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The association of albumin-corrected anion gap and acute kidney injury in heart failure patients: a competing risk model analysis

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Abstract

Background The combination of heart failure (HF) and acute kidney injury (AKI) increases the mortality of patients. It is critical to identify HF patients who may have a high risk for AKI. Albumin-corrected anion gap (ACAG) is a new indicator, but there are no studies on ACAG and the risk of AKI in HF patients.

Methods Data for HF patients was obtained from the MIMIC-IV database. Receiver operating characteristic (ROC) analysis and decision curve analysis (DCA) were employed to evaluate the clinical value of ACAG in predicting AKI risk. Logistic regression analysis and restricted cubic spline (RCS) curve were conducted to explore the relationship between ACAG and AKI. A competing risk model was developed to further investigate the relationship between ACAG on AKI.

Results The study analyzed 5,972 HF patients, with 49.82% (2886/5972) suffering from AKI. The prediction performance of ACAG on AKI was good (AUC:0.656). Continuous ACAG was associated with AKI after adjusting for various significant variables (Model 1: OR = 1.094, 95%CI: 1.078–1.110; Model 2: OR = 1.150, 95%CI: 1.133–1.166; Model 3: OR = 1.035, 95%CI. 1.017–1.054). All High ACAG groups showed a higher risk of AKI (all $P < 0.001$). ACAG was also linked to in-hospital mortality ($P < 0.001$). The competing risks model revealed that high ACAG was still a risk factor for AKI when in-hospital mortality served as a competing risk event ($P < 0.001$).

Conclusion High ACAG was associated with the risk of AKI in HF patients. Clinicians can risk-stratify HF patients by combining ACAG levels.

Keywords Acute kidney injury, Heart failure, Prognosis, Competing risk, Albumin-corrected anion gap

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Introduction

Acute kidney injury (AKI) is characterized by a rapid increase in serum creatinine and/or a decrease in urine output. Approximately 10–15% of hospitalized patients and more than 50% of patients in the intensive care unit (ICU) may have AKI, which is a common comorbid syndrome in patients with heart failure (HF) [1, 2]. More than 26 million people worldwide are reported to have HF, and the prevalence of HF continues to increase, creating a serious economic burden on society [3, 4]. Research suggests that by 2030, HF will affect over 8 million individuals in the United States, marking a 46% increase from 2012 [5]. Currently, over 1 million hospitalizations annually are related to HF in the US and Europe. In the US, approximately 10-51% of HF inpatients are admitted to ICU [6, 7]. AKI is more prevalent among HF patients in the ICU [8]. Studies indicated that cardiac and renal diseases interact in a complex, bidirectional, and interdependent manner in both acute and chronic states, with the coexistence of HF and kidney disease resulting in high mortality rates [9]. The comorbidity rate of AKI in HF patients is 33.0%, and HF patients with AKI have a higher mortality risk than non-AKI patients, with a two-fold increased risk of in-hospital mortality [10]. Consequently, identifying HF patients at high risk for AKI in the ICU is crucial for improving their prognosis.

The anion gap (AG) is an indicator of the balance between positive and negative ions [11]. It has been shown that AG is associated with prognosis and AKI occurrence in patients with HF [12, 13]. However, AG levels are less stable and are influenced by various factors such as albumin. Albumin-related bias has been adjusted by the emergence of the novel indicator albumin-corrected anion gap (ACAG), which more accurately reflects the presence of unmeasured anions [14]. In patients with acute ischemic stroke, ACAG predicts the occurrence of AKI better than AG [15]. Currently, ACAG is associated with decreased renal function in hypertensive patients [16], and the mortality of AKI patients admitted to the ICU and HF patients [17, 18]. However, the relationship between ACAG and AKI risk in HF patients remains unexplored. This study conducted a retrospective study using the MIMIC-IV database to fill this gap.

Methods

Data source and study population

This research utilized data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, which was established by the Laboratory of Computational Physiology at the Massachusetts Institute of Technology (MIT), the Beth Israel Deaconess Medical Center (BIDMC) at Harvard Medical School (HMS), and Philips Healthcare. The database anonymized patient information to protect privacy and was accessible to researchers worldwide. Thus, ethical approval or patient consent was not required. The study included first-time ICU hospitalized HF patients. The ICD codes for patients with HF are listed in Supplementary Table 1. From 2008 to 2019, the database recorded 24,079 HF patients. Patients who lacked AKI and ACAG data ($n = 13{,}726$) and were not admitted to the ICU ($n = 4{,}561$) were excluded, remaining 5,792 HF patients. Those aged under 18 years were also excluded ($n = 0$). The final analysis included 5792 adult HF patients. Figure 1 illustrates the inclusion process of participants.

Sampling size

The sample size was calculated according to the cross-sectional study sample size formula [1].

$$N = \frac{Z^2_{1-\alpha/2} p(1-p)}{d^2} \quad (1)$$

In the formula, $\alpha = 0.05$ and $Z = 1.96$. d is the tolerance error, taken as 0.05. p is the prevalence rate of AKI in HF patients. The prevalence of AKI was 33.0% according to previous studies [10]. Based on the formula [1], the required sample size was 340. In this study, the total number of analyzed participants was 5,792, which was greater than the required sample size. Therefore, this study was representative.

Calculation of ACAG

The ACAG was determined using the previously established formula [19]: ACAG = AG + [4.4– albumin (g/dL)] × 2.5.

Endpoints of interest

The primary outcome indicator in this study was the occurrence of AKI. Based on the AKI data, participants were categorized into the AKI group and non-AKI group. AKI was identified based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The criteria included [1] a reduction in urine output to less than 0.5 mL/kg/h for ≥ 6 h; [2] an increase in serum creatinine of at least 0.3 mg/dL within 48 h or a rise ≥ 1.5 times from the baseline level over the past week [20]. The secondary short-term outcome indicator was in-hospital mortality for the total HF patients, AKI patients, and non-AKI patients. The influence of ACAG on the long-term prognosis of HF patients such as half-year survival, 1-year survival, and 3-year survival was also expanded and analyzed.

Collected data

The study gathered demographic information such as age, gender, race, and alcohol use and smoking. The clinical data encompassed mechanical ventilation (MV),

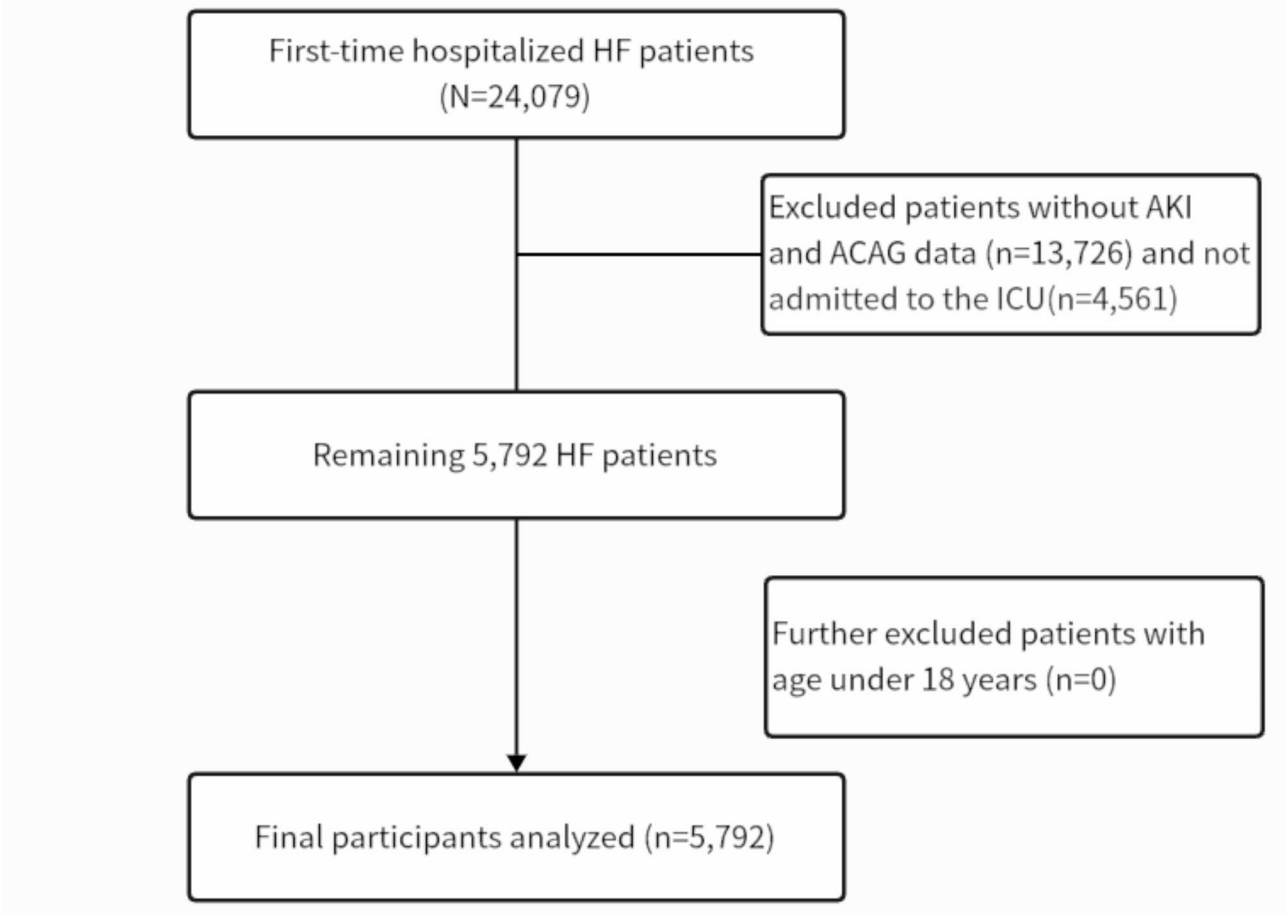

Fig. 1 Flow chart of patient selection

medication use, comorbidities, vital signs, laboratory data, and composite measures like the 24-hour Sequential Organ Failure Assessment (SOFA) score and Acute Physiology Score III (APSIII) score. Comorbidities included myocardial infarct (MI), peripheral vascular disease (PVD), cerebrovascular disease (CVD), chronic obstructive pulmonary disease (COPD), malignant cancer, diabetes, hypertension, and atrial fibrillation (AF). Medication use consisted of angiotensin receptor-neprilysin inhibitors (ARNi), anti-platelet, calcium channel blockers (CCBs), diuretics, angiotensin-converting enzyme inhibitors (ACEI), and adrenoceptor antagonists. Vital signs included systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). Laboratory data comprised albumin, blood urea nitrogen (BUN), alanine aminotransferase (ALT), AG, aspartate aminotransferase (AST), bicarbonate, calcium, chloride, creatinine, glucose, hemoglobin, international normalized ratio (INR), partial pressure of carbon dioxide (PCO_2), partial pressure of oxygen (PO_2), pondus Hydrogenii (pH), platelets, potassium, prothrombin time (PT), red blood cell (RBC), red blood cell distribution width (RDW), sodium, total bilirubin (TBil), white blood cell (WBC), lactate, alkaline phosphatase (ALP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and troponin-T (TnT). All laboratory variables were initially evaluated within the first 24 h of admission.

Statistical analysis

Random forest interpolation was employed for variables with < 25% missing data (ALT, AST, calcium, hemoglobin, glucose, INR, PCO_2, PH, PO_2, platelets, RBC, PT, RDW, TBil, WBC, lactate, and ALP) using the miss Forest package, as it effectively captures nonlinear relationships and is less affected by outliers [21, 22]. Variables > 25% missing data were potentially biased by direct imputation, so they (NT-proBNP and TnT) were converted to categorical variables with dummy variables [23].

Given that continuous data in this study did not follow a normal distribution after normality testing, median and quartiles were utilized for presentation, and the Mann-Whitney U test was applied for comparison between groups. For categorical variables, counts and percentages were used for statistical description, with Chi-square tests employed for statistical inferences. Collinearity analysis was utilized to address multi-collinearity, which

in this study was considered to be present if variance inflation factor (VIF) > 3 [24]. Additionally, the least absolute shrinkage and selection operator (LASSO) regression was applied to identify significant variables for subsequent analysis, with selection based on the 1-standard error (SE) criterion. LASSO regression is typically applied to high-dimensional data, but some findings suggest that LASSO regression is equally well suited to low-event per variable of low-dimensional data [25]. Therefore, LASSO regression was used to screen variables in this study.

The predictive value of ACAG for AKI risk was evaluated using the receiver operating characteristic (ROC) curve and decision curve analysis (DCA). The Delong test was used to compare the significance of AUC values. Next, three models were developed using logistic regression analysis to explore the association between continuous ACAG and the occurrence of AKI. Model 1 adjusted for disease severity variables: SOFA, APSIII, AKI stage. Model 2 adjusted for demographic characteristics, comorbidities, and medication use: gender, alcohol use, MI, malignant tumors, diabetes, hypertension, CCBs, and diuretics. Model 3 adjusted for laboratory indicators: BUN, creatinine, PCO_2, pH, PO_2, TBil, WBC, and lactate. ACAG was categorized by quartiles or best cutoff of ROC. Sensitivity analyses employed logistic analysis to explore the association between categorical ACAG and AKI. The relationship between ACAG and AKI was further explored using restricted cubic spline (RCS) analysis. AKI occurrence was the primary outcome of this study. The odds of the primary outcome may be confounded by competing risks of death [26]. The association between ACAG and in-hospital mortality was first explored, followed by the use of the Fine-Gray test and Nelson-Aalen cumulative risk curve to assess the risk of AKI. Furthermore, K-M curves were used to analyze the influence of ACAG on long-term prognosis in the total HF population. Data organization and analysis were performed using R software, with statistical significance set at $P < 0.05$.

Results

Participant baseline information

5,972 HF patients were included in this study, with 56.58% male patients and predominantly white race (67.52%). AKI was present in 49.82% (2886/5972) of the total HF patients. Table 1 demonstrates the categorical variables information for both AKI and non-AKI groups. The AKI group showed a higher percentage of male patients and alcohol users, but fewer smokers compared to the non-AKI group (all $P < 0.05$). Regarding comorbidities, the AKI group exhibited higher rates of MI, PVD, malignant cancer, and diabetes, but lower hypertension incidence than the non-AKI group (all $P < 0.05$). Medication usage patterns revealed lower utilization of anti-platelet drugs, adrenoceptor antagonists, and ACEI in the AKI group, while CCBs and diuretics use was higher than in the non-AKI group (all $P < 0.05$). NT-proBNP and TnT were different between the AKI group and non-AKI group (all $P < 0.05$). Supplementary Table 2 demonstrates the distribution of variables containing missing data before imputation. Table 2 illustrates the continuous variable information for both two groups after imputation. The results of data changes before and after imputation were not significant. Most variables showed significant differences (all $P < 0.05$). Among them, comprehensive indicators SOFA and APSIII and laboratory-related indicators such as HR, AG, ACAG, BUN, creatinine, ALT, AST, glucose, INR, PT, RDW, TBil, WBC, lactate, ALP, and potassium were higher in AKI group. Conversely, other laboratory indicators such as SBP, albumin, bicarbonate, sodium, calcium, hemoglobin, PCO_2, PH, PO_2, platelets, and RBC were lower than the non-AKI group.

Variable selection

Variables such as AG, albumin, sodium, potassium, chloride, and bicarbonate were excluded from further analysis due to their association with ACAG. The other 40 variables showing differences between AKI and non-AKI groups were included in the collinearity analysis, with VIF > 3 indicating collinearity. The results revealed collinearity for PT, INR, hemoglobin, RBC, AST, and ALT (Supplementary Table 3), which were excluded from subsequent analyses. LASSO regression analysis was performed on the remaining 34 variables. 20 variables were selected based on non-zero coefficients (Fig. 2A) and λ at lambda.1SE (right dashed line) (Fig. 2B). These selected variables encompassed AKI stage, gender, alcohol use, MI, malignant cancer, diabetes, hypertension, CCBs, diuretics, SOFA, APSIII, ACAG, BUN, creatinine, PCO_2, PH, PO_2, TBil, WBC, and lactate.

Prediction performance of ACAG on AKI

The performance of ACAG in predicting the occurrence of AKI was further evaluated by ROC analysis. The results revealed that the AUC of ACAG for predicting AKI (0.656) was significantly higher than that of the SOFA score (0.584) (Delong test $P < 0.001$). Although the AUC of ACAG was lower than that of the APSIII score (0.689) (Delong test $P < 0.001$), both of them exceeded 0.650. Notably, the specificity of ACAG (0.722) outperformed APSIII (0.594), reflecting a satisfactory overall predictive performance of ACAG (Supplementary Tables 4 & Supplementary Fig. 1A). The range of risk thresholds for ACAG, SOFA, and APSIII were 0.350–0.800, 0.420–0.700, and 0.230–0.800, respectively. DCA results were similar to the ROC results, demonstrating that ACAG provided a good net clinical benefit (Supplementary

Table 1 The categorical variables information of participants

Variables	Total (*n* = 5792)	non-AKI (*n* = 2906)	AKI (*n* = 2886)	χ^2	*P*-value
Gender, n(%)				21.847	< 0.001
Male	3277(56.58)	1556(53.54)	1721(59.63)		
Female	2515(43.4228)	1350(46.46)	1165(40.37)		
Race, n(%)				5.407	0.067
White	3911(67.52)	1987(68.38)	1924(66.67)		
non-White	989(17.08)	463(15.93)	526(18.22)		
Unknown	892(15.40)	456(15.69)	436(15.11)		
Alcohol use, n(%)				15.125	< 0.001
No	5145(88.83)	2628(90.43)	2517(87.21)		
Yes	647(11.17)	278(9.56)	369(12.79)		
Smoker, n(%)				4.033	0.045
No	4243(73.26)	2095(72.09)	2148(74.43)		
Yes	1549(26.74)	811(27.91)	738(25.57)		
MI, n(%)				14.001	< 0.001
No	3830(66.13)	1989(68.44)	1841(63.79)		
Yes	1962(33.87)	917(31.56)	1045(36.21)		
PVD, n(%)				5.394	0.020
No	4889(84.41)	2485(85.51)	2404(83.30)		
Yes	903(15.59)	421(14.49)	482(16.70)		
CVD, n(%)				0.853	0.356
No	4930(85.117)	2461(84.687)	2469(85.551)		
Yes	862(14.883)	445(15.313)	417(14.449)		
COPD, n(%)				1.418	0.234
No	3669(63.35)	1819(62.60)	1850(64.10)		
Yes	2123(36.65)	1087(37.40)	1036(35.90)		
Malignant cancer, n(%)				22.234	< 0.001
No	5156(89.02)	2643(90.95)	2513(87.08)		
Yes	636(10.98)	263(9.05)	373(12.92)		
Diabetes, n(%)				51.335	< 0.001
No	3542(61.15)	1910(65.73)	1632(56.55)		
Yes	2250(38.85)	996(34.27)	1254(43.45)		
Hypertension, n(%)				28.237	< 0.001
No	3586(61.91)	1701(58.53)	1885(65.31)		
Yes	2206(38.09)	1205(41.47)	1001(34.69)		
AF, n(%)				1.524	0.217
No	2901(50.09)	1479(50.90)	1422(49.27)		
Yes	2891(49.91)	1427(49.10)	1464(50.73)		
MV, n(%)				0.020	0.889
No	547(9.44)	276(9.50)	271(9.39)		
Yes	5245(90.56)	2630(90.50)	2615(90.61)		
Anti-platelet, n(%)				4.019	0.045
No	1362(23.51)	651(22.40)	711(24.64)		
Yes	4430(76.49)	2255(77.60)	2175(75.36)		
Adrenoceptor antagonist, n(%)				8.009	0.005
No	1550(26.76)	730(25.12)	820(28.41)		
Yes	4242(73.24)	2176(74.88)	2066(71.59)		
ARNI, n(%)				2.717	0.099
No	5262(90.85)	2622(90.23)	2640(91.48)		
Yes	530(9.15)	284(9.77)	246(8.52)		
ACEI, n(%)				10.629	0.001
No	5116(88.33)	2527(86.96)	2589(89.71)		
Yes	676(11.67)	379(13.04)	297(10.29)		

Table 1 (continued)

Variables	Total (*n* = 5792)	non-AKI (*n* = 2906)	AKI (*n* = 2886)	χ^2	*P*-value
CCBs, n(%)				9.021	0.003
No	4822(83.25)	2462(84.72)	2360(81.77)		
Yes	970(16.75)	444(15.28)	526(18.23)		
Diuretics, n(%)				47.024	< 0.001
No	865(14.93)	527(18.13)	338(11.71)		
Yes	4927(85.07)	2379(81.87)	2548(88.29)		
NT-proBNP, n(%)				122.247	< 0.001
29.0- 1723.0	393(6.78)	221(7.60)	172(5.96)		
1725.0-4559.0	393(6.78)	108(3.72)	285(9.88)		
4563.0-11535.0	393(6.78)	211(7.26)	182(6.30)		
11538.0-64845.0	394(6.81)	149(5.13)	245(8.49)		
missing	4219(72.85)	2217(76.29)	2002(69.37)		
TnT, n(%)				207.791	< 0.001
0.01–0.04	803(13.86)	334(11.49)	469(16.25)		
0.05–0.13	746(12.88)	305(10.50)	441(15.28)		
0.14–0.51	736(12.71)	294(10.11)	442(15.32)		
0.52–51.84	716(12.36)	299(10.29)	417(14.45)		
missing	2791(48.19)	1674(57.61)	1117(38.70)		

Abbreviation: Myocardial infarct, MI; Peripheral vascular disease, PVD; Cerebrovascular disease, CVD; Chronic obstructive pulmonary disease, COPD

Abbreviation: Atrial fibrillation, AF; Mechanical ventilation, MV; Angiotensin receptor-neprilysin inhibitor, ARNi; Calcium channel blockers, CCBs; Angiotensin-converting enzyme inhibitor, ACEI; N-terminal pro-brain natriuretic peptide, NT-proBNP; troponin-T, TnT

Fig. 1B). The SOFA and APSIII scores were widely used composite measures, so we combined ACAG with either SOFA or APSIII to assess its overall clinical utility. The ROC analysis revealed that the AUC for ACAG combined with SOFA or APSIII in predicting AKI was 0.673 (0.663–0.686) and 0.715 (0.701–0.728), which had higher predictive performance compared with single ACAG (Table 3). The combination of ACAG with APSIII demonstrated the highest predictive performance and net clinical benefit for AKI (Fig. 3A and B**).**

Association between ACAG and AKI in HF patients

The above results initially confirmed the important clinical value of ACAG in predicting AKI. Further investigation was conducted to explore the association between ACAG levels and AKI occurrence (Table 4). Logistic regression analysis was used to initially explore the relationship between continuous ACAG and AKI. The results showed that in models adjusting for different variables, continuous ACAG was associated with the occurrence of AKI (Model 1: OR = 1.094, 95%CI: 1.078–1.110; Model 2: OR = 1.150, 95%CI: 1.133–1.166; Model 3: OR = 1.035, 95% CI:1.017–1.054). Using the optimal ROC-derived cutoff value of 19.00, ACAG was categorized into low and high groups. The high ACAG group revealed a higher risk of AKI in the three models (all $P < 0.001$), which verified the association between ACAG and AKI. ACAG was further grouped according to quartiles and tested for trend, which showed that higher ACAG values were associated with a higher likelihood of AKI occurrence (all *P* for trend < 0.001).

RCS results indicated a nonlinear relationship between continuous ACAG and AKI occurrence in all three models. Model 1 showed a sharp initial increase in AKI risk with rising ACAG levels, followed by a plateau (Fig. 4A). Model 2 displayed a slow initial increase, then a sharp rise in AKI risk as ACAG levels increased (Fig. 4B). Model 3 exhibited a clear inverted U-shape relationship between ACAG and AKI occurrence. AKI risk initially increased with rising ACAG levels, then declined (Fig. 4C). The OR for AKI occurrence in the three models changed at ACAG about 19.00 mmol/L. This cutoff is similar to the optimal cutoff value for ACAG in the previous ROC results.

Estimation of the relationship of ACAG on AKI by a competing risk analysis

The preceding findings demonstrated a strong link between ACAG and AKI risk, and the association between ACAG and secondary outcomes (in-hospital mortality) was further explored (Fig. 5A-C). The high ACAG group exhibited a higher rate of in-hospital mortality compared to the low ACAG group among the total HF population, AKI group, and non-AKI group, with a significant difference in distribution (all $P < 0.001$). These results indicated that ACAG was associated with in-hospital mortality among patients.

Given that ACAG was linked to both AKI occurrence and in-hospital mortality, in-hospital mortality

Table 2 The continuous variables information of participants

Variables	Total ($n=5792$)	non-AKI ($n=2906$)	AKI ($n=2886$)	Z	*P*-value
Age, years	73.000[62.000,81.000]	72.000[62.000,81.000]	73.000[62.000,81.000]	-0.626	0.531
SOFA	2.000[0.000,4.000]	1.000[0.000,3.000]	2.000[1.000,4.000]	-11.091	< 0.001
APSIII	49.000[37.000,67.000]	42.000[33.000,56.000]	57.000[44.000,77.000]	-26.086	< 0.001
SBP, mmHg	119.000[104.000,137.000]	120.000[106.000,137.000]	117.000[102.000,136.000]	4.072	< 0.001
DBP, mmHg	64.000[54.000,77.000]	65.000[54.000,77.000]	64.000[53.000,78.000]	1.515	0.130
HR, bpm	87.000[76.000,102.000]	86.000[76.000,100.000]	88.000[76.000,104.000]	-3.636	< 0.001
Albumin, g/dL	3.300[2.800,3.700]	3.400[2.900,3.800]	3.200[2.700,3.600]	13.760	< 0.001
AG, mEq/L	15.000[13.000,18.000]	14.000[12.000,17.000]	16.000[13.000,19.000]	-15.804	< 0.001
ACAG, mmol/L	17.750[15.500,20.750]	16.750[14.750,19.250]	19.000[16.500,22.000]	-20.518	< 0.001
Bicarbonate, mEq/L	24.000[21.000,27.000]	25.000[22.000,28.000]	23.000[19.000,26.000]	17.472	< 0.001
BUN, mg/dL	26.000[18.000,41.000]	20.000[15.000,29.000]	34.000[23.000,53.000]	-30.692	< 0.001
Chloride, mEq/L	102.000[98.000,106.000]	102.000[98.000,106.000]	102.000[98.000,106.000]	-0.768	0.442
Creatinine, mg/dL	1.200[0.900,1.800]	1.000[0.800,1.200]	1.500[1.200,2.200]	-34.59	< 0.001
Sodium, mEq/L	139.000[136.000,141.000]	139.000[136.000,141.000]	138.000[135.000,141.000]	3.961	< 0.001
ALT, IU/L	26.000[16.000,47.000]	24.000[16.000,40.000]	27.000[17.000,57.270]	-7.385	< 0.001
AST, IU/L	34.000[22.000,62.000]	31.000[22.000,49.000]	38.000[24.000,83.000]	-11.333	< 0.001
Calcium, mg/dL	8.500[8.000,9.000]	8.600[8.100,9.100]	8.500[7.900,8.900]	6.325	< 0.001
Hemoglobin, g/dL	11.000[9.400,12.500]	11.300[9.800,12.800]	10.600[9.000,12.200]	9.974	< 0.001
Glucose, mg/dL	127.000[102.000,169.000]	123.000[101.000,157.000]	131.000[105.000,179.000]	-7.275	< 0.001
INR	1.300[1.100,1.600]	1.200[1.100,1.500]	1.300[1.100,1.700]	-10.508	< 0.001
PCO_2, mmHg	41.000[36.000,46.000]	41.000[37.000,45.570]	40.590[35.000,46.000]	3.177	0.001
pH	7.390[7.338,7.430]	7.400[7.360,7.430]	7.380[7.310,7.420]	12.807	< 0.001
PO_2, mmHg	112.000[65.000,216.000]	140.000[73.000,274.230]	93.000[57.000,164.400]	15.595	< 0.001
Platelets, K/μL	200.000[148.000,264.000]	205.000[155.000,265.000]	195.000[141.000,262.000]	4.996	< 0.001
RBC, m/μL	3.690[3.170,4.210]	3.800[3.280,4.280]	3.600[3.090,4.130]	8.544	< 0.001
PT, second	14.100[12.400,17.000]	13.700[12.200,16.000]	14.441[12.700,18.300]	-10.191	< 0.001
RDW, %	14.900[13.800,16.500]	14.600[13.600,16.100]	15.100[14.000,16.800]	-10.038	< 0.001
TBil, mg/dL	0.600[0.400,1.100]	0.600[0.400,0.900]	0.700[0.400,1.200]	-6.251	< 0.001
WBC, K/μL	9.900[7.200,14.100]	9.300[6.900,13.000]	10.700[7.600,15.200]	-8.999	< 0.001
Lactate, mmol/L	1.600[1.200,2.200]	1.550[1.200,2.000]	1.700[1.200,2.500]	-9.710	< 0.001
ALP, IU/L	84.240[64.000,117.000]	82.000[63.000,109.000]	89.000[66.000,127.000]	-6.978	< 0.001
Potassium, mEq/L	4.200[3.800,4.700]	4.100[3.800,4.500]	4.300[3.900,4.800]	-10.663	< 0.001

Abbreviation: Sequential Organ Failure Assessment, SOFA; Acute Physiology Score III, APSIII; Systolic blood pressure, SBP; Diastolic blood pressure, DBP; Heart rate, HR; Anion gap, AG; Albumin-corrected anion gap, ACAG; Blood urea nitrogen, BUN; Alanine aminotransferase, ALT; Aspartate aminotransferase, AST; International normalized ratio, INR

Abbreviation: Partial pressure of carbon dioxide, PCO_2; Pondus Hydrogenii, pH; Partial pressure of oxygen, PO_2; Red blood cell, RBC; Prothrombin time, PT; Red blood cell distribution width, RDW; White blood cell, WBC; Total bilirubin, TBil; Alkaline phosphatase, ALP

as a competing risk factor may reduce the occurrence of AKI. The relationship between ACAG on AKI was further investigated by constructing a competing risk model, treating AKI occurrence as the primary event of interest and in-hospital mortality as a competing event. Without considering ACAG levels, the cumulative incidence of AKI was consistently greater than the cumulative incidence of in-hospital mortality at each specific time point (Fig. 6A). After adjusting for the competing risk of in-hospital mortality, a significant difference was observed in the risk of AKI between the high and low ACAG groups ($P<0.001$), while no significant difference was found in the cumulative competing risk of in-hospital mortality between these groups ($P=0.470$) (Table 5). The Nelson-Aalen cumulative risk curve indicated that at each time point, the cumulative incidence of AKI was greater in the high ACAG group compared to the low ACAG group (Fig. 6B) Additional analysis showed that ACAG levels were also associated with long-term prognosis in HF patients (Supplementary Fig. 2).

Discussion

HF is a relatively prevalent disease, with AKI as its common complication. Due to the complex bidirectional mode of action of the heart and kidneys, when AKI occurs in HF patients, the mortality rate is increased and patients have a poorer prognosis [9]. It is crucial to identify HF patients at high risk of AKI to improve their prognosis. This study found that ACAG was associated with the development of AKI, in-hospital mortality, and long-term prognosis in HF patients.

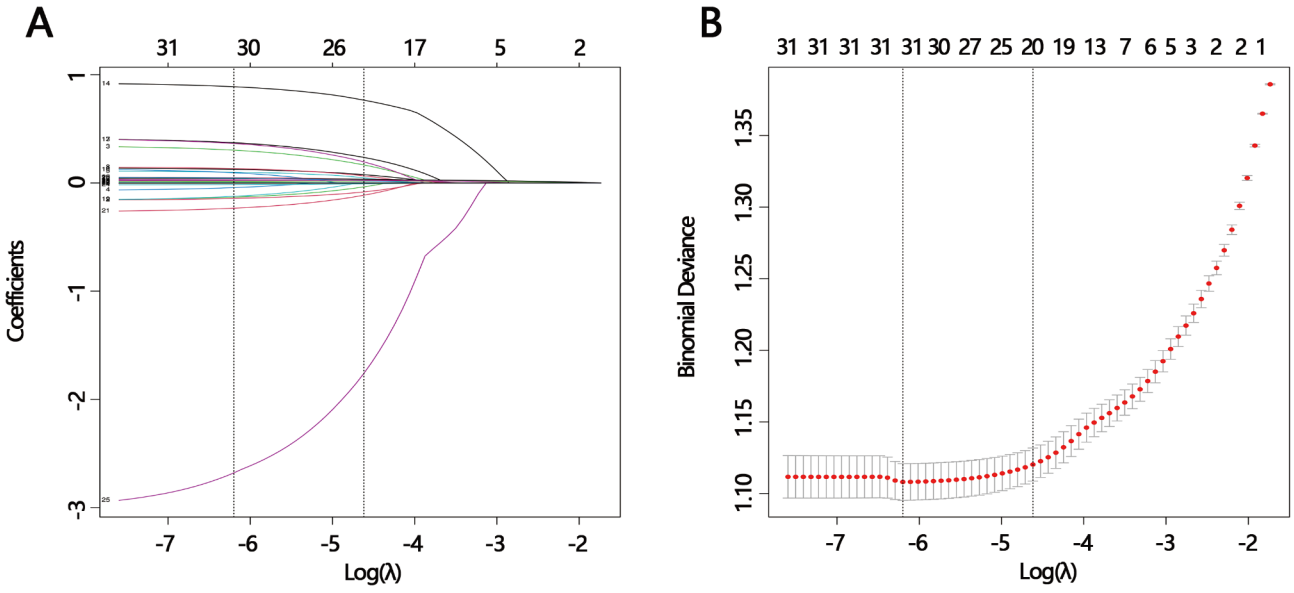

Fig. 2 LASSO regression analysis results for 34 variables. (**A**) LASSO coefficient of variables. (**B**) Cross-validation curve. The 1-SE Criteria (indicated by the right dotted line) was employed to select the optimum λ value in the Lasso regression. The standard error (SE) in this study was 0.01

Table 3 ROC analysis results for single ACAG and ACAG integrated SOFA or APSIII in AKI prediction

Variable	ACAG	ACAG + SOFA	ACAG + APSIII
AUC	0.656(0.638–0.669)	0.673(0.663–0.686)	0.715(0.701–0.728)
Sensitivity	0.510(0.482–0.676)	0.589(0.511–0.696)	0.675(0.659–0.765)
Specificity	0.722(0.557–0.754)	0.668(0.570–0.742)	0.648(0.556–0.670)
Best cutoff	19.000(17.500-19.250)	30.214(27.865–32.161)	47.218(44.083–47.883)
Accuracy	0.502(0.489–0.515)	0.503(0.490–0.515)	0.500(0.487–0.511)
Delong test	/	< 0.001	< 0.001

Abbreviation: Receiver operating characteristic, ROC; Acute kidney injury, AKI; Albumin-corrected anion gap, ACAG; Sequential Organ Failure Assessment, SOFA; Acute Physiology Score III, APSIII; Area under the curve, AUC

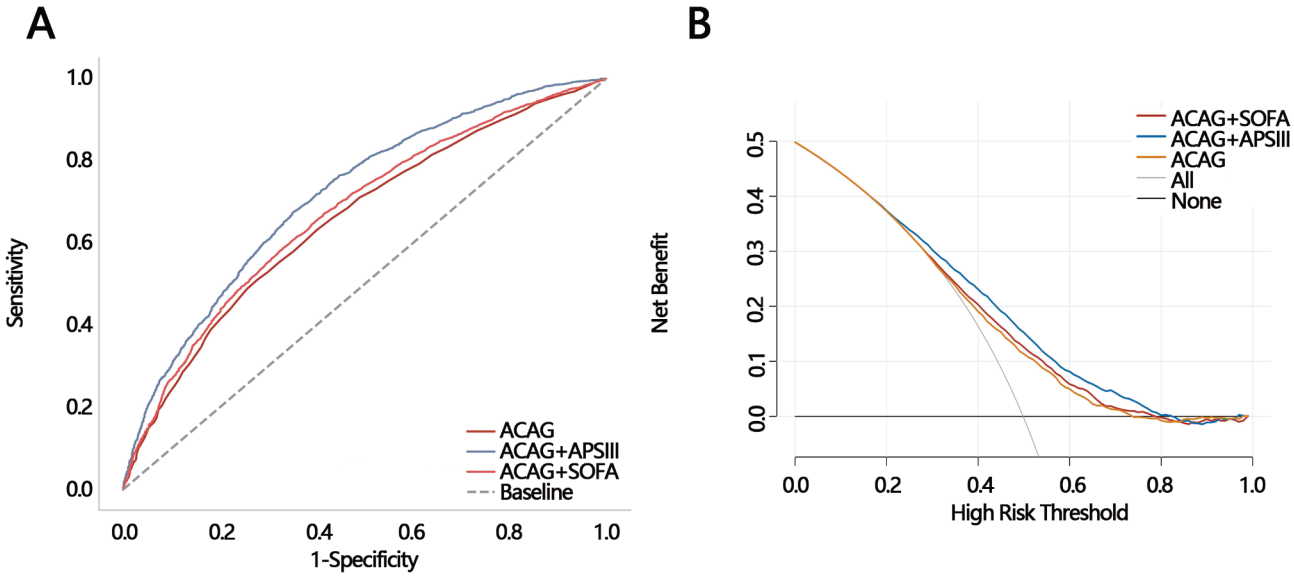

Fig. 3 AKI prediction performance of single ACAG and ACAG integrated SOFA or APSIII. (**A**) ROC comparison among single ACAG and ACAG integrated SOFA or APSIII. (**B**) The DCA of single ACAG and ACAG integrated SOFA or APSIII. Abbreviation: Acute kidney injury, AKI; Albumin-corrected anion gap, ACAG; Sequential Organ Failure Assessment, SOFA; Acute Physiology Score III, APSIII; Receiver operating characteristic, ROC; Decision curve analysis, DCA

Table 4 The association of different ACAG types with AKI by logistic regression

	Model 1	Model 2	Model 3
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Continuous ACAG	1.094(1.078,1.110) ***	1.150(1.133,1.166) ***	1.035(1.017,1.054) ***
Categorical ACAG by best cutoff			
Low ACAG			
High ACAG	2.008(1.788,2.256) ***	2.834(2.531,3.176) ***	1.378(1.206,1.575) ***
Categorical ACAG by quartiles			
6.00-15.50			
15.75–17.75	1.465(1.255,1.711) ***	1.551(1.333,1.805) ***	1.233(1.050,1.447) ***
18.00-20.75	1.984(1.702,2.312) ***	2.457(2.115,2.855) ***	1.428(1.211,1.685) ***
21.00-52.50	2.738(2.323,3.227) ***	4.547(3.871,5.340) ***	1.554(1.281,1.886) ***
P for trend	< 0.001	< 0.001	< 0.001

Model 1: adjusted for the variables of the severity of disease: SOFA, APSIII, and AKI stage

Model 2: adjusted for the variables of demographic, comorbidities, and medication use: gender, alcohol use, MI, malignant cancer, diabetes, hypertension, CCBs, and diuretics

Model 3: adjusted for laboratory indicators: BUN, creatinine, PCO_2, pH, PO_2, TBil, WBC, and lactate

****P* < 0.001

Abbreviation: Odds ratio, OR; Albumin-corrected anion gap, ACAG; Acute kidney injury, AKI; Sequential Organ Failure Assessment, SOFA; Acute Physiology Score III, APSIII; Myocardial infarct, MI; Calcium channel blockers, CCBs; Blood urea nitrogen, BUN; Partial pressure of carbon dioxide, PCO_2; Pondus Hydrogenii, pH; Partial pressure of oxygen, PO_2; White blood cell, WBC; Total bilirubin, TBil

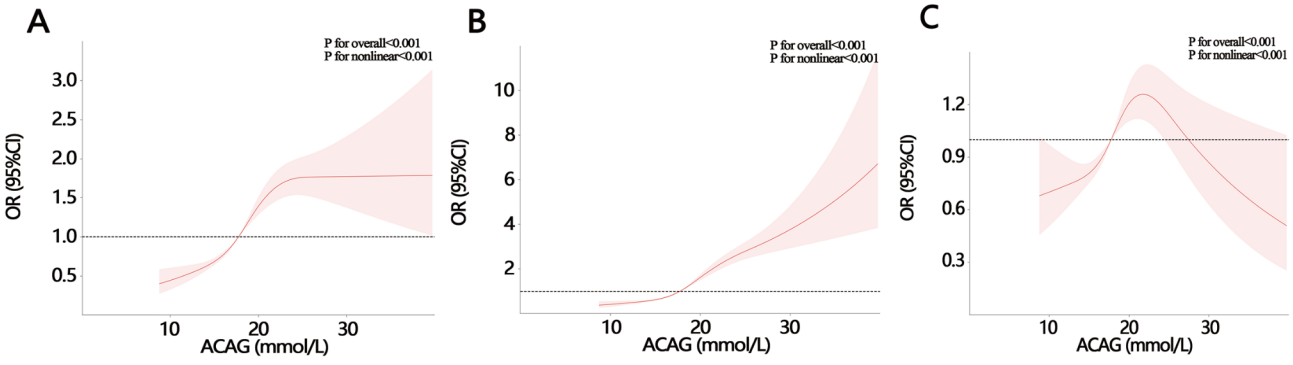

Fig. 4 The RCS results between ACAG and AKI in different adjusted models. (**A**) In model 1: adjusted for the variables of severity of disease: SOFA, APSIII, and AKI stage. (**B**) In model 2: adjusted for the variables of demographic, comorbidities, and medication use: gender, alcohol use, MI, malignant cancer, diabetes, hypertension, CCBs, and diuretics. (**C**) In Model 3: adjusted for laboratory indicators: BUN, creatinine, PCO_2, pH, PO_2, TBil, WBC, and lactate. Abbreviation: Restricted cubic spline, RCS; Odds ratio, OR; Albumin-corrected anion gap, ACAG; Acute kidney injury, AKI; Sequential Organ Failure Assessment, SOFA; Acute Physiology Score III, APSIII; Myocardial infarct, MI; Calcium channel blockers, CCBs; Blood urea nitrogen, BUN; Partial pressure of carbon dioxide, PCO_2; Pondus Hydrogenii, pH; Partial pressure of oxygen, PO_2; White blood cell, WBC; Total bilirubin, TBil

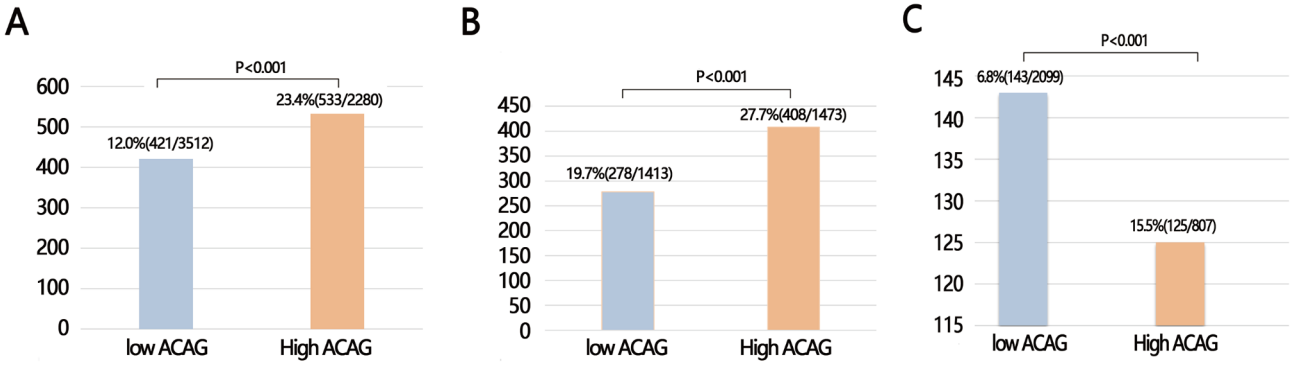

Fig. 5 The relationship between ACAG and in-hospital mortality. (**A**) In the whole HF population. (**B**) In AKI patients. (**C**) In non-AKI patients. Abbreviation: Albumin-corrected anion gap, ACAG; Heart failure, HF; Acute kidney injury, AKI

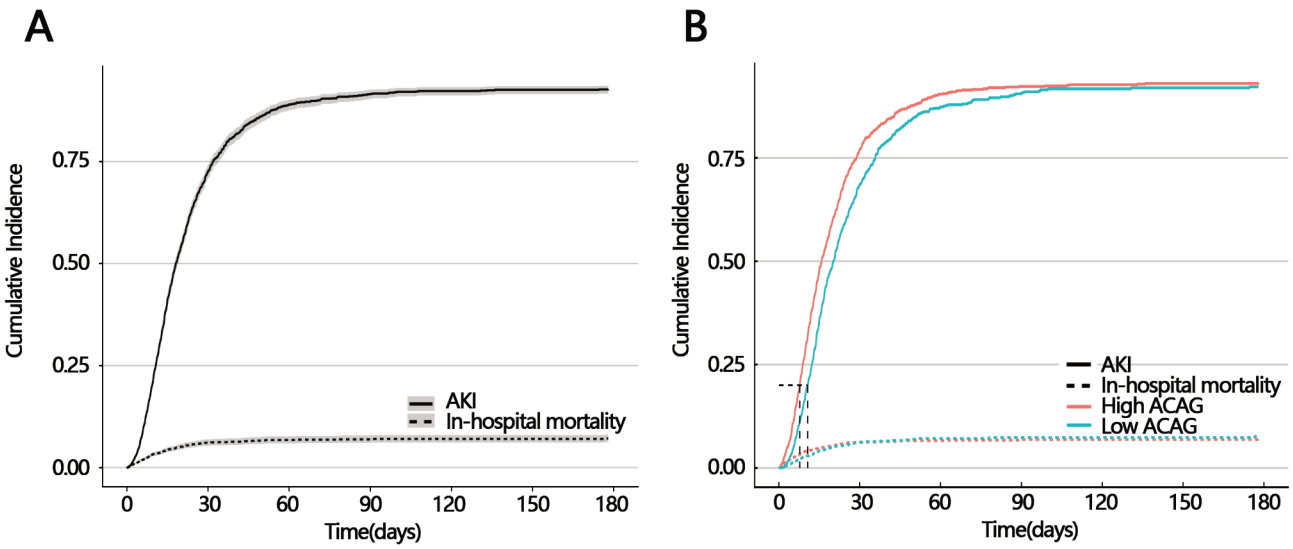

Fig. 6 The competing risk model by Nelson-Aalen cumulative risk curve. (**A**) The competing risk model about AKI and in-hospital mortality without considering ACAG. (**B**) The competing risk model about AKI and in-hospital mortality in low and high ACAG. Abbreviation: Albumin-corrected anion gap, ACAG; Acute kidney injury, AKI

Table 5 Association between ACAG and AKI with in-hospital mortality as a competing risk (Fine-Gray model)

Outcome	Statistic value	df	*P*-value
AKI	78.300	1.000	< 0.001
In-hospital mortality	0.514	1.000	0.470

Abbreviation: Acute kidney injury, AKI; Albumin-corrected anion gap, ACAG

AG is a simple-to-calculate indicator of metabolic acidosis, commonly elevated in both emergency and inpatient settings [27, 28]. It has been shown that high AG levels are associated with mortality in ICU patients with various diseases, such as aortic aneurysm, sepsis, and AKI, suggesting the potential of AG as a predictor of adverse clinical outcomes in ICU patients [29]. Elevated AG is associated with excessive secretion of organic acids [30]. Albumin possesses antioxidant and anti-inflammatory properties, as well as the ability to regulate acid-base balance, effectively reducing kidney damage [31]. However, albumin is a negatively charged protein, and its loss results in the retention of other negatively charged ions, potentially making AG appear less severe and influencing its predictive value [17]. ACAG addresses this albumin-related bias, more accurately reflecting the presence of unmeasured anions and serving as a more suitable indicator for diagnosing metabolic acidosis in the ICU [14]. This research found that high ACAG levels (> 19.00 mmol/L) were associated with AKI development in HF patients, possibly because acid retention in the body initiates a compensatory response that promotes tubulointerstitial fibrosis through intrarenal complement activation and upregulation of endothelin-1 (ET-1), angiotensin II, and aldosterone pathways, leading to kidney injury [32]. Cardiorenal syndrome describes a specific acute and chronic clinical presentation in which major dysfunctions of the heart or kidneys interact secondary to each other [33]. In HF, inadequate arterial filling stimulates pressure receptors, which in turn stimulate the Renin-Angiotensin-Aldosterone System (RAAS). The RAAS drives renal affinity for sodium and water leading to fluid retention and diminished urinary response to diuretics. Conversely, venous congestion prompts the release of natriuretic peptides, which inhibit sodium absorption [34].

In the RCS results adjusted for laboratory data, we observed an inverted U-shape of ACAG and AKI risk. In the early stages, acidosis causes slight impairment in kidney function and the release of ET-1 from the kidneys, which binds to endothelin A receptors, resulting in prolonged vasoconstriction. This binding may be associated with hyperfiltration or podocyte injury, which in turn leads to increased urinary excretion of proteins such as albumin [35, 36]. As ACAG continues to rise, the body may initiate compensatory mechanisms to address this imbalance. The kidneys might modify their metabolic and transport functions to boost albumin reabsorption and decrease its urinary excretion [37].

The results of this study showed that the combination of ACAG and APSIII improved the prediction performance of AKI. The ACAG provided clues to early metabolic disturbances of AKI by reflecting the accumulation of unmeasured anions and metabolic status, while the APSIII assessed the overall condition of the patient from a physiological perspective to assess the overall severity of the patient's condition, covering the functional status of multiple organ systems. This combination not only allowed for earlier identification of patients at high risk of

AKI but also provided a more comprehensive assessment of AKI severity and prognosis. This combined application can compensate for the limitations of single indicators, such as the insufficient sensitivity of ACAG for early AKI and the inadequate reflection of metabolic status by APSIII.

Research demonstrates that ACAG is linked to in-hospital mortality in sepsis-associated acute kidney injury, with better predictive power than albumin and AG [38]. Furthermore, higher ACAG levels at the initiation of continuous renal replacement therapy (CRRT) are associated with all-cause mortality in the ICU for AKI patients undergoing CRRT [39]. The results of the present study suggested that higher levels of ACAG were associated with long-term mortality or in-hospital mortality across various HF populations, including those with and without AKI, aligning with previous research. The relationship between ACAG and mortality in HF patients may be attributed to clinical symptoms of HF, ventricular dysfunction, and neurohormonal activation induced by heart failure medications, leading to cellular hypoxia, electrolyte imbalances, and metabolic acid-base disturbances [40, 41]. Persistent acid-base imbalance exacerbates the condition, resulting in poor outcomes [42].

High ACAG levels were associated with the occurrence and poor prognosis of AKI. Due to its easy calculation, rapid reflection of metabolic status, and indirect assessment of multi-organ function, ACAG can be used as an early warning tool to help identify patients at high risk of AKI and guide interventions. In addition, ACAG can also be used as a complementary measure in combination with other clinical data to improve the performance of predicting poor prognosis and effectively stratify the risk of HF patients.

This study was the first research to explore the relationship between ACAG and the risk of AKI in HF patients and use a competing risk model to adjust for the impact of in-hospital mortality on AKI occurrence. However, this study has the following limitations: [1] The study population only included HF patients admitted to the ICU, limiting the generalizability of the findings to non-ICU or outpatient HF populations; [2] This study did not differentiate between different HF types (e.g., preserved versus reduced ejection fraction), which may have different AKI risks and ACAG profiles; [3] It solely assessed the prognostic value of baseline ACAG for AKI in severe HF patients, disregarding the relationship between changes in ACAG dynamics during hospitalization and the risk of AKI or in-hospital mortality; [4] The present study was a cross-sectional study that does not allow to make causal inferences, and further research are necessitated to validate the association between ACAG and the risk of AKI in HF patients.

Conclusion

In summary, high levels of ACAG (> 19.00 mmol/L) were associated with the development of AKI in HF patients. ACAG was also associated with long-term prognosis and in-hospital mortality in HF patients, as well as in-hospital mortality in patients with or without AKI. Therefore, ACAG levels should be monitored in HF patients, and prompt pharmacological interventions should be implemented when abnormal ACAG changes are detected.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04723-7.

Supplementary Material 1: **Supplementary Figure 1**. AKI prediction performance of SOFA, APSIII, and ACAG. (A) ROC comparison among ACAG, SOFA, and APSIII. (B) The DCA of ACAG, SOFA, and APSIII. Abbreviation: Acute kidney injury, AKI; Albumin-corrected anion gap, ACAG; Sequential Organ Failure Assessment, SOFA; Acute Physiology Score III, APSIII; Receiver operating characteristic, ROC; Decision curve analysis, DCA

Supplementary Material 2: **Supplementary Figure 2**. The association between ACAG and long-term prognosis in HF patients. (A) half-year survival. (B)1-year survival. (C) 3-year survival. Abbreviation: Albumin-corrected anion gap, ACAG; Heart failure, HF.

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Acknowledgements
Not applicable.

Author contributions
AFR and JWZ contributed to the conception and design. AFR, SQS and XZL contributed to the collection and assembly of data. JWZ and TLC analyzed and interpreted the data. All authors wrote and approved the final manuscript.

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Data availability
Only publicly available MIMIC-IV data were utilized in this study. This data can be found here: https://physionet.org/content/mimiciv/3.1/. Access to the database required registration and successful completion of the Collaborative Institutional Training Initiative program.

Declarations

Ethics approval and consent to participate
The Ethics Committee of Hangzhou Lin'an District Hospital of Traditional Chinese Medicine deemed that this research is based on open-source data, so the need for ethics approval was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial
Not applicable.

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