Prognostic Value of Serum Ammonia in Critical Patients with Non-Hepatic Disease : A Prospective, Observational, Multicenter Study

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Research

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Abstract

Background: Non-hepatic hyperammonemia can damage the central nervous system (CNS) and possible prognostic factors are lacking. This study aimed to investigate the prognostic and risk factors for patients admitted to the intensive care unit (ICU).

Methods: This prospective, observational, multicenter study was conducted between November and December 2019 at 11 ICUs in the Chinese Heilongjiang province. Changes in blood ammonia level during and after ICU admission were continuously monitored, expressed as the high-level (H-), mean-level (M-), and initial-level (I-) of ammonia. The risk factors of poor prognosis were investigated by conducting univariate and multivariate logistic regression analyses. Receiver operating characteristic curve (ROC) analysis was conducted to compare predictive ability of APACHE-II score, lactic acid, TBil, M-ammonia.

Results: A total of 1060 patients were included in this study, of which 707 (67%) had a favorable prognosis and 353 (33%) had a poor prognosis. As shown by univariate models, a poor prognosis was associated with elevated serum levels of lactic acid, TBil, and ammonia ($P<0.05$), and pathologic scores from three assessments: APACHE-II, GCS, and SOFA. Multivariate analysis revealed that circulating mean ammonia levels in ICU patients were independently associated with a poor prognosis (OR=1.73, 95% CI: 1.07-2.80, P=0.02). However, the APACHE-II score (AUC: 0.714, sensitivity: 0.86, specificity: 0.68, $P <0.001$) remained the most predictive factor for patient prognosis by ROC analysis.

Conclusions: Elevated serum levels of ammonia in the blood were independently prognostic for ICU patients without liver disease.

Trial registration: ChiCTR1900026632. Registered 16 October 2014.

Background

Ammonia is a product of protein catabolism and the syndrome, hyperammonemia, results from metabolic defects.(1) Hyperammonemia is a life-threatening condition as it leads to encephalopathy, loss of consciousness, increased intracranial pressure, and may eventually progress to cerebral herniation.(2–4) Hyperammonemia is prevalent in patients with acute and chronic liver failure. However, it may also appear independently of liver disease as non-hepatic hyperammonemia (NHH).(5, 6) NHH occurs in up to 73% of critically ill patients.(7) At present, solicitous and continuous monitoring of blood ammonia for NHH is not standard practice in intensive care units (ICU).

Lactic acid is a product of the anaerobic glycolysis of glucose and can directly reflect tissue hypoperfusion and hypoxia conditions. As demonstrated by studies of metabolism during exercise, there is a linear relationship between blood ammonia and lactic acid levels due to a shared short-term energy pathway.(8, 9) During intense exercise, skeletal muscle generates adenosine triphosphate (ATP) through an adenylate kinase reaction, converting 2 adenosine diphosphate (ADP) molecules to 1 ATP molecule and 1 adenosine monophosphate (AMP) molecule.(10) Sustained exercise stimulates the deamidation of

AMP, generating ammonia as a byproduct, in order to maintain equilibrium states of AMP for the upstream adenylate kinase reaction. Therefore, high ammonia levels signify a state of rapid energy consumption or potential deficits in the aerobic tricarboxylic acid (TCA) cycle.(11–13) Accordingly, hyperammonemia can be representative of an insufficient energy supply or defective metabolism in critically ill patients.

Notably, increased blood ammonia levels are not solely acquired from liver diseases, and a particular attention should be paid to NHH in daily ICU practice. Patients with an underlying metabolic disorder are at particularly increased risk for NHH in the content of a critical injury or illness. A comprehensive metabolic assessment including blood ammonia, lactic acid, ketone body, and related indicators may have prognostic value in the ICU.(14–16) Two recent retrospective studies demonstrated that serum ammonia status was an independent prognostic predictor of mortality for NHH patients.(7, 17) Specifically, proactive monitoring of blood ammonia levels for the prompt detection of, and early intervention against, NHH may improve the prognosis of critically ill patients.

Irrespective of etiology, delayed diagnosis and treatment of hyperammonemia can lead to significant neurologic injury. When ammonia penetrates the blood-brain barrier by facilitated transport or passive diffusion, it is processed into glutamine, an osmolyte that induces astrocyte swelling. Since hyperammonemia is most commonly associated with hepatic dysfunction, elevated ammonia levels may be overlooked during the evaluation of other critically ill patients. Therefore, this prospective, multicenter study explored the prognostic value of ammonia levels in critically ill patients without hepatic dysfunction who were hospitalized in the ICU.

Methods

Patients

This was a prospective, observational, multicenter research that recruited 1,895 patients who were admitted to 11 general ICUs between November and December 2019. There were 4 centers in Harbin (the Second Affiliated Hospital of Harbin Medical University, Harbin Fifth Hospital, General Hospital of Heilongjiang Province Land Reclamatiom Bureau, and the First Hospital of Harbin), 3 centers in Daqing (the Fifth Affiliated Hospital of Harbin Medical University, Daqing Oilfield General Hospital, and the Longnan Hospital of Daqing), 2 centers in Jiamusi (the First Affiliated Hospital of Jiamusi University and Jamusi Central Hospital), and 2 centers in Mudanjiang (Hongqi Hospital affiliated with Mudanjiang Medical University and Mudanjiang City Second People's Hospital).

We only included patients (1) older than 18 years of age, and (2) who were directly admitted to the ICU and treated there for over 24h during the study period. The exclusion criteria were as follows: (1) patients with acute liver failure (ALF), (2) patients with Chronic Liver Diseases (CLDs), (3) patients readmitted to the ICU. We assigned patients to a favorable prognosis group (treated or transferred out of the ICU) and poor prognosis group (recalcitrant to treatment or experienced death as a primary endpoint).

The study protocol was approved by the ethics committee of each allied center (approval number KY2019-184), and signed informed consent forms wereaa collected from all study subjects or their families.

Data collection

Statistical data were collected at admission including demographic characteristics, a history of other diseases, patients' medical status, acute physiological assessment and the Acute Physiology And Chronic Health Evaluation II (APACHE-II) score.(18) Blood samples were drawn from the artery at admission and at 9 a.m. daily, and were immediately stored in a 4°C refrigerator or wrapped in ice packs. Measurements were performed within 30 min after sample collection. At admission, we performed a basic metabolic panel for blood levels of Na^+, K^+, lactic acid, serum glucose, leukocyte, platelet, hematocrit (HCT), total bilirubin (TBil), creatinine (Crea), Urea, albumin (ALB), and ammonia. Blood ammonia and lactic acid levels, the Glasgow Coma Scale (GCS) score, and the Sepsis-related Organ Failure Assessment (SOFA) score were examined at 9 a.m. daily during ICU hospitalization.

NHH was defined as the presence of high blood ammonia level (> 35 μmol/L) in patients without a history of liver diseases and was classified as mild-NHH (36–99 μmol/L) and severe-NHH (≥ 100 μmol/L) according to blood ammonia level.(19, 20) The I-ammonia was defined as the serum ammonia level at admission, M- and H-ammonia were the mean, and the highest serum ammonia levels during hospitalization at ICU respectively. SOFA scoring evaluates the incidence, occurrence and development of multiple organ dysfunction syndrome (MODS). It is a sequential assessment which assigns each organ system (respiratory, hematology, respiratory, cardiovascular, renal, and hepatic) a score from 0–4 for a maximum total score of 24. (21)

APACHE II uses a point scoring system based on initial values for 12 routine physiologic measurements combined with age and previous health status to provide a general measure of severity of disease.(18) The APACHE-II score is used in conjunction with a patient's disease status to predict mortality. Due to its close relationship with clinical outcomes, is often used as a control observation to test the sensitivity and specificity of other scoring systems.

The Glasgow Coma Scale (GCS) score uses a Coma Index, which sums the scores in three areas, including eye-opening response, verbal response and body movement to evaluate the degree of coma of patients.(22, 23) Healthy people have the maximum score of 15, and with scores decreasing by coma severity: ≤ 15 indicates consciousness, 3–8 indicates a coma, and scores < 3 are seen comatose patients who are unable to speak due to intubation.

Clinical Outcomes

The favorable prognosis group was comprised of patients released from the hospital or transferred out of the ICU to recover, while poor prognosis group was defined as the group of patients recalcitrant to treatment or who experienced death as a primary endpoint.

Statistical analysis

Data were statistically analyzed using SPSS 20.0 (IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), and were analyzed by using the Student's *t*-test. Categorical variables, presented as n (%), were compared via the Chi-square test. Logistic regression analysis was employed to differentiate whether mean and initial serum ammonia levels were statistically significant for predicting the prognosis of ICU patients. Univariate logistic regression analyses were used to identify factors with a significant association to prognosis ($P < 0.05$). To evaluate the independence of factors, bidirectional stepwise forward selection was used for multivariate logistic analysis of APACHE II, GCS, lactic acid, TBil, and M-ammonia. The receiver operating characteristic (ROC) curve was drawn, and the area under the curve (AUC) was calculated to assess the prognostic power of APACHE II, M-ammonia, lactic acid and TBil. A P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics and outcomes

We obtained records from 1,895 patients admitted to 11 ICUs across Heilongjiang province. A total 835 were ineligible, of which 143 were less than 18 years old (18%), 187 had CLDs (22%), 234 had acute liver failure (ALF) (28%), 67 were readmissions to the ICU (8%), and 204 failed to provide signed informed consent forms (24%) (Fig. 1). A total of 1060 patients met the inclusion criteria for analysis, and were divided into favorable prognosis (707 (67%); 62.26 ± 17.15 years) and poor prognosis groups (353 (33%); 63.7 ± 14.53 years).

The demographic characteristics of NHH patients included in this study are presented in Table 1. Patients with a poor prognosis had a significantly faster heart rate (95.61 ± 21.85 vs 104.87 ± 24.67 bmp, P = 0.001) and higher levels of lactic acid (1.96 ± 1.88 vs 2.87 ± 2.80 mmol/L, P < 0.001), TBil (15.79 ± 13.70 vs 20.31 ± 18.54, P = 0.004), Crea (126.78 ± 142.12 vs 161.99 ± 183.95, P = 0.005), urea (9.33 ± 6.81 vs 11.58 ± 8.97, P = 0.002), and M-ammonia (25.11 ± 21.35 vs 30.12 ± 23.56, P = 0.001). Surprisingly more patients with a favorable prognosis experienced respiratory failure (131 (18.53%) vs 92 (26.06%), P = 0.005), disturbance of consciousness (175 (24.75%) vs 122 (34.56%), P = 0.005), or underwent surgery (221 (31.26%) vs 41 (11.61%), P < 0.001). Baseline APACHE-II (15 ± 8 vs 21 ± 8, P < 0.001) and SOFA (7 ± 4 vs 9 ± 4, P < 0.001) scores were higher and GCS scores (12 ± 4 vs 10 ± 3, P < 0.001) were lower in the poor prognosis group as compared to the favorable prognosis group. The length of stay in the ICU for patients with poor prognosis was significantly longer than that for patients with favorable = prognosis (3.26 ± 2.33 vs. 4.25 ± 3.14 days, P = 0.008) (Table 1).

Table 1
Baseline characteristics of patients in the ICU with a favorable or poor prognosis.

Variables	Favorable Prognosis (n = 707)	Poor Prognosis (n = 353)	*P-value*
Demography			
Age, years	62.26 ± 17.15	63.7 ± 14.53	0.068
Sex, M	397 (56.15%)	183 (51.84%)	0.389
Harbin (4 center)	392 (55.45%)	208 (58.92%)	0.293
Daqing (3 center)	88 (12.45%)	42 (11.90%)	0.843
Jiamusi (2 center)	121 (17.11%)	53 (15.01%)	0.429
Mudanjiang (2 center)	106 (14.99%)	50 (14.16%)	0.714
Vital signs			
Temperature, ℃	37.00 ± 0.82	37.02 ± 0.84	0.807
HR, bmp	95.61 ± 21.85	104.87 ± 24.67	**0.001**
RR, bmp	20.57 ± 8.58	21.24 ± 8.41	0.414
SBP, mmHg	91.34 ± 45.33	94.10 ± 49.54	0.334
DBP, mmHg	63.55 ± 17.54	63.09 ± 16.90	0.257
MBP, mmHg	72.42 ± 24.03	74.22 ± 36.62	0.305
Laboratory parameters			
PH	7.37 ± 0.24	7.37 ± 0.13	0.911
Na^+, mmol/L	137.83 ± 10.39	137.43 ± 8.54	0.676
K^+, mmol/L	3.97 ± 0.64	3.95 ± 0.72	0.721
Lactic acid, mmol/L	1.96 ± 1.88	2.87 ± 2.80	**0.001**
Serum glucose, mmol/L	8.91 ± 3.41	9.16 ± 4.23	0.130
Leukocyte, $\times 10^9$/L	13.28 ± 8.60	13.96 ± 6.77	0.344

Data were expressed as mean ± SD and n (%). P < 0.05 was considered statistically significant.

NHH, non-hepatic hyperammonemia; M, male; BMI, body mass index; T, temperature; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HCT, hematocrit; TBil, total bilirubin; Crea, Creatinine; ALB, albumin; APACHE-II, acute physiologic assessment and chronic health evaluation II; GCS, glasgow coma scale; SOFA, sequential organ failure assessment; ICU, intensive care unit; H-, M-, and I- separately means the highest-level, the mean-level, the initial-level.

Variables	Favorable Prognosis (n = 707)	Poor Prognosis (n = 353)	*P-value*
Platelet, $\times 10^9$/L	168.26 ± 82.25	165.90 ± 84.05	0.726
HCT, %	35.03 ± 9.69	36.67 ± 14.68	0.140
TBil, mg/dl	15.79 ± 13.70	20.31 ± 18.54	**0.004**
Crea, μmol/L	126.78 ± 142.12	161.99 ± 183.95	**0.005**
Urea, mmol/L	9.33 ± 6.81	11.58 ± 8.97	**0.002**
ALB, g/L	32.52 ± 6.36	32.44 ± 7.56	0.893
Ammonia, μmol/L			
normal	345 (48.80%)	130 (36.83%)	**0.004**
mild-NHH	318 (44.98%)	169 (47.88%)	0.395
severe-NHH	44 (6.22%)	54 (15.30%)	**0.001**
I-Ammonia, μmol/L	29.22 ± 25.10	32.27 ± 21.90	0.051
H-Ammonia, μmol/L	40.65 ± 30.64	43.14 ± 25.31	0.066
M-Ammonia, μmol/L	25.11 ± 21.35	30.12 ± 23.56	**0.001**
Disease type			
Gastrointestinal bleeding	25 (3.54%)	11 (3.12%)	0.213
Sepsis	56 (7.92%)	31 (8.78%)	0.636
Obesity	45 (6.36%)	20 (5.67%)	0.687
Shock	90 (12.73%)	56 (15.86%)	0.185
Respiratory failure	131 (18.53%)	92 (26.06%)	**0.005**
Heart failure	53 (7.50%)	37 (10.48%)	0.103

Data were expressed as mean ± SD and n (%). P < 0.05 was considered statistically significant.

NHH, non-hepatic hyperammonemia; M, male; BMI, body mass index; T, temperature; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HCT, hematocrit; TBil, total bilirubin; Crea, Creatinine; ALB, albumin; APACHE-II, acute physiologic assessment and chronic health evaluation II; GCS, glasgow coma scale; SOFA, sequential organ failure assessment; ICU, intensive care unit; H-, M-, and I- separately means the highest-level, the mean-level, the initial-level.

Variables	Favorable Prognosis (n = 707)	Poor Prognosis (n = 353)	*P-value*
Kidney failure	24 (3.39%)	17 (4.82%)	0.310
Disturbance of consciousness	175 (24.75%)	122 (34.56%)	**0.001**
Poisoning	29 (4.10%)	13 (3.68%)	0.867
Epilepsy	20 (2.83%)	13 (3.68%)	0.457
Surgery	221 (31.26%)	41 (11.61%)	**0.001**
Drug type			
Corticosteroids	89 (12.59%)	48 (7.92%)	0.698
Carbamazepine	11 (1.56%)	5 (1.42%)	0.989
Valproic acid	13 (1.84%)	6 (1.70%)	0.939
Score system			
APACHE-II	15 ± 8	21 ± 8	**0.001**
GCS	12 ± 4	10 ± 3	**0.001**
SOFA	7 ± 4	9 ± 4	**0.001**
Length of ICU stay, days	3.26 ± 2.33	4.25 ± 3.14	**0.008**
Data were expressed as mean ± SD and n (%). P < 0.05 was considered statistically significant.			
NHH, non-hepatic hyperammonemia; M, male; BMI, body mass index; T, temperature; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HCT, hematocrit; TBil, total bilirubin; Crea, Creatinine; ALB, albumin; APACHE-II, acute physiologic assessment and chronic health evaluation II; GCS, glasgow coma scale; SOFA, sequential organ failure assessment; ICU, intensive care unit; H-, M-, and I- separately means the highest-level, the mean-level, the initial-level.			

Blood ammonia levels predict patient prognosis

In univariate competing risk models shown in Table 2, serum level of lactic acid, TBil, APACHE-II, GCS, SOFA, serum ammonia were associated with the poor prognosis of the patients with in ICU (P < 0.05). The multivariate logistic regression analysis model found that lactic acid (OR = 1.83, 95% CI: 1.08–3.09, P = 0.02), TBil (OR = 2.01, 95% CI: 1.11–3.63; P = 0.02), APACHE-II (OR = 3.08, 95% CI: 1.63–5.80, P < 0.001), and SOFA (OR = 2.01, 95% CI: 1.93–4.59, P = 0.02) scores are independent factors associated with poor prognosis. M-Ammonia and other serum ammonia factors were inputted into a multivariate logistic regression analysis to avoid multicollinearity. The results revealed that M-ammonia level in ICU patients was independently associated with a poor prognosis (OR = 1.73, 95% CI: 1.07–2.80, P = 0.02).

Table 2
Univariate and multivariate logistic analysis of risk factors associated with a poor prognosis.

	Univariate analysis			Multivariate analysis		
	OR	**95%CI**	***P-value***	**OR**	**95%CI**	***P-value***
Age, years	1.56	0.89 2.73	0.13			
Sex, M	0.69	0.42 1.11	0.12			
MBP, mmHg	0.60	0.31 1.14	0.13			
Laboratory parameters						
PH	0.98	0.70 1.36	0.89			
Na^+, mmol/L	0.75	0.48 1.18	0.21			
K^+, mmol/L	0.64	0.37 1.10	0.11			
Lactic acid, mmol/L	1.84	1.13 3.00	**0.01**	1.83	1.08 3.09	0.02
Serum glucose, mmol/L	1.24	0.76 2.02	0.40			
Leukocyte, $\times 10^9$/L	0.83	0.49 1.39	0.48			
Platelet, $\times 10^9$/L	0.49	0.26 0.91	0.15			
HCT, %	1.36	0.84 2.20	0.21			
TBil, mg/dl	1.79	1.05 3.07	**0.04**	2.01	1.11 3.63	**0.02**
Crea, μmol/L	1.39	0.83 2.34	0.21			
Urea, mmol/L	1.36	0.84 2.19	0.21			
ALB, g/L	0.98	0.56 1.70	0.93			
I-Ammonia, μmol/L	1.80	1.16 2.80	**0.01**			
H-Ammonia, μmol/L	1.84	1.22 2.79	**< 0.001**			
M-Ammonia, μmol/L	1.99	1.24 3.18	**< 0.001**	1.73	1.07 2.80	**0.02**
Score system						
APACHE-II	4.22	2.50 7.12	**< 0.001**	3.08	1.63 5.80	**< 0.001**
GCS	0.31	0.18 0.52	**< 0.001**	0.52	0.28 1.00	0.05

Data were expressed as OR (95%CI). P < 0.05 was considered statistically significant.

NHH, non-hepatic hyperammonemia; M, male; MBP, mean blood pressure; HCT, hematocrit; TBil, total bilirubin; Crea, Creatinine; ALB, albumin; APACHE-II, acute physiologic assessment and chronic health evaluation II; GCS, glasgow coma scale; SOFA, sequential organ failure assessment; H-, M-, and I- separately means the highest-level, the mean-level, the initial-level.

	Univariate analysis			Multivariate analysis		
	OR	**95%CI**	***P-value***	**OR**	**95%CI**	***P-value***
SOFA	2.47	1.72 5.52	**0.01**	2.01	1.93 4.59	**0.02**
Data were expressed as OR (95%CI). P < 0.05 was considered statistically significant.						
NHH, non-hepatic hyperammonemia; M, male; MBP, mean blood pressure; HCT, hematocrit; TBil, total bilirubin; Crea, Creatinine; ALB, albumin; APACHE-II, acute physiologic assessment and chronic health evaluation II; GCS, glasgow coma scale; SOFA, sequential organ failure assessment; H-, M-, and I- separately means the highest-level, the mean-level, the initial-level.						

Furthermore, the ROC curve analysis for the prognostic power of APACHE-II score, ammonia, lactic acid, TBil level revealed that the value of AUC was 0.714 (P < 0.001), 0.548 (P = 0.004), 0.589 (P = 0.002), 0.560 (P = 0.108). Lactic acid showed highest sensitivity (0.86) and specificity (0.68), followed by APACHE-II (sensitivity: 0.71, specificity: 0.65), ammonia (sensitivity: 0.67, specificity: 0.56). The cut-off point of the APACHE-II score was 15 and ammonia was 36.95 μmol/L for the prediction of poor prognosis, respectively (Fig. 2 and Table 3).

Table 3
ROC for the factors to predict prognosis.

	AUC	**Sensitivity**	**Specificity**	**Cut-off value**	***P-value***
APACHE-II	0.714	0.71	0.65	15	< 0.001
Ammonia, μmol/L	0.548	0.67	0.56	36.95	0.004
Lactic acid, mmol/L	0.589	0.86	0.68	1.35	0.002
TBil, mg/dl	0.560	0.37	0.23	18.3	0.108
APACHE-II, acute physiologic assessment and chronic health evaluation II; TBil, total bilirubin.					

Discussion

This prospective, multicenter study reveals prognostic biomarkers of NHH for critically ill patients who were hospitalized at ICUs, in which 1,060 patients from 11 ICUs were recruited. Our findings indicated that patients with poor prognosis had higher levels of M-Ammonia, and serum lactic acid, ammonia, TBil and APACHE-II scores on admission to ICU were independent predictors of prognosis. Moreover, the SOFA score was common risk factors for ICU patients with poor prognosis.

Increased blood lactic acid and ammonia levels are byproducts of ATP production and associated with higher levels of anaerobic metabolic activity.(24) Critically ill patients are at a higher risk of hyperammonemia because of increased ammonia generation and decreased blood ammonia clearance. Infection by bacteria which rely on urease to hydrolyze urea to carbon dioxide and ammonia, as well as pneumonia, fever, and other stressors may ultimately result in NHH.(25) Further, gastrointestinal bleeding

or steroid hormone-induced damages to the gastrointestinal tract can lead to increased protein breakdown and promote ammonia generation.(26) Moreover, several factors may hinder blood ammonia clearance: (1) acute/chronic liver failure caused by drugs or toxins, infections, and autoimmune diseases, leading to diminished ammonia clearance by the liver; (2) salicylic acid, valproic acid, and other drugs may diminish the mitochondrial function of liver cells and inhibit the activity of rate-limiting enzymes in the urea cycle, causing urea cycle disorders and subsequently increased blood ammonia level; (3) uremia caused by a decreased renal blood flow, glomerular filtration rate, and renal handling of urea in acute kidney injury may result in an increased blood ammonia level.(27) Therefore, a higher blood ammonia level can indicate both loss of hepatic ammonia clearance and a state of disordered energy metabolism.

Changes in energy metabolism are prevalent in critically ill patients admitted to ICU and can lead to a significant increase in blood ammonia levels.(28) However, to date, only a limited number of studies have reported the incidence of NHH. Nonetheless, a prospective study conducted by Prado et al. indicated that the incidence of NHH in patients with severe diseases was as high as 73%, and blood ammonia levels were significantly correlated with the rate of mortality. Our previous research confirmed that an increased serum ammonia level is not only commonly observed in ICU patients, but also is correlated to the disease severity and patient prognosis.(29) However, it is easy to overlook NHH as hyperammonemia is not related to liver disease in these patients. To date, no multicenter, prospective study on NHH patients admitted to ICU has been conducted. Thus, the current research was carried out to eliminate the mentioned clinical gap.

Patients with congestive heart failure often have high blood ammonia levels associated with reduced cardiac function. Recently, Bing et al. hypothesized that treating elevated circulating ammonia levels may prevent and reverse heart failure.(16) Elevated cardiac loads change the metabolic balance and lead to an ammonia surplus eventually causing myocardial cell apoptosis. A therapeutic strategy targeting hyperammonemia can prevent adverse cardiac events in early stages and reverse heart failure in later stages.(13)

It is noteworthy that ammonia is involved in the functional metabolism in multiple organs, such as liver, brain, kidney, muscles, and gastrointestinal tract. Therefore, hyperammonemia can indicate multiple organ dysfunction. It may also be involved in in the pathogenesis of septic shock via inflammatory responses and impaired tissue perfusion.(30, 31) In the present research, we examined whether there could be differences in the different prognosis between distinct types of diseases (e.g., Sepsis, Kidney failure), and no significant differences were identified, consistent with previously reported results in severity of hyperammonemia.(17) This may be attributed to the diverse and complicated etiology of NHH, which indicating the prognosis. Overall energy expenditure and severity of disease are the key factors contributing to the occurrence of NHH.

Our findings demonstrated that patients with poor prognoses had higher levels of average serum ammonia as well as a higher incidence of severe diseases (a higher APACHE-II score) and organ dysfunction (an increased SOFA score), lower level of consciousness, longer period of hospitalization,

and higher costs associated with the length of stay at ICU compared with cases with a favorable prognosis. Our previous single-center study revealed that severe NHH patients (serum ammonia level ≥ 100 μmol/L) required specialized treatments(29). As for the prognosis of patients, the logistic regression and ROC curve analyses demonstrated the competitive power of disease severity (the APACHE-II score) or serum ammonia in predicting a poor prognosis of severe NHH patients. Due to the extremely fast clearance of blood ammonia in the body, about 7.7 h, an occasional increase in the blood ammonia level can only reflect a transient high metabolic state in the body.(32, 33) M-ammonia is defined as continuously increased blood ammonia level, and is accompanied by a high mortality rate, demonstrating that solicitous and continuous monitoring of serum ammonia level is valuable in the prediction of the prognosis of ICU patients.

The serum ammonia level has widely been used as a biomarker for the diagnosis and treatment of liver failure, and for identification of hepatic associated with hyperammonemia.(34) Treating high serum ammonia levels effectively restores consciousness, attenuates the incidence of cerebral edema, and improves overall morbidity and mortality. However, the clinical significance of NHH as a prognostic indicator has long been neglected. The present study reveals that an elevated serum ammonia level is indicator of disease severity and prognosis in patients without liver diseases. At present, the majority of commonly used ammonia-lowering drugs are targeted at hyperglycemia-related hyperammonemia and hepatic encephalopathy caused by liver diseases.(35, 36) Thus, further research is warranted to indicate whether they improve outcomes in NHH patients.

Several limitations in the present study must be acknowledged. First, as our study enrolled heterogenous patients with normal or hyperammonemia, the causal relationship between non-hepatic hyperammonemia and poor outcome cannot be fully determined based on the present study. As we recruited patients from more than 10 centers, inter-center consistency needs to be considered. Expectedly, although NHH is a common metabolic disorder in daily ICU practice, its incidence varies among different medical centers. This may be explained by the differences in the number of participants, detection instruments and protocols, and prevalence of underlying diseases. Furthermore, since hyperammonemia was frequent in patients who died in the hospital, it is possible that early death (before ammonia measurement) could have led to further underreporting.

Conclusions

High blood ammonia level is frequent among patients who have been admitted to ICU, and is an independent predictor of the patients' clinical prognosis. Evaluating levels of M-ammonia in the blood may improve prediction of disease prognosis in ICU patients.

Abbreviations

NHH

Non-hepatic hyperammonemia; ICU:Intensive care unit; APACHE-II:Acute Physiologic Assessment and Chronic Health Evaluation II; SOFA:Sequential Organ Failure Assessment; GCS:Glasgow Coma Scale; ALF:Acute liver failure; CLD:Chronic liver disease; SD:Standard deviation; ANOVA:One-way analysis of variance; ROC:Receiver operating characteristic; AUC:Area under the curve; CNS:Central nervous system; H-:high-level; M-:mean-level; I-:initial-level; L-:low-level

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of each allied center (approval number KY2019-184), and signed informed consent forms wereaa collected from all study subjects or their families.

Consent for publication

Written informed consent was obtained from the patient for publication. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Li Y, Yao ZP, and Wang HL designed the research; Li Y, Yao ZP and Wang HL performed the research; Yao ZP analyzed the data; Li Y wrote the paper; Li YL, Yang ZY, Li M, Chen ZD, Liu SJ, Gong JG, Huang LB, Xu P, Li Y, Li HH, Liu X, Zhang L, Zhang GX collected data.

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Figures

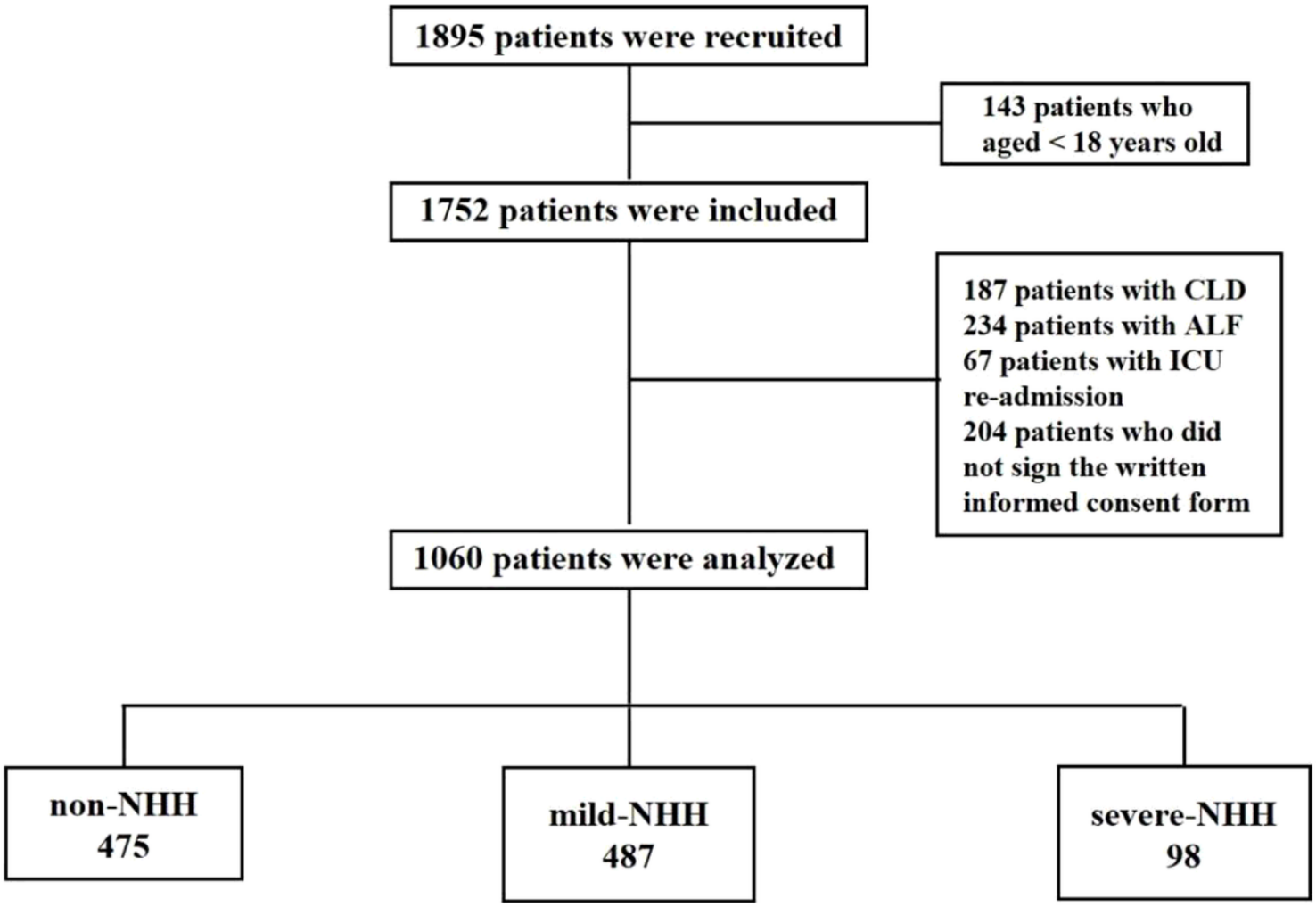

Figure 1

Flowchart of the patients involved in the study.

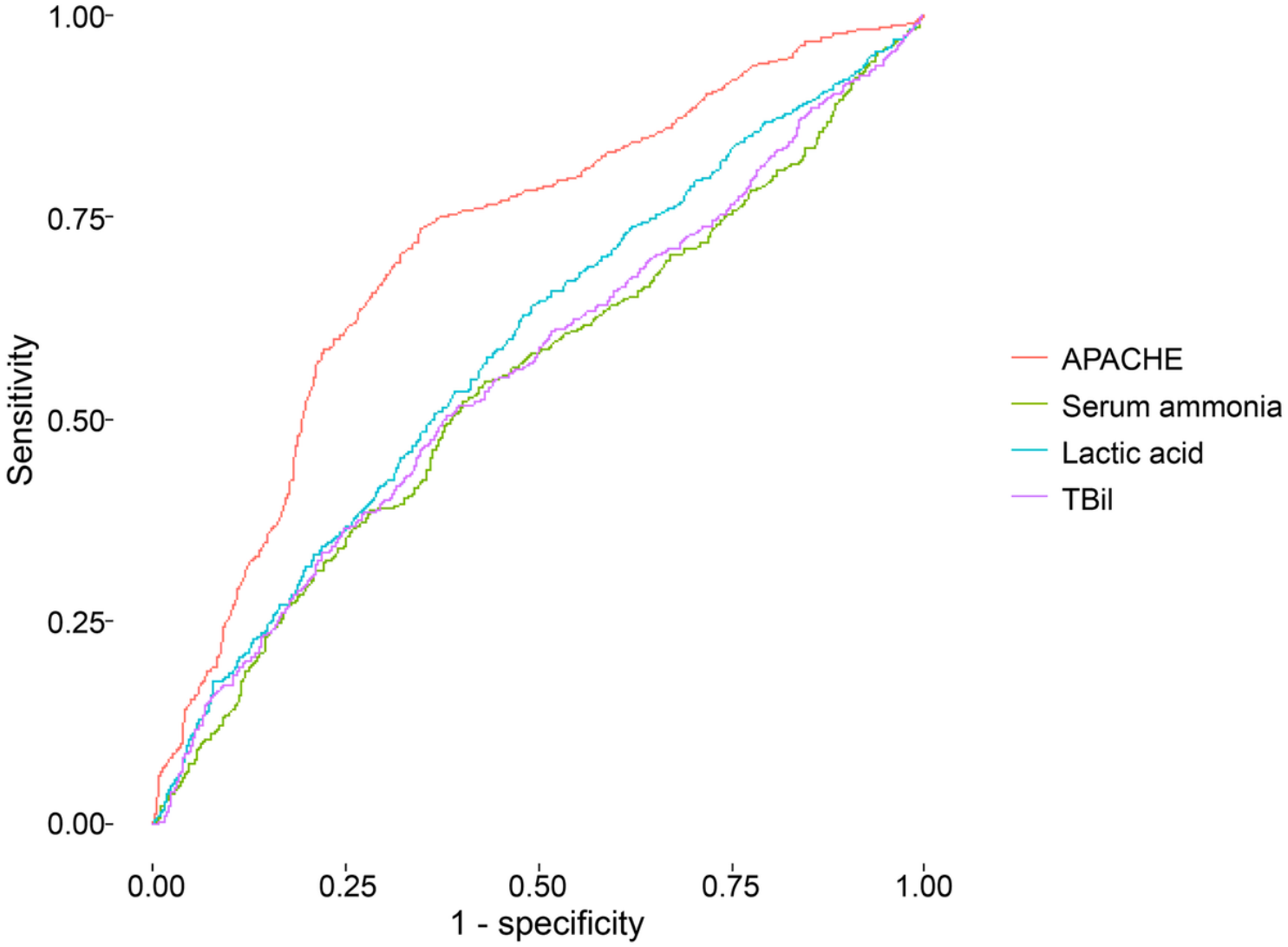

Figure 2

ROC predicting the risk of poor prognosis in ICU critically ill patients without liver disease.