



## Preoperative Serum Bicarbonate Levels Predict Acute Kidney Injury after Cardiac Surgery

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**Abstract : Background:** Cardiac surgery has been associated with impaired renal parenchymal function precisely in the tubular system. This causes Acute Kidney Injury (AKI), which started from the operation and persisted to postoperative in various time span. This decrease in kidney function leads to the accumulation of residual plasma products, such as urea and creatinine. Metabolic acidosis characterized by decreased serum bicarbonate concentration is thought to play a role in the pathogenesis of renal injury. Acidosis worsens renal tubular damage by increasing the production of ammonia in the renal tubular, which activates the complement system and triggers tubulointerstitial damage in the kidneys. **Methods:** This retrospective cohort study of 103 patients underwent coronary artery bypass graft (CABG) or valve surgery at the Haji Adam Malik General Hospital from January 2017 to December 2017. All patients will be examined for preoperative and postoperative laboratory. The patients were divided into 3 groups based on preoperative serum bicarbonate level, which represented group 1 (below normal levels) <22 mEq/L; group 2 (normal levels) 22 to 24 mEq/L, and group 3 (elevated levels) > 24 mEq/L. Then the patient will be followed during hospitalization. Then conducted analysis to see association between serum bicarbonate level and incidence of cardiac surgery-associated acute kidney injury (CSA-AKI). **Results:** CSA-AKI was more common in group 1 compared to group 2 and 3. CSA-AKI developed in 26 patients (65%) in group 1, 11 patients (27.5%) in group 2, and 3 patients (7.5%) in group 3 (P = 0.022). Multivariate analysis showed that serum bicarbonate <22 mEq/L was the most dominant risk factor affecting the incidence of CSA-AKI [OR 6.99 (1.68-29.15), p = 0.008]. **Conclusion:** Low serum bicarbonate levels (<22 mEq/L) is a strong predictor of the incidence CSA-AKI with OR 6.99.

**Keywords :** serum bicarbonate, AKI, cardiac surgery.

### Introduction

Cardiac surgery has been associated with impaired function of various organ systems, one of which is renal damage. Damage to the kidneys occur in the renal parenchyma precisely on the tubular system. This

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causes Acute Kidney Injury (AKI), which started from the operation and persisted until postoperative in various time span.<sup>1</sup>

The term AKI is used to describe a rapid (hour to day) declining in kidney function. This decrease in kidney function leads to the accumulation of residual plasma products, such as urea and creatinine. AKI is also known to induce damage to distant organs, thereby contributing to morbidity and mortality.<sup>2</sup> Overall mortality after cardiac surgery ranges from 2-8% .<sup>3</sup> However, the risk of death increases exponentially in patients with postoperative AKI, with mortality rate above 60% .<sup>4</sup>

Patients who have cardiac surgery associated AKI (CSA-AKI) often require dialysis, which in turn leads to increased ICU care and increases long-term morbidity. Mild impaired renal function after cardiac surgery that does not require dialysis is also significantly associated with poor clinical outcome.<sup>5</sup>

Several factors responsible for the occurrence of AKI post cardiac surgery have been known, such as reactive oxygen, inflammatory cytokines, ischemic injury due to reperfusion, and haemolysis.<sup>6</sup> Although the pathogenesis of postoperative AKI events is not fully known, the possibility of multifactorial interactions between hemodynamic, inflammatory, and direct injury lead to nephrotoxic mechanism.

Metabolic acidosis is defined as a decrease in serum bicarbonate ( $\text{HCO}_3$ ) concentration, which is often associated with a decrease in blood pH. Metabolic acidosis is thought to play a role in the pathogenesis of renal injury. Acidosis worsens renal tubular damage by increasing the production of ammonia in the renal tubular, which activates the complement system and triggers tubulointerstitial damage in the kidney.<sup>7</sup> In addition, acidosis is thought to activate the renin angiotensin system in the kidneys.

## Methods

This study was an observational study with a retrospective cohort design and single center to prove preoperative bicarbonate serum levels as a predictor of AKI post cardiac surgery. The inclusion criteria are all patients undergoing CABG surgery and / or heart valve surgery. Exclusion criteria for patients <18 years of age, history of hemodialysis or peritoneal dialysis prior to cardiac surgery, received alkaline therapy prior to cardiac surgery and chronic kidney disease. Patients undergoing cardiac surgery were grouped into 3 groups: group 1, patients with serum bicarbonate <22 mEq/L (low), group 2 with 22-24 mEq/L serum bicarbonate (normal), and group 3 with serum levels bicarbonate > 24 mEq/L (high). The primary outcome assessed was the incidence of AKI post cardiac surgery. Secondary outcomes assessed were duration of care in ICU, length of hospital stay, in-hospital mortality and mortality within 30 days after discharge from hospital.

The patient's data were filled in sheets containing clinical and laboratory data. Clinical data consist of age, sex, comorbidity, and type of surgery. Laboratory tests were performed before and after cardiac surgery at the hospital. Blood tests were conducted in the Clinical Pathology laboratory of Adam Malik Hospital. For preoperative laboratory data taken within 7 days before surgery and postoperative laboratory was taken within 48 hours after surgery. When more than one creatinine laboratory result is found within 48 hours postoperatively, the highest serum creatinine is taken as postoperative data. The data were collected by the researcher and then analyzed.

The categorical variable is presented with the number or frequency (n) and percentage (%). The numerical variables are assigned with mean (mean) and standard deviation values for normally distributed data, whereas non-distributed numerical data use median (middle value), which then compared with student's t-test or Mann Whitney U test. Normality test in numerical variables of all subjects using one sample Kolmogorov Smirnov ( $n > 50$ ) or Shapiro Wilk ( $n < 50$ ). For samples that was found significant in the bivariate analysis test, the next step is a multivariate test. Statistical data analysis using statistical software,  $p < 0.05$  is considered to be statistically significant.

## Results

The total number of study subjects was 103 people, consisting of 71 men and 32 women. This study found subjects with AKI was 40 people (38.8%) and non AKI 63 people (61.2%). The mean age of the study subjects with AKI was 55.7 years versus 47.5 years in non-AKI subjects. There were 27 people (38%) men who

had AKI post cardiac surgery and 44 people (62%) did not have AKI post cardiac surgery. Of the cardiac surgery types, patients who underwent CABG 65 people (63.1%), heart valve surgery 36 people (35%), and 2 (1.9%) CABG and heart valves surgery.

We found a statistically significant difference between the AKI and non-AKI groups in terms of laboratory examination. The AKI group had lower Hb levels than the non-AKI group of 13 versus 14 ( $p = 0.047$ ). In the case of  $\text{HCO}_3$ , it appears that the AKI group has a lower value than the non-AKI group that is 21 to 22.2 ( $p = 0.016$ ). The mean value of GFR in the lower AKI group was 76.1 while in the non-AKI group was higher with 88 ( $p = 0.026$ ). The AKI group had a higher average BUN value compared to the non-AKI group of 13 to 11.5 ( $p = 0.010$ ).

There was a statistically significant difference in risk factors for AKI events between the AKI and non-AKI groups. There were 13 patients with DM in the AKI group and 9 in the non-AKI group. For hypertension, there were 28 people in the AKI group and 31 people in the non-AKI group. (Table 1)

**Table 1. Baseline Characteristics of AKI Patients and Non-AKI Patients**

VARIABLE	ALL (n=103)	AKI (n=40)	Non-AKI (n=63)	P Value
Age ( years)	51.12±13.35	55.67±10.55	47.46±15.53	0.003
Male (%)	71 (68.9%)	27 (67.5%)	15 (69.8%)	0.802
BMI (kg/m <sup>2</sup> )	24.36±4.06	24.35±3.21	24.11±4.67	0.807
Diabetes mellitus (%)	22 (21.4%)	13 (32.5%)	9 (14.3%)	0.028
Hypertension (%)	59 (57.3%)	28 (70%)	31 (49.2%)	0.038
<b>Type of surgery</b>				
CABG (%)	66 (64.1%)	29 (72.5%)	37 (58.7%)	0.156
Valve (%)	35 (34%)	9 (22.5%)	26 (41.3%)	0.053
CABG + Valve (%)	2 (1.9%)	2 (5%)	0 (0%)	0.148
Hemoglobin (g/dL)	13.33±1.57	12.98±1.50	13.60±1.64	0.047
Serum bicarbonate (mEq/L)	21.65±3.50	20.98±3.22	22.27±3.45	0.016
Serum glucose(mg/dL)	105 (56-479)	109 (75-313)	104.5 (56-479)	0.105
HbA1C(%)	5.5 (3.9-12.6)	5.65 (4.30-12.60)	5.5 (3.90-11.80)	0.623
Creatinine (mg/dL)	0.86 (0.4-3.0)	0.98 (0.56-2.44)	0.83 (0.4-3.0)	0.222
BUN (mg/dL)	12 (5-37)	13 (6-32)	11.5 (5-37)	0.010
Albumin (g/dL)	3.69±0.41	3.76±0.44	3.64±0.41	0.296
GFR (mL/min/1,73 m <sup>2</sup> )	82.47±26.82	76.15±24.57	88.00±27.55	0.026
Total cholesterol (mg/dL)	160.57±34.21	163.22±37.69	155.71±31.39	0.175
pH urine	6 (5-8)	6 (5-7)	6 (5-8)	0.305

**Tabel 2. Comparison of Postoperative ICU Stay, Hospital Stay, In-hospital Mortality and Mortality within 30 Days after Discharge From Hospital.**

Variabel	AKI (n=39)	Non-AKI (n=62)	P Value
ICU stay	3.56±1.93	1.84±1.45	0.001
	AKI (n=35)	Non-AKI (n=62)	
Hospital stay	11.91±3.50	8.65±2.90	0.000
	AKI (n=40)	Non-AKI (n=63)	
In-hospital mortality	5 (12.5%)	1(1.6%)	0.021
	AKI (n=35)	Non-AKI (n=62)	
Mortality within 30 days	2(5.7%)	1(1.6%)	0.262

The study also found that the duration of ICU care in patients who had AKI post cardiac surgery was  $3.56 \pm 1.93$  days versus  $1.84 \pm 1.45$  days in non-AKI patients with P value 0.001. Similarly, longer duration of hospitalization in patients with AKI post cardiac surgery was  $11.91 \pm 3.50$  days versus  $8.65 \pm 2.90$  days in non-AKI patients with P value 0.000. Data on mortality showed a significant in-hospital mortality rates in 5 patients (12.5%) with AKI post cardiac surgery compared with 1 patient (1.6%) in non AKI with P value 0.021 . Meanwhile, for 30 days mortality showed no significant difference, 2 patients (5.7%) with AKI post cardiac surgery and 1 patient (1.6%) in non-AKI patients with P value 0.262. (Table 2)

The data showed that the highest incidence of AKI post cardiac surgery occurred at low serum bicarbonate level (group 1) compared to group 2 and 3. In group 1 we found 26 people with AKI post cardiac surgery (65%) while in group 2 there were 11 people (27.5%) and group 3 there were 3 people (7.5%) with P value 0.022. (Table 3)

**Table 3. AKI Stage and Serum Bicarbonate Levels Group**

VARIABLE	Group 1 (<22 mEq/L) (n=52)	Group 2 (22-24 mEq/L) (n=31)	Group 3 (>24 mEq/L) (n=20)	P Value
AKI (%)	26 (50%)	11 (35.5%)	3 (15%)	0.022

**Table 4. Bivariate Logistic Regression Analysis of Cardiac Surgery-Associated AKI**

VARIABLE	OR	95% CI	P Value
Serum bicarbonate			
Group 1	5.66	1.48-21.69	0.011
Group 2	3.11	0.74-13.03	0.119
Group 3	Reference		
Age $\geq 60$ years	4.82	1.96-11.85	0.001
Male	0.89	0.38-2.10	0.802
Hypertension	2.40	1.04-5.56	0.038
Diabetes mellitus	2.88	1.09-7.60	0.028
Type of surgery (CABG)	1.97	0.84-4.64	0.118
Hemoglobin <13 g/dL	0.98	0.44-2.19	0.972
BUN >20 (mg/dL)	2.41	1.04-5.56	0.040
GFR <60 (mL/min/1.73m <sup>2</sup> )	2.27	0.84-6.12	0.103

Based on the results of bivariate analysis logistic regression, we found risk factors for the incidence of CSA-AKI. Patients in group 1 [OR 5.66 (1.48-21.69), p = 0.011] and group 2 [OR 3.11 (0.74-12.03), p =

0.119] were higher for CSA-AKI events compared with patients in group 3, indicating that low preoperative bicarbonate serum levels increased CSA-AKI events. Age  $\geq 60$  years [OR 4.82 (0.84-4.64),  $p = 0.001$ ], hypertension [OR 2.40 (1.04-5.56),  $p = 0.040$ ], DM type 2 [OR 2.88 (1.09-7.60),  $p = 0.032$ ], GFR  $<60$  [OR 2.27 (0.84-6.12),  $p = 0.103$ ], and BUN [OR 2.40 (1.04-5.56),  $p = 0.040$ ] was significantly associated with the incidence of postoperative heart AKI. (Table 4)

We used multivariate analysis to know which independent variables are the most dominant and affect the incidence of CSA-AKI. Multivariate analysis showed that only 2 independent factors that can predict the occurrence of CSA-AKI: serum bicarbonate group 1 with serum bicarbonate value  $<22$  (low) and patient age  $\geq 60$  years. Group 1 bicarbonate serum is the most dominant risk factor affecting the incidence of CSA-AKI [OR 6.99 (1.68-29.15),  $p = 0.008$ ]. (Table 5)

**Table 5. Multivariate Logistic Regression Analysis of Cardiac Surgery-Associated AKI**

VARIABLE	OR	95% CI	P Value
<b>Serum bicarbonate</b>			
<b>Group 1</b>	6.99	1.68-29.15	0.008
<b>Group 2</b>	4.62	0.99-21.44	0.051
<b>Age <math>\geq 60</math> years</b>	4.51	1.71-11.86	0.002

## Discussion

Subjects in this study were collected consecutively from patients undergoing CABG and or heart valve surgery from January to December 2017. In this study data were taken from medical records of cardiac surgery patients from January to December 2017. There were 103 patients who have met the inclusion and exclusion criteria.

This study showed that lower-than-normal serum bicarbonate values were associated with decreased renal function and poorer outcome in patients undergoing heart surgery.

AKI post cardiac surgery is a common complication of heart surgery. From previous studies show  $\pm 30\%$  of patients undergoing heart surgery will have AKI postcardiac surgery. According to RIFLE and AKIN criteria, the incidence of AKI post cardiac surgery ranges from 9-39% depends on the clinical profile of the analyzed patients and the type of heart surgery.<sup>8</sup> In this study, the incidence of AKI post cardiac surgery was 38.8%, and higher rate in CABG than in valve surgery. This probably happened because the patients undergoing CABG were older with more comorbidity than the patients undergoing valve surgery.

AKI post cardiac surgery is also known to be associated with mortality and morbidity, including postoperative and infectious complications. In accordance with previous studies, the length of postoperative in intensive care and hospital care duration was significantly higher in patients with AKI post cardiac surgery. Similarly, postoperative mortality rates were higher in patients with AKI post cardiac surgery. However, for death within 30 days after returning from the hospital showed no statistically significant difference despite a higher mortality rate in patients with AKI post cardiac surgery. This is possible because the number of study subjects is small compared with previous studies.

A study by Shah et al showed that serum bicarbonate levels  $\leq 22$  mEq/L were associated with an increase of 54% of renal disease progression compared with serum bicarbonate levels of 25-26 mEq/L.<sup>9</sup> This study also showed that low serum bicarbonate levels were associated with a higher incidence of AKI post cardiac surgery. Whereas in this research we found the incidence of AKI post cardiac surgery on low bicarbonate level ( $<22$  mEq/L) was 65%, normal bicarbonate level (22-24 mEq/L) 27.5%, and high bicarbonate level ( $> 24$  mEq/L) 7.5%. This makes it possible that low levels of bicarbonate will affect the clinical outcome worse than normal or high levels of bicarbonate.

In this study, bivariate analysis showed that low and normal serum bicarbonate level, age  $\geq 60$  years, hypertension, diabetes mellitus, GFR  $<60$ , and type of cardiac surgery had significant value. However, after a multivariate analysis, only two independent factors were able to predict the occurrence of AKI post cardiac

surgery, low serum bicarbonate level <22 mEq/L and patient age  $\geq 60$  years with the most dominant risk factor affecting the incidence of AKI post cardiac surgery was low serum bicarbonate level <22 mEq/L [OR 6.99 (1.68-29.15),  $p = 0.008$ ].

The exact mechanisms underlying the association of low serum bicarbonate concentrations with the incidence of AKI post cardiac surgery remain unclear. But there are several possibilities, metabolic acidosis characterized by decreased serum bicarbonate concentration induces increased production of ammonia in the renal medulla thus activating complement pathways and tubular inflammation. In addition, these excess acids activate the renin-angiotensin-aldosterone system causing injury to the renal tubulointerstitial resulting in decreased renal function.<sup>10</sup>

**Conflict of interest:** None declared

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