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Clinical impact of arterial ammonia levels in ICU patients with different liver diseases

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Abstract Purpose: Increased arterial ammonia levels are associated with high mortality in patients with acute liver failure (ALF). Data on the prognostic impact of arterial ammonia is lacking in hypoxic hepatitis (HH) and scarce in critically ill patients with cirrhosis.

Methods: The patient cohort comprised 72 patients with HH, 43 patients with ALF, 100 patients with liver cirrhosis and 45 patients without evidence for liver disease. Arterial ammonia concentrations were assessed on a daily basis in all patients and the results were compared among these four patient groups and between 28-day survivors and 28-day non-survivors overall and in each group.

Results: Overall 28-day mortality rates in patients with HH, ALF and cirrhosis and in the control group were 54, 30, 49 and 27 %, respectively. Peak arterial ammonia levels differed significantly between transplant-free 28-day survivors and non-survivors in the HH and ALF groups ($p < 0.01$ for both). Multivariate regression identified peak arterial ammonia concentrations as an independent predictor of 28-day mortality or liver transplantation in patients with HH and ALF, respectively ($p < 0.01$). There was no association between mortality and arterial ammonia in patients with liver cirrhosis and in the control group. Admission arterial ammonia levels were independently

linked to hepatic encephalopathy grades 3/4 in patients with HH ($p < 0.01$), ALF ($p < 0.05$) and cirrhosis ($p < 0.05$), respectively.

Conclusions: Elevated arterial ammonia levels indicate a poor prognosis in acute liver injury and are associated with advanced HE in HH, ALF and cirrhosis. Arterial ammonia levels provide additional information in the risk assessment of critically ill patients with liver disease.

Keywords Hypoxic hepatitis · Acute liver failure · Liver cirrhosis · Ammonia · Mortality

Abbreviations

ALF	Acute liver failure
AUROC	Area under receiver operating characteristic (ROC) curve
CPR	Cardiopulmonary resuscitation
CT	Computed tomography
HE	Hepatic encephalopathy
HH	Hypoxic hepatitis
ICU	Intensive care unit
INR	International normalized ratio
MELD	Model of end stage liver disease
SIRS	Systemic inflammatory response syndrome
SAPS II	Simplified acute physiology score II
SOFA	Sequential organ failure assessment score

Introduction

Elevated arterial ammonia levels are frequently observed in patients with acute liver failure (ALF) and/or liver cirrhosis [1–4]. Diminished ammonia-detoxification capacity and porto-systemic shunting have been deemed responsible for the increased circulating ammonia levels and consequent development of hepatic encephalopathy (HE) [5–9]. In ALF, elevated ammonia levels have been linked to clinical features of HE [10], cerebral complications [1–3, 11] and increased mortality [2]. In contrast, arterial ammonia levels do not predict either the severity of encephalopathy or mortality in cirrhotic patients with HE grades 3/4 in the intensive care unit (ICU) [12]. Hypoxic hepatitis (HH), also known as shock liver or ischemic hepatitis, occurs in approximately 10 % of all patients admitted to medical ICUs and is associated with high morbidity and mortality [13–16]. Yet, arterial ammonia levels in patients with HH and the clinical relevance of these levels have not been investigated.

The primary aim of this study was to compare peak arterial ammonia levels between survivors and non-survivors in a patient cohort of critically ill individuals with different entities of liver disease.

Materials and methods

Patients

The patient cohort comprised 226 critically ill patients who had been admitted to medical ICU 13H1 of the Medical University Vienna. These patients were classified into four groups based on the entity of liver disease (see “Definitions”) or the absence thereof: HH (72 patients), ALF (43 patients), liver cirrhosis (100 patients) and control (= no evidence of liver disease; 45 patients).

All data were collected on a daily basis. Arterial ammonia concentration was determined as part of the routine daily laboratory assessment as described below. Twenty-eight-day mortality was assessed in all patients on site or by contacting the patients or their respective attending physician. Presence of HE was assessed by the attending physician and is part of the routine physical examination for patients with liver disease at our unit. The Simplified Acute Physiology Score II (SAPS II) [17], Sequential Organ Failure Assessment (SOFA) score [18], Systemic inflammatory response syndrome (SIRS) score [19] and Model of End-stage Liver Disease (MELD) score were calculated on admission to assess the severity of illness [20]. The study was approved by

the ethics committee of the Medical University Vienna, which waived the need for informed consent due to the observational character of the study. Data of patients with HH and cirrhosis and of the control group were collected prospectively between 2008 and 2010 in consecutively admitted patients. The results of this study have been presented in part at the annual congress of the Society of Intensive Care Medicine 2010 [21]; data on patients of the ALF group were collected and analyzed retrospectively.

Therapeutic management of patients

All patients were treated following standardized protocols. Patients meeting shock criteria received fluids intravenously and vasopressors to maintain mean arterial pressure at >65 mmHg. Renal replacement therapy (RRT) was initiated in patients with renal failure and/or metabolic acidosis. Broad-spectrum antibiotics were empirically given to each patient; antimicrobial therapy was initiated and adapted to the culture results where necessary. Cirrhotic patients with signs of HE, but not ALF, and HH patients received L-ornithine-L-aspartate and lactulose. N-acetylcysteine was administered to ALF patients with suspected acetaminophen intoxication. Patients showing HE \geq grade 3 were intubated and mechanically ventilated.

Definitions

Hypoxic hepatitis

Hypoxic hepatitis was diagnosed according to well-established criteria: (1) a clinical setting of cardiac, circulatory or respiratory failure; (2) a sharp increase in serum aminotransferase levels to at least 20-fold the upper limit of normal; (3) exclusion of other potential causes for increased aminotransferase levels [14, 15, 22]. Patients with HH accompanying cirrhosis were excluded from the analysis.

Acute liver failure

Acute liver failure was diagnosed in patients presenting with evidence of coagulation abnormality [international normalized ratio (INR) > 1.5] and any degree of mental alteration (encephalopathy) in the absence of pre-existing cirrhosis and with duration of illness <26 weeks [23].

Liver cirrhosis

Presence of liver cirrhosis was defined based on histological findings, if available, or by a combination of characteristic clinical (ascites, caput medusae, spider angiomas, among others), laboratory and radiological findings [typical morphological changes of the liver, signs of portal hypertension, etc. in ultrasonography or computed tomography (CT) scanning].

Hepatic encephalopathy

Hepatic encephalopathy was classified according to West–Haven criteria as HE grade 1 (trivial lack of awareness, shortened attention span, tremor, apraxia, incoordination of muscles), HE grade 2 (lethargy or apathy, disorientation, personality change, asterixis, ataxia, dysarthria), HE grade 3 (somnia to semistupor, confusion, responsive to stimuli, asterixis, ataxia) and HE grade 4 (coma \pm decerebration, unresponsive) [24–26]. Patients requiring intubation due to neurologic deterioration were considered HE stage 4. Clinical signs of HE were assessed in HH patients who were not intubated or sedated on or before admission to the ICU (22 %) for reasons other than encephalopathy [e.g. respiratory insufficiency, cardiopulmonary resuscitation (CPR), among others]. In sedated HH patients without contraindications for transportation [27], presence of HE was suggested by signs of intracranial hypertension on the CT/magnetic resonance imaging scans [28] or autopsy. Patients who had received CPR [29, 30] and those with pre-existing cerebral/cerebrovascular diseases were excluded from HE assessment.

Systemic inflammatory response syndrome)/sepsis/septic shock

Systemic inflammatory response syndrome, sepsis and septic shock were diagnosed as defined previously [31–33].

Cardiogenic shock

Cardiogenic shock was diagnosed in patients presenting with (1) low arterial blood pressure (systolic blood pressure <90 mmHg) without use of inotropes or requirement for vasopressors; (2) signs of decreased cardiac output (low cardiac output measured by any method, low mixed or central venous oxygen saturation, acute myocardial infarction); (3) absence of hypovolemia; (4) signs of organ malperfusion [34–36].

Measurement of arterial ammonia levels

Plasma ammonia levels were measured on a Beckman Coulter AU2700 chemistry analyzer (Beckman Coulter Diagnostics, Fullerton, CA) using the Ammonia Ultra reagents provided by Sentinel Diagnostics (Sentinel CH, Milan, Italy). The method is based on a glutamate dehydrogenase-mediated enzymatic transformation and UV detection of NADH to NAD⁺ that is proportionally dependent on the ammonia concentration in the plasma sample examined. The site of blood sampling was the radial artery in all patients. To avoid falsely high results, EDTA-anticoagulated blood samples were immediately placed on ice after blood sampling and typically processed within minutes. Only hemolysis-free plasma samples were eligible for analysis.

Data analysis and statistics

Data are presented as the median and 25–75 % interquartile range (IQR). Metric variables were compared using the Mann–Whitney test, dichotomous variables using chi-square analysis. The primary aim of this study was to compare arterial ammonia levels between survivors and non-survivors as well as between patients with and without signs of HE in different entities of liver disease (HH, ALF and cirrhosis). Differences in peak arterial ammonia were also studied between survivors and non-survivors without liver disease (control group). A post hoc correction of Bonferroni was performed to correct for these seven primary tests; thus, the needed p value for significant results in the primary analyses was lowered to $p < 0.0071$ ($p < 0.05/7$). All further analyses performed were exploratory. Suitable threshold values for predictive metric variables were derived from receiver operating characteristic (ROC) analysis. A forward stepwise procedure was used to identify the most potent predictors for the respective outcome parameter. Model fit for logistic regression models was assessed via the Hosmer–Lemeshow test and Nagelkerke R^2 . For all exploratory analyses, a p value of <0.05 was considered to be statistically significant. PASW Statistics ver. 17.0 (SPSS, Chicago, IL) was used for all analyses.

Results

Patients

Hypoxic hepatitis

The leading causes for the occurrence of HH among our patient cohort were cardiogenic ($n = 31$) and septic shock ($n = 31$), respectively. Other precipitating events were

hypoxia/respiratory failure ($n = 4$), temporary hypotension ($n = 2$), pericardial effusion ($n = 2$) and arrhythmogenic heart disease ($n = 2$). All patients had only one episode of HH during their stay in the ICU. Cerebral herniation occurred in only one patient with low arterial ammonia levels as a consequence of hypoxic brain injury following CPR.

Acute liver failure

Causes of ALF were viral ($n = 12$), amanita intoxication ($n = 8$), non-acetaminophen drug-induced ($n = 7$), autoimmune ($n = 5$), acetaminophen ($n = 4$), Wilson's disease ($n = 2$) and unknown ($n = 5$). Twenty-six patients (60 %) presented with HE < grade 3 on admission, and 17 (40 %) presented with HE grade 3/4. Sixteen patients were admitted with HE of < grade 3, but subsequently developed HE grade 3/4. Altogether, 33 patients (77 %) showed HE grade 3/4 during their stay in the ICU. The majority of ALF patients (91 %) presented signs of HE at admission. One patient died from cerebral herniation. Fifteen patients (35 %) underwent orthotopic liver transplantation during the observation period.

Liver cirrhosis

Underlying causes of cirrhosis among our patient cohort were alcoholic liver disease ($n = 53$), hepatitis C ($n = 16$), combined etiology (all alcoholic + hepatitis C; $n = 7$), cryptogenic ($n = 13$) and other ($n = 11$). The main admission diagnoses were severe sepsis/septic shock ($n = 46$), gastrointestinal bleeding ($n = 21$), coma hepaticum/HE grades 3/4 ($n = 10$), hepatorenal syndrome ($n = 9$) and other ($n = 14$). Electronic Supplemental Material (ESM) Table 1 presents the admission and peak ammonia levels and the clinical HE grades stratified according to the main admission diagnoses. Fifty-two patients (52 %) were admitted with HE \leq grade II and 33 (33 %) with HE grade 3/4; 15 (15 %) had no clinical signs of HE on admission. Six patients (6 %) were admitted with HE \leq grade 2, but subsequently developed HE grade 3/4. None of the patients died from cerebral herniation, and none of the patients underwent orthotopic liver transplantation within 28 days following ICU admission. The median Child–Pugh score on admission was 12 (IQR 10–13).

Control

The control group consisted of 45 critically ill patients. Of these, 19 (42 %) had septic shock, and 26 (58 %) suffered from cardiogenic shock without signs of severe liver injury, viral or drug-induced hepatitis or cirrhosis or had

serum aminotransferase levels that were less than fivefold the upper limit of normal and serum bilirubin levels that were less than 2 mg/dl. The median age of control patients was 61 (IQR 52–75) years. Sixteen patients were female (36 %). The median SOFA score on admission was 11 (IQR 8–12) and median SAPS II score was 61 (IQR 46–74). Twelve patients (27 %) died within 28 days following ICU admission. The SAPS II and SOFA scores did not differ significantly between the control group and the HH group ($p = 0.87$ and $p = 0.78$, respectively), although the SOFA score in cirrhotics was significantly higher (Table 1; $p < 0.01$) and SAPS score in ALF significantly lower (Table 1; $p < 0.01$).

The main clinical characteristics of patients with liver disease stratified according to 28-day survival are shown in Table 1.

Arterial ammonia levels

The laboratory features of the four study groups are illustrated in Table 2. Peak values of arterial ammonia were observed on day 2 (IQR 1–3 days) in HH and ALF patients, respectively, and on day 1 (IQR 1–3) in patients with cirrhosis following ICU admission. Distribution of measured peak arterial ammonia concentrations in 28-day survivors and non-survivors is shown in Fig. 1. The ESM figure illustrates the time course of arterial ammonia levels in the different study groups.

Arterial ammonia and 28-day mortality

The predictive value of arterial ammonia levels with respect to 28-day mortality or transplantation, respectively, is shown in Tables 1 and 4.

HH: arterial ammonia and 28-day mortality

There was a trend for lower arterial ammonia levels on admission in 28 day-survivors compared to non-survivors ($p = 0.087$; Table 1). Peak arterial ammonia levels were significantly higher in 28-day non-survivors ($p = 0.0042$; Table 1). Peak arterial ammonia concentrations of $>75 \mu\text{mol/l}$ were significantly associated with 28-day mortality (Fig. 2). In the multivariate logistic regression analysis, peak arterial ammonia levels of $>75 \mu\text{mol/l}$ remained an independent predictor of 28-day mortality [odds ratio (OR) 8.59, 95 % confidence interval (CI) 2.15–34.43, $p < 0.01$] after adjustment for the admission SOFA score and peak INR, which were also associated with 28-day mortality in the univariate analysis (Hosmer–Lemeshow test chi-square 7.2, $df = 8$, $p = 0.52$; Nagelkerke $R^2 = 0.343$).

Table 1 Characteristics of patients with liver disease admitted to the intensive care unit stratified according to 28-day survival

Parameter	Hypoxic hepatitis (n = 72)		Acute liver failure (n = 43)		Cirrhosis (n = 100)		p value
	28-day survivors	28-day non-survivors	Transplant-free 28-day survivors	28-day non-survivors and/or transplant	28-day survivors	28-day non-survivors	
Number of patients	33 (46 %)	39 (54 %)	17 (40 %)	26 (60 %)	51 (51 %)	49 (49 %)	
Admission characteristics							
Age (years)	65 (49–75)	64 (55–76)	40 (30–58)	50 (36–60)	53 (45–63)	56 (50–62)	0.225
Sex (female)	14 (42 %)	14 (36 %)	11 (65 %)	16 (62 %)	19 (37 %)	17 (35 %)	0.834
SOFA score	9 (6–11)	12 (8–15)	6 (3.5–8.5)	10 (6–13)	11 (7–13)	14 (11–15)	<0.01
SAPS II	50 (38–68)	67 (55–80)	26 (15–36)	40 (30–58)	53 (40–65)	72 (46–81)	<0.01
GCS	15 (12–15)	14 (4–15)	15 (12.5–15)	13 (7–15)	8 (3–13)	9 (3–15)	0.439
SIRS score	2 (2–3)	3 (2–3)	1 (1–2)	2 (1–2)	2 (1–3)	2 (1–3)	0.963
MELD score	18.3 (11.2–26.6)	19.1 (12.5–25.4)	31.2 (13.6–38.3)	38.6 (30.7–40.0)	20.7 (14.7–29)	29.3 (23.7–39.0)	<0.01
Treatment during stay in ICU							
Vasopressor	23 (70 %)	37 (95 %)	4 (24 %)	10 (39 %)	18 (35 %)	39 (80 %)	<0.01
Renal replacement therapy	6 (18 %)	13 (33 %)	4 (24 %)	12 (46 %)	11 (22 %)	21 (43 %)	<0.05
Mechanical ventilation	21 (64 %)	35 (90 %)	3 (18 %)	14 (54 %)	26 (51 %)	28 (57 %)	0.54
Laboratory parameters							
Adm INR	1.4 (1.2–2.1)	1.5 (1.2–2.2)	2.6 (1.4–3.6)	3.7 (2.3–7.4)	1.5 (1.4–2.0)	2.0 (1.7–2.8)	<0.01
Peak INR	1.9 (1.5–2.7)	2.2 (1.8–3.5)	2.8 (1.7–5.6)	8.1 (4.8–8.1)	1.9 (1.5–2.4)	2.9 (2.1–4.8)	<0.01
Adm creatinine (μmol/l)	1.8 (1.1–2.5)	2.0 (1.4–2.6)	0.9 (0.6–1.6)	1.0 (0.8–1.6)	1.3 (0.8–2.3)	2.2 (1.3–3.4)	<0.01
Peak creatinine (μmol/l)	2.5 (1.4–3.2)	2.8 (1.9–3.7)	1.2 (0.7–3.7)	1.4 (1.0–3.2)	1.5 (1.0–2.7)	2.6 (1.6–3.4)	<0.01
Arterial ammonia (NH ₃)							
Adm NH ₃ (μmol/l)	50.2 (35.7–73.5)	68.6 (47.3–121.1)	72 (55.2–133.2)	108.1 (67.6–155.4)	64.4 (47.3–95.1)	66.7 (53.5–86.4)	0.86
Peak NH ₃ ^a (μmol/l)	52.2 (36.8–106.6)	77.0 (53.1–125.6)	90.9 (60.9–126.4)	160.2 (119.6–194.9)	72.6 (54.9–128.8)	84.1 (63.7–122.5)	0.45

Data are presented as the median with the interquartile range (IQR) in parenthesis, or as the number with the percentage in parenthesis, where appropriate

SOFA Sequential Organ Failure Assessment, SAPS Simplified Acute Physiology Score, GCS Glasgow Coma Scale, SIRS Systemic inflammatory response syndrome, MELD Model of End-stage Liver Disease, ICU intensive care unit, INR international normalized ratio, Adm admission, NH₃ arterial ammonia concentration

^a Primary parameter of interest: after Bonferroni correction significant differences were found in patients with hypoxic hepatitis (HH) and acute liver failure (ALF) ($p < 0.0071$ for both)

Table 2 Admission and peak laboratory characteristics of 260 patients admitted to the medical ICU

Parameter	Hypoxic hepatitis (n = 72)	Acute liver failure (n = 43)	Cirrhosis (n = 100)	Control (n = 45)
Number of patients	72	43	100	45
On admission				
AST (U/l) ^{a, b, c, d, e}	262 (63–1,046)	1,507 (194–2,478)	75 (52–134)	54 (35–101)
ALT (U/l) ^{a, b, c, d, e}	142 (36–750)	2,224 (296–4,113)	32 (21–58)	36 (25–56)
INR ^{a, b, c, d, e, f}	1.4 (1.2–2.1)	3.1 (2.0–5.7)	1.8 (1.5–2.2)	1.2 (1.1–1.5)
Bilirubin (mg/dl) ^{a, b, c, d, e, f}	1.2 (0.7–2.2)	14.4 (5.2–25.8)	5.5 (2.6–16.7)	0.8 (0.5–1.2)
Creatinine (mg/dl) ^{a, c, d, f}	1.9 (1.2–2.5)	1.0 (0.7–1.6)	1.7 (1.0–3.0)	1.2 (1.0–1.7)
NH ₃ (μmol/l) ^{a, c, d, e, f}	65 (38.5–92.2)	95.9 (61.4–139.0)	66.0 (49.2–90.5)	31.8 (26.2–37.2)
Peak values				
AST (U/l) ^{a, b, c, d, e}	3,035 (1,568–6,942)	1,780 (452–3,110)	115 (68–205)	90 (55–170)
ALT (U/l) ^{b, c, d, e}	1,668 (869–3,123)	2,720 (485–4,680)	42 (29–74)	54 (28–88)
INR ^{a, c, d, e, f}	2.0 (1.7–3.0)	6.3(2.8–8.1)	2.2 (1.8–3.0)	1.4 (1.2–1.7)
Bilirubin (mg/dl) ^{a, b, c, d, e, f}	2.3 (1.5–4.4)	21.2 (9.8–32.2)	9.2 (3.9–19.3)	1.2 (0.9–1.8)
Creatinine (mg/dl) ^{a, b, c, f}	2.5 (1.6–3.5)	1.3 (1.0–3.1)	2.1 (1.1–3.2)	1.3 (1.1–2.0)
NH ₃ (μmol/l) ^{a, b, c, d, e, f}	65 (41.9–100.6)	122.0 (90.9–179.9)	78.3 (60.3–126.5)	40 (32.6–52.2)

Data are presented as the median with the IQR in parenthesis

AST Aspartate aminotransferase, ALT alanine aminotransferase

^{a, b, c, d, e, f} Exploratory analyses: ^a $p < 0.05$ HH vs. ALF; ^b $p < 0.05$ HH vs. cirrhosis; ^c $p < 0.05$ HH vs. control; ^d $p < 0.05$ ALF vs. cirrhosis; ^e $p < 0.05$ ALF vs. control; ^f $p < 0.05$ cirrhosis vs. control

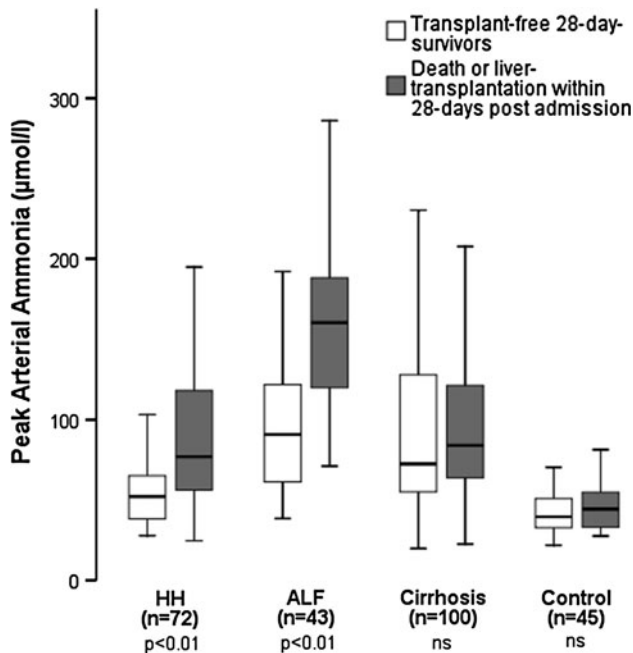


Fig. 1 Arterial ammonia levels in survivors and non-survivors in the intensive care unit. Peak arterial ammonia levels in the four study groups (HH hypoxic hepatitis, ALF acute liver failure) categorized into transplant-free 28 day-survivors vs. non-survivors/transplanted patients. Box plot marks median (thick horizontal line), interquartile range (box) and extreme values (whiskers)

ALF: arterial ammonia and transplant-free 28-day survival

There was a trend for lower arterial ammonia concentrations in 28-day transplant-free survivors at admission ($p = 0.101$), whereas peak arterial ammonia levels were

significantly lower in 28-day transplant-free survivors compared to patients who died or underwent liver transplantation ($p = 0.00056$; Table 1). The impact of peak arterial ammonia levels of $>100 \mu\text{mol/l}$ is shown in a Kaplan–Meier plot (Fig. 2). After adjustment for SOFA score and peak INR, which were associated with 28-day mortality in the univariate analysis (Table 1), peak arterial ammonia levels of $>100 \mu\text{mol/l}$ remained significantly linked to 28-day mortality or transplantation in the multivariate regression analysis (OR 11.21, 95 % CI 1.33–94.41, $p < 0.05$). (Hosmer–Lemeshow test chi-square 3.5, $df = 8$, $p = 0.90$; Nagelkerke $R^2 = 0.663$). Predictive values of peak arterial ammonia levels in comparison to commonly used scoring systems in ALF is shown in ESM Table 2.

Liver cirrhosis: arterial ammonia and 28-day mortality

Neither admission nor peak arterial ammonia levels differed significantly between 28-day non-survivors and 28-day survivors ($p = 0.860$ and $p = 0.452$, respectively; Table 1). The SOFA score (OR 1.23, 95 % CI 1.07–1.43, $p < 0.01$) and presence of septic shock (OR 3.72, 95 % CI 1.42–9.74, $p < 0.01$) remained significant predictors of 28-day mortality in the stepwise multivariate logistic regression model. (Hosmer–Lemeshow test chi-square 2.9, $df = 8$, $p = 0.94$, Nagelkerke $R^2 = 0.307$).

Controls: arterial ammonia and 28-day mortality

Admission and peak arterial ammonia concentrations, respectively, did not differ significantly between 28-day survivors and non-survivors [survivors: median 30 (IQR

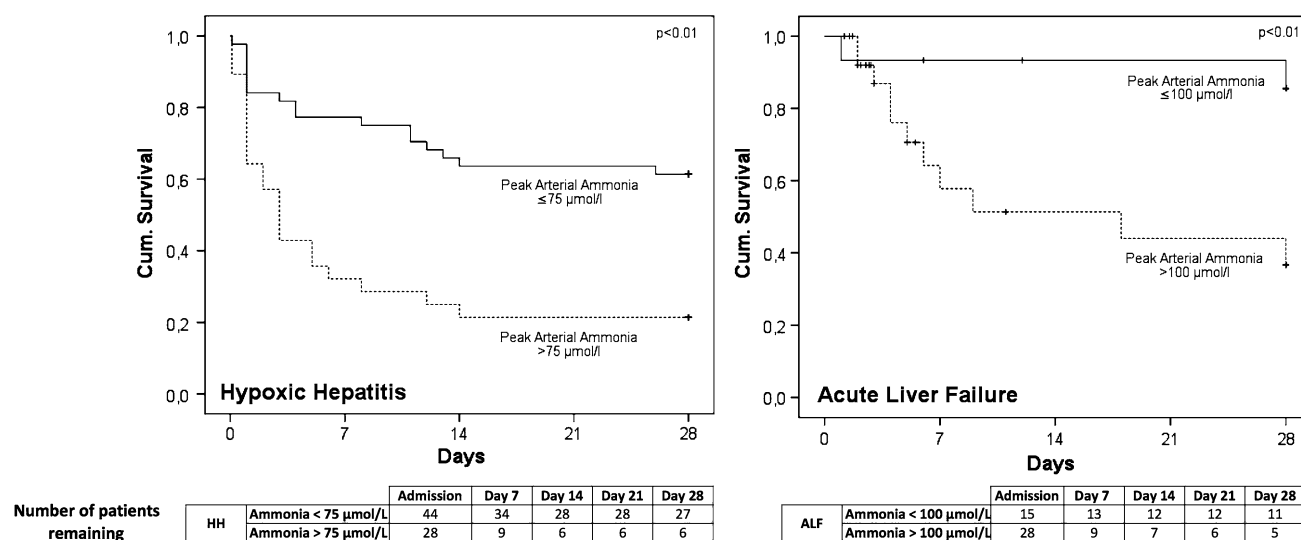


Fig. 2 Kaplan–Mayer plot of 28-day transplant-free survival in patients with HH (left) and ALF (right) with respect to peak arterial ammonia concentrations

27.2–34.6) vs. 35.6 (IQR 25.8–47.3) $\mu\text{mol/L}$, respectively, $p = 0.204$; non-survivors: median 39.6 (IQR 33.6–51.4) vs. 44.5 (IQR 32.7–55.6) $\mu\text{mol/L}$, respectively, $p = 0.676$]. The SOFA score differed significantly between 28-day survivors and non-survivors [median 9 (IQR 7–11) vs. 11.5 (IQR 11–14.75); $p < 0.05$].

Arterial ammonia and HE

Features of patients with and without advanced HE are illustrated in Table 3.

HH: arterial ammonia and signs of HE

Signs of HE were present in 12 of 35 patients who were included in the HE evaluation (Table 3). The prognostic value of arterial ammonia levels in predicting signs of HE in HH is shown in Table 4. None of the HH patients with signs of HE died from cerebral herniation, and the main causes of death in these patients were septic shock ($n = 4$), cardiogenic shock ($n = 2$), mixed cardiogenic and septic shock ($n = 1$) and cardiac arrest ($n = 1$).

ALF: arterial ammonia and HE

The predictive value of arterial ammonia levels in predicting HE grade 3/4 in ALF patients is shown in Tables 3 and 4. Twenty-six ALF patients were admitted to the ICU with HE \leq grade 2, of whom 16 subsequently developed HE grades 3/4 and showed significantly higher arterial ammonia levels than those who did not [median 86.6 (IQR 67.3–123.7) vs. 60.0 (IQR 50.0–61.9) $\mu\text{mol/L}$, respectively;

$p < 0.01$]. The area under the receiver operating characteristic curve (AUROC) for admission arterial ammonia levels in predicting new onset of HE grades 3/4 in ALF was 0.825 (95 % CI 0.659–0.991, $p < 0.01$). There was a trend for higher SIRS scores in patients with peak HE grades 3/4 compared to those with HE < grade 3 (Table 3).

Liver cirrhosis: arterial ammonia and encephalopathy

Both admission and peak ammonia levels were associated with peak HE grades 3/4 (Tables 3, 4). In patients who were admitted with HE \leq grade 2, neither admission nor peak arterial ammonia levels predicted new onset of HE grades 3/4 ($p = 0.69$ and $p = 0.43$, respectively). Admission SIRS scores were significantly higher in cirrhotic patients admitted with HE \leq grade 2 who subsequently developed HE grades 3/4 (median 3 (IQR 2.5–3.25) vs. 2 (IQR 1–2), respectively, $p < 0.05$). The AUROC for admission SIRS score in predicting new onset of HE grades 3/4 was 0.776 (95 % CI 0.568–0.984, $p < 0.05$). In the multivariate regression analysis, an admission SIRS score >2 (OR 9.65, 95 % CI 2.38–39.14, $p < 0.01$) and admission arterial ammonia levels of $>75 \mu\text{mol/L}$ (OR 8.37, 95 % CI 1.81–38.78, $p < 0.01$) remained independent predictors for peak HE grades 3/4. (Hosmer–Lemeshow test chi-square 4.6, $df = 2$, $p = 0.10$, Nagelkerke $R^2 = 0.382$).

Discussion

To the best of our knowledge, this is the first study to compare the clinical impact of arterial ammonia levels among critically ill patients with different entities of liver disease.

Table 3 Clinical and laboratory features of patients with HE in liver disease admitted to the ICU

Variable	Hypoxic hepatitis (n = 35)		Acute liver failure (n = 43)		Cirrhosis (n = 100)		p value
	No signs of HE (n = 23)	Signs of HE (n = 12)	HE ≤ grade 2 (n = 10)	HE 3/4 (n = 33)	HE ≤ grade 2 (n = 39)	HE 3/4 (n = 61)	
Age (years)	64 (47–75)	66 (49–77)	44 (31–61)	49 (32–59)	57 (49–62)	51 (46–62)	0.165
Sex (female)	11 (48 %)	3 (25 %)	7 (70 %)	20 (61 %)	22 (36 %)	14 (36 %)	0.986
Vasopressor	18 (78 %)	9 (75 %)	1 (10 %)	13 (39 %)	37 (61 %)	20 (51 %)	0.356
RRT	6 (26 %)	4 (33 %)	1 (10 %)	15 (46 %)	17 (28 %)	15 (39 %)	0.268
SIRS score	3 (2–3)	3 (1–3)	1 (0–2)	2 (1–2)	2 (1–2)	3 (2–3)	<0.01
Laboratory results							
Adm INR	1.3 (1.1–1.6)	1.6 (1.2–2.3)	3.3 (1.6–3.9)	2.9 (2.0–6.9)	1.7 (1.5–2.2)	1.8 (1.4–2.3)	0.824
Peak INR	2 (1.6–3.0)	3 (1.8–3.7)	3.5 (1.7–4.3)	8.1 (3.9–8.1)	2.2 (1.6–3.1)	2.3 (1.9–3.0)	0.567
Adm creatinine (mg/dl)	1.9 (1.2–3.1)	2.5 (1.8–2.9)	0.8 (0.6–1.0)	1.2 (0.7–1.7)	1.7 (1.0–2.8)	1.8 (0.8–3.1)	0.813
Peak creatinine (mg/dL)	2.7 (1.4–3.7)	2.9 (2.3–3.8)	1.0 (0.6–2.1)	1.4 (1.0–3.6)	2.1 (1.0–3.2)	2.1 (1.4–3.2)	0.78
Arterial ammonia (NH ₃)							
NH ₃ admission (μmol/l)	60.2 (35.0–74.8)	104.4 (69.4–147.8)	60.9 (50.0–61.9)	112 (73.3–170.5)	62.5 (46.8–72.9)	81.6 (54.9–145.9)	<0.01
NH ₃ peak ^a (μmol/l)	65.9 (58.3–81.7)	104.4 (79.5–218.5)	72.1 (59.2–98.9)	149.3 (113.1–187.8)	70.1 (55.4–100.5)	97.9 (76.4–155.9)	<0.001

NH₃ indicates arterial ammonia concentration

SIRS Systemic Inflammatory Response Syndrome, INR international normalized ratio, RRT Renal replacement therapy

^a primary parameter of interest: after Bonferroni correction differences remained significant in all three groups ($p < 0.0071$ for all)

Ammonia and 28-day mortality

Our results suggest that peak arterial ammonia values during the first 72 h following ICU admission are associated with 28-day mortality or transplantation, respectively, in patients with liver disease admitted to the ICU (Table 1). However, the predictive value of arterial ammonia levels for 28-day mortality was restricted to HH and ALF among our patient cohort (Fig. 2). Neither admission nor peak arterial ammonia levels predicted 28-day mortality in our cirrhotic patients, which is in keeping with the results of previous studies [12, 37]. Chronic elevation of ammonia levels in cirrhosis would seem to abolish the predictive potential of ammonia observed in patients with acute liver injury.

Ammonia and HE

Both admission and peak arterial ammonia levels were associated with HE grades 3/4 independent of the etiology of liver disease (Table 3). Recent publications indicate that the SIRS score, but not arterial ammonia levels, differs significantly between cirrhotic patients with HE grade 3 and HE grade 4 [12]. In our exploratory analysis, arterial ammonia levels and admission SIRS scores were independently linked to HE grades 3/4 in our cirrhotic patients. This association may be explained by the different study populations observed (HE grades 3/4 in [12] vs. all cirrhotic patients with all grades of HE in our study population). Our results further support the crucial role of systemic inflammation for the development of HE in cirrhosis as high SIRS scores on admission were associated with new onset of HE grades 3/4 in cirrhotic patients initially presenting HE ≤ grade 2.

Arterial ammonia in clinical practice

High arterial ammonia levels are an active contributor to HE and a prognostic marker in patients with acute liver injury admitted to the ICU. However, it remains unclear whether a therapy targeting the lowering of ammonia levels would improve outcome. In ALF, treatment with L-ornithine-L-aspartate failed to lower ammonia levels or improve survival [38]. A recent meta-analysis of ten prospective trials investigating the use of extracorporeal liver support devices in ALF did not show significant survival benefits for patients treated with these devices, although an improvement in HE was observed [39]. Mechanisms other than HE seem to contribute to high mortality in ALF. Accordingly, we observed higher peak arterial ammonia levels in patients (HH, ALF and cirrhosis) requiring RRT versus those who did not [median 97.7 (IQR 61.2–162.8) vs. 73.2 (55.0–121.2) μmol/l, respectively; $p < 0.05$]. Thus, patients showing high peak

Table 4 Predictive features of arterial ammonia in the different study groups

Arterial ammonia in the prediction of 28-day-mortality in patients with liver disease admitted to the ICU									
	AUROC (95 % CI)	<i>p</i> value	Derived NH ₃ cut-off (μmol/l)	Sensitivity (%)	Specificity (%)	PPV	NPV	LRP	LRN
Admission ammonia level									
Liver disease in the ICU									
(HH/ALF/cirrhosis)	0.579 (0.499–0.659)	0.052	–	–	–	–	–	–	–
HH	0.631 (0.488–0.774)	0.087	–	–	–	–	–	–	–
ALF	0.649 (0.478–0.821)	0.101	–	–	–	–	–	–	–
Cirrhosis	0.510 (0.395–0.625)	0.86	–	–	–	–	–	–	–
Controls	0.626 (0.417–0.835)	0.201	–	–	–	–	–	–	–
Peak ammonia									
Liver disease in the ICU									
(HH/ALF/cirrhosis)	0.634 (0.556–0.711)	<0.01	75	66	60	0.65	0.61	1.6	0.6
HH	0.677 (0.538–0.815)	<0.05	75	56	82	0.79	0.61	3.1	0.5
ALF	0.814 (0.677–0.951)	<0.01	100	88	71	0.82	0.8	3	0.2
Cirrhosis	0.544 (0.429–0.658)	0.452	–	–	–	–	–	–	–
Controls	0.533 (0.330–0.735)	0.742	–	–	–	–	–	–	–
Arterial ammonia in the prediction of HE signs in patients with HH and HE grade 3/4 in association with liver disease admitted to the ICU									
	AUROC (95 % CI)	<i>p</i> value	Derived NH ₃ cut-off (μmol/l)	Sensitivity (%)	Specificity (%)	PPV	NPV	LRP	LRN
Admission ammonia level									
Liver disease in the ICU									
(HH/ALF/cirrhosis)	0.764 (0.692–0.837)	<0.01	75	68	82	0.78	0.73	3.8	0.4
HH	0.794 (0.621–0.967)	<0.01	75	75	83	0.75	0.83	4.5	0.3
ALF	0.888 (0.788–0.987)	<0.01	85	70	90	0.95	0.47	7	0.3
Cirrhosis	0.687 (0.576–0.798)	<0.01	75	59	80	0.66	0.75	3	0.5
Peak ammonia									
Liver disease in the ICU									
(HH/ALF/cirrhosis)	0.782 (0.714–0.850)	<0.01	75	85	65	0.68	0.82	2.4	0.2
HH	0.841 (0.700–0.981)	<0.01	75	83	74	0.63	0.89	3.2	0.2
ALF	0.858 (0.730–0.985)	<0.01	100	90	80	0.93	0.53	3.9	0.3
Cirrhosis	0.699 (0.592–0.806)	<0.01	75	77	64	0.58	0.81	2.1	0.4

Exploratory analyses: AUROC Area under the receiver operating characteristic curve, PPV positive predictive value, NPV negative predictive value, LRP likelihood ratio positive, LRN likelihood ratio negative

ammonia levels were more severely ill and required RRT more frequently. Future studies are needed to clarify potential benefits of targeted ammonia-lowering therapies, such as lactulose, rifaximin or even extracorporeal support systems, not only for patients with HE but also on survival in patients with HH and ALF.

There are several limitations to our study. First, the sample sizes of the patient groups were rather small, which limits the applicability of multivariate regression models. However, our sample sizes are comparable those of other studies in this field. Second, this study was conducted in a medical ICU. Thus, the conclusions drawn by the authors may not entirely be applicable to patients in surgical wards. Third, there was no blinding to arterial ammonia levels during HE assessment.

In conclusion, in our study elevated arterial ammonia levels were almost exclusively found in critically ill patients with acute and acute-on-chronic liver disease. High arterial ammonia levels predicted poor outcome in our HH and ALF patients and were associated with advanced encephalopathy in those patients with acute and acute-on-chronic liver disease. Future studies should clarify whether targeted ammonia-lowering interventions may improve outcome in critically ill patients with acute hepatic injury.

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Conflicts of interest None.

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