Elevated strong ion gap: A predictor of the initiation of continuous renal replacement therapy in acute kidney injury

Bulent Gucyetmez, MD[1], Zeynep Tugce Sarikaya, MD[1] and Filiz Tuzuner, MD[2]

[1] Department of Anesthesiology and Reanimation, Acıbadem Mehmet Ali Aydınlar University School of Medicine, Istanbul, Turkey; [2] General Intensive Care, Acıbadem Taksim Hospital, Istanbul, Turkey

ABSTRACT

Background: There is no optimal timing for continuous renal replacement therapy (CRRT) in acute kidney injury (AKI). AKI is a reason for the increased unmeasured anions, which refers to the increased organic acids in the blood, and they can be detected by calculating strong ion gap (SIG). SIG level at the moment of the AKI diagnosis may be a predictor for the initiation of CRRT.

Methods: Patients who were diagnosed with AKI in the first week of the intensive care unit (ICU) period were included in this prospective observational study. At the moment of the AKI diagnosis, blood gas samples were recorded, and SIG was calculated.

Results: The median level of SIG at the moment of the AKI diagnosis of CRRT (+) patients was significantly higher than CRRT (-) patients (7.4 and 3.2 mmol L^{-1}, respectively). In the multivariate Cox regression analysis, the likelihood of the initiation of CRRT was increased 1.16-fold (1.01-1.33) and 4.0-fold (1.9-8.7) by only 1 mmol L^{-1} increases in SIG and SIG ≥6 mmol L-1 at the moment of AKI diagnosis, respectively ($p = 0.035$ and $p < 0.001$).

Conclusions: Increased SIG at the moment of the AKI diagnosis in patients with AKI may be a predictive marker to initiate CRRT.

Key Indexing Terms: Strong ion gap; Acute kidney injury; CRRT. **[Am J Med Sci 2024;367(2):112–118.]**

INTRODUCTION

In patients with acute kidney injury (AKI), the most crucial question is when continuous renal replacement therapy (CRRT) should be initiated if there are no urgent indications. The Clinical Practice Guideline for Acute Kidney Injury Guidelines (KDIGO) for AKI states that there is no optimal time for CRRT.[1] In the last six years, some notable studies have focused on some biomarkers and the interval between the moment of AKI diagnosis and the initiation of the CRRT or other time variables.[2–9] However, controversial results were observed in these studies, including meta-analyses. The secretion of organic acids is one of the physiological functions of the kidney, and intact kidneys remove most of the metabolism-generated acid via ammonia generation.[10–12] In AKI, this function can deteriorate, causing organic acids to accumulate in the blood. Therefore, AKI is known to be one reason for high organic acids, which are represented as unmeasured anions (UAs).[13,14] UAs are also detected by calculating the Stewart approach's strong ion gap (SIG), in which a higher SIG means higher UAs.[15] Hence, a high SIG at the moment of the AKI diagnosis may be used as a predictor of the need for CRRT, a topic we thought was worth investigating.

METHODS

Study design, population, definitions, and formulas

This prospective observational study was approved by the local ethics committee (Acıbadem University and Acıbadem Healthcare Institutions Medical Research Ethics Committee -ATADEK- 2019-14/18, Chief: Prof. Dr. Ismail Hakkı Ulus) and complied with the Declaration of Helsinki. Written informed consent was obtained from all participants before the examination. In three tertiary general intensive care units (ICUs) between 12 September 2019 and 1 January 2021, patients who were >18 years old and were diagnosed with AKI in the first week of their ICU period were included in the study. Patients with diabetic ketoacidosis, drug intoxication, chronic renal failure, liver failure, and cancer were excluded from the study because these conditions can increase SIG. Patients to whom

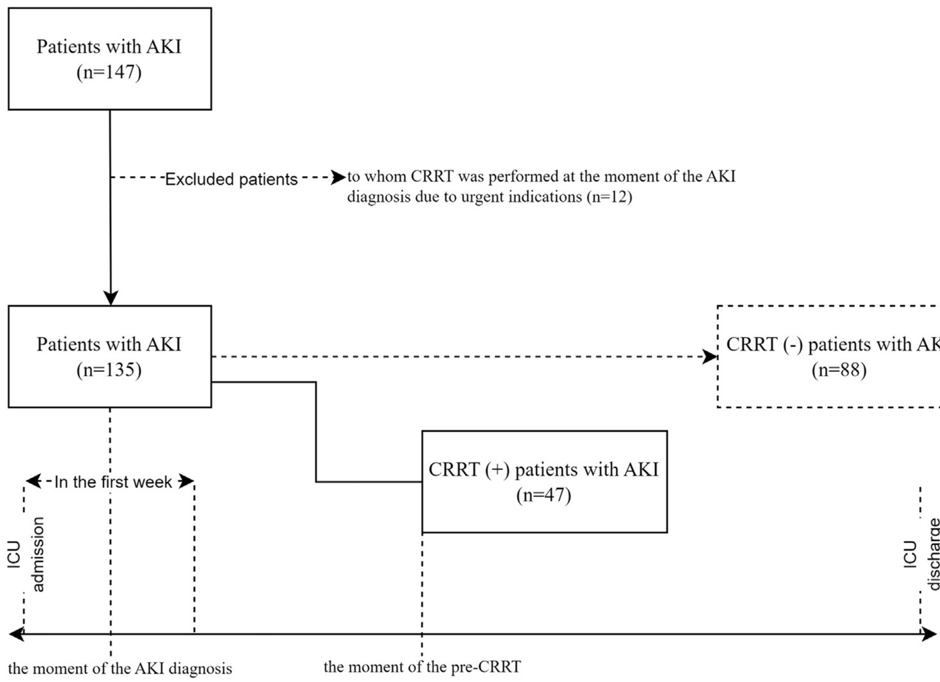

FIG. 1. Study flowchart.

CRRT was performed at the moment of the AKI diagnosis due to urgent indications (pH < 7.2, K>6 $mmolL^{-1}$, pulmonary edema, and uremic complications) were also excluded (Fig. 1).

The KDIGO guidelines were used for AKI definition and staging.[1] According to KDIGO, severe acidosis (pH < 7.2), hyperkalemia (K>6.0 mmol L^{-1}), anuria, volume overload despite diuretic usage, and uremic encephalopathy were used as indicators to initiate CRRT by the ICU doctor teams.[1,16]

At the moments of the AKI diagnosis (for all patients) and the pre-CRRT (for only CRRT (+) patients), arterial blood gas samples, albumin (Alb), magnesium (Mg), and inorganic phosphorus (P_i) levels were recorded by an assigned intensivist in each ICU doctor team. Other doctors did not know any calculated SIG values.

For all patients, age (years), sex, body mass index (BMI) (kg m^{-2}), Charlson comorbidity index (CCI), APACHE $II_{Cr\text{-}corr}$ (creatinine-corrected APACHE II), $SOFA_{Cr\text{-}corr}$ (creatinine-corrected SOFA) score, the main diagnoses, CRRT indications, pH, $PaCO_2$ (mmHg), HCO_3 (mmol L^{-1}), standard base excess (SBE) (mmol L^{-1}), Na (mmol L^{-1}), K (mmol L^{-1}), Ca (mmol L^{-1}), Mg (mg dL^{-1}), Cl (mmol L^{-1}), lactate (mmol L^{-1}), Alb (g L^{-1}), P_i (mg dL^{-1}), SIG (mmol L^{-1}), anion gap (AG) (mmol L^{-1}), urea (mg dL^{-1}), creatinine (mg dL^{-1}), length of ICU stay, dialysis requirements, and mortality were recorded.

SIG and AG were calculated for each patient by using the formula;[15]

$$SIG = (Na + K + Ca + Mg - Cl - lactate) - \left(0.003 \times P_aCO_2 \times 10^{(pH-6.1)}\right) - \left(Alb(g\,L^{-1}) \times [0.123 \times pH - 0.631]\right) - \left(P_i(mmol\,L^{-1}) \times [0.309 \times pH - 0.469]\right)$$

$$AG = Na + K - Cl - HCO3$$

Milligram values for Mg and P_i were converted to mmol by using these formulas;[17,18]

$$Mg(mmolL^{-1}) = Mg(mgdL^{-1}) \times 0.41152$$

$$P_i(mmolL^{-1}) = P_i(mgL^{-1}) \times 0.323$$

Blood gas data were acquired by using an ABL 800 (Radiometer, Denmark, Copenhagen) blood gas device, which employs ion-selective electrodes. Alb, Mg, P_i, urea, and creatinine were acquired by using a Cobas C 303 device (Roche, Rotkreuz, Switzerland). A Fresenius multifiltrate CRRT machine (Hamburg, Germany) was used to perform CRRT.

Statistical analysis

Descriptive data are presented as mean ± sd, median (quartiles), and percentages. The Kolmogorov–Smirnov and Shapiro–Wilcox tests were used to detect normality. To compare CRRT (+) and (-) groups, Student's t, Mann–Whitney U, and chi-square (Fisher's exact) tests were used. In CRRT (+) patients, parameters of the moments of the AKI diagnosis and the pre-CRRT were compared by using paired Student's t and Wilcoxon rank tests. For the likelihood of the initiation of CRRT, univariate and multivariate Cox regression analyses were used by adding all significantly different parameters in the CRRT (+) group. The Enter method was used in the model. The generalized R^2 value for the multivariate Cox regression models was calculated by using 1-exp(XLR^2/n) formula.[19] The primary goal was to investigate whether or not the SIG value at the moment of AKI diagnosis was a predictor for the initiation of CRRT. The cut-off value and area under the curve (AUC) of SIG for initiation of CRRT were detected by using ROC analysis. The estimated power of this study was detected as 1.0 by using the independent t-test for means (as per CRRT (+) and (-) groups' sizes [88 and 47], the mean difference of groups' SIG levels at the moment of AKI diagnosis [4.6 mmol L^{-1}] and $\alpha = 0.05$). SPSS version 28 was used for all statistical analyses, and the *p*-value of <0.05 was accepted for significance.

RESULTS

One hundred thirty-five of 147 patients with AKI were included in the study. Twelve patients were excluded because CRRT was performed on them at the moment of AKI diagnosis due to urgent indications. CRRT was performed on only 47 of 135 patients (35.4 %). The mortality rates for all patients with AKI and only CRRT (+) patients were 27.4 % and 48.9 %, respectively (Table 1).

Patients with stages I, II, and III numbered 49 (36.3 %), 69 (51.1 %), and 17 (12.6 %), respectively (Table 1). CRRT was only performed in stage II (32/69; 46.4 %) and stage III patients (15/17; 88.2 %) (Table 1).

In CRRT (+) patients, $SOFA_{Cr\text{-}corr}$, K, SIG, AG, urea, creatinine, dialysis requirement, length of ICU stay, and mortality were significantly higher. In contrast, pH, P_aCO_2, HCO_3, SBE and albumin were significantly lower than in CRRT (-) patients ($p = 0.042$, $p = 0.017$, $p < 0.001$, $p < 0.001$, $p = 0.006$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.005$, $p = 0.035$, $p < 0.001$, $p < 0.001$ and $p = 0.033$, respectively) (Table 2).

For initiation CRRT, the cut-off value of SIG at the moment of the AKI diagnosis was detected as ≥6mmol L-1. For this cut-off value, AUC (CI 95 %), sensitivity, specificity, positive and negative predictive values, positive likelihood ratio, and accuracy values were 0.88 (0.81-0.95) ($p < 0.001$), 0.75, 0.94, 0.88, 0.87, 13.1 and 0.87 respectively.

In the univariate Cox regression analysis, SIG≥6 mmol L^{-1}, SIG (mmol L^{-1}), SBE, HCO_3, urea, creatinine, K, $PaCO_2$, AG, and pH at the moment of the AKI diagnosis were related to the initiation of the CRRT ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.003$, $p = 0.010$, $p = 0.017$ and $p = 0.023$ respectively) (Table 3). However, in the multivariate Cox regression analysis Model I and II, the likelihood of performing CRRT was increased 1.16-fold (1.01-1.33) and 4.0-fold (1.9-8.7) by only one mmol L^{-1} increase in SIG

Table 1. Patients' characteristics and outcomes.

n	135
Age, (year)	79 (70-85)
Male, n (%)	77 (57.0)
BMI, (kg/m^2)	26.9 (23.4-31.3)
CCI	7 (5-8)
APACHE $II_{Cr\text{-}corr}$	21±8
SOFA $Score_{Cr\text{-}corr}$	6 (3-8)
Diagnosis, n (%)	
Sepsis	103 (76.3)
Hypovolemia	19 (14.1)
Heart failure	13 (9.6)
The day that AKI was diagnosed	
At the ICU admission	102 (75.6)
2nd day	6 (4.4)
3rd day	13 (9.6)
Between 4th – 7th days	14 (10.4)
AKI stages	
Stage I	49 (36.3)
Stage II	69 (51.1)
Stage III	17 (12.6)
CRRT (+) patients, n (%)	47 (34.8)
Stage I	0 (0.0)
Stage II	32 (68.1)
Stage III	15 (31.9)
Indications for CRRT, n (%)	19 (40.4)
Uremic encephalopathy	15 (31.9)
Volume overload	8 (17.0)
Severe metabolic acidosis	3 (6.4)
Anuria	2 (4.3)
Severe hyperpotassemia	
Blood gas and laboratory parameters at the moment of AKI diagnosed	
pH	7.39 (7.31-7.47)
P_aCO_2, (mmHg)	36.1 (30.9-44.7)
HCO_3, (mmol L^{-1})	22.36 ± 6.0
SBE, (mmol L^{-1})	-2.3 ± 7.0
Na, (mmol L^{-1})	138 (134-142)
Cl, (mmol L^{-1})	105 (99-109)
Na-Cl difference, (mmol L^{-1})	33 ± 7
K, (mmol L^{-1})	4.0 (3.6-4.6)
Ca, (mmol L^{-1})	1.12 (1.6-1.18)
Mg, (mg dL^{-1})	2.1 (1.8-2.5)
Lactate, (mmol L^{-1})	1.9 (1.3-3.3)
Albumin, (g L^{-1})	26 (23-30)
P_i, (mg dL^{-1})	4.7 ± 1.8
SIG, (mmol L^{-1})	4.5 (3.5-6.3)
AG, (mmol L^{-1})	14 (12-17)
Urea, (mg dL^{-1})	99 (72-144)
Creatinine, (mg dL^{-1})	2.0 (1.5-2.8)
Outcomes	
Dialysis requirement, n (%)	15 (11.1)
Length of ICU stay, days	10 (5-21)
Mortality, (%)	37 (27.4)
Mortality in CRRT (+) patients, n (%)	23 (48.9)

AG, anion gap; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CCI, Charlson Comorbidity Index; Cr-corr, creatinine corrected; CRRT, continuous renal replacement therapy; SOFA, Sequential Organ Failure Assessment

Table 2. Comparisons between CRRT (-) and (+) groups at the moment of the AKI diagnosis.

	CRRT (-) (*n* = 88)	CRRT (+) (*n* = 47)	p
Age, (year)	80 (71-87)	79 (66-82)	0.199
Male, n (%)	47 (53.4)	30 (63.8)	0.244
BMI	27.2 ± 6.7	28.6 ± 5.4	0.227
CCI	7 (5-8)	7 (6-8)	0.527
APACHE $II_{Cr\text{-}corr}$	20 ± 7	22 ± 8	0.060
SOFA $Score_{Cr\text{-}corr}$	6 ± 3	7 ± 3	***0.042***
Diagnosis, n (%)			0.206
Sepsis	71 (80.7)	32 (68.1)	
Hypovolemia	11 (12.5)	8 (17.0)	
Heart failure	6 (6.8)	7 (14.9)	
The day that AKI was diagnosed			0.993
At the ICU admission	65 (73.9)	37 (78.7)	
AKI stages, n (%)			***<0.001***
Stage I	49 (55.7)	0 (0.0)	
Stage II	37 (42.0)	32 (68.1)	
Stage III	2 (2.3)	15 (31.9)	
Blood gas and laboratory parameters			
pH	7.40±0.09	7.33 ± 0.14	***0.005***
P_aCO_2, (mmHg)	38.2 (31.3-46.0)	33.1 (30.0-39.2)	***0.035***
HCO_3, (mmol L^{-1})	23.9±5.2	20.2 ± 6.6	***<0.001***
SBE, (mmol L^{-1})	-0.6±6.0	-5.5 ± 7.7	***<0.001***
Na, (mmol L^{-1})	139 (135-142)	138 (132-141)	0.105
Cl, (mmol L^{-1})	106 (101-110)	104 (98-108)	0.172
Na-Cl difference, (mmol L^{-1})	33±6	33 ± 7	0.667
K, (mmol L^{-1})	3.9 (3.5-4.4)	4.3 (3.8-4.7)	***0.017***
Ca (mmol L^{-1})	1.11 (1.06-1.16)	1.14 (1.08-1.20)	0.147
Mg (mg dL^{-1})	2.1 (1.8-2.6)	2.0 (1.8-2.5)	0.808
Lactate, (mmol L^{-1})	1.9 (1.3-3.2)	2.0 (1.4-3.5)	0.450
Albumin, (g L^{-1})	26 (23-31)	25 (22-27)	***0.033***
P_i, (mg dL^{-1})	4.5±1.7	5.1±2.1	0.079
SIG (mmol L^{-1})	3.2 (1.4-4.9)	7.4 (5.7-8.8)	***<0.001***
AG, (mmol L^{-1})	14 (11-16)	17 (15-19)	***<0.001***
Urea, (mg dL^{-1})	92 (66-132)	121 (87-170)	***0.006***
Creatinine, (mg dL^{-1})	1.9 (1.4-2.4)	2.6 (1.8-3.5)	***<0.001***
Outcomes			
Duration between AKI and CRRT, (h)	-	24 (9-42)	
Duration of CRRT, (h)	-	144 (72-291)	
Dialysis requirement, n (%)	0 (0.0)	15 (31.9)	***<0.001***
Length of ICU stay, days	8 (5-14)	13 (8-28)	***<0.001***
Mortality, (%)	14 (15.9)	23 (48.9)	***<0.001***

AG, anion gap; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CCI, charlson comorbidity index; CRRT, continuous renal replacement therapy; ICU, intensive care unit; SBE, standard base-excess; SIG, strong ion gap; SOFA, sequential organ failure assessment.

and SIG≥ 6 mmol L^{-1} at the of the AKI diagnosis respectively (p = 0.035 and $p < 0.001$) (Table 3). In patients with CRRT (+), Na, Na-Cl difference, Ca, SIG, AG, urea, and creatinine at the moment of the AKI diagnosis significantly differed from the levels at the moment of the pre-CRRT, whereas pH, P_aCO_2, HCO_3, SBE, K, Cl and P_i were similar between the two times (Table 4).

DISCUSSION

This study reports two essential results: 1) increased SIG at the moment of AKI diagnosis was found to be the most notable predictor of the need for CRRT. 2) Increased organic acids was found to be the most important reason for metabolic acidosis in patients with CRRT (+).

Recent studies have generally concentrated on some biomarkers and the time between AKI diagnosis and the initiation of CRRT.[2–9,20] We think that these studies should be discussed from the point of view of optimal CRRT timing.

Biomarkers such as blood/urine cystatin C, blood/urine NGAL, KIM-1, and TIMP-2xIGFBP-7 give us some information about kidney functions in AKI.[21] However,

Table 3. Cox regression analysis for the risk of the initiating CRRT in patients with AKI (for variables at the moment of the AKI diagnosis).

	Univariate		Multivariate Model I		Multivariate Model II	
	HR (CI 95 %)	p	HR (CI 95 %)	p	HR (CI 95 %)	p
SIG ≥ 6mmol L^{-1}	4.3 (2.2-8.4)	***<0.001***			4.0 (1.9-8.7)	***<0.001***
SIG, (mmol L^{-1})	1.10 (1.05-1.16)	***<0.001***	1.16 (1.01-1.33)	***0.035***		
SBE, (mmol L^{-1})	0.90 (0.87-0.94)	***<0.001***	0.90 (0.73-1.11)	0.330	0.96 (0.78-1.16)	0.651
HCO_3, (mmol L^{-1})	0.90 (0.86-0.95)	***<0.001***	0.91 (0.84-1.05)	0.521	0.85 (0.77-1.12)	0.737
Urea, (mg dL^{-1})	1.01 (1.00-1.02)	***<0.001***	1.00 (0.99-1.01)	0.647	1.00 (0.99-1.01)	0.415
Creatinine, (mg dL^{-1})	1.41 (1.22-1.62)	***<0.001***	1.17 (0.94-1.46)	0.164	1.13 (0.91-1.40)	0.258
K, (mmol L^{-1})	1.50 (1.15-1.94)	***0.003***	0.96 (0.63-1.45)	0.837	0.89 (0.57-1.38)	0.597
P_aCO_2, (mmHg)	0.96 (0.93-0.99)	***0.010***	1.00 (0.91-1.10)	0.953	0.96 (0.88-1.05)	0.422
AG, (mmol L^{-1})	1.06 (1.01-1.12)	***0.017***	0.92 (0.82-1.04)	0.175	0.97 (0.89-1.04)	0.965
pH	0.67 (0.01-0.69)	***0.023***	1.01 (0.89-1.14)	0.885	0.98 (0.97-1.09)	0.667
SOFA $Score_{Cr\text{-}corr}$	1.02 (0.93-1.12)	0.707				
Albumin, (g L^{-1})	0.96 (0.90-1.02)	0.123				

AG, anion gap; AKI, acute kidney injury; CI, confidence interval; CRRT, continuous renal replacement therapy; SBE, standard base-excess; SIG, strong ion gap
Enter method was used in the multivariate Cox regression analysis. The omnibus tests significances were <0.001 for both models, and the generalized R^2 for Model I and II were 0.78 and 0.81 repectively.

biomarker studies have mainly focused on the early prediction of AKI, not of CRRT.[21] As for other studies of the optimal timing of CRRT, their results are controversial because of their limited number, limited evidence, and heterogeneous data.[6] Finally, the most important limitation of biomarkers is their costs. We did not measure any biomarkers in this study. This can be accepted as a limitation, but SIG is a more practical and less expensive parameter. Additionally, SIG could be a biomarker of glomerular filtration and tubular secretion of organic acids.

Interestingly, recent notable studies, such as AKIKI-1 and 2, STARRT-AKI, and ELAIN, have only focused on the interval between the moments of AKI diagnosis and CRRT.[2,3,7,9] However, each study had different definitions for early or delayed strategies. In these studies, CRRT was generally performed in the 6th, 8th, or 12th hours after observing urgent indications. This can be troubling because these studies did not make it clear why we should wait or not wait. The primary outcome of these studies was mortality, which cannot be a reason

Table 4. Comparison between blood gas and laboratory parameters at the moment of AKI diagnosis and the pre-CRRT in CRRT (+) patients.

	at the moment of AKI diagnosis	at the moment of the pre-CRRT	p
Patients, n (%)	47 (34.8)		
Duration between the moment of the AKI diagnosis and CRRT, (h)	24 (9-42)		
Blood gas and laboratory parameters			
pH	7.33 ± 0.14	7.34 ± 0.12	0.667
P_aCO_2, (mmHg)	33.1 (30.0-39.2)	36.8 (29.9-41.9)	0.310
HCO_3, (mmol L^{-1})	20.2 ± 6.6	20.6 ± 5.5	0.636
SBE, (mmol L^{-1})	-5.5 ± 7.7	-4.9 ± 7.0	0.466
Na, (mmol L^{-1})	138 (132-141)	140 (135-144)	***<0.001***
Cl, (mmol L^{-1})	103 ± 8	104±7	0.255
Na-Cl difference, (mmol L^{-1})	33±7	35±6	***<0.001***
K, (mmol L^{-1})	4.3 (3.8-4.7)	4.3 (3.76-4.8)	1.000
Ca, (mmol L^{-1})	1.13 ± 0.11	1.09 ± 0.13	***0.002***
Mg, (mg/dL)	2.0 (1.8-2.5)	2.2 (1.8-3.0)	0.118
Lactate, (mmol L^{-1})	2.0 (1.4-3.5)	1.8 (1.2-3.3)	0.360
Albumin, (g/L)	25 (22-27)	25 (22-29)	0.874
P_i, (mg dL^{-1})	5.1 ± 2.1	5.0 ± 2.1	0.672
SIG, (mmol L^{-1})	7.4 (5.7-8.8)	9.5 (7.6-12.1)	***<0.001***
AG, (mmol L^{-1})	17 (15-19)	19 (17-21)	***<0.001***
Urea, (mg dL^{-1})	121 (87-170)	163 (112-211)	***<0.001***
Creatinine, (mg dL^{-1})	2.6 (1.8-3.5)	2.9 (2.1-4.0)	***<0.001***

AG, anion gap; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; SBE, standard base-excess; SIG, strong ion gap for initiating CRRT. Furthermore, their results about mortality are already controversial in these studies, including meta-analyses.[2,3,6–9] For instance, in one study, although mortality was similar between the early and delayed groups, mortality in the delayed group was higher than that in the early group when excluding all CRRT (-) patients.[3] In that study, all CRRT (-) patients were in the delayed group, and there was no explanation why these patients did not need CRRT. In another review, the authors suggest “not too early, not too late, but just at the right time for each specific patient”.[20] What does “the right time” mean? How can we determine “the right time”? In our opinion, the study’s primary outcome regarding this topic should be searching for a predictor of the need for CRRT, not mortality or an unclear time. Our study demonstrates that SIG levels could be one of the parameters to indicate the right time for initiating CRRT in AKI.

In our study, the most crucial difference between CRRT (+) and (-) patients at the moment of the AKI diagnosis was metabolic acidosis due to lower pH, HCO_3, and SBE (Table 2). Two main reasons for metabolic acidosis in AKI are known: hyperchloremia and high UAs.[13,14,22] We did not observe hyperchloremia in our CRRT (+) patients (Table 2). Lactate could not be a reason for acidosis because it was similar between the groups (Table 2). On the other hand, the urea level of CRRT (+) patients at the moment of the AKI diagnosis was significantly higher than that of CRRT (-) patients (Table 2). However, urea is a neutral molecule and cannot be a reason for metabolic acidosis.[23] Given these circumstances, the only reason for metabolic acidosis in CRRT (+) patients can be high UAs caused by deteriorated glomerular filtration and secretion of organic acids. Furthermore, when we compared parameters at the moments of the AKI diagnosis and the pre-CRRT in CRRT (+) patients, the only reason for metabolic acidosis was an elevated SIG at both times (Table 4). Additionally, SIG was significantly increased at the moment of the pre-CRRT over the AKI diagnosis. Indeed, AG is also used to determine UAs. However, it should be corrected for albumin, at least.[24] Moreover, if it is fully corrected, it becomes SIG. For this reason, SIG seems like a better marker than AG in this study (Table 3).

In Table 4, increases in Na and the Na-Cl difference point to an alkaline effect, probably due to sodium bicarbonate usage until CRRT. Increases in cations at the moment of pre-CRRT, especially in Na, explain the similar pH, HCO_3, and SBE at both moments, although SIG was higher at that time. At the same time, this result indicates that administering cations such as sodium bicarbonate may regulate pH or HCO_3 levels; however, it cannot change the existence of the increased organic acid. Obviously, if the reason for the acidosis is increased organic acids, the only way to correct this situation is to remove them from the body by the kidney itself or an artificial filter. We believe that SIG levels can show the need for an artificial filter. Removing UA with CRRT by itself would not change the prognosis; however, it is the presence of CRRT use that likely makes the difference, where removal of SIG is just a marker of being a marker on CRRT.

On the other side, SIG levels in 12 excluded patients to whom CRRT was performed at the moment of AKI

Table 5. Patients performed CRRT caused by urgent indications at the moment of the AKI diagnosis (excluded patients).

Patients, n	12
Age, years	71 ± 14
Male, n (%)	7 (63.6)
BMI, (kg/m^2)	30.6 ± 7.7
CCI	6 ± 2
APACHE $II_{Cr\text{-}corr}$	24 ± 7
SOFA $Score_{Cr\text{-}corr}$	8 ± 4
Diagnosis, n (%)	
Sepsis	7 (58.3)
Hypovolemia	2 (16.7)
Heart failure	3 (25.0)
AKI stage, n (%)	
Stage I	0 (0.0)
Stage II	6 (50.0)
Stage III	6 (50.0)
Indications for CRRT, n (%)	
Uremic encephalopathy	5 (41.7)
Severe metabolic acidosis (pH<7.2)	4 (33.3)
Anuria	2 (16.7)
Hyperpotassemia (K>6.0)	1 (8.3)
Blood gas parameters at the moment of the AKI diagnosed	
pH	7.34 (7.20-7.39)
P_aCO_2, (mmHg)	34.3 ± 9.5
HCO_3, ($mmol\ L^{-1}$)	16.3 ± 5.5
SBE, ($mmol\ L^{-1}$)	-10.1 ± 7.6
Na, ($mmol\ L^{-1}$)	139 ± 7
Cl, ($mmol\ L^{-1}$)	105 ± 8
Na-Cl difference, ($mmol\ L^{-1}$)	33 ± 7
K, ($mmol\ L^{-1}$)	4.9 ± 0.9
Ca, ($mmol\ L^{-1}$)	1.10 ± 0.08
Mg, ($mg\ dL^{-1}$)	2.2 ± 0.6
Lactate, ($mmol\ L^{-1}$)	2.3 (1.3-6.4)
Albumin, ($g\ L^{-1}$)	25 ± 5.0
P_i, ($mg\ dL^{-1}$)	5.3 ± 1.8
SIG, ($mmol\ L^{-1}$)	9.6 (7.5-13.4)
AG, ($mmol\ L^{-1}$)	21 ± 8
Urea, ($mg\ dL^{-1}$)	187 ± 99
Creatinine, ($mg\ dL^{-1}$)	3.9 ± 1.6
Outcomes	
Duration of CRRT, hours	167 ± 88
Dialysis requirement, n (%)	3 (25.0)
Length of ICU stay, days	15 ± 12
Mortality, n(%)	5 (41.7)

AG, anion gap; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CCI, charlson comorbidity index; CRRT, continuous renal replacement therapy; ICU, intensive care unit; SBE, standard base-excess; SIG, strong ion gap; SOFA, sequential organ failure assessment.

diagnosis due to urgent indications and 47 patients to whom CRRT was performed a few hours later (median value: 24 hours) from AKI diagnosis were similar (9.6 [7.5-13.4] mmol L^{-1} and 9.5 [7.6-12.1] mmol L^{-1}, respectively) (Table 4 and 5). If the elevated SIG at the moment of the AKI diagnosis is an independent predictor of the need for CRRT, delaying the CRRT in those patients means that these patients will be exposed to an ever-increasing organic acid load, and CRRT will be inevitable.

CONCLUSIONS

Increased SIG was found to be the most important reason for metabolic acidosis in AKI. Increased SIG at the moment of AKI diagnosis was found to be a predictor for the initiation of CRRT in patients with AKI. Moreover, it could be a suitable marker that indicates the ‘right time’ for initiating CRRT, especially if its value is over 6 mmol L^{-1} at the moment of the AKI diagnosis. For these reasons, we suggest that SIG should be insistently and carefully monitored during AKI.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. KDIGO clinical practice guideline for acute kidney injury.; 2012.
2. **Zarbock A, Kellum JA, Schmidt C, et al.** Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN randomized clinical trial. *JAMA*. 2016;315 (20):2190–2199.
3. **Gaudry S, Hajage D, Schortgen F, et al.** Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med*. 2016;375 (2):122–133.
4. **Park JY, An JN, Jhee JH, et al.** Early initiation of continuous renal replacement therapy improves survival of elderly patients with acute kidney injury: a multicenter prospective cohort study. *Crit Care*. 2016;20(1):260.
5. **Lai TS, Shiao CC, Wang JJ, et al.** Earlier versus later initiation of renal replacement therapy among critically ill patients with acute kidney injury: a systematic review and meta-analysis of randomized controlled trials. *Ann Intensive Care*. 2017;7(1):38.
6. **Klein SJ, Brandtner AK, Lehner GF, et al.** Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med*. 2018;44(3):323–336.
7. **STARRT-AKI Investigators, Canadian Critical Care Trials Group. Australian and New Zealand Intensive Care Society Clinical Trials Group.** Timing of initiation of renal-replacement therapy in acute kidney injury. *N Engl J Med*. 2020;383(3):240–251.
8. **Gaudry S, Hajage D, Benichou N, et al.** Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet*. 2020;395(10235):1506–1515.
9. **Gaudry S, Hajage D, Martin-Lefevre L, et al.** Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. *Lancet*. 2021;397(10281):1293–1300.
10. **Hall JE.** *Guyton and Hall Textbook of Medical Physiology*. Elsevier Health Sciences; 2016.
11. **Weiner ID, Verlander JW.** Renal ammonia metabolism and transport. *Compr Physiol*. 2013;3(1):201–220.
12. **Wagner CA, Imenez Silva PH, Bourgeois S.** Molecular Pathophysiology of Acid-Base Disorders. *Semin Nephrol*. 2019;39(4):340–352.
13. **Zheng CM, Liu WC, Zheng JQ, et al.** Metabolic acidosis and strong ion gap in critically ill patients with acute kidney injury. *Biomed Res Int*. 2014;2014: 819528.
14. **Fidkowski C, Helstrom J.** Diagnosing metabolic acidosis in the critically ill: bridging the anion gap, Stewart, and base excess methods. *Can J Anaesth*. 2009;56(3):247–256.
15. **Kellum JA, Elbers PWG.** *Stewart's Textbook of Acid-Base*. Lulu Press, Inc; 2013.
16. **Jörres A.** Timing of acute renal replacement therapy. annual update in intensive care and emergency medicine. 2016:111-116. doi:10.1007/978-3-319-27349-5_10.
17. Magnesium Unit Conversion Page :: MediCalculator ::: ScyMed ::: http://www.scymed.com/en/smnxps/psxrq261_c.htm. Accessed June 18, 2022.
18. ScyMed. MediCalc. http://www.scymed.com/en/smnxtb/tbcbktk1.htm. Accessed June 18, 2022.
19. Use of generalized R-squared in Cox regression. https://apha.confex.com/apha/134am/techprogram/paper_135906.htm. Accessed May 16, 2023.
20. **Kipnis E, Garzotto F, Ronco C.** Timing of RRT initiation in critically-ill patients: time for precision medicine. *J Thorac Dis*. 2016;8(10):E1242–E1243.
21. **Pickkers P, Darmon M, Hoste E, et al.** Acute kidney injury in the critically ill: an updated review on pathophysiology and management. *Intensive Care Med*. 2021;47(8):835–850.
22. **Rein JL, Coca SG.** I don’t get no respect”: the role of chloride in acute kidney injury. *Am J Physiol-Renal Physiol*. 2019;316(3):F587–F605. https://doi.org/10.1152/ajprenal.00130.2018.
23. **Wang H, Ran J, Jiang T.** Urea. subcellular biochemistry. 2014:7-29. doi:10.1007/978-94-017-9343-8_2.
24. **Hatherill M, Waggie Z, Purves L, Reynolds L, Argent A.** Correction of the anion gap for albumin in order to detect occult tissue anions in shock. *Arch Dis Child*. 2002;87(6):526–529.

Submitted January 20, 2023; accepted November 14, 2023.

Corresponding author: Bulent Gucyetmez, MD, Department of Anesthesiology and Reanimation, Acıbadem Mehmet Ali Aydınlar University School of Medicine, İçerenköy, Kayışdağı Cd. No: 32 34752 Ataşehir, Istanbul, Turkey. (E-mail: bulentgucyetmez@gmail.com).