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ORIGINAL ARTICLE

Assessment of β2-Microglobulin as a Marker for Acute Kidney Injury in Patients with Intracerebral Hemorrhage in Medical Intensive Care Unit

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ABSTRACT

Background: Released into the bloodstream at a steady rate, β2-microglobulin (β2-MG) is readily filtered by the glomeruli, fully reabsorbed, and catabolized in the renal tubules. Due to these characteristics, it may be the best endogenous biomarker for estimating glomerular filtration rate. **Aim of work:** To examine whether β2-MG in patients who have experienced intracerebral haemorrhage is a marker of AKI. **Materials and methods:** Our prospective case control study was done in the Intensive Care Unit of Zagazig University Hospitals, Sharkia governorate, Egypt on 94 cases. All selected patients were classified AKI according to kidney disease improving global outcomes (KDIGO) 2012 criteria. Every patient in this study underwent a thorough clinical examination as well as a comprehensive history taking. The Glasgow Coma Scale (GCS) and the Acute Physiology and Chronic Health Evaluation (APACHE) II Score, which are frequently used scoring systems in intensive care units (ICUs) for critically sick patients, were employed to assess severity. β2-MG testing was one of the laboratory investigations carried out. **Results:** β2-MG levels were significantly higher in patients with AKI compared to non – AKI. At cutoff of value ≥4.6915 with accuracy of 84%, β2-MG had a sensitivity of (85.1%), and specificity of (83%) in prediction of AKI in patients with non-traumatic cerebral haemorrhage with PPV of 83.3% and NPV of 84.8%. **Conclusion:** When patients in the intensive care unit (ICU) have intracerebral haemorrhage (ICH), β2-MG can be used as a predictive marker of the onset of AKI.

Keywords: β2-microglobulin; AKI; ICU; Kidney.

INTRODUCTION

Intracerebral hemorrhage (ICH) is caused by a rupture in the weak arterial vasculature, which allows blood to seep into the surrounding brain parenchyma. High rates of death and disability are linked to ICH. It is true to state that studies have revealed that death rates can approach 70% after five years and 59% after one year, with over 80% of survivors suffering from lifelong disabilities **[1]**. The basal ganglia are the most frequently affected areas of the brain, followed by the cortex, brainstem, cerebellum, and other deep brain regions. The prevalence of ICH is increasing as the population ages, risk factors including obesity, diabetes, alcoholism, and hypertension rise, and the use of

anticoagulant medications becomes more common **[1]**.

Acute kidney injury (AKI) is a common and deadly condition that increases the risk of chronic kidney disease (CKD), which can result in end-stage renal disease (ESRD) and eventually death in severely ill individuals. Furthermore, intracerebral hemorrhage (ICH) is a dangerous condition **[2]**. The gold standard for identifying and categorizing AKI in contemporary clinical practice is a series of serum creatinine measurements. Regretfully, serum creatinine measurements are particularly unreliable during acute changes in renal function because of their many intrinsic limitations **[3]**. First, it's possible that serum creatinine levels won't alter until 50% of renal function is permanently lost. Second, it could take several days to attain a steady state, at which point the serum creatinine test may not be a meaningful indicator of renal function. Finally, blood levels of creatinine are influenced by several non-renal criteria, such as age, gender, race, and muscle mass, in addition to elements like medication metabolism, protein intake, perioperative fluid supply, and hydration status **[4]**. The diagnosis of AKI is significantly delayed because of all these causes. Because serum creatinine is not a reliable enough biomarker to diagnose acute kidney injury (AKI) and provide treatment planning information once AKI is diagnosed, more reliable biomarkers are needed **[5]**.

All nucleated cells contain β2-MG, an 11.8 kDa no glycosylated polypeptide that is age- and gender-independent. Due to its low molecular weight, β2-MG is liberated into the bloodstream gradually, filtered freely by the glomeruli, fully reabsorbed, and catabolized in the renal tubules. Due to these characteristics, it may be the best endogenous biomarker for estimating glomerular filtration rate **[6]**.

This study was performed to examine whether β2-microglobulin (β2 MG) in patients who have experienced intracerebral hemorrhage is a marker of AKI.

PATEINTS AND METHODS

Technical design

Our prospective case-control study was conducted in the ICU of Zagazig University Hospitals, Sharkia governorate, Egypt on 94 cases (31 females & 63 males) who were divided into 2 groups. Group A (AKI) which included ICU patients experiencing spontaneous, non-traumatic ICH and were complicated with AKI. Group B (Non-AKI): were included ICU patients experiencing spontaneous, non-traumatic ICH and were not complicated with AKI. Approval was asked from the institutional review board (IRB). Exclusion criteria was (i) male and female Patients younger than 18 years old, (ii) Patients with histories of kidney transplantation, preexisting hemodialysis or peritoneal dialysis, and missing serum creatinine data, (iii) Patients with Subdural hemorrhage, (iv) Patients with traumatic cerebral hematoma, and (v) Patients with cerebral infarction.

Methods

All selected patients were classified AKI according to kidney disease improving global outcomes (KDIGO) 2012 criteria by (Khwaja, 2012) (An increase in serum creatinine by greater than or equal to 0.3 mg/dL within 48 hours; or An increase in serum creatinine by greater than or equal to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or A urine volume less than 0.5 ml/kg/h for 6 hours) into 2 groups (i) Group A (AKI): included ICU patients experiencing spontaneous, non-traumatic ICH and were complicated with AKI (ii) Group B (Non-AKI): included ICU patients experiencing spontaneous, non-traumatic ICH and were not complicated with AKI **[7].** Within the study period, 115 adult patients with non-traumatic ICH were screened for inclusion into this study. After applying the exclusion criteria, 94 patients (31 females & 63 males) were ultimately included in the analysis. Every patient in this study underwent a thorough clinical examination as well as a comprehensive history taking. The Glasgow Coma Scale (GCS) and the Acute Physiology and Chronic Health Evaluation (APACHE) II Score, which are frequently used scoring systems in intensive care units (ICUs) for critically sick patients, were employed to assess severity. A resting 12-lead electrocardiogram (ECG) was performed. Additionally, we carried out pelvic-abdominal US, brain computed tomography (CT) scan, echocardiography, and chest X-ray. Whole blood count (CBC), random blood glucose level, HbA1c, liver function tests, PT, PTT, INR, kidney function tests, serum electrolytes (Na, K, C-reactive protein), arterial blood gases, serum sodium and potassium,

erythrocyte sedimentation rate (ESR), lipid profile (total cholesterol, triglycerides, HDL, and LDL), alkaline phosphatase, serum calcium and phosphorous, urine analysis, and B2-microglobulin test were among the laboratory investigations conducted. Initial measurements of serum creatinine were made on the day of hospital admission.

Administrative considerations

Every participant provided written informed consent, comatose patients' consents were taken from their first-degree relatives and the study was authorized by the Zagazig University Faculty of Medicine's Institutional Research Board IRB (research ethics committee). The work has been completed in compliance with the Declaration of Helsinki, the World Medical Association's code of ethics for human subjects' research.

STATISTICAL ANALYSIS

SPSS for Windows, version 22.0 (SPSS, Chicago, IL), was used for all analyses. Based on their b2-MG readings and clinical outcomes, we classified the patients into two groups using Chi square automated interaction detection (CHAID) and classification and regression trees (CART). Continuous variables can be shown as medians and interquartile ranges, or as means and standard deviations. Mann-Whitney U-tests or 2-sample t tests were used to analyze these variables. The Chi-square test was used when necessary to compare categorical data, which were reported as frequencies and percentages. To determine a b2-MG cut-off value, the relationships between b2-MG levels and clinical outcomes were initially assessed using a receiver operating characteristic (ROC) curve analysis. We determined the area under the curve (AUC), noted the value's sensitivity and specificity, and documented the 95% confidence interval (CI) to investigate the predictive usefulness of the b2-MG level for predicting AKI and death. Multivariable logistic regression analyses were used to obtain the odds ratio (OR) and 95% confidence interval (CI) to evaluate the effect of b2-MG levels on AKI prediction. To ascertain the mortality risk factors and pinpoint the statistically relevant variables to be incorporated into the multivariable Cox proportional hazards analysis, a univariate Cox logistic regression was employed. The independent NICU patient prognostic factors were found using this study. The relationship between b2-MG levels and 1-year mortality was ascertained using the Kaplan-Meier survival analysis and log-rank testing. We examined b2-MG levels as both continuous and categorical factors in this investigation. A P-value with two tails less than.05. was deemed statistically significant.

RESULTS

β2-MG levels were considerably greater in AKI patients than in non-AKI patients, as Table (1) illustrates. The data presented in Table (2) indicates a statistically significant negative connection between β2-MG and GCS, serum bicarbonate, and eGFR. β2-MG has a statistically significant positive connection with WBCs, the APACHE II score, serum urea, creatinine, and fasting blood glucose. The most significant predictor of AKI in patients with ICH, according to univariate analysis, was β2-MG, which was followed by the APACHE II score, WBCs, e GFR, bicarbonate, and GCS. Multivariate analysis revealed that in individuals with ICH, AKI was strongly and independently correlated with β2-MG and eGFR Table (3). Table (4) demonstrates that β2-MG had a sensitivity of 85.1% and specificity of 83% at a cutoff value of ≥4.6915 with accuracy of 84% in predicting AKI in patients with non-traumatic cerebral hemorrhage with PPV of 83.3% and NPV of 84.8%. When eGFR was used to predict AKI in patients with non-traumatic cerebral hemorrhage, it had a sensitivity of 83%, specificity of 87.2%, and NPV of 83.7% at a threshold value of ≤64 with a 95% accuracy rate.

Table (1) Comparison between studied groups regarding serum beta-2 microglobulin

	Group A (AKI)	Group B (Non-AKI)	t	p
	Median (IQR)	**Median (IQR)**		
Beta 2 microglobulin (Ug/L)	8.65(6.51 – 13.65)	2.97(2.55 – 4.34)	-5.43	<0.001**

Z= Mann Whitney test. p≤0.001 is statistically highly significant. IQR= interquartile range

Table (2) Correlation between serum beta-microglobulin 2 and study parameters:

	r	p
Age (year)	0.142	0.173
Systolic blood pressure (mmHg)	0.131	0.209
Diastolic blood pressure (mmHg)	0.149	0.151
GCS	-0.358	<0.001**
APACHE II	0.459	<0.001**
PH	-0.03	0.776
PaO2 (mmHg)	-0.088	0.4
PaCO2 (mmHg)	0.109	0.295
HCO3 (mmol/L)	-0.26	0.011*
Uric acid (mg/dl)	0.025	0.813
Hemoglobin (g/dl)	-0.105	0.316
RBCs (10^6/mm^3)	0.052	0.62
WBCs (10^3/mm^3)	0.294	0.004*
Platelet count (10^3/mm^3)	0.096	0.367
Albumin (g/dl)	-0.107	0.303
AST (U/L)	0.135	0.195
ALT (U/L)	0	0.999
INR	0.006	0.951
HbA1c	0.141	0.176
Fasting blood glucose (mg/dl)	0.225	0.029*
2-hour postprandial blood glucose (mg/dl)	0.176	0.089
Serum urea (mg/dl)	0.467	<0.001**
Serum creatinine (mg/dl)	0.468	<0.001**
eGFR (CKD-EPI creatinine equation) (mL/min/1.73m2)	-0.474	<0.001**
eGFR (MDRD equation) (mL/min/1.73m2)	-0.454	<0.001**
Calcium (mg/dl)	0.029	0.781
Potassium (mmol/L)	-0.138	0.183
Sodium (mmol/L)	-0.094	0.37

r= Spearman rank correlation coefficient. $p<0.05$ is statistically significant. $p\leq0.001$ is statistically highly significant.

Table (3) Univariate & multivariate logistic regression analysis of B2-MG ability to predict AKI in patients with ICH.

	Univariate			Multivariate		
	OR	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Age	1.03	0.99 – 1.07	0.098	-		-
Sex (female)	1.62	0.68 – 3.87	0.274			
Comorbidities:						
No	1	Reference	0.748			
DM	1292375013.9	(0 -)	0.999			
DM&HPN	2202911955.5	(0 -)	0.999			
NPN	1453921890.6	(0 -)	0.999			
Smoking	0.59	0.26 – 1.35	0.209			
SBP	1.02	0.99 – 1.04	0.183			
Fasting Blood sugar	0.99	0.98 – 1	0.081			
Urea	5.01	0.38 – 66.5	0.222			
eGFR	0.91	0.88 – 0.95	<0.001**	0.87	0.78 – 0.97	0.014*
WBCs	1.36	1.16 – 1.59	<0.001**	1.48	0.81 – 2.69	0.203
HCO3	0.84	0.75 – 0.93	0.001**	0.62	0.34 – 1.14	0.203
APACHE II	1.38	1.19 – 1.6	<0.001**	1.89	0.97 – 3.68	0.06
GCS	0.61	0.46 – 0.81	0.001**	4.93	0.46 – 52.78	0.187
B2microglobulin	1.39	1.21 – 1.59	<0.001**	1.36	1.03 – 1.81	0.032*
Creatinine	$4.14*10^{51}$	0 -	0.964			
Uric acid	210072610 -	0 -	0.955			

COR crude odds ratio. CI confidence interval. AOR adjusted odds ratio.

Table (4) Validity of APACHE and B2-microglobulin in prediction of AKI in patients with ICH:

	Cutoff	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**	**p**
β2microglobulin	≥4.6915	0.837	85.1%	83%	83.3%	84.8%	84%	<0.001**
eGFR	≤64	0.953	83%	87.2%	86.7%	83.7%	95.2%	<0.001**

p≤0.001 is statistically highly significant. PPV positive predictive value. NPV negative predictive value.

AUC area under curve.

DISCUSSION

Due to the limitations of serum creatinine, more reliable indicators are needed for the diagnosis of acute renal damage and to provide predictive information on outcomes once AKI has been established **[8]**. Several investigations have demonstrated that the β2-MG level is a unique, early predictor of AKI in critically sick children, recipients of liver transplants, and recipients of renal allografts. According to clinical investigations, β2-MG is a useful biomarker for forecasting unfavorable outcomes in patients suffering from cardiovascular and renal diseases, such as end-stage renal disease (ESRD) **[9]**.

The findings of our investigation demonstrated that patients with AKI had considerably greater levels of β2-MG than those without AKI. Like us, Wang et al. found that in hospitalized patients with ICH, serum β2-MG levels at admission are associated with the development of AKI. 6.4% more people had AKI for every 100 mg/L increase in serum β2-MG concentration. According to the same previously mentioned study, a β2-MG cut-off level of 2026.85 mg/L may be helpful for the early diagnosis of AKI in individuals with low serum creatinine values. The serum β2-MG concentration may also be an early and relevant biomarker for predicting AKI **[10]**. Furthermore, Herrero et al. proposed that serum β2-MG level could be a novel and helpful biomarker for identifying AKI in critically unwell children, with a higher diagnostic accuracy than serum creatinine **[11]**. Similar to this, Stefanovic et al. showed that cleaved urine β2-MG could be a useful marker for identifying tubular injury early in aristolochic acid nephropathy and Balkan endemic nephropathy **[12]**. Consistent with the present investigation, Wang et al.'s study also demonstrated that serum β2-MG levels are predictive of patients' prognoses with ICH. After controlling for all clinical indices, individuals with ICH classified into the β2-MG level >2123.50mg/L group had a 2-fold increased risk of in-hospital death compared to those in the lower β2-MG group **[9]**. Furthermore, in the trial, the high β2-MG group had a higher one-year mortality risk compared to the lower β2-MG group. With AUCs of 0.767 and 0.788, respectively, it was revealed that serum β2-MG levels assessed upon ICU admission are predictive of both in-hospital and one-year mortality. One year following ICU admission, a survival analysis revealed that serum β2-MG levels could also predict patients' one-year mortality **[9]**.

The present study's findings showed a statistically significant inverse relationship between β2-MG and eGFR, serum bicarbonate, and GCS. Additionally, β2-MG showed a statistically significant positive connection with WBCs, urea, creatinine, fasting blood glucose, and APACHE II score. Only serum creatinine has a substantial independent association with serum β2-MG among parameters that are strongly connected with it. The most significant predictor of AKI in patients with ICH, as determined by a univariate logistic regression analysis model, was β2-MG. This was followed by the APACHE II score, WBCs, e GFR, bicarbonate, and GCS. In individuals with ICH, β2-MG and eGFR were found to be significantly independently related with AKI in multivariate analysis. Wang et al. discovered that the combination of the serum β2-MG level and the APACHE II score offers a more accurate forecast of AKI, in-hospital mortality, and 1-year mortality in the target patient group than either value alone. These results are consistent with our own **[9]**. Furthermore, Kim et al. reported using a computed delta-neutrophil index (DNI) to predict sepsis-associated AKI in the ER. The DNI represents the fraction of immature WBC. In their cohort study subjects, severe AKI was independently associated with 30-day death, and WBCs were an independent predictor of severe AKI **[13]**. These findings were consistent with those of Fuhrman, who found substantial independent associations between AKI and WBCs, eGFR, bicarbonate, and GCS as well as the APACHE II score **[14]**.

In patients with non-traumatic cerebral hemorrhage, β2-MG had a sensitivity of 85.1% and specificity of 83% in predicting AKI using the ROC curve, with a cutoff value of ≥4.6915 and accuracy of 84%. The patients' PPV and NPV were 83.3% and 84.8%, respectively. In patients with non-traumatic cerebral hemorrhage with PPV of 86.7% and NPV of 84.8%, eGFR exhibited a sensitivity of 83% and specificity of 87.2% in predicting AKI at a cutoff value of ≤64 with accuracy of 95%. According to Wang's (2020) research, the likelihood of suffering AKI rose in tandem with elevated β2-MG levels. The prevalence of AKI was greater in the group with β2-MG levels >2.12350 mg/L than in the group with β2-MG levels ≤2.12350 mg/L (OR, 3.024; 95% CI, 1.504–6.079; P =.002). Additionally, they employed ROC curve analysis to identify the ideal β2-MG cut-

off, which came out to be 2.02685 mg/L (AUC, 0.712; 95% CI, 0.652–0.772), with a 57.5% sensitivity and 79.4% specificity **[9]**. In Zhang's (2020) study, the B2MG cut off, sensitivity, and specificity for β2-MG to detect AKI were determined using ROC analysis. The calculated cut-off value was 3.49 mg/L (AUC, 0.689; 95% CI, 0.586–0.791), with a 0.787 specificity and 0.487 sensitivity **[15]**. They believe that urine NGAL and α1-MG levels, as well as serum Cys-C and β2-MG, are early and specific markers of kidney injury following hypoxia. The varied population of unwell babies and the use of the newborn group could be the cause of the discrepancy in the results.

CONCLUSION

This study indicated that, to prevent potentially harmful events, the first objective of a physician treating patients with ICH should be the early and accurate diagnosis of AKI. When patients in the intensive care unit (ICU) have intracerebral hemorrhage (ICH), B2-MG can be used as a predictive marker of the onset of AKI. As we outline the most recent guidelines for diagnosis and treatment of these patients, we advise considering the measurement of β2-MG as a method to achieve early detection of AKI in individuals with ICH. More research is required to fully examine this problem.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Author Contributions.

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