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중증 급성 중독 환자에서 급성 신장 손상과 병원 내 사망률을 예측하기 위한 강이온차(Strong Ion Gap)의 중요성

심태진 · 조재완 · 이미진 · 정해원 · 박정배 · 서강석

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The Significance of the Strong Ion Gap in Predicting Acute Kidney Injury and In-hospital Mortality in Critically Ill Patients with Acute Poisoning

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Purpose: A high anion gap (AG) is known to be a significant risk factor for serious acid-base imbalances and death in acute poisoning cases. The strong ion difference (SID), or strong ion gap (SIG), has recently been used to predict in-hospital mortality or acute kidney injury (AKI) in patients with systemic inflammatory response syndrome. This study presents a comprehensive acid-base analysis in order to identify the predictive value of the SIG for disease severity in severe poisoning.
Methods: A cross-sectional observational study was conducted on acute poisoning patients treated in the emergency intensive care unit (ICU) between December 2015 and November 2020. Initial serum electrolytes, base deficit (BD), AG, SIG, and laboratory parameters were concurrently measured upon hospital arrival and were subsequently used along with Stewart's approach to acid-base analysis to predict AKI development and in-hospital death. The area under the receiver operating characteristic curve (AUC) and logistic regression analysis were used as statistical tests.
Results: Overall, 343 patients who were treated in the intensive care unit were enrolled. The initial levels of lactate, AG, and BD were significantly higher in the AKI group (n=62). Both effective SID [SIDe] (20.3 vs. 26.4 mEq/L, p<0.001) and SIG (20.2 vs. 16.5 mEq/L, p<0.001) were significantly higher in the AKI group; however, the AUC of serum SIDe was 0.842 (95% confidence interval [CI]=0.799-0.879). Serum SIDe had a higher predictive capacity for AKI than initial creatinine (AUC=0.796, 95% CI=0.749-0.837), BD (AUC=0.761, 95% CI=0.712-0.805), and AG (AUC=0.660, 95% CI=0.607-0.711). Multivariate logistic regression analyses revealed that diabetes, lactic acidosis, high SIG, and low SIDe were significant risk factors for in-hospital mortality.
Conclusion: Initial SIDe and SIG were identified as useful predictors of AKI and in-hospital mortality in intoxicated patients who were critically ill. Further research is necessary to evaluate the physiological nature of the toxicant or unmeasured anions in such patients.

Key Words: Poisoning; Acute kidney injury; Anion gap; Strong ion difference; Electrolytes

INTRODUCTION

Metabolic abnormality and acute kidney injury (AKI) are common but serious complications in critically ill patients. They occur in 20%-33% of patients in intensive care units (ICUs) and represent major risk factors for adult fatality[1-3]. The Henderson-Hasselbalch equation, which is traditionally used to interpret acid-base disorders, is coupled with the anion gap (AG) and clinical assessment to define acid-base imbalances. However, these variables for quantifying the degree of acid-base disturbances are dependent on normal

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plasma composition[1]. The traditional method has been criticized for not considering the impact of hypoalbuminemia and phosphatemia as well as the presence and impact of unmeasured anions when the patient is exposed to toxins. A simplistic clinical interpretation of acid-base derangements may be misleading when electrolyte and protein abnormalities are present[1].

An alternative paradigm for the interpretation of acid-base disorders is explained by Stewart' s approach, which allows for quantifying the effects of changes in the strong ion difference (SID), albumin and phosphate levels, and unmeasured anions-i.e., the strong ion gap (SIG). It has been used to predict AKI in septic patients or those with systemic inflammatory response syndrome. While several studies have shown that the SIG correlates with clinical outcomes in critically ill patients[2-4], some others have confirmed that these factors are not useful in such patients[1,5,6]. Although the physicochemical theory proposed by Stewart has served as the basis for understanding the mechanisms of metabolic acid-base disorders, it remains unclear how the laboratory parameters involved in acidosis or AKI influence clinical outcomes in critically ill patients with acute poisoning.

In the current study, we evaluated AKI and metabolic imbalances occurring at earlier stages of acute poisoning, and then used the Stewart model for acid-base analysis to predict subsequent poisoning severity.

MATERIALS AND METHODS

1. Study design and population

Between December 2015 and November 2020, 370 acute poisoning patients treated in the emergency ICU were recruited. Patients were considered eligible for ICU admission if they had a Poisoning Severity Score (PSS) of 3 or higher, or if they had a PSS of 2 and required monitoring and intervention[7]. The following patients were excluded from the study: cases below 15 years of age or with end-stage renal disease; those transferred from another hospital after undergoing hemodialysis or receiving intravenous sodium bicarbonate ($NaHCO_3$) for the treatment of acid-base imbalances; and patients arriving at the hospital 12 h or more after poisoning[8-10] (Fig. 1).

For each patient, medical records were carefully examined, and the following information was collected by 2 investigators: demographic data (e.g., sex and age), toxicology data, laboratory data, disease severity according to the Acute Physiology and Chronic Health Evaluation (APACHE) II and

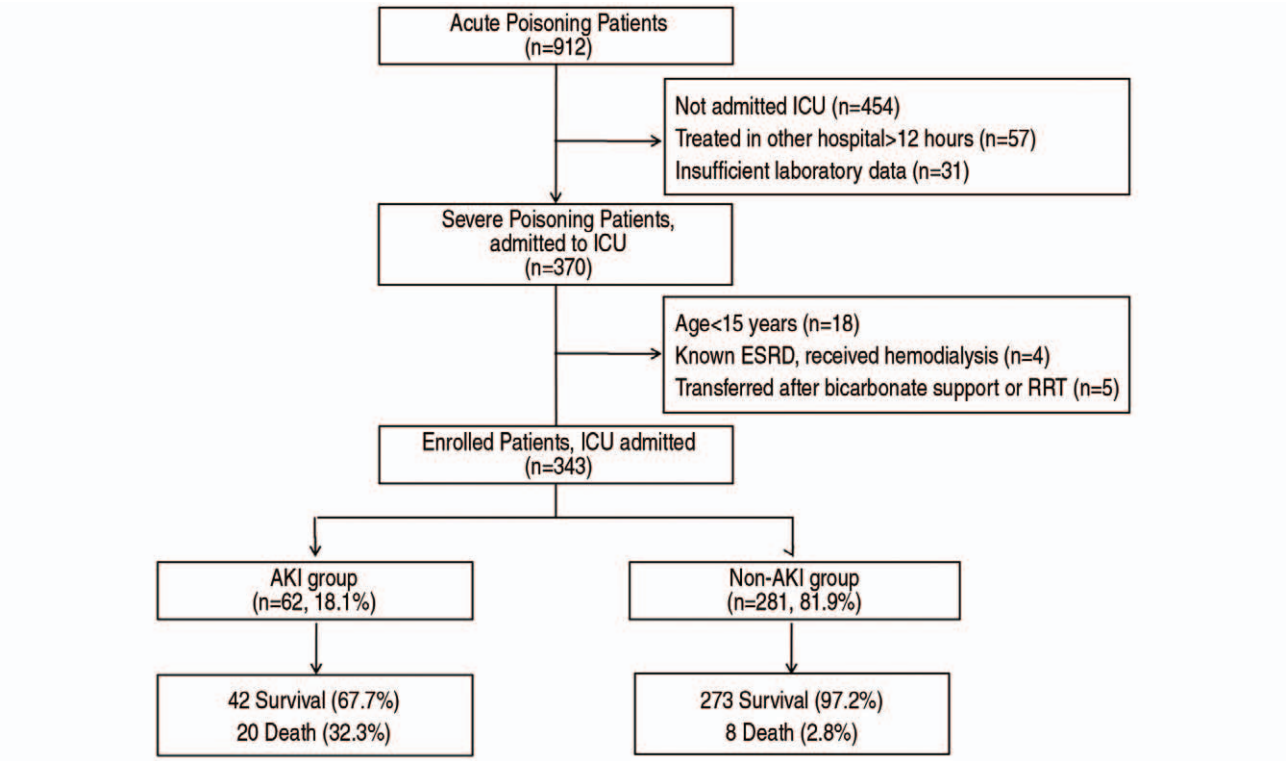

Fig. 1. Study flow diagram of severe poisoning.
ICU: intensive care unit, ESRD: end-stage renal disease, RRT: renal replacement therapy, AKI: acute kidney injury.

Sequential Organ Failure Assessment (SOFA) scores, clinical outcomes, treatments, and fatality. Blood samples for arterial blood gas analysis and electrolyte measurement (Na^+, K^+, Cl^-, HCO_3^-, and Ca^{2+}) were drawn simultaneously in the emergency department. We determined the nature of the toxins, the reasons for and routes of poisoning, the time intervals between poisoning and hospitalization, and the amounts of ingested drugs. The time of ingestion was reported by each patient or guardian, while the emergency physician identified the type of the toxin to which the patient had been exposed, using the bottle label as well as the patient's original prescription. Normal ranges were defined as follows: 7.35-7.45 for pH and 6-14 mEq/L for the AG[11]. Base deficit (BD) 〉6.0 mEq/L and 4.0 mmol/L were considered high[12,13]. Hypoalbuminemia was defined as albumin levels 〈3.5 g/dL [14].

2. AKI definition

AKI was defined according to the serum creatinine level and estimated glomerular filtration rate (eGFR) recommended by the Acute Kidney Injury Network (AKIN) classification system[8]. The eGFR was calculated using the Modification of Diet in Renal Disease equation. AKI was defined as an abrupt (within 48 h) decrease in kidney function, characterized by an absolute increase in serum creatinine levels by ≥0.3 mg/dL or a percentage increase in serum creatinine by ≥50% (1.5-fold from baseline). As recommended by the Kidney Disease Improving Global Outcomes guidelines[9,10], the first documented serum creatinine value of the episode-rather than a historical creatinine value or a calculated value based on a presumed GFR of 75 mL/min-was used as baseline.

3. AG and SIG calculation (Stewart Method)

According to data from blood gas analysis and biochemical tests at admission, the serum AG was initially calculated as follows: $AG=Na^+-(Cl^-+HCO_3^-)$. To adjust for the effect of abnormal serum albumin concentrations, we added 2.5 mEq/L to the calculated AG for every 1 g/dL decrease in albumin: (4.5 g/dL-measured serum albumin in g/dL)×2.5[11].

The apparent SID (SIDa) is simply the difference between the activity of all abundant cations (Na^+, K^+, Mg^{2+}, Ca^{2+}) and that of all abundant anions (Cl^-, lactate, and urate), which is usually approximately 40 mEq/L. The effective SID (SIDe) is given by the relationship between pH, carbon dioxide (CO_2), phosphate, and proteins. Therefore, it represents a measure of the remaining anions and is normally -40 mEq/L. Serum albumin and inorganic phosphate levels mainly represent total plasma concentrations of nonvolatile weak acids[15-18].

The modified Stewart's method was used to calculate SIDa, SIDe, and SIG. This difference is usually approximately 40 mEq/L. Calculations were performed using the following formulas:

$SIDa=[Na^+]+[K^+]+[Mg^{2+}]+[Ca^{2+}]-[Cl^-]-[lactate]$, with all concentrations being in mEq/L;

$SIDe=2.46\times10^{(pH-8)}\times PaCO_2+[albumin]\times(0.12\times pH-0.631)+[phosphate]\times(0.309\times pH-0.469)$, with $PaCO_2$ being in mmHg, albumin in g/L, and phosphate in mmol/L;

SIG=SIDa-SIDe, with all concentrations being in mEq/L. Both the BD and SIG become more positive as the concentration of unmeasured anions increases.

4. Statistical analysis

IBM SPSS Statistics software version 25 (IBM co., Armonk, NY, USA) and MedCalc version 15 (MedCalc Software, Mariakerke, Belgium) were used to conduct all analyses. Descriptive statistics of the patient population included frequency and percentage for categorical variables and median and interquartile range (25^{th}-75^{th} percentiles) for continuous variables. The significance of inter-group differences was tested using the Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact tests for categorical variables.

Receiver operating characteristic (ROC) curves were used to evaluate diagnostic characteristics of the SIG. ROC curves were constructed to determine the optimal thresholds (using Youden's index) for the rates of change in baseline creatinine, HCO_3^-, and SIG levels for predicting AKI, including likelihood ratios, sensitivities, and specificities. All variables found in univariate analyses to be significantly different between the surviving and non-surviving groups were entered into a multivariate logistic regression model. P〈0.05 was considered statistically significant.

RESULTS

1. Comparison of parameters between non-AKI and AKI groups

Of the 343 ICU patients, 62 (18.1%) developed AKI during their ICU stay (Fig. 1). The most common poisons leading to AKI were pesticides (54.8%), followed by antipsychotics (22.6%). Renal replacement therapy (RRT) was recommended

by the attending nephrologist in 18 cases (Table 1). Compared with the non-AKI group, AKI patients had a significantly higher crude ICU mortality rate (2.8% vs. 32.3%, $p<0.001$), but not a longer duration of ICU stay. Table 1 presents general patient characteristics as well as acid-base and electrolyte data for the study population.

2. Comparison of laboratory characteristics on hospital admission

Only 27 patients (43.5%) in the AKI group had an initial creatinine level above 1.5 mg/dL when visiting the emergency department (ED) (Table 2). AKI developed within 24 h of ED admission in 43 patients (69.4%) and 24-72 h following the acute onset of disease in 19 patients (30.6%). Univariate analysis revealed that AKI was more likely to occur in patients who had previously experienced metabolic acidosis and had increased creatinine levels (Table 2). Additionally, the incidence of elevated lactate, AG, and BD levels was significantly higher in the AKI than the non-AKI group. Moreover, the SIDe was marked lesser comparable between the non-AKI and AKI groups (26.4 vs. 20.3 mEq/L, $p<0.001$). Therefore, the SIG was significantly higher in the AKI than the non-AKI group (20.2 vs. 16.5 mEq/L, $p<0.001$, Fig. 2A).

Table 1. Comparison of parameters between the non-AKI and AKI groups

	Overall (n=343)	Non-AKI (n=281)	AKI (n=62)	*p*-value*
Age (years)	55.0 (42.5-73.0)	54.0 (42.0-69.0)	68.5 (51.0-79.0)	0.001*
Male gender, n (%)	168 (49.0%)	129 (45.9%)	39 (63.9%)	0.015*
Route of exposure, ingestion	336 (98.0%)	276 (97.9%)	60 (98.4%)	0.807
Poisoned materials, n (%)				
Sedatives/Antipsychotics	122 (35.6%)	108 (38.4%)	14 (22.6%)	
Pesticides	111 (32.4%)	77 (27.3%)	34 (54.8%)	
Antidepressants/TCA	27 (7.9%)	25 (8.9%)	2 (3.2%)	
Antihistamines/AAP	27 (7.9%)	26 (9.3%)	1 (1.6%)	
Plants/Natural toxins/CO	24 (7.0%)	20 (7.1%)	4 (6.5%)	
Alkali/Acid	12 (3.5%)	8 (2.8%)	4 (6.5%)	
Cardiovascular drugs	12 (3.5%)	9 (3.2%)	3 (4.8%)	
Unknown	8 (2.3%)	8 (2.8%)	0 (0.0%)	
GCS at presentation	15.0 (10.5-15.0)	15.0 (11.0-15.0)	14.0 (8.0-15.0)	0.102
Vital signs, initial				
Mean arterial pressure (mmHg)	88.0 (79.7-103.3)	88.3 (82.0-103.3)	88.0 (70.3-102.0)	0.496
Pulse rate (beats per min)	84.0 (68.0-100.0)	83.0 (67.0-98.0)	89.5 (75.0-108.0)	0.024*
Comorbidities, n (%)†				
Diabetes	48 (14.0%)	33 (11.7%)	15 (24.2%)	0.011*
Hypertension	106 (30.9%)	80 (28.5%)	26 (41.9%)	0.038*
Cerebrovascular accidents	16 (4.7%)	11 (3.9%)	5 (8.1%)	0.161
Gastric decontamination				
Gastric lavage, n (%)	108 (31.5%)	88 (31.3%)	20 (32.3%)	0.885
Activated charcoal, n (%)	150 (43.7%)	125 (44.5%)	25 (40.3%)	0.550
ICU admission				
Mechanical ventilation, n (%)	38 (11.1%)	15 (5.3%)	23 (37.1%)	<0.001*
Vasoactive drug, n (%)	31 (9.0%)	14 (5.0%)	17 (27.4%)	<0.001*
APACHE II	38.0 (14.0-42.0)	38.0 (14.0-41.0)	33.0 (16.0-45.0)	0.231
SOFA	7.0 (3.0-8.0)	7.0 (3.0-8.0)	8.0 (7.0-12.0)	<0.001*
Clinical Outcomes				
ICU mortality	28 (8.2%)	8 (2.8%)	20 (32.3%)	<0.001*
HD or recommended RRT	23 (6.7%)	5 (1.8%)	18 (29.0%)	<0.001*

ED: emergency department, GCS: Glasgow Coma Scale, SBP: systolic blood pressure, ICU: intensive care unit, CVP: central venous pressure, APACHE: Acute Physiologic and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, ICU: intensive care unit, HD: hemodialysis, RRT: renal replacement therapy.

Continuous data are expressed as median (25th to 75th percentiles). Categorical variables are reported as event number (column percentage).

* *p*-value<0.05, when making comparisons between the non-AKI and AKI groups.

† Unknown or not determined data: comorbidities (n=2).

Table 2. Comparison of laboratory characteristics on hospital admission

	Overall (n=343)	Non-AKI (n=281)	AKI (n=62)	*p*-value*
Initial renal dysfunction index				
BUN (mg/dL, NR: 6.0 to 20.0)	15.4 (11.6-20.0)	14.7 (11.3-20.0)	20.0 (14.9-25.7)	<0.001*
Creatinine (mg/dL, NR: 0.6 to 1.3)	0.78 (0.66-0.99)	0.74 (0.63-0.90)	1.27 (0.82-1.84)	<0.001*
Cr>1.5 mg/dL	27 (7.9%)	0 (0 %)	27 (43.5%)	<0.001*
AKIN stage, n (%)				
Stage 1	23 (6.7%)	-	23 (37.1%)	
Stage 2	20 (5.8%)	-	20 (32.3%)	
Stage 3	19 (5.5%)	-	19 (30.6%)	
Initial laboratory findings				
Sodium (mEq/L, NR: 136 to 146)	140 (137-142)	140 (138-142)	139 (135-143)	0.182
Potassium (mEq/L, NR: 3.3 to 5.1)	3.9 (3.5-4.2)	3.9 (3.5-4.1)	4.0 (3.2-4.5)	0.444
ALT (IU/L, NR: 0 to 41)	19.0 (13.0-26.0)	19.0 (13.0-25.0)	19.0 (13.0-32.0)	0.302
Albumin (mg/dL, NR: 3.2 to 4.8)	4.2 (3.8-4.5)	4.2 (3.9-4.5)	4.0 (3.5-4.3)	0.001*
Ammonia (μmol/L, NR: 9 to 33)	31.0 (19.0-43.0)	30.5 (19.0-43.0)	32.0 (19.5-54.0)	0.155
Lactate (mmol/L, NR: 0.7 to 2.1)	2.5 (1.7-4.1)	2.4 (1.5-3.3)	4.0 (2.4-8.5)	<0.001*
Arterial blood gas analysis				
pH (NR: 7.35 to 7.45)	7.41 (7.37-7.44)	7.42 (7.38-7.45)	7.36 (7.27-7.40)	<0.001*
pCO_2 (mmHg, NR: 32 to 45)	31.4 (28.0-36.1)	31.6 (28.6-36.1)	28.1 (22.2-35.8)	0.001*
pO_2 (mmHg, NR: 83 to 108)	66.9 (43.9-89.7)	65.2 (43.9-89.6)	72.7 (52.5-93.3)	0.266
HCO_3^- (mEq/L, NR: 22 to 26)	21.1 (18.6-23.6)	21.6 (19.5-23.6)	16.3 (13.2-21.5)	<0.001*
Base deficit (mmol/L)	2.2 (0.2-4.5)	1.8 (0.2-3.5)	7.2 (2.5-12.0)	<0.001*
Anion gap	14.8 (12.1-17.8)	14.3 (11.8-17.0)	20.7 (15.4-25.0)	<0.001*
Corrected AG	15.7 (13.1-19.2)	15.3 (12.4-17.9)	21.4 (15.8-27.1)	<0.001*
Strong Ion Differences				
SIDa (mEq/L)	42.9 (40.7-45.2)	43.1 (41.1-45.3)	41.5 (37.6-44.2)	0.002*
SIDe (mEq/L)	25.8 (23.6-28.1)	26.4 (24.5-28.4)	20.3 (17.6-23.5)	<0.001*
SIG (mEq/L)	17.0 (14.8-19.4)	16.5 (14.6-18.8)	20.2 (16.5-23.7)	<0.001*

NR: normal ranges of data level, BUN: blood urea nitrogen, Cr: creatinine, AKIN: acute kidney injury network, ALT: alanine aminotransferase, AG: anion gap, SID: Strong Ion Difference, SIDa: apparent strong ion difference, SIDe: effective strong ion difference, SIG: Strong Ion Gap.

Continuous data are expressed as median (25th to 75th percentiles). Categorical variables are reported as event number (column percentage).

* *p*-value<0.05, when comparing the non-AKI group with the AKI group.

3. Discriminative power of each model for predicting AKI

The ROC curve of initial SIDe levels showed that the highest specificity and sensitivity for the prediction of AKI were 86.9% and 75.8%, respectively, at the cut-off value of 23.5 mEq/L (Table 3, Fig. 3A). When comparing SIDs with other parameters (e.g., initial creatinine, BD, lactate, and AG) in terms of the area under the ROC curve (AUC), sensitivity, specificity, and likelihood ratios, we found that SIDe was superior to other laboratory parameters in predicting AKI (Table 3). The AUCs of the serum SIDe, corrected AG, and HCO_3^- for predicting AKI were 0.842 with a 95% confidence interval (CI) of 0.799-0.879, 0.767 (95% CI, 0.719-0.811), and 0.743 (95% CI, 0.693-0.788).

4. Comparison of variables between the surviving and non-surviving groups

Of the 343 ICU patients, 28 (8.2%) died during their ICU stay (Table 4). Patients in the non-surviving group were older and more often had diabetes than those in the surviving group (all p=0.020). Non-survivors underwent a significantly higher rate of hemodialysis or RRT, as compared to survivors (46.4% vs. 3.2%, p<0.001). Significant differences were observed between the 2 groups regarding laboratory parameters, AG, pH, BD, bicarbonate, lactate, albumin, SIDs, and SIG. Table 4 presents general patient characteristics as well as acid-base and electrolyte data for the study population.

The AUC of the SIDe was 0.872 (95% CI, 0.831-0.905) with a sensitivity and specificity of 77.1% and 85.7%, suggesting its excellent predictive value for mortality at the cut-off value of 23.9 mEq/L (Fig. 3B). In contrast, the AUCs of the corrected

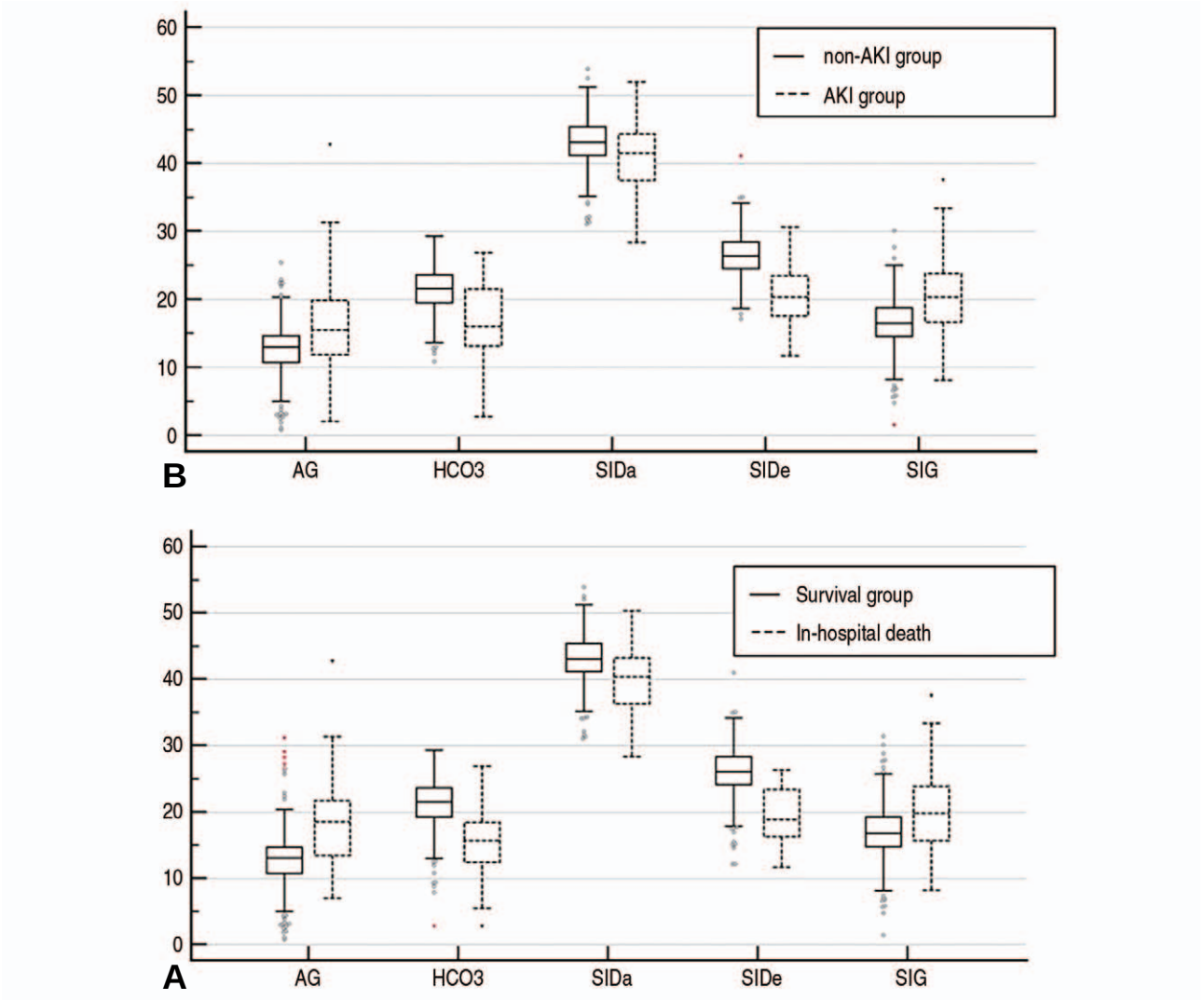

Fig. 2. Box plots of initial anion gap, HCO_3^-, SIDs, and SIG for comparing non-AKI and AKI groups (**A**) and for in-hospital mortality (**B**).

Table 3. Discriminative power of each model for predicting AKI

	Cut-off*	AUC (95% CI)	Sensitivity	Specificity	+LR	-LR
Creatinine	>1.08	0.796 (0.749 to 0.837)	61.3	91.8	7.49	0.42
Anion gap	>15.3	0.660 (0.607 to 0.711)	52.4	81.3	2.81	0.58
Corrected AG	>19.2	0.767 (0.719 to 0.811)	64.5	84.7	4.22	0.42
pH	<7.359	0.731 (0.681 to 0.778)	59.6	79.3	2.89	0.51
Base deficit	>5.5	0.761 (0.712 to 0.805)	58.0	90.7	6.28	0.46
HCO_3^-	<17.3	0.743 (0.693 to 0.788)	58.0	91.4	6.80	0.46
Lactate	>3.4	0.736 (0.686 to 0.782)	61.2	76.1	2.58	0.52
SIDa	<42.0	0.626 (0.572 to 0.677)	59.7	65.8	1.75	0.61
SIDe	<23.5	0.842 (0.799 to 0.879)	75.8	86.9	5.76	0.28
SIG	>19.3	0.737 (0.687 to 0.783)	61.3	80.5	3.05	0.50

AUC: area under the curve, AG: Anion Gap, CI: confidence interval, LR: likelihood ratio, SID: Strong Ion Difference, SIDa: apparent strong ion difference, SIDe: effective strong ion difference, SIG: Strong Ion Gap.
* Associated cut-off criteria were defined as values corresponding to the maximal Youden's index J.

AG, pH, BD, and creatinine levels for predicting in-hospital mortality were 0.811 (95% CI, 0.766-0.851), 0.721 (95% CI, 0.670-0.768), 0.831 (95% CI, 0.787-0.870), and 0.758 (95% CI, 0.709-0.803) (Fig. 3B).

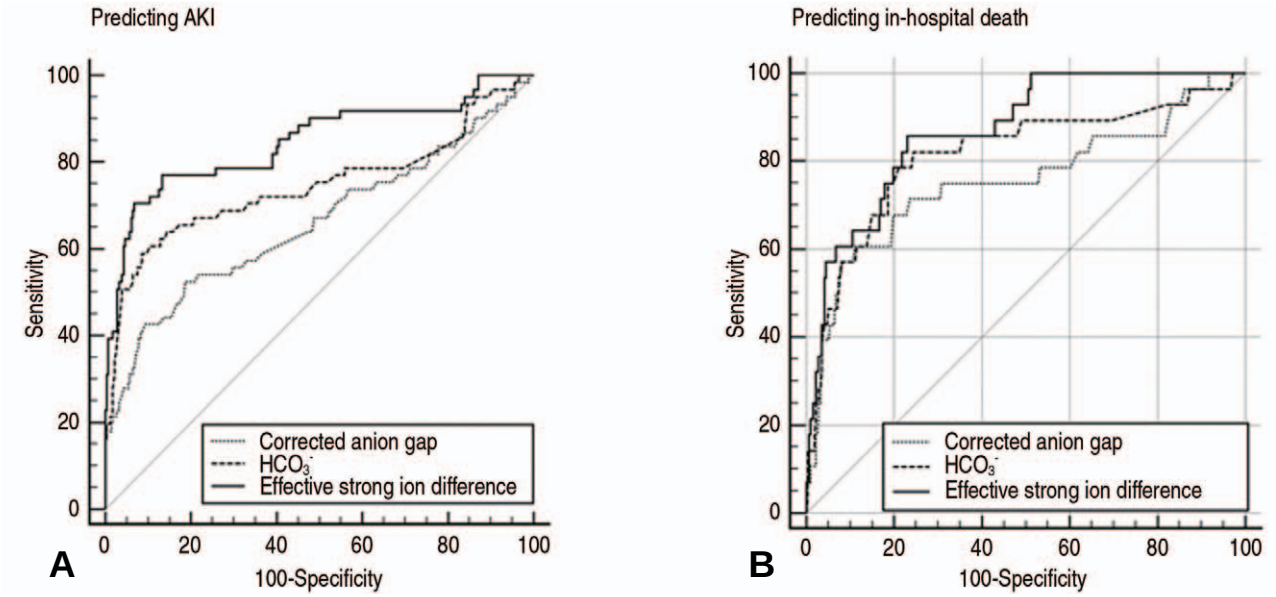

Fig. 3. The receiver operating characteristic curves of initial SIDe, creatinine, pH, HCO_3^-, and corrected anion gap levels for predicting AKI (**A**) and in-hospital mortality (**B**).
(**A**) For predicting AKI, the areas under the serum SIDe, corrected AG, and HCO_3^- curves were 0.842 (95% CI: 0.799 to 0.879), 0.767 (0.719 to 0.811), and 0.743 (0.693 to 0.788).
(**B**) Additionally, the areas under the serum SIDe, corrected AG, pH, base deficit, and creatinine curves were 0.872 (95% CI: 0.831 to 0.905), 0.811 (0.766 to 0.851), 0.721 (0.670 to 0.768), 0.831 (0.787 to 0.870) and 0.758 (0.709 to 0.803) for predicting in-hospital mortality, respectively.

5. Logistic regression analyses of predictive factors for in-hospital mortality in severe poisoning patients

Old age, high AG, lactic acidosis, diabetes, acidemia, high SIG, and low SIDe were determined as significant risk factors for death in univariate analyses (all other p values <0.05, Table 5) and were subsequently entered into a multivariable logistic regression model for in-hospital mortality prediction (Table 5), which revealed diabetes, lactic acidosis, high SIG, and low SIDe as significant risk factors for death (Fig. 4). However, results of the multivariate analysis showed no statistical significance for high AG and acidemia (Table 5).

DISCUSSION

This study examined whether novel parameters could be used as predictors of AKI in adult patients with acute poisoning. Our approach to exploring the relationship between poisoning and AKI differed in several important respects from those of previous reports; that is, we (1) evaluated the incidence of AKI in emergency ICU settings and (2) analyzed individual and baseline ED factors that were highly predictive of progression to AKI, as well as reference baseline cut-off values. Furthermore, we demonstrated the utility of the SIG (calculated from blood samples obtained upon arrival at the hospital) for predicting AKI or in-hospital mortality. It has also been reported that the SIG-which shows the difference between the levels of fully dissociated cations and anions in the serum-is useful in predicting the prognosis of critically ill patients.

Metabolic acidosis usually provokes nausea, vomiting, fatigue, and altered mentality in patients with poisoning. Worsening acidosis may result in falling blood pressure, shock, and death. It is, therefore, important to evaluate the acid-base status of patients with acute poisoning[11]. There are 3 approaches to assessing acid-base disturbances, namely the physiological approach, the BE approach, and the physicochemical approach. The physiological approach uses the Henderson-Hasselbalch equation, in which arterial pH is determined by the balance between arterial CO_2 and plasma HCO_3^-. The BE approach is similar to the physiological approach, except that it uses BE instead of HCO_3^- to define the metabolic component of acid-base disorders. It includes the AG with or without correction for hypoalbuminemia (AG correction) to define whether excess anions other than Cl^- and HCO_3^- are present[5].

There is a recent physicochemical approach, also called Stewart's approach to acid-base analysis, for quantifying acid-

Table 4. Comparison of variables between the surviving and non-surviving groups

	Overall (n=343)	Survival (n=315)	Death (n=28)	*p*-value*
Age (years)	55.0 (42.5-73.0)	55.0 (42.0-71.0)	72.5 (56.0-78.8)	0.002*
Elderly (>65 years)	117 (34.1%)	100 (31.7%)	17 (60.7%)	0.002*
Male gender, n (%)	168 (49.0%)	154 (48.9%)	14 (50.0%)	0.910
Route of exposure, ingestion	336 (98.0%)	309 (98.1%)	27 (96.4%)	0.550
GCS at presentation	15.0 (10.5-15.0)	15.0 (11.0-15.0)	13.5 (9.0-15.0)	0.232
Vital signs, initial				
Mean arterial pressure (mmHg)	88.0 (79.7-103.3)	88.3 (81.0-103.3)	84.7 (70.7-104.3)	0.176
Comorbidities, n (%)†				
Diabetes	48 (14.0%)	40 (12.7%)	8 (28.6%)	0.020*
Hypertension	106 (30.9%)	96 (30.5%)	10 (35.7%)	0.565
Cerebrovascular accidents	16 (4.7%)	14 (4.4%)	2 (7.1%)	0.516
Gastric decontamination				
Gastric lavage, n (%)	108 (31.5%)	93 (29.5%)	15 (53.6%)	0.009*
Activated charcoal, n (%)	150 (43.7%)	133 (42.2%)	17 (60.7%)	0.059
Initial laboratory findings				
Sodium (mEq/L)	140 (137-142)	140 (137-142)	142 (137-144)	0.157
Potassium (mEq/L)	3.9 (3.5-4.2)	3.9 (3.5-4.2)	4.0 (3.2-4.6)	0.611
Albumin (g/dL)	4.2 (3.8-4.5)	4.2 (3.8-4.5)	4.0 (3.5-4.3)	0.016*
Hypoalbuminemia (≤3.4 g/dL)	39 (11.4%)	33 (9.6%)	6 (1.7%)	0.080
Lactate (mmol/L)	2.5 (1.7-4.1)	2.3 (1.5-3.5)	5.0 (3.2-9.9)	<0.001*
Arterial blood gas analysis				
pH (NR: 7.35 to 7.45)	7.41 (7.37-7.44)	7.41 (7.37-7.45)	7.35 (7.23-7.41)	<0.001*
HCO_3^- (mEq/L, NR: 22 to 26)	21.1 (18.6-23.6)	21.5 (19.2-23.6)	15.7 (12.2-18.5)	<0.001*
Base deficit (mmol/L)	2.2 (0.2-4.5)	1.9 (0.2-3.9)	9.0 (5.1-12.7)	<0.001*
Anion gap	14.8 (12.1-17.8)	14.5 (11.9-17.4)	22.7 (17.3-26.9)	<0.001*
Corrected AG	15.7 (13.1-19.2)	15.5 (12.7-18.4)	24.0 (17.9-28.2)	<0.001*
Strong Ion Differences				
SIDa (mEq/L)	42.9 (40.7-45.2)	43.0 (41.1-45.3)	40.3 (36.2-43.4)	0.001*
SIDe (mEq/L)	25.8 (23.6-28.1)	26.1 (24.1-28.3)	18.8 (15.8-23.5)	<0.001*
SIG (mEq/L)	17.0 (14.8-19.4)	16.8 (14.8-19.3)	19.8 (15.6-23.9)	0.007*
Clinical Outcomes				
APACHE II	38.0 (14.0-42.0)	38.0 (14.0-41.0)	36.5 (18.0-44.0)	0.141
HD or recommended RRT	23 (6.7%)	10 (3.2%)	13 (46.4%)	<0.001*

GCS: Glasgow Coma Scale, AG: anion gap, SID: Strong Ion Difference, SIDa: apparent strong ion difference, SIDe: effective strong ion difference, SIG: Strong Ion Gap, APACHE: Acute Physiologic and Chronic Health Evaluation, HD: hemodialysis, RRT: renal replacement therapy.

Continuous data are expressed as median (25th to 75th percentiles). Categorical variables are reported as event number (column percentage).

* *p*-value<0.05, when making comparisons between the surviving and dead groups.

base imbalances[5]. Based on the degree of dissociation in solution, electrolytes may yield strong ions (e.g., Na^+, K^+, Mg^{2+}, Ca^{2+}, SO_4^{2-}, and Cl^-; complete dissociation) and weak ions (e.g., protein, phosphate, and HCO_3^-; incomplete dissociation). Taking into account weak ions such as albumin and phosphate, this approach makes it possible to identify acid-base abnormalities that may otherwise be overlooked by traditional methods[19]. Recent evidence suggests that SIG abnormalities are associated with inflammation severity, which in turn implies that abnormal Stewart's acid-base status may have pathogenic consequences and prognostic significance. This approach is more comprehensive than the other ones and can identify subtle or combined acid-base disturbances that fail to be detected using pH or BE alone[5].

There have been several studies on the relationship between the SIG and its clinical outcomes in critically ill patients. For example, it has been indicated that SIG values can predict both short- and long-term mortality in ICU patients with metabolic acidosis and AKI[9]. Another study has found unfavorable outcomes in cardiac arrest patients with elevated SIG values 12 h after the return of spontaneous circulation[20]. In the case of pancreatitis, the SIG has been identified as a strong independent predictor of severity and mortality, as well as a possible early marker for AKI[2]. In a study of patients with adult burn injury

Table 5. Univariate and multivariate analyses of predictive factors for in-hospital mortality in severe poisoning patients

	Univariate		Multivariate	
	p-value	Odds ratio* (95% confidence interval)	*p*-value	Odds ratio* (95% confidence interval)
Elderly (>65 years)	0.004	3.227 (1.458 to 7.141)	0.107	2.267 (0.838 to 6.131)
Diabetes	0.025	2.750 (1.136 to 6.660)	0.026	3.768 (1.171 to 12.125)
High Anion Gap (>14.1)	<0.001	5.789 (2.463 to 13.606)	0.591	0.701 (0.192 to 2.558)
Lactic acidosis (>4.0 mmol/L)	<0.001	12.001 (4.884 to 29.481)	0.001	7.417 (2.290 to 24.030)
Acidemia (pH<7.35)	<0.001	5.848 (2.617 to 13.068)	0.532	1.475 (0.436 to 4.984)
Acidosis (base deficit>6)	<0.001	15.389 (6.495 to 36.459)	0.574	1.518 (0.353 to 6.524)
SIDe ≤23.9†	<0.001	19.541 (6.569 to 58.124)	0.024	5.207 (1.248 to 21.723)
SIG >21.9†	<0.001	10.053 (4.307 to 23.466)	0.009	4.529 (1.462 to 14.032)

AG: Anion Gap, SID: Strong Ion Difference, SIG: Strong Ion Gap.
Values shown are odds ratios (95% confidence interval).
* Statistical logistic regression analysis was performed using the enter method. To determine the logistic model calibration, we calculated the Hosmer-Lemeshow goodness of fit (p=0.341).
† Associated cut-off values were defined as values corresponding to the maximal Youden's index J using the receiver operating characteristic curves.

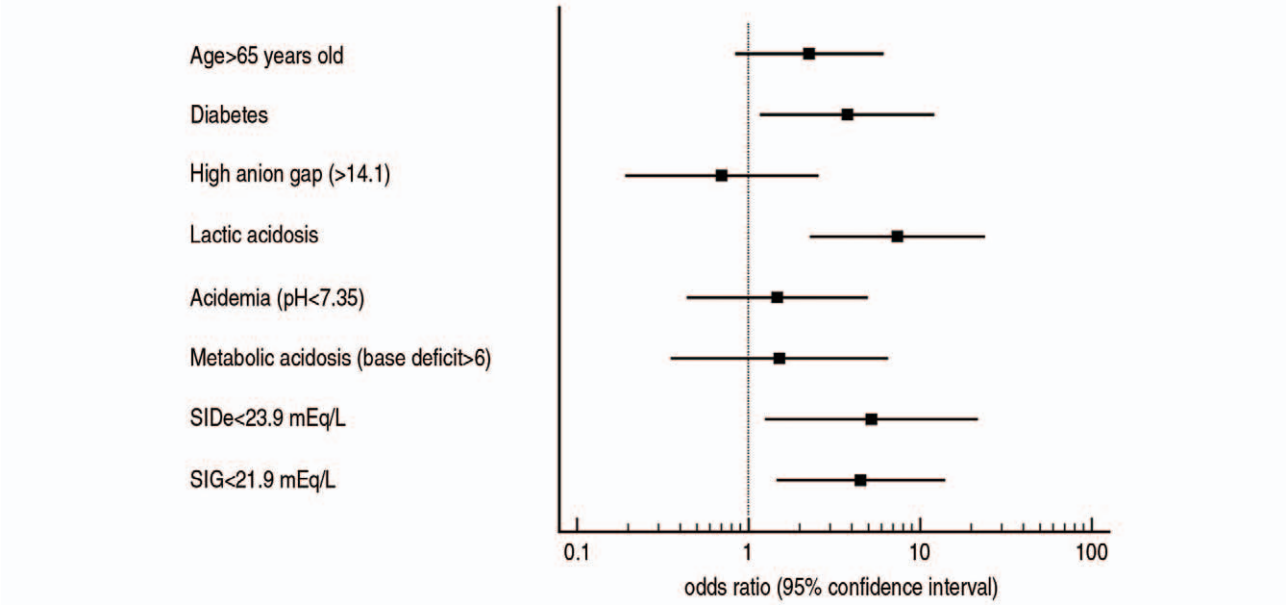

Fig. 4. Forest plots associated with in-hospital mortality in severe poisoning patients. The odds ratios for mortality are significant in diabetes, lactic acidosis, SIG and SIDe.

and blunt trauma, the SIG has been reported as a predictor of mortality, hospital length of stay, and ventilator day[3,4].

Unlike the AG or BD, the role of SIG in the prediction of AKI and death in acute poisoning patients is ill-defined. Previous studies of poisoning patients have shown that mortality is significantly higher in cases with higher AG vales than in those with normal or low AG vales[11,21]. This finding suggests that the AG is a surrogate marker for serious pathophysiological processes following acute poisoning. However, the predictive powers of the AG and BE for mortality still remain controversial. The main reason may be that the AG is oversimplified without considering the effects of albumin and phosphate. It also lacks sensitivity and specificity[2,5,22]. According to studies on SIG levels in critically ill patients, hypoperfusion and microcirculation disturbances might be the main reasons for elevated unmeasured anions, which may in turn affect the SIG. Besides, elevation of BUN and creatinine suggests that impaired renal excretion of unmeasured anions may contribute to such SIG alterations[2]. There are many unmeasured anions and exotoxins in patients with acute poisoning, all of which affect the SIG. Multiorgan failure, including renal toxicity, may also affect the SIG as in the case of other critically ill patients.

This indicates that, in patients with acute severe poisoning, the SIG may help identify metabolic acid-base abnormalities that cannot be detected by pH or BE alone.

The BD and AG have been investigated as prognosticators in critically ill patients, including DI. With respect to the SIG and SID, which are new parameters, there is not enough data available because research is still ongoing. In a study analyzing the initial SIG in critically ill patients at the ED, the cut-off value, which distinguishes survival from death on the ROC curve, was found to be 13.3 mEq/L[17]. In another study of the SIG in cardiac arrest patients treated with therapeutic hypothermia, Kaplan-Meier survival analysis revealed that elevated SIG values (〉8.9) 12 h after the return of spontaneous circulation were associated with poor outcomes[20].

As in the previous study, SIDa analysis showed controversial results; that is to say, the lower the SIDe and the higher the SIG, the higher the severity of the patient (Fig. 2). However, there is a slight difference in the standard value (about 8-13 mEq/L), and this study is about 19 mEq/L. Thus, further research is needed in the future.

This study has several limitations despite presenting important findings. First, the sample size was small; hence, we could not conduct subgroup validations according to intoxicant, age group, and combined sepsis or chronic renal disease. Additional research is needed to evaluate the physiological nature of the toxicant or unmeasured anions in such patients in the future[23]. Second, this was a single-center retrospective study; thus, not all relevant assessment variables were obtainable. Third, of the AKIN criteria for AKI, we used only serum creatinine and eGFR criteria, leaving out urine output. Fourth, patients were not followed up to obtain serial measurements of SIG levels. Serial measurements of SIG levels prevent false-negative results that arise from early sampling before renal insult occurs. Thus, future large-scale prospective studies that address these shortcomings should be conducted to validate our findings. Fifth, the mean age of the AKI group was significantly higher than that of the non-AKI group, which is attributable to the increased prevalence of CKD with age[23]. For this reason, it is possible that the occurrence of AKI might not be a direct effect of the SIG, but rather a secondary outcome and an interpretation error due to age. Sixth, hopeless discharge was a case of transfer because ventilator weaning was not possible, and this case was treated as a survival group. In the case of transfer, patients were transferred for supportive care after clinical improvement, and this was also treated as a survival group. It is possible that this might have affected the sample of the survival group. Finally, SIG calculation requires a more complex formula compared to traditional AG and BD values. Nevertheless, this complexity can be automatically handled using the APACHE II and SOFA scoring systems as soon as patients enter the ICU through their electronic medical records.

CONCLUSION

In conclusion, we assessed the predictive value of the SIG in severe poisoning patients with AKI. Our study demonstrated that an elevated SIG was a useful predictor of AKI and in-hospital mortality at earlier stages of poisoning. Complex acid-base disorders are easier to understand, explain, and rationalize using Stewart' s method compared with the traditional model. Moreover, our study suggests that Stewart' s method can be used in the triage, risk stratification, management, and prognostication of such patients in the future.

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