Prognosis of Patients with Sepsis and Non-Hepatic Hyperammonemia: A Cohort Study

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Background: Hyperammonemia has been reported in some critically ill patients with sepsis who do not have hepatic failure. A significant proportion of patients with non-hepatic hyperammonemia have underlying sepsis, but the association between non-hepatic hyperammonemia and prognosis is unclear.

Material/Methods: Information about patients with sepsis and non-hepatic hyperammonemia was retrieved from the Medical Information Mart for Intensive Care-III database. Survival rates were analyzed using the Kaplan-Meier method. Multivariate logistic regression models were employed to identify prognostic factors. Receiver operating characteristic (ROC) curve analysis was used to measure the predictive ability of ammonia in terms of patient mortality.

Results: A total of 265 patients with sepsis were enrolled in this study. Compared with the non-hyperammonemia group, the patients with hyperammonemia had significantly higher rates of hospital (59.8% *vs.* 43.0%, *P*=0.007), 30-day (47.7% *vs.* 34.8%, *P*=0.036), 90-day (61.7% *vs.* 43.7%, *P*=0.004), and 1-year mortality (67.3% *vs.* 49.4%, *P*=0.004). In the survival analysis, hyperammonemia was associated with these outcomes. Serum ammonia level was an independent predictor of hospital mortality. The area under the ROC curve for the ammonia levels had poor discriminative capacity. The hyperammonemia group also had significantly lower Glasgow Coma Scale scores (*P*=0.020) and higher incidences of delirium (15.9% *vs.* 8.2%, *P*=0.034) and encephalopathy (37.4% *vs.* 19.6%, *P*=0.001). Intestinal infection and urinary tract infection with organisms such as *Escherichia coli* may be risk factors for hyperammonemia in patients who have sepsis.

Conclusions: Higher ammonia levels are associated with poorer prognosis in patients with sepsis. Ammonia also may be associated with sepsis-associated encephalopathy. Therefore, we recommend that serum ammonia levels be measured in patients who are suspected of having sepsis.

MeSH Keywords: *Escherichia coli* Infections • Hyperammonemia • Prognosis Sepsis

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Background

Sepsis is a serious medical condition responsible for approximately 19.77% of all deaths worldwide [1,2]. The mortality is a result of the systemic inflammation and end-organ dysfunction associated with these infections [3]. The rate of mortality in patients diagnosed with sepsis is 30%, and 50% in individuals with severe sepsis. In patients in whom the disease progresses to septic shock, the mortality rate can rise to as high as 80%. As an individual's infection worsens, the risk of mortality gradually increases [4]. Sepsis-associated encephalopathy (SAE) can be found in up to 70% of patients with severe sepsis and it is a common neurological complication [5], with a mortality rate of up to 70% [6].

Ammonia is a major factor in the pathogenesis of hepatic encephalopathy and it crosses the blood-brain barrier readily, resulting in significant neurotoxicity [7]. Disorders of ammonia metabolism can lead to hyperammonemia, which usually is a consequence of hepatic failure. Hyperammonemia also can occur in critically ill patients who do not have hepatic disease [8], including individuals with sepsis, gastrointestinal bleeding, kidney failure, elevations in sodium, and exposure to valproate [8,9]. In recent reports, serum ammonia has been suggested as a possible predictor of 28-day mortality and hospital stay in patients with sepsis. While elevation in ammonia level has been reported as a novel biomarker for sepsis [10,11], its roles in long-term prognosis and as a risk factor for non-hepatic hyperammonemia in patients with sepsis are unclear. The relationship between serum ammonia and the development of sepsis and its prognosis in patients with the condition remains under-explored.

The aim of this study was to determine the significance of elevated serum ammonia levels to both the short- and long-term prognosis of patients with sepsis. We also explored risk factors for non-hepatic hyperammonemia in sepsis and the association between non-hepatic hyperammonemia and SAE.

Material and Methods

Database

This was a retrospective study based on information recorded in the publicly available Medical Information Mart for Intensive Care (MIMIC-III) database between 2001 and 2012. Use of the database was approved by the Massachusetts Institute of Technology (Cambridge, Massachusetts, U.S.A.) and the Institutional Review Board of Beth Israel Deaconess Medical Center (Boston, Massachusetts, U.S.A.). Individual patient consent was not required because the study was a retrospective review of publicly available, anonymized data and the analysis did not affect the care of individual patients. The raw data were extracted using structure query language (SQL) with Navicat and further processed with R software.

Patient population

Inclusion criteria for the study were as follows: (1) a diagnosis of sepsis, severe sepsis, or septic shock according to International Classification of Diseases, Ninth Revision (ICD-9) codes; (2) age ≥18 and ≤89 years; (3) admission for >24 hours in the intensive care unit (ICU); and documentation of blood ammonia levels. A blood ammonia level >35 μmol/L was defined as hyperammonemia in the MIMIC-III database.

Exclusion criteria for the study were as follows: (1) a history of acute or chronic liver disease, including hepatitis, hepatic cirrhosis, hepatic encephalopathy, hepatorenal syndrome, hepatic injury, and other chronic liver disease, according to ICD-9 diagnosis codes on patient discharge (Supplementary Table 1); and (2) no documentation of vital signs or ICD-9 diagnostic codes.

Data extraction

R statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used to collect data on baseline characteristics information such as age, sex, and vital signs and laboratory parameters during the first 24 hours of ICU admission. The maximum value for ammonia during each patient's ICU stay also was retrieved. Infection type (Supplementary Table 2), microbiology type (Supplementary Table 3), and patient comorbidities (Supplementary Table 4) were determined according to the primary ICD-9 codes, as documented in each patient's discharge summary. We retrieved the SQL scripts from the GitHub website (*https://github.com/MIT-LCP/mimic-code/tree/master/concepts/severity-scores*) and used them to calculate the severity scores. Simplified Acute Physiology Score (SAPSII), Sequential Organ Failure Assessment (SOFA) score, and Glasgow Coma Scale (GCS) ratings also were recorded during the first 24 hours of each patient's ICU stay. Outcomes of patient conditions such as delirium, encephalopathy, mechanical ventilation, renal replacement therapy (Supplementary Table 5), and survival status were recorded. Relevant information was obtained about patients who were diagnosed with "sepsis," "severe sepsis," and "septic shock" on discharge, according to ICD-9 codes (Supplementary Table 6).

Patients were assigned to the hyperammonemia and non-hyperammonemia groups based on serum ammonia levels. They were also divided into conscious (GCS=15), sub-coma (GCS 9–14), and deep coma groups (GCS 3–8) based on GCS scores.
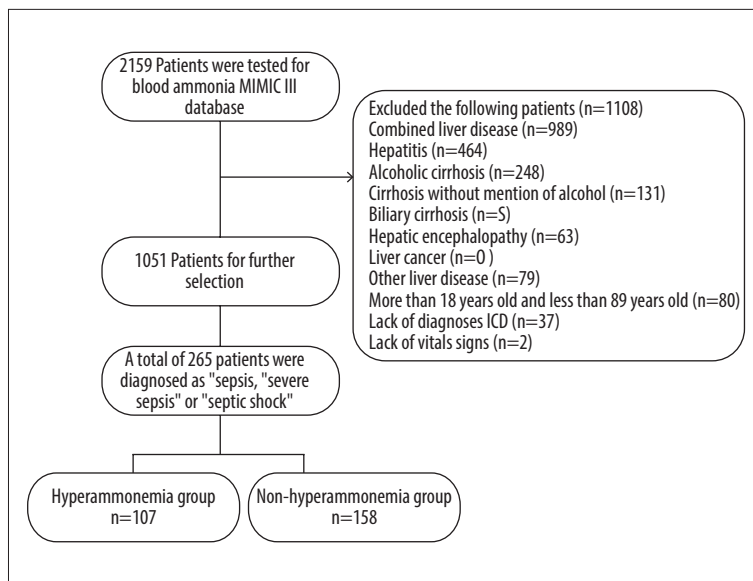
Figure 1. Flowchart of the enrolled patients. MIMIC-III – Medical Information Mart for Intensive Care-III.

Statistical analysis

The statistical analysis compared the hyperammonemia and non-hyperammonemia groups. Data distribution was tested using the Shapiro-Wilk test. Continuous variables were expressed as means with standard deviation for normal distributed data, and for non-normally distributed data, medians (interquartile range [IQR]) were expressed. Categorical variables were represented as frequencies with percentage and compared using a chi-square test. Variables with missing data are relatively common in the MIMIC-III database and we replaced them with median values (Supplementary Material 1).

A non-parametric test (Mann-Whitney U or Kruskal-Wallis) was used for comparisons between the baseline characteristics and outcomes in the hyperammonemia and non-hyperammonemia groups and the relationship between serum ammonia and consciousness. Kaplan-Meier curves were analyzed using log-rank tests for comparison of hospital mortality between the hyperammonemia and non-hepatic hyperammonemia groups. A Cox regression model was used to screen for variables associated with hospital mortality in survivors versus non-survivors. A 2-tailed *P*<0.05 was considered statistically significant. All statistical analyses were performed with R software (version 3.4.3).

Results

Baseline patient characteristics

The patient inclusion flowchart is shown in Figure 1. A total of 2159 patients were tested for blood ammonia according to information in the MIMIC-III database. Using the inclusion

and exclusion criteria, 1051 patients were identified for further screening. Of those patients, 265 were diagnosed with "sepsis," "severe sepsis," or "septic shock" on discharge, according to ICD-9 codes, and were enrolled in the study. The incidence of non-hepatic hyperammonemia was 40.4% with a 67.3% rate of 1-year mortality.

Information on the patients' baseline characteristics, vital signs, laboratory parameters, infection type, microbiology type, and comorbid diseases is summarized in Table 1. There were 107 patients in the hyperammonemia group and 158 patients in the non-hyperammonemia group.

Patients in the hyperammonemia group had significantly more intestinal infections (23.4% *vs.* 13.3%, *P*=0.034) and urinary tract infections (UTIs) (45.8% *vs.* 24.7%, *P*<0.001) than patients in the non-hyperammonemia group. Patients with hyperammonemia were more likely to be infected with *Escherichia coli* (42.1% *vs.* 22.8%, *P*=0.001). Patients in the hyperammonemia group had lower GCS scores than patients in the non-hyperammonemia group (*P*=0.020). No correlation was found between ammonia levels and respiratory infection, gastrointestinal bleeding, heart failure, kidney failure, or infection in other tissues by *E. coli*. In addition, there were no significant differences in SAPSII or SOFA scores between the 2 groups.

Patient outcomes

Table 2 shows the outcomes in the hyperammonemia and non-hyperammonemia groups. As illustrated, a greater proportion of patients in the hyperammonemia group were diagnosed with delirium (15.9% *vs.* 8.2%, *P*=0.034) and encephalopathy (37.4% *vs.* 19.6%, *P*=0.001). Patients with hyperammonemia also had higher rates of short- and long-term mortality

Table 1. Baseline characteristics of the hyperammonemia and non-hyperammonemia groups.

	Hyperammonemia group n=107		Non-hyperammonemia group n=158		P value
Baseline variable					
Age, median (IQR)	69.0	(56.1–76.6)	66.8	(55.6–75.6)	0.451
Sex, n (%)					
Female	43	(40.2)	67	(42.4)	0.719
Male	64	(59.8)	91	(57.6)	
Vital signs, median (IQR)/(x±s)					
Heart rate (bpm)	89.7±15.3		91.6±16.6		0.435
Systolic blood pressure (mmHg)	111.7	(104.3–123.9)	110.1	(102.6–126.5)	0.654
Diastolic blood pressure (mmHg)	56.1	(49.4–61.5)	57.7	(52.1–65.4)	0.058
Respiratory rate (bpm)	19.5	(16.8–22.8)	19.8	(16.7–23.9)	0.729
Temperature (ºC)	36.9±0.76		36.9±0.76		0.537
Laboratory parameters, median (IQR)					
Alanine aminotransferase (IU/L)	23	(15–35)	24	(12–39.0)	0.923
Aspartate aminotransferase (IU/L)	32	(21–52.0)	36	(23–52.3)	0.468
Creatinine (mg/dL)	1.7	(1.0–2.8)	1.5	(1.0–2.6)	0.355
Hemoglobin(g/dL)	9.3	(8.2–10.7)	9.2	(8.4–10.5)	0.917
Platelet (×10⁹/L)	197	(121–275)	167.0	(104.8–244.5)	0.091
Partial thromboplastin time(s)	36.3	(29.8–46.9)	38.4	(30.5–49.9)	0.341
International normalized ratio	1.4	(1.2–1.8)	1.4	(1.2–1.8)	0.996
Prothrombin time(s)	15.6	(13.8–19.0)	15.7	(13.9–19.0)	0.822
Blood urea nitrogen (mg/dL)	36	(22–55)	31	(18–57)	0.255
White blood cell count (×10⁹/L)	12.6	(8.6–18.2)	13.1	(8.9–19.1)	0.373
Ammonia (µmol/L)	63	(46–131)	24	(18–30)	<0.001
Infection type, n (%)					
Intestinal infection	25	(23.4)	21	(13.3)	0.034
Urinary tract infection	49	(45.8)	39	(24.7)	<0.001
Lung infection	63	(58.9)	86	(54.4)	0.474
Microbiology type, n (%)					
Pseudomonas aeruginosa	21	(19.6)	32	(20.3)	0.900
Klebsiella pneumoniae	22	(20.6)	44	(27.8)	0.178
Viridans streptococci	0	(1)	8	(5.1)	0.018
Stenotrophomonas maltophilia	10	(9.3)	9	(5.7)	0.259
Pneumocystis carinii positive	1	(0.9)	0	(0)	0.223
Staphylococcus, coagulase negative	45	(42.1)	82	(51.9)	0.116
Staphylococcus aureus coagulase positive	37	(34.6)	62	(39.2)	0.442
Positive for methicillin-resistant *Staphylococcus aureus*	10	(9.3)	18	(11.4)	0.595
Enterococcus sp.	30	(28.0)	43	(27.2)	0.883
Enterococcus faecium	9	(8.4)	21	(13.3)	0.219

Table 1 continued. Baseline characteristics of the hyperammonemia and non-hyperammonemia groups.

	Hyperammonemia group n=107		Non-hyperammonemia group n=158		P value
Gram negative rod(s)	22	(20.6)	47	(29.7)	0.095
Escherichia coli	45	(42.1)	36	(22.8)	0.001
Clostridium difficile	10	(9.3)	22	(13.9)	0.262
Bacteroides fragilis group	6	(5.6)	6	(3.8)	0.487
Aspergillus fumigatus	4	(3.7)	0	(0)	0.014
Yeast	61	(57.0)	90	(57.0)	0.994
Candida albicans	20	(18.7)	24	(15.2)	0.452
Comorbid disease, n (%)					
Gastrointestinal bleeding	12	(11.2)	33	(20.9)	0.004
Heart failure	77	(72.0)	120	(75.9)	0.466
Kidney failure	32	(29.9)	50	(31.6)	0.764
Score system, median (IQR)					
SAPSII	42	(34–52)	40	(30–53)	0.400
SOFA	6.0	(4.0–8.0)	6.0	(4.0–9.0)	0.422
GCS	14.0	(9.0–15.0)	15	(13–15)	0.020

IQR – interquartile range; SAPSII – Simplified Acute Physiology Score; SOFA – Sequential Organ Failure Assessment score; GCS – Glasgow Coma Scale. $P<0.05$ indicates statistical significance.

Table 2. Outcomes in the hyperammonemia and non-hyperammonemia groups.

Outcome	Hyperammonemia group n=107		Non-hyperammonemia group n=158		P value
Mechanical ventilation, n (%)	64	(59.8)	97	(61.4)	0.959
Renal replacement therapy, n (%)	10	(9.3)	23	(14.6)	0.207
Delirium, n (%)	17	(15.9)	13	(8.2)	0.034
Encephalopathy, n (%)	40	(37.4)	31	(19.6)	0.001
Length of stay, median (IQR)					
In ICU	4.0	(2.1–13.3)	5.0	(2.1–13.7)	0.748
In hospital	14	(6–28)	14	(7–28)	0.726
Mortality, n (%)					
Hospital mortality	64	(59.8)	68	(43.0)	0.007
30-day	51	(47.7)	55	(34.8)	0.036
90-day	66	(61.7)	69	(43.7)	0.004
1-year	72	(67.3)	78	(49.4)	0.004

ICU – intensive care unit; IQR – interquartile range. $P<0.05$ indicates statistical significance.
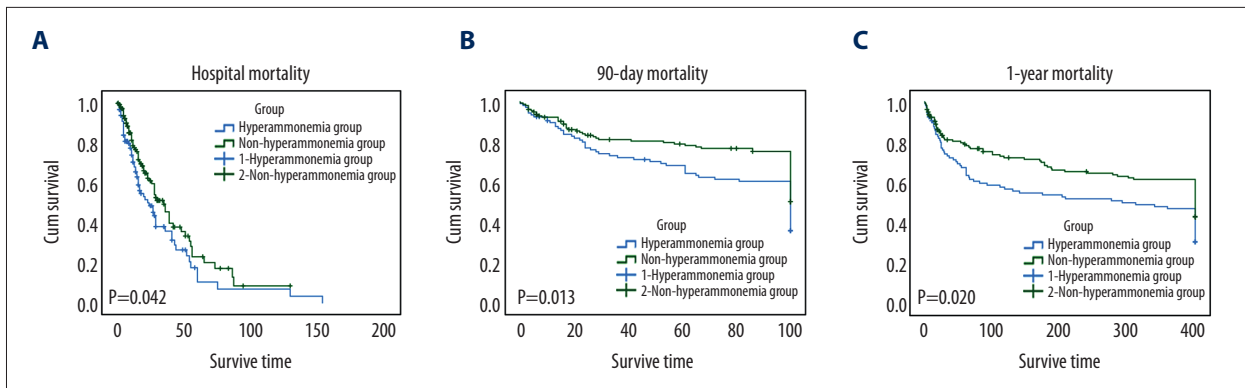
Figure 2. Probability of mortality curve for patients with sepsis by ammonia levels. (**A**) hospital mortality. (**B**) Ninety-day survival. (**C**) One-year mortality. *P* values were calculated using log-rank and Mantel tests. *P*<0.05 was considered statistically significant.

Table 3. Univariate and multivariate analysis of risk factors for hospital mortality.

	Univariate analysis				Multivariate analysis			
		95.0% CI				95.0% CI		
	RR	Lower	Upper	*P* value	RR	Lower	Upper	*P* value
Age, median (IQR)	1.015	1.003	1.028	0.015	1.014	1.002	1.027	0.027
Sex n (%)	0.955	0.671	1.360	0.799				
Laboratory parameters, median (IQR)								
Alanine aminotransferase (IU/L)	1.002	0.997	1.008	0.404				
Aspartate aminotransferase (IU/L)	1.001	0.999	1.003	0.425				
Creatinine (mg/dL)	1.089	1.011	1.172	0.024	1.072	0.994	1.155	0.071
Blood urea nitrogen (mg/dL)	1.001	0.995	1.006	0.839				
Hemoglobin (g/dL)	1.088	0.991	1.194	0.078				
Platelet (×10^9/L)	0.999	0.998	1.001	0.390				
Partial thromboplastin time(s)	0.998	0.991	1.004	0.512				
International normalized ratio	1.072	0.921	1.247	0.370				
Prothrombin time	1.002	0.988	1.017	0.745				
White blood cell count (×10^9/L)	0.997	0.981	1.013	0.689				
Ammonia (umol/L)	1.010	1.006	1.014	<0.001	1.009	1.006	1.013	<0.001

CI – confidence interval; IQR, interquartile range; RR – relative risk. *P*<0.05=statistically significant.

(in-hospital, 59.8% *vs.* 43.0%; 30-day, 47.7% *vs.* 34.8%; 90-day, 61.7% *vs.* 43.7%; 1-year, 67.3% *vs.* 49.4%).

Ammonia was an independent prognostic predictor in patients with sepsis

Patients in the hyperammonemia group had worse survival rates (in-hospital, 90-day, and 1-year mortality) (Figure 2). Furthermore, univariate and multivariate Cox analysis was performed of baseline variables (age and sex) and results of laboratory tests (alanine aminotransferase, aspartate aminotransferase, creatinine, blood urea nitrogen, hemoglobin, platelet count, partial thromboplastin time, international normalized ratio, prothrombin time, white blood cell count, and ammonia). The factors significantly correlated with survival were adjusted for in the multivariate analysis. The analysis revealed that ammonia remained an independent prognostic factor in patients with sepsis. (*P*<0.01 or *P*<0.05) (Table 3).
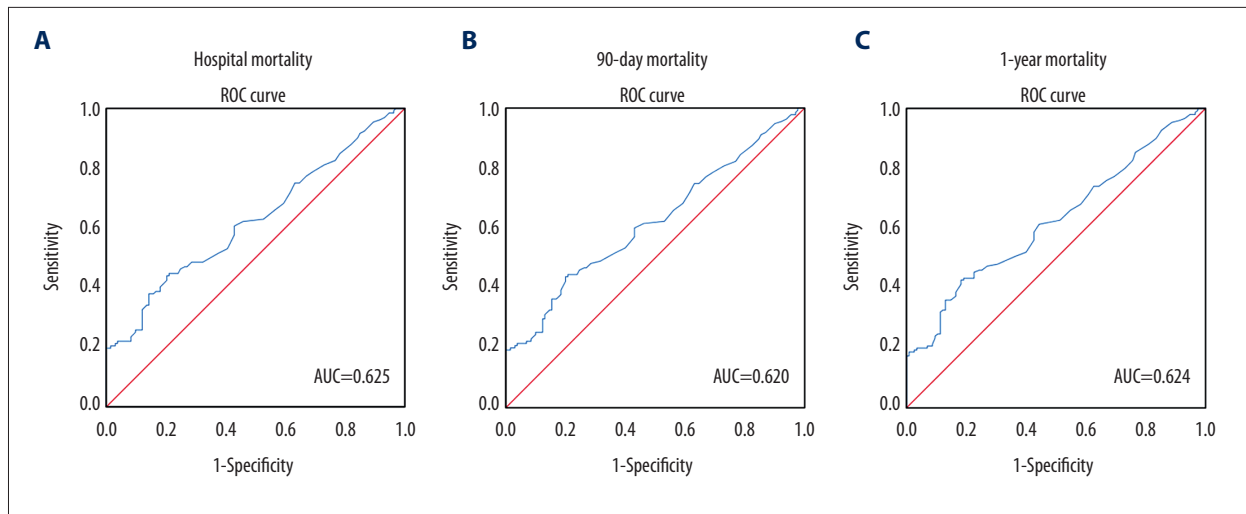
Figure 3. Receiver operating characteristic curves for ammonia for predicting mortality. (**A**) Hospital mortality. (**B**) Ninety-day mortality. (**C**) One-year mortality.

Receiver operating characteristic curves of ammonia indices for predicting mortality

To further confirm the reliability of ammonia, we plotted the area under the receiver operating characteristic (ROC) curve for 90-day and 1-year survival, and in-hospital mortality. The discriminative ability of ammonia levels based on the ROC curve analysis was 0.625 for in-hospital mortality, 0.620 for 90-day survival, and 0.624 for 1-year survival (Figure 3).

Relationship between serum ammonia and consciousness

Patients were divided into conscious (n=109), sub-coma (n=112), and deep coma groups (n=44) based on GCS score. As shown in Figure 4, patients with lower GCS scores had higher serum ammonia levels. The serum ammonia levels were highest in the deep coma group, compared with the other 2 groups (*P*<0.001), and they were significantly higher in the sub-coma group than in the conscious group (*P*<0.001) (Figure 4).

Discussion

Our study demonstrated that the incidence of non-hepatic hyperammonemia is 40.4% in patients with sepsis and the incidence of sepsis with encephalopathy in patients with non-hepatic hyperammonemia is 37.4%. Serum ammonia level may be a predictor of mortality in patients with sepsis who do not have hepatic disease.

In addition, we found that intestinal infection, UTI, and infections in other tissues caused by *E. coli* were risk factors for non-hepatic hyperammonemia in patients with sepsis.
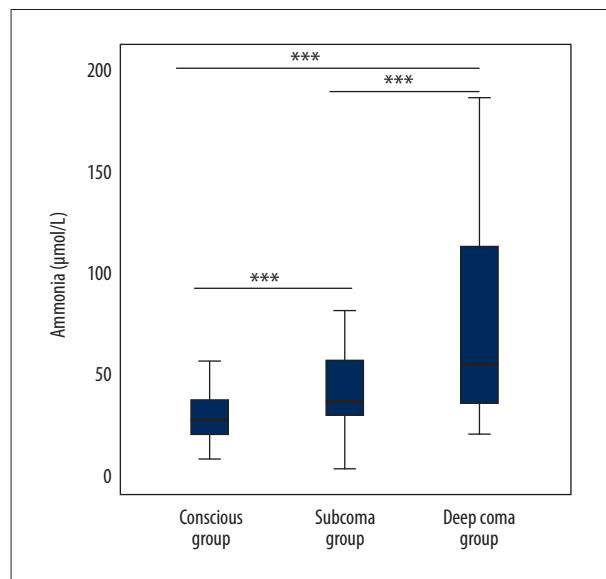
Figure 4. Serum ammonia levels in patients who were conscious, in a sub-coma, and in a deep coma. Patients in the conscious group had significantly lower serum ammonia levels than the sub-coma and deep coma groups. Serum ammonia levels of patients in the deep coma group were significantly higher than those in the other groups. *** *P*<0.001.

We also found that the rate of hospital mortality in patients with sepsis who had non-hepatic hyperammonemia was 59.8%, which was significantly higher than in patients with sepsis who had normal serum ammonia levels (46.4%) [1]. A higher serum ammonia level may be a risk factor for mortality. Our results are consistent with the findings of Zhao et al., which showed that in patients with sepsis, an increased serum ammonia level on admission to the emergency department was correlated

with an increased rate of mortality at 28 days. Our study explored mortality levels for up to 1 year, and we found that serum ammonia is an independent risk factor for long-term prognosis in patients with sepsis. In a case series, McEwan et al. suggested that higher serum ammonia levels are related to adverse clinical outcomes, which correlates with our findings. However, Zhao et al. showed that serum ammonia levels had a robust ability to predict the 28-day mortality rate in patients with sepsis, with an area under the ROC curve of 0.813, which is in contrast to our findings. That discrepancy may be attributable to differences in basic patient characteristics between the 2 studies. It suggests that serum ammonia level may be a new prognostic marker for patients with sepsis.

An interesting finding in our study is that non-hepatic hyperammonemia may be associated with an increased risk of SAE [12]. SAE is mainly characterized by symptoms of delirium with changes in a patient's consciousness, and it also can lead to coma [13]. Our study demonstrated that patients with hyperammonemia had lower GCS scores. In the absence of previous cerebrovascular and encephalopathic brain disease, SAE is more likely to occur as the serum ammonia level increases. SAE is a diffuse brain dysfunction that occurs secondary to sepsis in the body without overt infection of the central nervous system. Its pathogenesis is multifaceted and is attributed to a combination of astrocyte swelling, an increase in glutamine synthesis, and a disproportionate ratio of aromatic amino acids to branched chain amino acids [14–16]. Based on our study results, we hypothesize that non-hepatic hyperammonemia may be associated with SAE. Unfortunately, in our study, some primary brain diseases (such as cerebral hemorrhage and cerebral infarction) and some secondary brain diseases (such as metabolic encephalopathy and pulmonary encephalopathy) were not excluded. The association between non-hepatic hyperammonemia and SAE needs to be validated in future well-designed experimental trials.

Intestinal infection, UTI, and infection of other tissues by *E. coli* may be risk factors for non-hepatic hyperammonemia in patients with sepsis. Our results showed that the incidence of intestinal infections in the hyperammonemia group was 23.4% higher than in the non-hyperammonemia group. This is consistent with research by Wang et al., which found that in patients with infection-induced hepatic encephalopathy, levels of plasma ammonia were significantly higher in association with intestinal tract infection compared with other sites of infection. Their results, along with our findings, support the notion that intestinal infection is related to hyperammonemia [17]. A possible explanation for the link between intestinal infection and non-hepatic hyperammonemia is intestinal flora. Colonic bacteria have been known to produce ammonia from amino acid deamination or via urease, the hydrolysis of urea into carbon dioxide and ammonia [18]. When the body develops sepsis,

the composition of intestinal microbes changes, due to factors such as antibiotic usage, systemic inflammation, and intestinal leakage [19]. In the patient's feces, the composition of the microbial components changes rapidly, the microbial diversity is largely lost, and the proportion of anaerobic bacteria significantly reduced and of *Enterobacteriaceae* increased [20]. Ammonia production is increased by converting nitrate to nitrite, and subsequently to ammonia [21].

Our results are consistent with previous studies, in which an increase in ammonia was associated with higher rates of infection by *Enterobacteriaceae* [3,13,22]. Therefore, serum ammonia should be measured when risk factors are present, such as intestinal infection or infection by *E. coli*. Our study showed that UTI is significantly associated with non-hepatic hyperammonemia in patients with sepsis, which is in line with the literature [23–25]. The possible explanation for the link between non-hepatic hyperammonemia and UTI is urease-producing bacteria and distal renal tubular acidosis [26]. With the entry of urea into the urinary tract, urease-producing bacteria form "ammonia," which results in alkalinization of the urine. The pH of the urine, when relatively high compared with that of the blood, enhances the diffusion of "ammonia" into the bloodstream [27,28].

Another plausible explanation for the linkage between hyperammonemia and UTI is distal renal tubular acidosis. Severe UTIs occasionally are accompanied by altered distal renal tubular function, which results in reduced bicarbonates, and in turn, leads to increased renal "ammonia" production [29]. The last explanation could be urinary retention associated with a neurogenic bladder. As the pressure in the bladder increases, the area of the bladder expands and promotes drainage of more ammonia directly into the inferior vena cava via the internal iliac veins [30]. Therefore, in patients with UTIs, serum ammonia levels should be closely monitored and timely measures taken to reduce them.

Several limitations of the present study must be acknowledged. First, the result suggests a link between higher serum ammonia levels and lower GCS scores. Because of the nature of the retrospective analysis, the onset times of coma were not always available or documented, and some patients with primary and secondary encephalopathy in this study were not excluded. Therefore, whether there is a causal relationship between ammonia and SAE cannot be determined based on our results. Second, due to the limitations of the database, information was missing on some clinical variables, such as bilirubin, albumin, and intravenous nutrition. Inclusion of those data may have led to a more comprehensive understanding of the role of other biomarkers in sepsis with non-hepatic hyperammonemia. Third, our cohort study used ICD-9 diagnostic codes for sepsis, severe sepsis, and septic shock, but the

concept of severe sepsis was eliminated in Sepsis 3.0, which may have led to bias in our research results.

Conclusions

Non-hepatic hyperammonemia is associated with mortality in patients with sepsis. The present study was essentially a pilot that requires validation. We recommend that serum ammonia levels be measured in patients who have risk factors, such as intestinal infection, UTI, and *E. coli* infection. Infection caused by *E. coli* is a potential biomarker for sepsis in patients who have non-hepatic hyperammonemia. Our study also demonstrated a correlation between non-hepatic hyperammonemia and an increased risk of SAE.

Conflict of interests

None.

Availability of data and materials

The MIMIC-III database (version 1.4) is publically available from *https://mimic.physionet.org/*. Any researcher who adheres to the data use requirements is permitted access to the database.

Ethics approval and consent to participate

The use of the database was approved by the Massachusetts Institute of Technology (Cambridge, Massachusetts, U.S.A.) and the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, Massachusetts, U.S.A.).

Conflict of interests

None.

Supplementary Data

Supplementary Table 1. Exclusion of patients with acute and chronic liver disease from the MIMIC-III database according to International Classification of Diseases, Ninth Revision codes.

ICD9-code	Description
700	Hepatitis A with coma
0701	Viral hepatitis A without mention of hepatic coma
07020	Viral hepatitis B with hepatic coma, acute or unspecified, without mention of hepatitis delta
07021	Viral hepatitis B with hepatic coma, acute or unspecified, with hepatitis delta
07022	Chronic viral hepatitis B with hepatic coma without hepatitis delta
07023	Chronic viral hepatitis B with hepatic coma with hepatitis delta
07030	Viral hepatitis B without mention of hepatic coma, acute or unspecified, without mention of hepatitis
07031	Viral hepatitis B without mention of hepatic coma, acute or unspecified, with hepatitis delta
07032	Chronic viral hepatitis B without mention of hepatic coma without mention of hepatitis delta
07033	Chronic viral hepatitis B without mention of hepatic coma with hepatitis delta
07041	Acute hepatitis C with hepatic coma
07042	Hepatitis delta without mention of active hepatitis B disease with hepatic coma
07043	Hepatitis E with hepatic coma
07044	Chronic hepatitis C with hepatic coma
07049	Other specified viral hepatitis with hepatic coma
07051	Acute hepatitis C without mention of hepatic coma
07052	Hepatitis delta without mention of active hepatitis B disease or hepatic coma
07053	Hepatitis E without mention of hepatic coma
07054	Chronic hepatitis C without mention of hepatic coma
07059	Other specified viral hepatitis without mention of hepatic coma
0706	Unspecified viral hepatitis with hepatic coma

Supplementary Table 1 continued. Exclusion of patients with acute and chronic liver disease from the MIMIC-III database according to International Classification of Diseases, Ninth Revision codes.

ICD9-code	Description
07070	Unspecified viral hepatitis C without hepatic coma
07071	Unspecified viral hepatitis C with hepatic coma
0709	Unspecified viral hepatitis without mention of hepatic coma
5712	Alcoholic cirrhosis of liver
5713	Alcoholic liver damage, unspecified
57140	Chronic hepatitis, unspecified
57141	Chronic persistent hepatitis
57142	Autoimmune hepatitis
57149	Other chronic hepatitis
5715	Cirrhosis of liver without mention of alcohol
5716	Biliary cirrhosis
5718	Other chronic nonalcoholic liver disease
5719	Unspecified chronic liver disease without mention of alcohol
5722	Hepatic encephalopathy
5724	Hepatorenal syndrome
5728	Other sequelae of chronic liver disease
5738	Other specified disorders of liver
5735	Hepatopulmonary syndrome
5734	Hepatic infarction
5733	Hepatitis, unspecified
5732	Hepatitis in other infectious diseases classified elsewhere
5731	Hepatitis in viral diseases classified elsewhere
5730	Chronic passive congestion of liver
V0260	Viral hepatitis carrier, unspecified
V0261	Hepatitis B carrier
V0262	Hepatitis C carrier
V0269	Other viral hepatitis carrier
86400	Injury to liver without mention of open wound into cavity, unspecified injury
86401	Injury to liver without mention of open wound into cavity, hematoma and contusion
86402	Injury to liver without mention of open wound into cavity, laceration, minor
86403	Injury to liver without mention of open wound into cavity, laceration, moderate
86404	Injury to liver without mention of open wound into cavity, laceration, major
86405	Injury to liver without mention of open wound into cavity laceration, unspecified
86409	Other injury to liver without mention of open wound into cavity
86410	Injury to liver with open wound into cavity, unspecified injury
4560	Esophageal varices with bleeding
4561	Esophageal varices without mention of bleeding
45620	Esophageal varices in diseases classified elsewhere, with bleeding
45621	Esophageal varices in diseases classified elsewhere, without mention of bleeding

Supplementary Table 2. Type of Microbiology type and org_itemid.

org_itemid	Description
Microbiology type	
80026	*Pseudomonas aeruginosa*
80155	*Staphylococcus*, coagulase negative
80223	*Probable enterococcus*
80023	*Staph aureus* coag +
80155	*Staphylococcus*, coagulase negative
80280	*Viridans streptococci*
80081	Gram positive bacteria
80075	Yeast
80004	*Klebsiella pneumoniae*
80060	*Albicans*
80254	*Candida albicans*, presumptive identification
80058	Gram negative rod(s)
80260	Positive for pneumocystis carinii
80002	*Escherichia coli*
80053	*Enterococcus* sp.
80293	Positive for methicillin resistant staph aureus
80168	*Enterococcus faecium*
80139	*Clostridium difficile*
80112	*Bacteroides fragilis* group
80087	*Stenotrophomonas* (xanthomonas) maltophilia
80066	*Aspergillus fumigatus*

Supplementary Table 3. Type of infection and International Classification of Diseases, Ninth Revision codes.

ICD9 code	Description
Intestinal infection	
845	Intestinal infection due to *Clostridium difficile*
847	Intestinal infection due to other gram-negative bacteria
88	Intestinal infection due to other organism, not elsewhere classified
90	Infectious colitis, enteritis, and gastroenteritis
93	Diarrhea of presumed infectious origin
56081	Intestinal or peritoneal adhesions with obstruction (postoperative) (postinfection)
56982	Ulceration of intestine
56983	Perforation of intestine
Urinary tract infection	
5990	Urinary tract infection

Supplementary Table 3 continued. Type of infection and International Classification of Diseases, Ninth Revision codes.

ICD9 code	Description
lung infection	
322	*Salmonella pneumonia*
1160	Tuberculous pneumonia [any form], unspecified
1161	Tuberculous pneumonia [any form], bacteriological or histological examination not done
1162	Tuberculous pneumonia [any form], bacteriological or histological examination unknown (at present)
1163	Tuberculous pneumonia [any form], tubercle bacilli found (in sputum) by microscopy
1164	Tuberculous pneumonia [any form], tubercle bacilli not found (in sputum) by microscopy, but found by bacterial culture
1165	Tuberculous pneumonia [any form], tubercle bacilli not found by bacteriological examination, but tuberculosis confirmed histologically
413	*Klebsiella pneumoniae*
551	*Postmeasles pneumonia*
382	Pneumococcal septicemia [*Streptococcus pneumoniae* septicemia]
11505	Histoplasm caps pneumon
11515	Infection by *Histoplasma duboisii*, pneumonia
11595	Histoplasmosis, unspecified, pneumonia
730	Ornithosis with pneumonia
48249	Other *Staphylococcus pneumonia*
48281	Pneumonia due to anaerobes
48282	Pneumonia due to *Escherichia coli*
48283	Pneumonia due to other gram-negative bacteria
4800	Pneumonia due to adenovirus
4801	Pneumonia due to respiratory syncytial virus
4802	Pneumonia due to parainfluenza virus
4803	Pneumonia due to SARS-associated coronavirus
4808	Pneumonia due to other virus not elsewhere classified
4809	Viral pneumonia, unspecified
481	Pneumococcal pneumonia [*Streptococcus pneumoniae* pneumonia]
4820	Pneumonia due to *Klebsiella pneumoniae*
4821	Pneumonia due to *Pseudomonas*
4822	Pneumonia due to *Hemophilus influenzae* [*H. influenzae*]
48230	Pneumonia due to *Streptococcus*, unspecified
48231	Pneumonia due to *Streptococcus*, group A
48232	Pneumonia due to *Streptococcus*, group B

Supplementary Table 3 continued. Type of infection and International Classification of Diseases, Ninth Revision codes.

ICD9 code	Description
48239	Pneumonia due to other *Streptococcus*
48240	Pneumonia due to *Staphylococcus*, unspecified
48241	Methicillin susceptible pneumonia due to *Staphylococcus aureus*
48242	Methicillin resistant pneumonia due to *Staphylococcus aureus*
48284	Pneumonia due to Legionnaires' disease
48289	Pneumonia due to other specified bacteria
4829	Bacterial pneumonia NOS Bacterial pneumonia, unspecified
4830	Pneumonia due to mycoplasma pneumoniae
4831	Pneumonia due to chlamydia
4838	Pneumonia due to other specified organism
4841	Pneumonia in cytomegalic inclusion disease
4843	Pneumonia in whoop cough
4845	Pneumonia in anthrax
4846	Pneum in aspergillosis
4847	Pneumonia in other systemic mycoses
4848	Pneumonia in other infectious diseases classified elsewhere
485	Bronchopneumonia, organism unspecified
486	Pneumonia, organism unspecified
4870	Influenza with pneumonia
4871	Influenza with other respiratory manifestations
4878	Influenza with other manifestations
48801	Influenza due to identified avian influenza virus with pneumonia
48802	Influenza due to identified avian influenza virus with other respiratory manifestations
48809	Influenza due to identified avian influenza virus with other manifestations
48811	Influenza due to identified 2009 H1N1 influenza virus with pneumonia
48812	Influenza due to identified 2009 H1N1 influenza virus with other respiratory manifestations
48819	Influenza due to identified 2009 H1N1 influenza virus with other manifestations
48881	Influenza due to identified novel influenza A virus with pneumonia
48882	Influenza due to identified novel influenza A virus with other respiratory manifestations
48889	Influenza due to identified novel influenza A virus with other manifestations
51630	Idiopathic interstitial pneumonia, not otherwise specified
51635	Idiopathic lymphoid interstitial pneumonia
51636	Cryptogenic organizing pneumonia

Supplementary Table 3 continued. Type of infection and International Classification of Diseases, Ninth Revision codes.

ICD9 code	Description
51637	Desquamative interstitial pneumonia
5171	Rheumatic pneumonia
7700	Congenital pneumonia
V066	Need for prophylactic vaccination and inoculation against streptococcus pneumoniae [pneumococcus] and influenza
99731	Ventilator associated pneumonia
99732	Postprocedural aspiration pneumonia
V0382	Other specified vaccinations against *Streptococcus pneumoniae* [pneumococcus]
1166	Tuberculous pneumonia [any form], tubercle bacilli not found by bacteriological or histological examination, but tuberculosis confirmed by other methods [inoculation of animals]
3453	Grand mal status

Supplementary Table 4. Type of disease and International Classification of Diseases, Ninth Revision codes.

Disease	ICD9-Code	Description
Gastrointestinal bleeding		
	5789	Hemorrhage of gastrointestinal tract, unspecified
	5780	Hematemesis
	5781	Blood in stool
	5693	Hemorrhage of rectum and anus
	4560	Esophageal varices with bleeding
	45620	Esophageal varices in diseases classified elsewhere, with bleeding
	53100	Acute gastric ulcer with hemorrhage, without mention of obstruction
	53101	Acute gastric ulcer with hemorrhage, with obstruction
	53120	Acute gastric ulcer with hemorrhage and perforation, without mention of obstruction
	53121	Acute gastric ulcer with hemorrhage and perforation, with obstruction
	53300	Acute peptic ulcer of unspecified site with hemorrhage, without mention of obstruction
	53320	Acute peptic ulcer of unspecified site with hemorrhage and perforation, without mention of obstruction
	53321	Acute peptic ulcer of unspecified site with hemorrhage and perforation, with obstruction
	53200	Acute duodenal ulcer with hemorrhage, without mention of obstruction
	53201	Acute duodenal ulcer with hemorrhage, with obstruction
	53220	Acute duodenal ulcer with hemorrhage and perforation, without mention of obstruction
	53221	Acute duodenal ulcer with hemorrhage and perforation, with obstruction
	53400	Acute gastrojejunal ulcer with hemorrhage, without mention of obstruction
	53401	Acute gastrojejunal ulcer, with hemorrhage, with obstruction
	53420	Acute gastrojejunal ulcer with hemorrhage and perforation, without mention of obstruction
	53421	Acute gastrojejunal ulcer with hemorrhage and perforation, with obstruction
	53501	Acute gastritis, with hemorrhage

Supplementary Table 4 continued. Type of disease and International Classification of Diseases, Ninth Revision codes.

Disease	ICD9-Code	Description
Heart failure		
	4280	Congestive heart failure, unspecified
	4281	Left heart failure
	42830	Diastolic heart failure, unspecified
	42831	Acute diastolic heart failure
	42832	Chronic diastolic heart failure
	42833	Acute on chronic diastolic heart failure
	42840	Combined systolic and diastolic heart failure, unspecified
	42841	Acute combined systolic and diastolic heart failure
	42842	Chronic combined systolic and diastolic heart failure
	42843	Acute on chronic combined systolic and diastolic heart failure
	39891	Rheumatic heart failure (congestive)
Kidney failure		
	5845	Acute kidney failure with lesion of tubular necrosis
	5846	Acute kidney failure with lesion of renal cortical necrosis
	5848	Acute kidney failure with other specified pathological lesion in kidney
	5849	Acute kidney failure, unspecified
	5852	Chronic kidney disease, Stage II (mild)
	5853	Chronic kidney disease, Stage III (moderate)
	5854	Chronic kidney disease, Stage IV (severe)
	5855	Chronic kidney disease, Stage V
	5856	End stage renal disease

Supplementary Table 5. Outcome of patients in the hyperammonemia and non-hyperammonemia groups and International Classification of Diseases, Ninth Revision codes.

ICD9-code	Description
Delirium	
29041	Vascular dementia, with delirium
29043	Vascular dementia, with depressed mood
29281	Drug-induced delirium
2910	Alcohol withdrawal delirium
2930	Delirium due to conditions classified elsewhere
Encephalopathy	
4372	Hypertensive encephalopathy
34982	Toxic encephalopathy
34831	Metabolic encephalopathy
34830	Encephalopathy, unspecified
34839	Other encephalopathy

Supplemrentary Table 6. Definition of sepsis based on International Classification of Diseases, Ninth Revision codes.

ICD9-code	Description
99591	Sepsis
99592	Severe sepsis
78552	Septic shock

ICD-9 – International Classification of Diseases, Ninth Revision.

Supplementary Material 1. Data profiling report.

Supplementary Material 1 available from the corresponding author on request.

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