic liver disease/cirrhosis, associated with a high 28-d mortality, following an acute hepatic insult[4]. The conditions associated with ACLF vary from hepatitis B reactivation, super infection with hepatitis E, bacterial fungal or parasitic infections, drug-induced liver injury, alcohol abuse, autoimmune hepatitis flare, acute variceal bleeding, and also relative adrenal insufficiency[4-6].

Although ammonia is widely recognized as the main factor involved in the pathogenesis of HE, the association with the severity of HE is much clearer in acute liver failure than in chronic liver disease, suggesting that in the latter there might be other factors involved, such as systemic inflammation that could lower the threshold for neurological impairment caused by ammonia[7]. Patients with acute liver failure and high ammonia levels may experience cerebral edema, followed by subsequent herniation and death[8]. Although cerebral edema has been traditionally associated with acute liver failure, several studies also reported cerebral edema in patients with LC[9,10] as well as in some cases of ACLF[11,12]. High serum ammonia levels are found in patients with chronic liver disease as well as in patients with ACLF, with higher levels being reported in the latter category[13]. However, the relation between high ammonia levels and HE in patients with ACLF has not been adequately described. Although there is data indicating hyperammonemia as a potential mechanism for HE from experimental ACLF models, there are only a few studies to demonstrate this relation in clinical settings[8]. Moreover, there is still conflicting data concerning the risk of in-hospital death for patients with ACLF and high ammonia levels. While several studies found that hyperammonemia was associated with increased mortality[14,15], others did not show worse prognosis in the cases with peak ammonia levels[16,17]. Moreover, ammonia levels are not currently influencing the clinical management of the patients with HE, and further evidence is needed to demonstrate this biomarker's utility in predicting the mortality of patients with advanced liver disease[18].

This study aimed to assess the prognostic value of ammonia in patients with ACLF in terms of in-hospital mortality.

MATERIALS AND METHODS

Study design

We conducted a retrospective study on patients hospitalized in "St. Spiridon" University Hospital, Iasi, Romania between January 2017 and January 2019. We included consecutive cirrhotic patients admitted for non-elective indications such as ascites, HE, upper GI bleeding, or bacterial infections that fulfilled the APASL diagnostic criteria of ACLF. Patients diagnosed with non-hepatic malignancy, human immunodeficiency virus infection, hematological disease as well as pregnant women were excluded from the study. LC was diagnosed based on clinical criteria, laboratory tests, typical imagistic findings, and upper digestive endoscopy consistent with portal hypertension. The end-point of the study was considered in-hospital death.

Patient electronic records were analyzed and information regarding sex, demographics, etiology of liver disease, duration of hospitalization and the in-hospital death rates was recorded. The abdominal ultrasound and upper digestive endoscopy results were obtained. Laboratory tests from fasting venous blood taken at admission were noted. Complete blood count, serum transaminase levels, total serum bilirubin, albumin, creatinine, international normalized ratio (INR), lactate, C-reactive protein (CRP), sodium, and ammonia levels were retrieved.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of "Grigore T. Popa" University of Medicine and Pharmacy of Iasi. There was no requirement for the informed written consent because of the retrospective nature of the study; all of the patients signed an informed consent upon hospitalization agreeing to receive treatment.

Definitions

ACLF was defined according to APASL criteria. APASL ACLF Research Consortium (AARC) score was calculated using the online calculator available at http://www.aclf.in/ and ACLF grade was established accordingly. APASL definition for

ACLF was chosen because electronic records from our database did not contain information regarding the PaO_2 or the FiO_2 and thus the European Foundation for the Study of Chronic Liver Failure (EF-CLIF) Consortium definition criteria for ACLF could not be evaluated. HE was defined using the West Haven criteria[19]. Acute kidney injury was defined according to the International Club of Ascites (ICA-AKI) definition[20].

Statistical analysis

IBM SPSS version 22.0 was used for the statistical analysis. Continuous variables were expressed either as mean ± SD or as median (interquartile ratio), according to the parametric or non-parametric distribution. The Kolmogorov–Smirnov test was used to assess the distribution. The Student's *t*-test, Chi-square or Fischer's exact tests were used for the analysis of continuous and categorical variables respectively. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used for the assessment of accuracy in predicting the outcome for Child-Pugh, model for end-stage liver disease (MELD), AARC scores and venous ammonia (VA). The cohort was then divided and further analyzed according to the cut-off value obtained for VA. Univariate and multivariate analysis was performed to assess the risk factors for in-hospital mortality. The statistical methods of the study were reviewed by a biomedical statistician.

RESULTS

Five hundred and twenty patients were screened. After applying the exclusion criteria 74 patients were removed from further analysis, thus 446 patients were included in the study. The median age of the participants was 59 (50-65) years and 57.4% of the patients were men. The main etiology of LC was alcohol (78.7%), followed by hepatitis C virus (HCV) infection (11.2%), hepatitis B virus (HBV) infection (6.1%), alcohol and HBV (1.8%), alcohol and HVC (1.3%), HBV and HVC (0.7%). The patients' general characteristics are presented in Table 1.

Most of the patients had advanced liver disease, as indicated by the high values of the traditional Child-Pugh and MELD prognosis scores of 11 (10-12) and 19.13 ± 6.79 respectively. The median novel AARC score was 7 (6-8), consistent with the predominance of grade I ACLF found in the majority of the patients; 66.4% of the participants had ACLF grade I, 31.2% ACLF grade II, and 2.5% ACLF grade III. Non-contrast computed tomography (CT) cranial scans were performed in 34 patients and no evidence of cerebral edema was described.

Mortality analysis

In-hospital mortality was 7.8% (Table 2). The mean survival of the deceased patients was 5 (3-10) d. The causes of death were: multi-organ failure in 19 patients, severe HE in 9 patients, and hemorrhagic shock in 7 patients. Non-survivors had higher levels of bilirubin, higher INR, lower albumin, and consequently higher Child-Pugh and MELD scores, consistent with more advanced liver disease than survivors. However, a higher inflammatory response expressed through higher CRP and higher white blood cells (WBC) count was also noted in the deceased, independently of the presence of bacterial infections, thus suggesting the important role of an exacerbated inflammatory response in the prognostic of patients with ACLF and HE. As expected, most of the non-survivors had grade II and III ACLF (62.9%, 22.9% respectively), while most of the survivors had grade I ACLF (70.8%).

HE was diagnosed in 94.3% of the non-survivors and in 83% of the survivors (P = 0.081). However, 84% of the deceased had severe HE (grade III or IV), compared to 23.5 % of the survivors (P < 0.001). Overall VA was higher in the deceased than in the survivors' group [100 (75-139) μmol/L *vs* 198 (125-345) μmol/L, P < 0.001]. ROC analysis showed a slightly better accuracy for the prediction of in-hospital mortality for the AARC score (AUC = 0.886) than for the MELD score (AUC = 0.816) and the VA (AUC = 0.812). The accuracy of the Child-Pugh score in predicting mortality was fair (AUC = 0.799) (Figure 1).

Subsequently, cut-off values for the prediction of mortality were identified for VA (152.5 μmol/L, sensitivity = 0.706, 1-specificity = 0.190), AARC score (8.5, sensitivity = 0.743, 1-specificity = 0.102), MELD score (22.5, sensitivity = 0.771, 1-specificity = 0.286), and Child-Pugh score (12.5, sensitivity = 0.576, 1-specificity = 0.144).

Univariate analysis found that acute kidney injury (AKI) [odds ratio (OR) = 5.636, confidence interval (CI) (2.634-12.063)], severe HE (grade III or IV) [OR = 18.270, CI

Table 1 General cohort characteristics

Variable	Value
Age, median (IQR)	59 (50-65)
Male sex, *n* (%)	256 (57.4)
Etiology of liver disease, *n* (%)	
Alcohol	351 (78.7)
Hepatitis C virus	50 (11.2)
Hepatitis B virus	28 (6.1)
Alcohol + hepatitis B virus	8 (1.8)
Alcohol + hepatitis C virus	6 (1.3)
Hepatitis B and C virus	3 (0.7%)
Albumin (g/dL), mean ± SD	2.38 ± 0.59
Bilirubin (mg/dL), median (IQR)	2.53 (1.41-4.82)
INR, median (IQR)	1.47 (1.29-1.74)
Platelets (× 10^9/L), median (IQR)	128 (90-178)
WBC (× 10^9/L), median (IQR)	7.41 (5.45-10.36)
CRP (mg/dL), median (IQR)	1.51 (0.82-3.1)
Venous ammonia (μmol/L), median (IQR)	103 (78-148)
Sodium (mmol/L), median (IQR)	134 (130-137)
Creatinine (mg/dL), median (IQR)	0.815 (0.63-1.27)
Lactate (mmol/L), median (IQR)	1.7 (1.2-2.1)
Child-Pugh score, median (IQR)	11 (10-12)
Child-Pugh class, *n* (%)	
A	3 (0.7)
B	84 (19.2)
C	350 (80.1)
MELD, mean ± SD	19.13 ± 6.79
AARC score, median (IQR)	7 (6-8)
ACLF, *n* (%)	
Grade I	296 (66.4)
Grade II	139 (31.2)
Grade III	11(2.5)
Ascites, *n* (%)	408 (91.5)
Grade I	37(9.1)
Grade II	112 (27.5)
Grade III	259 (63.5)
HE, *n* (%)	374 (83.9)
Grade I	127 (34)
Grade II	139 (37.2)
Grade III	88(23.5)
Grade IV	20(5.3)
Precipitating factors, *n* (%)	
Alcohol	146 (32.7)

Upper GI bleeding	89 (19.9)
Infections	94 (21)
Hepatitis B virus activation	7 (1.5)
Unknown	110 (24.6)
Upper GI bleeding, *n* (%)	89 (20)
SBP, *n* (%)	24 (5.4)
Other infections, *n* (%)	70 (15.7)
UTI	28 (38.4)
Pneumonia	7 (9.6)
CDI	20 (27.4)
Sepsis	5 (6.8)
Cutaneous	11 (15.1)
Oral candidiasis	2 (2.7)
AKI, *n* (%)	52 (11.7)
HCC, *n* (%)	11 (2.5)
Hospital stay (d), median (IQR)	8 (5-11)
In-hospital death rate, *n* (%)	35 (7.8)

IQR: Interquartile range; SD: Standard deviation; INR: International normalized ratio; WBC: White blood cells; CRP: C-reactive protein; MELD: Model for end-stage liver disease; AARC score: APASL ACLF Research Consortium score; HE: Hepatic encephalopathy; GI: Gastrointestinal; UTI: Urinary tract infection; CDI: *Clostridium Difficile* infection; AKI: Acute kidney injury; SBP: Spontaneous bacterial peritonitis; HCC: Hepatocellular carcinoma.

(6.830-48.870)], VA ≥ 152.5 μmol/L [OR = 7.976, CI (3.950-16.104)], MELD score ≥ 22.5 [OR = 8.282, CI (3.657-18.752)], Child-Pugh score ≥ 12.5 [OR = 8.096, CI (3.846-17.041)], and AARC score ≥ 8.5 [OR = 25.381, CI (1.151-57.770)] was associated with in-hospital mortality. However, multivariate analysis identified AARC score ≥ 8.5 and VA ≥ 152 μmol/L to be independent predictors of in-hospital mortality (Table 3).

HE and high VA analysis

HE was diagnosed in 83.9% of patients, with 34% having grade I, 37.2% grade II, 23.5% grade III, and 5.3% grade IV HE. Patients with HE had lower levels of albumin and higher levels of bilirubin, MELD, Child-Pugh and AARC scores. Moreover, Patients with HE presented more often ascites and AKI, as a consequence of the higher severity of their liver disease (Table 4).

VA median value was 103 (78-148) μmol/L, with higher levels in the HE than in the non-HE groups [111 (86-158) *vs* 74 (60-93), respectively, $P < 0.001$]. When further analyzing the subgroup of patients with high VA levels (≥ 152 μmol/L), significant differences were found concerning the distribution of cases with HE, severe HE, and ascites. Patients with high VA levels had a more advanced liver disease, as shown by the high MELD and AARC scores and a significantly higher in-hospital death rate (Table 5).

DISCUSSION

This study provided evidence for the utility of VA in predicting the short-term prognosis in patients with ACLF. We found a statistically significant risk for in-hospital mortality in patients with high VA that was independent of the disease severity as evaluated by the classic and novel prognostic scores.

There is still much controversy regarding the use of VA in patients with LC, concerning its value as a predictor for the development of HE, as well as its role in predicting short-term mortality. VA is considered to be unspecific for the severity of HE[21] and thus it is not being used to guide the treatment in this setting[18]. However, the utility of VA might reside in its prognostic value. For the vast majority of patients with decompensated LC, VA has not been established as an adequate indicator for

Table 2 Mortality analysis

Variable	Survivors, *n* (%) 411 (92.2)	Non-survivors, *n* (%) 35 (7.8)	*P* value
Age, median (IQR)	59 (50-65)	60 (49-66)	0.956
Male sex, *n* (%)	239 (58.2)	17 (48.6)	0.271
Albumin (g/dL), mean ± SD	2.4 ± 0.59	2.16 ± 0.5	0.022
Bilirubin (mg/dL), median (IQR)	2.33 (1.37-4.67)	3.52 (1.93-6.49)	0.013
INR, median (IQR)	1.45 (1.27-1.68)	1.81 (1.5-2.6)	0.005
Creatinine (mg/dL), median (IQR)	0.82 (0.63-1.26)	0.77 (0.62-1.32)	0.397
Platelets (× 10^9/L), median (IQR)	132 (92-180)	123 (82-173)	0.481
WBC (× 10^9/L), median (IQR)	7.24 (5.37-9.89)	11.04 (6.79-13.45)	0.014
CRP (mg/dL), median (IQR)	1.36 (0.8-2.98)	3.15 (1.7-4.67)	0.001
Venous ammonia (μmol/L), median (IQR)	100 (75-139)	198 (125-345)	< 0.001
Venous ammonia > 152.5 μmol/L, *n* (%)	75 (19)	24 (70.6)	< 0.001
Sodium (mmol/L), median (IQR)	134 (130-137)	133 (130-137)	0.215
Child-Pugh score, median (IQR)	11 (10-12)	13 (11-15)	< 0.001
Child-Pugh score ≥ 12.5	58 (14.4)	19 (57.6)	< 0.001
Child-Pugh class, *n* (%)			
A	3 (0.7)	0	
B	84 (20.8)	0	
C	317 (78.5)	33 (100)	
MELD score, mean ± SD	18.43 ± 6.26	27.31 ± 7.37	< 0.001
MELD score ≥ 22.5	119 (29)	27 (77.1)	< 0.001
AARC score, median (IQR)	7 (6-8)	9 (9-11)	< 0.001
AARC score ≥ 8.5	42 (10.2)	26 (74.3)	< 0.001
ACLF, *n* (%)			
Grade I	291 (70.8)	5(14.3)	
Grade II	117 (28.5)	22 (62.9)	
Grade III	3 (0.7)	8(22.9)	
Ascites, *n* (%)	376 (91.5)	32 (91.4)	0.991
HE, *n* (%)	341 (83)	33 (94.3)	0.081
Grade I	126 (37)	1 (3)	
Grade II	135 (39.6)	4 (12.1)	
Grade III	76 (22.3)	12 (36.4)	
Grade IV	4 (1.2)	16 (48.5)	
Grade I or II HE, *n* (%)	261 (76.5)	5 (15.2)	< 0.001
Grade III or IV HE, *n* (%)	80 (23.5)	84.8 (28)	
Upper GI bleeding, *n* (%)	82 (20)	7 (21.2)	0.862
SBP, *n* (%)	22 (5.4)	2 (5.9)	0.705
Other infections, *n* (%)	63 (15.3)	7 (20)	0.466
AKI, *n* (%)	39 (9.5)	13 (38.1)	< 0.001
HCC, *n* (%)	9 (2.2)	2 (5.7)	0.211
Hospital stay (d), median (IQR)	8 (6-11)	5 (3-10)	0.160

IQR: Interquartile range; SD: Standard deviation; INR: International normalized ratio; WBC: White blood cells; CRP: C-reactive protein; MELD: Model for end-stage liver disease; AARC score: APASL ACLF Research Consortium score; HE: Hepatic encephalopathy; GI: Gastrointestinal; AKI: Acute kidney injury; SBP: Spontaneous bacterial peritonitis; HCC: Hepatocellular carcinoma.

Table 3 Multivariate analysis of the predictive factors for in-hospital mortality

Variables in the equation								
Step 1[1]	B	SE	Wald	df	Sig	Exp (B)	95%CI for EXP (B)	
							Lower	Upper
AKI	0.593	0.577	1.055	1	0.304	1.809	0.584	5.607
MELD score ≥ 22.5	0.815	0.610	1.787	1	0.181	2.259	0.684	7.463
Child-Pugh score ≥ 12.5	0.366	0.568	0.415	1	0.520	1.442	0.473	4.394
AARC score ≥ 8.5	1.849	0.642	8.305	1	0.004	6.354	1.807	22.349
HE grade III or IV	1.154	0.628	3.383	1	0.066	3.172	0.927	10.853
Venous ammonia ≥ 152 μmol/L	-1.813	0.508	12.763	1	0.000	0.163	0.060	0.441
Constant	-2.795	1.368	4.172	1	0.041	0.061		

[1]Variable(s) entered on step 1: AKI, MELD score ≥ 22.5, Child-Pugh score ≥ 12.5, AARC score ≥ 8.5, HE grade III or IV, Venous ammonia ≥ 152 μmol/L.AKI: Acute kidney injury; MELD: Model for end-stage liver disease; AARC score: APASL ACLF Research Consortium score; HE: Hepatic encephalopathy; Sig: Significant; SE: Standard error; CI: Confidence interval.

poor outcome[17,21]. This is mainly due to the intricate mechanisms that lead to hyperammonemia. These mechanisms are found in numerous conditions associated with LC, such as sarcopenia, GI bleeding, infection, and AKI, all of which are associated with poor prognostic in patients with LC and ACLF[22]. There is data suggesting that sepsis and systemic inflammation exacerbate the deleterious effects that ammonia exercise on the brain[12]. Thus, patients with sepsis and LC could present HE even in the absence of high VA. By analyzing only patients with ACLF in our study, we found that elements suggestive of systemic inflammation such as WBC and CRP presented higher values in the group of non-survivors, without relation to bacterial infections. These findings are indicative of alternative pathways of developing an exacerbated inflammatory response in ACLF, other than through infection, such as endotoxemia which is secondary to bacterial translocation from the gut[23]. However, no statistically significant differences were noted in patients with and without HE or high ammonia levels regarding these inflammatory markers. These results suggest that an exacerbated inflammatory response poses a risk for in-hospital mortality in patients with ACLF, mostly determined by other physiopathological mechanisms leading to different organ dysfunctions, such as AKI. The results also indicate that the relationship between systemic inflammation and HE is complex, requiring a more in-depth analysis.

The management of patients with advanced liver disease has been greatly improved by the efforts made to identify the groups with high-risk for mortality, *via* numerous prognostic scores[24]. This stratification has been of paramount importance for the in-hospital management, facilitating decisions such as admission to the intensive care unit, or urgent liver transplantation[25]. The traditional prognostic scores, namely Child-Pugh and MELD scores seem to be more adequate for the prediction of outcome in the setting of decompensated LC, but not ACLF[26]. In our study, the novel AARC score presented a good accuracy for predicting mortality, better than the Child-Pugh and MELD scores. Moreover, VA showed good accuracy for predicting the outcome, similarly to the accuracy of the MELD score. We identified a cut-off value of 152.5 μmol/L for VA which accurately predicted mortality in our cohort. These observations are in accordance with recent data which supports the theory that ammonia has an independent role in the risk for short-term mortality[15]. As discussed, VA levels can be increased in the presence of several conditions frequently associated with LC, among which sarcopenia, AKI, GI bleeding, and infection, thus ammonia levels could represent an additional marker of advanced liver disease, indicative of the altered homeostasis of patients with LC and ACLF[22]. VA could therefore aid in the

Table 4 Comparison of patient characteristics based on the presence of hepatic encephalopathy

Variable	HE, *n* (%) 374 (83.9)	No. HE, *n* (%) 72 (16.1)	*P* value
Age, median (IQR)	60 (50-65)	56 (47-65)	0.413
Male sex, *n* (%)	211 (56.4)	45 (62.5)	0.339
Albumin (g/dL), mean ± SD	2.33 ± 0.55	2.60 ± 0.74	< 0.001
Bilirubin (mg/dL), median (IQR)	2.62 (1.54-5.11)	1.72 (0.73-3.30)	0.015
INR, median (IQR)	1.49 (1.31-1.75)	1.34 (1.14-1.57)	0.054
Creatinine (mg/dL), median (IQR)	0.82 (0.63-1.26)	0.77 (0.62-1.32)	0.520
Platelets (× 10^9/L), median (IQR)	127 (90-173)	154 (93-193.5)	0.054
WBC (×10^9/L), median (IQR)	7.5 (5.41-10.45)	7.12 (5.76-9.09)	0.898
CRP (mg/dL), median (IQR)	1.53 (0.83-3.15)	1.29 (0.72-2.24)	0.795
Venous ammonia (μmol/L), median (IQR)	111 (86-158)	74 (60-93)	< 0.001
Venous ammonia > 152.5 μmol/L, *n* (%)	96 (26.6)	3 (4.5)	< 0.001
Sodium (mmol/L), median (IQR)	134 (129-137)	135 (131-138)	0.883
Child-Pugh score, median (IQR)	11 (10-12)	9 (8-11)	< 0.001
Child-Pugh class, *n* (%)			
A	1 (0.3)	2 (3)	
B	47 (12.7)	37 (55.2)	
C	322 (87)	28 (41.8)	
MELD, mean ± SD	19.74 ± 6.88	15.97 ± 5.24	< 0.001
AARC score, median (IQR)	7 (6-8)	9 (9-11)	< 0.001
ACLF, *n* (%)			
Grade I	224 (59.9)	72(100)	
Grade II	139 (37.2)	0	
Grade III	11 (2.9)	0	
Ascites, *n* (%)	337 (90.1)	71 (98.6)	0.018
Upper GI bleeding, *n* (%)	71 (19)	18 (25)	0.247
SBP, *n* (%)	23 (6.1)	1 (1.4)	0.150
Other infections, *n* (%)	64 (17.1)	6 (8.3)	0.061
AKI, *n* (%)	51 (13.6)	1 (1.4)	0.003
HCC, *n* (%)	10 (2.7)	1 (1.4)	0.520
Hospital stay (d), median (IQR)	8 (6-11)	5 (3-10)	0.061
In-hospital death rate, *n* (%)	33 (8.8)	2 (2.8)	0.081

IQR: Interquartile range; SD: Standard deviation; INR: International normalized ratio; WBC: White blood cells; CRP: C-reactive protein; MELD: Model for end-stage liver disease; AARC score: APASL ACLF Research Consortium score; HE: Hepatic encephalopathy; GI: Gastrointestinal; AKI: Acute kidney injury; SBP: Spontaneous bacterial peritonitis; HCC: Hepatocellular carcinoma.

stratification of ACLF patients regarding in-hospital prognostic and serve as a marker of severity for this category.

In our study, comprising of patients with advanced liver disease, the presence of HE, in general, was not associated with increased mortality. However, grade III or IV HE posed a statistically significant high risk for in-hospital death and was associated with high levels of VA. These results are in accordance with the findings reported by Bajaj *et al*[27]. The authors analyzed 1560 patients, from which 516 presented HE, 371 grade 1-2 and 145 grade 3-4. Grade 3-4 but not grad 1-2 HE was associated with both higher in-hospital and 30-day mortality rates[27]. Ammonia levels correlate with HE grade in ACLF patients[14], but high ammonia levels have also been associated with the

Table 5 Comparison of patient characteristics based on the presence of high venous ammonia

Variable	Venous ammonia > 152.5 μmol/L, *n* (%) 99 (23.1)	Venous ammonia ≤ 152.5 μmol/L, *n* (%) 329 (76.9)	*P* value
Age, median (IQR)	57 (48-65)	60 (50-65)	0.481
Male sex, *n* (%)	58 (58.6)	190 (57.8)	0.883
Albumin (g/dL), mean ± SD	2.33 ± 0.54	2.38 ± 0.59	0.452
Bilirubin (mg/dL), median (IQR)	2.7 (1.48-5)	2.33 (1.37-4.7)	0.230
INR, median (IQR)	1.5 (1.31-1.83)	1.46 (1.27-1.72)	0.584
Creatinine (mg/dL), median (IQR)	0.85 (0.63-1.54)	0.81 (0.63-1.18)	0.397
Platelets (× 10^9/L), median (IQR)	121 (73-173)	134 (93-182)	0.134
WBC (× 10^9/L), median (IQR)	8.39 (5.251-11.02)	7.26 (5.47-9.92)	0.359
CRP (mg/dL), median (IQR)	1.4 (0.84-4.16)	1.5 (0.8-2.98)	0.682
HE, *n* (%)	265 (80.5)	96 (97)	< 0.001
HE grade III or IV, *n* (%)	55 (20.8)	49 (51)	< 0.001
Sodium (mmol/L), median (IQR)	134 (131-137)	134 (129-137)	0.970
Child-Pugh score, median (IQR)	11 (10-12)	11 (10-12)	0.173
Child-Pugh class, *n* (%)			
A	1 (1)	2 (0.6)	
B	12 (12.4)	70 (21.4)	
C	84 (86.6)	255 (78)	
MELD, mean ± SD	20.76 ± 7.72	18.61 ± 6.34	0.013
AARC score, median (IQR)	7 (6-8)	9 (9-11)	< 0.001
ACLF, *n* (%)			
Grade I	47 (47.5)	238 (72.3)	
Grade II	46 (46.5)	87 (26.4)	
Grade III	6 (6.1)	4 (1.2)	
Ascites, *n* (%)	82 (82.8)	308 (93.6)	0.001
Upper GI bleeding, *n* (%)	22 (22.4)	57 (17.3)	0.252
SBP, *n* (%)	4 (4)	20 (6.1)	0.440
Other infections, *n* (%)	16 (16.2)	49 (14.9)	0.758
AKI, *n* (%)	16 (16.2)	32 (9.7)	0.075
HCC, *n* (%)	5 (5.1)	6 (1.8)	0.137
Hospital stay (d), median (IQR)	8 (6-11)	5 (3-10)	0.969
In-hospital death rate, *n* (%)	24 (24.2)	10 (3)	< 0.001

IQR: Interquartile range; SD: Standard deviation; INR: International normalized ratio; WBC: White blood cells; CRP: C-reactive protein; MELD: Model for end-stage liver disease; AARC score: APASL ACLF Research Consortium score; HE: Hepatic encephalopathy; GI: Gastrointestinal; AKI: Acute kidney injury; SBP: Spontaneous bacterial peritonitis; HCC: Hepatocelular carcinoma.

development of organ failure in the setting of ACLF, other than HE, thus contributing to the unfavorable prognostic of these patients[15]. Our data suggest that the main risk factor for in-hospital mortality in patients with high VA remains severe HE, thus optimal management of these patients is required.

There are several limitations to our study. As a single-center retrospective study, the possibility of selection bias could not be eliminated. Also, as per hospital protocol, arterial ammonia was not available and therefore not comparable with VA regarding the outcome. Furthermore, CT cranial scan was not routinely performed for patients with ACLF and HE, thus the frequency and the impact of cerebral edema on survival

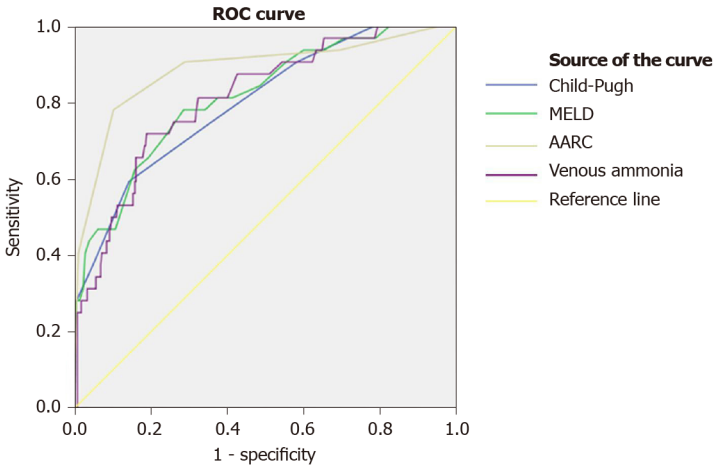

Figure 1 Receiver operating characteristics curve analysis. Diagonal segments are produced by ties. ROC: Receiver operating characteristics; MELD: Model for end-stage liver disease; AARC: Asian Pacific Association for the Study of the Liver Acute-on-chronic Liver Failure Research Consortium.

could not be optimally analyzed.

CONCLUSION

Our results suggest that VA presents a good predictive value for in-hospital mortality in patients with ACLF and that high levels of VA are associated with severe HE. VA has the potential to be used as an additional prognostic marker in the evaluation of patients with ACLF. However, prospective additional studies are required to confirm whether the use of ammonia lowering agents guided by VA levels can improve survival in these patients.

ARTICLE HIGHLIGHTS

Research background

High venous ammonia (VA) values have been proven to be a part of the mechanism of hepatic encephalopathy in patients with liver cirrhosis (LC) as well as acute hepatitis. Moreover, VA has been associated with poor prognosis and high mortality in these clinical settings.

Research motivation

VA has been associated with hepatic encephalopathy (HE) and mortality and has been used by clinicians in acute settings. However, the role of ammonia in acute-on-chronic liver failure (ACLF) has not yet been clearly established and a cut-off value for the prediction of in-hospital mortality is not currently available.

Research objectives

We aimed to adequately assess the role of VA in predicting in-hospital mortality of cirrhotic patients with ACLF in a tertiary care center and to establish an indicative cut-off value for poor prognosis in these patients.

Research methods

We retrospectively included consecutive cirrhotic patients fulfilling the Asian Pacific Association for the Study of the Liver (APASL) criteria for ACLF that were hospitalized for acute non-elective indications such as ascites, HE, upper gastrointestinal bleeding, or bacterial infections. The study was conducted in "St. Spiridon" University Hospital, Iasi, Romania, a tertiary care center, between January 2017 and January 2019. Patients diagnosed with non-hepatic malignancy, human immunodeficiency virus infection, hematological disease as well as pregnant women were excluded. ACLF was defined according to the APASL criteria. The APASL ACLF Research Consortium (AARC) score was calculated and ACLF grade was established

accordingly. West-haven classification was used for HE. Statistical analysis was performed using IBM SPSS version 22.0.

Research results

Five hundred and twenty patients were screened and after applying the exclusion criteria 446 patients were included, aged 59 (50-65) years, 57.4% men. The main etiology of LC was alcohol (78.7%), followed by hepatitis C virus (HCV) infection (11.2%), hepatitis B virus (HBV) infection (6.1%), alcohol and HBV (1.8%), alcohol and HVC (1.3%), HBV and HVC (0.7%). 66.4% had ACLF grade I, 31.2% ACLF grade II, and 2.5% ACLF grade III. HE was diagnosed in 83.9%, 34% grade I, 37.2% grade II, 23.5% grade III, and 5.3% grade IV. Overall mortality was 7.8% and the mean survival of the deceased patients was 5 (3-10) d. ROC analysis showed good accuracy for the prediction of in-hospital mortality for the AARC score [Area under the curve (AUC) = 0.886], model for end-stage liver disease (MELD) score (AUC = 0.816), VA (AUC = 0.812) and a fair accuracy for the Child-Pugh score (AUC = 0.799). A cut-off value for the prediction of mortality was identified for VA (152.5 μmol/L, sensitivity = 0.706, 1-specificity = 0.190). We identified acute kidney injury, severe HE (grade III or IV), VA ≥ 152.5 μmol/L, MELD score ≥ 22.5, Child-Pugh score ≥ 12.5, and AARC score ≥ 8.5 to be associated with in-hospital mortality. Multivariate analysis found AARC score ≥ 8.5 and venous ammonia ≥ 152 μmol/L to be independent predictors of in-hospital mortality.

Research conclusions

Our data indicated that VA represented a useful prognostic marker for patients with ACLF diagnosed according to the APASL definition. Moreover, the cut-off value of 152.5 μmol/L was independently associated with the risk of death with a sensitivity = 0.706 for a 1-specificity = 0.190.

Research perspectives

Prospective large additional studies should be performed in order to confirm whether the use of ammonia lowering agents guided by VA levels could improve survival in patients with ACLF.

REFERENCES

1 **Jaeger V**, DeMorrow S, McMillin M. The Direct Contribution of Astrocytes and Microglia to the Pathogenesis of Hepatic Encephalopathy. *J Clin Transl Hepatol* 2019; **7**: 352-361 [PMID: 31915605 DOI: 10.14218/JCTH.2019.00025]

2 **Laish I**, Ben Ari Z. Noncirrhotic hyperammonaemic encephalopathy. *Liver Int* 2011; **31**: 1259-1270 [PMID: 21745294 DOI: 10.1111/j.1478-3231.2011.02550.x]

3 **Triplett KE**, Murray R, Anstey M. Multifactorial non-cirrhotic hyperammonaemic encephalopathy. *BMJ Case Rep* 2018; **2018** [PMID: 29523611 DOI: 10.1136/bcr-2017-223245]

4 **Sarin SK**, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, Saigal S, Saraf N, Soin AS, Devarbhavi H, Kim DJ, Dhiman RK, Duseja A, Taneja S, Eapen CE, Goel A, Ning Q, Chen T, Ma K, Duan Z, Yu C, Treeprasertsuk S, Hamid SS, Butt AS, Jafri W, Shukla A, Saraswat V, Tan SS, Sood A, Midha V, Goyal O, Ghazinyan H, Arora A, Hu J, Sahu M, Rao PN, Lee GH, Lim SG, Lesmana LA, Lesmana CR, Shah S, Prasad VGM, Payawal DA, Abbas Z, Dokmeci AK, Sollano JD, Carpio G, Shresta A, Lau GK, Fazal Karim M, Shiha G, Gani R, Kalista KF, Yuen MF, Alam S, Khanna R, Sood V, Lal BB, Pamecha V, Jindal A, Rajan V, Arora V, Yokosuka O, Niriella MA, Li H, Qi X, Tanaka A, Mochida S, Chaudhuri DR, Gane E, Win KM, Chen WT, Rela M, Kapoor D, Rastogi A, Kale P, Rastogi A, Sharma CB, Bajpai M, Singh V, Premkumar M, Maharashi S, Olithselvan A, Philips CA, Srivastava A, Yachha SK, Wani ZA, Thapa BR, Saraya A, Shalimar, Kumar A, Wadhawan M, Gupta S, Madan K, Sakhuja P, Vij V, Sharma BC, Garg H, Garg V, Kalal C, Anand L, Vyas T, Mathur RP, Kumar G, Jain P, Pasupuleti SSR, Chawla YK, Chowdhury A, Alam S, Song DS, Yang JM, Yoon EL; APASL ACLF Research Consortium (AARC) for APASL ACLF working Party. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. *Hepatol Int* 2019; **13**: 353-390 [PMID: 31172417 DOI: 10.1007/s12072-019-09946-3]

5 **Piano S**, Favaretto E, Tonon M, Antonelli G, Brocca A, Sticca A, Mareso S, Gringeri E, Scaroni C, Plebani M, Russo FP, Burra P, Cillo U, Angeli P. Including Relative Adrenal Insufficiency in Definition and Classification of Acute-on-Chronic Liver Failure. *Clin Gastroenterol Hepatol* 2020; **18**: 1188-1196.e3 [PMID: 31589973 DOI: 10.1016/j.cgh.2019.09.035]

6 **Trifan A**, Chiriac S, Stanciu C. Update on adrenal insufficiency in patients with liver cirrhosis. *World J Gastroenterol* 2013; **19**: 445-456 [PMID: 23382623 DOI: 10.3748/wjg.v19.i4.445]

7 **Seyan AS**, Hughes RD, Shawcross DL. Changing face of hepatic encephalopathy: role of

inflammation and oxidative stress. *World J Gastroenterol* 2010; **16**: 3347-3357 [PMID: 20632436 DOI: 10.3748/wjg.v16.i27.3347]

8 **Liotta EM**, Kimberly WT. Cerebral edema and liver disease: Classic perspectives and contemporary hypotheses on mechanism. *Neurosci Lett* 2020; **721**: 134818 [PMID: 32035166 DOI: 10.1016/j.neulet.2020.134818]

9 **Kale RA**, Gupta RK, Saraswat VA, Hasan KM, Trivedi R, Mishra AM, Ranjan P, Pandey CM, Narayana PA. Demonstration of interstitial cerebral edema with diffusion tensor MR imaging in type C hepatic encephalopathy. *Hepatology* 2006; **43**: 698-706 [PMID: 16557540 DOI: 10.1002/hep.21114]

10 **Häussinger D**. Low grade cerebral edema and the pathogenesis of hepatic encephalopathy in cirrhosis. *Hepatology* 2006; **43**: 1187-1190 [PMID: 16729329 DOI: 10.1002/hep.21235]

11 **Joshi D**, O'Grady J, Patel A, Shawcross D, Connor S, Deasy N, Willars C, Bernal W, Wendon J, Auzinger G. Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. *Liver Int* 2014; **34**: 362-366 [PMID: 23844567 DOI: 10.1111/liv.12257]

12 **Sawhney R**, Holland-Fischer P, Rosselli M, Mookerjee RP, Agarwal B, Jalan R. Role of ammonia, inflammation, and cerebral oxygenation in brain dysfunction of acute-on-chronic liver failure patients. *Liver Transpl* 2016; **22**: 732-742 [PMID: 27028317 DOI: 10.1002/lt.24443]

13 **Hu C**, Huang K, Zhao L, Zhang F, Wu Z, Li L. Serum ammonia is a strong prognostic factor for patients with acute-on-chronic liver failure. *Sci Rep* 2020; **10**: 16970 [PMID: 33046732 DOI: 10.1038/s41598-020-73603-1]

14 **Shalimar**, Sheikh MF, Mookerjee RP, Agarwal B, Acharya SK, Jalan R. Prognostic Role of Ammonia in Patients With Cirrhosis. *Hepatology* 2019; **70**: 982-994 [PMID: 30703853 DOI: 10.1002/hep.30534]

15 **Kumar R**, Shalimar, Sharma H, Prakash S, Panda SK, Khanal S, Acharya SK. Persistent hyperammonemia is associated with complications and poor outcomes in patients with acute liver failure. *Clin Gastroenterol Hepatol* 2012; **10**: 925-931 [PMID: 22521861 DOI: 10.1016/j.cgh.2012.04.011]

16 **Jacoby KJ**, Singh P, Prekker ME, Leatherman JW. Characteristics and outcomes of critically ill patients with severe hyperammonemia. *J Crit Care* 2020; **56**: 177-181 [PMID: 31935606 DOI: 10.1016/j.jcrc.2019.12.005]

17 **Shawcross DL**, Sharifi Y, Canavan JB, Yeoman AD, Abeles RD, Taylor NJ, Auzinger G, Bernal W, Wendon JA. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. *J Hepatol* 2011; **54**: 640-649 [PMID: 21163546 DOI: 10.1016/j.jhep.2010.07.045]

18 **Haj M**, Rockey DC. Ammonia Levels Do Not Guide Clinical Management of Patients With Hepatic Encephalopathy Caused by Cirrhosis. *Am J Gastroenterol* 2020; **115**: 723-728 [PMID: 31658104 DOI: 10.14309/ajg.0000000000000343]

19 **Dharel N**, Bajaj JS. Definition and nomenclature of hepatic encephalopathy. *J Clin Exp Hepatol* 2015; **5**: S37-S41 [PMID: 26041955 DOI: 10.1016/j.jceh.2014.10.001]

20 **Khwaja A**. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; **120**: c179-c184 [PMID: 22890468 DOI: 10.1159/000339789]

21 **Ong JP**, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, Arroliga AC, Mullen KD. Correlation between ammonia levels and the severity of hepatic encephalopathy. *Am J Med* 2003; **114**: 188-193 [PMID: 12637132 DOI: 10.1016/s0002-9343(02)01477-8]

22 **Patwardhan VR**, Jiang ZG, Risech-Neiman Y, Piatkowski G, Afdhal NH, Mukamal K, Curry MP, Tapper EB. Serum Ammonia is Associated With Transplant-free Survival in Hospitalized Patients With Acutely Decompensated Cirrhosis [corrected]. *J Clin Gastroenterol* 2016; **50**: 345-350 [PMID: 26565968 DOI: 10.1097/MCG.0000000000000443]

23 **Takaya H**, Namisaki T, Sato S, Kaji K, Tsuji Y, Kaya D, Fujinaga Y, Sawada Y, Shimozato N, Kawaratani H, Moriya K, Akahane T, Mitoro A, Yoshiji H. Increased Endotoxin Activity Is Associated with the Risk of Developing Acute-on-Chronic Liver Failure. *J Clin Med* 2020; **9** [PMID: 32422875 DOI: 10.3390/jcm9051467]

24 **Chen BH**, Tseng HJ, Chen WT, Chen PC, Ho YP, Huang CH, Lin CY. Comparing Eight Prognostic Scores in Predicting Mortality of Patients with Acute-On-Chronic Liver Failure Who Were Admitted to an ICU: A Single-Center Experience. *J Clin Med* 2020; **9** [PMID: 32443729 DOI: 10.3390/jcm9051540]

25 **Trebicka J**, Sundaram V, Moreau R, Jalan R, Arroyo V. Liver Transplantation for Acute-on-Chronic Liver Failure: Science or Fiction? *Liver Transpl* 2020; **26**: 906-915 [PMID: 32365422 DOI: 10.1002/lt.25788]

26 **Weil D**, Levesque E, McPhail M, Cavallazzi R, Theocharidou E, Cholongitas E, Galbois A, Pan HC, Karvellas CJ, Sauneuf B, Robert R, Fichet J, Piton G, Thevenot T, Capellier G, Di Martino V; METAREACIR Group. Prognosis of cirrhotic patients admitted to intensive care unit: a meta-analysis. *Ann Intensive Care* 2017; **7**: 33 [PMID: 28321803 DOI: 10.1186/s13613-017-0249-6]

27 **Bajaj JS**, O'Leary JG, Tandon P, Wong F, Garcia-Tsao G, Kamath PS, Maliakkal B, Biggins SW, Thuluvath PJ, Fallon MB, Subramanian RM, Vargas HE, Lai J, Thacker LR, Reddy KR. Hepatic Encephalopathy Is Associated With Mortality in Patients With Cirrhosis Independent of Other Extrahepatic Organ Failures. *Clin Gastroenterol Hepatol* 2017; **15**: 565-574. e4 [PMID: 27720916 DOI: 10.1016/j.cgh.2016.09.157]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com