European Review for Medical and Pharmacological Sciences 2023; 27: 2964-2970

The serum anion gap is associated with the prognosis of coronary artery bypass grafting (CABG): analysis based on the MIMIC-IV database

X.-M. WANG[1], Y.-S. DENG[1], B. HE[2], J.-W. LIU[1], Z.-H. ZHANG[1], Z.-D. YE[2], P. LIU[1,2]

[1]Department of Cardiovascular Surgery, Peking University China-Japan Friendship School of Clinical Medicine, Beijing, China
[2]Department of Cardiovascular Surgery, China-Japan Friendship Hospital, Beijing, China

Abstract. – OBJECTIVE: The serum anion gap (AG) has been reported to be an important prognostic indicator for patients in intensive care units. To explore the potential relationship between the serum AG and 30-day mortality in patients who underwent CABG.

PATIENTS AND METHODS: All data were collected from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. We divided patients into 3 groups according to AG tertiles. The primary outcome of our study was the 30-day mortality of patients who underwent CABG. The relationship between the serum AG and mortality in individuals who underwent CABG was estimated using Cox proportional hazard models. Subgroup analysis for effect modification was conducted with a likelihood ratio test.

RESULTS: A total of 5,102 eligible subjects were included in our analysis. After adjusting for confounding factors, every unit increase in the AG was associated with a 22% higher odds of 30-day mortality in patients who underwent CABG [hazard ratio (HR), 95% confidence interval (CI): 1.22, 1.13-1.33] When the AG was converted into a categorical variable, the high AG group had a higher risk of 30-day mortality than the low AG group in the fully adjusted model (HR, 95% CI: 3.99, 1.35-11.76). Tests for trends were statistically significant (p-value < 0.05). Subgroup analysis demonstrated that higher mortality was related to the subgroups of people ≥ 70 years and females.

CONCLUSIONS: The serum AG was an independent predictor of short-term prognosis in patients who underwent CABG. A high AG was associated with an increased risk of 30-day mortality after CABG.

Key Words:
Serum anion gap, Metabolic acidosis, Coronary artery bypass grafting, MIMIC-IV.

Introduction

Coronary artery disease (CAD), mainly caused by the development of atherosclerotic plaques that block the coronary vessel or rupture, contributes to myocardial infarction (MI) and other ischemic heart diseases. CAD has been the leading cause of mortality globally[1]. Coronary artery bypass grafting (CABG) is considered a well-established procedure to reduce myocardial ischemic injury and subsequent mortality by recovering coronary flow. Although this surgical technique has been considerably developed over the past few years, it still carriers a considerable risk of perioperative or postoperative morbidity and mortality[2]. The identification of useful and effective markers that could help clinicians judge the prognosis of CABG is urgently needed. The serum anion gap (AG), which is calculated based on the measured cation and anion concentrations ([Na (+)] - ([HCO (3) (-)] + [Cl (-)]), is a simple indicator to assess acid-based balance[3]. It has been clinically used for years. Recently, the AG seems to have renewed usage as a prognostic predictor. A high AG usually predicts severe illness or poor outcomes, such as acute kidney injury, acute pancreatitis, aortic aneurysm, and cerebral infarction[4-7]. In addition, a high AG is associated with cardiovascular events[8,9]. However, whether a high AG could lead to a status deterioration in patients who undergo CABG remains unclear. In this study, we try to explore the potential association between the serum AG and the prognosis of CABG.

Corresponding Author: P. Liu, MD; e-mail: liupeng6618@yeah.net

Patients and Methods

Data Source

We retrieved all data from the Medical Information Mart for Intensive Care IV (MIMIC-IV version 1.0), which contained more than 250 thousand patients admitted to Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2008 to 2019[10]. We collected patient parameters, including age, sex, admission date, discharge date, comorbidities, vital signs, and laboratory results. The study was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, MA, USA). Identity was hidden to protect patient privacy; thus, informed consent was not required.

Population Selection Criteria

We included patients who underwent CABG according to the Ninth and Tenth Revisions of the International Classification of Diseases (ICD-9 and ICD-10, respectively), and the exclusion criteria were as follows: (1) intensive care unit (ICU) stay<24 hours, (2) transfer to the ICU before surgery or more than one day after surgery and (3) missing anion gap data (Figure 1).

Data Collection

We used Structured Query Language (SQL) with PostgreSQL (version 11.13) to extract data from the MIMIC-IV. Demographic data, comorbidities, vital signs, laboratory test results, system scores, and other variables were collected. Demographic data included sex, age, race, height, and weight. Comorbidities included MI, congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease, chronic pulmonary disease, and so on. Vital signs, including heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and body temperature were collected. The results of laboratory tests, which were performed within 24 hours of ICU admission, included the white blood cell (WBC) count, hemoglobin, he-

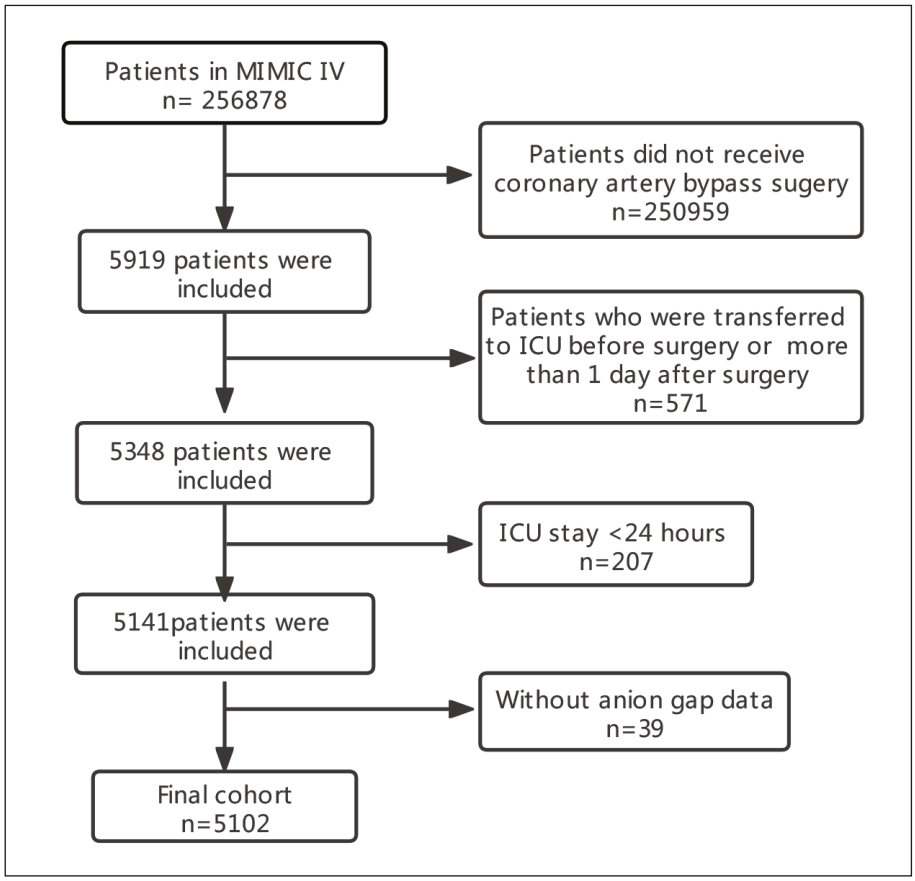

Figure 1. Study flowchart of subject screening.

matocrit, platelet count, sodium, potassium, AG, international standardized ratio (INR), prothrombin time (PT), and partial thromboplastin time (PTT). We also extracted the scores from the Glasgow Coma Scale (GCS), Logistic Organ Dysfunction System (LODS), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiological Score II (SAPSII) assessments. The end point of our study was all-cause mortality at 30 days from the date of admission to the ICU. All analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.3[11].

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation (SD) or the median and interquartile range (IQR), while categorical data are expressed as frequencies and percentages. We used the Chi-square test, one-way analysis of variance (ANOVA), and the Kruskal-Wallis' H test to determine whether there was a significant difference between two groups. Cox proportional risk models were conducted to assess the relationship between the AG and 30-day mortality in patients, and the results are expressed as 95% confidence intervals (CIs) of the hazard ratio (HR). Subgroup analyses were performed using a stratified Cox proportional risk model with likelihood ratios to test for subgroup modifications and interactions. All probability values were two-sided, and statistical significance was defined as p-values <0.05.

Results

Patient Characteristics

Patients were divided into three groups based on the AG, and the baseline characteristics are described in Table I. We extracted information for a total of 5,102 eligible subjects from the MIMIC-IV, including information for 3,942 males and 1,160 females. The high AG group (≥14 mmol/L) was more likely to have a history of obesity, MI, CHF, and renal disease and had a higher WBC count, creatinine, sodium, potassium, blood glucose, lactate, INR, PT, and PTT than the low AG group (<12 mmol/L). GCS, SAPSII, LODS, and SOFA scores were also significantly higher in the high AG group (AG≥ 14 mmol/L) than in the low AG group (AG < 12 mmol/L).

Outcomes

Patients with a high AG were found to have higher mortality than those with a low AG (Table II). We used Cox proportional hazard regression models to determine the relationship between the AG and 30-day all-cause mortality in patients who underwent CABG (Table III). With the low AG (AG < 12 mmol/L) group as a reference, in model I, after adjusting for age and sex, a high AG (AG ≥ 14 mmol/L) was significantly associated with an increased risk of all-cause death (HR, 95% CI: 10.32, 3.72-28.64). In model II, after adjusting for confounding factors, including age, sex, race, MI, CHF, PVD, cerebrovascular disease, chronic pulmonary disease, renal disease, heart rate, SBP, DBP, MBP, respiratory rate, pulse oxygen saturation (SpO_2), WBC count, hemoglobin, hematocrit, platelet count, creatinine, potassium, glucose, lactate, INR, PT, PTT, urine output, GCS score, SOFA score, LODS score, and SAPSII, the high AG group (AG ≥ 14 mmol/L) still had a higher risk of 30-day mortality than the low AG group (HR, 95% CI: 3.99, 1.35-11.76).

Subgroup Analyses

The interaction test was statistically significant in several subgroups ($p < 0.05$). As shown in Table II, higher mortality was observed in the subgroups of individuals ≥ 70 years and females.

Discussion

The principal finding of this research is that the serum AG has a strong relationship with the prognosis of CABG. A higher AG (AG>14 mmol/L) was related to a higher risk of 30-day mortality in the targeted population. In addition, the serum AG was positively associated with SBP, and there was a 0.48 mmHg increase in SBP with each milliequivalent-per-liter increase in the serum AG (95% CI: 0.28 to 0.69 mmHg)[12]. In healthy persons aged 20-49 years, a high AG often predicts worse cardiopulmonary fitness and greater insulin resistance[13,14]. The involvement of these factors is typically associated with a higher incidence of cardiovascular events. This predictive effect of the AG was still significant even following adjustment for other factors, such as age, sex, comorbidities, other laboratory test results, and clinical system scores in model I and model II (HR, 95% CI: 10.32, 3.72-28.64, and HR, 95% CI: 3.99, 1.35-11.76, respectively). Notably, although the mortality difference between the low

Table I. Baseline characteristics of the study population.

Variables	Total (n = 5,102)	< 12 (n = 1,701)	≥12 and <14 (n = 1,496)	≥14 (n = 1,905)	*p*-value
Age (years)	68.8 ± 10.2	68.6 ± 9.9	68.9 ± 10.3	68.8 ± 10.5	0.648
Gender, n (%)					0.065
Female	1,160 (22.7)	359 (21.1)	337 (22.5)	464 (24.4)	
Male	3,942 (77.3)	1,342 (78.9)	1,159 (77.5)	1,441 (75.6)	
Race, n (%)					0.948
0	1393 (27.3)	461 (27.1)	413 (27.6)	519 (27.2)	
1	3,709 (72.7)	1,240 (72.9)	1,083 (72.4)	1,386 (72.8)	
BMI (kg/m^2)	30.3 ± 5.7	29.9 ± 5.5	30.3 ± 5.8	30.7 ± 5.9	< 0.001
Comorbidities, n (%)					
Myocardial infarction	1,968 (38.6)	563 (33.1)	563 (37.6)	842 (44.2)	< 0.001
Congestive heart failure	1,273 (25.0)	323 (19)	338 (22.6)	612 (32.1)	< 0.001
Peripheral vascular disease	674 (13.2)	211 (12.4)	210 (14)	253 (13.3)	0.394
Cerebrovascular disease	532 (10.4)	168 (9.9)	156 (10.4)	208 (10.9)	0.593
Chronic pulmonary disease	989 (19.4)	331 (19.5)	294 (19.7)	364 (19.1)	0.919
Renal disease	952 (18.7)	209 (12.3)	261 (17.4)	482 (25.3)	< 0.001
Vital signs					
Heart rate (beats/minute)	82.8 ± 8.8	82.9 ± 8.4	82.7 ± 8.7	82.9 ± 9.2	0.665
SBP (mmHg)	111.5 ± 7.3	111.6 ± 6.9	111.9 ± 7.3	111.2 ± 7.5	0.011
DBP (mmHg)	56.4 ± 6.3	56.7 ± 5.7	56.6 ± 6.2	56.0 ± 6.8	< 0.001
MBP (mmHg)	73.6 ± 5.4	73.7 ± 5.0	73.7 ± 5.3	73.5 ± 5.7	0.283
Respiratory rate (times/minute)	17.7 ± 2.5	17.4 ± 2.4	17.7 ± 2.4	18.0 ± 2.5	< 0.001
SpO_2 (%)	97.9 ± 1.3	98.0 ± 1.2	97.8 ± 1.3	97.9 ± 1.5	0.004
Laboratory results					
WBC (10^9/L)	16.9 ± 7.7	15.8 ± 5.8	16.7 ± 7.2	18.1 ± 9.3	< 0.001
Hemoglobin (g/dL)	11.4 ± 1.5	11.1 ± 1.3	11.5 ± 1.5	11.7 ± 1.7	< 0.001
Hematocrit (%)	34.3 ± 4.3	33.2 ± 3.7	34.5 ± 4.1	35.2 ± 4.6	< 0.001
Platelet (10^9/L)	187.1 ± 60.9	179.3 ± 54.7	185.2 ± 56.9	195.5 ± 67.9	< 0.001
Creatinine (mEq/L)	1.2 ± 1.0	1.0 ± 0.4	1.1 ± 0.6	1.5 ± 1.4	< 0.001
Potassium (mmol/L)	5.2 (4.9, 5.7)	5.2 (4.9, 5.7)	5.2 (4.9, 5.7)	5.3 (4.9, 5.7)	0.121
Sodium (mmol/L)	139.2 ± 2.9	138.9 ± 2.7	139.4 ± 2.7	139.4 ± 3.1	< 0.001
Glucose (mg/dL)	183.0 (164.0, 209.0)	178.0 (162.0, 201.0)	181.0 (163.0, 207.0)	190.0 (168.0, 215.0)	< 0.001
Lactate (mmol/L)	2.9 ± 1.5	2.6 ± 0.9	2.7 ± 1.1	3.3 ± 2.0	< 0.001
INR	1.5 ± 0.4	1.4 ± 0.2	1.5 ± 0.5	1.5 ± 0.4	< 0.001
PT (seconds)	16.2 ± 5.0	15.7 ± 2.0	16.0 ± 5.0	16.7 ± 6.6	< 0.001
PTT (seconds)	40.4 ± 20.3	38.1 ± 16.7	39.5 ± 20.2	43.1 ± 22.9	< 0.001
Urine output (ml)	1,933.1 ± 893.5	2,069.0 ± 888.5	1,942.9 ± 848.7	1,803.9 ± 913.8	< 0.001
GCS	12.7 ± 3.9	13.0 ± 3.7	12.9 ± 3.8	12.4 ± 4.1	< 0.001
SOFA	5.7 ± 2.9	5.2 ± 2.4	5.4 ± 2.6	6.5 ± 3.3	< 0.001
LODS	4.8 ± 2.7	4.3 ± 2.3	4.5 ± 2.4	5.4 ± 3.1	< 0.001
SAPSII	38.2 ± 11.9	36.7 ± 10.9	37.5 ± 11.4	40.1 ± 12.7	< 0.001

BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO_2, pulse oxygen saturation; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; GCS, Glass Score; SOFA, Sequential Organ Failure Assessment; LODS, Logistic Organ dysfunction score system; SAPSII, Simplified Acute Physiology Score II.

AG group (AG < 12 mmol/L) and the median AG group (12 mmol/L< AG < 14 mmol/L) was not significant (HR, 95% CI: 2, 0.62-6.47, p=0.246), the trend test showed that this AG change was meaningful for predicting patient outcomes (HR, 95% CI: 2, 1.24-3.21, p=0.004).

Table II. Subgroup analysis of the association between 30 days all-cause mortality and AG.

Subgroup	n. total	n. event (%)	HR (95% CI)	*p*-value
Overall				
Crude	5,102	61(1.2)	1.31 (1.26-1.35)	
Adjusted	5,102	61(1.2)	1.22 (1.13-1.33)	
Age				
<70	2,691	25 (0.9)	0.9 (0.76-1.07)	0.015
>=70	2,411	36 (1.5)	1.38 (1.2-1.59)	
Gender				
Female	1,160	24 (2.1)	1.52 (1.27-1.82)	<0,001
Male	3,942	37 (0.9)	0.99 (0.86-1.13)	
Myocardial infarction				
No	3,134	23 (0.7)	1.12 (0.91-1.37)	0.416
Yes	1,968	38 (1.9)	1.16 (1.02-1.31)	
Peripheral vascular disease				
No	4,428	36 (0.8)	1.09 (0.97-1.23)	0.823
Yes	674	25 (3.7)	1.29 (1.03-1.62)	
Cerebrovascular disease				
No	4,570	45 (1)	1.11 (0.99-1.24)	0.085
Yes	532	16 (3)	1.75 (1.01-3.04)	
Creatinine				
<1	2,489	11 (0.4)	1 (0.77-1.29)	0.002
>=1	2,613	50 (1.9)	1.09 (0.98-1.22)	
PT				
<15.6	2,523	11 (0.4)	1.13 (0.79-1.63)	0.974
>=15.6	2,579	50 (1.9)	1.14 (1.02-1.27)	
PTT				
<33.5	2,524	9 (0.4)	0.87 (0.61-1.23)	0.91
>=33.5	2,578	52 (2)	1.17 (1.05-1.3)	
GCS				
<14	1,237	29 (2.3)	1.05 (0.89-1.24)	<0,001
>=14	3,865	32 (0.8)	1.07 (0.93-1.22)	
SAPSII				
<36	2,393	7 (0.3)	1.4 (0.85-2.3)	0.664
>=36	2,709	54 (2)	1.16 (1.05-1.29	

HR, hazard ratio; CI, confidence interval; PT, prothrombin time; PTT, partial thromboplastin time; GCS, Glass Score; SAPSII, Simplified Acute Physiology Score II.

Table III. Relationship between AG and 30 days all-cause mortality in different models.

Variable	Crude model HR (95% CI)	*p*-value	Model 1 HR (95% CI)	*p*-value	Model 2 HR (95% CI)	*p*-value
Anion gap (mmol/L)	1.31 (1.26-1.35)	<0.001	1.36 (1.3-1.42)	<0.001	1.22 (1.13-1.33)	<0.001
Anion gap (tertile) (mmol/L)						
<12	1(Ref)		1(Ref)		1(Ref)	
≥12, <14	2.85 (0.89-9.08)	0.077	2.79 (0.88-8.9)	0.083	2 (0.62-6.47)	0.246
≥14	10.61 (3.82-29.46)	<0.001	10.32 (3.72-28.64)	<0.001	3.99 (1.35-11.76)	0.012
Trend. Test	3.42 (2.2-5.31)	<0.001	3.38 (2.18-5.25)	<0.001	2 (1.24-3.21)	0.004

Crude model: no covariates were adjusted. Model I adjusted for: age and gender. Model II adjusted for: age, gender, race, BMI, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, renal disease, heart rate, SBP, DBP, MBP, respiratory rate, SpO_2, WBC, platelets, creatinine, potassium, glucose, INR, PT, PTT, urine output, GCS, and SAPSII. HR: hazard ratio; CI: confidence interval; BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO_2, pulse oxygen saturation; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; GCS, Glass Score; SAPSII, Simplified Acute Physiology Score II.

2968

Prior studies[5] have noted the importance of the serum AG in death and complications of critical diseases in the ICU. Gong found that the number of all-cause deaths increased with the serum AG at 90 days (HR 1.88, 95% CI 1.04-3.41, p=0.037). Liu suggested that a high AG is related to increased risks of short-term mortality (30-day HR 2.45, 95% CI 1.21-4.97)[7]. However, at one year follow-up, the predictive ability of a high AG declines (365-day HR 1.56, 95% CI 0.87-2.78). Such predictive capability also applies to the cardiovascular system. Sahu et al[9] also revealed that the initial AG was associated with death in acute MI (OR 4.2, 95% CI 2.3-7.5). Yang et al[8] found that each milliequivalent-per-liter increase in AG was correlated with a higher grade of cardiac function (2.1%) and a higher risk of mortality in CAD (HR 1.069, 95% CI 1.020-1.121). Our finding that the serum AG predicts poor outcomes is consistent with the findings of previous studies[15,16]. The kidney is an important organ for acid excretion. Dehydrogenase dysfunction in acute kidney injury leads to endogenous acid accumulation, and the resulting high AG may offset our conclusion. However, after we adjusted for renal disease in model II, a higher AG still predicted worse outcomes. In our subgroup analysis, higher creatine seemed to indicate a worse prognostic outcome, but the difference was not statistically significant (HR 1.09, 95% CI 0.98-1.22). Moreover, we found that females and elderly individuals were more likely to develop all-cause mortality within 30 days.

We can only speculate on the mechanism behind this relationship because of the lack of detailed data. In metabolic acidosis, which is the main predictor of prognosis, the protons could combine with bicarbonate and contribute to unmeasured anions[17]. Most metabolic acidosis in the ICU could be attributable to an increase in unmeasured anions[18]. Excessive production of organic acids or decreased renal excretion, as occur in lactic acidosis and ketoacidosis, are the main reasons for an elevated AG[19]. Clinicians can quickly infer acid-base equilibrium status due to an elevated AG. Hypotension is a common phenomenon in metabolic acidosis that is mainly caused by reduced cardiac contraction and resistance to catecholamines[20,21]. However, the opinion that acidosis directly damages cardiovascular function has not been demonstrated experimentally[3]. In addition, studies[22] have shown that acute metabolic acidosis, including high-AG metabolic acidosis, can suppress immune function, making patients more susceptible to infection.

Limitations

There are several limitations in our study. First, selection bias was inevitable, as this was a single-center retrospective observational study. Second, we collected only the initial AG and, therefore, did not evaluate dynamic changes in the AG, which may provide more prognostic information. In addition, because of missing data, we did not include serum albumin, which may influence the AG, in our analyses[23]. Finally, we did not reveal the potential mechanism underlying the relationship between the serum AG and higher mortality in CABG.

Conclusions

In summary, the serum AG can serve as a simple and easily available means to predict the short-term prognosis of patients who undergo CABG. Early discovery of a high serum AG will help raise awareness about the severity of the disease.

Conflicts of Interestt

The authors declare that they have no conflict of interests.

Informed Consent and Ethics Approval

The informed consent was obtained for the original data collection. Thus, the ethical approval and the need for informed consent were waived for the studies on this database.

Funding

The authors received no financial support for this article's research, authorship, and/or publication.

Authors' Contribution

X.-M. Wang and Y.-S. Deng: Methodology, Software, Formal analysis, Data Curation, Writing - Original Draft; B. He: Writing - Original Draft, Formal analysis; J.-W. Liu and Z.-H. Zhang: Formal analysis and Data Curation; Z.-D. Ye: Supervision, Writing - Review & Editing; P. LIU: Conceptualization, Supervision, Writing - Review and Editing. X.-M. Wang and Y.-S. Deng contributed equally to this work.

ORCID ID

P. Liu: 0000-0002-2653-0718

Availability of Data and Materials

The datasets presented in the current study are available in the MIMIC IV database (https://mimic-iv.mit.edu/).

References

1) Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019; 40: 87-165.
2) Nalysnyk L, Fahrbach K, Reynolds MW, Zhao SZ, Ross S. Adverse events in coronary artery bypass graft (CABG) trials: a systematic review and analysis. Heart Br Card Soc 2003; 89: 767-772.
3) Kraut JA, Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. Nat Rev Nephrol 2010; 6: 274-285.
4) Cheng B, Li D, Gong Y, Ying B, Wang B. Serum Anion Gap Predicts All-Cause Mortality in Critically Ill Patients with Acute Kidney Injury: Analysis of the MIMIC-III Database. Dis Markers 2020; 2020: 6501272.
5) Gong F, Zhou Q, Gui C, Huang SH, Qin Z. The Relationship Between the Serum Anion Gap and All-Cause Mortality in Acute Pancreatitis: An Analysis of the MIMIC-III Database. Int J Gen Med 2021; 14: 531-538.
6) Gao Y, Hong Z, Shen R, Zhang S, You GC, Chen J, Guo X, Peng S, Huang K. Association between anion gap and mortality of aortic aneurysm in intensive care unit after open surgery. BMC Cardiovasc Disord 2021; 21: 458.
7) Liu X, Feng Y, Zhu X, Shi Y, Lin M, Song X, Tu J, Yuan E. Serum anion gap at admission predicts all-cause mortality in critically ill patients with cerebral infarction: evidence from the MIMIC-III database. Biomark Biochem Indic Expo Response Susceptibility Chem 2020; 25: 725-732.
8) Yang SW, Zhou YJ, Zhao YX, Liu YY, Tian XF, Wang ZJ, Jia DA, Han HY, Hu B, Shen H, Gao F, Wang L, Lin J, Pan GZ, Zhang J, Guo ZF, Du J, Hu DY. The serum anion gap is associated with disease severity and all-cause mortality in coronary artery disease. J Geriatr Cardiol JGC 2017; 14: 392-400.
9) Sahu A, Cooper HA, Panza JA. The initial anion gap is a predictor of mortality in acute myocardial infarction. Coron Artery Dis 2006; 17: 409-412.
10) Goldberger AL, Amaral LA, Glass L, Ivanov PC, Mark RG, Mietus JE, Moody GB, Peng CK, Stanley HE. PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. Circulation 2000; 101: E215-220.
11) Yang Q, Zheng J, Chen W, Chen X, Wen D, Chen W, Xiong X, Zhang Z. Association Between Preadmission Metformin Use and Outcomes in Intensive Care Unit Patients with Sepsis and Type 2 Diabetes: A Cohort Study. Front Med 2021; 8: 640785.
12) Taylor EN, Forman JP, Farwell WR. Serum anion gap and blood pressure in the national health and nutrition examination survey. Hypertension 2007; 50: 320-324.
13) Farwell WR, Taylor EN. Serum bicarbonate, anion gap and insulin resistance in the National Health and Nutrition Examination Survey. Diabet Med J Br Diabet Assoc 2008; 25: 798-804.
14) Abramowitz MK, Hostetter TH, Melamed ML. Lower serum bicarbonate and a higher anion gap are associated with lower cardiorespiratory fitness in young adults. Kidney Int 2012; 81: 1033-1042.
15) Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE. Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. Lancet Lond Engl 2005; 365: 871-875.
16) Kurtz I, Maher T, Hulter HN, M Schambelan, Sebastian A. Effect of diet on plasma acid-base composition in normal humans. Kidney Int 1983; 24: 670-680.
17) Gunnerson KJ. Clinical review: the meaning of acid-base abnormalities in the intensive care unit part I - epidemiology. Crit Care Lond Engl 2005; 9: 508-516.
18) Maciel AT, Park M. Unmeasured anions account for most of the metabolic acidosis in patients with hyperlactatemia. Clin Sao Paulo Braz 2007; 62: 55-62.
19) Gabow PA, Kaehny WD, Fennessey PV, Goodman SI, Gross PA, Schrier RW. Diagnostic importance of an increased serum anion gap. N Engl J Med 1980; 303: 854-858.
20) Mitchell JH, Wildenthal K, Johnson RL. The effects of acid-base disturbances on cardiovascular and pulmonary function. Kidney Int 1972; 1: 375-389.
21) Davies AO. Rapid desensitization and uncoupling of human beta-adrenergic receptors in an in vitro model of lactic acidosis. J Clin Endocrinol Metab 1984; 59: 398-405.
22) Kellum JA, Song M, Li J. Science review: extracellular acidosis and the immune response: clinical and physiologic implications. Crit Care Lond Engl 2004; 8: 331-336.
23) Feldman M, Soni N, Dickson B. Influence of hypoalbuminemia or hyperalbuminemia on the serum anion gap. J Lab Clin Med 2005; 146: 317-320.