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Albumin corrected anion gap and clinical outcomes in elderly patients with acute kidney injury caused or accompanied by sepsis: a MIMIC-IV retrospective study

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Abstract

Background Elderly acute kidney injury (AKI) occurring in the intensive care unit (ICU), particularly when caused or accompanied by sepsis, is linked to extended hospital stays, increased mortality rates, heightened prevalence of chronic diseases, and diminished quality of life. This study primarily utilizes a comprehensive critical care database to examine the correlation of albumin corrected anion gap (ACAG) levels with short-term prognosis in elderly patients with AKI caused or accompanied by sepsis, thus assisting physicians in early identification of high-risk patients.

Methods This study utilized data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, v2.0) database. The patient population was divided into death and survival groups based on a 14-day prognosis. Subsequently, the entire population was further categorized into a normal ACAG group (12–20 mmol/L) and a high ACAG group (> 20 mmol/L) based on ACAG levels. The LASSO regression cross-validation method was employed to identify significant risk factors for inclusion in multivariate Cox regression analyses. A restricted cubic spline (RCS) was then employed to visually represent the correlation between ACAG levels and the risk of mortality in patients. Kaplan–Meier curves were utilized to plot the cumulative survival rates at 14 and 30 days for both patient groups. The robustness of the findings was subsequently evaluated through subgroup analyses.

Results Our study identified a total of 3741 eligible subjects, revealing higher all-cause mortality rates at both 14-day and 30-day intervals in the high ACAG group compared to the normal ACAG group ($\chi2 = 87.023$, $P < 0.001$; $\chi2 = 90.508$, $P < 0.001$). Cox regression analysis further demonstrated that an elevated ACAG on ICU admission independently posed a risk factor for both 14- and 30-day prognosis within this population. In addition, the analysis conducted using RCS revealed a non-linear association between the levels of ACAG and the risk of mortality at both 14 and 30 days in the patient cohort ($\chi2 = 18.220$, $P < 0.001$; $\chi2 = 18.360$, $P < 0.001$). The application of Kaplan–Meier analysis demonstrated a statistically significant decrease in cumulative survival rates among individuals with high ACAG levels ($P < 0.001$). Subgroup analyses indicated that ACAG levels interacted with cerebrovascular disease and acute pancreatitis on 14-day mortality ($P < 0.05$ for interaction).

Conclusion Elevated ACAG levels at ICU admission are an independent risk factor for poor short-term prognosis, correlating with increased all-cause mortality at 14 and 30 days in elderly patients with AKI caused or accompanied

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by sepsis. This highlights the importance of monitoring ACAG in critically ill patients to identify those at higher risk of adverse outcomes early.

Keywords Albumin corrected anion gap, Acute kidney injury, Sepsis, Prognosis, MIMIC-IV database

Background

Sepsis, a critical illness encountered in the intensive care unit (ICU), is characterized by organ dysfunction resulting from an aberrant response of the organism to infection [1]. Acute kidney injury (AKI), a commonly observed complication in ICU patients, is linked to unfavorable short- and long-term outcomes [2–4]. The interconnection between AKI and sepsis is widely acknowledged [5], as sepsis escalates the likelihood of AKI development, affecting approximately two-thirds of patients with sepsis or septic shock [6, 7]. Conversely, AKI is associated with an elevated occurrence of emerging infections or sepsis [8, 9]. Severe AKI, defined as KDIGO stage 2 or 3 [10], is associated with prolonged hospital stays, increased mortality rates, a higher prevalence of chronic diseases, and reduced quality of life, particularly when caused or accompanied by sepsis [7, 9]. Furthermore, with the global population experiencing an aging trend, there is a growing demand for the admission of elderly individuals to the ICU [11, 12]. Extensive research has demonstrated that advancing age is a distinct factor linked to unfavorable outcomes in both AKI and sepsis [13, 14]. Consequently, it is imperative to promptly identify elderly AKI patients with sepsis in clinical settings to enable timely intervention and enhance prognosis.

Despite ongoing investigations, the precise pathophysiological mechanisms of AKI with sepsis remain incompletely understood. Nevertheless, preclinical studies consistently indicate the involvement of microcirculatory dysfunction and a hyperinflammatory response state [5, 9]. Severe sepsis often leads to metabolic acidosis, with the kidneys playing a crucial role in maintaining acid–base balance [15]. Malnutrition, particularly in the form of hypoalbuminemia, is commonly observed in elderly patients [16]. Albumin corrected anion gap (ACAG), a newly identified inflammatory marker, combines the two conditions of metabolic acidosis and hypoalbuminemia [17]. Previous research has demonstrated a link between ACAG and mortality in patients with sepsis [18], acute myocardial infarction (AMI) [19],cardiac arrest (CA) [20],and AKI necessitating renal replacement therapy [21]. Therefore, we hypothesize that there may be a correlation between ACAG levels and unfavorable prognosis in elderly AKI patients with sepsis.

This study primarily utilizes a comprehensive critical care database to examine the correlation of ACAG levels with short-term prognosis in elderly patients with AKI caused or accompanied by sepsis, thus assisting physicians in early identification of high-risk patients.

Methods

Data source

This study utilized data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, v2.0) database [22]. The funding for the database was provided by the National Institutes of Health, the Massachusetts Institute of Technology, and Beth Israel Deaconess Medical Center. It was developed collaboratively by emergency physicians, critical care physicians, and computer science experts. The database encompasses patients who were admitted to the ICU at Beth Israel Deaconess Medical Center from 2008 to 2019. Our authors are granted unrestricted access to the database upon acceptance of the Data Use Agreement and successful completion of the Protection of Human Subjects Training (certification number: 51774135; 53446653). Patient consent and ethical approval were not deemed necessary for this study, and all patient identifiers were appropriately removed.

Study participants

The eligible participants for this study consisted of elderly patients from the MIMIC-IV database. Accurately defining the precise timing or causality of AKI and sepsis occurrences poses clinical challenges. Therefore, we use the term "AKI caused or accompanied by sepsis" to refer to the simultaneous fulfillment of diagnostic criteria for both conditions. The selection of subjects was based on the following inclusion criteria: (1) adult patients aged 65 years or older; (2) patients meeting the diagnostic criteria for Sepsis 3.0 [1]; (3) patients meeting the 7-day diagnostic criteria for AKI as defined by Kidney Disease: Improving Global Outcomes (KDIGO) [23]; and (4) for patients with multiple admissions, only the initial hospitalization was considered in our study. Subjects were excluded based on specific criteria, including ICU stays of less than 24 h, patients who died within 24 h of ICU admission, patients with chronic kidney disease (CKD) stage 5, and patients lacking key variables such as ACAG.

Variable extraction

The data extraction tool used for obtaining various variables, including demographics (age, sex), clinical severity scores, laboratory data, treatment information, coexisting illnesses, and length of ICU stay, was Structured Query

Language (SQL) with PostgreSQL 10.13. The laboratory data encompassed measurements such as anion gap (AG), albumin, white blood cell (WBC), hemoglobin, platelet, hematocrit, red cell distribution width (RDW), mean corpuscular volume (MCV), bicarbonate, blood urea nitrogen (BUN), creatinine, prothrombin time (PT), glucose, sodium, potassium, chloride, calcium and phosphorus. Treatment records included the use of mechanical ventilation (MV), continuous renal replacement therapy (CRRT), transthoracic echocardiography (TTE), norepinephrine, and dopamine. Additionally, information on coexisting illnesses such as hypertension, diabetes, chronic pulmonary disease (CPD), cerebrovascular disease, severe liver disease, malignant tumor, acute pancreatitis, AMI, atrial fibrillation (AF), CA, cardiogenic shock, and catheter-related bloodstream infection (CRBSI) was also extracted. An assessment of severity at admission was based on Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score II (SAPS II). The ACAG value was calculated using the formula: ACAG (mmol/L) = AG + [44—albumin(g/L)] * 0.25 [24]. All laboratory variables were sampled on the initial day of ICU admission and scores were based on indicators within the first 24 h of admission.

Groups and endpoints

The patient population was divided into death ($n=927$) and survival groups ($n=2,814$) based on a 14-day prognosis. Subsequently, the entire population was further categorized into a normal ACAG group (12–20 mmol/L, $n=2,076$) and a high ACAG group (>20 mmol/L, $n=1,665$) according to the previous research [25]. The primary endpoint of our study was 14-day all-cause mortality from the date of ICU admission. The secondary endpoint was 30-day all-cause mortality.

Statistical analyses

The t-test was employed to compare continuous variables that exhibited a normal distribution, with results presented as mean ± standard deviation. For variables not following a normal distribution, the Mann–Whitney U test was utilized, with medians and interquartile ranges reported. Categorical variables were expressed as numbers (percentages) and analyzed using the Chi-square test.

Significant risk factors were identified by screening for inclusion in multivariate Cox regression analyses, which was facilitated by the least absolute shrinkage and selection operator (LASSO) regression cross-validation method. The outcomes were expressed in terms of hazard ratio (HR) and 95% confidence interval (CI). Model I was not adjusted for any variables. Model II was adjusted for age, SOFA score, SAPS II, RDW, and PT. Model III was adjusted for all variables in model II, as well as MV, norepinephrine use, diabetes, cerebrovascular disease, malignant tumor, CA, cardiogenic shock and CRBSI.

Restricted cubic spline (RCS) analysis was employed to visually represent the correlation between ACAG levels and the risk of mortality in patients. Kaplan–Meier curves were utilized to plot the cumulative survival rates at 14 and 30 days for both groups.

Subsequently, subgroup analyses were conducted to investigate the relationship between ACAG levels and 14-day mortality. Subgroups were defined based on key demographic and clinical characteristics, including age (≥80 years vs. <80 years), gender (male vs. female), presence of comorbidities, and availability of treatment modalities. Within each subgroup, multivariate Cox regression models were employed to determine the HRs associated with elevated ACAG levels, adjusting for potential confounding variables.

The statistical analysis was conducted using Stata14.0 software and the R programming language (version 4.2.0). A two-tailed P value of less than 0.05 was considered statistically significant.

Results

Patient demographics and baseline characteristics

The MIMIC-IV database included a total of 76,943 patients admitted to the ICU. Following the screening process, there were 16,966 adult patients who were initially admitted to the ICU and diagnosed with both sepsis and AKI. Through the application of exclusion criteria, a subset of 3741 eligible subjects were selected for inclusion in our study. Complete data of the inclusion and exclusion procedures can be found in Fig. 1. The average age of the patients included in the study was 78.06 ± 8.17 years, with males accounting for 54.93% of the sample. Among

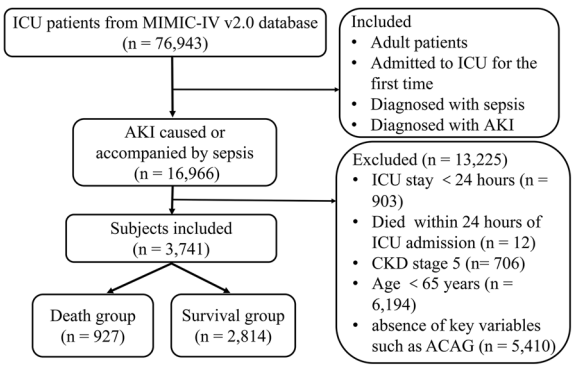

Fig. 1 Complete data regarding the inclusion and exclusion processes. *ICU* intensive care unit, *MIMIC-IV* Medical Information Mart for Intensive Care IV, *AKI* acute kidney injury, *CKD* chronic kidney disease, *ACAG* albumin corrected anion gap

these patients, a 14-day all-cause mortality rate of 24.78% ($n=927$) was observed, leading to their classification as non-survivors. In comparison to the group of survivors, the deceased patients exhibited advanced age, higher SOFA scores and SAPSII scores, as well as higher levels of AG, ACAG, WBC, RDW, MCV, BUN, creatinine, PT, potassium, and phosphorus (all $P<0.05$). Conversely, the survivors demonstrated significantly higher levels of albumin, hemoglobin, platelet, bicarbonate, and calcium. The death group also had a higher proportion of patients requiring MV, CRRT, norepinephrine, and dopamine, as well as higher rates of hypertension, severe liver disease, malignant tumor, AMI, CA, and cardiogenic shock. Patient demographics and baseline characteristics are presented in Table 1.

Comparison of mortality

Table 2 reveals that the high ACAG group exhibited elevated rates of both 14-day and 30-day all-cause mortality in comparison to the normal ACAG group (32.13% vs 18.88, $\chi2=87.023$, $P<0.001$; 42.34% vs 27.50%, $\chi2=90.508$, $P<0.001$).

Risk factors screening and Cox regression analysis

The LASSO regression cross-validation method, utilizing the R language glmnet package, successfully identified significant risk factors by considering the 14-day survival of patients as the dependent variable and the 38 characteristics listed in Table 1 as the independent variables. The analysis revealed that the following 14 variables had non-zero parameters at the optimal λ (λ = 0.015, i.e., lambda.1se): ACAG, age, SOFA score, SAPS II score, RDW, PT, MV, norepinephrine use, diabetes, cerebrovascular disease, malignant tumor, CA, cardiogenic shock, and CRBSI. Figure 2 displays the screening of these 14 variables, highlighting their significance in predicting patient outcomes.

To further explore the relationship between ACAG and mortality, we conducted a multivariate Cox regression analysis that adjusted for the 13 other variables identified in the LASSO analysis, excluding ACAG itself. The findings, presented in Table 3, indicated that in comparison to the baseline, the HRs with 95%CIs for all-cause mortality at 14 and 30 days in the high ACAG group were 1.860 (1.633–2.119) and 1.733 (1.552–1.936), respectively, in model I, which did not adjust for any variables. These results indicated a significant correlation between elevated ACAG levels and increased short-term mortality among elderly AKI patients with sepsis. In Model II, which adjusted for age, SOFA score, SAPS II score, RDW, and PT, the HRs for all-cause mortality in the high ACAG group were 1.330 (95% CI 1.161–1.524) at 14 days and 1.271 (95% CI 1.133–1.426) at 30 days. In model III, which adjusted for various confounding factors, elevated ACAG levels were identified as an independent risk factor for short-term mortality, with HRs of 1.367 (95% CI 1.191–1.569, $P<0.001$) and 1.297 (95% CI 1.154–1.457, $P<0.001$) at 14 and 30 days, respectively.

RCS analysis and Kaplan–Meier survival curves

The application of RCS analysis revealed a non-linear association between ACAG levels and the risk of 14- and 30-day mortality ($\chi2=18.220$, $P<0.001$; $\chi2=18.360$, $P<0.001$). Specifically, when the ACAG level reached approximately 19.62, the HR was 1. The graphical representation in Fig. 3a and b demonstrated a gradual deceleration and stabilization in the increase of death risk with higher ACAG levels.

The findings from the Kaplan–Meier analysis, as depicted in Fig. 4, indicated a significant disparity in the cumulative survival rates at both 14 and 30 days between patients classified in the high ACAG group and those in the normal ACAG group (log-rank test, $\chi2=92.110$, $P<0.001$; $\chi2=99.780$, $P<0.001$).

Subgroup analyses

In order to further explore the relationship between ACAG and 14-day mortality across various subgroups, subgroup analyses were conducted and the results are illustrated in Fig. 5. The outcomes suggested that ACAG levels interacted with cerebrovascular disease and acute pancreatitis in influencing 14-day mortality ($P<0.05$ for interaction). Specifically, in patients without cerebrovascular disease, elevated ACAG levels were associated with a significantly increased risk of mortality (HR = 1.456, 95% CI 1.249–1.697), whereas in patients with this comorbidity, the impact was not significant (HR = 1.060, 95% CI 0.760–1.478). Similarly, compared to patients with acute pancreatitis, the association between ACAG levels and mortality was more pronounced in patients without acute pancreatitis (HR = 1.326, 95% CI 1.154–1.524). In addition, no significant interaction was observed in the other subgroups ($p>0.05$ for interaction).

Discussion

Elderly patients are at a higher risk of AKI and sepsis due to the high prevalence of underlying diseases and compromised immune function, resulting in elevated mortality rates [26, 27].In this study, a retrospective analysis was conducted on a sample of 3741 patients from the MIMIC database. The findings revealed that elderly AKI patients with sepsis had a 14-day mortality rate of 24.78% and a 30-day mortality rate of 34.11%, which were higher than the mortality rates reported in previous studies for elderly patients with sepsis or AKI [13, 26]. Cox regression analysis demonstrated that elevated ACAG levels on

Table 1 Patient demographics and baseline characteristics in the death and survival groups

Variable	Overall population (*n* = 3,741)	Death group (*n* = 927)	Survival group (*n* = 2,814)	t/Z/χ2 value	*P* value
Demographics					
Age (years)	78.06 ± 8.17	79.26 ± 8.20	77.67 ± 8.13	− 5.141	< 0.001
Male, n (%)	2,055 (54.93)	489 (52.75)	1,566 (55.65)	2.368	0.124
Scores					
SOFA score	7.85 ± 3.96	9.62 ± 4.19	7.27 ± 3.70	− 16.229	< 0.001
SAPS II score	48.04 ± 14.00	55.77 ± 15.34	45.50 ± 12.53	− 20.423	< 0.001
Laboratory parameters					
AG (mmol/L)	17.17 ± 5.06	18.30 ± 5.60	16.79 ± 4.81	− 7.926	< 0.001
Albumin (g/L)	31.31 ± 6.71	29.52 ± 7.29	31.90 ± 6.39	9.507	< 0.001
ACAG (mmol/L)	20.34 ± 5.09	21.92 ± 5.58	19.82 ± 4.81	− 11.085	< 0.001
WBC ($\times 10^9$/L)	12.0 (8.2, 17.0)	13.20 (8.60, 19.20)	11.46 (8.10, 16.50)	− 5.354	< 0.001
Hemoglobin (g/L)	108.28 ± 24.26	111.33 ± 23.86	114.10 ± 23.34	3.354	< 0.001
Platelet ($\times 10^9$/L)	200 (141, 278)	198 (128, 276)	201 (145, 279)	2.022	0.043
Hematocrit (%)	34.07 ± 7.21	33.68 ± 7.30	33.68 ± 7.30	1.892	0.059
RDW (%)	15.47 ± 2.37	16.03 ± 2.62	15.28 ± 2.24	− 8.447	< 0.001
MCV (fl)	92.76 ± 7.58	93.32 ± 8.21	92.57 ± 7.36	− 2.589	0.010
Bicarbonate (mmol/L)	21.69 ± 5.39	20.83 ± 5.80	21.98 ± 5.22	5.622	< 0.001
BUN (mmol/L)	9.97 (6.76, 16.02)	12.10 (7.83, 18.87)	9.61 (6.41, 14.95)	− 9.138	< 0.001
Creatinine (umol/L)	114.92 (79.56, 167.96)	123.76 (88.40, 194.48)	106.08 (79.56, 159.12)	− 6.001	< 0.001
PT (s)	14.4 (12.7, 18.3)	15.60 (13.30, 21.40)	14.20 (12.60, 17.20)	− 9.199	< 0.001
Glucose (mmol/L)	7.78 (6.17, 10.50)	7.83 (6.06, 11.00)	7.78 (6.22, 10.33)	− 0.086	0.932
Sodium (mmol/L)	138.31 ± 6.47	138.54 ± 6.88	138.24 ± 6.33	− 1.246	0.213
Potassium (mmol/L)	4.44 ± 0.96	4.57 ± 1.02	4.39 ± 0.94	− 4.823	< 0.001
Chloride (mmol/L)	102.86 ± 7.35	102.82 ± 7.92	102.87 ± 7.15	0.153	0.878
Calcium (mmol/L)	2.07 ± 0.25	2.05 ± 0.26	2.08 ± 0.24	2.724	0.007
Phosphorus (mmol/L)	1.29 ± 0.51	1.42 ± 0.54	1.25 ± 0.49	− 8.748	< 0.001
Therapies, n (%)					
MV	2,751 (73.54)	764 (82.42)	1,987 (70.61)	49.936	< 0.001
CRRT	279 (7.46)	113 (12.19)	166 (5.90)	39.983	< 0.001
TTE	1,147 (30.66)	300 (32.36)	847 (30.10)	1.680	0.195
Norepinephrine	1,718 (45.92)	568 (61.27)	1,150 (40.87)	116.918	< 0.001
Dopamine	265 (7.08)	98 (10.57)	167 (5.93)	22.781	< 0.001
Coexisting illness, n (%)					
Hypertension	1,661 (44.40)	377 (40.67)	550 (19.55)	6.950	0.008
Diabetes	1,313 (35.10)	303 (32.69)	1,010 (35.89)	3.146	0.076
CPD	1,100 (29.40)	282 (30.42)	818 (29.07)	0.614	0.433
Cerebrovascular disease	628 (16.79)	170 (18.34)	458 (16.28)	2.124	0.145
Severe liver disease	240 (6.42)	73 (7.87)	167 (5.93)	4.372	0.037
Malignant tumor	755 (20.18)	254 (27.40)	501 (17.80)	39.863	< 0.001
Acute pancreatitis	127 (3.39)	27 (2.91)	100 (3.55)	0.874	0.350
AMI	650 (17.38)	183 (19.74)	467 (16.60)	4.806	0.028
AF	1,671 (44.67)	418 (45.09)	1,253 (44.53)	0.090	0.764
CA	236 (6.31)	115 (12.41)	121 (4.30)	77.512	< 0.001
Cardiogenic shock	375 (10.02)	143 (15.43)	232 (8.24)	39.874	< 0.001
CRBSI	28 (0.75)	2 (0.22)	26 (0.92)	0.083	0.773
Length of ICU stay (day)	4.14 (2.33, 7.75)	3.89 (2.15, 6.57)	4.22 (2.43, 8.30)	4.708	0.030

SOFA Sequential Organ Failure Assessment, *SAPS II* Simplified Acute Physiology Score II, *AG* anion gap, *ACAG* albumin corrected anion gap, *WBC* white blood cell, *RDW* red cell distribution width, *MCV* mean corpuscular volume, *BUN* blood urea nitrogen, *PT* prothrombin time, *MV* mechanical ventilation, CRRT continuous renal replacement therapy, *TTE* transthoracic echocardiography, *CPD* chronic pulmonary disease, *AMI* acute myocardial infarction, *AF* atrial fibrillation, *CA* cardiac arrest,

Table 1 (continued)

CRBSI catheter-related bloodstream infection, *ICU* intensive care unit

Table 2 Comparison of clinical outcomes at different points between the normal and high ACAG groups

Variables	Normal ACAG ($n=2,076$)	High ACAG ($n=1,665$)	χ2	*P*
14-day mortality, *n*(%)	392 (18.88)	535 (32.13)	87.023	< 0.001
30-day mortality, *n*(%)	571 (27.50)	705 (42.34)	90.508	< 0.001

ACAG albumin corrected anion gap

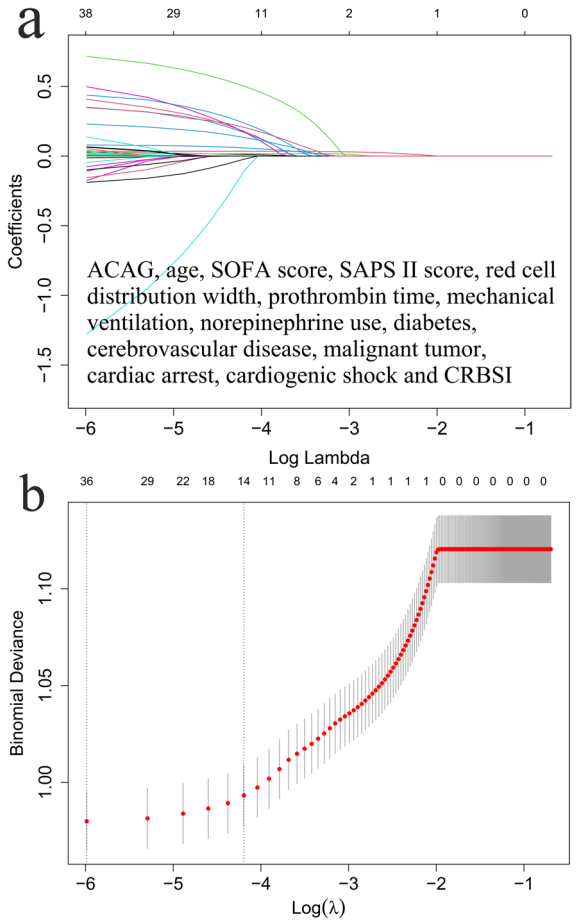

Fig. 2 LASSO regression model for variables screening of clinical data. **a** LASSO coefficient profiles of the 38 candidate variables; b tuning parameter (λ) selection using LASSO logistic regression with tenfold cross-validation. *LASSO* least absolute shrinkage and selection operator, *ACAG* albumin corrected anion gap, *SOFA* Sequential Organ Failure Assessment, *SAPS II* Simplified Acute Physiology Score II, *CRBSI* catheter-related bloodstream infection

ICU admission were an independent risk factor for short-term prognosis in this specific population. Furthermore, the analysis conducted using RCS revealed a non-linear association between ACAG and the risk of mortality at both 14 and 30 days in older critically ill patients with AKI caused or accompanied by sepsis. To the best of our knowledge, this is the first study to investigate the correlation between ACAG and clinical outcomes in this specific patient population.

Determining the timing and causality of AKI and sepsis is challenging in clinical practice, as both conditions are multifactorial and have complex pathophysiology. Notably, acid–base disturbances significantly contribute to the progression of AKI in patients suffering from sepsis. Patients diagnosed with sepsis in the ICU typically experience severe illness, characterized by the occurrence of ischemia and hypoxia, along with disturbances in acid–base balance, particularly metabolic acidosis [15]. Conventional markers such as blood pH, lactate levels, and base excess have been employed to assess the body's acid–base status. While the anion gap (AG), unaffected by respiratory function, provides a direct indication of the metabolic acid–base status and aids in identifying the specific type of metabolic acidosis [28]. Research has demonstrated that serum AG serves as an independent risk factor for mortality at both the 30- and 90-day marks in sepsis patients, surpassing lactate in its predictive capacity (30-day AUC: AG 0.703, lactate 0.502; 90-day AUC: AG 0.696, lactate 0.501) [29]. The presence of elevated AG in patients with AKI is attributed to impaired renal acid excretion, which exacerbates acidosis. Consequently, acidosis hampers renal blood flow, triggers the release of inflammatory mediators, and ultimately worsens the condition of AKI patients. In their study, Bihuan C et al. [30] identified a U-shaped relationship between AG levels and 30-day all-cause mortality in patients with severe AKI. Furthermore, they found that higher AG levels (AG ≥ 14 mmol/L) were a more reliable indicator of both short- and long-term mortality, even after accounting for potential confounding factors such as lactate, pH, and bicarbonate.

Furthermore, it has been proposed that the interplay between the inflammatory response and malnutrition

Table 3 Different Cox proportional hazard models for relationship between ACAG and mortality among elderly critically ill patients with AKI caused or accompanied by sepsis

Variable	Model I			Model II			Model III		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
14-day mortality									
Normal ACAG	1.0 (ref)			1.0 (ref)			1.0 (ref)		
High ACAG	1.860	1.633–2.119	< 0.001	1.330	1.161–1.524	< 0.001	1.367	1.191–1.569	< 0.001
30-day mortality									
Normal ACAG	1.0 (ref)			1.0 (ref)			1.0 (ref)		
High ACAG	1.733	1.552–1.936	< 0.001	1.271	1.133–1.426	< 0.001	1.297	1.154–1.457	< 0.001

Model I was not adjusted for any variables

Model II was adjusted for age, SOFA score, SAPS II score, RDW, and PT

Model III was adjusted for all variables in model II, as well as MV, norepinephrine use, diabetes, cerebrovascular disease, malignant tumor, CA, cardiogenic shock and CRBSI

ACAG albumin corrected anion gap, *AKI* acute kidney injury, *HR* hazard ratio, *CI* confidence interval, *SOFA* Sequential Organ Failure Assessment, *SAPS II* Simplified Acute Physiology Score II, *RDW* red cell distribution width, *PT* prothrombin time, *MV* mechanical ventilation, *CA* cardiac arrest, *CRBSI* catheter-related bloodstream infection

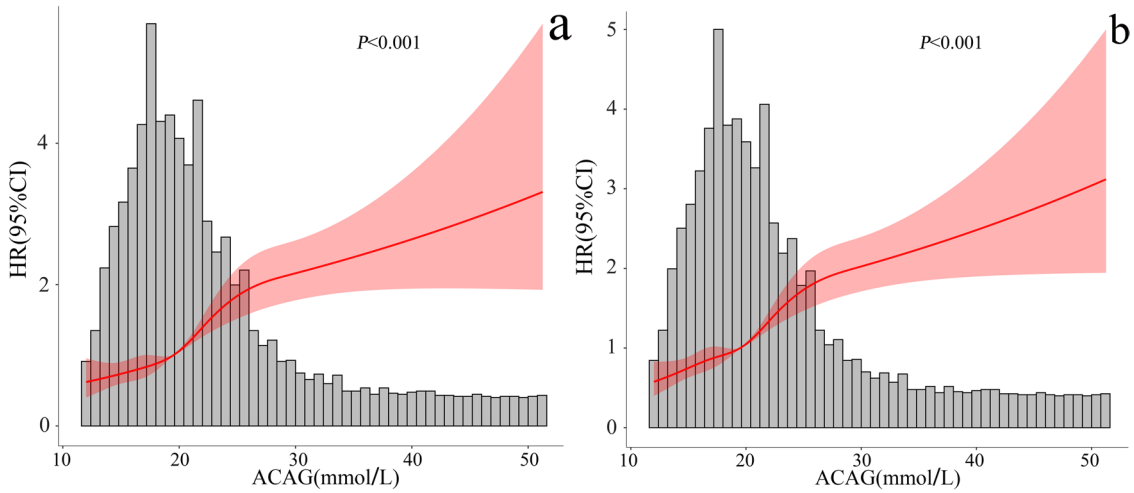

Fig. 3 Correlation of ACAG with the risk of 14-day (**a**) and 30-day (**b**) mortality. *ACAG* albumin corrected anion gap, *HR* hazard ratio, *CI* confidence interval

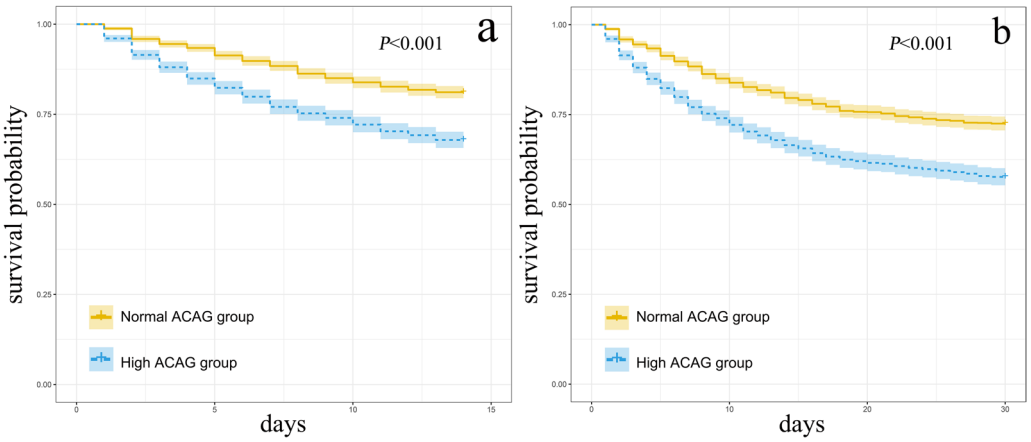

Fig. 4 Kaplan–Meier curves of 14-day (**a**) and 30-day (**b**) cumulative survival rates for both groups of patients. *ACAG* albumin corrected anion gap

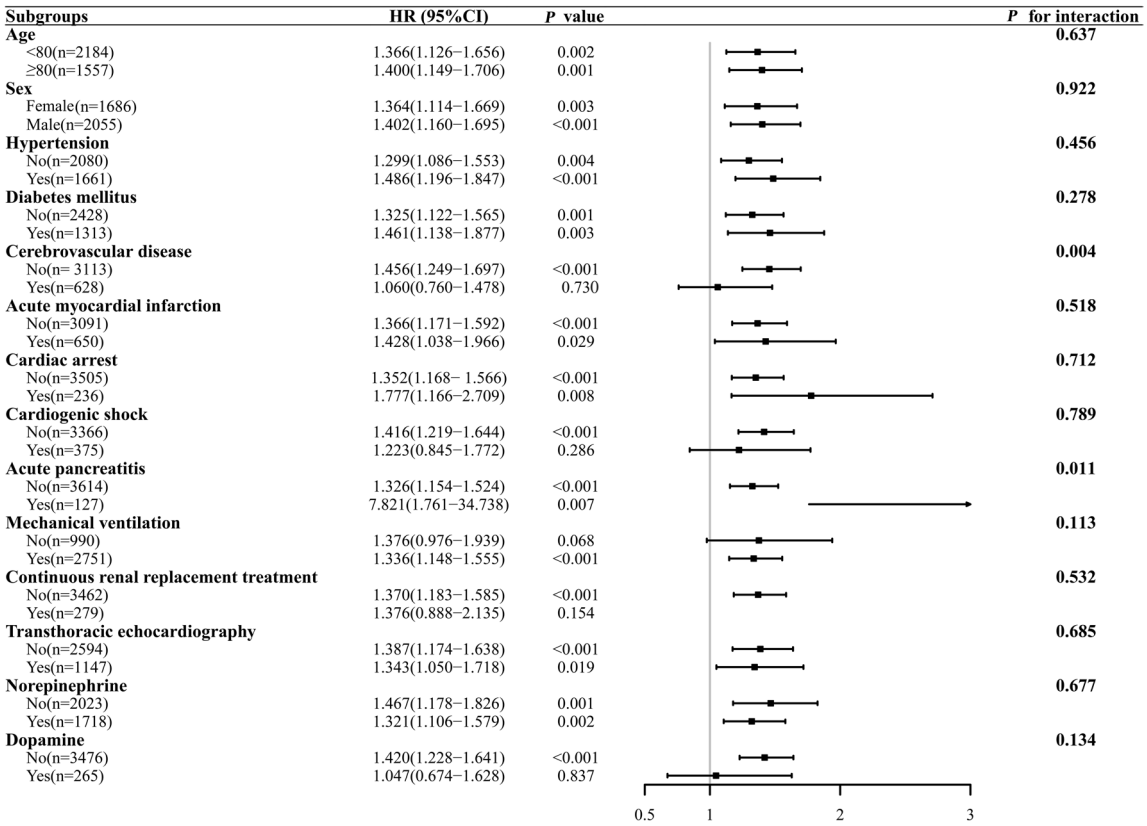

Fig. 5 The association between ACAG and 14-day mortality in different subgroups. *ACAG* albumin corrected anion gap, *HR* hazard ratio, *CI* confidence interval

holds significant relevance in the pathogenesis of AKI with sepsis among elderly individuals [31]. Serum albumin, a major constituent of plasma proteins, can serve as a valuable marker for assessing the nutritional status and inflammatory condition of patients [32]. Notably, patients with sepsis, characterized by heightened inflammation and metabolism, exhibit enhanced albumin catabolism. One study demonstrated a correlation between low levels of albumin and unfavorable prognosis in septic patients [33], while another study found that serum albumin independently predicted mortality in elderly patients with sepsis [34]. Furthermore, albumin possesses antioxidant and anti-inflammatory properties, along with the ability to regulate acid–base balance, which effectively mitigates renal injury [35, 36].Consistent with these findings, our study observed a significantly lower albumin concentration in the death group compared to the survival group. Concurrently, the presence of a negative charge in albumin renders hypoalbuminemia capable of impacting the evaluation of acid–base imbalances by AG [37].Consequently, the notion of ACAG has been introduced, posited as a superior marker for identifying acidosis and monitoring hidden anions in serum when compared to AG [17, 38].

Previous studies have established a correlation between elevated serum ACAG levels and adverse outcomes. For instance, Zhao B et al. [19] found that higher ACAG levels were associated with increased heart failure incidence after myocardial infarction, with renal function decline and hyperinflammatory states partially mediating this relationship. Additionally, a propensity score matching analysis involving septic ICU patients confirmed a significant association between ACAG and in-hospital mortality, both pre- and post-matching [18].Notably, ROC curve analyses indicated that ACAG demonstrated superior predictive value for mortality compared to albumin and AG. However, research specifically exploring the relationship between ACAG and prognosis in elderly AKI patients with sepsis remains limited. Therefore, our study aims to investigate the independent role of ACAG as a risk factor for short-term prognosis in this population.

Scholars have suggested several biomarkers, including microRNA, serum neutrophil gelatinase-related lipid carrier protein (NGAL), urinary kidney injury molecule 1 (uKIM-1), serum cystatin and urocystatin,

as potential indicators of poor prognosis in elderly AKI patients with sepsis [39–41]. However, these biomarkers are often costly and challenging to implement in clinical practice. Furthermore, certain emerging technologies and methodologies, such as machine learning, have been employed in the prognostication of AKI in elderly individuals with sepsis [42, 43]. However, further clinical investigations are necessary to determine their efficacy. In contrast, ACAG serves as a novel prognostic indicator that is cost-effective and readily accessible. Our research findings complement prior studies on ACAG, indicating that elevated ACAG levels are associated with an increased risk of unfavorable outcomes in elderly AKI patients with sepsis. Consequently, healthcare practitioners should exercise heightened vigilance when managing this particular patient population.

Despite the potential of ACAG as a biomarker, it is important to acknowledge several notable limitations. Firstly, the study design was retrospective, introducing potential biases that may restrict the generalizability of the findings. Secondly, although the investigation focused on all-cause mortality, there was a lack of comprehensive examination for specific causes of death. Lastly, the discussion solely pertains to the association between initial ACAG values upon admission to the ICU and prognosis, without considering the evaluation of dynamic fluctuations in ACAG levels. However, it is important to note that these findings are preliminary and require further confirmation through additional randomized controlled trials.

Conclusions

Notably, elevated ACAG levels at ICU admission have been identified as an independent risk factor for a poor prognosis, specifically relating to higher short-term all-cause mortality in older critically ill patients with AKI caused or accompanied by sepsis. Consequently, healthcare professionals should prioritize the monitoring and intervention of elderly patients exhibiting elevated ACAG levels in order to mitigate potential negative outcomes.

Abbreviations

AKI	Acute kidney injury
ICU	Intensive care unit
ACAG	Albumin corrected anion gap
MIMIC-IV	Medical Information Mart for Intensive Care IV
RCS	Restricted cubic spline
AMI	Acute myocardial infarction
CA	Cardiac arrest
KDIGO	Kidney disease: improving global outcomes
CKD	Chronic kidney disease
SQL	Structured Query Language
AG	Anion gap
WBC	White blood cell
RDW	Red cell distribution width
MCV	Mean corpuscular volume
BUN	Blood urea nitrogen
PT	Prothrombin time
MV	Mechanical ventilation
CRRT	Continuous renal replacement therapy
TTE	Transthoracic echocardiography
CPD	Chronic pulmonary disease
AF	Atrial fibrillation
CRBSI	Catheter-related bloodstream infection
SOFA	Sequential Organ Failure Assessment
SAPS II	Simplified Acute Physiology Score II
LASSO	Least absolute shrinkage and selection operator
HR	Hazard ratio
CI	Confidence interval

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Author contributions

YW and LZ: provided the idea of the research and designed the research; LZ, JM and JZ: acquired the data and drafted the manuscript. JL helped with data collection and statistical analysis. JS: revised the manuscript. All the authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The establishment of this de-identified database was approved by the Institutional Review Board at the Beth Israel Deaconess Medical Center. Written informed consent for participation was not required for this project in accordance with the national legislation and the institutional requirements. To gain access to the database, we completed the Collaborative Institutional Training Initiative examination (certification number: 51774135; 53446653), and no additional ethical approval was required for this study.

Competing interests

The authors declare no competing interests.

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