

# Impact of Non-Hepatic Hyperammonemia on Mortality in Intensive Care Unit Patients: A Retrospective Cohort Study

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## Research

**Keywords:** hyperammonemia, non-hepatic disease, intensive care unit, acute brain failure, mortality

**Posted Date:** December 17th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-129350/v1>

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## Abstract

**Background:** The effect of hyperammonemia on the mortality in patients with liver cirrhosis is well documented. However, little is known about the impact of hyperammonemia on mortality in intensive care unit patients without hepatic disease. We aimed to investigate factors associated with non-hepatic hyperammonemia in intensive care unit patients and evaluate the factors related to 90-day mortality.

**Methods:** Between February 2016 and February 2020, 972 cases in 948 intensive care unit patients without hepatic disease were retrospectively enrolled and classified as hyperammonemia grades 0 ( $\leq 80$   $\mu\text{g}/\text{dL}$ ; n=585 (60.2%)), 1 ( $\leq 160$   $\mu\text{g}/\text{dL}$ ; n=291 (29.9%)), 2 ( $\leq 240$   $\mu\text{g}/\text{dL}$ ; n=55 (5.7%)), and 3 ( $> 240$   $\mu\text{g}/\text{dL}$ ; n=41 (4.2%)). Factors associated with hyperammonemia and 90-day mortality were evaluated by multivariate logistic regression analysis and Cox regression analysis, respectively. Kaplan-Meier survival curves for 90-day mortality were constructed.

**Results:** The independent risk factors for hyperammonemia were male sex (odds ratio, 1.517), age (0.984 per year), acute brain failure (2.467), acute kidney injury (1.437), prothrombin time-international normalized ratio (2.272 per unit), and albumin (0.694 per g/dL). The 90-day mortality rate in the entire cohort was 24.3% and gradually increased with increasing hyperammonemia grade at admission (17.9%, 28.2%, 43.6%, and 61.0% in patients with grades 0, 1, 2, and 3, respectively). Additionally, non-hepatic hyperammonemia was an independent predictor of 90-day mortality in intensive care unit patients.

**Conclusions:** Non-hepatic hyperammonemia is common (39.8%) and associated with 90-day mortality in intensive care unit patients. Therefore, clinicians must examine serum ammonia levels in patients before admission to intensive care unit.

## Background

Hyperammonemia is defined as a raised level of serum ammonia, a nitrogen-containing compound. In adults, this is associated with liver cirrhosis in 90% of cases [1]. Hepatic hyperammonemia may play a central role in the development of acute life-threatening encephalopathy that can lead to cerebral edema, brain stem herniation, and death [2]. In a recent study, serum ammonia level was correlated to encephalopathy severity and was an independent predictor of mortality in patients with liver cirrhosis [3]. Hepatic hyperammonemia has neurotoxic effects and causes inflammation and injury to several organs. [4] In general, hyperammonemia directly causes hepatic injury, immune system dysfunction, and hepatic stellate cell activation [5-8].

On the other hand, serum ammonia levels can be increased by non-hepatic factors. Hyperammonemia may occur from either increased ammonia production or decreased ammonia elimination. The etiology of increased ammonia production includes infection [9, 10], hematologic malignancy [11, 12], organ transplantation [13], and protein load and increased catabolism. Protein load and increased catabolism arise due to seizures, trauma, intensive exercise, starvation, steroid use, total parenteral nutrition (TPN), and gastrointestinal (GI) bleeding [14-17]. The etiology of decreased ammonia elimination includes

portosystemic shunts [18], uretersigmoidostomy [19], drugs (valproate and carbamazepine) [20, 21], and inborn errors of metabolism [22].

Most patients with non-hepatic hyperammonemia present with confusion and coma [23, 24]. Non-hepatic hyperammonemia in intensive care unit (ICU) patients has especially high morbidity and mortality [25, 26]. There are several reviews and case reports on hyperammonemia in non-hepatic disease and ICU patients, but large observational studies on non-hepatic hyperammonemia are limited [24, 26]. Fabrizio et al. reported that ammonia levels affect the mortality rates of ICU patients with non-hepatic disease and were correlated with mortality by univariate analysis using the chi-square test in 100 patients with non-hyperammonemia [26]. Additionally, no significant factors associated with non-hepatic hyperammonemia were found in the Cox regression analysis.

This retrospective large observational cohort study was designed to evaluate the characteristics of ICU patients with non-hepatic hyperammonemia. This study aimed to investigate factors associated with non-hepatic hyperammonemia in ICU patients and elucidate whether ammonia levels affect mortality of ICU patients with non-hepatic diseases.

## Materials And Methods

### Study population

This retrospective study included 4,205 cases in 3,767 critically ill patients consecutively admitted to the Gyeongsang National University Changwon Hospital (GNUCH) ICU from February 2016 to February 2020. The exclusion criteria were as follows: (1) patient ammonia levels were not measured ( $n=2,973$ ); (2) hyperbilirubinemia ( $> 2 \text{ mg/dL}$ ;  $n=207$ ); (3) liver cirrhosis ( $n=21$ ); (4) hepatitis A, B, or C virus infections ( $n=9$ ); (5) liver cancer ( $n=6$ ); (6) portosystemic shunt ( $n=2$ ); and (7) age  $< 18$  years ( $n=15$ ). The remaining 972 cases in 948 patients admitted to the ICU whose ammonia levels were measured were finally selected for analysis (Additional file 1: Figure S1). The study was approved by the institutional review board of GNUCH.

### Data collection

The patients' medical histories were reviewed to gather demographic data, including age; sex; body mass index; alcohol consumption; concomitant diseases, such as diabetes, congestive heart failure, extrahepatic malignancy, and end-stage renal disease; and laboratory data, including total bilirubin, white blood cell (WBC), hemoglobin, creatinine, albumin, total cholesterol, and prothrombin time-international normalized ratio (PT-INR).

Ammonia levels were measured with the Beckman Coulter AU 5800 clinical chemistry analyzer (Beckman Coulter, Brea, CA, USA). The normal blood ammonia level for an adult is  $\leq 80 \text{ } \mu\text{g/dL}$  using this device. Therefore, we defined hyperammonemia as an ammonia level  $> 80 \text{ } \mu\text{g/dL}$ . Additionally, we extracted information on potential risk factors for hyperammonemia: generalized seizures; hematologic

malignancy; acute kidney injury (AKI); GI bleeding; gastric bypass surgery; TPN; infection; trauma; and intake of drugs, such as valproate, carbamazepine, proton pump inhibitor (PPI), and steroids.

## Follow-up and definition

Medical charts were retrospectively reviewed to determine 90-day mortality and non-hepatic hyperammonemia at admission. The index date was the date of first admission to the ICU. Hyperammonemia grades were defined as follows (serum ammonia concentrations in parentheses): (1) grade 0 as patients without hyperammonemia ( $\leq 80 \text{ } \mu\text{g/dL}$ ); (2) grade 1 as ammonia levels 1 to 2 times the upper limit of normal (ULN) ( $81\text{--}160 \text{ } \mu\text{g/dL}$ ); (3) grade 2 as ammonia levels 2 to 3 times the ULN ( $161\text{--}240 \text{ } \mu\text{g/dL}$ ); and (4) grade 3 as ammonia levels  $> 3$  times the ULN ( $> 240 \text{ } \mu\text{g/dL}$ ). Further, AKI was defined as an absolute increase in serum creatinine by  $\geq 0.3 \text{ mg/dL}$  or  $\geq 50\%$  from baseline within 48 hours [27]. Acute brain failure was defined as a Glasgow Coma Scale (GCS) score less than 15 or a Full Outline of UnResponsiveness (FOUR) score less than 16 [28].

## Statistical analysis

Continuous variables are expressed as medians (interquartile range). The Mann-Whitney *U* test was performed to analyze quantitative data. The Fisher's exact and Pearson's chi-square tests were used for qualitative data. The factors associated with hyperammonemia were evaluated using a multivariate logistic regression model after adjusting for potential confounding variables. Risk analysis was performed by calculating the odds ratio (OR) and the 95% confidence interval (CI). Kaplan-Meier survival curves for 90-day mortality were constructed and compared using the log-rank test. Univariate and multivariate analyses were conducted using a Cox proportional regression model to identify potential factors associated with 90-day mortality. Risk was expressed as hazard ratios (HRs) and 95% CIs. A two-sided *P* value  $< 0.05$  was considered statistically significant for all analyses. All statistical operations were performed using PASW Statistics, version 18 (SPSS Inc., Chicago, IL, USA).

# Results

## Patient characteristics

A total of 972 cases from 948 ICU patients whose ammonia levels were measured were identified (Table 1). Hyperammonemia cases (585, 60.2%) were from significantly younger patients (median age, 66.0 years) than the patients with the 387 (39.8%) cases without hyperammonemia (median age, 69.0 years, *P* = 0.003). The proportion of men was higher among patients with hyperammonemia (59.7%) than among patients without hyperammonemia (47.9%, *P* < 0.001). Additionally, the proportions of endotracheal intubation and acute brain failure among patients with hyperammonemia were higher than those among patients without hyperammonemia. However, there were no significant differences between patients with and without hyperammonemia in the rates of diabetes, alcohol consumption  $> 40 \text{ g/day}$ , congestive heart failure, and end-stage renal disease. Laboratory findings revealed that patients with hyperammonemia

had higher ammonia, WBC, creatinine, and PT-INR levels but lower albumin and total cholesterol levels than patients without hyperammonemia.

### Potential factors associated with hyperammonemia

The rates of AKI, TPN, and infection were higher in patients with than in those without hyperammonemia (Additional file 1: Table S1). However, there were no significant differences between patients with and without hyperammonemia in the rates of generalized seizures, hematologic malignancy, GI bleeding, gastric bypass surgery, trauma, and drugs, such as valproate/carbamazepine, PPI, and steroids.

Additional file 1: Figure S2 shows the distribution of potential risk factors in the different hyperammonemia grades. Patients with AKI causing impaired urea excretion comprised 26.8%, 33.3%, 58.2%, and 68.3% of patients with hyperammonemia grades 0, 1, 2, and 3, respectively. Patients with infection causing urease-producing organism comprised 36.1%, 43.3%, 52.7%, and 52.1% of patients with hyperammonemia grades 0, 1, 2, and 3, respectively. Most patients (66.4%) in our cohort had acute brain failure, meaning decreased levels of consciousness. Serum ammonia levels were significantly and closely dependently associated with acute brain failure (Figure 1A). Patients with acute brain failure comprised 58.6%, 74.6%, 85.5%, and 92.7% of patients with hyperammonemia grades 0, 1, 2, and 3, respectively. At admission albumin was associated inversely, but WBC and PT-INR had a parallel relationship with ammonia levels (Additional file 1: Figure S3).

Univariate analysis showed that male sex, age, acute brain failure, AKI, infection, WBC, PT-INR, total cholesterol, and albumin were related to hyperammonemia (Table 2). On multivariate analysis, the independent factors for hyperammonemia were male sex, age, acute brain failure, AKI, PT-INR, and albumin (Table 2).

### Impact of ammonia level on 90-day mortality

The median ICU and hospital lengths of stay were 4.0 and 15.0 days, respectively. In our entire cohort, the 90-day mortality rate was 24.3%. The median ammonia level in non-survivors was higher than that of survivors (87.0 vs. 68.0 µg/dL,  $P < 0.001$ ). A strong stepwise association was observed between hyperammonemia severity and 90-day mortality (Figure 1B). The patients with grade 0 hyperammonemia (17.9%) had a lower 90-day mortality than those with grades 1 ( $28.2\%$ ,  $P < 0.001$ ), 2 ( $43.6\%$ ,  $P < 0.001$ ), and 3 ( $61.0\%$ ,  $P < 0.001$ ) (Figure 2).

The factors associated with 90-day mortality on univariate analysis were age; hyperammonemia grades 1, 2, and 3; acute brain failure; diabetes; extrahepatic malignancy; AKI; infection; platelet count; PT-INR; total cholesterol; and albumin (Table 3). The factors associated with 90-day mortality in the final multivariate analysis included age; hyperammonemia grades 1, 2, and 3; acute brain failure; platelet count; and albumin (Table 3).

## Discussion

This large retrospective observational study included patients whose ammonia levels were measured in the ICU. We found that the prevalence of non-hepatic hyperammonemia in the ICU was 39.8%. The 90-day mortality of patients with hyperammonemia was higher than that of those without hyperammonemia (33.9% vs. 17.9%,  $P < 0.001$ ). Additionally, the 90-day mortality rate was closely dependent and was affected by ammonia levels. This study showed that male sex, age, acute brain failure, AKI, PT-INR, and albumin are independent risk factors for the development of non-hepatic hyperammonemia. The occurrence of non-hepatic hyperammonemia in the ICU was an independent risk factor for 90-day mortality. In particular, non-hepatic hyperammonemia grade at admission correlated directly with adjusted 90-day mortality, and hyperammonemia grades were independent predictors of 90-day mortality.

Hyperammonemia results from increased ammonia production, decreased ammonia elimination, or both. Ammonia metabolism involves mainly five organs: liver, gut, kidney, muscle, and brain. Ammonia is produced primarily in the GI tract, but also in the kidneys and muscles [29]. Blood ammonia is metabolized to urea through the urea cycle in the liver. When the capacity of the liver to eliminate ammonia is overcome, ammonia metabolism is dependent on the kidney, muscles, and brain [30]. In the case of hyperammonemia, the kidney increases urinary excretion of ammonia. When the capacity of the kidney to metabolize ammonia is overwhelmed due to AKI, advanced hyperammonemia develops. Serum ammonia levels can be increased as a result of changes in acid-base status and GI bleeding [31]. In the case of increased muscle catabolism, through seizures, intense exercise, starvation, steroid use, or trauma, ammonia production increases. Moreover, TPN can lead to hyperammonemia by providing more protein to patients than usually consumed enterally [32]. It is well documented that drug-induced non-hepatic hyperammonemia is caused by valproate, carbamazepine, and PPI [33].

Male sex, age, acute brain failure, AKI, PT-INR, and albumin were associated with non-hepatic hyperammonemia in ICU patients. These factors are thought to reflect protein load, increased catabolism, or decreased ammonia elimination. Ammonia balance is controlled by a fine equilibrium, which may be affected by age. A positive correlation between ammonia level and age was previously reported [34]. However, the present study found that the adjusted OR (0.984 per year) for hyperammonemia decreased with age. This phenomenon is difficult to explain clearly, but ammonia metabolism could have been affected in the critically ill patients comprising our cohort. Acute brain failure, which entails a decreased level of consciousness, including cognitive impairment, abnormal neuropsychological test, and cerebral edema and herniation, reflects hyperammonemia. Because of the limitation of the retrospective nature of this study, we defined acute brain failure as a GCS score  $< 15$  or FOUR score  $< 16$  [28]. Patients with acute brain failure in our cohort consisted of patients with abnormal GCS (recorded at hospitalization in all ICU patients) or FOUR (mainly those undergoing endotracheal intubation or exhibiting abnormal respiration, confirmed through retrospective chart review) scores. A significant positive correlation was observed between grades of hyperammonemia and the rate of acute brain failure: prevalence of acute brain failure was 58.6%, 74.6%, 85.5%, and 92.7% in patients with hyperammonemia grades 0, 1, 2, and 3, respectively.

Few studies are available on the impact of non-hepatic hyperammonemia on mortality in ICU patients [24, 26]; Amra et al. found that serum ammonia levels in 167 ICU patients with non-hepatic hyperammonemia

were not associated with increased mortality. However, they did not compare patients with hyperammonemia with patients with normal ammonia levels [24]. Fabrizio et al. found that mortality rates in 100 ICU patients were significant among patients with mild and moderate non-hepatic hyperammonemia and those without non-hepatic hyperammonemia. However, they demonstrated a correlation only in univariate analysis because of the small number of patients. To the best of our knowledge, the present study demonstrated for the first time that non-hepatic hyperammonemia is an independent predictor of 90-day mortality using multivariate analysis in a large population of ICU patients. The 90-day mortality rate gradually increased with increasing hyperammonemia grades at admission. Additionally, we found approximately 0.3-, 1.2-, and 3.1-fold increases in the risk of 90-day mortality in ICU patients with hyperammonemia grades 1, 2, and 3, respectively, than that in patients without hyperammonemia. In previous studies involving cirrhotic patients, serum ammonia levels correlated with the severity of hepatic encephalopathy and were an independent risk factor for mortality [3, 35]. Our study showed that hyperammonemia is a significant predictor of mortality in ICU patients without hepatic disease.

The present study has a few limitations because of its retrospective nature. Of the 4,205 cases screened in the ICU, 2,973 cases from patients whose ammonia levels were not measured at admission were excluded. Of the 972 cases finally selected, we were unable to collect serial ammonia data after the initial ammonia level check. Therefore, we could not assess response to hyperammonemia treatment for prognosis. Further, our results did not show arterial ammonia levels, which do not usually correlate with venous ammonia levels (venous ammonia levels vary locally) [36]. However, Ong et al. found that venous and arterial ammonia levels were similar in their correlation with encephalopathy severity [35]. Despite these limitations, the present study was conducted in a large population of ICU patients, and clearly showed a significant correlation between hyperammonemia grades and 90-day mortality.

## Conclusions

Male sex, younger age, acute brain failure, AKI, prolonged PT-INR, and decreased albumin levels were associated with hyperammonemia in ICU patients without hepatic disease. Our observations suggest that hyperammonemia occurs commonly in ICU patients without hepatic disease and has a significant effect on 90-day mortality. Additionally, classification of hyperammonemia grades as in the present study may help predict prognosis for ICU patients with non-hepatic disease.

## Abbreviations

ICU, intensive care unit; OR, odds ratio; TPN, total parenteral nutrition; GI, gastrointestinal; GNUBH, Gyeongsang National University Changwon Hospital; WBC, white blood cell; PT-INR, prothrombin time-international normalized ratio; AKI, acute kidney injury; PPI, proton pump inhibitor; ULN, upper limit of normal; GCS, Glasgow Coma Scale; FOUR, Full Outline of UnResponsiveness; CI, confidence interval; HR, hazard ratio.

# Declarations

## Ethics approval and consent to participate

The study was approved by the institutional review board of Gyeongsang National University Changwon Hospital (IRB File No. 2020-11-011). Informed consent was waived given that all of the personal data obtained were anonymized before analysis.

## Consent for publication

Not applicable.

## Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to ethical and confidentiality reasons but are available from the corresponding author on reasonable request under the Gyeongsang National University Changwon Hospital and Gyeongsang National University Hospital Ethics Committee's approval. The data that support the findings of this study are available on request to the correspondence author. (Sang Soo Lee, Email:3939lee@naver.com)

## Competing interests

The authors declare that they have no competing interests.

## Funding

There was no financial support for this study.

**Authors' Contributions:** SSL conceived and designed the study. JHK, HJ, HeeJK, RRC, HyunJK, and JML performed data collection. JHK and HJ performed data analysis and interpretation. JHK, HJ, and SSL wrote the initial version, and all authors edited, contributed, and approved the final version of this manuscript. All authors read and approved the final manuscript.

## Acknowledgements

We would like to thank Editage ([www.editage.co.kr](http://www.editage.co.kr)) for English language editing. There was no financial support for writing assistance.

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## Tables

Table 1. Baseline characteristics at admission according to the initial ammonia level

Characteristics	Overall	Normal ammonia	High ammonia	P
No.	972 (100%)	585 (60.2%)	387 (39.8%)	
Age, year	68.0 (55.0 - 77.8)	69.0 (57.0 - 78.0)	66.0 (54.0 - 76.0)	0.003
Male gender	511 (52.6%)	280 (47.9%)	231 (59.7%)	<0.001
BMI, m/kg <sup>2</sup>	23.1 (20.6 - 25.6)	23.1 (20.7 - 25.5)	23.1 (20.2 - 25.7)	0.790
Diabetes	286 (29.4%)	168 (28.7%)	118 (30.5%)	0.566
Alcohol > 40 g/day	44 (4.5%)	24 (4.1%)	20 (5.2%)	0.435
CHF	42 (4.3%)	24 (4.1%)	18 (4.7%)	0.748
ESRD	33 (3.4%)	19 (3.2%)	14 (3.6%)	0.857
Extrahepatic malignancy	52 (5.3%)	28 (4.8%)	24 (6.2%)	0.383
Endotracheal intubation	504 (51.9%)	253 (43.2%)	251 (51.9%)	<0.001
Acute brain failure	645 (66.4%)	343 (58.6%)	302 (78.0%)	<0.001
Serum ammonia, $\mu/dL$	72.0 (54.0 - 101.0)	58.0 (46.0 - 68.0)	111.0 (92.0 - 160.0)	<0.001
WBC, $10 \times 10^9/L$	12.0 (7.9 - 16.5)	11.3 (7.8 - 15.3)	13.1 (8.0 - 18.1)	0.001
Hemoglobin, g/dL	12.4 (10.6-13.9)	12.5 (10.7-13.8)	12.3 (10.4 - 14.1)	0.993
Platelet, $\times 10^9/L$	222.0 (168.0 - 275.7)	222.0 (172.0 - 269.0)	223.0 (160.0 - 286.0)	0.753
Creatinine, mg/dL	0.93 (0.65 - 1.48)	0.86 (0.65 - 1.33)	1.03 (0.67 - 1.80)	0.001
Bilirubin, mg/dL	0.68 (0.50 - 0.93)	0.68 (0.51 - 0.91)	0.68 (0.48 - 1.00)	0.962
Albumin, g/dL	3.6 (2.9-4.1)	3.8 (3.1 - 4.2)	3.3 (2.8 - 3.9)	<0.001
Total cholesterol, mg/dL	153.0 (116.0 - 189.0)	159.0 (123.0 - 196.5)	145.0 (112.0 - 179.0)	<0.001
PT-INR	1.07 (0.99-1.25)	1.04 (0.98 - 1.16)	1.15 (1.03 - 1.37)	<0.001

Abbreviation: BMI, body mass index; CHF, congestive heart failure; ESRD, end-stage renal disease; WBC, white blood cell; PT-INR, prothrombin time- international normalized ratio.

P: Mann-Whitney U-test and Chi-squared test.

Data are presented as the median (interquartile range) for continuous data and percentages for categorical data.

Table 2. Univariate and multivariate analyses showing significant associated factors of hyperammonemia (n=972)

Variable	Univariate analysis		Multivariate analysis	
	P	OR (95% CI)	P	OR (95% CI)
Male	<0.001	1.613 (1.244 - 2.092)	0.004	1.517 (1.138 - 2.021)
Age, per year	0.006	0.988 (0.980 - 0.997)	0.001	0.984 (0.974 - 0.993)
Acute brain failure	<0.001	2.507 (1.873 - 3.355)	<0.001	2.467 (1.812 - 3.359)
AKI	<0.001	1.861 (1.416 - 2.445)	0.027	1.437 (1.041 - 1.982)
Infection	0.003	1.478 (1.138 - 1.921)	0.771	0.950 (0.672 - 1.342)
WBC per $10 \times 10^9/L$	0.001	1.031 (1.013 - 1.050)	0.126	1.015 (0.996 - 1.035)
PT-INR	<0.001	3.350 (2.156 - 5.207)	<0.001	2.272 (1.473 - 3.506)
Total cholesterol per $mg/dL$	<0.001	0.996 (0.993 - 0.998)	0.788	1.000 (0.997 - 1.004)
Albumin per $g/dL$	<0.001	0.642 (0.544 - 0.757)	0.002	0.694 (0.549 - 0.878)

Abbreviation: OR, odds ratio; CI, confidence interval; AKI, acute kidney injury; TPN, total parenteral nutrition; WBC, white blood cell; PT-INR, prothrombin time- international normalized ratio.

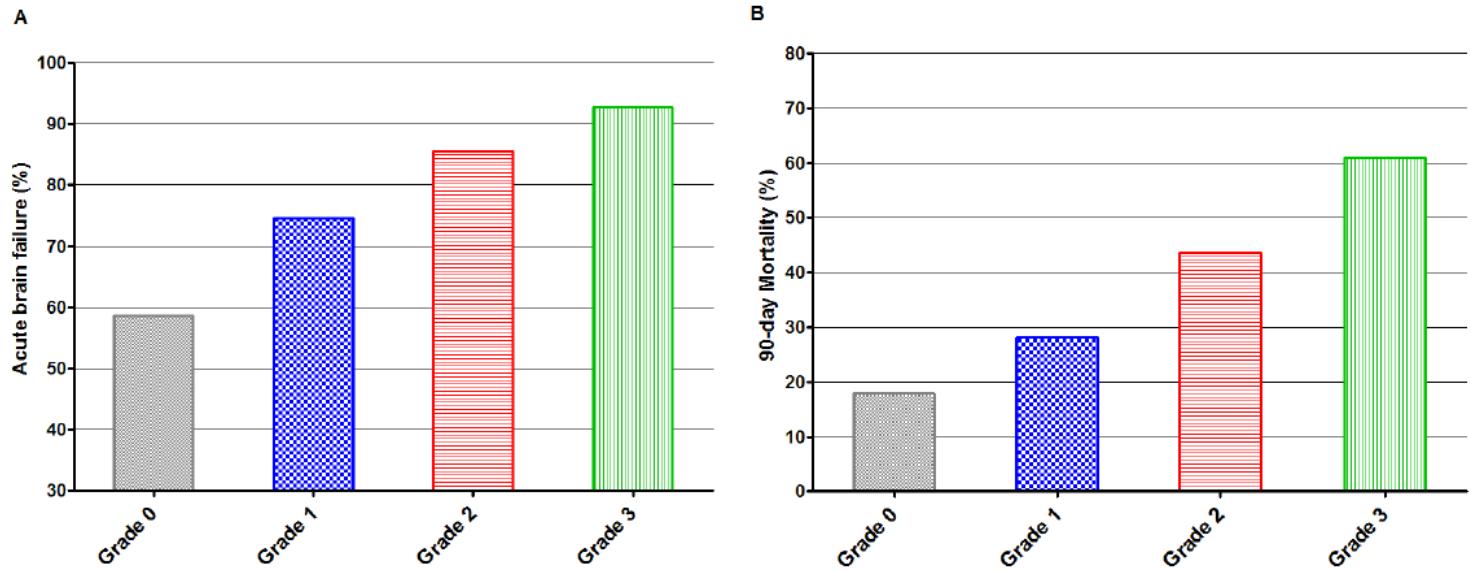
Table 3. Univariate and multivariate analyses showing significant predictive factors of 90-days mortality (n=972)

Variable	Univariate analysis		Multivariate analysis	
	P	HR (95% CI)	P	HR (95% CI)
Age, per year	<0.001	1.025 (1.015 - 1.035)	<0.001	1.025 (1.014 - 1.035)
*Ammonia level				
Grade 0	Reference			
Grade 1	0.001	1.623 (1.216 - 2.167)	0.037	1.372 (1.019 - 1.847)
Grade 2	<0.001	3.039 (1.950 - 4.738)	0.001	2.158 (1.345 - 3.463)
Grade 3	<0.001	4.988 (3.220 - 7.724)	<0.001	4.145 (2.594 - 6.623)
Acute brain failure	<0.001	3.461 (2.406 - 4.978)	<0.001	3.026 (2.085 - 4.390)
Diabetes	0.004	1.475 (1.132 - 1.921)	0.572	1.084 (0.820 - 1.433)
Extrahepatic malignancy	0.006	1.859 (1.198 - 2.882)	0.157	1.392 (0.880 - 2.201)
AKI	<0.001	1.663 (1.285 - 2.154)	0.771	1.044 (0.779 - 1.400)
Infection	<0.001	2.087 (1.614 - 2.699)	0.087	1.302 (0.963 - 1.762)
Platelet, $\times 10^9/L$	0.005	0.998 (0.996 - 0.999)	0.003	0.998 (0.997 - 0.999)
PT-INR per unit	0.005	1.146 (1.042 - 1.261)	0.789	0.978 (0.829 - 1.153)
Total cholesterol per mg/dL	<0.001	0.994 (0.992 - 0.997)	0.964	1.000 (0.997 - 1.003)
Albumin per g/dL	<0.001	0.559 (0.484 - 0.647)	0.001	0.714 (0.582 - 0.876)

Abbreviation: HR, hazard ratio; CI, confidence interval; AKI, acute kidney injury; PT-INR, prothrombin time-international normalized ratio.

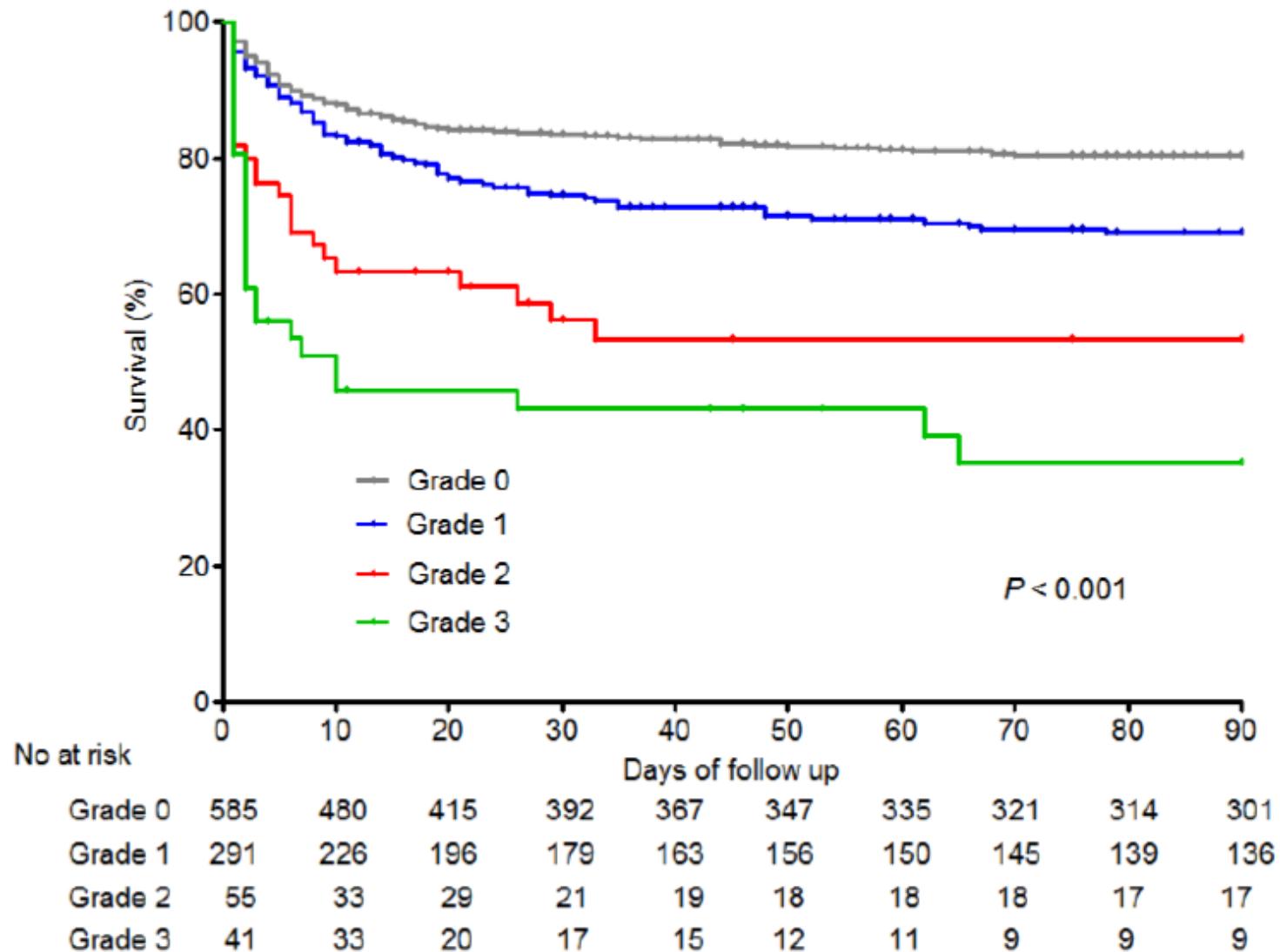
\*Ammonia level: Grade 0  $\leq$  80  $\mu\text{mol}/\text{dL}$ , 80  $\mu\text{mol}/\text{dL} <$  Grade 1  $\leq$  160  $\mu\text{mol}/\text{dL}$ , 160  $\mu\text{mol}/\text{dL} <$  Grade 2  $\leq$  240  $\mu\text{mol}/\text{dL}$ , and Grade 3  $>$  240  $\mu\text{mol}/\text{dL}$ .

## Figures



**Figure 1**

Rates of acute brain failure and 90-day mortality based on initial ammonia levels at admission (n=972).



## **Figure 1**

Kaplan-Meier survival curves for 90-day mortality according to initial ammonia levels (n=972).

## **Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalfileFigureS3.tif
- AdditionalfileFigureS2.tif
- AdditionalfileFigureS1.tif
- AdditionalfileTableS1.docx