Association of anion gap and albumin corrected anion gap with acute kidney injury in patients with acute ischemic stroke

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Abstract

Background. Acute kidney injury (AKI) has become a common complication of acute ischemic stroke (AIS) and may have a significant impact on clinical outcomes. Anion gap (AG)/albumin corrected anion gap (ACAG) are used to assess acid-base balance status and help identify the severity of metabolic acidosis.

Objectives. To explore the association of AG and ACAG with the risk of AKI in AIS patients admitted to the intensive care unit (ICU).

Materials and methods. Data of AIS patients in this retrospective cohort study were extracted from the electronic ICU (eICU) databases (2014–2015). The outcome was the occurrence of AKI after ICU admission. The covariates included demographic data, vital signs, comorbidities, laboratory parameters, and medication use. The association of AG and ACAG levels with AKI risk in AIS patients was evaluated using univariate and multivariate logistic regression models with odds ratios (ORs) and 95% confidence intervals (95% CIs). The predictive performance of AG and ACAG for the risk of AKI in AIS patients was assessed with the area under the curve (AUC). To further explore the association of AG and ACAG levels with AKI risk, subgroup analyses were performed according to comorbidities.

Results. Of the 1,260 AIS patients, 546 (43%) developed AKI. Elevated AG (OR = 1.73, 95% CI: 1.32–2.29) and ACAG (OR = 1.57, 95% CI: 1.21–2.04) were associated with the risk of AKI in AIS patients. The AUC of ACAG was superior to AG for predicting the risk of AKI (0.581 vs 0.558; p = 0.024). Elevated ACAG levels were associated with the risk of AKI in AIS patients without ischemic heart disease (OR = 1.60, 95% CI: 1.19–2.15), diabetes (OR = 1.58, 95% CI: 1.19–2.10) and hypertension (OR = 1.69, 95% CI: 1.24–2.30).

Conclusions. Albumin corrected anion gap was a better predictor than AG for AKI risk in AIS patients, which may help clinicians identify high-risk patients for AKI.

Key words: acute kidney injury, acute ischemic stroke, anion gap, albumin corrected anion gap

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Background

Acute ischemic stroke (AIS) is a cerebral infarction caused by cerebral vascular occlusion or hemorrhage and is a common vascular event of the central nervous system.[1] Acute ischemic stroke affects approx. 95 individuals per 100,000 population worldwide every year and is a significant cause of disability and death.[2] Evidence showed that a common complication in patients with AIS is acute kidney injury (AKI), which occurs in about 19% of patients with AIS.[3,4] Acute kidney injury can deteriorate the medical status of patients with AIS and predict a worse clinical prognosis, including longer hospital stay and higher mortality.[5,6] Identification of high-risk patients who may develop AKI is essential for the management and improvement of outcomes in patients with AIS.

Acid-base disorders (particularly metabolic acidosis) are common problems in critically ill patients and are closely related to patient morbidity and mortality.[7] Evidence shows that acid-base disorders and altered electrolyte concentrations are early biochemical responses in AIS, leading to continuous tissue oxidative damage and increased inflammation.[8] The serum anion gap (AG) is an index reflecting the concentration of unmeasured anions, which is used to assess acid-base balance status.[9] However, due to albumin molecules carrying a charge, the results will appear falsely negative, leading to misjudgment of the AG level, a situation that often occurs in critically ill patients with hypoalbuminemia.[10] To avoid the fluctuation of the AG with differing albumin concentrations, the albumin-corrected anion gap (ACAG) was proposed.[11] The AG level is a significant predictor of in-hospital mortality in patients with AIS, and high AG levels are linked to high mortality in AIS patients.[12] However, the relationship between ACAG levels and the prognosis of AIS patients is unclear. Moreover, AG and ACAG levels have been reported to be linked to a higher incidence of and mortality in AKI.[13,14] The link between AG and ACAG levels and the risk of AKI in AIS patients deserves to be explored.

Objectives

This study aimed to evaluate the associations of AG and ACAG levels with AKI risk in patients with AIS who were admitted to the intensive care unit (ICU) and assessed the predictive effect of AG and ACAG for AKI risk.

Materials and methods

Study population

This retrospective cohort study extracted AIS patient data from the electronic ICU (eICU) database (https://eicu-crd.mit.edu/gettingstarted/overview/). The eICU database is a publicly available multicenter database that covers highly granular data on more than 200,000 patients admitted to ICUs across the continental USA from 2014 to 2015.[15] The overall information includes vital sign measurements, severity of illness measures, care plan documentation, treatment information, and diagnosis information. The participant's informed consent was waived because the data were anonymized.

The inclusion criteria included: 1) participants ≥18 years of age and 2) participants diagnosed with AIS at ICU admission.[16] The exclusion criteria were: 1) ICU stay shorter than 24 h; 2) patients with missing data about survival; 3) patients with missing data of sodium, potassium, chloride, bicarbonate, albumin, and AKI grade; 4) patients diagnosed with end-stage renal disease (ESRD)[17,18]; and 5) patients with a history of kidney transplantation.

Definition of AG and ACAG

Anion gap and ACAG were calculated based on the following equation[19]: AG (mmol/L) = (sodium + potassium) – (chloride + bicarbonate) and ACAG (mmol/L) = [4.4 – {albumin(g/dL)}] * 2.5 + AG. The measurements of sodium, potassium, chloride, bicarbonate, and albumin were based on the patient's records at the time of initial admission to the ICU. The AG and ACAG levels were categorized into high- and low-level groups based on the value corresponding to the maximum of Youden's J statistic as the cutoff value (Supplementary Fig. 1). The AG and ACAG levels were categorized as AG levels (low-level (<12.15 mmol/L) and high-level (≥12.15 mmol/L)) and ACAG levels (low-level (<15.075 mmol/L) and high-level (≥15.075 mmol/L)).

Potential covariates

Potential covariates were age, gender, race, height, weight, ICU type, body mass index (BMI), cardiogenic shock, ischemic heart disease, diabetes, hypertension, vasopressor therapy, thrombolysis, thrombectomy, antiplatelet, anticoagulation, antihypertension, ventilation, diastolic blood pressure (DBP), respiratory rate, heart rate, alanine aminotransferase (ALT), systolic blood pressure (SBP), aspartate aminotransferase (AST), serum creatinine (SCR), blood urea nitrogen (BUN), mean arterial pressure (MAP), platelets, white blood cell count (WBC), red blood cell distribution width (RDW), hemoglobin, bilirubin, glucose, international normalized ratio (INR), and estimated glomerular filtration rate (eGFR).

Outcome and follow-up

The AKI was defined by the Kidney Disease Improving Global Outcomes (KDIGO)[20] as follows: an increase in SCR level ≥0.3 mg/dL within 48 h, an increase in SCR levels to ≥1.5 times than the level at ICU admission within 7 days, or urine volume <0.5 mL/kg/h for 6 h. The outcome in this

cohort was the occurrence of AKI after ICU admission. Follow-up began on ICU admission and was terminated when the patient was discharged from the ICU or AKI developed.

Statistical analyses

Normally distributed continuous data were reported as the mean ± standard deviation (mean (±SD)) and tested using t-tests. Non-normally continuous data were presented as medians and quartiles (Me (Q1, Q3)) and tested using a Mann–Whitney U test. Categorical data were presented as the number and percentage (n (%)) and tested using a χ^2 test or Fisher's exact test.

The outcome and exposure variables were not missing, covariates with greater than 20% missing were deleted, and covariates with less than 20% missing were interpolated using multiple interpolations (Supplementary Table 1). Missing data were interpolated 5 times using multiple interpolations through the R package "mice" (v. 3.15.0),[21] with the means of the 5 interpolations taken for continuous variables and the mode of the 5 interpolations taken for categorical variables. Sensitivity analyses were performed on the data before and after interpolation (Supplementary Table 2). Covariates were screened using the adaptive best–subset selection (ABESS) method.[22] All variables except exposure and composite index calculation variables (e.g., height, weight, SBP, DBP, SCR, sodium, potassium, chloride, bicarbonate, and albumin) were selected using the "abbess" R package (v. 0.4.8) based on the generalized information criterion (GIC) (Supplementary Table 3).[22] A variance inflation factor (VIF) was used to assess the linearity between variables, and a VIF ≥ 5 was considered multicollinearity (Supplementary Table 4). The Box–Tidwell test was applied to evaluate the linearity of numerical variables using Logit(P), and a p-value >0.05 satisfied the linear requirement (Supplementary Table 5). The best subsets of covariates after screening were BMI, ischemic heart disease, ventilation, WBC, and platelets. The logistic regression models were used for analyzing the association between AG and ACAG levels and AKI risk in AIS patients, and the results were presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). Model 1 was adjusted for all covariates, including BMI, ischemic heart disease, ventilation, WBC, and platelets. Model 2 was adjusted for albumin based on Model 1. The area under the curve (AUC) was applied to evaluate the predictive effect of AG and ACAG on the AKI risk of AIS patients. The Hosmer–Lemeshow test was utilized to assess the model's goodness-of-fit (Supplementary Table 6). The associations were performed in different subgroups of ischemic heart disease (yes or no), diabetes (yes or no) and hypertension (yes or no).

Data cleaning, missing value imputation, covariate screening, data modeling, prediction performance evaluation, and subgroup analysis were performed using R software v. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). SAS 9.4 software (SAS Institute Inc., Cary, USA) was used for descriptive statistical analysis and sensitivity analysis. A p-value <0.05 was considered statistically significant for all analyses.

Results

Patients' characteristics

A flowchart of AIS patients is presented in Fig. 1. A total of 3,005 patients with AIS admitted to ICU were screened. Among them, 1,745 patients were excluded from the study, including 97 patients aged <18 years, 280 patients with an ICU stay of less than 24 h, 1,331 patients with missing sodium, potassium, chloride, bicarbonate, albumin, and AKI grade data, and 37 patients with a diagnosis of ESRD. The mean age of all patients was 67.70 ±13.38 years, with a median follow-up time of 2 (1, 4) days. Table 1 displays AIS patient characteristics with and without AKI. There were significant differences in age, weight, BMI, ICU type, cardiogenic shock, ischemic heart disease, diabetes, hypertension, vasopressor, ventilation, thrombolysis, antiplatelet therapy, heart rate, respiratory rate, WBC, hemoglobin, RDW, bilirubin, SCR, INR, albumin, BUN, glucose, AST, bicarbonate, and eGFR.

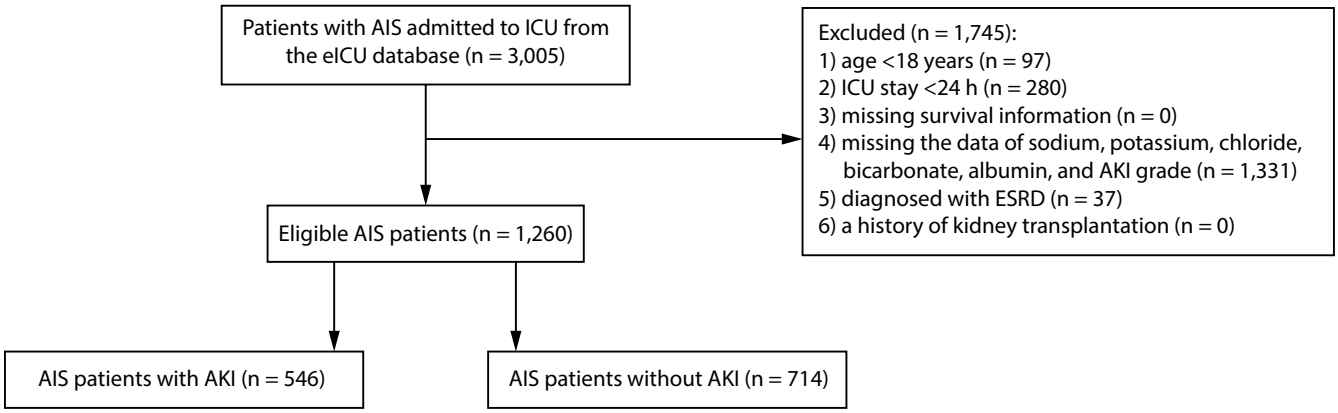

Fig. 1. The screening flowchart of acute ischemic stroke (AIS) patients

ICU – intensive care unit; AKI – acute kidney injury; ESRD – end-stage renal disease.

Table 1. Characteristics of patients with acute ischemic stroke (AIS)

Variables		Total (n = 1,260)	Non-AKI (n = 714)	AKI (n = 546)	Statistics	p-value
AG [mmol/L] mean ±SD		14.52 ±4.32	14.12 ±4.20	15.03 ±4.42	t = –3.73	<0.001
AG, n (%)	high-level (≥12.15 mmol/L)	880 (69.84)	463 (64.85)	417 (76.37)	χ^2 = 19.520	<0.001
	low-level (<12.15 mmol/L)	380 (30.16)	251 (35.15)	129 (23.63)		
ACAG [mmol/L], mean ±SD		16.84 ±4.32	16.23 ±4.14	17.65 ±4.41	t = –5.87	<0.001
ACAG, n (%)	high-level (≥15.075 mmol/L)	823 (65.32)	416 (58.26)	407 (74.54)	χ^2 = 36.193	<0.001
	low-level (<15.075 mmol/L)	437 (34.68)	298 (41.74)	139 (25.46)		
Age [years] mean ±SD		67.70 ±13.38	67.04 ±14.00	68.56 ±12.47	t = –2.03	0.043
Age, years, n (%)	<65	477 (37.86)	285 (39.92)	192 (35.16)	χ^2 = 2.969	0.085
	≥65	783 (62.14)	429 (60.08)	354 (64.84)		
Gender, n (%)	female	609 (48.33)	346 (48.46)	263 (48.17)	χ^2 = 0.010	0.918
	male	651 (51.67)	368 (51.54)	283 (51.83)		
Race, n (%)	African-American	124 (9.84)	72 (10.08)	52 (9.52)	χ^2 = 0.236	0.889
	Caucasian	982 (77.94)	557 (78.01)	425 (77.84)		
	other	154 (12.22)	85 (11.90)	69 (12.64)		
Height [cm], mean ±SD		168.99 ±11.57	169.46 ±10.67	168.37 ±12.63	t = 1.63	0.103
Weight [kg], mean ±SD		82.54 ±22.44	81.28 ±21.47	84.18 ±23.56	t = –2.25	0.025
BMI [kg/m^2], Me (Q1, Q3)		27.58 (24.08, 32.02)	27.31 (23.84, 31.09)	28.02 (24.52, 33.43)	Z = 2.815	0.005
BMI [kg/m^2], n (%)	<25	391 (31.03)	237 (33.19)	154 (28.21)	χ^2 = 8.652	0.013
	25–30	431 (34.21)	253 (35.43)	178 (32.60)		
	≥30	438 (34.76)	224 (31.37)	214 (39.19)		
ICU type, n (%)	CICU	114 (9.05)	50 (7.00)	64 (11.72)	χ^2 = 10.336	0.016
	NICU	440 (34.92)	266 (37.25)	174 (31.87)		
	SICU	72 (5.71)	42 (5.88)	30 (5.49)		
	other	634 (50.32)	356 (49.86)	278 (50.92)		
Cardiogenic shock, n (%)	no	1,250 (99.21)	712 (99.72)	538 (98.53)	–	0.024
	yes	10 (0.79)	2 (0.28)	8 (1.47)		
Ischemic heart disease, n (%)	no	964 (76.51)	593 (83.05)	371 (67.95)	χ^2 = 39.274	<0.001
	yes	296 (23.49)	121 (16.95)	175 (32.05)		
Diabetes, n (%)	no	1074 (85.24)	632 (88.52)	442 (80.95)	χ^2 = 14.065	<0.001
	yes	186 (14.76)	82 (11.48)	104 (19.05)		
Hypertension, n (%)	no	905 (71.83)	532 (74.51)	373 (68.32)	χ^2 = 5.867	0.015
	yes	355 (28.17)	182 (25.49)	173 (31.68)		
Vasopressor, n (%)	no	1137 (90.24)	675 (94.54)	462 (84.62)	χ^2 = 34.581	<0.001
	yes	123 (9.76)	39 (5.46)	84 (15.38)		
Ventilation, n (%)	no	959 (76.11)	619 (86.69)	340 (62.27)	χ^2 = 101.507	<0.001
	yes	301 (23.89)	95 (13.31)	206 (37.73)		
Thrombolysis, n (%)	no	874 (69.37)	467 (65.41)	407 (74.54)	χ^2 = 12.153	<0.001
	yes	386 (30.63)	247 (34.59)	139 (25.46)		
Thrombectomy, n (%)	no	1243 (98.65)	706 (98.88)	537 (98.35)	χ^2 = 0.648	0.421
	yes	17 (1.35)	8 (1.12)	9 (1.65)		
Antiplatelet, n (%)	no	1122 (89.05)	647 (90.62)	475 (87.00)	χ^2 = 4.157	0.041
	yes	138 (10.95)	67 (9.38)	71 (13.00)		
Anticoagulation, n (%)	no	1197 (95.00)	681 (95.38)	516 (94.51)	χ^2 = 0.496	0.481
	yes	63 (5.00)	33 (4.62)	30 (5.49)		
Antihypertension, n (%)	no	1056 (83.81)	604 (84.59)	452 (82.78)	χ^2 = 0.747	0.387
	yes	204 (16.19)	110 (15.41)	94 (17.22)		
Heart rate [bpm], mean ±SD		84.37 ±19.84	82.66 ±18.72	86.62 ±21.04	t = –3.48	<0.001
Respiratory rate [times/min], mean ±SD		19.07 ±4.99	18.72 ±4.54	19.54 ±5.50	t = –2.82	0.005

Table 1. Characteristics of patients with acute ischemic stroke (AIS) – cont.

Variables		Total (n = 1,260)	Non-AKI (n = 714)	AKI (n = 546)	Statistics	p-value
SBP [mm Hg], mean ±SD		146.38 ±28.94	147.32 ±27.46	145.14 ±30.74	t = 1.31	0.191
DBP [mm Hg], mean ±SD		80.47 ±19.45	81.10 ±18.36	79.64 ±20.78	t = 1.30	0.193
MAP [mm Hg], mean ±SD		102.44 ±20.03	103.18 ±18.91	101.47 ±21.40	t = 1.47	0.141
WBC [k/mcL], Me (Q_1, Q_3)		9.40 (7.30, 12.60)	8.82 (7.20, 11.20)	10.51 (7.60, 14.30)	Z = 6.075	<0.001
Platelets [K/mcL], Me (Q_1, Q_3)		218.50 (176.00, 267.50)	222.00 (180.00, 267.00)	215.00 (169.00, 269.00)	Z = –1.814	0.070
Hemoglobin [g/dL], mean ±SD		13.05 ±2.32	13.19 ±2.23	12.86 ±2.41	t = 2.44	0.015
RDW [%], mean ±SD		14.38 ±1.87	14.23 ±1.73	14.58 ±2.02	t = –3.22	0.001
Billirubin [mg/dL], Me (Q_1, Q_3)		0.60 (0.40, 0.80)	0.50 (0.40, 0.70)	0.60 (0.40, 0.90)	Z = 5.461	<0.001
SCR [mg/dL], Me (Q_1, Q_3)		0.97 (0.78, 1.27)	0.94 (0.76, 1.20)	1.00 (0.80, 1.40)	Z = 3.655	<0.001
INR, Me (Q_1, Q_3)		1.06 (1.00, 1.20)	1.00 (1.00, 1.10)	1.10 (1.00, 1.24)	Z = 7.382	<0.001
Albumin [g/dL], mean ±SD		3.47 ±0.61	3.56 ±0.58	3.35 ±0.63	t = 5.88	<0.001
BUN [mg/dL], Me (Q_1, Q_3)		18.00 (13.00, 25.00)	17.00 (13.00, 23.00)	19.00 (14.00, 28.00)	Z = 3.859	<0.001
Glucose [mg/dL], Me (Q_1, Q_3)		128.00 (105.00, 161.00)	121.00 (102.00, 148.00)	138.00 (110.00, 178.00)	Z = 6.165	<0.001
ALT [U/L], Me (Q_1, Q_3)		23.90 (17.00, 35.00)	24.00 (17.00, 34.00)	23.00 (17.00, 36.00)	Z = 0.016	0.987
AST [U/L], Me (Q_1, Q_3)		24.00 (18.00, 34.00)	23.00 (18.00, 31.00)	25.00 (19.00, 41.00)	Z = 5.088	<0.001
Sodium [mmol/L], mean ±SD		138.73 ±4.42	138.62 ±4.11	138.88 ±4.79	t = –1.01	0.313
Potassium [mmol/L], mean ±SD		4.03 ±0.57	4.00 ±0.51	4.06 ±0.64	t = –1.85	0.065
Chloride [mmol/L], mean ±SD		103.71 ±5.41	103.70 ±5.04	103.73 ±5.86	t = –0.11	0.916
Bicarbonate [mmol/L], mean ±SD		24.53 ±3.92	24.80 ±3.64	24.18 ±4.23	t = 2.75	0.006
eGFR [mL/min/1.7 3m^2], Me (Q_1, Q_3)		77.28 (56.89, 93.57)	80.58 (61.31, 95.81)	71.75 (52.34, 91.22)	Z = –4.525	<0.001
Status, n (%)	survival	1169 (92.78)	696 (97.48)	473 (86.63)	χ^2 = 54.348	<0.001
	dead	91 (7.22)	18 (2.52)	73 (13.37)		

t – statistics for t-test; Z – statistics of Wilcoxon–Mann–Whitney test; χ^2 – statistics for χ^2 test. These tests were used to compare the differences in characteristics between patients with acute kidney injury (AKI) and those without AKI. SD – standard deviation; Me – median; Q1 – 1st quartile; Q3– 3rd quartile; AG – anion gap; ACAG – albumin corrected anion gap; BMI – body mass index; CICU – cardiac intensive care unit; NICU – neuro intensive care unit; SICU – surgical intensive care unit; SBP – systolic blood pressure; DBP – diastolic blood pressure; MAP – mean arterial pressure; WBC – white blood cell count; RDW – red cell volume distribution width; SCR – serum creatinine; INR – international normalized ratio; BUN – blood urea nitrogen; ALT – alanine aminotransferase; AST – aspartate aminotransferase; eGFR – estimated glomerular filtration rate.

Association between AG and ACAG levels and the AKI risk in patients with AIS

The relationship between AG and ACAG levels and the risk of AKI in AIS patients is presented in Table 2. An elevated AG was associated with the AKI risk in patients with AIS (OR = 1.73, 95% CI: 1.32–2.29; p < 0.001), after adjustments for BMI, ischemic heart disease, ventilation, WBC, platelets, and albumin. A high level of ACAG was associated with the AKI risk in AIS patients (OR = 1.57, 95% CI: 1.21–2.04; p = 0.001), after adjustments for BMI, ischemic heart disease, ventilation, WBC, and platelets.

The predictive performance of AG and ACAG for the risk of AKI in AIS patients

Figure 2 shows the predictive performance of AG and ACAG concerning AKI risk in patients with AISs. The AUC for predicting the AKI risk was 0.558 (95% CI: 0.533–0.583) and 0.581 (95% CI: 0.556–0.607) for AG and ACAG, respectively (Table 3). Moreover, the predictive performance of ACAG was superior to that of AG (p = 0.024).

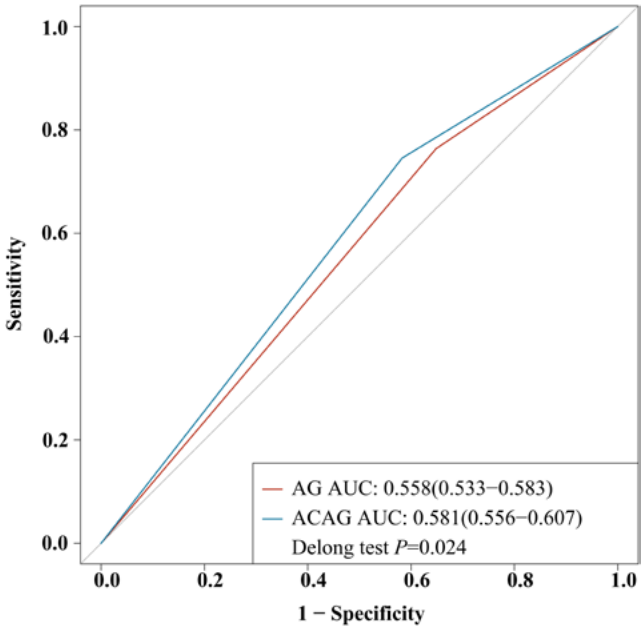

Fig. 2. The receiver operating characteristic (ROC) curves of AG and ACAG for predicting the risk of AKI in AIS patients

AG – anion gap; ACAG – albumin corrected anion gap; AKI – acute kidney injury; AIS – acute ischemic stroke; AUC – area under the curve

Table 2. Associations of AG and ACAG with the risk of AKI in AIS patients

Variables		Crude model		Model 1		Model 2	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
AG	low-level	Ref.	–	Ref.	–	Ref.	–
	high-level	1.75 (1.37–2.25)	<0.001	1.57 (1.20–2.05)	0.001	1.73 (1.32–2.29)	<0.001
ACAG	low-level	Ref.	–	Ref.	–	–	–
	high-level	2.10 (1.65–2.68)	<0.001	1.57 (1.21–2.04)	0.001	–	–

OR – odd ratio; 95% CI – 95% confidence interval; AG – anion gap; ACAG – albumin corrected anion gap; AKI – acute kidney injury; AIS – acute ischemic stroke; AG levels (low-level (<12.15 mmol/L) and high-level (≥12.15 mmol/L)); ACAG levels (low-level (<15.075 mmol/L) and high-level (≥15.075 mmol/L)). Crude model – univariate model; Model 1 – adjusted for body mass index (BMI), ischemic heart disease, ventilation, white blood cells count (WBC), and platelets; Model 2 – adjusted for BMI, ischemic heart disease, ventilation, WBC, platelets, and albumin.

Table 3. The predictive performance of AG and ACAG for the AKI risk in patients with AIS

Variables	AG	ACAG
AUC (95% CI)	0.558 (0.533–0.583)	0.581 (0.556–0.607)
Accuracy (95% CI)	0.530 (0.502–0.558)	0.560 (0.532–0.587)
Specificity (95% CI)	0.352 (0.317–0.387)	0.417 (0.381–0.454)
Sensitivity (95% CI)	0.764 (0.728–0.799)	0.745 (0.709–0782)
PPV (95% CI)	0.474 (0.441–0.507)	0.495 (0.460–0.529)
NPV (95% CI)	0.661 (0.613–0.708)	0.682 (0.638–0726)

AG – anion gap; ACAG – albumin corrected anion gap; AKI – acute kidney injury; AIS – acute ischemic stroke; AUC – area under the curve; 95% CI – 95% confidence interval; PPV – positive predictive value; NPV – negative predictive value.

Association of ACAG with AKI in AIS patients based on ischemic heart disease, diabetes and hypertension

Further analyses were conducted to explore this association in AIS patients with regard to different subgroups of ischemic heart disease, diabetes and hypertension patients (Fig. 3). The results showed that the high ACAG levels were associated with the AKI risk in AIS patients without ischemic heart disease (OR = 1.60, 95% CI: 1.19–2.15), diabetes (OR = 1.58, 95% CI: 1.19–2.10) and hypertension (OR = 1.69, 95% CI: 1.24–2.30).

Discussion

We investigated the effects of AG and ACAG levels on AKI risk in AIS patients. Our findings showed that high AG and ACAG levels were associated with AKI risk in AIS patients. The performance of ACAG was superior to AG for predicting the risk of AKI. We also found that high levels of ACAG were associated with the AKI risk in AIS patients without ischemic heart disease, diabetes and hypertension.

The AG and ACAG are clinical indicators to evaluate acid-base imbalances, and high AG and ACAG levels indicate the occurrence of metabolic acidosis.[23,24] Previous studies have found that high levels of AG and ACAG were positively associated with poor outcomes in a variety of diseases, including AKI and AIS.[12,25–28] Jhou et al.[12] reported that an elevated AG was associated with poor outcomes and a higher in-hospital mortality risk in patients with AIS. Cheng et al.[25] found that an elevated AG was associated with increased short-term and long-term all-cause mortality in AKI patients. Zhao et al.[28] reported that a high level of ACAG was associated with the AKI risk in patients who were admitted to the ICU. However, the association of AG and ACAG levels with AKI risk in AIS patients remains unclear. In our study, we found that an elevated AG and ACAG were associated with AKI risk in patients with AIS. Our findings regarding the relationship between AG and ACAG and the risk of AKI in AIS patients are consistent with previous studies on AKI risk. The receiver operating characteristic (ROC) curve showed that both AG and ACAG could predict the AKI risk in AIS patients, and the predictive performance of ACAG was superior to AG. As mentioned earlier, ACAG is a more accurate predictor of metabolic acidosis in critically ill patients with hypoalbuminemia. Hu et al.[24] reported the association of high ACAG levels with the risk of 1-year mortality in critically ill patients with sepsis, and the predictive performance of ACAG was superior to AG.

We further evaluated the relationship between ACAG levels and AKI risk in different populations. Our study indicated that a high level of ACAG was associated with AKI risks in AIS patients without ischemic heart disease, diabetes and hypertension. The high ACAG levels were not associated with an increased AKI risk in AIS patients with ischemic heart disease, diabetes and hypertension. This reason may be that the values of acid-base imbalance markers change with the progression of the disease. Evidence suggests that ischemic heart disease, diabetes and hypertension can cause low serum albumin levels, hyperlactatemia and electrolyte disturbances, which may affect ACAG levels.[29–33] Dinh et al.[34] conducted a retrospective study that found ACAG to perform poorly in the diagnosis of hyperlactatemia.

The mechanism by which a high level of ACAG was associated with higher odds of AKI in patients with AIS may involve acid-base disorders. The kidneys are an important organ system for regulating acid-base balance, which mainly

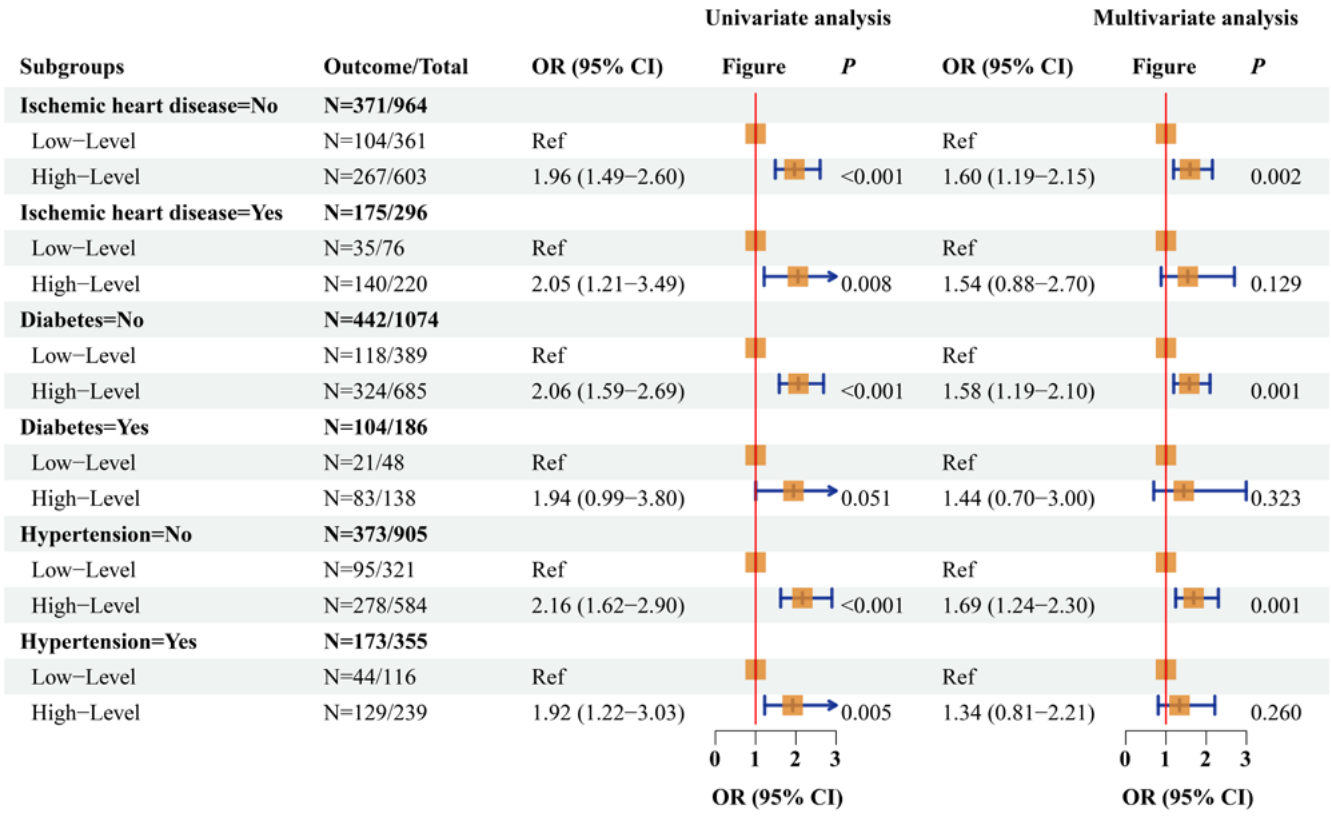

Fig. 3. Association between ACAG and AKI in AIS patients based on ischemic heart disease, diabetes and hypertension. Multivariate analysis adjusted for body mass index (BMI), ischemic heart disease (unadjusted for analysis of ischemic heart disease), ventilation, white blood cells count (WBC), and platelets

ACAG – albumin corrected anion gap; AKI – acute kidney injury; AIS – acute ischemic stroke. OR – odds ratio; 95% CI – 95% confidence interval.

promotes acid-base balance by maintaining bicarbonate homeostasis and acid excretion.[35] Acute kidney injury occurs in 9.62% of patients with ischemic stroke[4,36]; such patients are characterized by high SCR levels and kidney function impairments such as acid-base balance, electrolytes and fluids, and is associated with high mortality.[37,38] In addition, acid-base disorders and altered electrolyte concentrations are early biochemical responses in AIS, leading to continuous tissue oxidative damage and increased inflammation, further aggravating kidney injury and metabolic acidosis.[8]

Clinically, the ACAG level may be used as a potential prognostic indicator for the pre-bed management of AIS patients, which can help clinicians in the early identification of AIS patients with a high risk for AKI. This may provide certain references for risk stratification management and early intervention treatment of AIS patients.

Limitations

When interpreting our findings, it is important to consider the limitations of this retrospective cohort study. The database did not record AIS infarct size. This study highlights the relationship between AG and ACAG at ICU admission and AKI risk in AIS patients. However, the AG and ACAG at different time points were not explored due to the lack of data. Moreover, the association between dynamic changes in AG and ACAG levels during ICU admission and the risk of AKI is still not clear. Future well-designed prospective studies should be conducted to confirm our findings.

Conclusions

Our results demonstrated that high levels of AG and ACAG were linked to higher odds of AKI in AIS patients. In AIS patients, ACAG levels are a better predictor of AKI risk than AG. Monitoring ACAG levels before bed can help clinicians identify individuals at risk for AKI and intervene with treatment early.

Supplementary data

The Supplementary materials are available at https://doi.org/10.5281/zenodo.10851301. The package includes the following files:

Supplementary Table 1. Proportion of missing values for variables.

Supplementary Table 2. Comparison for the missing data before and after data interpolation.

Supplementary Table 3. The optimum subset of covariates and their coefficients screened using the ABESS method.

Supplementary Table 4. Multicollinearity test between variables using VIF.

Supplementary Table 5. The Box–Tidwell test for subsets of optimal covariates.

Supplementary Table 6. The Hosmer–Lemeshow test for the model goodness-of-fit.

Supplementary Fig. 1. Youden's J statistic for categorizing AG and ACAG levels.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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