Persistent Hyperammonemia Is Associated With Complications and Poor Outcomes in Patients With Acute Liver Failure

RAMESH KUMAR,* SHALIMAR,* HANISH SHARMA,* SHYAM PRAKASH,* SUBRAT KUMAR PANDA,‡ SHANKAR KHANAL,§ and SUBRAT KUMAR ACHARYA*

*Department of Gastroenterology, ‡Department of Pathology, and §Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

BACKGROUND & AIMS: Patients admitted to the hospital with acute liver failure (ALF) and high arterial levels of ammonia are more likely to have complications and poor outcomes than patients with lower levels of ammonia. ALF is a dynamic process; ammonia levels can change over time. We investigated whether early changes (first 3 days after admission) in arterial levels of ammonia were associated with complications and outcomes and identified factors associated with persistent hyperammonemia. **METHODS:** We performed a prospective observational study that measured arterial ammonia levels each day for 5 days in 295 consecutive patients with ALF. We analyzed associations of changes in ammonia levels during the first 3 days with complications and outcomes. **RESULTS:** Patients with persistent arterial hyperammonemia (≥122 μmol/L for 3 consecutive days), compared with those with decreasing levels, had lower rates of survival (23% vs 72%; $P < .001$) and higher percentages of cerebral edema (71% vs 37%; $P < .001$), infection (67% vs 28%; $P = .003$), and seizures (41% vs 7.7%; $P < .001$). Patients with persistent hyperammonemia had greater mortality, with an odds ratio (OR) of 10.7, compared with patients with baseline levels of ammonia ≥122 μmol/L (OR, 2.4). Patients with persistent hyperammonemia were more likely to progress to and maintain advanced hepatic encephalopathy than those with decreasing levels. Patients with persistent, mild hyperammonemia (≥85 μmol/L for 3 days) were also more likely to have complications or die ($P < .001$) than patients with serial ammonia levels <85 μmol/L. Infections (OR, 4.17), renal failure (OR, 2.20), and decreased arterial pH (OR, 0.003) were independent predictors of persistent hyperammonemia. **CONCLUSIONS: Patients with ALF and persistent arterial hyperammonemia for 3 days after admission are more likely to develop complications and have greater mortality than patients with decreasing levels or high baseline levels. Infection, renal failure, and decreased arterial pH are independent predictors of persistent hyperammonemia.**

Keywords: Prognostic Factor; Hepatic Encephalopathy (HE); Central Nervous System; Risk Factor; Liver Failure.

Ammonia levels in blood are acutely elevated in patients with acute liver failure (ALF). Substantial evidence links ammonia to the development of various complications and poor outcome in patients with ALF.[1–5] High levels of ammonia have been implicated in the development of hepatic encephalopathy (HE),[2–4] cerebral edema (CE),[1–4] and brain herniation[1] in ALF patients. Recent evidence has also implicated ammonia in the causation of neutrophil dysfunction,[5] which might predispose ALF patients to various infections that are quite common in ALF patients.[6]

Arterial ammonia level at admission predicts complications and survival in ALF patients.[1–3] Because ammonia levels are dynamic and alteration in levels may precede evolving clinical features, a declining level might predict lesser complications and better survival than the persistently elevated level. Thus, the measurement of serial arterial ammonia may assist us to identify objectively ALF patients at high risk of complications and death. Factors associated with persistent hyperammonemia in ALF patients are not known. The identification of such factors may indicate whether existing medical treatment strategy can be improved. Therefore, this prospective study was designed to evaluate whether early changes (first 3 days after admission) in arterial ammonia levels were associated with complications and outcomes and to identify factors associated with persistent hyperammonemia in ALF. Our situation provided us opportunity to assess the above hypothesis prospectively because liver transplantation was not available, and all patients were managed medically until recovery or death.

Methods

Between January 2004 and June 2009, 302 consecutive adult patients with ALF were evaluated at the Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi, India. After excluding 7 patients who died on day 1 of admission, the study cohort consisted of 295 ALF patients. The study was approved by the ethics committee of the institute, and consent was obtained from the nearest relative of each patient.

Definitions of Variables

ALF was defined by occurrence of HE within 4 weeks of symptoms in absence of preexisting liver disease. We followed the recommendations of the International Association for the Study of the Liver subcommittee on nomenclature of acute and subacute liver failure.[7]

Abbreviations used in this paper: ALF, acute liver failure; ARF, acute renal failure; CE, cerebral edema; CI, confidence interval; HE, hepatic encephalopathy; INR, international normalized ratio; OR, odds ratio; ROC, receiver operating characteristic.

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CE was defined by the presence of spontaneous or inducible decerebrate posturing or presence of any 2 of the following: hypertension (blood pressure, ≥150/90 mm Hg), bradycardia (heart rate, <60/min), pupillary dilatation or decreased reactivity to light, and neurogenic hyperventilation.[8] Hyperventilation was termed *neurogenic* only in presence of at least one more sign of CE and in absence of metabolic acidosis or respiratory tract infection.

Infection was diagnosed by the presence of pyrexia (>101°F) or hypothermia (<98°F) and neutrophilic leukocytosis (>15,000/mm^3, with ≥80% polymorphonuclear leukocytes), and one or more of positive blood culture, positive urine culture, or radiologic evidence of pneumonitis.[8]

Acute renal failure (ARF) was diagnosed if patients developed decreased urine output (<400 mL in 24 hours), with serum creatinine >1.5 mg/dL and blood urea >40 mg/dL, despite hydration, objectively assessed by central venous pressure of 10 cm of saline or more.[8]

Management Protocol

All patients were managed in intensive care unit with a uniform management protocol that included stress ulcer prophylaxis, glycemic control, and elective ventilation for patients with grade IV encephalopathy or grade III encephalopathy with CE. The fluid resuscitation was done with crystalloid, with the aim to maintain central venous pressure around 10 cm of saline. The vasopressor (noradrenaline) was recommended when systemic hypotension persisted after correction of volume status, and the goal was to maintain a mean arterial pressure >60 mm Hg. Intravenous mannitol was used to control CE. Prophylactic antibiotics with daily microbiological surveillance were used to detect infection. Renal replacement therapy (hemodialysis) was used for refractory metabolic acidosis, severe hyperkalemia, and fluid overload. Only 10% of ALF patients with ARF (6 of 60) underwent dialysis.

Estimation of Arterial Ammonia

Arterial ammonia levels were estimated by an enzymatic method (Randox Lab Ltd, Crumlin, UK) in heparinized plasma at admission and then every 24 hours for the next 5 days. Samples for ammonia were obtained in fasting state before the dose of mannitol and before dialysis if needed. Although doubtful, any agents that may alter gut flora and hence ammonia levels, such as lactulose, probiotics, prebiotics, or nonabsorbable antibiotics, were avoided during hospitalization.

Categorization of Patients on the Basis of Serial Ammonia Levels

On the basis of a discriminatory cutoff value of baseline arterial ammonia (≥122μmol/L) identified on receiver operating characteristic (ROC) curve, patients were initially categorized into high (≥122 μmol/L) and low (<122 μmol/L) ammonia groups. The patients in high ammonia group were further divided into 2 subgroups, namely subgroup A, which included patients in whom arterial ammonia persisted ≥122 μmol/L for 3 consecutive days, and subgroup B, in whom the ammonia declined to <122 μmol/L by day 3. The patients in low ammonia group were also categorized into 2 subgroups on the basis of another discriminatory cutoff (85 μmol/L) on ROC curve associated with mortality. The subgroup C included patients in whom arterial ammonia was between 122 and 85 μmol/L at baseline but persisted to levels ≥85 μmol/L for 3 consecutive days. The subgroup D included patients in whom baseline as well as subsequent 3-day ammonia level was <85 μmol/L. The patients who died before day 3 were categorized as per 2 days of consecutive levels of arterial ammonia, keeping the cutoff levels the same. The persistent hyperammonemia was defined as persistence of arterial ammonia levels ≥122 μmol/L for 3 days among patients with high baseline ammonia (≥122 μmol/L) and persistence of arterial ammonia levels ≥85 μmol/L for 3 days among patients with low baseline ammonia levels (<122 μmol/L).

Statistical Analysis

Data were analyzed by using SPSS software verson 15.0 (SPSS, Chicago, IL). Normally distributed continuous variables were expressed as mean (standard deviation), and the continuous variables with skewed distribution were expressed as median (range). Factors that independently determined outcomes were identified by using multiple regression analysis. A ROC curve technique was used to identify an appropriate cutoff of arterial ammonia for predicting mortality and CE. Comparisons were done by using the Mann–Whitney *U* test or *t* test for continuous variables and the χ^2 or Fisher test for discrete variables, wherever applicable. Multivariable logistic regression was performed to identify significantly important variables associated with persistent hyperammonemia. The variables with significance of $P \leq .10$ in the univariate analysis were taken in the multivariable analysis. Odds ratios (ORs) with 95% confidence interval (CI) for each variable in the final multivariable analysis were reported.

Results

Baseline Characteristics and Predictors of Outcome in Acute Liver Failure Patients

The demographic, clinical, and laboratory characteristics of 295 ALF patients are depicted in Table 1. With medical treatment, 138 patients (46.7%) died, and 157 patients (53.2%) survived. The median interval from admission to death was 5 days (2–24 days). The median baseline arterial ammonia level in patients who died (159 [23–866] μmol/L) was significantly higher than those who survived (102 [17–640] μmol/L), $P < .001$. Other variables that differed significantly between patients who died and those who survived are depicted in Table 1. In multivariate analysis, variables that independently predicted mortality were age (OR, 1.04; 95% CI, 1.01–1.08), HE (OR, 1.88; 95% CI, 1.24–2.85), CE (OR, 2.0; 95% CI, 2.02–4.26), international normalized ratio (INR) (OR, 3.13; 95% CI, 2.16–4.53), and arterial ammonia (OR, 2.40; 95% CI, 1.32–4.38). A cutoff of baseline arterial ammonia at ≥122 μmol/L had modest discrimination of outcome (area under ROC, 0.69).

Serial Arterial Ammonia Levels in Patients With Baseline Hyperammonemia ≥122 μmol/L

Of 157 patients in this category, 92 patients (59%) belonged to subgroup A, and 65 patients (41%) belonged to subgroup B. Patients of subgroup A, compared with subgroup B, had lower rates of survival (23% vs 72%; $P < .001$) and higher percentages of CE (71% vs 37%; $P < .001$), infection (67% vs 28%; $P = .003$), HE progression (42% vs 17%; $P = .001$), and seizures

Table 1. Baseline Characteristics of ALF Patients (N = 295) and Comparisons of Variables Between Patients Who Died and Survived

Parameters	Total patients (N = 295)	Patients who died (n = 138)	Patients who survived (n = 157)
Age (*y*)[a]	25 (12–76)	26 (13–76)	24 (12–60)
Male:female	132:163	55:83	77:80
Icterus encephalopathy interval (*d*)	03 (0–30)	04 (0–30)	03 (0–28)
HE,[a] n (%)			
I–II	81 (27.4)	21 (15.2)	60 (38.2)
III–IV	214 (72.6)	117 (84.8)	97 (61.8)
CE, n (%)[a]	116 (39)	76 (55)	40 (25)
Bilirubin (*mg/dL*)[a]	13.9 (2.8–72.8)	15.6 (3.6–72.8)	13 (2.8–57)
Aspartate transaminase (*IU/L*)	536 (44–8710)	533 (44–8710)	540 (57–5950)
Alanine transaminase (*IU/L*)	1023 (23–5980)	889 (26–5980)	1164 (40–3550)
Alkaline phosphatase (*U/L*)	275 (63–1544)	289 (99–1429)	260 (63–1544)
Albumin (*g/dL*), mean ± SD	2.9 ± 0.5	2.8 ± 0.6	2.9 ± 0.5
Sodium (*mEq/dL*), mean ± SD	141 ± 7.5	141.5 ± 7.6	140 ± 7.6
Urea (*mg/dL*)	19 (10–144)	19 (10–121)	19 (13–144)
Creatinine (*mg/dL*)[a]	0.9 (0.3–10)	1.0 (0.4–10)	0.8 (0.3–2.7)
Hemoglobin (*g/dL*)	11.8 (5.6–18.8)	11.4 (5.6–17.2)	12.2 (6.2–18)
Total leukocyte count/mm^3	14,000 (2100–49,700)	13,900 (2100–45,700)	14,000 (4600–49,700)
Platelet/mm^3	2.03 (0.4–19.4)	2.02 (0.4–6.7)	2.04 (0.4–19.4)
INR[a]	5.03 ± 1.7	5.84 ± 1.5	4.31 ± 1.5
Arterial pH[a]	7.45 ± 0.07	7.43 ± 0.08	7.46 ± 0.06
Arterial ammonia (*μmol/L*)[a]	134 (17–866)	159 (23–866)	102 (17–640)
Etiology, n (%)[a]			
Hepatitis E	135 (45.8)	46 (33.3)	89 (56.7)
Hepatitis B	31 (10.5)	22 (15.2)	09 (5.7)
Hepatitis A	06 (02)	02 (1.4)	04 (2.5)
Dual acute viral infection	31 (10.5)	19 (13.8)	12 (7.6)
Antituberculosis drugs	07 (2.3)	05 (3.6)	02 (1.3)
Other[b]	78 (26.4)	39 (28.2)	39 (25)

NOTE. All data are in median (range) unless specified otherwise. All patients had INR >1.5.
HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; SD, standard deviation.
[a]Significantly different between patients who died and survived (bivariate *P* value: age, .04; bilirubin, .004; pH and creatinine, .01; others, <.001).
[b]59 patients indeterminate; 11 patients HBsAg+; 5 patients anti-HBc+; 3 patients anti-HCV+.

(41% vs 7.7%; $P < .001$) (Table 2). The persistent hyperammonemia ≥122 μmol/L for 3 days predicted mortality with higher OR (10.7; 95% CI, 3.5–32.8) than baseline arterial ammonia ≥122 μmol/L (OR, 2.4; 95% CI, 1.3–4.4). Also, although baseline arterial ammonia did not independently predict CE, persistent arterial hyperammonemia predicted the same (OR, 3; 95% CI, 1.3–6.6; $P < .006$). The Kaplan–Meier survival plots revealed a better discrimination in outcome when patients were stratified according to early changes in ammonia levels than the baseline levels (Figure 1).

Table 2. Comparison of Outcome and Complications Between Patients With Baseline and Persistent Arterial Hyperammonemia

	Baseline arterial hyperammonemia ≥122 μmol/L			Persistent arterial hyperammonemia ≥122 μmol/L		
Parameters	Yes (n = 157)	No (n = 138)	*P* value	Yes (n = 92)	No (n = 65)	*P* value
Outcome, n (%)						
Died	89 (57)	49 (35)	.001	71 (77)	18 (28)	<.001
Survived	68 (43)	89 (65)		21 (23)	47 (72)	
CE, n (%)	63 (40)	53 (38)	.76	65 (71)	24 (37)	<.001
HE, n (%)						
Grade I–II	43 (27.4)	38 (27)	1.0	19 (21)	24 (37)	.03
Grade III–IV	114 (72.6)	100 (73)		73 (79)	41 (73)	
Progression from early to advanced HE, n (%)	12/43 (28)	9/38 (24)	.66	8/19 (42)	4/24 (17)	.05
Seizure, n (%)	43 (27)	24 (17)	.05	38 (41)	5 (7.7)	<.001
Infection, n (%)	90 (57)	77 (56)	.81	62 (67)	28 (28)	.003

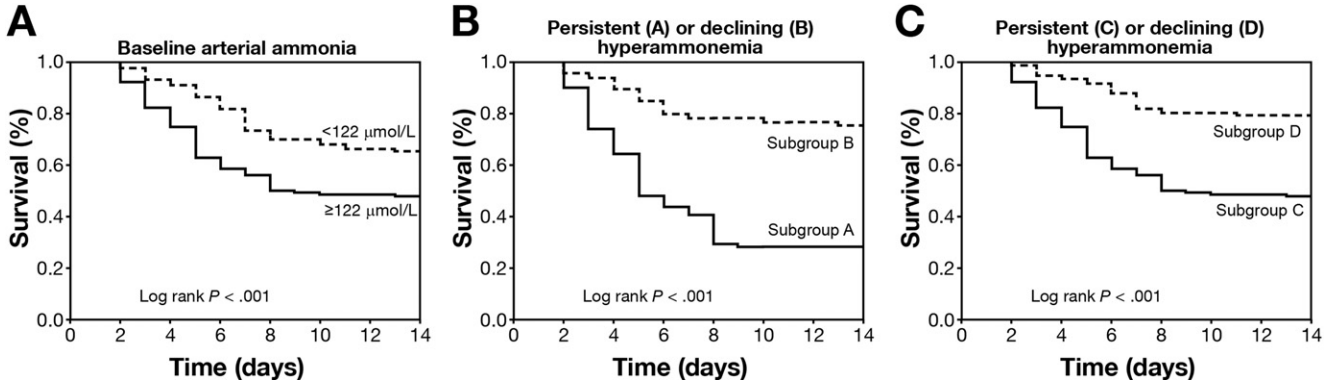

Figure 1. Kaplan–Meier plots showing 2-week survival (%) in ALF patients stratified according to severity of baseline ammonia (levels ≥122 and <122 μmol/L, *A*) or persistent hyperammonemia; (*B*) persistent levels ≥122 μmol/L for 3 days (subgroup A), and declining levels to <122 μmol/L by 3 days (subgroup B); and (*C*) persistent levels ≥85 μmol/L for 3 days (subgroup C), and low declining levels <85 μmol/L for 3 days (subgroup D).

Serial Arterial Ammonia Levels in Patients With Baseline Hyperammonemia <122 μmol/L

Of 138 patients in this category, 58 patients (42%) belonged to subgroup C, and 80 patients (58%) belonged to subgroup D (declining ammonia). Patients of subgroup C, compared with subgroup D, had lower rates of survival (45% vs 79%; $P < .001$) and higher percentages of HE progression (63% vs 7%; $P = .001$), infection (70% vs 45%; $P = .003$), and seizures (31% vs 7.5%; $P = .001$) (Table 3). Multivariate regression analysis in this group of patients revealed that subgroup C patients were 2.8 times more likely to die than patients of subgroup D (95% CI, 1.1–7.1; $P = .02$).

Serial Arterial Ammonia Levels and Cerebral Edema

At admission, 116 patients (39%) had CE, and the median baseline ammonia levels were similar between patients with (n = 116) or without (n = 179) CE (136 [18.7–469] vs 132 [17–866] μmol/L; $P = .58$). The frequency of CE was similar between patients with or without baseline ammonia ≥122 μmol/L (40% vs 38%; $P = .76$). However, the frequency of CE was significantly higher in patients with persistent hyperammonemia (subgroup A) than in those without (subgroup B), 71% vs 37%, $P < .001$. Among patients in whom CE improved (40 of 116), arterial ammonia was <122 μmol/L at baseline and declined progressively over time. In contrast, in patients (n = 76) in whom CE remained persistent throughout hospitalization, arterial ammonia levels were >122 μmol/L at baseline and did not show significant decline subsequently. Of 179 patients without CE at presentation, 117 patients revealed progressively decreasing levels of arterial ammonia and never developed CE (Figure 2*A*). In contrast, 62 patients who developed CE after hospitalization had higher (>122 μmol/L) and nondeclining levels of arterial ammonia (Figure 2*B*). No cutoff value of arterial ammonia could predict CE with acceptable accuracy.

Table 3. Comparison of Outcome and Complications Between Patients With Mild Persistent Hyperammonemia[a] Among Patients With Baseline Arterial Ammonia[b]

	Persistent low arterial hyperammonemia (≥85 μmol/L)		
Parameters	Yes (n = 58)	No (n = 80)	*P* value
Outcome, n (%)			
Died	32 (55)	17 (21)	.001
Survived	26 (45)	63 (79)	
CE, n (%)	27 (46)	26 (27)	.09
HE, n (%)			
Grade I–II	11 (19)	27 (34)	
Grade III–IV	47 (81)	53 (66)	.82
Progression from early to advanced HE, n (%)	7/11 (63)	2/27 (7)	.001
Seizure, n (%)	18 (31)	6 (7.5)	.001
Infection, n (%)	41 (70)	36 (45)	.003

[a]≥85 μmol/L for 3 days.
[b]<122 μmol/L.

Serial Ammonia Levels and Hepatic Encephalopathy

The median arterial ammonia levels were similar between patients with early (grade I–II) or advanced HE (grade III–IV) at admission (133.2 vs 134 μmol/L; $P = .78$). Among patients with early HE at presentation (n = 81), HE improved in 60 patients (74%) and progressed in 21 patients (26%). The median baseline ammonia levels were similar between patients whose HE either improved (128 μmol/L) or deteriorated (139 μmol/L), $P = .17$. However, patients whose HE progressed had persistently higher levels of arterial ammonia and those with HE recovered (Figure 2*C*). Among patients with advanced HE at presentation, 117 patients (55.6%) maintained advanced HE, whereas 97 patients (45.3%) showed HE improvement. The baseline as well as serial levels of arterial ammonia were significantly higher in patients with persistent advanced HE compared with those with improved HE (Figure 2*D*).

Serial Ammonia Levels and Infection

Infection was documented in 167 patients (56.6%). The patients with infection had higher mortality than those without infection (63% vs 25%; $P < .001$). During the first 2 days of hospitalization, arterial ammonia levels were similar between pa-

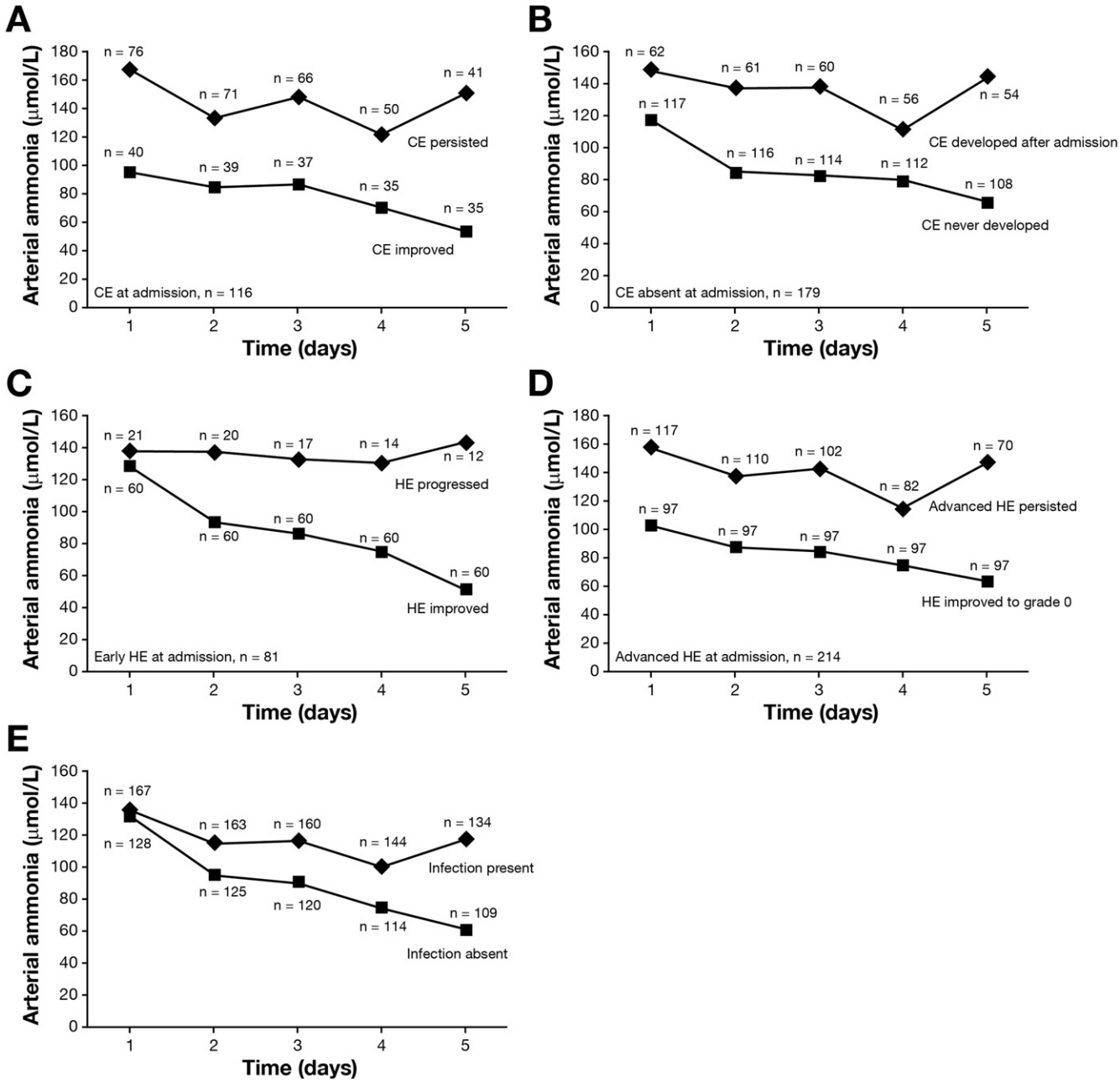

Figure 2. Serial arterial ammonia levels in patients with CE at presentation (*A*, n = 116) or without CE at presentation (*B*, n = 179). Serial ammonia levels in patients presenting with early HE (*C*, n = 81) and advanced HE (*D*, n = 214). Serial arterial ammonia levels in patients with or without documented infection (*E*).

tients with or without infection; however, the subsequent levels were significantly higher in patients with infection (Figure 2*E*).

Factors Associated With Persistent Hyperammonemia

Univariate analysis was performed to compare the relevant variables between patients with persistent hyperammonemia (n = 150) and those with progressive declining levels of ammonia (n = 145) (Table 4). Although our attempt was to include only baseline variables as far as possible, certain variables that could have influence on serial ammonia levels (eg, infection, ARF, and gastrointestinal bleeding) were also included if they were found within 3 days of hospitalization. In this circumstance, INR, arterial pH, serum alkaline phosphatase, etiology of ALF, infection, gastrointestinal bleeding, and ARF were significantly different between the 2 groups. However, in multivariate analysis, independent predictors of persistent hyperammonemia were infection (OR, 4.17; 95% CI, 2.30–7.56), ARF (OR, 2.20; 95% CI, 1.07–4.52), and lower pH (OR, 0.003; 95% CI, 0.00–0.12).

Discussion

The results of our study suggest the early changes in ammonia levels predict complications and outcome better than

Table 4. Factors Associated With Persistent Hyperammonemia (Univariate and Multivariate Analysis)

	Univariate analysis			Multivariate analysis		
Variables[a]	Persistent hyperammonemia present (n = 150)	Persistent hyperammonemia absent (n = 145)	*P* value	OR	95% CI	*P* value
Age (*y*) ± SD	27.7 ± 9.6	26.2 ± 8.9	.09			
Sex, male:female	52:78	60:75	.53			
Icterus encephalopathy interval (*d*)	03 (0–30)	03 (0–28)	.66			
Serum bilirubin (*mg/dL*)	14.05 (2.8–72.8)	13.4 (3.9–56.9)	.89			
Aspartate transaminase (*IU/L*)	522 (48–3686)	536 (44–6950)	.98			
Alanine transaminase (*IU/L*)	951 (52–4200)	1091 (26–4130)	.22			
Serum albumin (*g/dL*), mean ± SD	2.8 ± 0.6	2.8 ± 0.5	.72			
Alkaline phosphatase (*U/L*)	291 (91–1000)	244 (63–1544)	.01			
Sodium (*mEq/dL*)	140 ± 7.02	140.3 ± 7.8	.69			
Potassium (*mEq/dL*)	4.1 ± 0.89	4.1 ± 0.78	.85			
Arterial pH	7.43 ± 0.08	7.47 ± 0.07	.002	0.002	0.00–0.12	.003
Blood urea (*mg/dL*)	18 (10–81)	17.5 (13–144)	.31			
Serum creatinine (*mg/dL*)	0.8 ± 0.78	0.94 ± 0.59	.28			
INR	5.43 ± 1.5	4.53 ± 1.6	.001			
Total leukocyte counts/mm^3	13,800 (2100–40,000)	14,000 (3600–49,700)	.99			
Platelets/mm^3	190 (43–638)	224 (47–194)	.08			
Infection, n (%)	94 (73.2)	54 (40)	<.001	4.17	2.30–7.56	.001
ARF, n (%)	43 (33)	17 (12.6)	<.001	2.20	1.07–4.52	.032
Gastrointestinal bleeding, n (%)	14 (10.9)	06 (4.4)	.049			
Etiology, n (%)			.004			
Hepatitis E	45 (35)	77 (57)				
Non–hepatitis E	84 (62)	57 (42)				

SD, standard deviation.
[a]Normally distributed variables are expressed as mean (SD), and variables with skewed distribution are expressed as median (range).

static baseline levels. Association between early dynamicity of variables and outcome of ALF has earlier been demonstrated in paracetamol-induced ALF, whereas patients with a rising prothrombin time between days 3 and 4 after overdose had revealed higher mortality compared with patients in whom the prothrombin time improved (93% vs 22%).[9] The reason we preferred to study kinetics of arterial ammonia was that ammonia has a direct pathogenic role in various complications of ALF.[1–5] In patients with high arterial ammonia (≥122 μmol/L) at admission, the discrimination of outcome was better when serial ammonia levels were followed for 3 consecutive days (Table 2). Because 35% of patients also died among those with arterial ammonia <122 μmol/L at admission, another cutoff (85 μmol/L) was chosen to discriminate the outcomes in this group of ALF patients, and we found that the serial ammonia levels across 85 μmol/L for 3 days could identify patients at high risk of complications and death (Figure 1*C*, Table 3).

In the brain, ammonia is detoxified to glutamine,[10,11] which is accumulated in astrocytes, leading to astrocyte swelling and CE. In a small study (n = 17), Tofteng et al[12] demonstrated that persistent hyperammonemia resulted in elevation of brain glutamine, which correlated with intracranial pressure. Recently, Bernal et al[3] demonstrated that nonreduction of hyperammonemia was associated with development of CE. However, these studies did not evaluate the association of changing ammonia levels with other complications and outcome. In our study, the association between baseline ammonia and CE was not strong, and no single cutoff value of baseline arterial ammonia had an acceptable combined sensitivity and specificity for predicting CE. Only persistent, and not baseline, hyperammonemia (≥122 μmol/L) independently predicted CE. The frequency of CE was higher in patients with persistent hyperammonemia than in those without (71% vs 37%; $P < .001$). Also, CE did not respond to osmotic therapy in case of nonreduction of hyperammonemia (Figure 2*A*). Therefore, serial ammonia estimation may help in identifying patients at high risk of developing CE as well as subsequent courses of CE. Ammonia has also been implicated in the pathogenesis of HE.[2,3,13,14] However, utility of single value of arterial ammonia for predicting severity of HE is limited.[15,16] In our study, the levels of arterial ammonia were similar in patients who presented with either early or advanced HE. However, the progression of HE and persistence of advanced HE were higher in patients with persistent hyperammonemia.

Infection, renal failure, and arterial pH were independent predictors of persistent hyperammonemia. The patients with infection were 4 times more likely to have persistent hyperammonemia than those without. Ammonia is known to cause neutrophil dysfunctions,[5,17] and certain infections can contribute to hyperammonemia.[18] Thus, in ALF patients, aggravation of hyperammonemia by infections may further predispose such patients to infections by causing neutrophil dysfunctions. The kidneys and blood pH also play important roles in the ammonia metabolism. In a state of acute hyperammonemia, normal kidneys have the ability to acutely diminish systemic ammonia release and excrete as high as 70% of total ammonia produced in the kidney.[19] Therefore, decreased ammonia clearance by kidney during renal failure can possibly be one of the mechanisms contributing to persistent hyperammonemia.

The existing prognostic models of ALF are based on admission parameters that have poor accuracy in predicting outcome. By using serial ammonia estimation, the risk stratification in

ALF patients can be made dynamic, which can be more useful in therapeutic decision. In our study, among patients with baseline arterial ammonia ≥122 μmol/L, 72% of survivors (47 of 68) had declining ammonia levels, whereas 77% of nonsurvivors (71 of 92) had persistent hyperammonemia (Table 2). The survival in patients with serial ammonia levels <85 μmol/L for 3 consecutive days (80%) was comparable to that obtained after emergency liver transplantation in ALF.[20] A limitation of serial ammonia estimation for predicting outcome in ALF is the fact that it takes 3 days. However, only by day 3, changes in ammonia levels were more noticeable across the discriminatory cutoff and more accurately associated with the outcome. The performance of 2 days of ammonia was not expected to be better than the baseline levels. The ammonia-lowering interventions should be strongly considered in ALF patients with persistent hyperammonemia. An effective control of infection and renal replacement therapy may reduce arterial ammonia levels. A recent large study on human ALF patients revealed that L-ornithine L-aspartate was ineffective in lowering ammonia.[21]

Although ammonia is a surrogate marker of hepatocyte insufficiency, because of direct pathogenic role, we believe that ammonia itself is a harbinger of poor outcome. The persistent hyperammonemia increases mortality in ALF patients by several mechanisms such as increased risk of CE, persistence of CE, HE progression, persistent advanced HE, and seizures. By causing neutrophil dysfunctions, ammonia might predispose ALF patients to increased infections.[5,17] Both ammonia and CE predicted mortality independently, but the 2 variables were not exclusively interrelated, and in multivariate analysis, their individual variance inflation factor was low (<1.5).

The strength of our study is prospective data on a large number of ALF patients from a single center, which ensures a homogenous cohort managed with similar treatment protocol. A comprehensive natural history was studied in all patients without interruption by liver transplantation. A weakness of our study is the definition of CE based on clinical parameters that could have underestimated the frequency of CE.

In conclusion, persistence of arterial hyperammonemia in ALF has better association with complications and poor outcome than the baseline levels. Infection, renal failure, and low arterial pH are independent predictors of persistent hyperammonemia.

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Reprint requests

Address requests for reprints to: Subrat K. Acharya, MD, DM, Professor and Head, Department of Gastroenterology and Human Nutrition, Room 3105, 3rd Floor, Teaching Block, All India Institute of Medical Sciences, New Delhi 110029, India. e-mail: subratacharya@hotmail.com; fax: 91-11-2659641.

Conflicts of interest

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