BMJ Open

Albumin corrected anion gap is associated with the prognosis of cardiogenic shock: a multi-center retrospective study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-081597
Article Type:	Original research
Date Submitted by the Author:	01-Nov-2023
Complete List of Authors:	Wang, Yuxing; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Tao, Yuhang; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Yuan, Ming; Zhejiang University School of Medicine Sir Run Run Shaw Hospital yu, pengcheng; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Zhang, Kai; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Ying, Hangying; Zhejiang University School of Medicine Sir Run Run Shaw Hospital jiang, ruhong; Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INTENSIVE & CRITICAL CARE, CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Albumin corrected anion gap is associated with the prognosis of cardiogenic shock: a multi-center retrospective study

Yuxing Wang[1*], Yuhang Tao[1*], Ming Yuan[1], Pengcheng Yu[1], Kai Zhang[1],Hangying Ying[1†], Ruhong Jiang[1†]

Affiliations:
1 Department of Cardiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

* Co-first authors contributed equally

† Co-corresponding authors contributed equally

Address for Corresponding Authors:
Hangying Ying, M.D.
Department of Cardiology, Sir Run Run Shaw Hospital
Zhejiang University School of Medicine
3 East Qingchun Road
Hangzhou, Zhejiang, 310016, P.R. China.
E-mail: yinghangying@zju.edu.cn

Ruhong Jiang, M.D.
Department of Cardiology, Sir Run Run Shaw Hospital
Zhejiang University School of Medicine
3 East Qingchun Road
Hangzhou, Zhejiang, 310016, P.R. China.
E-mail: jrh@zju.edu.cn

Declarations of interest: none

Abstract:

Objectives: We aimed to investigate the association between albumin corrected anion gap (ACAG) and the prognosis of cardiogenic shock (CS).

Design: A multi-center retrospective cohort study.

Setting: Data were collected from the Medical Information Mart for Intensive Care (MIMIC-IV) and eICU Collaborative Research Database (eICU-CRD) datasets.

Participants: A total of 808 and 700 individuals diagnosed with CS from MIMIC-IV and eICU-CRD respectively.

Primary and secondary outcome: The primary endpoint is short-term all-cause mortality including ICU, in-hospital, and 28-day mortality. The secondary endpoints are 28-day free from ICU and length of time intensive care needed.

Results: CS patients were divided into two groups according to the admission ACAG value: normal ACAG group (≤20 mmol/L) and high ACAG group (> 20 mmol/L). CS patients with a higher ACAG level exhibited increased short-term all cause mortality rates, including ICU mortality (MIMIC-IV cohort: adjusted HR:1.43, 95%CI=1.05-1.93, p=0.022; eICU-CRD cohort: adjusted HR:1.38, 95%CI=1.02-1.86, p=0.036), in-hospital mortality (MIMIC-IV cohort: adjusted HR:1.31, 95%CI=1.01-1.71, p=0.03; eICU-CRD cohort: adjusted HR:1.47, 95%CI=1.12-1.94, p=0.006), and 28-day mortality (adjusted HR: 1.42, 95%CI: 1.11-1.83, p=0.007). A positive linear correlation was observed between ACAG values and short-term mortality rates by restricted cubic splines. In comparison to AG, ACAG displayed a larger area under the curve for short-term mortality prediction. Besides, the duration of intensive care was longer while 28-day free from ICU was shorter in patients with a higher ACAG level in both cohorts.

Conclusion: ACAG value was independently and strongly associated with the prognosis of CS, which was superior than the conventional AG.

Strengths and limitations of this study:

1.This is the first study to explore the association between ACAG and the prognosis of CS.

2.CS patients are from a diverse and heterogeneous population with mixed etiologies from two distinct high-quality datasets.

3. As a nature of retrospective, the selection bias cannot be avoided and detailed information about cardiac function are not available.

Keywords: Albumin corrected anion gap, anion gap, cardiogenic shock, intensive care unit, acute cardiovascular care

1.Introduction

Cardiogenic shock (CS), a life-threatening clinical condition, is characterized by acute end-organ hypoperfusion resulting from reduced cardiac output [1]. Despite substantial progress achieved in CS management over the past three decades, the mortality rate of CS remains unexpectedly high, making it a formidable challenge within the intensive care unit (ICU)[2]. It is worth noting the one-year mortality rate in CS patients is approximately 50%-60%, with a substantial portion of cases (70% to 80%) occurring within the initial 30 to 60 days[3]. Therefore, early identification of CS patients with a poor prognosis holds paramount clinical importance for tailoring effective risk reduction strategies.

Anion gap (AG), a biomarker reflecting unmeasured anions, is calculated using the following formula: AG (mmol/l) = (sodium + potassium) - (chloride + bicarbonate)[4]. It is extensively utilized to assess the acid-base disorders and to evaluate the prognosis of various diseases in clinical practice[5]. Nevertheless, the accuracy of AG in predicting the prognosis of patients in the ICU remains debatable. While some studies have suggested that AG can effectively predict short-term mortality in patients with critical illness, others have yielded inconclusive results[6]. In 1985, Gabow observed that the AG value could be influenced by serum albumin levels[7]. Given that albumin carries a negative charge, any fluctuations in albumin levels can impact the final AG measurement[8]. Consequently, for patients with critical illness in the ICU, AG may sometimes appear to be pseudo-normal since hypoalbuminemia is very common in the setting of intensive care[9]. In order to address this problem, Figge J et al. introduced the concept of the albumin corrected anion gap (ACAG) in 1998[10]. Hatherill et al. discovered that ACAG exhibited superior predictive capabilities for metabolic acidosis compared to AG in pediatric patients with shock[11]. Furthermore, numerous studies have demonstrated the association between ACAG and the prognosis of critical conditions including cardiac arrest[12], acute myocardial infarction[13], acute kidney injury[14], sepsis[15], and acute pancreatitis[16].

However, to the best of our knowledge, the relationship between ACAG and the prognosis of CS has not been investigated. Furthermore, it remains uncertain whether ACAG offers an improved predictive capability for short-term mortality when compared to AG. Therefore, in this study, our objectives are as follows: 1) to exam the correlation between ACAG and short-term mortality in patients with CS; 2) to compare the admission values of AG and ACAG for predicting CS mortality and assessing the severity.

2.Materials and methods

2.1 Datasets and ethics

In this study, we utilized the following two publicly-accessible dataset: (1) Medical Information Mart for Intensive Care IV/MIMIC-IV v2.2 dataset (2008–2019)[17]; (2) eICU Collaborative Research Database/eICU-CRD dataset (2014–2015)[18]. MIMIC-IV is an updated version of the MIMIC-III, containing de-personalized data of 73,181 ICU stays for 50,906 unique patients at the Beth Israel Deaconess Medical Center between 2008 and 2019 (a single center dataset). The eICU-CRD is also a de-identified database and

contains 200,859 ICU stays for 139,367 unique patients admitted to 335 ICUs at 208 hospitals across the United States (a multi-center dataset). Importantly, as there is no shared hospital involvement between the MIMIC and eICU program, the eICU-CRD dataset remains entirely independent of MIMIC-IV.

The first author has successfully completed the online course and passed the Examination for Protecting Human Research Participants (Record ID: 11841860). Hence, he was granted permission to extract data from the two datasets mentioned above. Given that all identifying information had been removed, our study was considered exempt from ethical review by the institutional research board. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

2.2 Study population and endpoints

This is a multi-center, retrospective, observational study. We screened all patients diagnosed with CS in MIMIC-IV dataset and eICU-CRD dataset. We excluded those who aged younger than 18 years old, length of stay (LOS) in ICU or hospital less than 24 hours, and lack of AG or albumin value within the first 24 hours of ICU admission. In cases of patients with multiple ICU admissions, we only included the first ICU stay for analysis. AG was calculated by the following formula: AG (mmol/l) = (sodium + potassium) - (chloride + bicarbonate). ACAG was determined as follows: ACAG (mmol/l) = [4.4-{albumin(g/dl)}] *2.5 + AG[11]. Additionally, we categorized the enrolled patients into two groups according to the admission values of ACAG based on the previous studies[14,15]: the normal ACAG group (< 20 mmol/l) and the higher ACAG group (≥20 mmol/l).

The primary endpoint of this study was short-term all-cause mortality, which included ICU mortality, in-hospital mortality, as well as 28-day mortality (not available in eICU-CRD). The secondary endpoints encompassed 28-day free from ICU (not available in eICU-CRD) and LOS in ICU. 28-day free from ICU is a composite outcome which integrates both mortality and LOS in ICU. It was calculated as 28 minus the days spent in the ICU during the first 28 day and the dead patients were assigned the value of zero. LOS in ICU was defined as the duration that intensive care was required and was calculated based on the time to discharge alive from ICU, with death in ICU as a completing risk.

2.3 Variable extraction

We extracted the variables with structured query language in Navicat Premium (version 15.0.12). The codes for data extraction were based on https://github.com/MIT-LCP/mimic-code and https://github.com/MIT-LCP/eicu-code. For each patient, we collected a wide range of variables including demographic information, comorbidities, Sequential Organ Failure Assessment (SOFA) score, vital signs, and laboratory data. Demographic information included age at admission, gender, weight/body mass index, and race. Acute myocardial infarction, hypertension, atrial fibrillation, valvular disease,

cardiomyopathy, acute kidney injury/acute renal failure, chronic obstructive pulmonary disease, diabetes, and malignancy were identified as comorbidities. Vital signs encompassed heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, and oxygen saturation. Additionally, we collected laboratory data, which included white blood cell, hemoglobin, platelet, bilirubin, creatinine, sodium, potassium, chloride, bicarbonate, albumin, AG, and ACAG.

All vital signs, laboratory data, and the SOFA score were extracted and calculated within the first 24 hours of ICU admission. If a variable was measured multiple times within the initial 24 hours of ICU admission, we used the first recorded value for analysis.

2.4 Statistical analysis

To address missing values, we initially conducted multiple imputation using chained equations. In the MIMIC-IV cohort, the percentage of incomplete cases was 3.1%, and in the eICU-CRD cohort, it was 16.7%. Accordingly, we generated 5 datasets for MIMIC-IV and 17 datasets for eICU-CRD for further analysis and the results were combined according to the Rubin's rules[19].

We compared the baseline characteristics of the enrolled patients based on their hospital survival status and ACAG levels. Categorical variables were presented as numbers plus percentages and compared using Pearson's chi-square test. Shapiro-Wilk tests were performed to assess the distribution of continues variables. Since all continuous variables in two cohorts were both skewed-distributed, they were expressed as median [inter-quartile range (IQR)] and compared by Wilcoxon rank sum test.

Pearson correlation analyses were utilized to investigate the association between AG/ACAG values and the SOFA score. The ability of AG and ACAG to predict short-term mortality was compared by the area under curves (AUC) of the receiver operating characteristic curves (ROC). Z test was used to compare the predictive ability of AG and ACAG following the method of Delong et al[20]. Threshold values were determined by identifying the values that provided the highest specificity and sensitivity by calculating the Youden Index.

To evaluate the relationship between ACAG and ICU, in-hospital, and 28-day all-cause mortality, ACAG was initially analyzed as a categorical variable (normal ACAG group and high ACAG group) and then as a continuous variable (ACAG values). Kaplan-Meier survival curves and Cox proportional hazards regression models were employed to calculate hazard ratios (HR) and 95% confidence intervals. Furthermore, we investigated the association between ACAG values and short-term mortality using restricted cubic splines with four knots at 25%, 50%, 75% and 95%. Based on the previous studies and theoretical considerations, we selected clinically relevant confounding factors as covariates in the regression model. Variance inflation factor was used to test the multicollinearity between each covariate and the covariates with a high degree of collinearity (variance inflation factor > 5) were removed from the regression model. Finally, we constructed two models for adjustments. In model I, we adjusted for confounders including age, gender, race, and weight/body mass index. In model II, we further adjusted acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular heart disease, diabetes, chronic obstructive pulmonary disease, acute kidney injury,

SOFA score, mean blood pressure, oxygen saturation, potassium, chloride, creatinine, and total bilirubin.

Since ICU expire resulted in a shorter LOS, the correlation between ACAG and LOS in ICU was analyzed using the Fine-Gray competing risk model. In this model, a higher HR for earlier alive ICU discharge indicated a shorter LOS while a lower HR indicated a longer LOS in ICU.

Subgroup analyses were conducted to evaluate the relationship between ACAG levels and 28-day all-cause mortality within various subpopulations, including age (<65 years, ≥65 years), gender (male, female), acute myocardial infarction, atrial fibrillation, valvular disorders, cardiomyopathy, chronic obstructive pulmonary disease, diabetes mellitus, acute kidney injury/acute renal failure, hypoalbuminemia (<3.5 g/dL, ≥3.5 g/dL), and SOFA score (<8, ≥8) using the stratified multivariable Cox proportional hazards model.

All statistical analysis were performed with R version 4.1.2. A P value < 0.05 for two sides is considered statistical significance.

3.Results

3.1 Baseline characteristics of enrolled patients

The flowchart of our study was presented in *Fig.1*. Overall, a total of 808 and 700 individuals diagnosed with CS were enrolled from the MIMIC-IV dataset and eICU-CRD dataset respectively. The short-term mortality rates of CS patients were similar in both cohorts. Specifically, the ICU mortality rates were 29%, 30% while in-hospital mortality rates were 36%, 37% in MIMIC-IV cohort and eICU-CRD cohort, respectively. In the MIMIC-IV cohort, the 28-day all-cause mortality rates were 39%.

Table1 summarized the baseline characteristic of enrolled patients stratified according to the ACAG level. Obviously, patients with a higher ACAG level exhibited a greater predisposition to acute kidney injury/acute renal failure and had elevated values of the SOFA score, white blood cell count, sodium, potassium, creatinine, and total bilirubin. In comparison to the normal ACAG group, the short-term mortality rates (including ICU mortality, in-hospital mortality, and 28-day mortality) were significantly higher while the 28-day free from ICU were notably shorter (20 [2-25] vs 9 [0-23], p<0.001) in patients with a higher ACAG level.

Furthermore, the baseline characteristic of enrolled patients stratified according to the hospital survival status were summarized in *eTable1*. Notably, we found that the ACAG value was significantly higher in the group of patients who did not survive in hospital, both in the MIMIC-IV cohort (21.0 [18.0-25.3] vs 19.0 [16.5-22.5], p<0.001) and the eICU-CRD cohort (22.0 [17.7-27.0] vs 19.0 [16.2-23.0], p<0.001). Additionally, among the non-survivors during hospitalization, we observed a higher rate of acute kidney injury/acute renal failure, lower values of hemoglobin, albumin, bicarbonate, and higher levels of age, creatinine, SOFA score.

3.2 Comparison of AG and ACAG for mortality prediction and severity assessment

The predictive performance of ACAG versus AG for ICU, in-hospital, and 28-day all-cause mortality was assessed through ROC curve analysis (e*Fig.1*). As shown in *Table2*, ACAG outperformed AG for short-term mortality prediction, including ICU mortality (MIMIC-IV cohort: AUC: 0.654 [95%CI: 0.613-0.696] vs 0.632 [95%CI: 0.589-0.674], Z = 2.99, p= 0.003; eICU-CRD cohort: AUC: 0.613 [95%CI: 0.566-0.660] vs 0.594 [95%CI: 0.546-0.642], Z = 2.99, p=0.003), in-hospital mortality (MIMIC-IV cohort: ACU: 0.629 [95%CI: 0.589-0.669] vs 0.599 [95%CI: 0.558-0.641], Z =4.13, p< 0.001; eICU-CRD cohort: AUC: 0.628 [95%CI: 0.585-0.671] vs 0.603 [95%CI: 0.559-0.647], Z = 3.92, p< 0.001), and 28-day mortality prediction (MIMIC-IV cohort: AUC: 0.641 [95%CI:0.602-0.680] vs 0.614 [95%CI: 0.574-0.654], Z = 3.95, p< 0.001).

Additionally, we conducted correlation analyses to investigate the association between AG/ACAG values and the SOFA score using Pearson's method. as depicted in eFigure2. In both cohorts, we observed positive correlations between both AG and ACAG values and the SOFA score (both p-values < 0.001). Intriguingly, we found that the correlation coefficient for ACAG was significantly higher than that of AG (MIMIC-IV cohort: AG: R=0.28 vs ACAG: R=0.35; eICU-CRD cohort: AG: R=0.30 vs ACAG: R=0.35). These findings highlight the stronger positive correlation between ACAG and the SOFA score, underscoring its potential as a valuable prognostic indicator.

3.3 Increased ACAG level correlates with higher risk of short-term morality

As demonstrated in *eFig.3*, the Kaplan–Meier survival curve showed an increased 28-day all-cause mortality rate among patients with a higher ACAG level (HR: 1.85, 95%CI: 1.48-2.32, log-rank test, p-value <0.001) in the MIMIC-IV cohort. Furthermore, even after adjusting for confounding variables in model II, we observed that the individuals with an evaluated ACAG level still exhibited an increased 28-day all-cause mortality rate (adjusted HR: 1.42, 95%CI: 1.11-1.83, p=0.007).

Similarly, the relationship between ACAG levels and ICU/in-hospital mortality was assessed through multivariable Cox regression models as well. As presented in *Table3*, in comparison to the normal ACAG group, the results showed that the CS patients with a higher ACAG level experienced increased rates of ICU mortality (MIMIC-IV cohort: adjusted HR:1.43, 95%CI=1.05-1.93, p=0.022; eICU-CRD cohort: adjusted HR:1.38, 95%CI=1.02-1.86, p=0.036) and in-hospital mortality (MIMIC-IV cohort: adjusted HR:1.31, 95%CI=1.01-1.71, p=0.03; eICU-CRD cohort: adjusted HR:1.47, 95%CI=1.12-1.94, p=0.006).

3.4 Linear relationship of ACAG value and short-term all-cause mortality

We extended our analysis to assess the association between ACAG values and short-term all-cause mortality rates. As presented in *Table3*, the adjusted HRs with 95%CI were 1.05 (1.03-1.07) for 28-day mortality, 1.04 (1.01-1.06) for ICU mortality, and 1.04 (1.02-1.07) for in-hospital mortality in the MIMIC-IV cohort while 1.06 (1.03-1.09) for ICU mortality and 1.05 (1.02-1.07) for in-hospital mortality in the eICU-CRD cohort respectively.

To further investigate the relationship between ACAG values and short-term all-

cause mortality rates, we utilized the adjusted restricted cubic splines. As shown in *Fig.2*, we observed a linear correlation between ACAG and short-term all-cause mortality, which includes 28-day mortality (MIMIC-IV cohort: p for overall<0.001, p for non-linear=0.651), ICU mortality (MIMIC-IV cohort: p for overall<0.001, p for non-linear=0.693; eICU-CRD cohort: p for overall<0.001, p for non-linear=0.183), and in-hospital mortality (MIMIC-IV cohort: p for overall<0.001, p for non-linear=0.948; eICU-CRD cohort: p for overall<0.001, p for non-linear=0.404) in both cohorts. These findings suggest that a 1-unit increase in ACAG value is associated with approximately 5% increase in short-term all-cause mortality rates among patients with CS.

3.5 Association of ACAG and earlier alive discharge in ICU

Cumulative incidence ratio (CIR) of earlier discharge alive in ICU among ACAG levels was shown in *eFig.4*. Obviously, the unadjusted CIR for earlier alive discharge in ICU was significantly higher in lower ACAG group. The robustness of the results was further confirmed using Fine-Gray competing risk models after adjusting for confounding variables (e*Table2*). In the MIMIC-IV cohort, the adjusted HR (95%CI) for the relationship between ACAG level and earlier alive discharge in ICU was 0.77 (95% CI= 0.65–0.92; p = 0.004). However, in the eICU-CRD cohort, this relationship did not reach statistical significance (adjusted HR: 0.85, 0.69–1.04; p = 0.140).

Additionally, ACAG was analyzed as a continuous variable. Intriguingly, the association between ACAG value and earlier discharge alive was statistically significant in both cohorts, with adjusted HRs (95%CI) of 0.96 (95% CI=0.94-0.98; p <0.001) in the MIMIC-IV cohort and 0.97 (95% CI=0.95-0.99; p=0.001) in the eICU-CRD cohort. In summary, the ACAG value was inversely associated with earlier discharge alive in the ICU for patients with CS.

3.6 Subgroup analysis

Subgroup analysis was conducted to assess the stability of the consistency for the relationship between ACAG levels and 28-day all-cause mortality across various subpopulations, including age group (<65 years, ≥65 years), gender group (male, female), SOFA score (<8, ≥8), and different clinical conditions such as acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular disorders, chronic obstructive pulmonary disease, diabetes mellitus, acute kidney injury, hypoalbuminemia (<3.5 g/dL, ≥3.5 g/dL). Adjustments for confounding factors were made as in Model II. As depicted in e*Fig.5*, all p-values for interaction tests within different subgroups were greater than 0.05, indicating that the relationship between ACAG level and 28-day all-cause mortality remained stable and consistent across the various subpopulations.

4.Discussion

In this large-sample retrospective study based on two distinct public-accessible datasets, we investigate the association of ACAG, a novel biomarker indicating metabolic acid load, and the short-term prognosis of CS patients with mixed etiologies. The main findings of our study are as follows: (1) ACAG is strongly and independently associated with short-term all-cause mortality rates (including ICU, in-hospital, and 28-day mortality)

and the duration of intensive care required in patients with CS, even after adjusting for disease severity using SOFA score; (2) ACAG outperforms AG in its ability to predict short-term mortality and evaluate the severity of CS.

It is widely acknowledged that metabolic acidosis is a frequent event in the setting of intensive care and has been consistently demonstrated to be associated with adverse outcomes in individuals with critical illness[21]. Notably, in patients with severe cardiovascular disorders, particularly those suffering from CS, acidemia may trigger a detrimental cycle via impairing cardiac contractile function, inducing malignant arrhythmias, and exacerbating circulatory failure[22]. Additionally, severe acidemia may further compromise the responses to catecholamines of cardiovascular systems and weaken the effectiveness of vasopressors to reverse hypotension[23]. A prior study has demonstrated that the severity of acidosis is strongly and positively correlated with both the degree of shock and short-term mortality rates in CS patients[24].

As one of the simplest methods for assessing acid-base balance, the anion gap (AG) is a widely used biomarker in clinical practice. The relationship between AG and short-term mortality in patients with critical illness has been extensively investigated[25]. A previous study demonstrated a J-shaped association between AG value and the 30-day all-cause mortality rate in patients with CS based on MIMIC-III dataset[26]. Similarly, our study revealed that AG values were significantly higher in non-survivors when compared to survivors (MIMIC-IV cohort: 18 [15-22] vs 16 [14-20], p<0.001; eICU-CRD cohort: 18 [14-23] vs 16 [13-19], p<0.001) in our study. Moreover, AG has also been used for risk stratification in the setting of acute cardiovascular care. Recently, a study has combined the AG and SOFA to create the AG-SOFA score, which displayed improved predictive capabilities for short-term mortality in cardiovascular intensive care units[27]. Similarly, Eric et al incorporated AG into the BOS,MA2 score and exhibited superior performance than other pre-existing risk scores systems for CS prognostication[28]. However, the physiological AG primarily consists of inorganic phosphate and albuminate, which is a weak anion derived from serum albumin[5]. Given the involvement of albumin in the acid-base equilibrium, it may perplex the interpretation of acid-base data[29]. Theoretically, hypoalbuminemia can lead to a decrease in albuminate levels, resulting in a reduction in AG values[10]. Therefore, in the case of a patient with hypoalbuminemia and a normal AG value, it might indicate the presence of plasma acids. Similarly, we might underestimate the severity of metabolic acidosis based on the AG values for patients with low albumin levels. Notably, hypoalbuminemia is very frequent among patients with critical illness and has been demonstrated to be associated with unfavorable outcomes including higher rates of short-term mortality and longer LOS in ICU. The incidence of hypoalbuminemia is striking in patients with CS, with a reported rate of 75% from the previous CardShock study[30]. Similarly, our study also observed an exceptionally high frequency of hypoalbuminemia in patients with CS. Specifically, the incidence of hypoalbuminemia (defined as albumin < 3.5 g/dL) is 58.4% (472/808) in the MIMIC-IV cohort and 74.1% (519/700) in the eICU-CRD cohort respectively. Furthermore, a recent study has established that serum albumin is an independent predictor for short-term mortality in CS patients [20]. Likewise, in this study, we found that the value of albumin was significantly lower in hospital death group than survival group (MIMIC-IV cohort: 3.4

[3.0-3.7] vs 3.1 [2.7-3.6], p<0.001; eICU-CRD cohort: 3.1 [2.7-3.6] vs 2.9 [2.5-3.3], p<0.001).

ACAG, which combines the AG and serum albumin, has been proposed as a replacement for AG in differentiating acidosis caused by acid load or base deficit from a panel of expert's consensus about metabolic acidosis management[31]. As a ubiquitous abnormality in patients with critical illness, hypoalbuminemia has been demonstrated to complicate the interpretation of acid–base data when using diagnostic methods based on base excess or plasma bicarbonate concentration alongside AG [29]. In the presence of hypoalbuminemia, taking albumin levels into account can reveal the presence of plasma acid, which might otherwise be overlooked when relying solely on AG or base excess values. Previous studies have demonstrated that ACAG is a superior predictor compared to conventional AG for short-term prognosis prediction in patients with critical illness like cardiopulmonary arrest[12], acute myocardial infarction[13], and sepsis[15]. Therefore, we hypothesized that ACAG may perform better than AG, particularly in a population at high risk of metabolic acidosis and hypoalbuminemia. As previously discussed, patients with CS are not only prone to hypoalbuminemia, but are also susceptible to metabolic acidosis. Hence, we posited that ACAG might outperform AG for risk stratification in the setting of CS. In this study, we compared AG and ACAG for mortality prediction and severity assessment for CS patients in two cohorts. Through the ROC curve analysis, we found that ACAG exhibited the highest AUC and Youden's index for short-term morality prediction in both cohorts, suggesting the better short-term mortality predicting capacity than AG for CS. Furthermore, using the Spearman's methods, we discovered that both AG and ACAG were positively correlated with the SOFA score. Importantly, the correlation coefficients with the SOFA score were significantly higher for ACAG when compared to AG. Taken together, our findings support the superiority of ACAG in predicting prognosis and estimating disease severity in patients with CS.

As a medical emergency requiring prompt evaluation and intervention, the mortality risk of CS is highest during the initial 48 hours following the onset of shock[32]. Therefore, mortality assessment in CS patients should be performed as early as possible after ICU admission. Given the rapid and widespread availability of AG and albumin in clinical practice, we recommend the inclusion of baseline ACAG levels in the prognostic biomarkers for patients with CS.

Indeed, our study has notable strengths. Firstly, it represents the pioneering study to explore the association between ACAG and the prognosis of CS. Second, the CS patients are from a diverse and heterogeneous patient population with mixed etiologies, enhancing its relevance and applicability to real-world clinical scenarios. Third, the data in this study are derived from two distinct high-quality datasets and the results are consistent with each other. However, several limitations of this study are deserved discussion. First, as the nature of retrospective, selection bias cannot be avoided. Second, detailed information about cardiac function (like left ventricular ejection fraction, ventricular size) and other important cardiac biomarkers (like troponin, N-terminal pro brain natriuretic peptide) are not included in this study due to a large amount of missing data. Third, the association between ACAG and the short-term mortality are established based on the first ACAG value within the first 24h of ICU admission. Monitoring the

dynamic changes of ACAG may be valuable for patients with CS. Further studies are needed to explore the relationship between the dynamic changes of ACAG and mortality of CS.

5.Conclusion

In conclusion, we found that the baseline ACAG value following ICU admission independently predicts the short-term mortality in patients with CS, which is better than AG. Given the high mortality risk of CS during the early phase of ICU admission, baseline ACAG value may help clinicians to identify patients at high risk of mortality. Therefore, we propose to incorporate the baseline ACAG into the risk stratification systems for CS.

Data availability

The datasets used in this study are available from the corresponding author upon reasonable request.

Author contributions

Yuxing Wang: Conceptualization, Formal analysis, Investigation, Software, Visualization, Writing - original draft, Data curation, Methodology, Resources. Yuhang Tao: Investigation, Software, Visualization, Writing - original draft. Ming Yuan: Writing - review & editing. Pengcheng Yu: Writing - review & editing. Kai Zhang: Writing - review & editing. Hangying Ying: Project administration, Supervision Validation, and Writing - review & editing. Ruhong Jiang: Project administration, Supervision Validation, and Writing - review & editing.

Declaration of Competing Interest

None

Reference:

1 Van Diepen S, Katz JN, Albert NM, *et al.* Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation*. 2017;136. doi: 10.1161/CIR.0000000000000525

2 Hunziker L, Radovanovic D, Jeger R, *et al.* Twenty-Year Trends in the Incidence and Outcome of Cardiogenic Shock in AMIS Plus Registry. *Circ: Cardiovascular Interventions*. 2019;12:e007293.

3 Berg DD, Bohula EA, Morrow DA. Epidemiology and causes of cardiogenic shock. *Current Opinion in Critical Care*. 2021;27:401–8.

4 Posen AK, Paloucek FP, Petzel R. Anion gap physiology and faults of the correction formula. *American Journal of Health-System Pharmacy*. 2022;79:446–51.

5 Kraut JA, Madias NE. Serum Anion Gap: Its Uses and Limitations in Clinical Medicine. *Clinical Journal of the American Society of Nephrology*. 2007;2:162–74.

6 Rocktaeschel J, Morimatsu H, Uchino S, *et al.* Unmeasured anions in critically ill patients: Can they predict mortality?*: *Critical Care Medicine*. 2003;31:2131–6.

7 Gabow PA. Disorders associated with an altered anion gap. *Kidney International*. 1985;27:472–83.

8 Figge J, Bellomo R, Egi M. Quantitative relationships among plasma lactate, inorganic phosphorus, albumin, unmeasured anions and the anion gap in lactic acidosis. *Journal of Critical Care*. 2018;44:101–10.

9 Gatta A, Verardo A, Bolognesi M. Hypoalbuminemia. *Intern Emerg Med*. 2012;7:193–9.

10 Figge J, Jabor A, Kazda A, *et al.* Anion gap and hypoalbuminemia: *Critical Care Medicine*. 1998;26:1807–10.

11 Hatherill M. Correction of the anion gap for albumin in order to detect occult tissue anions in shock. *Archives of Disease in Childhood*. 2002;87:526–9.

12 Hagiwara S, Oshima K, Furukawa K, *et al.* The Significance of Albumin Corrected Anion Gap in Patients with Cardiopulmonary Arrest. *Ann Thorac Cardiovasc Surg*. 2013;19:283–8.

13 Jian L. Association between albumin corrected anion gap and 30-day all-cause mortality of critically ill patients with acute myocardial infarction: a retrospective analysis based on the MIMIC-IV database. 2023.

14 Zhong L, Xie B, Ji X-W, *et al.* The association between albumin corrected anion gap and ICU mortality in acute kidney injury patients requiring continuous renal replacement therapy. *Intern Emerg Med*. 2022;17:2315–22.

15 Hu T, Zhang Z, Jiang Y. Albumin corrected anion gap for predicting in-hospital mortality among intensive care patients with sepsis: A retrospective propensity score matching analysis. *Clinica Chimica Acta*. 2021;521:272–7.

16 Li P, Shi L, Yan X, *et al.* Albumin Corrected Anion Gap and the Risk of in-Hospital Mortality in Patients with Acute Pancreatitis: A Retrospective Cohort Study. *JIR*. 2023;Volume 16:2415–22.

17 Johnson AEW, Bulgarelli L, Shen L, *et al.* MIMIC-IV, a freely accessible electronic health record dataset. *Sci Data*. 2023;10:1.

18 Pollard TJ, Johnson AEW, Raffa JD, *et al.* The eICU Collaborative Research Database, a freely available multi-center database for critical care research. *Sci Data*. 2018;5:180178.

19 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues

and guidance for practice. *Statist Med*. 2011;30:377–99.

20 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach. *Biometrics*. 1988;44:837.

21 Gunnerson KJ, Kellum JA. Acid–base and electrolyte analysis in critically ill patients: are we ready for the new millennium?: *Current Opinion in Critical Care*. 2003;9:468–73.

22 Kraut JA, Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. *Nat Rev Nephrol*. 2010;6:274–85.

23 Jentzer JC, Kashani KB, Wiley BM, *et al.* Laboratory Markers of Acidosis and Mortality in Cardiogenic Shock: Developing a Definition of Hemometabolic Shock. *Shock*. 2022;57:31–40.

24 Jentzer JC, Schrage B, Patel PC, *et al.* Association Between the Acidemia, Lactic Acidosis, and Shock Severity With Outcomes in Patients With Cardiogenic Shock. *JAHA*. 2022;11:e024932.

25 Glasmacher SA, Stones W. Anion gap as a prognostic tool for risk stratification in critically ill patients – a systematic review and meta-analysis. *BMC Anesthesiol*. 2015;16:68.

26 Zhang T, Wang J, Li X. Association Between Anion Gap and Mortality in Critically Ill Patients with Cardiogenic Shock. *IJGM*. 2021;Volume 14:4765–73.

27 Zhou Y-H, Pang S, Miao G-R, *et al.* Combining the anion gap with the sequential organ failure assessment score to evaluate the short-term prognosis of patients in the cardiac intensive care unit. *International Journal of Cardiology*. 2023;370:381–7.

28 Yamga E, Mantena S, Rosen D, *et al.* Optimized Risk Score to Predict Mortality in Patients With Cardiogenic Shock in the Cardiac Intensive Care Unit. *JAHA*. 2023;12:e029232.

29 Fencl V, Jabor A, Kazda A, *et al.* Diagnosis of Metabolic Acid–Base Disturbances in Critically Ill Patients. *Am J Respir Crit Care Med*. 2000;162:2246–51.

30 Jäntti T, Tarvasmäki T, Harjola V-P, *et al.* Hypoalbuminemia is a frequent marker of increased mortality in cardiogenic shock. *PLoS ONE*. 2019;14:e0217006.

31 for the Société de Réanimation de Langue Française (SRLF), the Société Française de Médecine d'Urgence (SFMU), Jung B, *et al.* Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. *Ann Intensive Care*. 2019;9:92.

32 Wigger O, Bloechlinger S, Berger D, *et al.* Baseline serum bicarbonate levels independently predict short-term mortality in critically ill patients with ischaemic cardiogenic shock. *European Heart Journal: Acute Cardiovascular Care*. 2018;7:45–52.

Figure lengeds:

Fig.1: The flow chart of this study.

LOS: length of stay, ICU: intensive care unit, AG: anion gap

Fig.2: Restricted cubic spline for the associations between ACAG value and short-term mortality

Fig.2A and Fig.2B showed the ICU mortality while Fig.3C and Fig.3D showed the in-hospital mortality in MIMIC-IV and eICU-CRD cohort respectively. 28-day mortality was shown in Fig.2E.

The solid lines represent the adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CI) after multivariable adjustment in Model II.

Histograms represent the distribution of concentrations of ACAG in two cohorts.

Table1: Baseline characteristics of enrolled patients stratified by ACAG level in two cohorts

	MIMIC-IV cohort (n=808)				eICU-CRD cohort (n=700)			
	Overall (n=808)	Normal ACAG (n=416)	Higher ACAG (n=392)	p-value	Overall (n=700)	Normal ACAG (n=353)	Higher ACAG (n=347)	p-value
Demographic characteristics								
Age	70 (60, 80)	71 (61, 81)	70 (60, 79)	0.3	67 (57, 76)	68 (57, 77)	67 (57, 75)	0.2
Gender				0.2				
Female	347 (43%)	188 (45%)	159 (41%)		255 (36%)	130 (37%)	125 (36%)	
Male	461 (57%)	228 (55%)	233 (59%)		445 (64%)	223 (63%)	222 (64%)	
Weight/BMI[a]	80 (68, 95)	79 (67, 94)	81 (68, 97)	0.2	28 (24, 33)	28 (24, 33)	28 (24, 33)	0.6
Ethnicity				0.3				0.016
White	497 (62%)	255 (61%)	242 (62%)		531 (76%)	276 (78%)	255 (73%)	
Black	71 (8.8%)	34 (8.2%)	37 (9.4%)		83 (12%)	32 (9.1%)	51 (15%)	
Hispanic	19 (2.4%)	12 (2.9%)	7 (1.8%)		32 (4.6%)	14 (4.0%)	18 (5.2%)	
Asian	18 (2.2%)	13 (3.1%)	5 (1.3%)		19 (2.7%)	15 (4.2%)	4 (1.2%)	
Others/unknown	203 (25%)	102 (25%)	101 (26%)		35 (5.0%)	16 (4.5%)	19 (5.5%)	
Comorbidities								
AMI	349 (43%)	187 (45%)	162 (41%)	0.3	270 (39%)	152 (43%)	118 (34%)	0.014
Hypertension	241 (30%)	143 (34%)	98 (25%)	0.004*	365 (52%)	186 (53%)	179 (52%)	0.8
Cardiomyopathy	206 (25%)	105 (25%)	101 (26%)	0.9	119 (17%)	69 (20%)	50 (14%)	0.070
Atrial fibrillation	393 (49%)	199 (48%)	194 (49%)	0.6	144 (21%)	77 (22%)	67 (19%)	0.4
VHD	293 (36%)	150 (36%)	143 (36%)	>0.9	99 (14%)	64 (18%)	35 (10%)	0.002
AKI/ARF[a]	573 (71%)	259 (62%)	314 (80%)	<0.001*	323 (46%)	150 (42%)	173 (50%)	0.051
COPD	71 (8.8%)	41 (9.9%)	30 (7.7%)	0.3	101 (14%)	53 (15%)	48 (14%)	0.7
Diabetes	283 (35%)	116 (28%)	167 (43%)	<0.001*	158 (23%)	70 (20%)	88 (25%)	0.080
Malignancy	80 (9.9%)	38 (9.1%)	42 (11%)	0.5	16 (2.3%)	6 (1.7%)	10 (2.9%)	0.3
SOFA	8 (5, 11)	7 (4, 10)	9 (6, 12)	<0.001*	8 (6, 11)	7 (5, 10)	9 (7, 12)	<0.001*
Vital signs								
Heart rate	90 (77, 108)	87 (74, 102)	93 (80, 111)	<0.001*	91 (78, 108)	90 (77, 105)	93 (78, 111)	0.088
Respiratory rate	20 (17, 24)	20 (16, 23)	21 (17, 26)	<0.001*	20 (17, 25)	19 (16, 24)	20 (17, 25)	0.083
Systolic BP	111 (97,	114 (99,	109 (95,	0.2	107 (91,	107 (92,	107 (90, 126)	0.8

	129)	127)	129)		122)	121)		
Mean BP	66 (54, 79)	66 (54, 79)	66 (54, 78)	0.5	62 (50, 75)	62 (50, 73)	62 (50, 77)	0.3
Diastolic BP	79 (68, 91)	79 (69, 91)	78 (66, 91)	0.4	77 (65, 89)	76 (67, 88)	78 (64, 91)	0.4
SpO2	97 (94, 100)	98 (94, 100)	97(93, 100)	0.12	97 (93, 100)	97 (94, 100)	98 (93, 100)	>0.9
Laboratory data								
White blood cell	13 (9, 17)	12 (9, 17)	13 (9, 18)	0.001*	12 (9, 18)	12 (9, 16)	13 (9, 20)	0.002*
Hemoglobin	11.5 (9.8, 13.4)	11.7 (10.1, 13.5)	11.4 (9.6, 13.1)	0.045*	12.1 (10.1, 13.9)	12.2 (10.3, 14.0)	11.8 (9.8, 13.7)	0.2
Platelet	211 (152, 278)	210 (154, 278)	213 (149, 278)	0.8	196 (145, 260)	203 (151, 253)	192 (139, 268)	0.4
Sodium	138 (134, 141)	138 (135, 141)	137 (133, 141)	0.2	137 (134, 141)	137 (135, 140)	138 (133, 141)	>0.9
Potassium	4.4 (3.9, 5.0)	4.3 (3.8, 4.7)	4.6 (3.9, 5.1)	<0.001*	4.2 (3.7, 4.9)	4.1 (3.7, 4.7)	4.4 (3.7, 5.2)	<0.001*
Chloride	103 (98, 107)	104 (100,108)	101 (96, 106)	<0.001*	103 (98, 107)	104 (100, 108)	101 (96, 105)	<0.001*
Bicarbonate	20 (17, 23)	22 (20, 25)	18 (15, 21)	<0.001*	22 (18, 25)	24 (21, 27)	19 (16, 22)	<0.001*
AG	13 (9, 17)	12 (9, 17)	13 (9, 18)	0.001*	167 (13, 21)	13 (12, 15)	21 (18, 24)	<0.001*
Albumin	3.3 (2.9, 3.7)	3.4 (3.0, 3.7)	3.2 (2.7, 3.6)	<0.001*	3.0 (2.6, 3.5)	3.1 (2.8, 3.6)	2.9 (2.5, 3.4)	<0.001*
ACAG	20.0 (17.0, 23.5)	17.1 (15.3, 18.5)	23.5 (21.8, 26.5)	<0.001*	19.9 (16.7, 24.2)	16.7 (14.8, 18.3)	24.2 (21.9, 28.0)	<0.001*
Creatine	1.4 (1.0, 2.3)	1.2 (0.9, 1.7)	1.8 (1.3, 2.9)	<0.001*	1.5 (1.1, 2.4)	1.3 (0.9, 1.8)	1.8 (1.3, 2.8)	<0.001*
Bilirubin	0.7 (0.4, 1.3)	0.7 (0.4, 1.0)	0.8 (0.5, 1.5)	<0.001*	0.8 (0.5, 1.4)	0.8 (0.5, 1.3)	0.9 (0.5, 1.6)	0.055
Outcomes								
LOS in ICU	5 (3, 9)	5 (3, 9)	5 (3, 9)	0.5	5 (3, 9)	5 (3, 8)	5 (3, 9)	0.3
LOS in hospital	10 (5, 17)	10 (6, 17)	10 (5, 18)	0.3	8 (5, 14)	9 (5, 15)	8 (4, 14)	0.017
ICU death	231 (29%)	85 (20%)	146 (37%)	<0.001*	211 (30%)	87 (25%)	124 (36%)	0.001*
Hospital death	289 (36%)	122 (29%)	167 (43%)	<0.001*	260 (37%)	102 (29%)	158 (46%)	<0.001*
28-day death[b]	315 (39%)	126 (30%)	189 (48%)	<0.001*				
28-day free from ICU[b]	17 (0, 24)	20 (2, 25)	9 (0, 23)	<0.001*				

Abbreviation: BMI: body mass index, AMI: acute myocardial infarction, AKI: acute kidney injury, ARF: acute renal failure, COPD: chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, BP: blood pressure, AG: anion gap, ACAG albumin

corrected anion gap, LOS: length of stay, ICU: intensive care unit

p<0.05*

a: body weight and acute kidney injury were shown in MIMIC-IV cohort while body mass index and acute renal failure were presented in eICU-CRD cohort due to data availability.

b: 28-day all-cause mortality and 28-day free from ICU were reported in MIMIC-IV cohort.

Table2: ROC curve analysis of AG/ACAG and short-term mortality

	Factor	AUC	95%CI	Cut-off	Sensitivity	Specificity	Youden's index
ICU mortality (MIMIC-IV)	AG	0.654	0.613-0.696	15.5	0.758	0.426	0.184
	ACAG	0.632	0.589-0.674	19.6	0.680	0.532	0.212
ICU mortality (eICU-CRD)	AG	0.594	0.546-0.642	18.1	0.526	0.654	0.180
	ACAG	0.613	0.566-0.660	25.4	0.351	0.857	0.208
Hospital mortality (MIMIC-IV)	AG	0.599	0.558-0.641	20.5	0.346	0.796	0.142
	ACAG	0.629	0.589-0.669	24.6	0.322	0.869	0.191
Hospital mortality (eICU-CRD)	AG	0.603	0.559-0.647	18.1	0.523	0.673	0.196
	ACAG	0.628	0.585-0.671	21.6	0.527	0.705	0.232
28-day mortality (MIMIC-IV))	AG	0.614	0.574-0.654	21.5	0.295	0.870	0.165
	ACAG	0.641	0.602-0.680	22.9	0.400	0.805	0.205

Abbreviation: AUC: area under curve, CI: confidence interval, AG: anion gap, ACAG: albumin corrected anion gap,

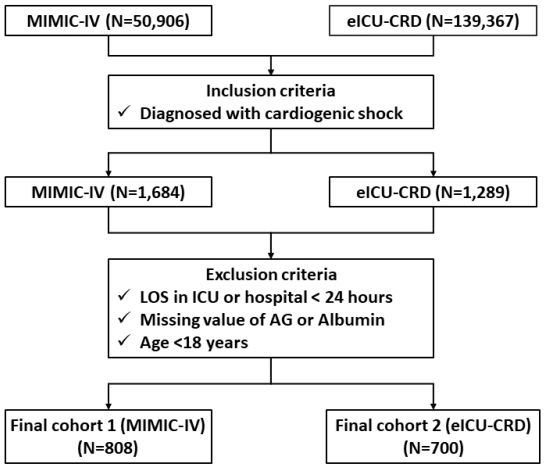
Table3: Association of ACAG and short-term all-cause mortality

	Crude Model		Model I		Model II	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
28-day mortality (MIMIC-IV cohort)						
ACAG (per 1 unit)	1.07 (1.06-1.09)	<0.001	1.08 (1.06-1.10)	<0.001	1.05 (1.03-1.07)	<0.001
Higher ACAG level	1.85 (1.48-2.32)	<0.001	1.90 (1.52-2.39)	<0.001	1.42 (1.11-1.83)	0.007
ICU mortality (MIMIC-IV cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.09)	<0.001	1.07 (1.05-1.09)	<0.001	1.04 (1.01-1.06)	0.005
Higher ACAG level	1.74 (1.33-2.28)	<0.001	1.87 (1.43-1.91)	<0.001	1.43 (1.05-1.93)	0.022
ICU mortality (eICU-CRD cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.08)	<0.001	1.07 (1.05-1.09)	<0.001	1.06 (1.03-1.09)	<0.001
Higher ACAG level	1.61 (1.22-2.11)	<0.001	1.65 (1.25-2.17)	<0.001	1.38 (1.02-1.86)	0.036
In-hospital mortality (MIMIC-IV cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.08)	<0.001	1.06 (1.04-1.08)	<0.001	1.04 (1.02-1.07)	<0.001
Higher ACAG level	1.51 (1.20-1.91)	<0.001	1.58 (1.25-2.01)	<0.001	1.31 (1.01-1.71)	0.041
In-hospital mortality (eICU-CRD cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.08)	<0.001	1.07 (1.05-1.09)	<0.001	1.05 (1.02-1.07)	<0.001
Higher ACAG level	1.81 (1.41-2.33)	<0.001	1.86 (1.44-2.39)	<0.001	1.47 (1.12-1.94)	0.006

Abbreviation: ACAG: albumin corrected anion gap, HR: hazard ratio, CI: confidence interval

Model I adjusted for age, gender, race, and weight/body mass index

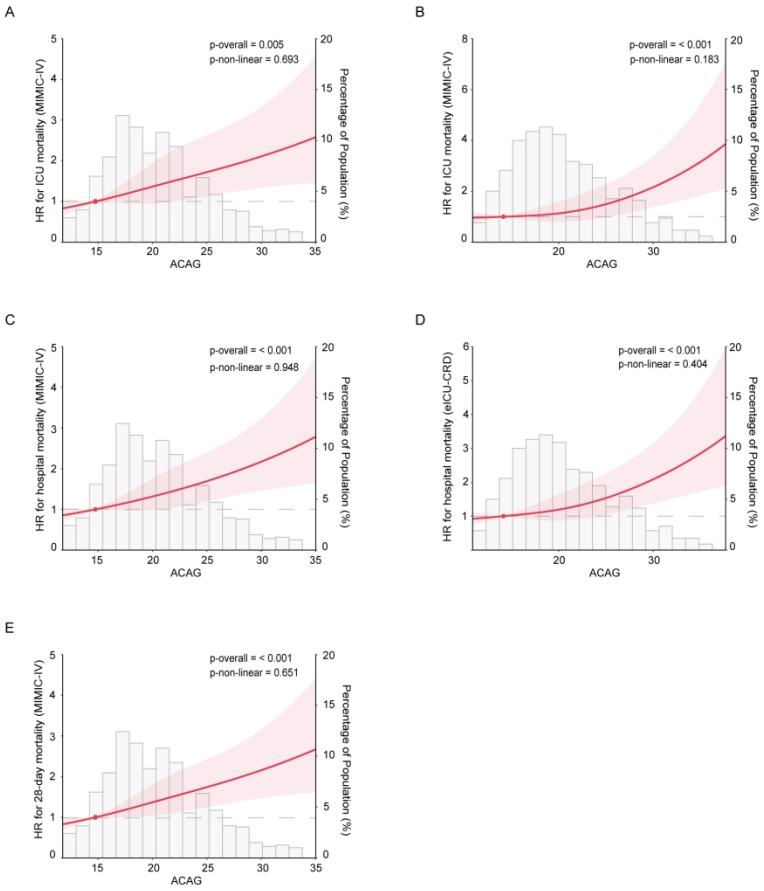
Model II adjusted for age, gender, race, weight/body mass index, acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular heart disease, diabetes, chronic obstructive pulmonary disease, acute kidney injury, SOFA score, mean blood pressure, oxygen saturation, potassium, chloride, creatine, and total bilirubin.



The flow chart of this study

338x190mm (96 x 96 DPI)

Fig.2



Restricted cubic spline for the associations between ACAG value and short-term mortality
Fig.2A and Fig.2B showed the ICU mortality while Fig.3C and Fig.3D showed the in-hospital mortality in MIMIC-IV and eICU-CRD cohort respectively. 28-day mortality was shown in Fig.2E.
The solid lines represent the adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CI) after multivariable adjustment in Model II.
Histograms represent the distribution of concentrations of ACAG in two cohorts.

174x234mm (300 x 300 DPI)

Albumin corrected anion gap is associated with the prognosis of cardiogenic shock: a multi-center retrospective study

Online Supplement material

eTable1: Baseline characteristics of enrolled patients stratified by hospital survival status in two cohorts

	MIMIC-IV cohort (n=808)				eICU-CRD cohort (n=700)			
	Overall (n=808)	Survivors (n=519)	Non-survivors (n=289)	p-value	Overall (n=700)	Survivors (n=440)	Non-survivors (n=260)	p-value
Demographic characteristics								
Age	70 (60, 80)	69 (59, 79)	74 (63, 81)	0.001*	67 (57, 76)	66 (55, 75)	70 (62, 79)	<0.001*
Gender				0.018*				0.4
Female	347 (43%)	207 (40%)	140 (48%)		255 (36%)	155 (35%)	100 (38%)	
Male	461 (57%)	312 (60%)	149 (52%)		445 (64%)	285 (65%)	160 (62%)	
Weight/BMI[a]	80 (68, 95)	80 (69, 95)	80 (66, 95)	0.7	28 (24, 33)	28 (24, 33)	28 (24, 33)	>0.9
Ethnicity				0.002*				>0.9
White	497 (62%)	336 (65%)	161 (56%)		531 (76%)	332 (75%)	199 (77%)	
Black	71 (8.8%)	51 (9.8%)	20 (6.9%)		83 (12%)	52 (12%)	31 (12%)	
Hispanic	19 (2.4%)	12 (2.3%)	7 (2.4%)		32 (4.6%)	20 (4.5%)	12 (4.6%)	
Asian	18 (2.2%)	13 (2.5%)	5 (1.7%)		19 (2.7%)	14 (3.2%)	5 (1.9%)	
Others/unknown	203 (25%)	107 (21%)	96 (33%)		35 (5.0%)	22 (5.0%)	13 (5.0%)	
Comorbidities								
AMI	349 (43%)	231 (45%)	118 (41%)	0.3	270 (39%)	181 (41%)	89 (34%)	0.070
Hypertension	241 (30%)	160 (31%)	81 (28%)	0.4	365 (52%)	226 (51%)	139 (53%)	0.6
Cardiomyopathy	206 (25%)	143 (28%)	63 (22%)	0.072	119 (17%)	80 (18%)	39 (15%)	0.3
Atrial fibrillation	393 (49%)	254 (49%)	139 (48%)	0.8	144 (21%)	88 (20%)	56 (22%)	0.6
VHD	293 (36%)	203 (39%)	90 (31%)	0.024*	99 (14%)	62 (14%)	37 (14%)	>0.9
AKI/ARF[a]	573 (71%)	334 (64%)	239 (83%)	<0.001*	323 (46%)	180 (41%)	143 (55%)	<0.001*
COPD	71 (8.8%)	46 (8.9%)	25 (8.7%)	>0.9	101 (14%)	56 (13%)	45 (17%)	0.10

Diabetes	283 (35%)	171 (33%)	112 (39%)	0.10	158 (23%)	94 (21%)	64 (25%)	0.3
Malignancy	80 (9.9%)	41 (7.9%)	39 (13%)	0.011*	16 (2.3%)	6 (1.4%)	10 (3.8%)	0.034*
SOFA	8 (5, 11)	7 (4, 10)	10 (7, 12)	<0.001*	8 (6, 11)	7 (5, 10)	10 (8, 13)	<0.001*
Vital signs								
Heart rate	90 (77, 108)	89 (75, 105)	92 (78, 111)	0.066	91 (78, 108)	90 (77, 105)	93 (78, 111)	0.088
Respiratory rate	20 (17, 24)	20 (17, 24)	21 (17, 26)	0.023*	20 (17, 25)	19 (16, 24)	20 (17, 25)	0.083
Systolic BP	111 (97, 129)	113 (98, 129)	110 (96, 125)	0.2	107 (91, 122)	107 (92, 12	107 (90, 126)	0.8
Mean BP	66 (54, 79)	67 (55, 79)	63 (52, 78)	0.022*	62 (50, 75)	62 (50, 73)	62 (50, 77)	0.3
Diastolic BP	79 (68, 91)	80 (69, 93)	78 (66, 90)	0.075	77 (65, 89)	76 (67, 88)	78 (64, 91)	0.4
SpO2	97 (94, 100)	97 (94, 100)	98 (94, 100)	0.4	97 (93, 100)	97 (94, 100)	98 (93, 100)	>0.9
Laboratory data								
White blood cell	13 (9, 17)	12 (9, 17)	13 (9, 19)	0.013*	12 (9, 18)	12 (9, 17)	13 (9, 20)	0.076
Hemoglobin	11.5 (9.8, 13.4)	11.8 (10.0, 13.7)	11.2 (9.4, 12.5)	<0.001*	12.1 (10.1, 13.9)	12.4 (10.4, 14.2)	11.6 (9.7, 13.4)	0.003*
Platelet	211 (152, 278)	216 (155, 282)	198 (146, 274)	0.076	196 (145, 260)	210 (157, 266)	182 (128, 242)	<0.001*
Sodium	138 (134, 141)	138 (134, 140)	138 (134, 141)	0.6	137 (134, 141)	137 (134, 140)	138 (134, 142)	0.13
Potassium	4.4 (3.9, 5.0)	4.4 (3.9, 4.9)	4.4 (3.8, 5.0)	>0.9	4.2 (3.7, 4.9)	4.2 (3.7, 4.8)	4.3 (3.7, 5.1)	0.15
Chloride	103 (98, 107)	103 (98, 107)	103 (98, 107)	0.6	103 (98, 107)	103 (99, 107)	103 (98, 107)	>0.9
Bicarbonate	20 (17, 23)	21 (18, 24)	20 (16, 23)	<0.001*	22 (18, 25)	22 (19, 25)	21 (17, 24)	0.002*
AG	17 (14, 21)	16 (14, 20)	18 (15, 22)	<0.001*	17 (13, 21)	16 (13, 19)	18 (14, 23)	<0.001*
Albumin	3.3 (2.9, 3.7)	3.4 (3.0, 3.7)	3.1 (2.7, 3.6)	<0.001*	3.0 (2.6, 3.5)	3.1 (2.7, 3.6)	2.9 (2.5, 3.3)	<0.001*
ACAG	20.0	19.0	21.0	<0.001*	19.9	19.0	22.0	<0.001*

	(17.0, 23.5)	(16.5, 22.5)	(18.0, 25.3)		(16.7, 24.2)	(16.2, 23.0)	(17.7, 27.0)	
Creatine	1.4 (1.0, 2.3)	1.4 (1.0, 2.1)	1.6 (1.1, 2.6)	<0.001*	1.5 (1.1, 2.4)	1.4 (1.1, 2.2)	1.6 (1.2, 2.4)	0.021*
Bilirubin	0.7 (0.4, 1.3)	0.7 (0.5, 1.2)	0.7 (0.4, 1.4)	0.4	0.8 (0.5, 1.4)	0.8 (0.5, 1.4)	0.9 (0.6, 1.5)	0.065

Abbreviation: BMI: body mass index, AMI: acute myocardial infarction, AKI: acute kidney injury, ARF: acute renal failure, COPD: chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, BP: blood pressure, AG: anion gap, ACAG albumin corrected anion gap, LOS: length of stay, ICU: intensive care unit

p<0.05*

a: body weight and acute kidney injury were shown in MIMIC-IV cohort while body mass index and acute renal failure were presented in eICU-CRD cohort due to data availability.

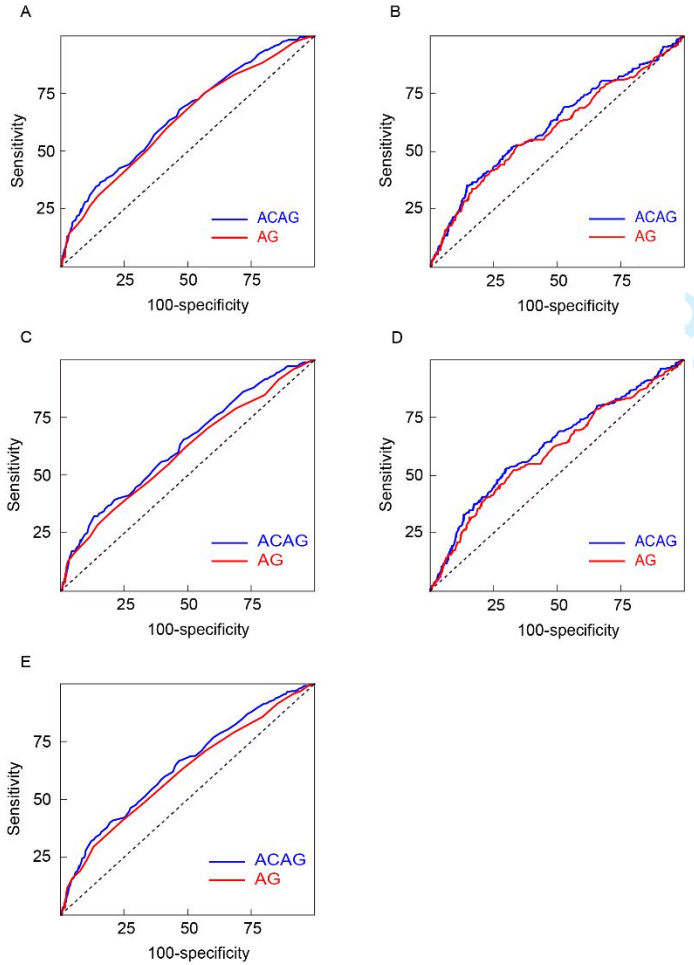
eTable2: Association of ACAG and earlier discharge alive in ICU

	Crude Model		Model I		Model II	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
LOS in ICU (MIMIC-IV cohort)						
ACAG	0.94 (0.92-0.95)	<0.001	0.94 (0.92-0.95)	<0.001	0.96 (0.94-0.98)	<0.001
Higher ACAG	0.62 (0.53-0.73)	<0.001	0.61 (0.52-0.72)	<0.001	0.77 (0.66-0.92)	0.004
LOS in ICU (eICU-CRD cohort)						
ACAG	0.96 (0.95-0.98)	<0.001	0.96 (0.94-0.98)	<0.001	0.97 (0.95-0.99)	0.001
Higher ACAG	0.74 (0.62-0.88)	<0.001	0.73 (0.61-0.88)	<0.001	0.85 (0.71-1.04)	0.140

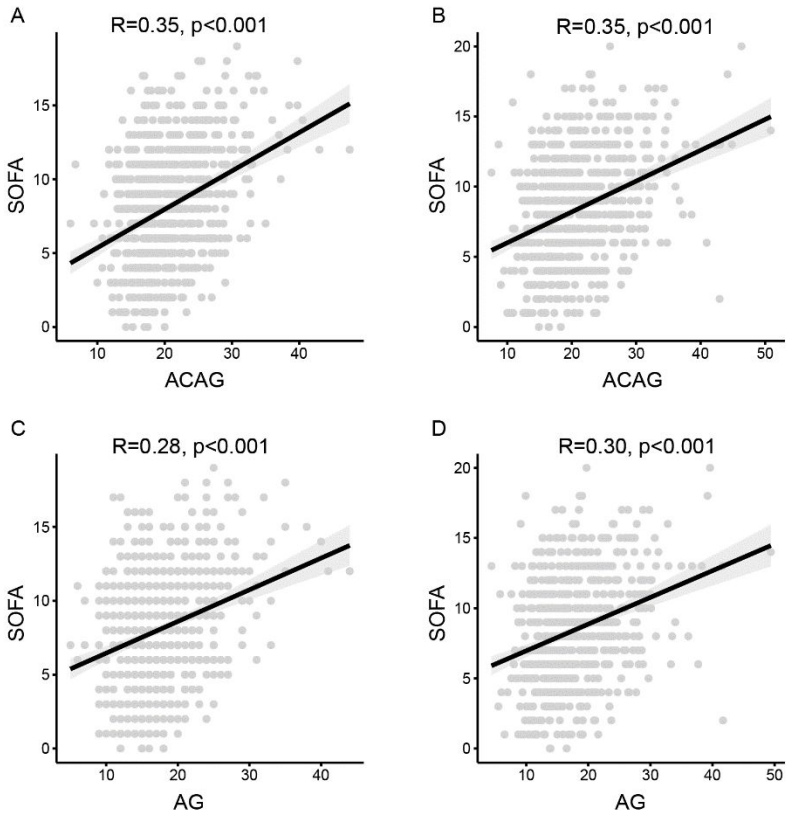
Model I adjusted for age, gender, race, and weight/body mass index

Model II adjusted for age, gender, race, weight/body mass index, acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular heart disease, diabetes, chronic obstructive pulmonary disease, acute kidney injury, SOFA score, mean blood pressure, oxygen saturation, potassium, chloride, creatinine, and total bilirubin.

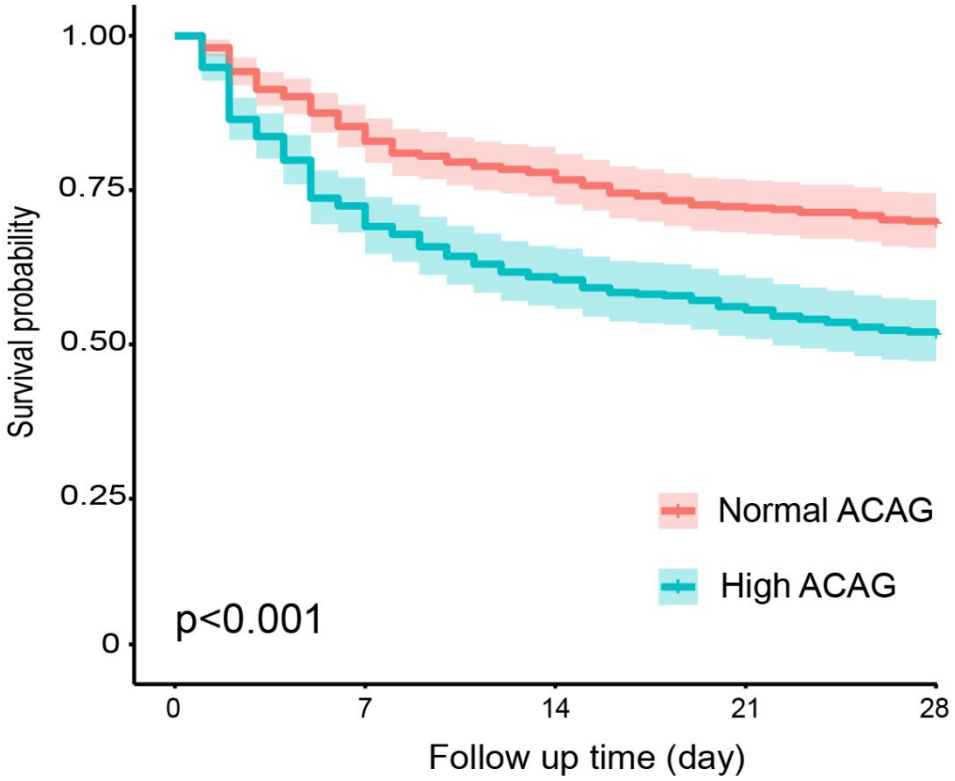
eFigure1: ROC curve analysis of AG, ACAG and ICU mortality (A: MIMIC-IV cohort; B: eICU-CRD cohort), in-hospital morality (C: MIMIC-IV cohort; D: eICU-CRD cohort), and 28-day mortality (E: MIMIC-IV cohort)



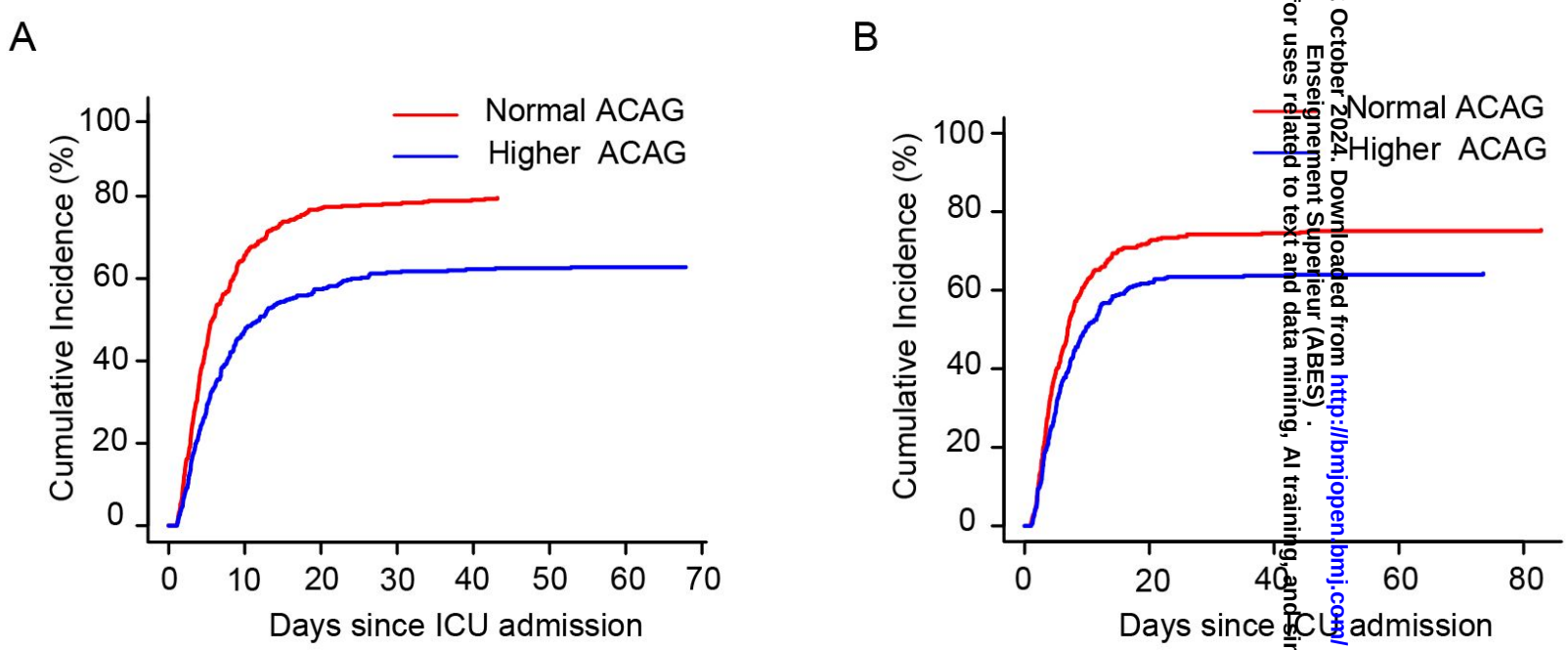
eFigure2: Pearson correlation analyses of AC/ACAG and SOFA score in MIMIC-IV cohort (A, C) and eICU-CRD cohort (B, D)



eFigure3: Kaplan–Meier survival curve of ACAG levels and 28-day all-cause mortality

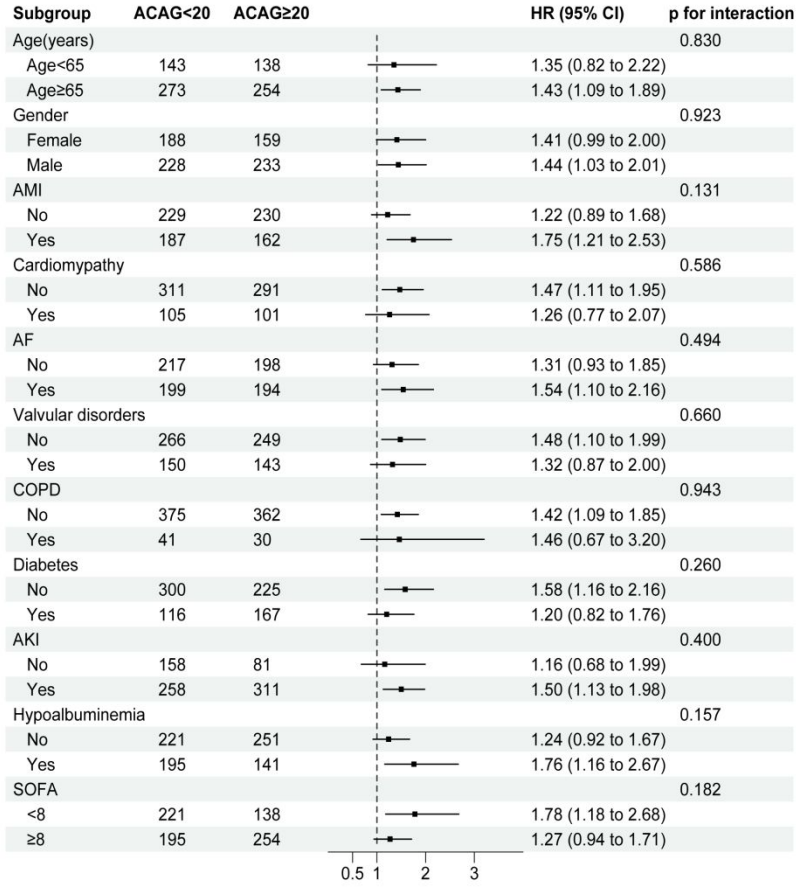


eFigure4: Cumulative incidence ratio of earlier discharge alive in the ICU in MIMIC-IV cohort (A) and eICU-CRD cohort (B)



eFigure5: Subgroup analysis

ACAG: albumin corrected anion gap, HR: hazard ratio, CI: confidence interval, AMI: acute myocardial infarction, AF:atrial fibrillation, COPD: chronic obstructive pulmonary disease, AKI: acute kidney injury, SOFA: Sequential Organ Failure Assessment



Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods	3

		of recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4
Bias	#9	Describe any efforts to address potential sources of bias	4
Study size	#10	Explain how the study size was arrived at	4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5
Statistical methods	#12c	Explain how missing data were addressed	5
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	5
Statistical methods	#12e	Describe any sensitivity analyses	5
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible,	6

		included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	6
Participants	#13c	Consider use of a flow diagram	6
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	6
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	4
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	7
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	7
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8

Discussion

Key results	#18	Summarise key results with reference to study objectives	8
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	9
Generalisability	#21	Discuss the generalisability (external validity) of the study results	10
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

 This checklist was completed on 01. November 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Albumin corrected anion gap is associated with the prognosis of cardiogenic shock: a multi-center retrospective study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-081597.R1
Article Type:	Original research
Date Submitted by the Author:	09-Jun-2024
Complete List of Authors:	Wang, Yuxing; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Tao, Yuhang; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Yuan, Ming; Zhejiang University School of Medicine Sir Run Run Shaw Hospital yu, pengcheng; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Zhang, Kai; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Ying, Hangying; Zhejiang University School of Medicine Sir Run Run Shaw Hospital jiang, ruhong; Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Emergency medicine, Intensive care
Keywords:	CARDIOLOGY, INTENSIVE & CRITICAL CARE, Cardiovascular Disease

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Albumin corrected anion gap is associated with the prognosis of cardiogenic shock: a multi-center retrospective study

Yuxing Wang[1*], Yuhang Tao[1*], Ming Yuan[1], Pengcheng Yu[1], Kai Zhang[1],Hangying Ying[1†], Ruhong Jiang[1†]

Affiliations:
1 Department of Cardiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

* Co-first authors contributed equally

† Co-corresponding authors contributed equally

Address for Corresponding Authors:
Hangying Ying, M.D.
Department of Cardiology, Sir Run Run Shaw Hospital
Zhejiang University School of Medicine
3 East Qingchun Road
Hangzhou, Zhejiang, 310016, P.R. China.
E-mail: yinghangying@zju.edu.cn

Ruhong Jiang, M.D.
Department of Cardiology, Sir Run Run Shaw Hospital
Zhejiang University School of Medicine
3 East Qingchun Road
Hangzhou, Zhejiang, 310016, P.R. China.
E-mail: jrh@zju.edu.cn

Declarations of interest: none

Abstract:

Objectives: We aimed to investigate the association between albumin corrected anion gap (ACAG) and the prognosis of cardiogenic shock (CS).

Design: A multi-center retrospective cohort study.

Setting: Data were collected from the Medical Information Mart for Intensive Care (MIMIC-IV) and eICU Collaborative Research Database (eICU-CRD) datasets.

Participants: A total of 808 and 700 individuals diagnosed with CS from MIMIC-IV and eICU-CRD respectively.

Primary and secondary outcome: The primary endpoint is short-term all-cause mortality including ICU, in-hospital, and 28-day mortality. The secondary endpoints are 28-day free from ICU and length of time intensive care needed.

Results: CS patients were divided into two groups according to the admission ACAG value: normal ACAG group (≤20 mmol/L) and high ACAG group (> 20 mmol/L). CS patients with a higher ACAG level exhibited increased short-term all cause mortality rates, including ICU mortality (MIMIC-IV cohort: adjusted HR:1.43, 95%CI=1.05-1.93, p=0.022; eICU-CRD cohort: adjusted HR:1.38, 95%CI=1.02-1.86, p=0.036), in-hospital mortality (MIMIC-IV cohort: adjusted HR:1.31, 95%CI=1.01-1.71, p=0.03; eICU-CRD cohort: adjusted HR:1.47, 95%CI=1.12-1.94, p=0.006), and 28-day mortality (adjusted HR: 1.42, 95%CI: 1.11-1.83, p=0.007). A positive linear correlation was observed between ACAG values and short-term mortality rates by restricted cubic splines. In comparison to AG, ACAG displayed a larger area under the curve for short-term mortality prediction. Besides, the duration of intensive care was longer while 28-day free from ICU was shorter in patients with a higher ACAG level in both cohorts.

Conclusion: ACAG value was independently and strongly associated with the prognosis of CS, which was superior than the conventional AG.

Strengths and limitations of this study:

1.This is the first study to explore the association between ACAG and the prognosis of CS.

2.CS patients are from a diverse and heterogeneous population with mixed etiologies from two distinct high-quality datasets.

3. As a nature of retrospective, the selection bias cannot be avoided and detailed information about cardiac function are not available.

Keywords: Albumin corrected anion gap, anion gap, cardiogenic shock, intensive care unit, acute cardiovascular care

1.Introduction

Cardiogenic shock (CS), a life-threatening clinical condition, is characterized by acute end-organ hypoperfusion resulting from reduced cardiac output [1]. Despite substantial progress achieved in CS management over the past three decades, the mortality rate of CS remains unexpectedly high, making it a formidable challenge within the intensive care unit (ICU)[2]. It is worth noting the one-year mortality rate in CS patients is approximately 50%-60%, with a substantial portion of cases (70% to 80%) occurring within the initial 30 to 60 days[3]. Therefore, early identification of CS patients with a poor prognosis holds paramount clinical importance for tailoring effective risk reduction strategies.

Anion gap (AG), a biomarker reflecting unmeasured anions, is calculated using the following formula: AG (mmol/l) = (sodium + potassium) - (chloride + bicarbonate)[4]. It is extensively utilized to assess the acid-base disorders and to evaluate the prognosis of various diseases in clinical practice[5]. Nevertheless, the accuracy of AG in predicting the prognosis of patients in the ICU remains debatable. While some studies have suggested that AG can effectively predict short-term mortality in patients with critical illness, others have yielded inconclusive results[6]. In 1985, Gabow observed that the AG value could be influenced by serum albumin levels[7]. Given that albumin carries a negative charge, any fluctuations in albumin levels can impact the final AG measurement[8]. Consequently, for patients with critical illness in the ICU, AG may sometimes appear to be pseudo-normal since hypoalbuminemia is very common in the setting of intensive care[9]. In order to address this problem, Figge J et al. introduced the concept of the albumin corrected anion gap (ACAG) in 1998[10]. Hatherill et al. discovered that ACAG exhibited superior predictive capabilities for metabolic acidosis compared to AG in pediatric patients with shock[11]. Furthermore, numerous studies have demonstrated the association between ACAG and the prognosis of critical conditions including cardiac arrest[12], acute myocardial infarction[13], acute kidney injury[14], sepsis[15], and acute pancreatitis[16].

However, to the best of our knowledge, the relationship between ACAG and the prognosis of CS has not been investigated. Furthermore, it remains uncertain whether ACAG offers an improved predictive capability for short-term mortality when compared to AG. Therefore, in this study, our objectives are as follows: 1) to exam the correlation between ACAG and short-term mortality in patients with CS; 2) to compare the admission values of AG and ACAG for predicting CS mortality and assessing the severity.

2.Materials and methods

2.1 Datasets and ethics

In this study, we utilized the following two publicly-accessible dataset: (1) Medical Information Mart for Intensive Care IV/MIMIC-IV v2.2 dataset (2008–2019)[17]; (2) eICU Collaborative Research Database/eICU-CRD dataset (2014–2015)[18]. MIMIC-IV is an updated version of the MIMIC-III, containing de-personalized data of 73,181 ICU stays for 50,906 unique patients at the Beth Israel Deaconess Medical Center between 2008 and 2019 (a single center dataset). The eICU-CRD is also a de-identified database and

contains 200,859 ICU stays for 139,367 unique patients admitted to 335 ICUs at 208 hospitals across the United States (a multi-center dataset). Importantly, as there is no shared hospital involvement between the MIMIC and eICU program, the eICU-CRD dataset remains entirely independent of MIMIC-IV.

The first author has successfully completed the online course and passed the Examination for Protecting Human Research Participants (Record ID: 11841860). Hence, he was granted permission to extract data from the two datasets mentioned above. Given that all identifying information had been removed, our study was considered exempt from ethical review by the institutional research board. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

2.2 Study population and endpoints

This is a multi-center, retrospective, observational study.. CS was defined based on the diagnostic codes from the MIMIC-IV and eICU-CRD databases. These codes are in accordance with the standard clinical definitions. We excluded those who aged younger than 18 years old, length of stay (LOS) in ICU or hospital less than 24 hours, and lack of AG or albumin value within the first 24 hours of ICU admission. In cases of patients with multiple ICU admissions, we only included the first ICU stay for analysis. AG was calculated by the following formula: AG (mmol/l) = (sodium + potassium) - (chloride + bicarbonate). ACAG was determined as follows: ACAG (mmol/l) = [4.4-{albumin(g/dl)}] *2.5 + AG[11]. Additionally, we categorized the enrolled patients into two groups according to the admission values of ACAG based on the previous studies[14,15]: the normal ACAG group (< 20 mmol/l) and the higher ACAG group (≥20 mmol/l).

The primary endpoint of this study was short-term all-cause mortality, which included ICU mortality, in-hospital mortality, as well as 28-day mortality (not available in eICU-CRD). The secondary endpoints encompassed 28-day free from ICU (not available in eICU-CRD) and LOS in ICU. 28-day free from ICU is a composite outcome which integrates both mortality and LOS in ICU. It was calculated as 28 minus the days spent in the ICU during the first 28 day and the dead patients were assigned the value of zero. LOS in ICU was defined as the duration that intensive care was required and was calculated based on the time to discharge alive from ICU, with death in ICU as a completing risk.

2.3 Variable extraction

We extracted the variables with structured query language in Navicat Premium (version 15.0.12). The codes for data extraction were based on https://github.com/MIT-LCP/mimic-code and https://github.com/MIT-LCP/eicu-code. For each patient, we collected a wide range of variables including demographic information, comorbidities, Sequential Organ Failure Assessment (SOFA) score, vital signs, and laboratory data. Demographic information included age at admission, gender, weight/body mass index, and race. Acute myocardial infarction, hypertension, atrial fibrillation, valvular disease,

cardiomyopathy, acute kidney injury/acute renal failure, chronic obstructive pulmonary disease, diabetes, and malignancy were identified as comorbidities. Vital signs encompassed heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, and oxygen saturation. Additionally, we collected laboratory data, which included white blood cell, hemoglobin, platelet, bilirubin, creatinine, sodium, potassium, chloride, bicarbonate, albumin, AG, and ACAG.

All vital signs, laboratory data, and the SOFA score were extracted and calculated within the first 24 hours of ICU admission. If a variable was measured multiple times within the initial 24 hours of ICU admission, we used the first recorded value for analysis.

2.4 Statistical analysis

To address missing values, we initially conducted multiple imputation using chained equations. In the MIMIC-IV cohort, the percentage of incomplete cases was 3.1%, and in the eICU-CRD cohort, it was 16.7%. Accordingly, we generated 5 datasets for MIMIC-IV and 17 datasets for eICU-CRD for further analysis and the results were combined according to the Rubin's rules[19].

We compared the baseline characteristics of the enrolled patients based on their hospital survival status and ACAG levels. Categorical variables were presented as numbers plus percentages and compared using Pearson's chi-square test. Shapiro-Wilk tests were performed to assess the distribution of continues variables. Since all continuous variables in two cohorts were both skewed-distributed, they were expressed as median [inter-quartile range (IQR)] and compared by Wilcoxon rank sum test.

Pearson correlation analyses were utilized to investigate the association between AG/ACAG values and the SOFA score. The ability of AG and ACAG to predict short-term mortality was compared by the area under curves (AUC) of the receiver operating characteristic curves (ROC). Z test was used to compare the predictive ability of AG and ACAG following the method of Delong et al[20]. Threshold values were determined by identifying the values that provided the highest specificity and sensitivity by calculating the Youden Index.

To evaluate the relationship between ACAG and ICU, in-hospital, and 28-day all-cause mortality, ACAG was initially analyzed as a categorical variable (normal ACAG group and high ACAG group) and then as a continuous variable (ACAG values). Kaplan-Meier survival curves and Cox proportional hazards regression models were employed to calculate hazard ratios (HR) and 95% confidence intervals. Furthermore, we investigated the association between ACAG values and short-term mortality using restricted cubic splines with four knots at 25%, 50%, 75% and 95%. Based on the previous studies and theoretical considerations, we selected clinically relevant confounding factors as covariates in the regression model. Variance inflation factor was used to test the multicollinearity between each covariate and the covariates with a high degree of collinearity (variance inflation factor > 5) were removed from the regression model. Finally, we constructed two models for adjustments. In model I, we adjusted for confounders including age, gender, race, and weight/body mass index. In model II, we further adjusted acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular heart disease, diabetes, chronic obstructive pulmonary disease, acute kidney injury,

SOFA score, mean blood pressure, oxygen saturation, potassium, chloride, creatinine, and total bilirubin.

Since ICU expire resulted in a shorter LOS, the correlation between ACAG and LOS in ICU was analyzed using the Fine-Gray competing risk model. In this model, a higher HR for earlier alive ICU discharge indicated a shorter LOS while a lower HR indicated a longer LOS in ICU.

Subgroup analyses were conducted to evaluate the relationship between ACAG levels and 28-day all-cause mortality within various subpopulations, including age (<65 years, ≥65 years), gender (male, female), acute myocardial infarction, atrial fibrillation, valvular disorders, cardiomyopathy, chronic obstructive pulmonary disease, diabetes mellitus, acute kidney injury/acute renal failure, hypoalbuminemia (<3.5 g/dL, ≥3.5 g/dL), and SOFA score (<8, ≥8) using the stratified multivariable Cox proportional hazards model.

All statistical analysis were performed with R version 4.1.2. A P value < 0.05 for two sides is considered statistical significance.

3.Results

3.1 Baseline characteristics of enrolled patients

The flowchart of our study was presented in *Fig.1*. The differences between included and excluded patients were summarized in *eTable1*.Overall, a total of 808 and 700 individuals diagnosed with CS were enrolled from the MIMIC-IV dataset and eICU-CRD dataset respectively. The short-term mortality rates of CS patients were similar in both cohorts. Specifically, the ICU mortality rates were 29%, 30% while in-hospital mortality rates were 36%, 37% in MIMIC-IV cohort and eICU-CRD cohort, respectively. In the MIMIC-IV cohort, the 28-day all-cause mortality rates were 39%.

Table1 summarized the baseline characteristic of enrolled patients stratified according to the ACAG level. Obviously, patients with a higher ACAG level exhibited a greater predisposition to acute kidney injury/acute renal failure and had elevated values of the SOFA score, white blood cell count, sodium, potassium, creatinine, and total bilirubin. In comparison to the normal ACAG group, the short-term mortality rates (including ICU mortality, in-hospital mortality, and 28-day mortality) were significantly higher while the 28-day free from ICU were notably shorter (20 [2-25] vs 9 [0-23], p<0.001) in patients with a higher ACAG level.

Furthermore, the baseline characteristic of enrolled patients stratified according to the hospital survival status were summarized in *eTable2*. Notably, we found that the ACAG value was significantly higher in the group of patients who did not survive in hospital, both in the MIMIC-IV cohort (21.0 [18.0-25.3] vs 19.0 [16.5-22.5], p<0.001) and the eICU-CRD cohort (22.0 [17.7-27.0] vs 19.0 [16.2-23.0], p<0.001). Additionally, among the non-survivors during hospitalization, we observed a higher rate of acute kidney injury/acute renal failure, lower values of hemoglobin, albumin, bicarbonate, and higher levels of age, creatinine, SOFA score.

3.2 Comparison of AG and ACAG for mortality prediction and severity

assessment

The predictive performance of ACAG versus AG for ICU, in-hospital, and 28-day all-cause mortality was assessed through ROC curve analysis (e*Fig.1*). As shown in *Table2*, ACAG outperformed AG for short-term mortality prediction, including ICU mortality (MIMIC-IV cohort: AUC: 0.654 [95%CI: 0.613-0.696] vs 0.632 [95%CI: 0.589-0.674], Z = 2.99, p= 0.003; eICU-CRD cohort: AUC: 0.613 [95%CI: 0.566-0.660] vs 0.594 [95%CI: 0.546-0.642], Z = 2.99, p=0.003), in-hospital mortality (MIMIC-IV cohort: ACU: 0.629 [95%CI: 0.589-0.669] vs 0.599 [95%CI: 0.558-0.641], Z =4.13, p< 0.001; eICU-CRD cohort: AUC: 0.628 [95%CI: 0.585-0.671] vs 0.603 [95%CI: 0.559-0.647], Z = 3.92, p< 0.001), and 28-day mortality prediction (MIMIC-IV cohort: AUC: 0.641 [95%CI:0.602-0.680] vs 0.614 [95%CI: 0.574-0.654], Z = 3.95, p< 0.001).

Additionally, we conducted correlation analyses to investigate the association between AG/ACAG values and the SOFA score using Pearson's method. as depicted in eFigure2. In both cohorts, we observed positive correlations between both AG and ACAG values and the SOFA score (both p-values < 0.001). Intriguingly, we found that the correlation coefficient for ACAG was significantly higher than that of AG (MIMIC-IV cohort: AG: R=0.28 vs ACAG: R=0.35; eICU-CRD cohort: AG: R=0.30 vs ACAG: R=0.35). These findings highlight the stronger positive correlation between ACAG and the SOFA score, underscoring its potential as a valuable prognostic indicator.

3.3 Increased ACAG level correlates with higher risk of short-term morality

As demonstrated in *eFig.3*, the Kaplan–Meier survival curve showed an increased 28-day all-cause mortality rate among patients with a higher ACAG level (HR: 1.85, 95%CI: 1.48-2.32, log-rank test, p-value <0.001) in the MIMIC-IV cohort. Furthermore, even after adjusting for confounding variables in model II, we observed that the individuals with an evaluated ACAG level still exhibited an increased 28-day all-cause mortality rate (adjusted HR: 1.42, 95%CI: 1.11-1.83, p=0.007).

Similarly, the relationship between ACAG levels and ICU/in-hospital mortality was assessed through multivariable Cox regression models as well. As presented in *Table3*, in comparison to the normal ACAG group, the results showed that the CS patients with a higher ACAG level experienced increased rates of ICU mortality (MIMIC-IV cohort: adjusted HR:1.43, 95%CI=1.05-1.93, p=0.022; eICU-CRD cohort: adjusted HR:1.38, 95%CI=1.02-1.86, p=0.036) and in-hospital mortality (MIMIC-IV cohort: adjusted HR:1.31, 95%CI=1.01-1.71, p=0.03; eICU-CRD cohort: adjusted HR:1.47, 95%CI=1.12-1.94, p=0.006).

3.4 Linear relationship of ACAG value and short-term all-cause mortality

We extended our analysis to assess the association between ACAG values and short-term all-cause mortality rates. As presented in *Table3*, the adjusted HRs with 95%CI were 1.05 (1.03-1.07) for 28-day mortality, 1.04 (1.01-1.06) for ICU mortality, and 1.04 (1.02-1.07) for in-hospital mortality in the MIMIC-IV cohort while 1.06 (1.03-1.09) for ICU mortality and 1.05 (1.02-1.07) for in-hospital mortality in the eICU-CRD cohort respectively.

To further investigate the relationship between ACAG values and short-term all-cause mortality rates, we utilized the adjusted restricted cubic splines. As shown in *Fig.2*, we observed a linear correlation between ACAG and short-term all-cause mortality, which includes 28-day mortality (MIMIC-IV cohort: p for overall<0.001, p for non-linear=0.651), ICU mortality (MIMIC-IV cohort: p for overall<0.001, p for non-linear=0.693; eICU-CRD cohort: p for overall<0.001, p for non-linear=0.183), and in-hospital mortality (MIMIC-IV cohort: p for overall<0.001, p for non-linear=0.948; eICU-CRD cohort: p for overall<0.001, p for non-linear=0.404) in both cohorts. These findings suggest that a 1-unit increase in ACAG value is associated with approximately 5% increase in short-term all-cause mortality rates among patients with CS.

3.5 Association of ACAG and earlier alive discharge in ICU

Cumulative incidence ratio (CIR) of earlier discharge alive in ICU among ACAG levels was shown in *eFig.4*. Obviously, the unadjusted CIR for earlier alive discharge in ICU was significantly higher in lower ACAG group. The robustness of the results was further confirmed using Fine-Gray competing risk models after adjusting for confounding variables (e*Table3*). In the MIMIC-IV cohort, the adjusted HR (95%CI) for the relationship between ACAG level and earlier alive discharge in ICU was 0.77 (95% CI= 0.65–0.92; p = 0.004). However, in the eICU-CRD cohort, this relationship did not reach statistical significance (adjusted HR: 0.85, 0.69–1.04; p = 0.140).

Additionally, ACAG was analyzed as a continuous variable. Intriguingly, the association between ACAG value and earlier discharge alive was statistically significant in both cohorts, with adjusted HRs (95%CI) of 0.96 (95% CI=0.94-0.98; p <0.001) in the MIMIC-IV cohort and 0.97 (95% CI=0.95-0.99; p=0.001) in the eICU-CRD cohort. In summary, the ACAG value was inversely associated with earlier discharge alive in the ICU for patients with CS.

3.6 Subgroup analysis

Subgroup analysis was conducted to assess the stability of the consistency for the relationship between ACAG levels and 28-day all-cause mortality across various subpopulations, including age group (<65 years, ≥65 years), gender group (male, female), SOFA score (<8, ≥8), and different clinical conditions such as acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular disorders, chronic obstructive pulmonary disease, diabetes mellitus, acute kidney injury, hypoalbuminemia (<3.5 g/dL, ≥3.5 g/dL). Adjustments for confounding factors were made as in Model II. As depicted in e*Fig.5*, all p-values for interaction tests within different subgroups were greater than 0.05, indicating that the relationship between ACAG level and 28-day all-cause mortality remained stable and consistent across the various subpopulations.

4.Discussion

In this large-sample retrospective study based on two distinct public-accessible datasets, we investigate the association of ACAG, a novel biomarker indicating metabolic acid load, and the short-term prognosis of CS patients with mixed etiologies. The main findings of our study are as follows: (1) ACAG is strongly and independently associated

with short-term all-cause mortality rates (including ICU, in-hospital, and 28-day mortality) and the duration of intensive care required in patients with CS, even after adjusting for disease severity using SOFA score; (2) ACAG outperforms AG in its ability to predict short-term mortality and evaluate the severity of CS.

It is widely acknowledged that metabolic acidosis is a frequent event in the setting of intensive care and has been consistently demonstrated to be associated with adverse outcomes in individuals with critical illness[21]. Notably, in patients with severe cardiovascular disorders, particularly those suffering from CS, acidemia may trigger a detrimental cycle via impairing cardiac contractile function, inducing malignant arrhythmias, and exacerbating circulatory failure[22]. Additionally, severe acidemia may further compromise the responses to catecholamines of cardiovascular systems and weaken the effectiveness of vasopressors to reverse hypotension[23]. A prior study has demonstrated that the severity of acidosis is strongly and positively correlated with both the degree of shock and short-term mortality rates in CS patients[24].

As one of the simplest methods for assessing acid-base balance, the anion gap (AG) is a widely used biomarker in clinical practice. The relationship between AG and short-term mortality in patients with critical illness has been extensively investigated[25]. A previous study demonstrated a J-shaped association between AG value and the 30-day all-cause mortality rate in patients with CS based on MIMIC-III dataset[26]. Similarly, our study revealed that AG values were significantly higher in non-survivors when compared to survivors (MIMIC-IV cohort: 18 [15-22] vs 16 [14-20], p<0.001; eICU-CRD cohort: 18 [14-23] vs 16 [13-19], p<0.001) in our study. Moreover, AG has also been used for risk stratification in the setting of acute cardiovascular care. Recently, a study has combined the AG and SOFA to create the AG-SOFA score, which displayed improved predictive capabilities for short-term mortality in cardiovascular intensive care units[27]. Similarly, Eric et al incorporated AG into the BOS,MA2 score and exhibited superior performance than other pre-existing risk scores systems for CS prognostication[28]. However, the physiological AG primarily consists of inorganic phosphate and albuminate, which is a weak anion derived from serum albumin[5]. Given the involvement of albumin in the acid-base equilibrium, it may perplex the interpretation of acid-base data[29]. Theoretically, hypoalbuminemia can lead to a decrease in albuminate levels, resulting in a reduction in AG values[10]. Therefore, in the case of a patient with hypoalbuminemia and a normal AG value, it might indicate the presence of plasma acids. Similarly, we might underestimate the severity of metabolic acidosis based on the AG values for patients with low albumin levels. Notably, hypoalbuminemia is very frequent among patients with critical illness and has been demonstrated to be associated with unfavorable outcomes including higher rates of short-term mortality and longer LOS in ICU. The incidence of hypoalbuminemia is striking in patients with CS, with a reported rate of 75% from the previous CardShock study[30]. Similarly, our study also observed an exceptionally high frequency of hypoalbuminemia in patients with CS. Specifically, the incidence of hypoalbuminemia (defined as albumin < 3.5 g/dL) is 58.4% (472/808) in the MIMIC-IV cohort and 74.1% (519/700) in the eICU-CRD cohort respectively. Furthermore, a recent study has established that serum albumin is an independent predictor for short-term mortality in CS patients [20]. Likewise, in this study, we found that the value of albumin

was significantly lower in hospital death group than survival group (MIMIC-IV cohort: 3.4 [3.0-3.7] vs 3.1 [2.7-3.6], p<0.001; eICU-CRD cohort: 3.1 [2.7-3.6] vs 2.9 [2.5-3.3], p<0.001).

ACAG, which combines the AG and serum albumin, has been proposed as a replacement for AG in differentiating acidosis caused by acid load or base deficit from a panel of expert's consensus about metabolic acidosis management[31]. As a ubiquitous abnormality in patients with critical illness, hypoalbuminemia has been demonstrated to complicate the interpretation of acid–base data when using diagnostic methods based on base excess or plasma bicarbonate concentration alongside AG [29]. In the presence of hypoalbuminemia, taking albumin levels into account can reveal the presence of plasma acid, which might otherwise be overlooked when relying solely on AG or base excess values. Previous studies have demonstrated that ACAG is a superior predictor compared to conventional AG for short-term prognosis prediction in patients with critical illness like cardiopulmonary arrest[12], acute myocardial infarction[13], and sepsis[15]. Therefore, we hypothesized that ACAG may perform better than AG, particularly in a population at high risk of metabolic acidosis and hypoalbuminemia. As previously discussed, patients with CS are not only prone to hypoalbuminemia, but are also susceptible to metabolic acidosis. Hence, we posited that ACAG might outperform AG for risk stratification in the setting of CS. In this study, we compared AG and ACAG for mortality prediction and severity assessment for CS patients in two cohorts. Through the ROC curve analysis, we found that ACAG exhibited the highest AUC and Youden's index for short-term morality prediction in both cohorts, suggesting the better short-term mortality predicting capacity than AG for CS. Furthermore, using the Spearman's methods, we discovered that both AG and ACAG were positively correlated with the SOFA score. Importantly, the correlation coefficients with the SOFA score were significantly higher for ACAG when compared to AG. Taken together, our findings support the superiority of ACAG in predicting prognosis and estimating disease severity in patients with CS.

As a medical emergency requiring prompt evaluation and intervention, the mortality risk of CS is highest during the initial 48 hours following the onset of shock[32]. Therefore, mortality assessment in CS patients should be performed as early as possible after ICU admission. Given the rapid and widespread availability of AG and albumin in clinical practice, we recommend the inclusion of baseline ACAG levels in the prognostic biomarkers for patients with CS.

Indeed, our study has notable strengths. Firstly, it represents the pioneering study to explore the association between ACAG and the prognosis of CS. Second, the CS patients are from a diverse and heterogeneous patient population with mixed etiologies, enhancing its relevance and applicability to real-world clinical scenarios. Third, the data in this study are derived from two distinct high-quality datasets and the results are consistent with each other. However, several limitations of this study are deserved discussion. First, as the nature of retrospective, selection bias cannot be avoided. Second, detailed information about cardiac function (like left ventricular ejection fraction, ventricular size) and other important cardiac biomarkers (like troponin, N-terminal pro brain natriuretic peptide) are not included in this study due to a large amount of missing data. Third, we could not calculate CS stages of Society for Cardiovascular Angiography

and Interventions accurately due to specific data limitations in the MIMIC-IV and eICU databases. Fourth, the association between ACAG and the short-term mortality are established based on the first ACAG value within the first 24h of ICU admission. Monitoring the dynamic changes of ACAG may be valuable for patients with CS. Further studies are needed to explore the relationship between the dynamic changes of ACAG and mortality of CS.

5.Conclusion

In conclusion, we found that the baseline ACAG value following ICU admission independently predicts the short-term mortality in patients with CS, which is better than AG. Given the high mortality risk of CS during the early phase of ICU admission, baseline ACAG value may help clinicians to identify patients at high risk of mortality. Therefore, we propose to incorporate the baseline ACAG into the risk stratification systems for CS.

Data availability

The datasets used in this study are available from the corresponding author upon reasonable request.

Funding

None

Author contributions

Yuxing Wang: Conceptualization, Formal analysis, Investigation, Software, Visualization, Writing - original draft, Data curation, Methodology, Resources. Yuhang Tao: Investigation, Software, Visualization, Writing - original draft. Ming Yuan: Writing - review & editing. Pengcheng Yu: Writing - review & editing. Kai Zhang: Writing - review & editing. Hangying Ying: Project administration, Supervision Validation, and Writing - review & editing. Ruhong Jiang: Project administration, Supervision Validation, and Writing - review & editing.

Declaration of Competing Interest

None

Reference:

1 Van Diepen S, Katz JN, Albert NM, *et al.* Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation*. 2017;136. doi: 10.1161/CIR.0000000000000525

2 Hunziker L, Radovanovic D, Jeger R, *et al.* Twenty-Year Trends in the Incidence and Outcome of Cardiogenic Shock in AMIS Plus Registry. *Circ: Cardiovascular Interventions*. 2019;12:e007293.

3 Berg DD, Bohula EA, Morrow DA. Epidemiology and causes of cardiogenic shock.

Current Opinion in Critical Care. 2021;27:401–8.

4 Posen AK, Paloucek FP, Petzel R. Anion gap physiology and faults of the correction formula. *American Journal of Health-System Pharmacy*. 2022;79:446–51.

5 Kraut JA, Madias NE. Serum Anion Gap: Its Uses and Limitations in Clinical Medicine. *Clinical Journal of the American Society of Nephrology*. 2007;2:162–74.

6 Rocktaeschel J, Morimatsu H, Uchino S, *et al.* Unmeasured anions in critically ill patients: Can they predict mortality?*: *Critical Care Medicine*. 2003;31:2131–6.

7 Gabow PA. Disorders associated with an altered anion gap. *Kidney International*. 1985;27:472–83.

8 Figge J, Bellomo R, Egi M. Quantitative relationships among plasma lactate, inorganic phosphorus, albumin, unmeasured anions and the anion gap in lactic acidosis. *Journal of Critical Care*. 2018;44:101–10.

9 Gatta A, Verardo A, Bolognesi M. Hypoalbuminemia. *Intern Emerg Med*. 2012;7:193–9.

10 Figge J, Jabor A, Kazda A, *et al.* Anion gap and hypoalbuminemia: *Critical Care Medicine*. 1998;26:1807–10.

11 Hatherill M. Correction of the anion gap for albumin in order to detect occult tissue anions in shock. *Archives of Disease in Childhood*. 2002;87:526–9.

12 Hagiwara S, Oshima K, Furukawa K, *et al.* The Significance of Albumin Corrected Anion Gap in Patients with Cardiopulmonary Arrest. *Ann Thorac Cardiovasc Surg*. 2013;19:283–8.

13 Jian L. Association between albumin corrected anion gap and 30-day all-cause mortality of critically ill patients with acute myocardial infarction: a retrospective analysis based on the MIMIC-IV database. 2023.

14 Zhong L, Xie B, Ji X-W, *et al.* The association between albumin corrected anion gap and ICU mortality in acute kidney injury patients requiring continuous renal replacement therapy. *Intern Emerg Med*. 2022;17:2315–22.

15 Hu T, Zhang Z, Jiang Y. Albumin corrected anion gap for predicting in-hospital mortality among intensive care patients with sepsis: A retrospective propensity score matching analysis. *Clinica Chimica Acta*. 2021;521:272–7.

16 Li P, Shi L, Yan X, *et al.* Albumin Corrected Anion Gap and the Risk of in-Hospital Mortality in Patients with Acute Pancreatitis: A Retrospective Cohort Study. *JIR*. 2023;Volume 16:2415–22.

17 Johnson AEW, Bulgarelli L, Shen L, *et al.* MIMIC-IV, a freely accessible electronic health record dataset. *Sci Data*. 2023;10:1.

18 Pollard TJ, Johnson AEW, Raffa JD, *et al.* The eICU Collaborative Research Database, a freely available multi-center database for critical care research. *Sci Data*. 2018;5:180178.

19 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statist Med*. 2011;30:377–99.

20 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach. *Biometrics*. 1988;44:837.

21 Gunnerson KJ, Kellum JA. Acid–base and electrolyte analysis in critically ill patients: are we ready for the new millennium?: *Current Opinion in Critical Care*. 2003;9:468–73.

22 Kraut JA, Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. *Nat Rev Nephrol*. 2010;6:274–85.

23 Jentzer JC, Kashani KB, Wiley BM, *et al.* Laboratory Markers of Acidosis and Mortality in Cardiogenic Shock: Developing a Definition of Hemometabolic Shock. *Shock*. 2022;57:31–40.

24 Jentzer JC, Schrage B, Patel PC, *et al.* Association Between the Acidemia, Lactic Acidosis, and Shock Severity With Outcomes in Patients With Cardiogenic Shock. *JAHA*. 2022;11:e024932.

25 Glasmacher SA, Stones W. Anion gap as a prognostic tool for risk stratification in critically ill patients – a systematic review and meta-analysis. *BMC Anesthesiol*. 2015;16:68.

26 Zhang T, Wang J, Li X. Association Between Anion Gap and Mortality in Critically Ill Patients with Cardiogenic Shock. *IJGM*. 2021;Volume 14:4765–73.

27 Zhou Y-H, Pang S, Miao G-R, *et al.* Combining the anion gap with the sequential organ failure assessment score to evaluate the short-term prognosis of patients in the cardiac intensive care unit. *International Journal of Cardiology*. 2023;370:381–7.

28 Yamga E, Mantena S, Rosen D, *et al.* Optimized Risk Score to Predict Mortality in Patients With Cardiogenic Shock in the Cardiac Intensive Care Unit. *JAHA*. 2023;12:e029232.

29 Fencl V, Jabor A, Kazda A, *et al.* Diagnosis of Metabolic Acid–Base Disturbances in Critically Ill Patients. *Am J Respir Crit Care Med*. 2000;162:2246–51.

30 Jäntti T, Tarvasmäki T, Harjola V-P, *et al.* Hypoalbuminemia is a frequent marker of increased mortality in cardiogenic shock. *PLoS ONE*. 2019;14:e0217006.

31 for the Société de Réanimation de Langue Française (SRLF), the Société Française de Médecine d'Urgence (SFMU), Jung B, *et al.* Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. *Ann Intensive Care*. 2019;9:92.

32 Wigger O, Bloechlinger S, Berger D, *et al.* Baseline serum bicarbonate levels independently predict short-term mortality in critically ill patients with ischaemic cardiogenic shock. *European Heart Journal: Acute Cardiovascular Care*. 2018;7:45–52.

Figure lengeds:

Fig.1: The flow chart of this study.

LOS: length of stay, ICU: intensive care unit, AG: anion gap

Fig.2: Restricted cubic spline for the associations between ACAG value and short-term mortality

Fig.2A and Fig.2B showed the ICU mortality while Fig.3C and Fig.3D showed the in-hospital mortality in MIMIC-IV and eICU-CRD cohort respectively. 28-day mortality was shown in Fig.2E.

The solid lines represent the adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CI) after multivariable adjustment in Model II.

Histograms represent the distribution of concentrations of ACAG in two cohorts.

Table1: Baseline characteristics of enrolled patients stratified by ACAG level in two cohorts

	MIMIC-IV cohort (n=808)				eICU-CRD cohort (n=700)			
	Overall (n=808)	Normal ACAG (n=416)	Higher ACAG (n=392)	p-value	Overall (n=700)	Normal ACAG (n=353)	Higher ACAG (n=347)	p-value
Demographic characteristics								
Age	70 (60, 80)	71 (61, 81)	70 (60, 79)	0.3	67 (57, 76)	68 (57, 77)	67 (57, 75)	0.2
Gender				0.2				
Female	347 (43%)	188 (45%)	159 (41%)		255 (36%)	130 (37%)	125 (36%)	
Male	461 (57%)	228 (55%)	233 (59%)		445 (64%)	223 (63%)	222 (64%)	
Weight/BMI[a]	80 (68, 95)	79 (67, 94)	81 (68, 97)	0.2	28 (24, 33)	28 (24, 33)	28 (24, 33)	0.6
Ethnicity				0.3				0.016
White	497 (62%)	255 (61%)	242 (62%)		531 (76%)	276 (78%)	255 (73%)	
Black	71 (8.8%)	34 (8.2%)	37 (9.4%)		83 (12%)	32 (9.1%)	51 (15%)	
Hispanic	19 (2.4%)	12 (2.9%)	7 (1.8%)		32 (4.6%)	14 (4.0%)	18 (5.2%)	
Asian	18 (2.2%)	13 (3.1%)	5 (1.3%)		19 (2.7%)	15 (4.2%)	4 (1.2%)	
Others/unknown	203 (25%)	102 (25%)	101 (26%)		35 (5.0%)	16 (4.5%)	19 (5.5%)	
Comorbidities								
AMI	349 (43%)	187 (45%)	162 (41%)	0.3	270 (39%)	152 (43%)	118 (34%)	0.014
Hypertension	241 (30%)	143 (34%)	98 (25%)	0.004*	365 (52%)	186 (53%)	179 (52%)	0.8
Cardiomyopathy	206 (25%)	105 (25%)	101 (26%)	0.9	119 (17%)	69 (20%)	50 (14%)	0.070
Atrial fibrillation	393 (49%)	199 (48%)	194 (49%)	0.6	144 (21%)	77 (22%)	67 (19%)	0.4
VHD	293 (36%)	150 (36%)	143 (36%)	>0.9	99 (14%)	64 (18%)	35 (10%)	0.002
AKI/ARF[a]	573 (71%)	259 (62%)	314 (80%)	<0.001*	323 (46%)	150 (42%)	173 (50%)	0.051
COPD	71 (8.8%)	41 (9.9%)	30 (7.7%)	0.3	101 (14%)	53 (15%)	48 (14%)	0.7
Diabetes	283 (35%)	116 (28%)	167 (43%)	<0.001*	158 (23%)	70 (20%)	88 (25%)	0.080
Malignancy	80 (9.9%)	38 (9.1%)	42 (11%)	0.5	16 (2.3%)	6 (1.7%)	10 (2.9%)	0.3
SOFA	8 (5, 11)	7 (4, 10)	9 (6, 12)	<0.001*	8 (6, 11)	7 (5, 10)	9 (7, 12)	<0.001*
Vital signs								
Heart rate	90 (77, 108)	87 (74, 102)	93 (80, 111)	<0.001*	91 (78, 108)	90 (77, 105)	93 (78, 111)	0.088
Respiratory rate	20 (17, 24)	20 (16, 23)	21 (17, 26)	<0.001*	20 (17, 25)	19 (16, 24)	20 (17, 25)	0.083
Systolic BP	111 (97,	114 (99,	109 (95,	0.2	107 (91,	107 (92,	107 (90, 126)	0.8

	129)	127)	129)		122)	121)		
Diastolic BP	66 (54, 79)	66 (54, 79)	66 (54, 78)	0.5	62 (50, 75)	62 (50, 73)	62 (50, 77)	0.3
Mean BP	79 (68, 91)	79 (69, 91)	78 (66, 91)	0.4	77 (65, 89)	76 (67, 88)	78 (64, 91)	0.4
SpO2	97 (94, 100)	98 (94, 100)	97(93, 100)	0.12	97 (93, 100)	97 (94, 100)	98 (93, 100)	>0.9
Laboratory data								
White blood cell	13 (9, 17)	12 (9, 17)	13 (9, 18)	0.001*	12 (9, 18)	12 (9, 16)	13 (9, 20)	0.002*
Hemoglobin	11.5 (9.8, 13.4)	11.7 (10.1, 13.5)	11.4 (9.6, 13.1)	0.045*	12.1 (10.1, 13.9)	12.2 (10.3, 14.0)	11.8 (9.8, 13.7)	0.2
Platelet	211 (152, 278)	210 (154, 278)	213 (149, 278)	0.8	196 (145, 260)	203 (151, 253)	192 (139, 268)	0.4
Sodium	138 (134, 141)	138 (135, 141)	137 (133, 141)	0.2	137 (134, 141)	137 (135, 140)	138 (133, 141)	>0.9
Potassium	4.4 (3.9, 5.0)	4.3 (3.8, 4.7)	4.6 (3.9, 5.1)	<0.001*	4.2 (3.7, 4.9)	4.1 (3.7, 4.7)	4.4 (3.7, 5.2)	<0.001*
Chloride	103 (98, 107)	104 (100,108)	101 (96, 106)	<0.001*	103 (98, 107)	104 (100, 108)	101 (96, 105)	<0.001*
Bicarbonate	20 (17, 23)	22 (20, 25)	18 (15, 21)	<0.001*	22 (18, 25)	24 (21, 27)	19 (16, 22)	<0.001*
AG	13 (9, 17)	12 (9, 17)	13 (9, 18)	0.001*	167 (13, 21)	13 (12, 15)	21 (18, 24)	<0.001*
Albumin	3.3 (2.9, 3.7)	3.4 (3.0, 3.7)	3.2 (2.7, 3.6)	<0.001*	3.0 (2.6, 3.5)	3.1 (2.8, 3.6)	2.9 (2.5, 3.4)	<0.001*
ACAG	20.0 (17.0, 23.5)	17.1 (15.3, 18.5)	23.5 (21.8, 26.5)	<0.001*	19.9 (16.7, 24.2)	16.7 (14.8, 18.3)	24.2 (21.9, 28.0)	<0.001*
Creatine	1.4 (1.0, 2.3)	1.2 (0.9, 1.7)	1.8 (1.3, 2.9)	<0.001*	1.5 (1.1, 2.4)	1.3 (0.9, 1.8)	1.8 (1.3, 2.8)	<0.001*
Bilirubin	0.7 (0.4, 1.3)	0.7 (0.4, 1.0)	0.8 (0.5, 1.5)	<0.001*	0.8 (0.5, 1.4)	0.8 (0.5, 1.3)	0.9 (0.5, 1.6)	0.055
Outcomes								
LOS in ICU	5 (3, 9)	5 (3, 9)	5 (3, 9)	0.5	5 (3, 9)	5 (3, 8)	5 (3, 9)	0.3
LOS in hospital	10 (5, 17)	10 (6, 17)	10 (5, 18)	0.3	8 (5, 14)	9 (5, 15)	8 (4, 14)	0.017
ICU death	231 (29%)	85 (20%)	146 (37%)	<0.001*	211 (30%)	87 (25%)	124 (36%)	0.001*
Hospital death	289 (36%)	122 (29%)	167 (43%)	<0.001*	260 (37%)	102 (29%)	158 (46%)	<0.001*
28-day death[b]	315 (39%)	126 (30%)	189 (48%)	<0.001*				
28-day free from ICU[b]	17 (0, 24)	20 (2, 25)	9 (0, 23)	<0.001*				

Abbreviation: BMI: body mass index, AMI: acute myocardial infarction, AKI: acute kidney injury, ARF: acute renal failure, COPD: chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, BP: blood pressure, AG: anion gap, ACAG albumin

corrected anion gap, LOS: length of stay, ICU: intensive care unit

p<0.05*

a: body weight and acute kidney injury were shown in MIMIC-IV cohort while body mass index and acute renal failure were presented in eICU-CRD cohort due to data availability.

b: 28-day all-cause mortality and 28-day free from ICU were reported in MIMIC-IV cohort.

Table2: ROC curve analysis of AG/ACAG and short-term mortality

	Factor	AUC	95%CI	Cut-off	Sensitivity	Specificity	Youden's index
ICU mortality (MIMIC-IV)	AG	0.654	0.613-0.696	15.5	0.758	0.426	0.184
	ACAG	0.632	0.589-0.674	19.6	0.680	0.532	0.212
ICU mortality (eICU-CRD)	AG	0.594	0.546-0.642	18.1	0.526	0.654	0.180
	ACAG	0.613	0.566-0.660	25.4	0.351	0.857	0.208
Hospital mortality (MIMIC-IV)	AG	0.599	0.558-0.641	20.5	0.346	0.796	0.142
	ACAG	0.629	0.589-0.669	24.6	0.322	0.869	0.191
Hospital mortality (eICU-CRD)	AG	0.603	0.559-0.647	18.1	0.523	0.673	0.196
	ACAG	0.628	0.585-0.671	21.6	0.527	0.705	0.232
28-day mortality (MIMIC-IV))	AG	0.614	0.574-0.654	21.5	0.295	0.870	0.165
	ACAG	0.641	0.602-0.680	22.9	0.400	0.805	0.205

Abbreviation: AUC: area under curve, CI: confidence interval, AG: anion gap, ACAG: albumin corrected anion gap,

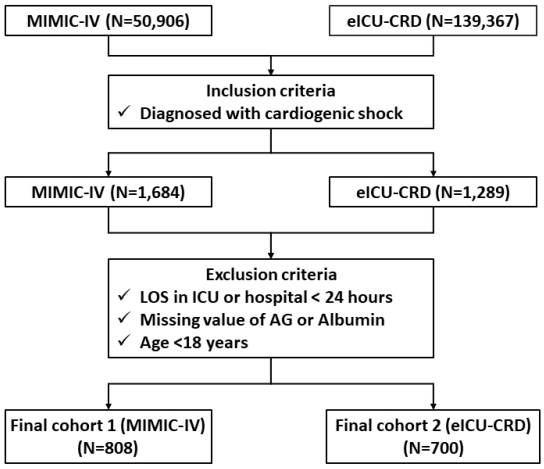
Table3: Association of ACAG and short-term all-cause mortality

	Crude Model		Model I		Model II	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
28-day mortality (MIMIC-IV cohort)						
ACAG (per 1 unit)	1.07 (1.06-1.09)	<0.001	1.08 (1.06-1.10)	<0.001	1.05 (1.03-1.07)	<0.001
Higher ACAG level	1.85 (1.48-2.32)	<0.001	1.90 (1.52-2.39)	<0.001	1.42 (1.11-1.83)	0.007
ICU mortality (MIMIC-IV cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.09)	<0.001	1.07 (1.05-1.09)	<0.001	1.04 (1.01-1.06)	0.005
Higher ACAG level	1.74 (1.33-2.28)	<0.001	1.87 (1.43-1.91)	<0.001	1.43 (1.05-1.93)	0.022
ICU mortality (eICU-CRD cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.08)	<0.001	1.07 (1.05-1.09)	<0.001	1.06 (1.03-1.09)	<0.001
Higher ACAG level	1.61 (1.22-2.11)	<0.001	1.65 (1.25-2.17)	<0.001	1.38 (1.02-1.86)	0.036
In-hospital mortality (MIMIC-IV cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.08)	<0.001	1.06 (1.04-1.08)	<0.001	1.04 (1.02-1.07)	<0.001
Higher ACAG level	1.51 (1.20-1.91)	<0.001	1.58 (1.25-2.01)	<0.001	1.31 (1.01-1.71)	0.041
In-hospital mortality (eICU-CRD cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.08)	<0.001	1.07 (1.05-1.09)	<0.001	1.05 (1.02-1.07)	<0.001
Higher ACAG level	1.81 (1.41-2.33)	<0.001	1.86 (1.44-2.39)	<0.001	1.47 (1.12-1.94)	0.006

Abbreviation: ACAG: albumin corrected anion gap, HR: hazard ratio, CI: confidence interval

Model I adjusted for age, gender, race, and weight/body mass index

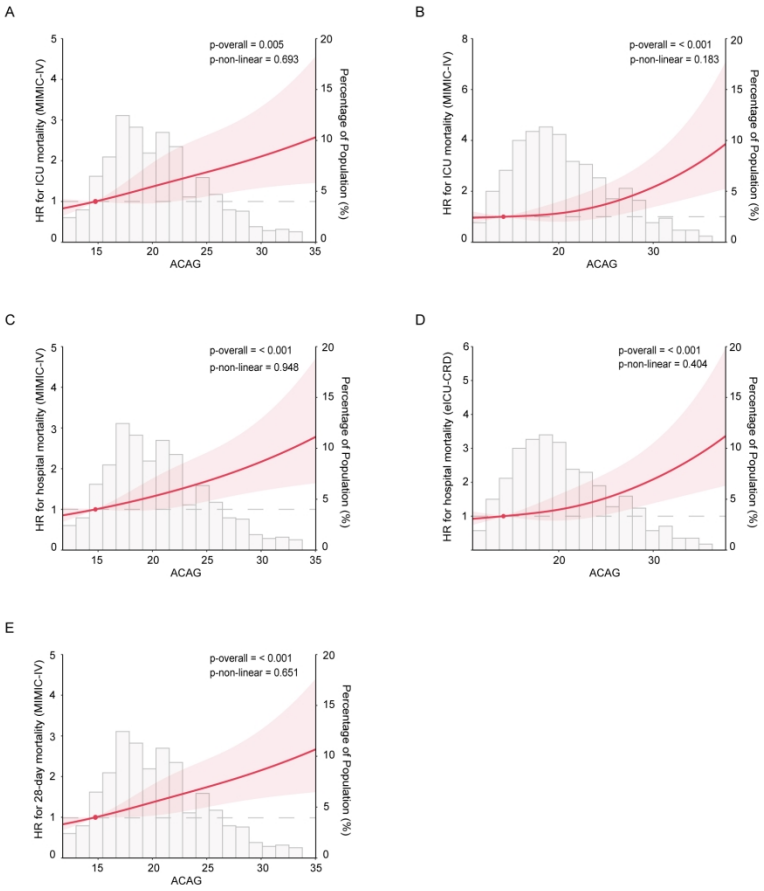
Model II adjusted for age, gender, race, weight/body mass index, acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular heart disease, diabetes, chronic obstructive pulmonary disease, acute kidney injury, SOFA score, mean blood pressure, oxygen saturation, potassium, chloride, creatine, and total bilirubin.



The flow chart of this study

338x190mm (96 x 96 DPI)

Fig.2



Restricted cubic spline for the associations between ACAG value and short-term mortality
Fig.2A and Fig.2B showed the ICU mortality while Fig.3C and Fig.3D showed the in-hospital mortality in MIMIC-IV and eICU-CRD cohort respectively. 28-day mortality was shown in Fig.2E.
The solid lines represent the adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CI) after multivariable adjustment in Model II.
Histograms represent the distribution of concentrations of ACAG in two cohorts.

174x234mm (300 x 300 DPI)

Albumin corrected anion gap is associated with the prognosis of cardiogenic shock: a multi-center retrospective study

Online Supplement material

eTable1: Baseline characteristics of included and excluded patients in two cohorts

	MIMIC-IV cohort (n=1684)				eICU-CRD cohort (n=1289)			
	Overall (n=1684)	Excluded (n=876)	Included (n=808)	p-value	Overall (n=1289)	Excluded (n=589)	Included (n=700)	p-value
Demographic characteristics								
Age	72 (61, 81)	73 (63, 81)	70 (60, 80)	0.006*	68 (57, 77)	69 (58, 78)	67 (57, 76)	0.2
Gender				0.062				0.8
Female	684 (41%)	337 (38%)	347 (43%)		473 (37%)	218 (37%)	255 (36%)	
Male	1000 (59%)	539 (60%)	461 (57%)		816 (64%)	371 (65%)	445 (62%)	
Weight/BMI[a]	80 (68, 95)	80 (68, 95)	80 (68, 95)	0.5	28 (24, 33)	28 (24, 33)	28 (24, 33)	0.4
Ethnicity				0.3				0.2
White	1072 (64%)	575 (66%)	497 (62%)		987 (77%)	456 (77%)	531 (76%)	
Black	144 (8.6%)	73 (8.3%)	71 (8.8%)		136 (11%)	53 (9.0%)	83 (12%)	
Hispanic	32 (1.9%)	13 (1.5%)	19 (2.4%)		62 (4.8%)	30 (5.1%)	32 (4.6%)	
Asian	40 (2.4%)	22 (2.5%)	18 (2.2%)		29 (2.2%)	10 (1.7%)	19 (2.7%)	
Others/unknown	396 (24%)	193 (22%)	203 (25%)		75 (5.8%)	40 (6.8%)	35 (5.0%)	
Comorbidities								
AMI	719 (43%)	370 (42%)	349 (43%)	0.7	489 (38%)	219 (37%)	270 (39%)	0.6
Hypertension	490 (29%)	249 (28%)	241 (30%)	0.5	666 (52%)	301 (51%)	365 (52%)	0.7
Cardiomyopathy	431 (26%)	225 (26%)	206 (25%)	>0.9	221 (17%)	102 (17%)	119 (17%)	0.9
Atrial fibrillation	856 (51%)	463 (53%)	393 (49%)	0.084	250 (19%)	106 (18%)	144 (21%)	0.2
VHD	660 (39%)	367 (42%)	293 (36%)	0.018*	184 (14%)	85 (14%)	99 (14%)	0.9
AKI/ARF[a]	1,118 (66%)	549 (63%)	569 (70%)	<0.001*	533 (41%)	210 (36%)	323 (46%)	<0.001*
COPD	142 (8.4%)	71 (8.1%)	71 (8.8%)	0.6	191 (14%)	90 (15%)	101 (14%)	0.7
Diabetes	609 (36%)	326 (37%)	283 (35%)	0.4	294 (23%)	136 (23%)	158 (23%)	0.8
Malignancy	146 (8.7%)	66 (7.5%)	80 (9.9%)	0.085	28 (2.2%)	12 (2.0%)	16 (2.3%)	0.8

SOFA	8 (5, 11)	8 (5, 10)	8 (5, 11)	0.003	8 (5, 11)	7 (4, 10)	8 (6, 11)	<0.001*
Vital signs								
Heart rate	89 (77, 105)	88 (77, 103)	90 (77, 108)	0.2	90 (77, 107)	88 (76, 105)	91 (78, 108)	0.2
Respiratory rate	20 (16, 24)	20 (16, 24)	20 (17, 24)	0.056	20 (16, 24)	20 (16, 24)	20 (17, 25)	0.11
Systolic BP	109 (95, 125)	108 (93, 123)	111 (97, 129)	<0.001	106 (90, 122)	104 (88, 122)	107 (91, 122)	0.056
Mean BP	78 (67, 89)	76 (66, 88)	79 (68, 91)	<0.001	76 (64, 88)	74 (64, 87)	77 (65, 89)	0.019*
Diastolic BP	64 (52, 77)	63 (51, 75)	66 (54, 79)	<0.001	60 (49, 74)	59 (49, 71)	62 (50, 75)	0.011*
SpO2	98 (94, 100)	98 (94, 100)	97 (94, 100)	0.6	97 (93, 100)	97 (93, 100)	97 (93, 100)	0.5
Laboratory data								
White blood cell	13 (9, 17)	12 (9, 17)	13 (9, 17)	0.5	12 (9, 18)	12 (9, 17)	12 (9, 18)	0.8
Hemoglobin	11.5 (9.5, 13.2)	11.4 (9.2, 13.2)	11.5 (9.8, 13.4)	0.058	11.8 (9.9, 13.7)	11.4 (9.6, 13.3)	12.1 (10.1, 13.9)	<0.001*
Platelet	201 (147, 269)	196 (142, 257)	211 (152, 278)	0.001	192 (143, 255)	189 (140, 251)	196 (145, 260)	0.3
Sodium	138 (135, 141)	138 (135, 141)	138 (134, 141)	0.015	138 (134, 141)	138 (134, 141)	137 (134, 141)	>0.9
Potassium	4.3 (3.9, 4.9)	4.3 (3.8, 4.8)	4.4 (3.9, 5.0)	0.022	4.2 (3.7, 4.9)	4.2 (3.7, 4.8)	4.2 (3.7, 4.9)	0.5
Chloride	103 (98, 107)	103 (98, 107)	103 (98, 107)	0.3	103 (98, 107)	103 (98, 108)	103 (98, 107)	0.5
Bicarbonate	21 (18, 24)	21 (18, 24)	20 (17, 23)	<0.001	22 (18, 25)	22 (18, 25)	22 (18, 25)	0.7
AG	17 (14, 20)	16 (13, 20)	17 (14, 21)	0.003	16 (13, 21)	16 (13, 20)	17 (13, 21)	0.035*
Albumin	3.3 (2.8, 3.7)	3.2 (2.6, 3.6)	3.3 (2.9, 3.7)	0.014	3.0 (2.6, 3.4)	2.9 (2.4, 3.4)	3.0 (2.6, 3.5)	0.004*
ACAG	20.3 (17.3, 24.0)	23.5 (19.0, 30.5)	20.0 (17.0, 23.5)	<0.001	20 (17, 25)	21 (18, 27)	20 (17, 24)	<0.001*

Creatine	1.4 (1.0, 2.1)	1.4 (1.0, 2.1)	1.4 (1.0, 2.3)	0.10	1.4 (1.0, 2.3)	1.4 (1.0, 2.3)	1.5 (1.1, 2.4)	0.061
Bilirubin	0.7 (0.5, 1.2)	0.7 (0.5, 1.2)	0.7 (0.4, 1.3)	0.6	0.8 (0.5, 1.4)	0.8 (0.5, 1.4)	0.9 (0.6, 1.4)	0.6

Abbreviation: BMI: body mass index, AMI: acute myocardial infarction, AKI: acute kidney injury, ARF: acute renal failure, COPD: chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, BP: blood pressure, AG: anion gap, ACAG albumin corrected anion gap, LOS: length of stay, ICU: intensive care unit

p<0.05*

a: body weight and acute kidney injury were shown in MIMIC-IV cohort while body mass index and acute renal failure were presented in eICU-CRD cohort due to data availability.

eTable2: Baseline characteristics of enrolled patients stratified by hospital survival status in two cohorts

	MIMIC-IV cohort (n=808)				eICU-CRD cohort (n=700)			
	Overall (n=808)	Survivors (n=519)	Non-survivors (n=289)	p-value	Overall (n=700)	Survivors (n=440)	Non-survivors (n=260)	p-value
Demographic characteristics								
Age	70 (60, 80)	69 (59, 79)	74 (63, 81)	0.001*	67 (57, 76)	66 (55, 75)	70 (62, 79)	<0.001*
Gender				0.018*				0.4
Female	347 (43%)	207 (40%)	140 (48%)		255 (36%)	155 (35%)	100 (38%)	
Male	461 (57%)	312 (60%)	149 (52%)		445 (64%)	285 (65%)	160 (62%)	
Weight/BMI[a]	80 (68, 95)	80 (69, 95)	80 (66, 95)	0.7	28 (24, 33)	28 (24, 33)	28 (24, 33)	>0.9
Ethnicity				0.002*				>0.9
White	497 (62%)	336 (65%)	161 (56%)		531 (76%)	332 (75%)	199 (77%)	
Black	71 (8.8%)	51 (9.8%)	20 (6.9%)		83 (12%)	52 (12%)	31 (12%)	
Hispanic	19 (2.4%)	12 (2.3%)	7 (2.4%)		32 (4.6%)	20 (4.5%)	12 (4.6%)	
Asian	18 (2.2%)	13 (2.5%)	5 (1.7%)		19 (2.7%)	14 (3.2%)	5 (1.9%)	
Others/unknown	203 (25%)	107 (21%)	96 (33%)		35 (5.0%)	22 (5.0%)	13 (5.0%)	
Comorbidities								
AMI	349 (43%)	231 (45%)	118 (41%)	0.3	270 (39%)	181 (41%)	89 (34%)	0.070
Hypertension	241 (30%)	160 (31%)	81 (28%)	0.4	365 (52%)	226 (51%)	139 (53%)	0.6
Cardiomyopathy	206 (25%)	143 (28%)	63 (22%)	0.072	119 (17%)	80 (18%)	39 (15%)	0.3
Atrial fibrillation	393 (49%)	254 (49%)	139 (48%)	0.8	144 (21%)	88 (20%)	56 (22%)	0.6
VHD	293 (36%)	203 (39%)	90 (31%)	0.024*	99 (14%)	62 (14%)	37 (14%)	>0.9
AKI/ARF[a]	573 (71%)	334 (64%)	239 (83%)	<0.001*	323 (46%)	180 (41%)	143 (55%)	<0.001*
COPD	71 (8.8%)	46 (8.9%)	25 (8.7%)	>0.9	101 (14%)	56 (13%)	45 (17%)	0.10
Diabetes	283 (35%)	171 (33%)	112 (39%)	0.10	158 (23%)	94 (21%)	64 (25%)	0.3
Malignancy	80 (9.9%)	41 (7.9%)	39 (13%)	0.011*	16 (2.3%)	6 (1.4%)	10 (3.8%)	0.034*

SOFA	8 (5, 11)	7 (4, 10)	10 (7, 12)	<0.001*	8 (6, 11)	7 (5, 10)	10 (8, 13)	<0.001*
Vital signs								
Heart rate	90 (77, 108)	89 (75, 105)	92 (78, 111)	0.066	91 (78, 108)	90 (77, 105)	93 (78, 111)	0.088
Respiratory rate	20 (17, 24)	20 (17, 24)	21 (17, 26)	0.023*	20 (17, 25)	19 (16, 24)	20 (17, 25)	0.083
Systolic BP	111 (97, 129)	113 (98, 129)	110 (96, 125)	0.2	107 (91, 122)	107 (92, 12	107 (90, 126)	0.8
Mean BP	66 (54, 79)	67 (55, 79)	63 (52, 78)	0.022*	62 (50, 75)	62 (50, 73)	62 (50, 77)	0.3
Diastolic BP	79 (68, 91)	80 (69, 93)	78 (66, 90)	0.075	77 (65, 89)	76 (67, 88)	78 (64, 91)	0.4
SpO2	97 (94, 100)	97 (94, 100)	98 (94, 100)	0.4	97 (93, 100)	97 (94, 100)	98 (93, 100)	>0.9
Laboratory data								
White blood cell	13 (9, 17)	12 (9, 17)	13 (9, 19)	0.013*	12 (9, 18)	12 (9, 17)	13 (9, 20)	0.076
Hemoglobin	11.5 (9.8, 13.4)	11.8 (10.0, 13.7)	11.2 (9.4, 12.5)	<0.001*	12.1 (10.1, 13.9)	12.4 (10.4, 14.2)	11.6 (9.7, 13.4)	0.003*
Platelet	211 (152, 278)	216 (155, 282)	198 (146, 274)	0.076	196 (145, 260)	210 (157, 266)	182 (128, 242)	<0.001*
Sodium	138 (134, 141)	138 (134, 140)	138 (134, 141)	0.6	137 (134, 141)	137 (134, 140)	138 (134, 142)	0.13
Potassium	4.4 (3.9, 5.0)	4.4 (3.9, 4.9)	4.4 (3.8, 5.0)	>0.9	4.2 (3.7, 4.9)	4.2 (3.7, 4.8)	4.3 (3.7, 5.1)	0.15
Chloride	103 (98, 107)	103 (98, 107)	103 (98, 107)	0.6	103 (98, 107)	103 (99, 107)	103 (98, 107)	>0.9
Bicarbonate	20 (17, 23)	21 (18, 24)	20 (16, 23)	<0.001*	22 (18, 25)	22 (19, 25)	21 (17, 24)	0.002*
AG	17 (14, 21)	16 (14, 20)	18 (15, 22)	<0.001*	17 (13, 21)	16 (13, 19)	18 (14, 23)	<0.001*
Albumin	3.3 (2.9, 3.7)	3.4 (3.0, 3.7)	3.1 (2.7, 3.6)	<0.001*	3.0 (2.6, 3.5)	3.1 (2.7, 3.5)	2.9 (2.5, 3.3)	<0.001*
ACAG	20.0 (17.0, 23.5)	19.0 (16.5, 22.5)	21.0 (18.0, 25.3)	<0.001*	19.9 (16.7, 24.2)	19.0 (16.2, 23.0)	22.0 (17.7, 27.0)	<0.001*
Creatine	1.4 (1.0, 2.3)	1.4 (1.0, 2.1)	1.6 (1.1, 2.6)	<0.001*	1.5 (1.1, 2.4)	1.4 (1.1, 2.3)	1.6 (1.2, 2.4)	0.021*

Bilirubin	0.7 (0.4, 1.3)	0.7 (0.5, 1.2)	0.7 (0.4, 1.4)	0.4	0.8 (0.5, 1.4)	0.8 (0.5, 1.4)	0.9 (0.6, 1.5)	0.065

Abbreviation: BMI: body mass index, AMI: acute myocardial infarction, AKI: acute kidney injury, ARF: acute renal failure, COPD: chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, BP: blood pressure, AG: anion gap, ACAG albumin corrected anion gap, LOS: length of stay, ICU: intensive care unit

$p<0.05$*

a: body weight and acute kidney injury were shown in MIMIC-IV cohort while body mass index and acute renal failure were presented in eICU-CRD cohort due to data availability.

eTable2: Baseline characteristics of enrolled patients stratified by hospital survival status in two cohorts

	MIMIC-IV cohort (n=1684)				eICU-CRD cohort (n=1289)			
	Overall (n=1684)	Excluded (n=876)	Included (n=808)	p-value	Overall (n=1289)	Excluded (n=589)	Included (n=700)	p-value
Demographic characteristics								
Age	72 (61, 81)	73 (63, 81)	70 (60, 80)	0.006*	68 (57, 77)	69 (58, 78)	67 (57, 76)	0.2
Gender				0.062				0.8
Female	684 (41%)	337 (38%)	347 (43%)		473 (37%)	218 (37%)	255 (36%)	
Male	1000 (59%)	539 (60%)	461 (57%)		816 (64%)	371 (65%)	445 (62%)	
Weight/BMI[a]	80 (68, 95)	80 (68, 95)	80 (68, 95)	0.5	28 (24, 33)	28 (24, 33)	28 (24, 33)	0.4
Ethnicity				0.3				0.2
White	1072 (64%)	575 (66%)	497 (62%)		987 (77%)	456 (77%)	531 (76%)	
Black	144 (8.6%)	73 (8.3%)	71 (8.8%)		136 (11%)	53 (9.0%)	83 (12%)	
Hispanic	32 (1.9%)	13 (1.5%)	19 (2.4%)		62 (4.8%)	30 (5.1%)	32 (4.6%)	
Asian	40 (2.4%)	22 (2.5%)	18 (2.2%)		29 (2.2%)	10 (1.7%)	19 (2.7%)	
Others/unknown	396 (24%)	193 (22%)	203 (25%)		75 (5.8%)	40 (6.8%)	35 (5.0%)	
Comorbidities								
AMI	719 (43%)	370 (42%)	349 (43%)	0.7	489 (38%)	219 (37%)	270 (39%)	0.6
Hypertension	490 (29%)	249 (28%)	241 (30%)	0.5	666 (52%)	301 (51%)	365 (52%)	0.7
Cardiomyopathy	431 (26%)	225 (26%)	206 (25%)	>0.9	221 (17%)	102 (17%)	119 (17%)	0.9
Atrial fibrillation	856 (51%)	463 (53%)	393 (49%)	0.084	250 (19%)	106 (18%)	144 (21%)	0.2
VHD	660 (39%)	367 (42%)	293 (36%)	0.018*	184 (14%)	85 (14%)	99 (14%)	0.9
AKI/ARF[a]	1,118 (66%)	549 (63%)	569 (70%)	<0.001*	533 (41%)	210 (36%)	323 (46%)	<0.001*
COPD	142 (8.4%)	71 (8.1%)	71 (8.8%)	0.6	191 (14%)	90 (15%)	101 (14%)	0.7
Diabetes	609 (36%)	326 (37%)	283 (35%)	0.4	294 (23%)	136 (23%)	158 (23%)	0.8
Malignancy	146 (8.7%)	66 (7.5%)	80 (9.9%)	0.085	28 (2.2%)	12 (2.0%)	16 (2.3%)	0.8

SOFA	8 (5, 11)	8 (5, 10)	8 (5, 11)	0.003	8 (5, 11)	7 (4, 10)	8 (6, 11)	<0.001*
Vital signs								
Heart rate	89 (77, 105)	88 (77, 103)	90 (77, 108)	0.2	90 (77, 107)	88 (76, 105)	91 (78, 108)	0.2
Respiratory rate	20 (16, 24)	20 (16, 24)	20 (17, 24)	0.056	20 (16, 24)	20 (16, 24)	20 (17, 25)	0.11
Systolic BP	109 (95, 125)	108 (93, 123)	111 (97, 129)	<0.001	106 (90, 122)	104 (88, 122)	107 (91, 122)	0.056
Mean BP	78 (67, 89)	76 (66, 88)	79 (68, 91)	<0.001	76 (64, 88)	74 (64, 87)	77 (65, 89)	0.019*
Diastolic BP	64 (52, 77)	63 (51, 75)	66 (54, 79)	<0.001	60 (49, 74)	59 (49, 71)	62 (50, 75)	0.011*
SpO2	98 (94, 100)	98 (94, 100)	97 (94, 100)	0.6	97 (93, 100)	97 (93, 100)	97 (93, 100)	0.5
Laboratory data								
White blood cell	13 (9, 17)	12 (9, 17)	13 (9, 17)	0.5	12 (9, 18)	12 (9, 17)	12 (9, 18)	0.8
Hemoglobin	11.5 (9.5, 13.2)	11.4 (9.2, 13.2)	11.5 (9.8, 13.4)	0.058	11.8 (9.9, 13.7)	11.4 (9.6, 13.3)	12.1 (10.1, 13.9)	<0.001*
Platelet	201 (147, 269)	196 (142, 257)	211 (152, 278)	0.001	192 (143, 255)	189 (140, 251)	196 (145, 260)	0.3
Sodium	138 (135, 141)	138 (135, 141)	138 (134, 141)	0.015	138 (134, 141)	138 (134, 141)	137 (134, 141)	>0.9
Potassium	4.3 (3.9, 4.9)	4.3 (3.8, 4.8)	4.4 (3.9, 5.0)	0.022	4.2 (3.7, 4.9)	4.2 (3.7, 4.8)	4.2 (3.7, 4.9)	0.5
Chloride	103 (98, 107)	103 (98, 107)	103 (98, 107)	0.3	103 (98, 107)	103 (98, 108)	103 (98, 107)	0.5
Bicarbonate	21 (18, 24)	21 (18, 24)	20 (17, 23)	<0.001	22 (18, 25)	22 (18, 25)	22 (18, 25)	0.7
AG	17 (14, 20)	16 (13, 20)	17 (14, 21)	0.003	16 (13, 21)	16 (13, 20)	17 (13, 21)	0.035*
Albumin	3.3 (2.8, 3.7)	3.2 (2.6, 3.6)	3.3 (2.9, 3.7)	0.014	3.0 (2.6, 3.4)	2.9 (2.4, 3.4)	3.0 (2.6, 3.5)	0.004*
ACAG	20.3 (17.3, 24.0)	23.5 (19.0, 30.5)	20.0 (17.0, 23.5)	<0.001	20 (17, 25)	21 (18, 27)	20 (17, 24)	<0.001*

Creatine	1.4 (1.0, 2.1)	1.4 (1.0, 2.1)	1.4 (1.0, 2.3)	0.10	1.4 (1.0, 2.3)	1.4 (1.0, 2.3)	1.5 (1.1, 2.4)	0.061
Bilirubin	0.7 (0.5, 1.2)	0.7 (0.5, 1.2)	0.7 (0.4, 1.3)	0.6	0.8 (0.5, 1.4)	0.8 (0.5, 1.4)	0.9 (0.6, 1.4)	0.6

Abbreviation: BMI: body mass index, AMI: acute myocardial infarction, AKI: acute kidney injury, ARF: acute renal failure, COPD: chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, BP: blood pressure, AG: anion gap, ACAG albumin corrected anion gap, LOS: length of stay, ICU: intensive care unit

p<0.05*

a: body weight and acute kidney injury were shown in MIMIC-IV cohort while body mass index and acute renal failure were presented in eICU-CRD cohort due to data availability.

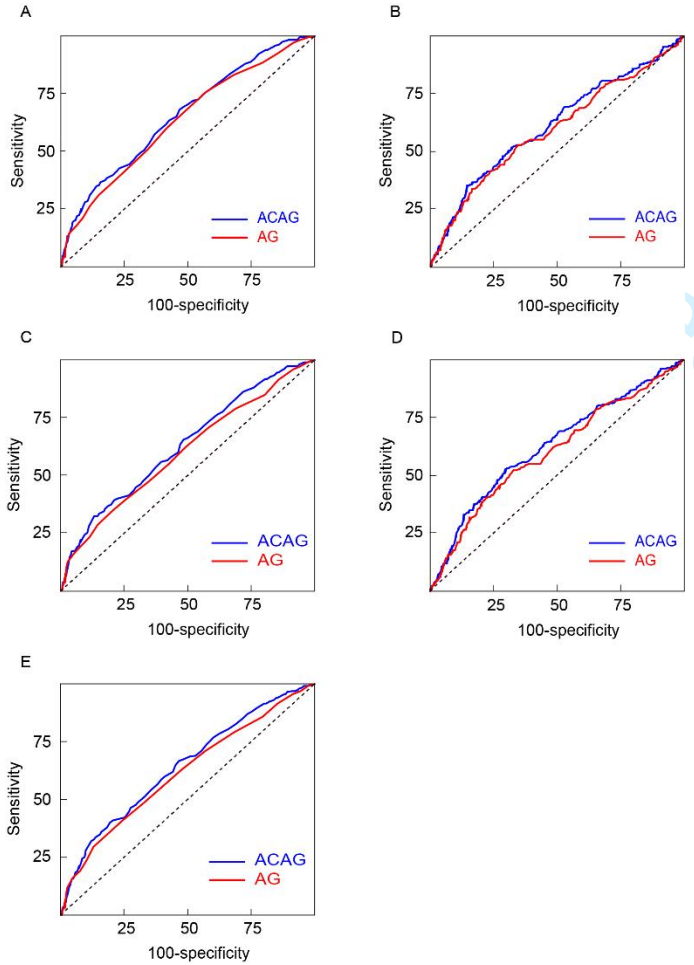
eTable2: Association of ACAG and earlier discharge alive in ICU

	Crude Model		Model I		Model II	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
LOS in ICU (MIMIC-IV cohort)						
ACAG	0.94 (0.92-0.95)	<0.001	0.94 (0.92-0.95)	<0.001	0.96 (0.94-0.98)	<0.001
Higher ACAG	0.62 (0.53-0.73)	<0.001	0.61 (0.52-0.72)	<0.001	0.77 (0.65-0.92)	0.004
LOS in ICU (eICU-CRD cohort)						
ACAG	0.96 (0.95-0.98)	<0.001	0.96 (0.94-0.98)	<0.001	0.97 (0.95-0.99)	0.001
Higher ACAG	0.74 (0.62-0.88)	<0.001	0.73 (0.61-0.88)	<0.001	0.85 (0.70-1.04)	0.140

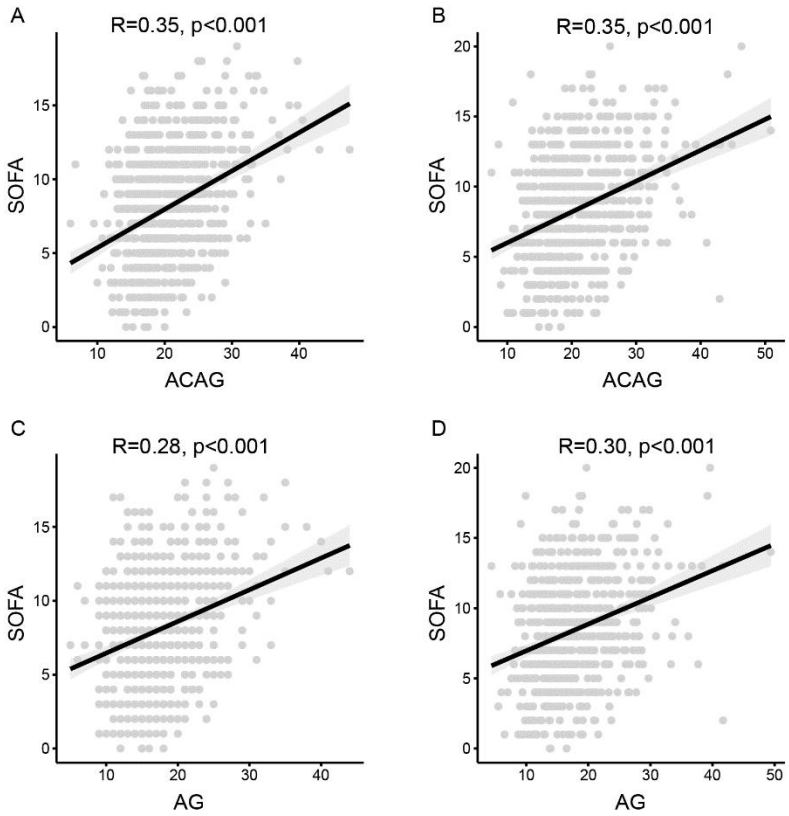
Model I adjusted for age, gender, race, and weight/body mass index

Model II adjusted for age, gender, race, weight/body mass index, acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular heart disease, diabetes, chronic obstructive pulmonary disease, acute kidney injury, SOFA score, mean blood pressure, oxygen saturation, potassium, chloride, creatinine, and total bilirubin.

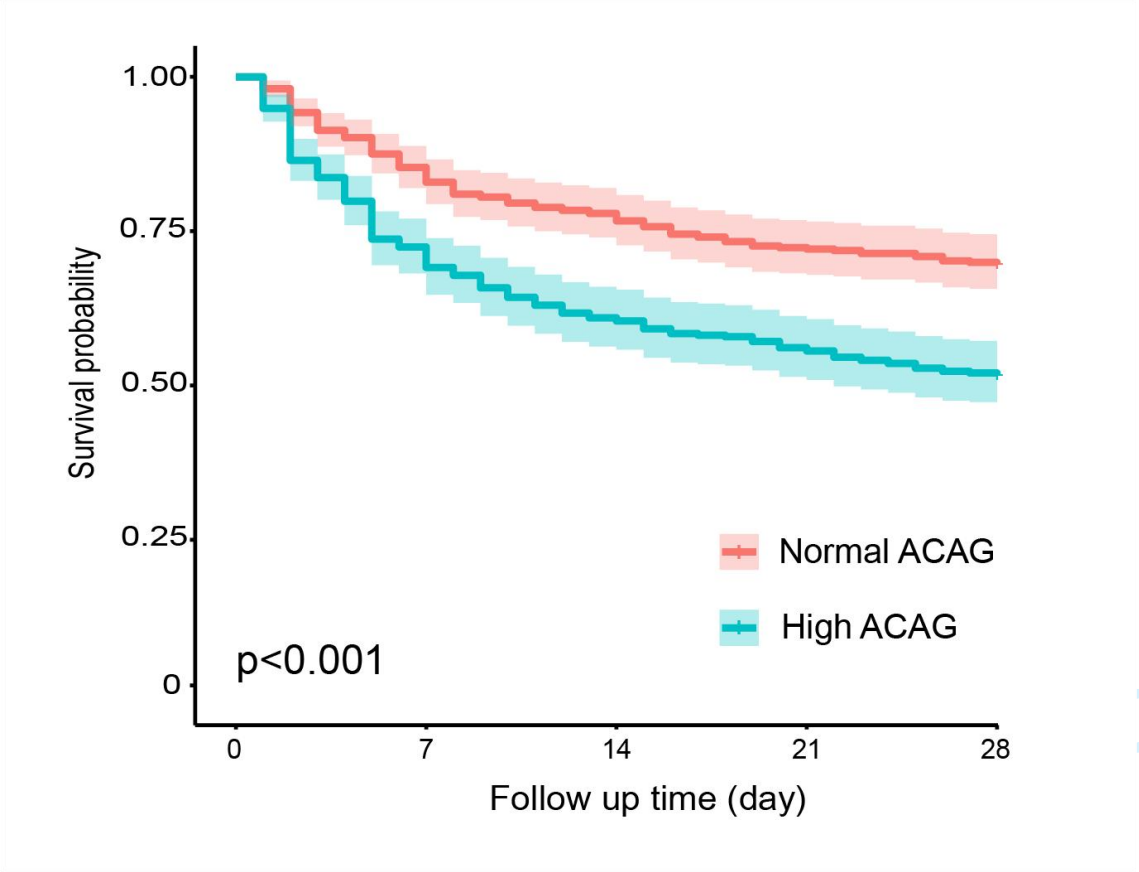
eFigure1: ROC curve analysis of AG, ACAG and ICU mortality (A: MIMIC-IV cohort; B: eICU-CRD cohort), in-hospital morality (C: MIMIC-IV cohort; D: eICU-CRD cohort), and 28-day mortality (E: MIMIC-IV cohort)



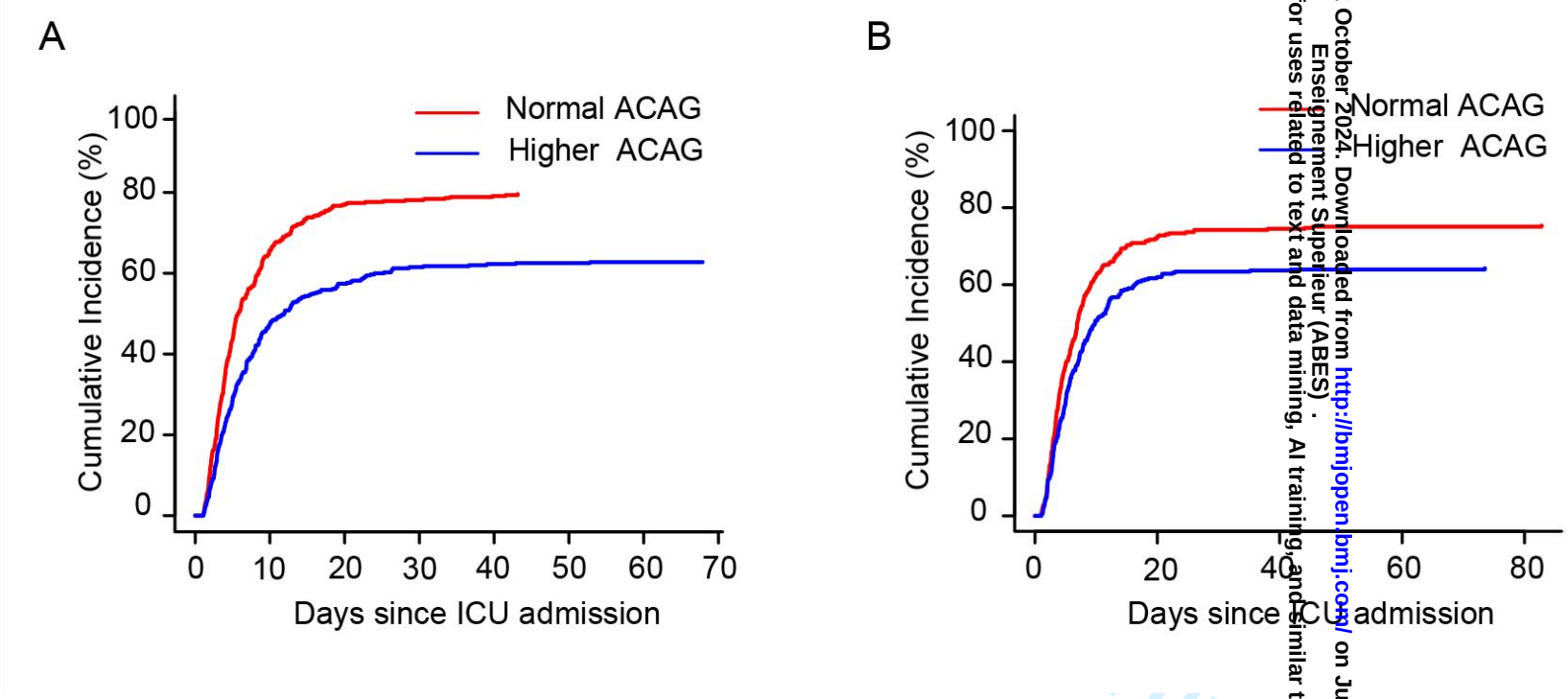
eFigure2: Pearson correlation analyses of AC/ACAG and SOFA score in MIMIC-IV cohort (A, C) and eICU-CRD cohort (B, D)



eFigure3: Kaplan–Meier survival curve of ACAG levels and 28-day all-cause mortality

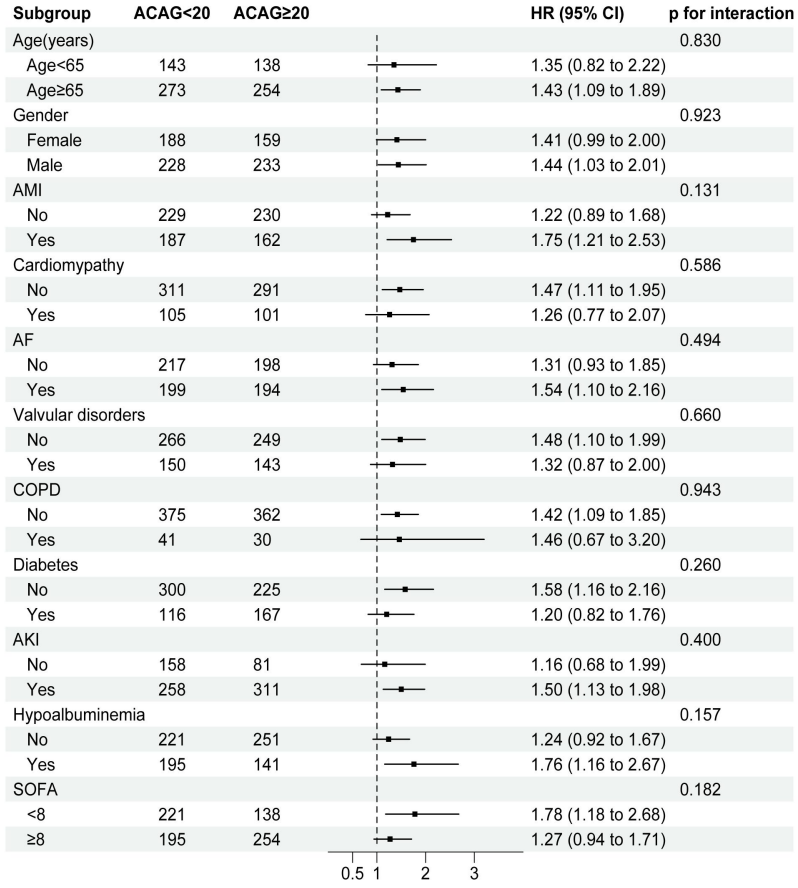


eFigure4: Cumulative incidence ratio of earlier discharge alive in the ICU in MIMIC-IV cohort (A) and eICU-CRD cohort (B)



eFigure5: Subgroup analysis

ACAG: albumin corrected anion gap, HR: hazard ratio, CI: confidence interval, AMI: acute myocardial infarction, AF:atrial fibrillation, COPD: chronic obstructive pulmonary disease, AKI: acute kidney injury, SOFA: Sequential Organ Failure Assessment



Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods	3

		of recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4
Bias	#9	Describe any efforts to address potential sources of bias	4
Study size	#10	Explain how the study size was arrived at	4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5
Statistical methods	#12c	Explain how missing data were addressed	5
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	5
Statistical methods	#12e	Describe any sensitivity analyses	5
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible,	6

		included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	6
Participants	#13c	Consider use of a flow diagram	6
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	6
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	4
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	7
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	7
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8

Discussion

Key results	#18	Summarise key results with reference to study objectives	8
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	9
Generalisability	#21	Discuss the generalisability (external validity) of the study results	10
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

 This checklist was completed on 01. November 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Relationship between the albumin-corrected anion gap and short-term prognosis among patients with cardiogenic shock: a retrospective analysis of the MIMIC-IV and eICU databases

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-081597.R2
Article Type:	Original research
Date Submitted by the Author:	08-Aug-2024
Complete List of Authors:	Wang, Yuxing; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Tao, Yuhang; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Yuan, Ming; Zhejiang University School of Medicine Sir Run Run Shaw Hospital yu, pengcheng; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Zhang, Kai; Zhejiang University School of Medicine Sir Run Run Shaw Hospital Ying, Hangying; Zhejiang University School of Medicine Sir Run Run Shaw Hospital jiang, ruhong; Zhejiang University School of Medicine Sir Run Run Shaw Hospital
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Emergency medicine, Intensive care
Keywords:	CARDIOLOGY, INTENSIVE & CRITICAL CARE, Cardiovascular Disease

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Relationship between the albumin-corrected anion gap and short-term prognosis among patients with cardiogenic shock: a retrospective analysis of the MIMIC-IV and eICU databases

Yuxing Wang[1*], Yuhang Tao[1*], Ming Yuan[1], Pengcheng Yu[1], Kai Zhang[1],Hangying Ying[1†], Ruhong Jiang[1†]

Affiliations:
1 Department of Cardiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

* Co-first authors contributed equally

† Corresponding authors contributed equally

Address for Corresponding Authors:
Hangying Ying, M.D.
Department of Cardiology, Sir Run Run Shaw Hospital
Zhejiang University School of Medicine
3 East Qingchun Road
Hangzhou, Zhejiang, 310016, P. R. China.
E-mail: yinghangying@zju.edu.cn

Ruhong Jiang, M.D.
Department of Cardiology, Sir Run Run Shaw Hospital
Zhejiang University School of Medicine
3 East Qingchun Road
Hangzhou, Zhejiang, 310016, P. R. China.
E-mail: jrh@zju.edu.cn

Conflicts of interest: None

Abstract:

Objectives: We aimed to investigate the association between the albumin-corrected anion gap (ACAG) and the prognosis of cardiogenic shock (CS).

Design: A multicentre retrospective cohort study.

Setting: Data were collected from the Medical Information Mart for Intensive Care (MIMIC-IV) and eICU Collaborative Research Database (eICU-CRD) datasets.

Participants: A total of 808 and 700 individuals from the MIMIC-IV and eICU-CRD, respectively, diagnosed with CS.

Primary and secondary outcomes: The primary endpoint was short-term all-cause mortality, including intensive care unit (ICU), in-hospital, and 28-day mortality. The secondary endpoints were the 28-day free from the ICU duration and the length of intensive care unit stay.

Results: CS patients were divided into two groups according to the admission ACAG value: the normal ACAG group (≤20 mmol/L) and the high ACAG group (> 20 mmol/L). CS patients with higher ACAG values exhibited increased short-term all-cause mortality rates, including ICU mortality (MIMIC-IV cohort: adjusted HR: 1.43, 95% CI=1.05–1.93, p=0.022; eICU-CRD cohort: adjusted HR: 1.38, 95% CI=1.02–1.86, p=0.036), in-hospital mortality (MIMIC-IV cohort: adjusted HR: 1.31, 95% CI=1.01–1.71, p=0.03; eICU-CRD cohort: adjusted HR: 1.47, 95% CI=1.12–1.94, p=0.006), and 28-day mortality (adjusted HR: 1.42, 95% CI: 1.11–1.83, p=0.007). A positive linear correlation was observed between the ACAG value and short-term mortality rates via restricted cubic splines. Compared with the AG, the ACAG presented a larger area under the curve for short-term mortality prediction. In addition, the duration of intensive care was longer, whereas the 28-day free from the ICU duration was shorter in patients with a higher ACAG value in both cohorts.

Conclusion: The ACAG value was independently and strongly associated with the prognosis of patients with CS, indicating that the ACAG value is superior to the conventional AG value.

Strengths and limitations of this study:

1. The included patients were from two distinct high-quality datasets with mixed aetiologies of CS.

2. We employed restricted cubic splines to reveal the association between the ACAG value and short-term mortality in CS patients.

3. Given its retrospective nature, selection bias cannot be avoided, and detailed information about cardiac function is not available.

Keywords: Albumin-corrected anion gap, anion gap, cardiogenic shock, intensive care unit, acute cardiovascular care

1. Introduction

Cardiogenic shock (CS), a life-threatening clinical condition, is characterized by acute end-organ hypoperfusion resulting from reduced cardiac output [1]. Despite substantial progress achieved in CS management over the past three decades, the mortality rate of CS remains unexpectedly high, making it a formidable challenge within the intensive care unit (ICU)[2]. Notably, the one-year mortality rate of CS patients is approximately 50%-60%, with a substantial portion of cases (70% to 80%) occurring within the initial 30 to 60 days[3]. Therefore, early identification of CS patients with a poor prognosis holds paramount clinical importance for tailoring effective risk reduction strategies.

The anion gap (AG), a biomarker reflecting unmeasured anions, is calculated via the following formula: AG (mmol/l) = (sodium + potassium) - (chloride + bicarbonate)[4]. It is extensively utilized to assess acid–base disorders and evaluate the prognosis of various diseases in clinical practice[5]. Nevertheless, the accuracy of the AG in predicting the prognosis of patients in the ICU remains debatable. While some studies have suggested that the AG can effectively predict short-term mortality in patients with critical illness, others have yielded inconclusive results[6]. In 1985, Gabow reported that the AG value could be influenced by serum albumin levels[7]. Given that albumin has a negative charge, any fluctuations in albumin levels can impact the final AG measurement[8]. Consequently, for patients with critical illness in the ICU, the AG may sometimes appear to be pseudonormal since hypoalbuminaemia is very common in the setting of intensive care[9]. To address this problem, Figge J et al. introduced the concept of the albumin-corrected anion gap (ACAG) in 1998[10]. Hatherill et al. discovered that the ACAG exhibited superior predictive capabilities for metabolic acidosis than did the AG in paediatric patients with shock[11]. Furthermore, numerous studies have demonstrated the association between the ACAG and the prognosis of critical conditions, including cardiac arrest[12], acute myocardial infarction[13], acute kidney injury[14], sepsis[15], and acute pancreatitis[16].

However, to the best of our knowledge, the relationship between the ACAG and the prognosis of CS patients has not been investigated. Furthermore, it remains uncertain whether the ACAG offers an improved ability to predict short-term mortality compared with the AG. Therefore, in this study, our objectives are as follows: 1) to examine the correlation between the ACAG and short-term mortality in patients with CS and 2) to compare the admission values of the AG and ACAG for predicting CS mortality and assessing severity.

2. Materials and methods

2.1 Datasets and ethics

In this study, we utilized the following two publicly accessible datasets: (1) the Medical Information Mart for Intensive Care IV/MIMIC-IV v2.2 dataset (2008–2019)[17] and (2) the eICU Collaborative Research Database/eICU-CRD dataset (2014–2015)[18]. The MIMIC-IV is an updated version of the MIMIC-III, containing depersonalized data of 73,181 ICU stays for 50,906 unique patients at the Beth Israel Deaconess Medical Center between 2008 and 2019 (a single centre dataset). The eICU-CRD is also a deidentified database and contains 200,859 ICU stays for 139,367 unique patients admitted to 335 ICUs at 208 hospitals across the United States (a multicentre dataset). Importantly, as there is no

shared hospital involvement between the MIMIC and eICU datasets, the eICU-CRD dataset remains entirely independent of the MIMIC-IV dataset.

The first author successfully completed the online course and passed the Examination for Protecting Human Research Participants (Record ID: 11841860). Hence, he was granted permission to extract data from the two datasets mentioned above. Given that all identifying information had been removed, our study was considered exempt from ethical review by the institutional research board. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

2.2 Patient and public involvement

Neither the patients nor the members of the public were involved in any part of this study.

2.3 Study population and endpoints

This was a multicentre, retrospective, observational study. CS was defined on the basis of the diagnostic codes from the MIMIC-IV and eICU-CRD databases. These codes are in accordance with standard clinical definitions. We excluded those who were younger than 18 years old, had a length of stay (LOS) in the ICU or hospital of less than 24 hours, or lacked AG values or albumin levels from within the first 24 hours of ICU admission. For patients with multiple ICU admissions, we included only the first ICU stay for analysis. The AG value was calculated via the following formula: AG (mmol/l) = (sodium + potassium) - (chloride + bicarbonate). The ACAG value was determined as follows: ACAG (mmol/l) = [4.4-{albumin(g/dl)}] *2.5 + AG[11]. Additionally, we categorized the enrolled patients into two groups according to the ACAG admission value and previous studies[14,15]: the normal ACAG group (<20 mmol/l) and the high ACAG group (≥20 mmol/l).

The primary endpoint of this study was short-term all-cause mortality, which included ICU mortality, in-hospital mortality, and 28-day mortality (not available in the eICU-CRD dataset). The secondary endpoints included 28-day free from the ICU duration (not available in the eICU-CRD dataset) and LOS in the ICU. The 28-day free from the ICU duration is a composite outcome that integrates both mortality and LOS in the ICU. It was calculated as 28 minus the days spent in the ICU during the first 28 days, and the dead patients were assigned a value of zero. The LOS in the ICU was defined as the duration that intensive care was required and was calculated on the basis of the time to discharge alive from the ICU, with death in the ICU as a completion risk.

2.4 Variable extraction

We extracted the variables with structured query language in Navicat Premium (version 15.0.12). The codes for data extraction were based on https://github.com/MIT-LCP/mimic-code and https://github.com/MIT-LCP/eicu-code. For each patient, we collected a wide range of variables, including demographic information, comorbidities, Sequential Organ Failure Assessment (SOFA) score, vital signs, and laboratory data. Demographic information included age at admission, sex, weight/body mass index, and

race. Acute myocardial infarction, hypertension, atrial fibrillation, valvular disease, cardiomyopathy, acute kidney injury/acute renal failure, chronic obstructive pulmonary disease, diabetes, and malignancy were identified as comorbidities. Vital signs included heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, and oxygen saturation. Additionally, we collected laboratory data, which included white blood cell count, haemoglobin, platelet, bilirubin, creatinine, sodium, potassium, chloride, bicarbonate, and albumin levels, and AG and ACAG values.

All vital signs, laboratory data, and SOFA scores were extracted and calculated within the first 24 hours of ICU admission. If a variable was measured multiple times within the initial 24 hours of ICU admission, we used the first recorded value for analysis.

2.5 Statistical analysis

To address missing values, we initially conducted multiple imputation using chained equations. In the MIMIC-IV cohort, the percentage of incomplete cases was 3.1%, and in the eICU-CRD cohort, it was 16.7%. Accordingly, we generated 5 datasets for MIMIC-IV and 17 datasets for eICU-CRD for further analysis, and the results were combined according to Rubin's rules[19].

We compared the baseline characteristics of the enrolled patients on the basis of their hospital survival status and ACAG value. Categorical variables are presented as numbers plus percentages and were compared via Pearson's chi-square test. Shapiro–Wilk tests were performed to assess the distribution of continuous variables. Since all the continuous variables in the two cohorts were skewed, they are expressed as medians [interquartile ranges (IQRs)] and were compared via the Wilcoxon rank sum test.

Pearson correlation analyses were used to investigate the associations between the AG/ACAG values and the SOFA score. The ability of the AG and ACAG values to predict short-term mortality was compared by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. A Z test was used to compare the predictive ability of the AG and ACAG values following the methods of Delong et al.[20]. Threshold values were determined by identifying the values that provided the highest specificity and sensitivity via the calculation of the Youden index.

To evaluate the relationships between the ACAG value and ICU, in-hospital, and 28-day all-cause mortality, the ACAG value was initially analysed as a categorical variable (normal ACAG group and high ACAG group) and then as a continuous variable (ACAG values). Kaplan–Meier survival curves and Cox proportional hazards regression models were used to calculate the hazard ratios (HRs) and 95% confidence intervals. Furthermore, we investigated the association between the ACAG value and short-term mortality via restricted cubic splines with four knots at 25%, 50%, 75% and 95%. On the basis of previous studies and theoretical considerations, we selected clinically relevant confounding factors as covariates in the regression model. The variance inflation factor was used to test the multicollinearity between each covariate, and the covariates with a high degree of collinearity (variance inflation factor > 5) were removed from the regression model. Finally, we constructed two models for adjustments. In Model I, we adjusted for confounders, including age, sex, race, and weight/body mass index. In Model II, we further adjusted for acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular heart

disease, diabetes, chronic obstructive pulmonary disease, acute kidney injury, SOFA score, mean blood pressure, oxygen saturation, and potassium, chloride, creatinine, and total bilirubin levels.

Since ICU death resulted in a shorter LOS, the correlation between the ACAG value and LOS in the ICU was analysed via the Fine–Grey competing risk model. In this model, a higher HR for earlier alive ICU discharge indicated a shorter LOS, whereas a lower HR indicated a longer LOS in the ICU.

Subgroup analyses were conducted to evaluate the relationships between the ACAG value and 28-day all-cause mortality within various subpopulations, including age (<65 years, ≥65 years), sex (male, female), acute myocardial infarction, atrial fibrillation, valvular disorders, cardiomyopathy, chronic obstructive pulmonary disease, diabetes mellitus, acute kidney injury/acute renal failure, hypoalbuminaemia (<3.5 g/dL, ≥3.5 g/dL), and SOFA score (<8, ≥8), via stratified multivariable Cox proportional hazards model.

All the statistical analyses were performed with R version 4.1.2. A two-sided P value < 0.05 was considered statistically significant.

3. Results

3.1 Baseline characteristics of the enrolled patients

The flowchart of our study is presented in *Fig. 1*. The differences between the included and excluded patients are summarized in eTable 1. Overall, a total of 808 and 700 individuals diagnosed with CS were enrolled from the MIMIC-IV dataset and eICU-CRD dataset, respectively. The short-term mortality rates of CS patients were similar in both cohorts. Specifically, the ICU mortality rates were 29% and 30%, whereas the in-hospital mortality rates were 36% and 37% in the MIMIC-IV cohort and eICU-CRD cohort, respectively. In the MIMIC-IV cohort, the 28-day all-cause mortality rate was 39%.

Table 1 summarizes the baseline characteristics of the enrolled patients stratified according to the ACAG value. Patients with a higher ACAG value clearly exhibited a greater predisposition to acute kidney injury/acute renal failure and had elevated SOFA scores; white blood cell counts; and sodium, potassium, creatinine, and total bilirubin levels. Compared with those in the normal ACAG group, the short-term mortality rates (including ICU mortality, in-hospital mortality, and 28-day mortality) were significantly greater, whereas the 28-day mortality rates in patients in the ICU were notably lower (20 [2-25] vs. 9 [0-23], p<0.001) in the high ACAG group.

Furthermore, the baseline characteristics of the enrolled patients stratified according to hospital survival status are summarized in *eTable 2*. Notably, we found that the ACAG value was significantly greater in the group of patients who did not survive in the hospital, both in the MIMIC-IV cohort (21.0 [18.0–25.3] vs. 19.0 [16.5–22.5], p<0.001) and in the eICU-CRD cohort (22.0 [17.7–27.0] vs. 19.0 [16.2–23.0], p<0.001). Additionally, among the nonsurvivors during hospitalization, we observed a higher rate of acute kidney injury/acute renal failure; lower haemoglobin, albumin, and bicarbonate levels; and higher age, creatinine levels, and SOFA scores.

3.2 Comparison of the AG and ACAG values for mortality prediction and

severity assessment

The predictive performance of the ACAG value versus the AG value for ICU, in-hospital, and 28-day all-cause mortality was assessed through ROC curve analysis (e*Fig. 1*). As shown in Table 2, the ACAG value outperformed the AG value for short-term mortality prediction, including ICU mortality (MIMIC-IV cohort: AUC: 0.654 [95% CI: 0.613–0.696] vs. 0.632 [95% CI: 0.589–0.674], Z = 2.99, p= 0.003; eICU-CRD cohort: AUC: 0.613 [95% CI: 0.566–0.660] vs. 0.594 [95% CI: 0.546–0.642], Z = 2.99, p=0.003), in-hospital mortality (MIMIC-IV cohort: ACU: 0.629 [95% CI: 0.589–0.669] vs. 0.599 [95% CI: 0.558–0.641], Z =4.13, p< 0.001; eICU-CRD cohort: AUC: 0.628 [95% CI: 0.585–0.671] vs. 0.603 [95% CI: 0.559–0.647], Z = 3.92, p< 0.001), and 28-day mortality prediction (MIMIC-IV cohort: AUC: 0.641 [95% CI: 0.602–0.680] vs 0.614 [95% CI: 0.574–0.654], Z = 3.95, p< 0.001).

Additionally, we conducted correlation analyses to investigate the association between the AG/ACAG values and the SOFA score via Pearson's method. As depicted in eFigure 2, in both cohorts, we observed positive correlations between both the AG and ACAG values and the SOFA score (both p values < 0.001). Intriguingly, we found that the correlation coefficient for the ACAG value was significantly greater than that for the AG value (MIMIC-IV cohort: AG: R=0.28 vs. ACAG: R=0.35; eICU-CRD cohort: AG: R=0.30 vs. ACAG: R=0.35). These findings highlight the strong positive correlation between the ACAG value and the SOFA score, underscoring its potential as a valuable prognostic indicator.

3.3 An increased ACAG value is correlated with increased risk of short-term morality

As shown in *eFig. 3*, the Kaplan–Meier survival curve revealed an increased 28-day all-cause mortality rate among patients with a higher ACAG value (HR: 1.85, 95% CI: 1.48–2.32, log-rank test, p value <0.001) in the MIMIC-IV cohort. Furthermore, even after adjusting for confounding variables in Model II, we observed that the individuals whose ACAG value was evaluated still presented an increased 28-day all-cause mortality rate (adjusted HR: 1.42, 95% CI: 1.11–1.83, p=0.007).

Similarly, the relationship between the ACAG value and ICU/in-hospital mortality was also assessed through multivariable Cox regression models. As presented in *Table 3*, in comparison with the normal ACAG group, the high ACAG group experienced increased rates of ICU mortality (MIMIC-IV cohort: 1.43, 95% CI=1.05–1.93, p=0.022; eICU-CRD cohort: adjusted HR: 1.38, 95% CI=1.02–1.86, p=0.036) and in-hospital mortality (MIMIC-IV cohort: adjusted HR: 1.31, 95% CI=1.01–1.71, p=0.03; eICU-CRD cohort: adjusted HR: 1.47, 95% CI=1.12–1.94, p=0.006).

3.4 Linear relationship between the ACAG value and short-term all-cause mortality

We extended our analysis to assess the association between the ACAG value and short-term all-cause mortality rates. As presented in *Table 3*, the adjusted HRs with 95% CIs were 1.05 (1.03–1.07) for 28-day mortality, 1.04 (1.01–1.06) for ICU mortality, and 1.04 (1.02–1.07) for in-hospital mortality in the MIMIC-IV cohort, and 1.06 (1.03–1.09) for ICU

mortality and 1.05 (1.02–1.07) for in-hospital mortality in the eICU-CRD cohort.

To further investigate the relationship between the ACAG value and short-term all-cause mortality rates, we utilized adjusted restricted cubic splines. As shown in *Fig. 2*, we observed a linear correlation between the ACAG value and short-term all-cause mortality, which included 28-day mortality (MIMIC-IV cohort: p for overall<0.001, p for nonlinear=0.651), ICU mortality (MIMIC-IV cohort: p for overall<0.001, p for nonlinear=0.693; eICU-CRD cohort: p for overall<0.001, p for nonlinear=0.183), and in-hospital mortality (MIMIC-IV cohort: p for overall<0.001, p for nonlinear=0.948; eICU-CRD cohort: p for overall<0.001, p for nonlinear=0.404) in both cohorts. These findings suggest that a 1-unit increase in the ACAG value is associated with an approximately 5% increase in short-term all-cause mortality rates among patients with CS.

3.5 Association of the ACAG value and earlier alive discharge from the ICU

The cumulative incidence ratio (CIR) of earlier discharge alive from the ICU among the different ACAG value groups is shown in *eFig. 4*. Obviously, the unadjusted CIR for earlier alive discharge from the ICU was significantly greater in the normal ACAG group. The robustness of the results was further confirmed via Fine–Grey competing risk models after adjusting for confounding variables (*eTable 3*). In the MIMIC-IV cohort, the adjusted HR (95% CI) for the relationship between the ACAG value and earlier alive discharge from the ICU was 0.77 (95% CI= 0.65–0.92; p = 0.004). However, in the eICU-CRD cohort, this relationship did not reach statistical significance (adjusted HR: 0.85, 0.69–1.04; p = 0.140).

Additionally, the ACAG value was analysed as a continuous variable. Intriguingly, the association between the ACAG value and earlier discharge was statistically significant in both cohorts, with adjusted HRs (95% CI) of 0.96 (95% CI=0.94–0.98; p<0.001) in the MIMIC-IV cohort and 0.97 (95% CI=0.95–0.99; p=0.001) in the eICU-CRD cohort. In summary, the ACAG value was inversely associated with earlier discharge from the ICU for patients with CS.

3.6 Subgroup analysis

Subgroup analysis was conducted to assess the consistency of the association between the ACAG value and 28-day all-cause mortality across various subpopulations, including age groups (<65 years, ≥65 years), sexes (male, female), SOFA scores (<8, ≥8), and different clinical conditions, such as acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular disorders, chronic obstructive pulmonary disease, diabetes mellitus, acute kidney injury, and hypoalbuminaemia (<3.5 g/dL, ≥3.5 g/dL). Adjustments for confounding factors were made as in Model II. As depicted in e*Fig. 5*, all p values for the interaction tests within different subgroups were greater than 0.05, indicating that the relationship between the ACAG value and 28-day all-cause mortality remained stable and consistent across the various subpopulations.

4. Discussion

In this large-sample retrospective study based on two distinct publicly accessible datasets, we investigated the association of the ACAG value, a novel biomarker indicating

metabolic acid load, with the short-term prognosis of CS patients with mixed aetiologies. The main findings of our study are as follows: (1) the ACAG value is strongly and independently associated with short-term all-cause mortality rates (including ICU, in-hospital, and 28-day mortality) and the duration of intensive care required in patients with CS, even after adjusting for disease severity via the SOFA score; (2) the ACAG value outperforms the AG value in its ability to predict short-term mortality and evaluate the severity of CS.

It is widely acknowledged that metabolic acidosis is a frequent event in the setting of intensive care and has been consistently demonstrated to be associated with adverse outcomes in individuals with critical illness[21]. Notably, in patients with severe cardiovascular disorders, particularly those suffering from CS, acidaemia may trigger a detrimental cycle by impairing cardiac contractile function, inducing malignant arrhythmias, and exacerbating circulatory failure[22]. Additionally, severe acidaemia may further compromise the response of the cardiovascular system to catecholamines and weaken the effectiveness of vasopressors to reverse hypotension[23]. A prior study demonstrated that the severity of acidosis is strongly and positively correlated with both the degree of shock and short-term mortality rates in CS patients[24].

As one of the simplest methods for assessing acid–base balance, the anion gap (AG) is a widely used biomarker in clinical practice. The relationship between the AG value and short-term mortality in patients with critical illness has been extensively investigated[25]. A previous study demonstrated a J-shaped association between the AG value and the 30-day all-cause mortality rate in patients with CS on the basis of the MIMIC-III dataset[26]. Similarly, our study revealed that the AG value was significantly greater in nonsurvivors than in survivors (MIMIC-IV cohort: 18 [15–22] vs. 16 [14–20], p<0.001; eICU-CRD cohort: 18 [14–23] vs. 16 [13–19], p<0.001) in our study. Moreover, the AG value has also been used for risk stratification in the setting of acute cardiovascular care. Recently, a study combined the AG value and SOFA score to create the AG-SOFA score, which displayed improved ability to predict short-term mortality in cardiovascular intensive care unit patients[27]. Similarly, Eric et al. incorporated the AG value into the BOS and MA2 scores and achieved superior performance over other preexisting risk score systems for CS prognostication[28]. However, the physiological AG value primarily consists of inorganic phosphate and albuminate, which are weak anions derived from serum albumin[5]. Given the involvement of albumin in acid–base equilibrium, the interpretation of acid–base data may be limited[29]. Theoretically, hypoalbuminaemia can lead to a decrease in albuminate levels, resulting in a reduction in AG values[10]. Therefore, in the case of a patient with hypoalbuminaemia and a normal AG value, it might indicate the presence of plasma acids. Similarly, we might underestimate the severity of metabolic acidosis on the basis of the AG value for patients with low albumin levels. Notably, hypoalbuminaemia is very common among patients with critical illnesses and has been demonstrated to be associated with unfavourable outcomes, including higher rates of short-term mortality and a longer LOS in the ICU. The incidence of hypoalbuminaemia is striking in patients with CS, with a reported rate of 75% from the previous CardShock study[30]. Similarly, our study revealed an exceptionally high frequency of hypoalbuminaemia in patients with CS. Specifically, the incidence of hypoalbuminaemia (defined as an albumin concentration < 3.5 g/dL) was 58.4%

(472/808) in the MIMIC-IV cohort and 74.1% (519/700) in the eICU-CRD cohort. Furthermore, a recent study established that the serum albumin concentration is an independent predictor of short-term mortality in CS patients [20]. Similarly, in this study, we found that the albumin level was significantly lower in the hospital death group than in the survival group (MIMIC-IV cohort: 3.4 [3.0–3.7] vs. 3.1 [2.7–3.6], p<0.001; eICU-CRD cohort: 3.1 [2.7–-3.6] vs. 2.9 [2.5–3.3], p<0.001).

The ACAG value, which combines the AG value and serum albumin level, has been proposed as a replacement for the AG value in differentiating acidosis caused by acid load or base deficit from an expert consensus panel in metabolic acidosis management[31]. As a ubiquitous abnormality in patients with critical illnesses, hypoalbuminaemia has been demonstrated to complicate the interpretation of acid–base data when diagnostic methods based on base excess or plasma bicarbonate concentration are used alongside the AG value [29]. In the presence of hypoalbuminaemia, taking albumin levels into account can reveal the presence of plasma acid, which might otherwise be overlooked when relying solely on the AG or base excess values. Previous studies have demonstrated that the ACAG value is a superior predictor compared with the conventional AG value for short-term prognosis prediction in patients with critical illnesses such as cardiopulmonary arrest[12], acute myocardial infarction[13], and sepsis[15]. Therefore, we hypothesized that the ACAG value may perform better than the AG value does, particularly in a population at high risk for metabolic acidosis and hypoalbuminaemia. As previously discussed, patients with CS are not only prone to hypoalbuminaemia but also susceptible to metabolic acidosis. Hence, we posited that the ACAG value might outperform the AG value for risk stratification in the context of CS. In this study, we compared the use of the AG and ACAG values for mortality prediction and severity assessment in CS patients in two cohorts. Through ROC curve analysis, we found that the ACAG value had the highest AUC and Youden's index for short-term mortality prediction in both cohorts, suggesting that the ACAG value has a better ability to predict short-term mortality than the AG value does for CS. Furthermore, using Spearman's methods, we discovered that both the AG and ACAG values were positively correlated with the SOFA score. Importantly, the correlation coefficients with the SOFA score were significantly greater for the ACAG value than for the AG value. Taken together, our findings support the superiority of the ACAG value in predicting prognosis and estimating disease severity in patients with CS.

As a medical emergency requiring prompt evaluation and intervention, the mortality risk of CS is highest during the initial 48 hours following the onset of shock[32]. Therefore, mortality assessment in CS patients should be performed as early as possible after ICU admission. Given the rapid and widespread availability of the AG value and albumin level in clinical practice, we recommend the inclusion of the baseline ACAG level as a prognostic biomarker for patients with CS.

Our study has notable strengths. First, this is a pioneering study to explore the association between the ACAG value and the prognosis of CS. Second, the CS patients were from a diverse and heterogeneous patient population with mixed aetiologies, enhancing its relevance and applicability to real-world clinical scenarios. Third, the data in this study are derived from two distinct high-quality datasets, and the results are consistent with each other. However, several limitations of this study deserve discussion. First, owing

to the retrospective nature of the study, selection bias cannot be avoided. Second, detailed information about cardiac function (such as left ventricular ejection fraction and ventricular size) and other important cardiac biomarkers (such as troponin and N-terminal pro-brain natriuretic peptide levels) was not included in this study because of the large amount of missing data. Third, we could not calculate the CS stages based on the Society for Cardiovascular Angiography and Interventions guidelines accurately because of specific data limitations in the MIMIC-IV and eICU databases. Fourth, the association between the ACAG value and short-term mortality was established on the basis of the first ACAG value within the first 24 h of ICU admission. Monitoring dynamic changes in the ACAG value may be valuable for patients with CS. However, further studies are needed to explore the relationship between dynamic changes in the ACAG value and mortality in patients with CS.

5. Conclusion

In conclusion, we found that the baseline ACAG value following ICU admission independently predicts short-term mortality in patients with CS, which is better than the AG value. Given the high mortality risk of CS during the early phase of ICU admission, the baseline ACAG value may help clinicians identify patients at high risk of mortality. Therefore, we propose incorporating the baseline ACAG value into risk stratification systems for CS.

Data availability

The datasets used in this study are available from the corresponding author upon reasonable request.

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval

The study was an analysis of third-party anonymised publicly available databases with pre-existing institutional review board approval. Informed consent was not required in this database study because of the non-identifying and anonymous nature of the databases.

Funding

None

Author contributions

Yuxing Wang: Conceptualization, Formal analysis, Investigation, Software, Visualization, Writing - original draft, Data curation, Methodology, Resources. Yuhang Tao: Investigation, Software, Visualization, Writing - original draft. Ming Yuan: Writing - review & editing. Pengcheng Yu: Writing - review & editing. Kai Zhang: Writing - review & editing. Hangying Ying: Project administration, Supervision Validation, and Writing - review & editing. Ruhong Jiang: Project administration, Supervision validation, and Writing - review & editing.
Ruhong Jiang and Hangying Ying are the guarantor.

Declaration of Competing Interests

None

References:

1 Van Diepen S, Katz JN, Albert NM, *et al.* Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation*. 2017;136. doi: 10.1161/CIR.0000000000000525

2 Hunziker L, Radovanovic D, Jeger R, *et al.* Twenty-Year Trends in the Incidence and Outcome of Cardiogenic Shock in AMIS Plus Registry. *Circ: Cardiovascular Interventions*. 2019;12:e007293.

3 Berg DD, Bohula EA, Morrow DA. Epidemiology and causes of cardiogenic shock. *Current Opinion in Critical Care*. 2021;27:401–8.

4 Posen AK, Paloucek FP, Petzel R. Anion gap physiology and faults of the correction formula. *American Journal of Health-System Pharmacy*. 2022;79:446–51.

5 Kraut JA, Madias NE. Serum Anion Gap: Its Uses and Limitations in Clinical Medicine. *Clinical Journal of the American Society of Nephrology*. 2007;2:162–74.

6 Rocktaeschel J, Morimatsu H, Uchino S, *et al.* Unmeasured anions in critically ill patients: Can they predict mortality?*: *Critical Care Medicine*. 2003;31:2131–6.

7 Gabow PA. Disorders associated with an altered anion gap. *Kidney International*. 1985;27:472–83.

8 Figge J, Bellomo R, Egi M. Quantitative relationships among plasma lactate, inorganic phosphorus, albumin, unmeasured anions and the anion gap in lactic acidosis. *Journal of Critical Care*. 2018;44:101–10.

9 Gatta A, Verardo A, Bolognesi M. Hypoalbuminemia. *Intern Emerg Med*. 2012;7:193–9.

10 Figge J, Jabor A, Kazda A, *et al.* Anion gap and hypoalbuminemia: *Critical Care Medicine*. 1998;26:1807–10.

11 Hatherill M. Correction of the anion gap for albumin in order to detect occult tissue anions in shock. *Archives of Disease in Childhood*. 2002;87:526–9.

12 Hagiwara S, Oshima K, Furukawa K, *et al.* The Significance of Albumin Corrected Anion Gap in Patients with Cardiopulmonary Arrest. *Ann Thorac Cardiovasc Surg*. 2013;19:283–8.

13 Jian L. Association between albumin corrected anion gap and 30-day all-cause mortality of critically ill patients with acute myocardial infarction: a retrospective

analysis based on the MIMIC-IV database. 2023.

14 Zhong L, Xie B, Ji X-W, *et al.* The association between albumin corrected anion gap and ICU mortality in acute kidney injury patients requiring continuous renal replacement therapy. *Intern Emerg Med*. 2022;17:2315–22.

15 Hu T, Zhang Z, Jiang Y. Albumin corrected anion gap for predicting in-hospital mortality among intensive care patients with sepsis: A retrospective propensity score matching analysis. *Clinica Chimica Acta*. 2021;521:272–7.

16 Li P, Shi L, Yan X, *et al.* Albumin Corrected Anion Gap and the Risk of in-Hospital Mortality in Patients with Acute Pancreatitis: A Retrospective Cohort Study. *JIR*. 2023;Volume 16:2415–22.

17 Johnson AEW, Bulgarelli L, Shen L, *et al.* MIMIC-IV, a freely accessible electronic health record dataset. *Sci Data*. 2023;10:1.

18 Pollard TJ, Johnson AEW, Raffa JD, *et al.* The eICU Collaborative Research Database, a freely available multi-center database for critical care research. *Sci Data*. 2018;5:180178.

19 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statist Med*. 2011;30:377–99.

20 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach. *Biometrics*. 1988;44:837.

21 Gunnerson KJ, Kellum JA. Acid–base and electrolyte analysis in critically ill patients: are we ready for the new millennium?: *Current Opinion in Critical Care*. 2003;9:468–73.

22 Kraut JA, Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. *Nat Rev Nephrol*. 2010;6:274–85.

23 Jentzer JC, Kashani KB, Wiley BM, *et al.* Laboratory Markers of Acidosis and Mortality in Cardiogenic Shock: Developing a Definition of Hemometabolic Shock. *Shock*. 2022;57:31–40.

24 Jentzer JC, Schrage B, Patel PC, *et al.* Association Between the Acidemia, Lactic Acidosis, and Shock Severity With Outcomes in Patients With Cardiogenic Shock. *JAHA*. 2022;11:e024932.

25 Glasmacher SA, Stones W. Anion gap as a prognostic tool for risk stratification in critically ill patients – a systematic review and meta-analysis. *BMC Anesthesiol*. 2015;16:68.

26 Zhang T, Wang J, Li X. Association Between Anion Gap and Mortality in Critically Ill Patients with Cardiogenic Shock. *IJGM*. 2021;Volume 14:4765–73.

27 Zhou Y-H, Pang S, Miao G-R, *et al.* Combining the anion gap with the sequential organ failure assessment score to evaluate the short-term prognosis of patients in the cardiac intensive care unit. *International Journal of Cardiology*. 2023;370:381–7.

28 Yamga E, Mantena S, Rosen D, *et al.* Optimized Risk Score to Predict Mortality in Patients With Cardiogenic Shock in the Cardiac Intensive Care Unit. *JAHA*. 2023;12:e029232.

29 Fencl V, Jabor A, Kazda A, *et al.* Diagnosis of Metabolic Acid–Base Disturbances in Critically Ill Patients. *Am J Respir Crit Care Med*. 2000;162:2246–51.

30 Jäntti T, Tarvasmäki T, Harjola V-P, *et al.* Hypoalbuminemia is a frequent marker of increased mortality in cardiogenic shock. *PLoS ONE*. 2019;14:e0217006.

31 for the Société de Réanimation de Langue Française (SRLF), the Société Française de Médecine d'Urgence (SFMU), Jung B, *et al.* Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. *Ann Intensive Care*. 2019;9:92.

32 Wigger O, Bloechlinger S, Berger D, *et al.* Baseline serum bicarbonate levels independently predict short-term mortality in critically ill patients with ischaemic cardiogenic shock. *European Heart Journal: Acute Cardiovascular Care*. 2018;7:45–52.

Figure legends:

Fig. 1: Flow chart of this study.

LOS: length of stay, ICU: intensive care unit, AG: anion gap.

Fig. 2: Restricted cubic spline for the associations between the ACAG value and short-term mortality.

Fig. 2A and Fig. 2B show the ICU mortality rates, whereas Fig. 3C and Fig. 3D show the in-hospital mortality rates in the MIMIC-IV and eICU-CRD cohorts, respectively. The 28-day mortality data are shown in Fig. 2E.

The solid lines represent the adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) after multivariable adjustment in Model II.

Histograms represent the distribution of the ACAG value in the two cohorts.

HR: hazard ratio; ICU: intensive care unit; ACAG: albumin-corrected anion gap.

Table 1: Baseline characteristics of the enrolled patients stratified by the ACAG value in the two cohorts

	MIMIC-IV cohort (n=808)				eICU-CRD cohort (n=700)			
	Overall (n=808)	Normal ACAG (n=416)	Higher ACAG (n=392)	p value	Overall (n=700)	Normal ACAG (n=353)	Higher ACAG (n=347)	p value
Demographic characteristics								
Age	70 (60, 80)	71 (61, 81)	70 (60, 79)	0.3	67 (57, 76)	68 (57, 77)	67 (57, 75)	0.2
Sex				0.2				
Female	347 (43%)	188 (45%)	159 (41%)		255 (36%)	130 (37%)	125 (36%)	
Male	461 (57%)	228 (55%)	233 (59%)		445 (64%)	223 (63%)	222 (64%)	
Weight/BMI[a]	80 (68, 95)	79 (67, 94)	81 (68, 97)	0.2	28 (24, 33)	28 (24, 33)	28 (24, 33)	0.6
Ethnicity				0.3				0.01*
White	497 (62%)	255 (61%)	242 (62%)		531 (76%)	276 (78%)	255 (73%)	
Black	71 (8.8%)	34 (8.2%)	37 (9.4%)		83 (12%)	32 (9.1%)	51 (15%)	
Hispanic	19 (2.4%)	12 (2.9%)	7 (1.8%)		32 (4.6%)	14 (4.0%)	18 (5.2%)	
Asian	18 (2.2%)	13 (3.1%)	5 (1.3%)		19 (2.7%)	15 (4.2%)	4 (1.2%)	
Others/unknown	203 (25%)	102 (25%)	101 (26%)		35 (5.0%)	16 (4.5%)	19 (5.5%)	
Comorbidities								
AMI	349 (43%)	187 (45%)	162 (41%)	0.3	270 (39%)	152 (43%)	118 (34%)	0.01*
Hypertension	241 (30%)	143 (34%)	98 (25%)	0.004*	365 (52%)	186 (53%)	179 (52%)	0.8
Cardiomyopathy	206 (25%)	105 (25%)	101 (26%)	0.9	119 (17%)	69 (20%)	50 (14%)	0.07
Atrial fibrillation	393 (49%)	199 (48%)	194 (49%)	0.6	144 (21%)	77 (22%)	67 (19%)	0.4
VHD	293 (36%)	150 (36%)	143 (36%)	>0.9	99 (14%)	64 (18%)	35 (10%)	0.001*
AKI/ARF[a]	573 (71%)	259 (62%)	314 (80%)	<0.001*	323 (46%)	150 (42%)	173 (50%)	0.05
COPD	71 (8.8%)	41 (9.9%)	30 (7.7%)	0.3	101 (14%)	53 (15%)	48 (14%)	0.7
Diabetes	283 (35%)	116 (28%)	167 (43%)	<0.001*	158 (23%)	70 (20%)	88 (25%)	0.08
Malignancy	80 (9.9%)	38 (9.1%)	42 (11%)	0.5	16 (2.3%)	6 (1.7%)	10 (2.9%)	0.3
SOFA	8 (5, 11)	7 (4, 10)	9 (6, 12)	<0.001*	8 (6, 11)	7 (5, 10)	9 (7, 12)	<0.001*
Vital signs								
Heart rate	90 (77, 108)	87 (74, 102)	93 (80, 111)	<0.001*	91 (78, 108)	90 (77, 105)	93 (78, 111)	0.088
Respiratory rate	20 (17, 24)	20 (16, 23)	21 (17, 26)	<0.001*	20 (17, 25)	19 (16, 24)	20 (17, 25)	0.083
Systolic BP	111 (97, 129)	114 (99, 127)	109 (95, 129)	0.2	107 (91, 122)	107 (92, 121)	107 (90, 126)	0.8

Diastolic BP	66 (54, 79)	66 (54, 79)	66 (54, 78)	0.5	62 (50, 75)	62 (50, 73)	62 (50, 77)	0.3
Mean BP	79 (68, 91)	79 (69, 91)	78 (66, 91)	0.4	77 (65, 89)	76 (67, 88)	78 (64, 91)	0.4
SpO2	97 (94, 100)	98 (94, 100)	97(93, 100)	0.12	97 (93, 100)	97 (94, 100)	98 (93, 100)	>0.9
Laboratory data								
White blood cell	13 (9, 17)	12 (9, 17)	13 (9, 18)	0.001*	12 (9, 18)	12 (9, 16)	13 (9, 20)	0.002*
Haemoglobin	11.5 (9.8, 13.4)	11.7 (10.1, 13.5)	11.4 (9.6, 13.1)	0.045*	12.1 (10.1, 13.9)	12.2 (10.3, 14.0)	11.8 (9.8, 13.7)	0.2
Platelet	211 (152, 278)	210 (154, 278)	213 (149, 278)	0.8	196 (145, 260)	203 (151, 253)	192 (139, 268)	0.4
Sodium	138 (134, 141)	138 (135, 141)	137 (133, 141)	0.2	137 (134, 141)	137 (135, 140)	138 (133, 141)	>0.9
Potassium	4.4 (3.9, 5.0)	4.3 (3.8, 4.7)	4.6 (3.9, 5.1)	<0.001*	4.2 (3.7, 4.9)	4.1 (3.7, 4.7)	4.4 (3.7, 5.2)	<0.001*
Chloride	103 (98, 107)	104 (100,108)	101 (96, 106)	<0.001*	103 (98, 107)	104 (100, 108)	101 (96, 105)	<0.001*
Bicarbonate	20 (17, 23)	22 (20, 25)	18 (15, 21)	<0.001*	22 (18, 25)	24 (21, 27)	19 (16, 22)	<0.001*
AG	13 (9, 17)	12 (9, 17)	13 (9, 18)	0.001*	167 (13, 21)	13 (12, 15)	21 (18, 24)	<0.001*
Albumin	3.3 (2.9, 3.7)	3.4 (3.0, 3.7)	3.2 (2.7, 3.6)	<0.001*	3.0 (2.6, 3.5)	3.1 (2.8, 3.6)	2.9 (2.5, 3.4)	<0.001*
ACAG	20.0 (17.0, 23.5)	17.1 (15.3, 18.5)	23.5 (21.8, 26.5)	<0.001*	19.9 (16.7, 24.2)	16.7 (14.8, 18.3)	24.2 (21.9, 28.0)	<0.001*
Creatine	1.4 (1.0, 2.3)	1.2 (0.9, 1.7)	1.8 (1.3, 2.9)	<0.001*	1.5 (1.1, 2.4)	1.3 (0.9, 1.8)	1.8 (1.3, 2.8)	<0.001*
Bilirubin	0.7 (0.4, 1.3)	0.7 (0.4, 1.0)	0.8 (0.5, 1.5)	<0.001*	0.8 (0.5, 1.4)	0.8 (0.5, 1.3)	0.9 (0.5, 1.6)	0.054
Outcomes								
LOS in ICU	5 (3, 9)	5 (3, 9)	5 (3, 9)	0.5	5 (3, 9)	5 (3, 8)	5 (3, 9)	0.3
LOS in hospital	10 (5, 17)	10 (6, 17)	10 (5, 18)	0.3	8 (5, 14)	9 (5, 15)	8 (4, 14)	0.014*
ICU death	231 (29%)	85 (20%)	146 (37%)	<0.001*	211 (30%)	87 (25%)	124 (36%)	0.001*
Hospital death	289 (36%)	122 (29%)	167 (43%)	<0.001*	260 (37%)	102 (29%)	158 (46%)	<0.001*
28-day death[b]	315 (39%)	126 (30%)	189 (48%)	<0.001*				
28-day free from the ICU duration[b]	17 (0, 24)	20 (2, 25)	9 (0, 23)	<0.001*				

Abbreviations: BMI: body mass index, AMI: acute myocardial infarction, AKI: acute kidney injury, ARF: acute renal failure, COPD: chronic obstructive pulmonary disease, SOFA: sequential organ failure assessment, BP: blood pressure, AG: anion gap, ACAG: albumin-

corrected anion gap, LOS: length of stay, ICU: intensive care unit.

p<0.05*

a: Body weight and acute kidney injury are shown for the MIMIC-IV cohort, whereas body mass index and acute renal failure are presented for the eICU-CRD cohort because of data availability.

b: Twenty-eight-day all-cause mortality and 28-day free from the ICU duration were reported for the MIMIC-IV cohort.

Table 2: ROC curve analysis of AG/ACAG values and short-term mortality

	Factor	AUC	95% CI	Cut-off	Sensitivity	Specificity	Youden's index
ICU mortality (MIMIC-IV)	AG	0.654	0.613-0.696	15.5	0.758	0.426	0.184
	ACAG	0.632	0.589-0.674	19.6	0.680	0.532	0.212
ICU mortality (eICU-CRD)	AG	0.594	0.546-0.642	18.1	0.526	0.654	0.180
	ACAG	0.613	0.566-0.660	25.4	0.351	0.857	0.208
Hospital mortality (MIMIC-IV)	AG	0.599	0.558-0.641	20.5	0.346	0.796	0.142
	ACAG	0.629	0.589-0.669	24.6	0.322	0.869	0.191
Hospital mortality (eICU-CRD)	AG	0.603	0.559-0.647	18.1	0.523	0.673	0.196
	ACAG	0.628	0.585-0.671	21.6	0.527	0.705	0.232
28-day mortality (MIMIC-IV))	AG	0.614	0.574-0.654	21.5	0.295	0.870	0.165
	ACAG	0.641	0.602-0.680	22.9	0.400	0.805	0.205

Abbreviations: AUC: area under curve, CI: confidence interval, AG: anion gap, ACAG: albumin-corrected anion gap.

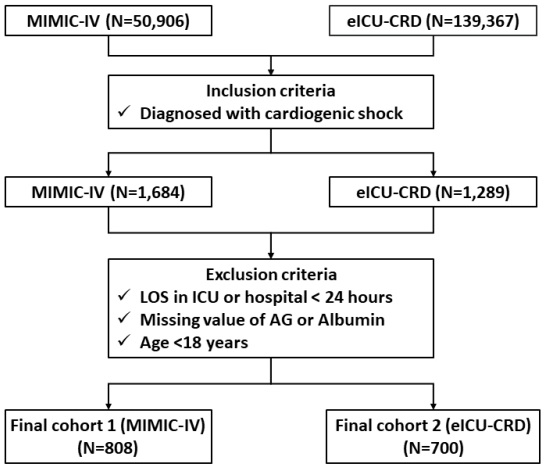
Table 3: Association between the ACAG value and short-term all-cause mortality

	Crude Model		Model I		Model II	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
28-day mortality (MIMIC-IV cohort)						
ACAG (per 1 unit)	1.07 (1.06-1.09)	<0.001	1.08 (1.06-1.10)	<0.001	1.05 (1.03-1.07)	<0.001
Higher ACAG level	1.85 (1.48-2.32)	<0.001	1.90 (1.52-2.39)	<0.001	1.42 (1.11-1.83)	0.007
ICU mortality (MIMIC-IV cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.09)	<0.001	1.07 (1.05-1.09)	<0.001	1.04 (1.01-1.06)	0.005
Higher ACAG level	1.74 (1.33-2.28)	<0.001	1.87 (1.43-1.91)	<0.001	1.43 (1.05-1.93)	0.022
ICU mortality (eICU-CRD cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.08)	<0.001	1.07 (1.05-1.09)	<0.001	1.06 (1.03-1.09)	<0.001
Higher ACAG level	1.61 (1.22-2.11)	<0.001	1.65 (1.25-2.17)	<0.001	1.38 (1.02-1.86)	0.036
In-hospital mortality (MIMIC-IV cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.08)	<0.001	1.06 (1.04-1.08)	<0.001	1.04 (1.02-1.07)	<0.001
Higher ACAG level	1.51 (1.20-1.91)	<0.001	1.58 (1.25-2.01)	<0.001	1.31 (1.01-1.71)	0.041
In-hospital mortality (eICU-CRD cohort)						
ACAG (per 1 unit)	1.06 (1.04-1.08)	<0.001	1.07 (1.05-1.09)	<0.001	1.05 (1.02-1.07)	<0.001
Higher ACAG level	1.81 (1.41-2.33)	<0.001	1.86 (1.44-2.39)	<0.001	1.47 (1.12-1.94)	0.006

Abbreviations: ACAG: albumin-corrected anion gap, HR: hazard ratio, CI: confidence interval.

Model I was adjusted for age, sex, race, and weight/body mass index.

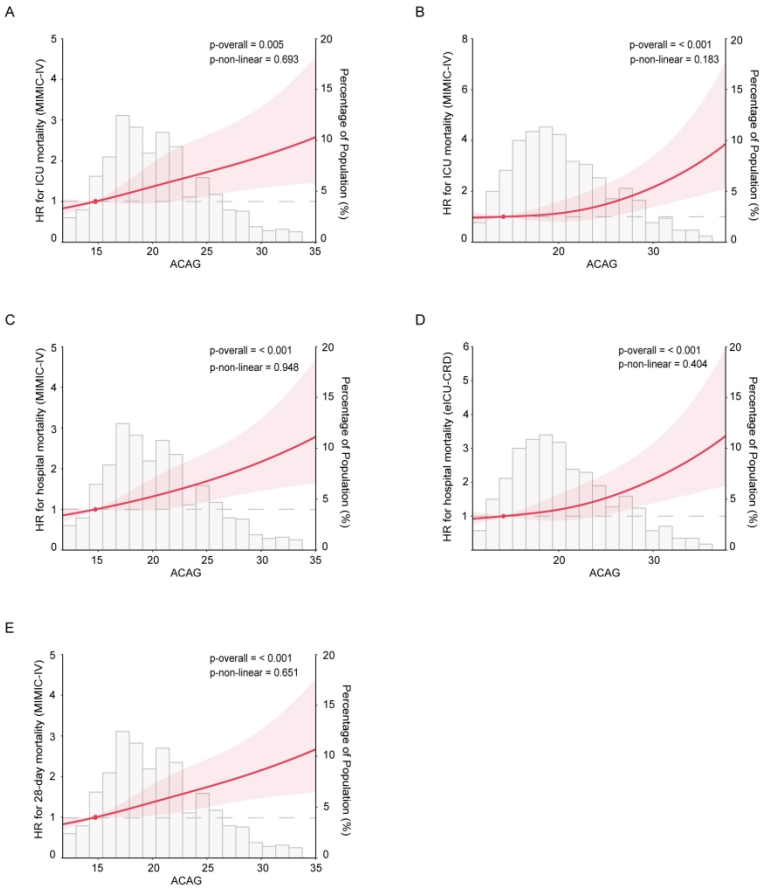
Model II was adjusted for age, sex, race, weight/body mass index, acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular heart disease, diabetes, chronic obstructive pulmonary disease, acute kidney injury, SOFA score, mean blood pressure, oxygen saturation, potassium, chloride, creatine, and total bilirubin.



The flow chart of this study

338x190mm (96 x 96 DPI)

Fig.2



Restricted cubic spline for the associations between ACAG value and short-term mortality
Fig.2A and Fig.2B showed the ICU mortality while Fig.3C and Fig.3D showed the in-hospital mortality in MIMIC-IV and eICU-CRD cohort respectively. 28-day mortality was shown in Fig.2E.
The solid lines represent the adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CI) after multivariable adjustment in Model II.
Histograms represent the distribution of concentrations of ACAG in two cohorts.

174x234mm (300 x 300 DPI)

Albumin corrected anion gap is associated with the prognosis of cardiogenic shock: a multi-center retrospective study

Online Supplement material

eTable1: Baseline characteristics of included and excluded patients in two cohorts

	MIMIC-IV cohort (n=1684)				eICU-CRD cohort (n=1289)			
	Overall (n=1684)	Excluded (n=876)	Included (n=808)	p-value	Overall (n=1289)	Excluded (n=589)	Included (n=700)	p-value
Demographic characteristics								
Age	72 (61, 81)	73 (63, 81)	70 (60, 80)	0.006*	68 (57, 77)	69 (58, 78)	67 (57, 76)	0.2
Gender				0.062				0.8
Female	684 (41%)	337 (38%)	347 (43%)		473 (37%)	218 (37%)	255 (36%)	
Male	1000 (59%)	539 (60%)	461 (57%)		816 (64%)	371 (65%)	445 (62%)	
Weight/BMI[a]	80 (68, 95)	80 (68, 95)	80 (68, 95)	0.5	28 (24, 33)	28 (24, 33)	28 (24, 33)	0.4
Ethnicity				0.3				0.2
White	1072 (64%)	575 (66%)	497 (62%)		987 (77%)	456 (77%)	531 (76%)	
Black	144 (8.6%)	73 (8.3%)	71 (8.8%)		136 (11%)	53 (9.0%)	83 (12%)	
Hispanic	32 (1.9%)	13 (1.5%)	19 (2.4%)		62 (4.8%)	30 (5.1%)	32 (4.6%)	
Asian	40 (2.4%)	22 (2.5%)	18 (2.2%)		29 (2.2%)	10 (1.7%)	19 (2.7%)	
Others/unknown	396 (24%)	193 (22%)	203 (25%)		75 (5.8%)	40 (6.8%)	35 (5.0%)	
Comorbidities								
AMI	719 (43%)	370 (42%)	349 (43%)	0.7	489 (38%)	219 (37%)	270 (39%)	0.6
Hypertension	490 (29%)	249 (28%)	241 (30%)	0.5	666 (52%)	301 (51%)	365 (52%)	0.7
Cardiomyopathy	431 (26%)	225 (26%)	206 (25%)	>0.9	221 (17%)	102 (17%)	119 (17%)	0.9
Atrial fibrillation	856 (51%)	463 (53%)	393 (49%)	0.084	250 (19%)	106 (18%)	144 (21%)	0.2
VHD	660 (39%)	367 (42%)	293 (36%)	0.018*	184 (14%)	85 (14%)	99 (14%)	0.9
AKI/ARF[a]	1,118 (66%)	549 (63%)	569 (70%)	<0.001*	533 (41%)	210 (36%)	323 (46%)	<0.001*
COPD	142 (8.4%)	71 (8.1%)	71 (8.8%)	0.6	191 (14%)	90 (15%)	101 (14%)	0.7
Diabetes	609 (36%)	326 (37%)	283 (35%)	0.4	294 (23%)	136 (23%)	158 (23%)	0.8
Malignancy	146 (8.7%)	66 (7.5%)	80 (9.9%)	0.085	28 (2.2%)	12 (2.0%)	16 (2.3%)	0.8

SOFA	8 (5, 11)	8 (5, 10)	8 (5, 11)	0.003	8 (5, 11)	7 (4, 10)	8 (6, 11)	<0.001*
Vital signs								
Heart rate	89 (77, 105)	88 (77, 103)	90 (77, 108)	0.2	90 (77, 107)	88 (76, 105)	91 (78, 108)	0.2
Respiratory rate	20 (16, 24)	20 (16, 24)	20 (17, 24)	0.056	20 (16, 24)	20 (16, 24)	20 (17, 25)	0.11
Systolic BP	109 (95, 125)	108 (93, 123)	111 (97, 129)	<0.001	106 (90, 122)	104 (88, 122)	107 (91, 122)	0.056
Mean BP	78 (67, 89)	76 (66, 88)	79 (68, 91)	<0.001	76 (64, 88)	74 (64, 87)	77 (65, 89)	0.019*
Diastolic BP	64 (52, 77)	63 (51, 75)	66 (54, 79)	<0.001	60 (49, 74)	59 (49, 71)	62 (50, 75)	0.011*
SpO2	98 (94, 100)	98 (94, 100)	97 (94, 100)	0.6	97 (93, 100)	97 (93, 100)	97 (93, 100)	0.5
Laboratory data								
White blood cell	13 (9, 17)	12 (9, 17)	13 (9, 17)	0.5	12 (9, 18)	12 (9, 17)	12 (9, 18)	0.8
Hemoglobin	11.5 (9.5, 13.2)	11.4 (9.2, 13.2)	11.5 (9.8, 13.4)	0.058	11.8 (9.9, 13.7)	11.4 (9.6, 13.3)	12.1 (10.1, 13.9)	<0.001*
Platelet	201 (147, 269)	196 (142, 257)	211 (152, 278)	0.001	192 (143, 255)	189 (140, 251)	196 (145, 260)	0.3
Sodium	138 (135, 141)	138 (135, 141)	138 (134, 141)	0.015	138 (134, 141)	138 (134, 141)	137 (134, 141)	>0.9
Potassium	4.3 (3.9, 4.9)	4.3 (3.8, 4.8)	4.4 (3.9, 5.0)	0.022	4.2 (3.7, 4.9)	4.2 (3.7, 4.8)	4.2 (3.7, 4.9)	0.5
Chloride	103 (98, 107)	103 (98, 107)	103 (98, 107)	0.3	103 (98, 107)	103 (98, 108)	103 (98, 107)	0.5
Bicarbonate	21 (18, 24)	21 (18, 24)	20 (17, 23)	<0.001	22 (18, 25)	22 (18, 25)	22 (18, 25)	0.7
AG	17 (14, 20)	16 (13, 20)	17 (14, 21)	0.003	16 (13, 21)	16 (13, 20)	17 (13, 21)	0.035*
Albumin	3.3 (2.8, 3.7)	3.2 (2.6, 3.6)	3.3 (2.9, 3.7)	0.014	3.0 (2.6, 3.4)	2.9 (2.4, 3.4)	3.0 (2.6, 3.5)	0.004*
ACAG	20.3 (17.3, 24.0)	23.5 (19.0, 30.5)	20.0 (17.0, 23.5)	<0.001	20 (17, 25)	21 (18, 27)	20 (17, 24)	<0.001*

Creatine	1.4 (1.0, 2.1)	1.4 (1.0, 2.1)	1.4 (1.0, 2.3)	0.10	1.4 (1.0, 2.3)	1.4 (1.0, 2.3)	1.5 (1.1, 2.4)	0.061
Bilirubin	0.7 (0.5, 1.2)	0.7 (0.5, 1.2)	0.7 (0.4, 1.3)	0.6	0.8 (0.5, 1.4)	0.8 (0.5, 1.4)	0.9 (0.6, 1.4)	0.6

Abbreviation: BMI: body mass index, AMI: acute myocardial infarction, AKI: acute kidney injury, ARF: acute renal failure, COPD: chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, BP: blood pressure, AG: anion gap, ACAG albumin corrected anion gap, LOS: length of stay, ICU: intensive care unit

p<0.05*

a: body weight and acute kidney injury were shown in MIMIC-IV cohort while body mass index and acute renal failure were presented in eICU-CRD cohort due to data availability.

eTable2: Baseline characteristics of enrolled patients stratified by hospital survival status in two cohorts

	MIMIC-IV cohort (n=808)				eICU-CRD cohort (n=700)			
	Overall (n=808)	Survivors (n=519)	Non-survivors (n=289)	p-value	Overall (n=700)	Survivors (n=440)	Non-survivors (n=260)	p-value
Demographic characteristics								
Age	70 (60, 80)	69 (59, 79)	74 (63, 81)	0.001*	67 (57, 76)	66 (55, 75)	70 (62, 79)	<0.001*
Gender				0.018*				0.4
Female	347 (43%)	207 (40%)	140 (48%)		255 (36%)	155 (35%)	100 (38%)	
Male	461 (57%)	312 (60%)	149 (52%)		445 (64%)	285 (65%)	160 (62%)	
Weight/BMI[a]	80 (68, 95)	80 (69, 95)	80 (66, 95)	0.7	28 (24, 33)	28 (24, 33)	28 (24, 33)	>0.9
Ethnicity				0.002*				>0.9
White	497 (62%)	336 (65%)	161 (56%)		531 (76%)	332 (75%)	199 (77%)	
Black	71 (8.8%)	51 (9.8%)	20 (6.9%)		83 (12%)	52 (12%)	31 (12%)	
Hispanic	19 (2.4%)	12 (2.3%)	7 (2.4%)		32 (4.6%)	20 (4.5%)	12 (4.6%)	
Asian	18 (2.2%)	13 (2.5%)	5 (1.7%)		19 (2.7%)	14 (3.2%)	5 (1.9%)	
Others/unknown	203 (25%)	107 (21%)	96 (33%)		35 (5.0%)	22 (5.0%)	13 (5.0%)	
Comorbidities								
AMI	349 (43%)	231 (45%)	118 (41%)	0.3	270 (39%)	181 (41%)	89 (34%)	0.070
Hypertension	241 (30%)	160 (31%)	81 (28%)	0.4	365 (52%)	226 (51%)	139 (53%)	0.6
Cardiomyopathy	206 (25%)	143 (28%)	63 (22%)	0.072	119 (17%)	80 (18%)	39 (15%)	0.3
Atrial fibrillation	393 (49%)	254 (49%)	139 (48%)	0.8	144 (21%)	88 (20%)	56 (22%)	0.6
VHD	293 (36%)	203 (39%)	90 (31%)	0.024*	99 (14%)	62 (14%)	37 (14%)	>0.9
AKI/ARF[a]	573 (71%)	334 (64%)	239 (83%)	<0.001*	323 (46%)	180 (41%)	143 (55%)	<0.001*
COPD	71 (8.8%)	46 (8.9%)	25 (8.7%)	>0.9	101 (14%)	56 (13%)	45 (17%)	0.10
Diabetes	283 (35%)	171 (33%)	112 (39%)	0.10	158 (23%)	94 (21%)	64 (25%)	0.3
Malignancy	80 (9.9%)	41 (7.9%)	39 (13%)	0.011*	16 (2.3%)	6 (1.4%)	10 (3.8%)	0.034*

SOFA	8 (5, 11)	7 (4, 10)	10 (7, 12)	<0.001*	8 (6, 11)	7 (5, 10)	10 (8, 13)	<0.001*
Vital signs								
Heart rate	90 (77, 108)	89 (75, 105)	92 (78, 111)	0.066	91 (78, 108)	90 (77, 105)	93 (78, 111)	0.088
Respiratory rate	20 (17, 24)	20 (17, 24)	21 (17, 26)	0.023*	20 (17, 25)	19 (16, 24)	20 (17, 25)	0.083
Systolic BP	111 (97, 129)	113 (98, 129)	110 (96, 125)	0.2	107 (91, 122)	107 (92, 12	107 (90, 126)	0.8
Mean BP	66 (54, 79)	67 (55, 79)	63 (52, 78)	0.022*	62 (50, 75)	62 (50, 73)	62 (50, 77)	0.3
Diastolic BP	79 (68, 91)	80 (69, 93)	78 (66, 90)	0.075	77 (65, 89)	76 (67, 88)	78 (64, 91)	0.4
SpO2	97 (94, 100)	97 (94, 100)	98 (94, 100)	0.4	97 (93, 100)	97 (94, 100)	98 (93, 100)	>0.9
Laboratory data								
White blood cell	13 (9, 17)	12 (9, 17)	13 (9, 19)	0.013*	12 (9, 18)	12 (9, 17)	13 (9, 20)	0.076
Hemoglobin	11.5 (9.8, 13.4)	11.8 (10.0, 13.7)	11.2 (9.4, 12.5)	<0.001*	12.1 (10.1, 13.9)	12.4 (10.4, 14.2)	11.6 (9.7, 13.4)	0.003*
Platelet	211 (152, 278)	216 (155, 282)	198 (146, 274)	0.076	196 (145, 260)	210 (157, 266)	182 (128, 242)	<0.001*
Sodium	138 (134, 141)	138 (134, 140)	138 (134, 141)	0.6	137 (134, 141)	137 (134, 140)	138 (134, 142)	0.13
Potassium	4.4 (3.9, 5.0)	4.4 (3.9, 4.9)	4.4 (3.8, 5.0)	>0.9	4.2 (3.7, 4.9)	4.2 (3.7, 4.8)	4.3 (3.7, 5.1)	0.15
Chloride	103 (98, 107)	103 (98, 107)	103 (98, 107)	0.6	103 (98, 107)	103 (99, 107)	103 (98, 107)	>0.9
Bicarbonate	20 (17, 23)	21 (18, 24)	20 (16, 23)	<0.001*	22 (18, 25)	22 (19, 25)	21 (17, 24)	0.002*
AG	17 (14, 21)	16 (14, 20)	18 (15, 22)	<0.001*	17 (13, 21)	16 (13, 19)	18 (14, 23)	<0.001*
Albumin	3.3 (2.9, 3.7)	3.4 (3.0, 3.7)	3.1 (2.7, 3.6)	<0.001*	3.0 (2.6, 3.5)	3.1 (2.7, 3.6)	2.9 (2.5, 3.3)	<0.001*
ACAG	20.0 (17.0, 23.5)	19.0 (16.5, 22.5)	21.0 (18.0, 25.3)	<0.001*	19.9 (16.7, 24.2)	19.0 (16.2, 23.0)	22.0 (17.7, 27.0)	<0.001*
Creatine	1.4 (1.0, 2.3)	1.4 (1.0, 2.1)	1.6 (1.1, 2.6)	<0.001*	1.5 (1.1, 2.4)	1.4 (1.1, 2.3)	1.6 (1.2, 2.4)	0.021*

Bilirubin	0.7 (0.4, 1.3)	0.7 (0.5, 1.2)	0.7 (0.4, 1.4)	0.4	0.8 (0.5, 1.4)	0.8 (0.5, 1.5)	0.9 (0.6, 1.5)	0.065

Abbreviation: BMI: body mass index, AMI: acute myocardial infarction, AKI: acute kidney injury, ARF: acute renal failure, COPD: chronic obstructive pulmonary disease, SOFA sequential organ failure assessment, BP: blood pressure, AG: anion gap, ACAG albumin corrected anion gap, LOS: length of stay, ICU: intensive care unit

p<0.05*

a: body weight and acute kidney injury were shown in MIMIC-IV cohort while body mass index and acute renal failure were presented in eICU-CRD cohort due to data availability.

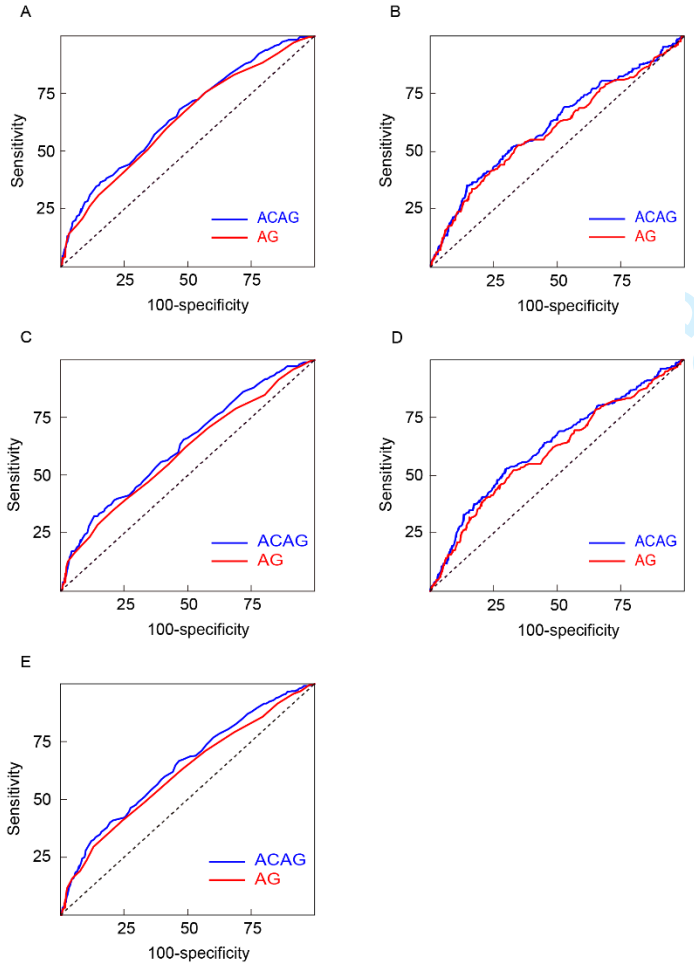
eTable3: Association of ACAG and earlier discharge alive in ICU

	Crude Model		Model I		Model II	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
LOS in ICU (MIMIC-IV cohort)						
ACAG	0.94 (0.92-0.95)	<0.001	0.94 (0.92-0.95)	<0.001	0.96 (0.94-0.98)	<0.001
Higher ACAG	0.62 (0.53-0.73)	<0.001	0.61 (0.52-0.72)	<0.001	0.77 (0.66-0.92)	0.004
LOS in ICU (eICU-CRD cohort)						
ACAG	0.96 (0.95-0.98)	<0.001	0.96 (0.94-0.98)	<0.001	0.97 (0.95-0.99)	0.001
Higher ACAG	0.74 (0.62-0.88)	<0.001	0.73 (0.61-0.88)	<0.001	0.85 (0.71-1.04)	0.140

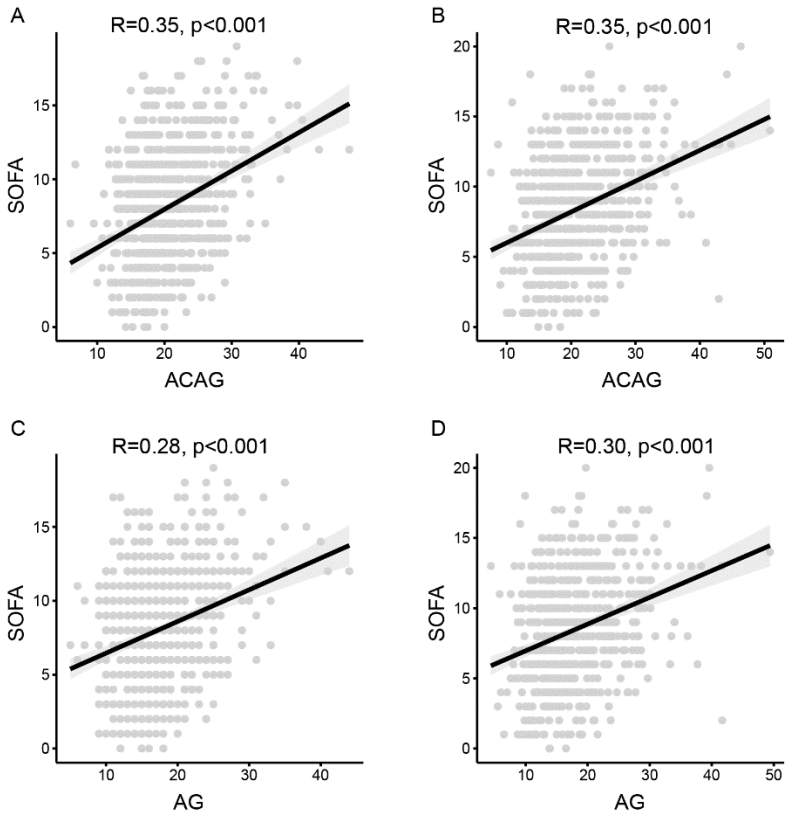
Model I adjusted for age, gender, race, and weight/body mass index

Model II adjusted for age, gender, race, weight/body mass index, acute myocardial infarction, cardiomyopathy, atrial fibrillation, valvular heart disease, diabetes, chronic obstructive pulmonary disease, acute kidney injury, SOFA score, mean blood pressure, oxygen saturation, potassium, chloride, creatinine, and total bilirubin.

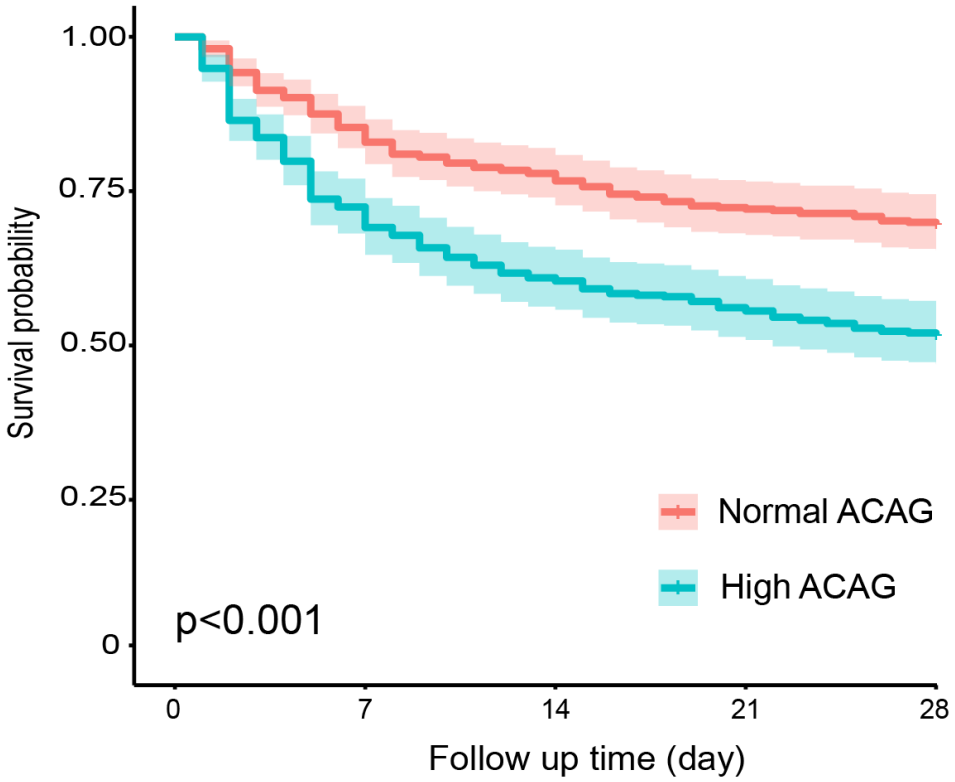
eFigure1: ROC curve analysis of AG, ACAG and ICU mortality (A: MIMIC-IV cohort; B: eICU-CRD cohort), in-hospital morality (C: MIMIC-IV cohort; D: eICU-CRD cohort), and 28-day mortality (E: MIMIC-IV cohort)



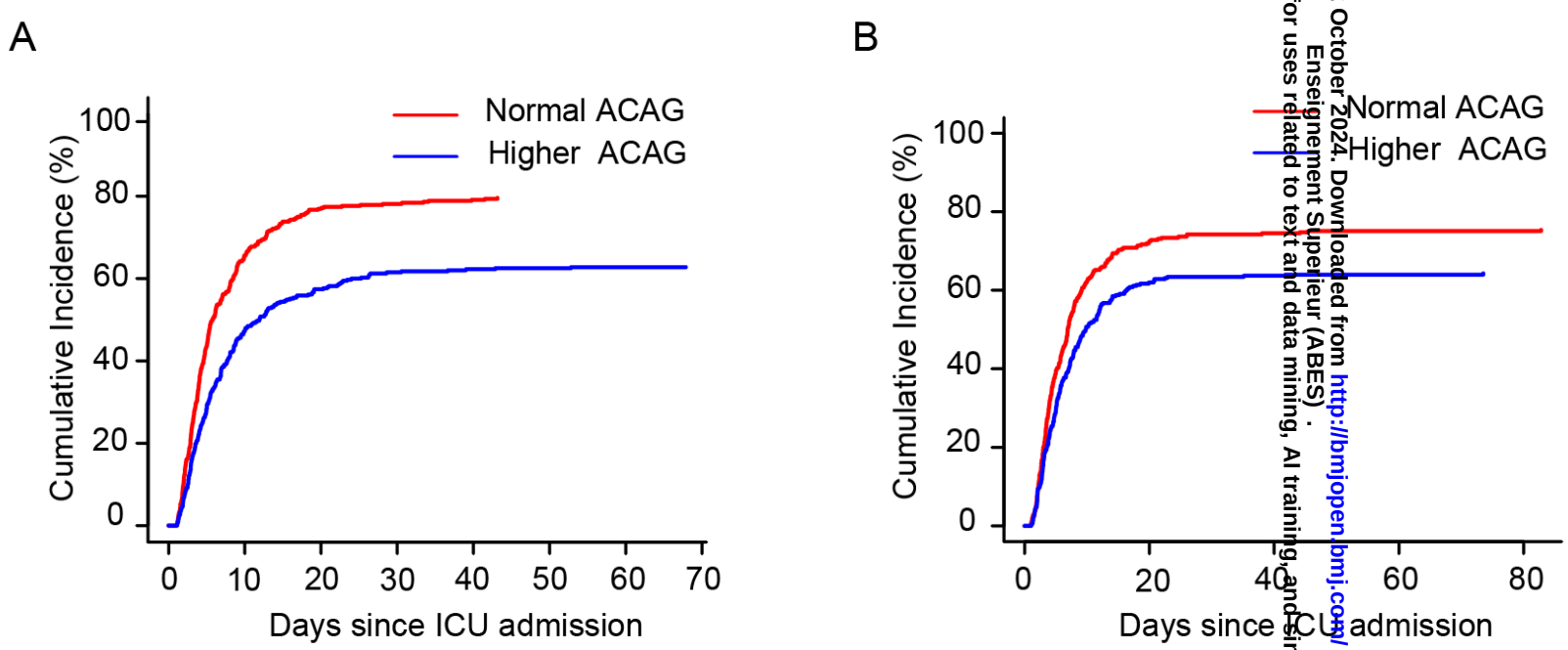
eFigure2: Pearson correlation analyses of AC/ACAG and SOFA score in MIMIC-IV cohort (A, C) and eICU-CRD cohort (B, D)



eFigure3: Kaplan–Meier survival curve of ACAG levels and 28-day all-cause mortality

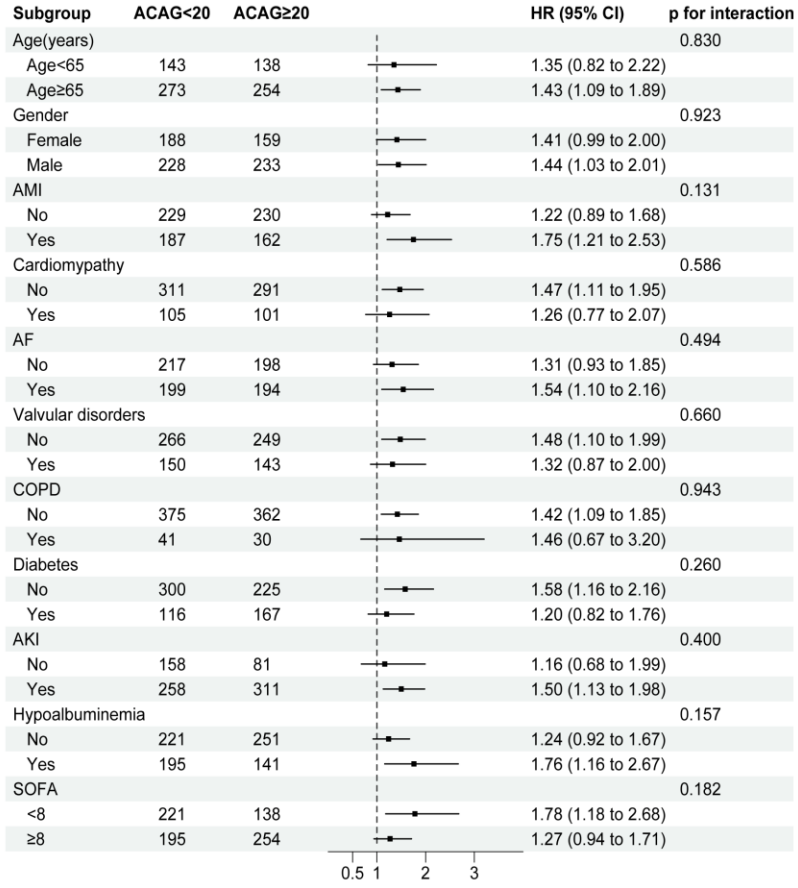


eFigure4: Cumulative incidence ratio of earlier discharge alive in the ICU in MIMIC-IV cohort (A) and eICU-CRD cohort (B)



eFigure5: Subgroup analysis

ACAG: albumin corrected anion gap, HR: hazard ratio, CI: confidence interval, AMI: acute myocardial infarction, AF:atrial fibrillation, COPD: chronic obstructive pulmonary disease, AKI: acute kidney injury, SOFA: Sequential Organ Failure Assessment



Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods	3

		of recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	4
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4
Bias	#9	Describe any efforts to address potential sources of bias	4
Study size	#10	Explain how the study size was arrived at	4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5
Statistical methods	#12c	Explain how missing data were addressed	5
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	5
Statistical methods	#12e	Describe any sensitivity analyses	5
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible,	6

		included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	6
Participants	#13c	Consider use of a flow diagram	6
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	6
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	4
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	7
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	7
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8

Discussion

Key results	#18	Summarise key results with reference to study objectives	8
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	10
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	9
Generalisability	#21	Discuss the generalisability (external validity) of the study results	10
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

 This checklist was completed on 01. November 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai