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β2-microglobulin is an independent indicator of acute kidney injury and outcomes in patients with intracerebral hemorrhage

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Abstract

Acute kidney injury (AKI), a serious complication in critically ill patients, is associated with poor clinical outcomes. We explored the hypothesis that β2-microglobulin (β2-MG) is an independent indicator of AKI development and outcomes in patients with intracerebral hemorrhage (ICH) in the neurosurgical intensive care unit (NICU).

Patients with ICH (n = 403) admitted to the NICU of Zhongnan Hospital, Wuhan University, between January 1, 2015 and December 31, 2016 were prospectively enrolled in this single-center, observational study. The primary outcome was the incidence of AKI, secondary outcomes were in-hospital mortality and 1-year mortality (from time of admission).

The overall AKI incidence, in hospital, was 35.2%; patients were diagnosed with stage 1 (22.1%), 2 (5.7%), and 3 (7.4%) AKI. β2-MG levels predicted AKI with an area under the curve of 0.712 (95% confidence interval [CI], 0.652–0.772) and a cut-off of 2026.85 μg/L (sensitivity, 57.5%; specificity, 79.4%). Compared with the group having lower β2-MG values, the group with higher values (β2-MG >2123.50 μg/L) had significantly higher risks of AKI (odds ratio, 2.606; 95% CI, 1.315–5.166), in-hospital mortality (hazard ratio [HR], 2.548; 95% CI, 1.318–4.924), and 1-year mortality (HR, 3.161; 95% CI, 1.781–5.611) in adjusted analyses.

β2-MG levels predict AKI development and outcomes in patients with ICH in the NICU.

Abbreviations: β2-MG = β2-microglobulin, AKI = acute kidney injury, APACHE II = acute physiology and chronic health evaluation II score, AUC = area under curve, CART = classification and regression tress, CHAID = Chi-square automatic interaction detection, CI = confidence intervals, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, ESRD = end-stage kidney disease, ICH = intracerebral hemorrhage, KDIGO = kidney disease improving global outcomes, NICU = neurosurgical intensive care unit, OR = odds ratio, ROC = receiver operating characteristic curve.

Keywords: β2-microglobulin, acute kidney injury, intracerebral hemorrhage, prognosis

1. Introduction

Intracerebral hemorrhage (ICH) is a critical disease, and acute kidney injury (AKI) is a common and serious disorder in critically ill patients that confers a high risk of chronic kidney disease (CKD) that may progress to end-stage renal disease (ESRD) and death.[1–4] A few studies have suggested that AKI is a more common complication in patients with ICH than in those with other types of stroke. However, the data relating AKI risk with ICH are limited.[5,6] Despite increased knowledge regarding the management of critically ill patients, the major obstacle to improving the clinical prognoses of patients with ICH and AKI is the inability to recognize patients at high risk of developing AKI and then to provide early-stage interventions. Despite its limitations, serum creatinine levels remain the clinical parameter used to define AKI. In fact, a rise in the serum creatinine level may not truly reflect kidney damage due to the many confounding factors, such as age, sex, muscle mass, and others. In early-stage AKI, nephron damage may precede changes in serum creatinine levels[7–10]; therefore, a new biomarker that predicts early-stage kidney injury is needed.

β2-microglobulin (β2-MG) is an 11.8 kDa, nonglycosylated polypeptide that is present in all nucleated cells[11,12] and is not affected by sex or age.[13,14] As a low molecular-weight protein, β2-MG is released into circulation at a constant rate, freely filtered by the glomeruli, and completely reabsorbed and catabolized in the renal tubules. These properties may make it an ideal endogenous biomarker for estimating the glomerular filtration rate.[13,15,16] Several studies found that the β2-MG level is a novel, early predictor of AKI in critically ill children,[17] renal allograft patients,[18] and liver transplant patients.[19] Furthermore, clinical studies have investigated β2-MG as a useful biomarker for predicting poor outcomes in patients with kidney (eg, ESRD) and cardiovascular diseases.[20–22]

Thus, the present study attempted to characterize the risk association between β2-MG levels and the incidence of AKI in patients with ICH in the neurosurgical intensive care unit (NICU). We hypothesized that β2-MG is an independent indicator of AKI in patients with ICH and suggests patient prognoses.

2. Materials and methods

2.1. Study design

This single-center, prospective, observational study included all patients, 18 to 90 years old, experiencing spontaneous, non-traumatic ICH admitted to the NICU of Zhongnan Hospital, Wuhan University, between January 1, 2015 and December 31, 2016. All patients who remained in the NICU for >48 hours and demonstrated symptom onset within 24 hours were enrolled. We excluded patients with histories of kidney transplantation, pre-existing hemodialysis or peritoneal dialysis, and missing serum creatinine data.

This study was approved by the hospital's ethics committee, and informed consent was obtained from each study participant.

2.2. Definitions

The kidney disease improving global outcomes (KDIGO) 2012 creatinine criteria were used to define and stage the severity of AKI.[23] The estimated glomerular filtration rate (eGFR) was determined using the baseline plasma creatinine level and calculated using the modification of diet in renal disease formula[24]; this equation is clinically valuable for estimating GFRs in adult patients with stable kidney status.[25] Baseline serum creatinine levels were measured on the first day of hospitalization as was each patient's acute physiology and chronic health evaluation II (APACHE II) score, widely used to describe the severity of disease and evaluate the prognoses of critically ill patients.[26] CKD was diagnosed if the patient had an eGFR of $<60 \, \text{mL/min/1.73 m}^2$) for >3 months before hospital admission, according to the Clinical Practice Guideline for Chronic Kidney Disease.[27] Brain hemorrhages, occurring at >2 sites, were detected using computed tomography. Anemia was defined as hemoglobin levels $<120 \, \text{g/L}$ (males) or $<110 \, \text{g/L}$ (females).

2.3. Data collection

The collected patient data included patient demographics (age, sex), pre-existing co-morbidities (diabetes, hypertension, coronary artery disease, chronic kidney disease), Glasgow Coma Scale and APACHE II scores (determined using validated methods and data from the admission physical exams), the site(s) of ICH-related bleeding determined using computed tomography (basal ganglia, frontal cortex, temporal lobe, parietal lobe, thalamus, multiple brain hemorrhages), serum creatinine values recorded upon NICU admission and routinely until discharge, blood samples upon NICU admission and before the start of treatment, and clinical outcomes (length of NICU stay, AKI occurrence, in-hospital mortality, 1-year mortality).

2.4. Biomarker measurements

Venous blood samples were obtained in plasma collection tubes; β2-MG concentrations were then determined in the central laboratory of Zhongnan Hospital, using a solid-phase, 2-site, chemiluminescent immunometric assay (Siemens Healthcare, Erlangen, Germany). The diagnostic ranges were established by the manufacturer, with serum β2-MG levels of 1000 to 3000 μg/L considered normal. The laboratory investigators were blinded to patient outcomes.

2.5. Outcomes

The primary outcome was the occurrence of AKI, diagnosed using the KDIGO criteria. Secondary outcomes were in-hospital mortality and all-cause mortality between admission and the 1-year follow up. The post-admission complications that were tracked included blood-stream infections, pulmonary infections, wound infections, need for mechanical ventilation, deep venous thrombosis, and death.

2.6. Statistical analysis

We used classification and regression trees (CART) and Chi-square automatic interaction detection (CHAID) to divide patients into 2 groups according to their β2-MG values and clinical outcomes. Continuous variables are presented as means and standard deviations or as medians and interquartile ranges. These variables were analyzed using 2-sample t tests or Mann–Whitney U-tests. Categorical variables, expressed as frequencies and percentages, were compared using the Chi-square test, as appropriate. The associations between β2-MG levels and clinical outcomes were first evaluated using a receiver operating characteristic (ROC) curve analysis to obtain a β2-MG cut-off value. To explore the predictive value of the β2-MG level for predicting AKI and mortality, we calculated the area under the curve (AUC) and recorded the sensitivity and specificity of the value and its corresponding 95% confidence interval (CI). The odds ratio (OR) and 95% CI were calculated using multivariable logistic regression analyses to assess the impact of β2-MG levels on AKI prediction. A univariate Cox logistic regression was used to determine mortality risk factors and identify the statistically significant variables for inclusion in the multivariable Cox proportional hazards analysis. This analysis was used to detect the independent indicators of NICU patient prognoses. The Kaplan–Meier survival analysis and log-rank tests were used to determine the association of β2-MG levels with 1-year mortality. In this study, we analyzed β2-MG levels as both continuous and categorical variables. A 2-tailed P-value $<.05$ was considered statistically significant; all analyses were performed using SPSS for Windows, version 22.0 (SPSS, Chicago, IL).

3. Results

3.1. Patient characteristics

Within the study period, 447 adult patients with ICH were screened for inclusion into this study. After applying the exclusion criteria, 403 patients (237 men, 166 women; median age, 59 [IQR, 50–69] years) were ultimately included in the analyses (Fig. 1). The locations of the ICH lesions were the basal ganglia (170 patients, 42.2%), brain lobe (82 patients, 20.3%), thalamus (51 patients, 12.7%), multiple brain locations (34 patients, 8.4%), brainstem (29 patients, 7.2%), intraventricular area (19 patients, 4.7%), cerebellum (18 patients, 4.2%).

3.2. β2-MG as a predictor of AKI

In the study, AKI developed in 142 patients (35.2%), including 89 (22.1%) with stage 1 AKI, 23 (5.7%) with stage 2, and 30 (7.4%) with stage 3 disease. The patients were grouped according to the presence/absence of AKI. Patients with AKI had higher levels of serum creatinine, blood glucose, blood urea nitrogen,
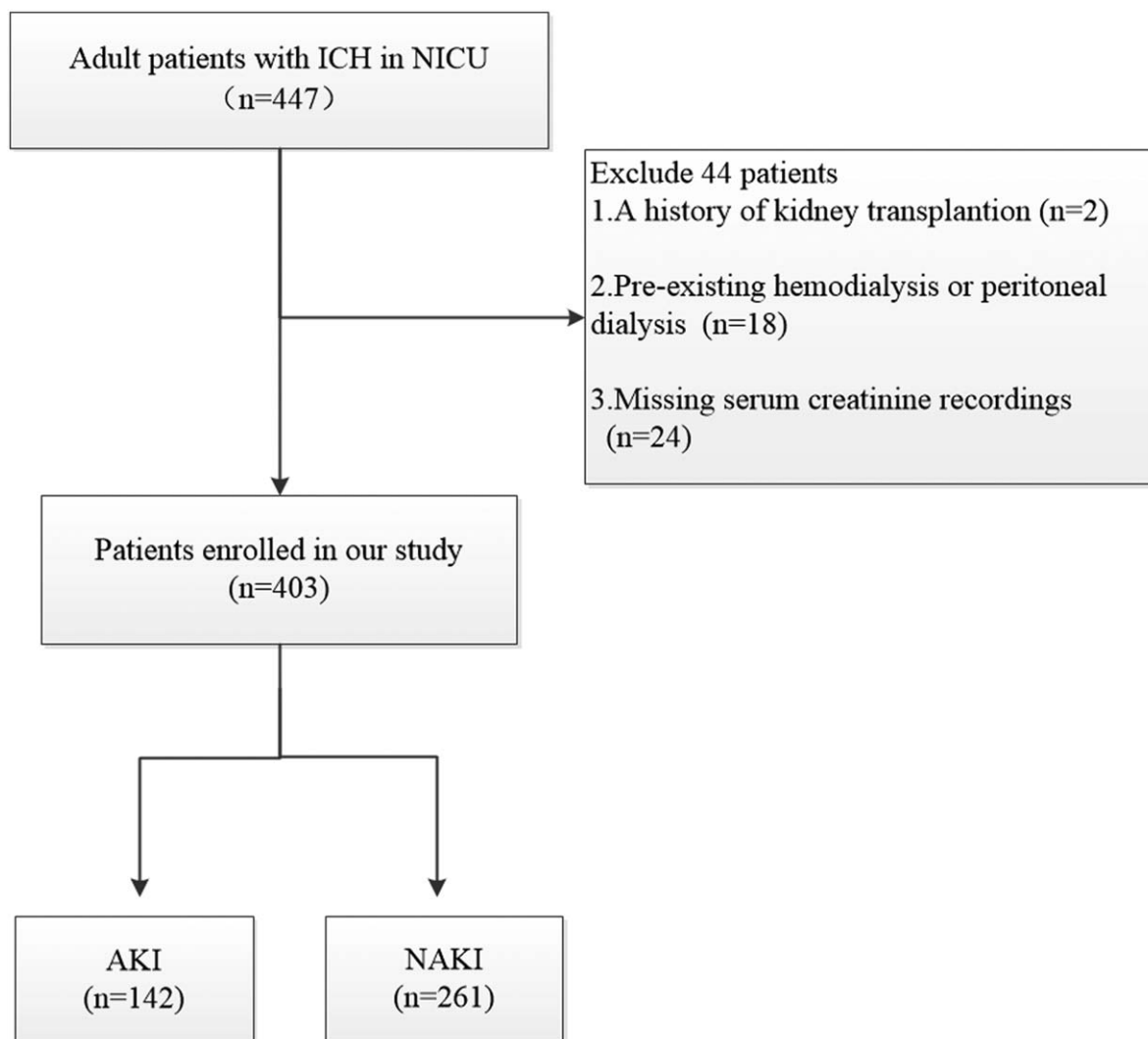
Figure 1. Flow chart for patient enrollment in the study. AKI = acute kidney injury, ICH = intracerebral hemorrhage, NICU = neurosurgical intensive care unit.

uric acid, and β2-MG; they also demonstrated higher leukocyte numbers, a higher mean arterial pressure, and lower serum bicarbonate concentrations. AKI was also more frequent in those with histories of chronic kidney disease or diabetes. In the AKI group, compared with the non-AKI group, the admission APACHE II scores were markedly higher while the Glasgow Coma Scale scores were lower. AKI was more likely to occur in patients with infections and in those who had undergone surgeries or used loop diuretics. Compared with those with AKI, patients without AKI were more frequently exposed to contrast media; the histories of mannitol exposure were similar between the groups (Table 1).

Figure 2 shows that as β2-MG levels increased, so did the risk of developing AKI. The relationship between AKI incidence and serum β2-MG levels was further investigated using multivariate regression. Higher circulating levels of β2-MG were associated with increased AKI risk, after adjusting for other variables. CART and CHAID were used to divide patients with ICH into 2 groups, according to their β2-MG values. Compared with the group with β2-MG levels ≤2123.50 μg/L, the prevalence of AKI (OR, 3.024; 95% CI, 1.504–6.079; P = .002) was higher in the group with β2-MG levels >2123.50 μg/L (Table 3). Furthermore, the β2-MG level measured on the first day of admission was an independent indicator of AKI when we analyzed the β2-MG level as a continuous variable in the regression model (OR, 1.068; 95% CI, 1.029–1.109; P < 001) (Table 2). In an attempt to predict AKI, we used the ROC curve analysis to calculate the optimal β2-MG cut-off; the cut-off value was determined to be 2026.85 μg/L (AUC, 0.712; 95% CI, 0.652–0.772), with a sensitivity of 57.5% and specificity of 79.4%. In the current study, the best cut-off value for the admission APACHE II score for predicting AKI was 17.5 (AUC, 0.823; 95% CI, 0.781–0.864) (Fig. 3A).

3.3. β2-MG as a predictor of mortality

During their hospitalizations, 84 (20.8%) patients died, including 31 (7.7%) in the β2-MG ≤2123.50 μg/L group and 53 (13.1%) in the β2-MG >2123.50 μg/L group. A univariate Cox proportional hazards analysis revealed that high β2-MG levels significantly increased the probability of in-hospital mortality. Further, high β2-MG levels were closely associated with in-

Table 1

Baseline characteristics of AKI and NAKI patients.

Variable	Total (n = 403)	NAKI (n = 261)	AKI (n = 142)	*P*-value
Demographics				
Age, yr	58.0 (50.0, 69.0)	59.0 (50.5, 67.0)	56.5 (48.8, 73.0)	.627
Males, N (%)	237 (58.8%)	141 (54.0%)	96 (67.6%)	.008
Medical history				
Diabetes, N (%)	40 (9.9%)	20 (7.7%)	20 (14.1%)	.039
Hypertension, N (%)	252 (62.5%)	157 (60.2%)	95 (66.9%)	.181
CHD, N (%)	24 (6.0%)	16 (6.1%)	8 (5.6%)	.847
CKD*, N (%)	9 (2.2%)	1 (0.4%)	8 (5.6%)	.001
Characteristics on admission				
Systolic BP, mm Hg	168.0 ± 31.3	164.4 ± 29.4	174.7 ± 33.7	.002
Diastolic BP, mm Hg	96.6 ± 19.8	94.9 ± 18.9	99.6 ± 21.1	.024
Mean arterial pressure, mm Hg	120.4 ± 21.7	118.1 ± 20.4	124.6 ± 23.6	.004
Serum creatinine, umol/L	65.2 (51.8, 79.7)	63.7 (52.4, 72.7)	71.3 (49.4, 97.3)	.003
eGFR[†], mL/min per 1.73 m^2	97.8 (79.8, 122.0)	99.0 (83.0, 120.7)	90.7 (68.0, 128.9)	.057
Leucocyte, ×10^9/L	11.7 (9.1, 15.2)	11.0 (8.6, 14.8)	13.0 (9.9, 17.0)	.001
Hemoglobin, g/L	132.3 ± 18.8	131.7 ± 15.9	133.4 ± 23.2	.425
Anemia (%)	60 (14.9%)	30 (11.5%)	30 (21.1%)	.009
Serum albumin, g/L	42.1 (38.3, 45.8)	42.0 (38.5, 45.4)	43.0 (37.7, 46.5)	.523
Blood glucose, mmol/L	7.5 (6.1, 9.3)	7.1 (5.8, 8.8)	7.9 (6.4, 11.6)	<.001
Blood urea nitrogen, mmol/L	5.3 (4.3, 6.5)	5.1 (4.2, 6.2)	5.8 (4.6, 7.0)	<.001
Uric acid, umol/L	295.1 (221.8, 368.6)	287.4 (217.9, 348.7)	316.7 (237.2, 414.7)	.002
Serum bicarbonate, mmol/L	89.8 (86.6, 92.9)	90.4 (87.1, 94.1)	88.5 (86.2, 91.6)	.007
β2-MG, ug/L	1724.8 (1319.9, 2339.1)	1560.9 (1247.9, 1950.3)	2129.2 (1582.2, 3151.8)	<.001
Prealbumin, mg/L	201.1 (156.1, 247.3)	201.1 (159.3, 247.8)	201.0 (147.6, 247.1)	.424
Serum sodium, mmol/L	137.9 (134.0, 140.5)	138.0 (135.0, 140.4)	137.0 (133.0, 140.6)	.203
Serum calcium, mmol/L	2.2 (2.1, 2.3)	2.2 (2.1, 2.3)	2.1 (2.0, 2.3)	.157
Red cell distribution width, %	13.1 (12.6, 13.7)	13.1 (12.7, 13.7)	13.0 (12.6, 13.6)	.737
GSC score	9.0 (4.0, 14.0)	12.0 (7.0, 14.0)	4.0 (3.0, 10.0)	<.001
APACHEII score	15.0 (10.0, 21.0)	12.0 (8.0, 17.0)	21.0 (17.0, 24.3)	<.001
Characteristics during hospitalization				
Infection, %	200 (49.6%)	115 (44.1%)	85 (59.9%)	.002
Surgery, %	260 (64.5%)	155 (59.4%)	105 (73.9%)	.004
Mechanical ventilation, %	248 (61.5%)	137 (52.5%)	111 (78.1%)	<.001
Mannitol, %	366 (90.8%)	233 (89.3%)	133 (93.7%)	.145
Loop diuretics, %	178 (44.2%)	93 (35.6%)	85 (59.9%)	<.001
Contrast medium, %	138 (34.2%)	99 (37.9%)	39 (27.5%)	.034
Length of stay, d	7.0 (4.0, 12.0)	6.0 (4.0, 10.0)	9.0 (5.0, 16.0)	<.001

Continuous variables was expressed as mean ± SD or median (IQR) according to their distribution. Categorical variables was expressed as n (%).

β2-MG = β2-microglobulin, AKI = acute kidney injury, APACHEII = acute physiology and chronic health evaluation ll, CHD = coronary heart disease, CKD = chronic kidney disease, eGFR = estimate glomerular filtration rate, GCS = Glasgow Coma Scale.

* Defined as preadmission eGFR <60 mL/per 1.73 m^2

† eGFR was calculated by the modification of diet in renal disease formula.
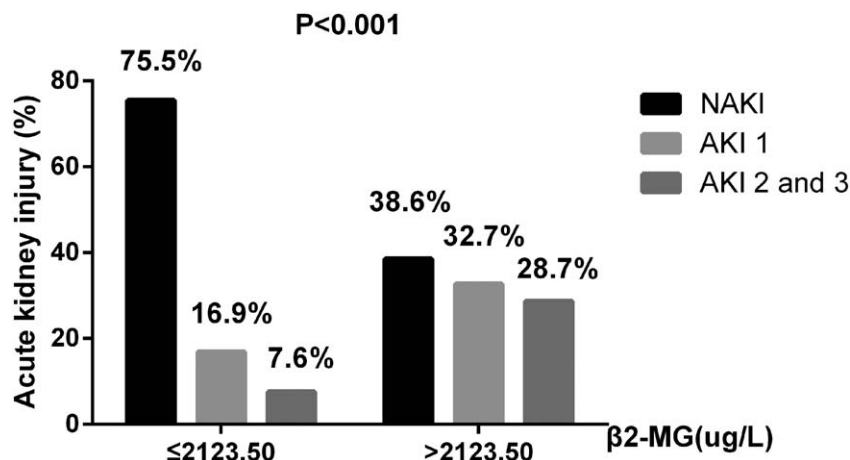

Figure 2. The prevalance of AKI in ICH patients, grouped according to the β2-MG level below or above of 2123.5 ug/L. AKI = acute kidney injury, ICH = intracerebral hemorrhage.

Table 2

Univariate and multivariate logistic regression analysis of the ability of β2-MG to predict AKI when analyzed as a continuous variable.

	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
β2-MG (per 100 ug/L)	1.079 (1.050–1.110)	<.001	1.068 (1.029–1.109)	<.001
Age, yr	0.997 (0.982–1.012)	.728	0.976 (0.954–0.999)	.044
Males	0.563 (0.367–0.863)	.008	0.577 (0.291–1.145)	.123
Diabetes	1.975 (1.024–3.810)	.042	1.282 (0.467–3.519)	.116
Anemia	2.062 (1.185–3.590)	.010	2.547 (1.089–5.957)	.031
Systolic BP, mm Hg	1.011 (1.004–1.018)	.002	1.005 (0.995–1.015)	.346
Uric acid, umol/L	1.003 (1.001–1.005)	<.001	1.001 (0.998–1.004)	.703
Leucocyte, ×10⁹/L	1.078 (1.032–1.126)	.001	1.021 (0.949–1.098)	.575
Blood glucose, mmol/L	1.127 (1.057–1.201)	<.001	1.029 (0.943–1.123)	.523
Blood urea nitrogen, mmol/L	1.224 (1.107–1.354)	<.001	1.014 (0.861–1.194)	.868
Serum bicarbonate, mmol/L	0.929 (0.880–0.981)	.008	0.997 (0.916–1.084)	.936
APACHEII score	1.228 (1.176–1.282)	<.001	1.198 (1.130–1.270)	<.001
eGFR	1.001 (0.997–1.005)	.689	1.009 (1.002–1.016)	.009
Prealbumin, mg/L	1.000 (0.997–1.002)	.820		
Serum calcium, mmol/L	0.359 (0.103–1.253)	.108		
Hypertension	1.339 (0.872–2.055)	.182		

Adjusted for age, gender, diabetes, anemia, systolic blood pressure, blood urea nitrogen, blood glucose, leucocyte, serum bicarbonate, uric acid, APACHEII score, eGFR.
β2-MG = β2-microglobulin, AKI=acute kidney injury, APACHEII = acute physiology and chronic health evaluation II, CI = confidence interval, OR = odds ratio.

hospital mortality, remaining significant after adjusting for age, sex, anemia, leukocyte count, blood glucose level, uric acid level, blood urea nitrogen level, prealbumin level, serum calcium level, and APACHE II scores (HR, 1.010; 95% CI, 1.001–1.020; *P*=.045) (Table 4). The in-hospital mortality risk in the high β2-MG group remained higher than that in the low β2-MG group even when β2-MG was analyzed as a categorical variable (HR, 2.397; 95% CI, 1.223–4.698; *P*=.011) (Table 5). The AUCs for the APACHE II and β2-MG ROC curves for predicting of in-hospital mortality were 0.801 (95% CI, 0.745–0.856) and 0.767 (95% CI, 0.704–0.830), respectively (Fig. 3B).

The median follow-up time for the overall cohort was 9.1 (range, 3.4–11.2) months, with a total of 115 patients (28.5%) dying within 1 year of NICU admission. The Cox proportional hazards analysis of 1-year mortalities is presented in Tables 6 and 7. The 1-year mortality rate was significantly higher among patients with high β2-MG levels than in those with low β2-MG levels (HR, 1.014; 95% CI, 1.005–1.022; *P*=.001). Further, the β2-MG level was a meaningful prognostic indicator of 1-year mortality (HR, 2.815; 95% CI, 1.568–5.051; *P*=.001), with a cut-off of 2014.7 μg/L being useful for predicting 1-year mortality (AUC, 0.788; 95% CI, 0.734–0.842) (Fig. 3C). The Kaplan–Meier survival curves, stratified by β2-MG level and AKI stage, are presented in Figure 4, further demonstrating the ability

Table 3

Univariate and multivariate logistic regression analysis of the ability of β2-MG to predict AKI when analyzed as a categorical variable.

	OR	95% CI	*P*-value
Model 1	4.906	2.981–8.074	<.001
Model 2	2.897	1.486–5.647	.002
Model 3	3.024	1.504–6.079	.002

Model 1: adjusted for unadjusted relative risk; Model 2: adjusted for age, gender, diabetes, anemia, systolic blood pressure, blood urea nitrogen, blood glucose, leucocyte, serum bicarbonate, uric acid, APACHEII score; Model 3: adjusted for model 2 plus mannitol, loop diuretics, contrast medium, infection, eGFR.
AKI=acute kidney injury, APACHEII = acute physiology and chronic health evaluation II, CI = confidence interval, OR = odds ratio.

of the β2-MG level to predict the 1-year mortality of patients with ICH in the NICU. The 1-year mortality rate was higher in patients with stage 2–3 AKI than in those without AKI or with stage 1 disease (log rank, *P*<.001) (Fig. 4A); patients in the low β2-MG group also had a significantly lower 1-year mortality rate (log rank, *P*<.001) (Fig. 4B). Figure 4C further reveals the additive effect on 1-year mortality risk, for all patients, when the factors are combined. Patients who developed AKI and had an β2-MG value >2123.50 μg/L had the highest 1-year mortality.

4. Discussion

In this study of 403 patients with ICH, AKI was a frequent complication of those in the NICU (incidence, 35.2%). George et al reported, in a prospective study of 2155 patients with acute, first-ever stroke, reported an AKI incidence of 27%.[5] Moreover, Burgess et al, using the AKI Network criteria to diagnose AKI, recently reported a prospective study that indicated that 31% of patients with ICH developed AKI while hospitalized.[28] The differences in the reported AKI incidences, between the studies, may be related to the sample sizes, AKI diagnostic criteria, stroke types, and so on.

AKI, a common complication after ischemic stroke and ICH, is strongly associated with poor prognoses, including short- and long-term increases in post-stroke mortality.[29,30] Therefore, there is an urgent need to find a reliable method for the early identification of patients with a high AKI risk. Unlike acute coronary syndrome, where biomarkers (such as troponin) for early diagnoses are available, biomarkers predicting AKI are lacking. Despite its unreliability, the serum creatinine level remains the most commonly used indicator of an AKI diagnosis, at present.[31] Hence, this study investigated β2-MG as an alternative and perhaps better predictor of AKI. The major finding of this study is that serum β2-MG levels, upon admission, are related to AKI development in hospitalized patients with ICH. For every 100 μg/L increase in serum β2-MG concentration, the prevalence of AKI increased by 6.4%. Further, the serum β2-MG concentration may be an early and useful biomarker for predicting AKI; a β2-MG cut-off level of 2026.85 μg/L may be advantageous for the early detection of AKI in patients with low

Prediction of AKI in ICH patients in NICU

Variable	best cutoff	sensitivity	specificity	AUC(95CI%)
APACHEII(pionts)	17.5	73.9%	77.8%	0.823(0.781-0.864)
β2-MG(ug/L)	2026.85	57.5%	79.4%	0.712(0.652-0.772)

Prediction of in-hospital mortality in ICH patients in NICU

Variable	best cutoff	sensitivity	specificity	AUC(95CI%)
APACHEII(pionts)	18.5	73.8%	73.0%	0.801(0.745-0.856)
β2-MG(ug/L)	2026.85	68.5%	75.8%	0.767(0.704-0.830)

Prediction of 1-year mortality in ICH patients in NICU

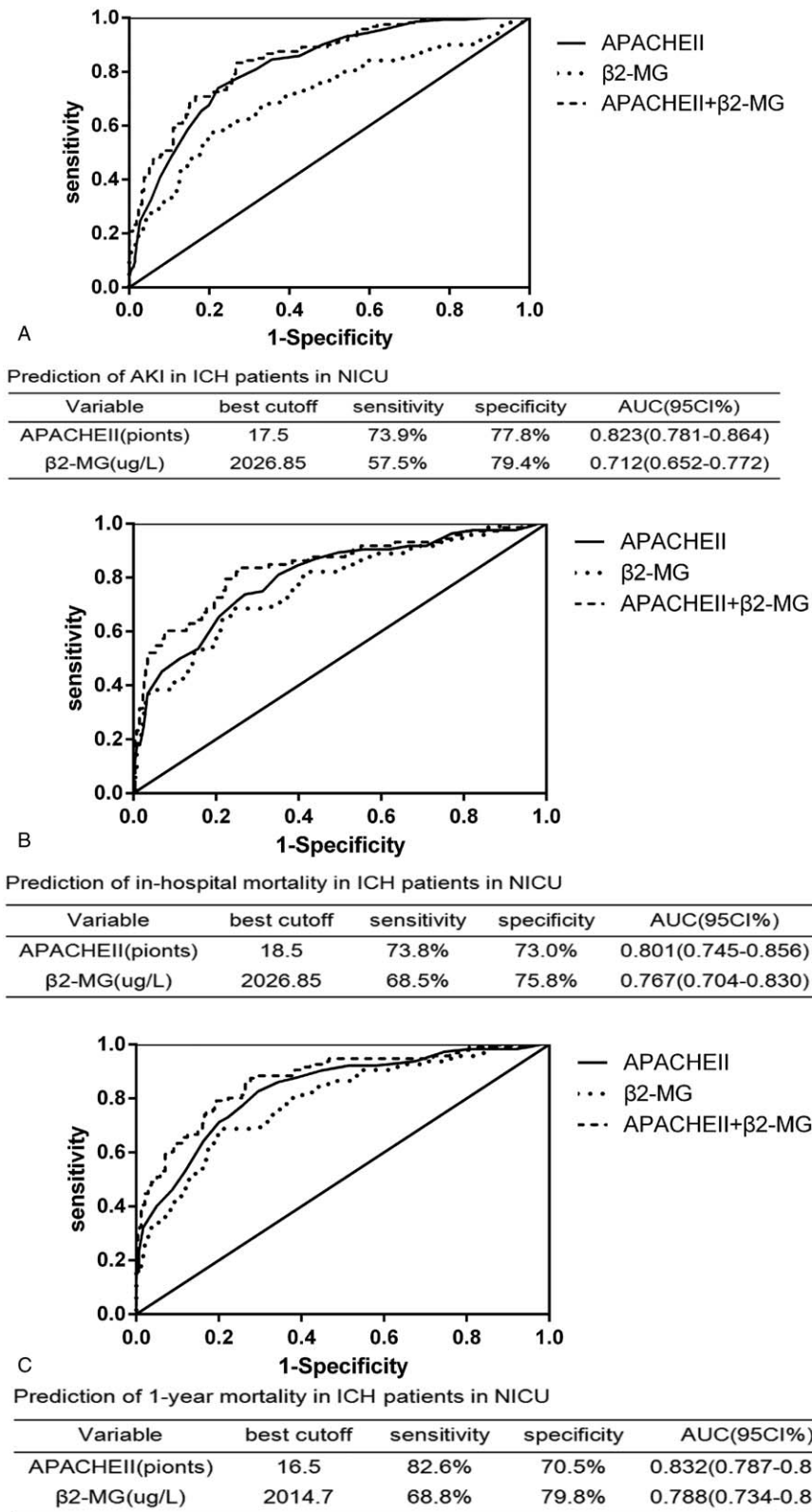| Variable	best cutoff	sensitivity	specificity	AUC(95CI%)
APACHEII(pionts)	16.5	82.6%	70.5%	0.832(0.787-0.876)
β2-MG(ug/L)	2014.7	68.8%	79.8%	0.788(0.734-0.842)

Figure 3. ROC analysis of β2-MG, APACHE II score, and β2-MG plus APACHE II score for AKI detection (A), in-hospital mortality (B) and 1-yr mortality (C) in all ICH patients in NICU. AKI=acute kidney injury, APACHEII = acute physiology and chronic health evaluation II, ICH=intracerebral hemorrhage, NICU= neurosurgical intensive care unit, ROC = receiver operating characteristic.

Table 4

Cox proportional hazards analysis of the ability of β2-MG to predict in-hospital mortality when analyzed as a continuous variable.

	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
β2-MG (per 100 ug/L)	1.012 (1.006–1.017)	<.001	1.010 (1.001–1.020)	.045
Age, yr	1.009 (0.994–1.025)	.221	1.014 (0.992–1.037)	.203
Males	0.804 (0.505–1.278)	.356	0.838 (0.402–1.749)	.638
Anemia	1.806 (1.120–2.913)	.015	0.774 (0.322–1.864)	.568
Leucocyte, ×10⁹/L	1.090 (1.046–1.136)	<.001	1.088 (1.023–1.156)	.007
Uric acid, umol/L	1.001 (1.000–1.003)	.087	1.000 (0.997–1.002)	.779
Prealbumin, mg/L	0.996 (0.992–1.000)	.029	0.997 (0.994–1.001)	.142
Blood glucose, mmol/L	1.063 (1.013–1.115)	.013	1.049 (0.975–1.128)	.199
Serum calcium, mmol/L	0.249 (0.070–0.884)	.031	0.510 (0.080–3.344)	.475
Blood urea nitrogen, mmol/L	1.084 (1.040–1.130)	<.001	1.042 (0.956–1.137)	.350
APACHEII score	1.119 (1.077–1.163)	<.001	1.081 (1.020–1.146)	.009
eGFR	0.997 (0.992–1.002)	.217	0.998 (0.989–1.007)	.659
Serum bicarbonate, mmol/L	0.959 (0.908–1.012)	.128		
Systolic BP, mm Hg	1.001 (0.995–1.008)	.743		
Hypertension	1.288 (0.806–2.060)	.290		
Diabetes	1.442 (0.809–2.572)	.214		

Adjusted for age, gender, anemia, leucocyte, blood glucose, uric acid, blood urea nitrogen, prealbumin, serum calcium, APACHEII score, eGFR.
β2-MG = β2-microglobulin, AKI = acute kidney injury, APACHEII = acute physiology and chronic health evaluation II, CI = confidence interval, eGFR = estimated glomerular filtration rate, HR = hazard ratio.

Table 5

Cox proportional hazards analysis of the ability of β2-MG to predict in-hospital mortality when analyzed as a categorical variable.

	HR	95% CI	P-value
Model 1	2.700	1.680–4.339	<.001
Model 2	2.078	1.093–3.951	.026
Model 3	2.397	1.223–4.698	.011

Model 1: adjusted for unadjusted relative risk; Model 2: adjusted for age, gender, anemia, leucocyte, blood glucose, uric acid, blood urea nitrogen, prealbumin, serum calcium, APACHEII score; Model 3: adjusted for model 2 plus mannitol, loop diuretics, contrast medium, infection, eGFR.
β2-MG = β2-microglobulin, CI = confidence interval, HR = hazard ratio.

Table 7

Cox proportional hazards analysis of the ability of β2-MG to predict 1-yr mortality when analyzed as a categorical variable.

	HR	95% CI	P-value
Model 1	4.840	3.201–7.318	<.001
Model 2	2.956	1.706–5.124	<.001
Model 3	2.815	1.568–5.051	.001

Model 1: adjusted for unadjusted relative risk; Model 2: adjusted for age, gender, diabetes, anemia, systolic blood pressure, blood urea nitrogen, blood glucose, leucocyte, serum bicarbonate, uric acid, prealbumin, serum calcium APACHEII score; Model 3: adjusted for model 2 plus mannitol, loop diuretics, contrast medium, infection, eGFR.
β2-MG = β2-microglobulin, CI = confidence interval, HR = hazard ratio.

serum creatinine values. Herrero-Morin et al also suggested that the serum β2-MG level may be a useful and novel biomarker, with greater diagnostic accuracy than serum creatinine, for detecting AKI in critically ill children.[17] Similar to our findings, cleaved urinary β2-MG may be a potential marker for

determining early tubular injury in Balkan endemic nephropathy and aristolochic acid nephropathy.[32]

The serum β2-MG level, measured at discharge, was proven to be a novel biomarker for predicting mortality and graft loss in a

Table 6

Cox proportional hazards analysis of the ability of β2-MG to predict 1-yr mortality when analyzed as a continuous variable.

	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
β2-MG (per 100 ug/L)	1.018 (1.013–1.022)	<.001	1.014 (1.005–1.022)	.001
Age, yr	1.020 (1.006–1.035)	.004	1.013 (0.994–1.033)	.178
Males	0.701 (0.477–1.032)	.072	1.092 (0.587–2.030)	.782
Diabetes	2.181 (1.346–3.535)	.002	1.967 (0.999–3.875)	.050
Anemia	2.262 (1.484–3.449)	<.001	1.253 (0.623–2.519)	.527
Systolic BP, mm Hg	1.008 (1.002–1.014)	.006	1.001 (0.993–1.009)	.748
Leucocyte, ×10⁹/L	1.106 (1.067–1.147)	<.001	1.009 (1.040–1.163)	.001
Uric acid, umol/L	1.003 (1.001–1.004)	<.001	1.001 (0.999–1.003)	.384
Prealbumin, mg/L	0.995 (0.992–0.998)	.001	0.997 (0.994–1.001)	.117
Blood glucose, mmol/L	1.094 (1.052–1.138)	<.001	1.055 (0.992–1.123)	.089
Blood urea nitrogen, mmol/L	1.126 (1.082–1.171)	<.001	0.967 (0.890–1.050)	.424
Serum bicarbonate, mmol/L	0.948 (0.907–0.991)	.019	1.002 (0.936–1.073)	.951
Serum calcium, mmol/L	0.255 (0.084–0.773)	.016	0.533 (0.109–2.599)	.437
APACHEII score	1.191 (1.153–1.230)	<.001	1.147 (1.092–1.204)	<.001
eGFR	0.994 (0.989–0.999)	.013	0.993 (0.985–1.001)	.069
Hypertension	1.386 (0.934–2.055)	.105		

Adjusted for age, gender, diabetes, anemia, systolic blood pressure, blood urea nitrogen, blood glucose, leucocyte, serum bicarbonate, uric acid, prealbumin, serum calcium, APACHEII score, eGFR.
β2-MG = β2-microglobulin, APACHEII = acute physiology and chronic health evaluation II, CI = confidence interval, eGFR = estimated glomerular filtration rate, OR = odds ratio.
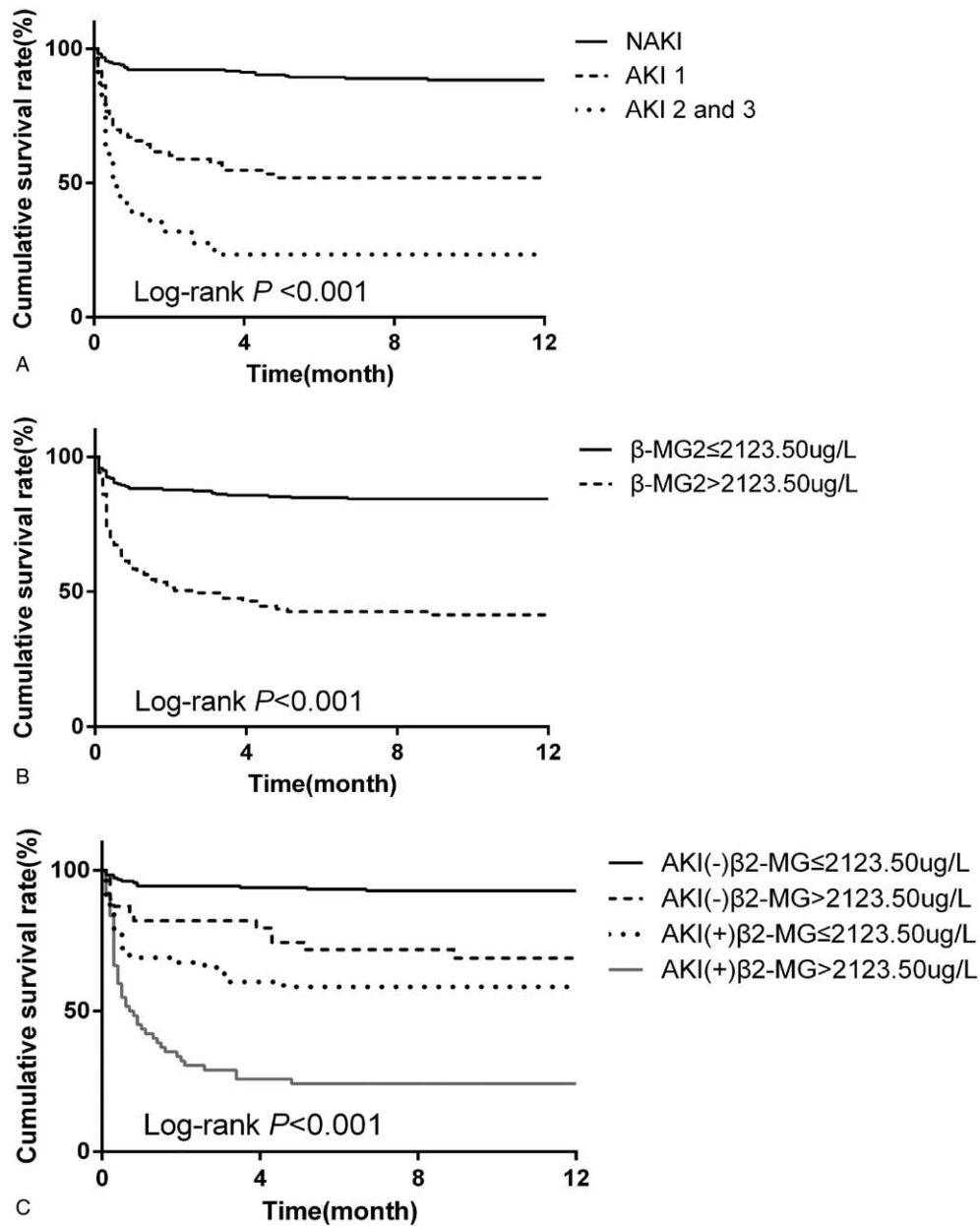
Figure 4. Kaplan–Meier plots for cumulative 1-yr survival according to the presence of AKI (A), β2-MG category (B) and their combination (C), respectively. AKI = acute kidney injury.

retrospective study of 2190 patients who underwent primary kidney transplantation.[20] Studies have shown that the serum β2-MG level is a strong, independent biomarker that is predictive of cardiovascular events and mortality in stable kidney transplant recipients[33] and in adults with CKD.[21] Supported by these reports, our study also shows that serum β2-MG levels predict the prognoses of patients with ICH. Patients with ICH categorized into the β2-MG level >2123.50 µg/L group had a 2-fold higher risk of in-hospital mortality than did patients in the lower β2-MG group, after adjusting for other clinical indices. Moreover, the 1-year mortality risk in the high β2-MG group was also higher than in the lower β2-MG group. Thus, this prospective study suggested that serum β2-MG levels, measured

upon NICU admission, are predictive of both in-hospital and 1-year mortality, with AUCs of 0.767 and 0.788, respectively. A survival analysis, conducted 1 year after NICU admission, further indicated that serum β2-MG levels could predict the 1-year mortality of the patients in this observational study.

We also found that the APACHE II score, calculated for each patient during the first 24 hours after NICU admission, was strongly associated with the development of AKI, in-hospital mortality, and 1-year mortality for patients with ICH. The APACHE II score is a well-known and important tool for accurately predicting critically ill patient outcomes; numerous studies have verified the score as an independent predictor of AKI in critically ill patients.[34,35] The present study also found that

the combined APACHE II score and serum β2-MG level provides a better prediction of AKI, in-hospital mortality, and 1-year mortality in the target patient population than either value, alone.

To our knowledge, this is the first study that has explored the potential association between serum β2-MG levels and the risks for AKI and all-cause mortality in NICU patients with ICH. Our study has several strengths, including its prospective design (prespecified protocol, analytical methods, surgical standards, and diagnostic criteria). The study also has some limitations. First, it was a single-center, observational study that recruited only 403 patients with ICH. A multi-center study, involving a larger study population is warranted to evaluate the value of β2-MG levels for predicting the incidence of AKI in NICU patients with ICH, as well as their overall prognosis. Second, only serum creatinine, and not urine output (particularly affected by the loop diuretics used by 44.2% of our patients), was used to diagnose AKI; thus, we may have underestimated the incidence of AKI. However, our study showed an AKI incidence that was consistent with a recent prospective study.[28] Third, the temporal changes in serum and urinary β2-MG levels were not determined. Several studies have reported that urinary β2-MG levels are an early and promising biomarker of AKI and may predict the prognoses of patients with idiopathic membranous nephropathy or immuno-globulin A nephropathy.[36,37] Furthermore, we did not evaluate the risks for ESRD or new cardiovascular events in patients with ICH and who developed AKI while hospitalized.

5. Conclusion

This prospective study showed that the serum β2-MG level, measured upon NICU admission, maybe an early and promising biomarker of AKI and adverse outcomes in patients with ICH in the NICU. Further research should confirm this finding, which may help clinicians take timely action to improve patient outcomes.

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Author contributions

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