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ORIGINAL RESEARCH

Association between albumin corrected anion gap (ACAG) and all-cause mortality in intensive care unit heart failure patients treated with inotropes and vasopressors

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Abstract

Background: To eliminate the influence of serum albumin level on anion gap, the albumin-corrected anion gap (ACAG) is introduced into clinic. There is increasing evidence suggesting that ACAG functions as an early prognostic indicator in patients with cardiovascular diseases and critical illnesses. However, as a novel parameter, many aspects of its clinical utility remain uncertain. In particular, the relationship between ACAG and the risk of in-hospital mortality in intensive care unit (ICU) heart failure patients treated with inotropes or vasopressors and whether ACAG could enhance sequential organ failure assessment (SOFA) and acute physiology score III (APS III) scores remains inconclusive. **Methods**: This study assessed patients with heart failure requiring inotropes or vasopressors from the eICU Collaborative Research Database (eICU-CRD) and the Medical Information Mart for Intensive Care IV database (MIMIC-IV). **Results**: Analysis of eICU-CRD data revealed that elevated ACAG was independently associated with all-cause mortality, with odds ratios of 1.14 (95% confidence interval (CI), 1.09–1.18), 1.41 (95% CI, 1.36–1.47), and 2.29 (95% CI, 2.20–2.38) for Q2 to Q4 groups compared to the lowest quartile for ACAG. The restricted cubic spline regression demonstrated a linear relationship, which remained consistent across various subgroups (p for interaction > 0.05 for all). Analysis of MIMIC-IV data indicated that the inclusion of ACAG significantly enhanced the prognostic value based on SOFA and APS III. In addition, the area under the curve for SOFA increased from 0.740 to 0.772 ($p < 0.001$), and for APS III increased from 0.815 to 0.824 ($p < 0.001$). **Conclusions**: ACAG was shown to be independently associated with the risk of all-cause mortality in heart failure patients requiring inotropes or vasopressors in the ICU, and it could serve as a potent supplement to SOFA and APS III.

Keywords

Anion gap; Heart failure; Intensive care unit; Mortality

1. Introduction

Heart failure manifests as a clinical syndrome marked by impaired cardiac pump function, which can lead to poor prognosis for patients. In developed nations such as the United States, approximately 10%–15% of hospitalized heart failure cases require intensive care unit (ICU) admission for advanced critical care [1]. In the ICU, these patients often necessitate inotropes and vasopressors, indicating more severe disease states and heightened mortality risks [2]. Thus, accurate evaluation of adverse event risks is essential for efficiently allocating medical resources and implementing proactive interventions. To assess risk in critically ill patients, existing scoring systems such as the Sequential Organ Failure Assessment (SOFA) and Acute Physiology Score III (APS III) scores are commonly utilized [2, 3]. However, these scores exhibit significant heterogeneity, and their effectiveness in assessing conditions varies across different populations [4–6], thereby presenting challenges in clinical decision-making and highlighting the need for more reliable prognostic factors to enhance the risk prediction system.

Notably, heart failure patients frequently develop metabolic acidosis as a result of hemodynamic disruptions and diuretic usage, which may significantly contribute to their poor prognosis [7]. The anion gap is a laboratory parameter commonly used for assessing metabolic acidosis [8]. Albumin, the primary unmeasured anion in plasma, plays a crucial role in maintaining a normal anion gap [9]. To counteract the impact of decreased albumin levels on the anion gap, researchers have introduced the concept of the albumin-corrected anion

gap (ACAG). Growing evidence indicates that ACAG serves as an indicator of poor prognosis in critically ill individuals. A retrospective analysis has demonstrated that ACAG levels could assess the risk of in-hospital mortality in ICU patients with sepsis, outperforming both the anion gap and albumin [10]. Another study indicated that elevated ACAG was a distinct risk factor for in-hospital mortality in ICU patients with cardiac arrest [11]. However, the association between ACAG and the risk of in-hospital mortality in ICU heart failure patients requiring inotropes and vasopressors remains uncertain.

In this study, we analyzed the clinical data from ICU patients diagnosed with congestive heart failure based on international classification of diseases (ICD-9 and ICD-10) codes and receiving inotropic and pressor therapy. We hypothesized that ACAG levels were associated with the risk of in-hospital mortality in those patients and may represent a valuable supplement to SOFA and APS III scores. The potential integration of ACAG could help mitigate the variability of scores and improve the risk assessment system.

2. Materials and methods

2.1 Study population

It was a retrospective analysis. Data was obtained from two databases: the eICU Collaborative Research Database (eICU-CRD) and the Medical Information Mart for Intensive Care IV (MIMIC-IV). The eICU-CRD, a multi-center database established by Philips Healthcare, contains a wide range of information, including demographic data, vital signs, laboratory test results, medication treatments, nursing records and severity of illness scores across more than 200 hospitals in the United States. MIMIC-IV, a single-center database, contains data on over 190,000 ICU patients from 2008 to 2019, including demographic records, vital signs from bedside monitors, laboratory tests, diagnoses coded by ICD-9 and ICD-10, and other important patient clinical characteristics.

2.2 Inclusion and exclusion criteria

Data on congestive heart failure patients were extracted from databases using ICD-9 and ICD-10 codes (**Supplementary Table 1**). The inclusion criteria comprised all patients diagnosed with congestive heart failure and treated with inotropes and vasopressors. The exclusion criteria were: (a) patients under the age of 18, (b) non-first ICU admissions, (c) ICU stays of less than 24 hours and (d) absence of treatment with inotropes and vasopressors. Ultimately, the eICU-CRD and MIMIC-IV databases were utilized to recruit 1622 and 4583 patients for this study, as illustrated in the study flowchart (Fig. 1). This study constituted a secondary analysis based on the datasets, with all patient privacy information de-identified, thereby obviating the need for obtaining patient informed consent.

2.3 Data collection and outcome definition

Clinical data were initially gathered within 24 hours following ICU admission, encompassing demographic characteristics (gender, age), comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease (COPD)), vital signs upon admission (arterial oxygen saturation (SpO_2), heart rate, respiratory rate, systolic and mean blood pressure), severity scores (SOFA and APS III), laboratory tests (white blood

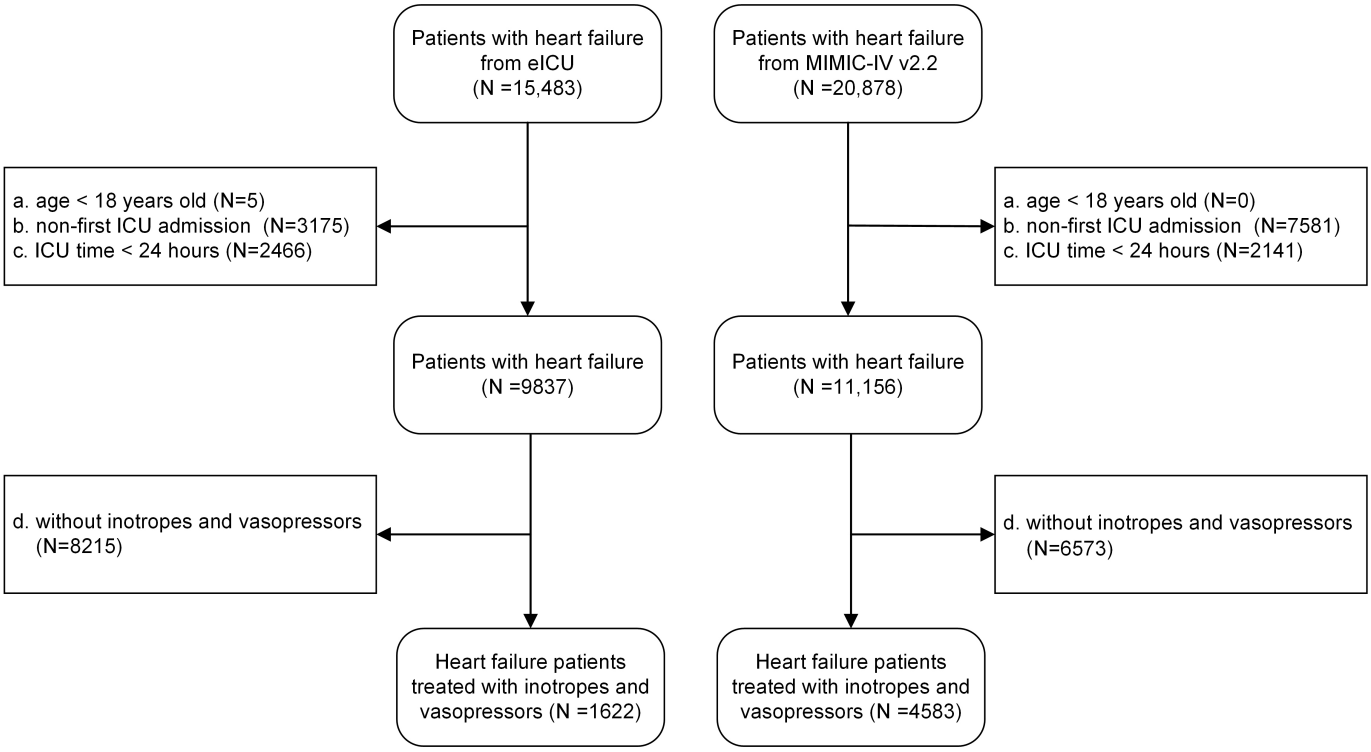

FIGURE 1. Flowchart of data selection from the eICU-CRD and MIMIC-IV datasets. eICU-CRD: The eICU Collaborative Research Database; MIMIC-IV: Medical Information Mart for Intensive Care IV.

cell count (WBC), platelets, neutrophils, hemoglobin, red cell distribution width (RDW), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, total protein, albumin, blood urea nitrogen (BUN), creatinine, anion gap (AG), bicarbonate), and treatments (dopamine, dobutamine, milrinone, phenylephrine, norepinephrine, epinephrine, vasopressin, mechanical ventilation, renal replacement therapy (RRT)). The same parameters were extracted from the MIMIC-IV database. Data extraction was conducted using the PostgreSQL programming language from both eICU-CRD and MIMIC-IV. Utilization of inotropes and vasopressors was defined as the necessity for dopamine, dobutamine, milrinone, phenylephrine, norepinephrine, epinephrine or vasopressin. ACAG was calculated using the following formula: ACAG (mmol/L) = AG (mmol/L) + [4.4 − albumin (g/dL)] × 2.5 [12]. The primary endpoint was defined as the occurrence of all-cause mortality during hospitalization.

2.4 Statistical analysis

Normally distributed variables were presented as mean ± standard deviation, non-normally distributed variables as median (interquartile range), and categorical variables as percentages. Clinical characteristics and mortality rates were compared across ACAG quartiles (Q1, Q2, Q3, Q4) using the Kruskal-Wallis H test, chi-square test, or analysis of variance, as appropriate.

In the eICU-CRD, this study investigated the association between AG or ACAG and in-hospital all-cause mortality. Initially, AG or ACAG was considered as a categorical variable (quartiles), ranked variable (per quartile increase), and continuous variable (per unit increase). Four distinct logistic regression models were employed to estimate the odds ratios (OR) and 95% confidence intervals (CI) for all-cause mortality, with corresponding tests for trends. Model 0 solely included AG or ACAG; Model 1 adjusted for gender and age; Model 2 adjusted for age, gender, SpO_2, neutrophils, RDW, albumin, BUN, sodium, chloride, mechanical ventilation and RRT; Model 3 adjusted for the same covariates as Model 2 plus SOFA and APS III scores. Subsequently, restricted cubic splines were employed to delineate the linear or curvilinear relationship between ACAG and all-cause mortality. Further, subgroup and interaction effect analyses for the association between ACAG and mortality were conducted.

In MIMIC-IV, this study investigated the incremental value of AG or ACAG on SOFA and APS III scores to enhance the robustness of the analysis results. Receiver operating characteristic (ROC) curves and clinical decision curves were generated, incorporating AG or ACAG, SOFA, APS III, AG or ACAG plus SOFA, and AG or ACAG plus APS III, to compare their predictive abilities regarding in-hospital mortality among ICU heart failure patients requiring inotropes and vasopressors. All statistical analyses were conducted using R (version 4.3.1), with significance level set at $p < 0.05$.

3. Results

3.1 Population baseline characteristics

Tables 1 and 2 presented the baseline characteristics of all participants, categorized by quartile of ACAG. The study included a total of 1622 patients from the eICU-CRD dataset and 4583 patients from the MIMIC-IV dataset. Among them, patients with higher ACAG demonstrated a higher proportion of RRT, elevated heart and respiratory rates, increased WBC counts, higher SOFA and APS III scores, more severe liver and kidney damage, and lower levels of albumin, chloride and bicarbonate. Endpoint events occurred in 24.97% (405/1622) and 17.41% (798/4583) of patients, respectively. Notably, patients with higher ACAG exhibited higher in-hospital mortality rates.

3.2 Odd ratios for all-cause mortality

Compared with AG, ACAG demonstrated a stronger prognostic effect on all-cause mortality risk (Table 3). In Model 3, the multivariable odds ratios (ORs) for all-cause mortality in the Q2, Q3 and Q4 groups of ACAG (with Q1 as the reference) were 1.14 (95% CI, 1.09–1.18), 1.41 (95% CI, 1.36–1.47), and 2.29 (95% CI, 2.20–2.38), respectively, after adjusting for age, gender, SpO_2, neutrophils, RDW, albumin, BUN, sodium, chloride, RRT, mechanical ventilation, SOFA and APS III cores (p for trend < 0.001) (Table 3). Treating ACAG as a ranking variable, each quartile increase in ACAG corresponded to a 22% increase in the multivariable mortality risk (OR 1.22, $p < 0.001$). Additionally, each unit increase in ACAG was associated with a 6% rise in the mortality risk (OR 1.06, 95% CI, 1.06–1.06) (Table 3). The multivariable restricted cubic spline (RCS) regression model revealed a linear correlation between ACAG and overall mortality risk (Fig. 2A) (p for nonlinearity = 0.306), indicating that as ACAG levels increased, the likelihood of all-cause mortality increased.

3.3 Subgroup analysis

The subgroup analysis assessed the association between ACAG and all-cause mortality in various subgroups stratified by age, gender, diabetes, hypertension, COPD, RRT, mechanical ventilation, SOFA and APS III. Furthermore, interaction effect tests were conducted (Fig. 2B). The results revealed that elevated ACAG levels were linked with increased all-cause mortality, and this positive association remained consistent across all subgroups (p for interaction > 0.05).

3.4 Additional prognostic value of ACAG

The results of ROC curve analysis demonstrated that the inclusion of ACAG to SOFA and APS III scores significantly improved the accuracy of prognostic assessment (Fig. 3). Notably, ACAG provided a more substantial enhancement. Specifically, the area under the ROC curve (AUC) for ACAG was higher than for AG (0.719 *vs.* 0.690, $p < 0.001$). When AG or ACAG was combined with SOFA (AUC 0.740), the AUC increased to 0.763 or 0.772 (DeLong's test for 0.763 and 0.772, $p < 0.001$), and when combined with APS III (AUC 0.815), the AUC increased from 0.822 to 0.824 (DeLong's test for 0.822 and 0.824, $p = 0.005$). Furthermore, decision curve analysis revealed similar results.

TABLE 1. Baseline characteristics of eICU-CRD participants according to quartiles of albumin-corrected anion gap.

Characteristic	Overall (n = 1622)	Q1 (n = 405)	Q2 (n = 406)	Q3 (n = 405)	Q4 (n = 406)	*p* value
Male, n (%)	943 (58.1)	240 (59.3)	244 (60.1)	233 (57.5)	226 (55.7)	0.587
Diabetes, n (%)	617 (38.0)	150 (37.0)	150 (36.9)	151 (37.3)	166 (40.9)	0.599
Hypertension, n (%)	1030 (63.5)	242 (59.8)	270 (66.5)	252 (62.2)	266 (65.5)	0.170
COPD, n (%)	231 (14.2)	64 (15.8)	60 (14.8)	48 (11.9)	59 (14.5)	0.419
Age (mean (SD))	70.28 (13.19)	71.96 (12.45)	70.64 (13.97)	70.01 (13.40)	68.54 (12.71)	0.003
BMI (mean (SD))	29.31 (6.94)	29.33 (7.07)	29.32 (6.83)	29.14 (6.80)	29.44 (7.08)	0.938
SOFA (mean (SD))	7.99 (3.37)	7.56 (3.11)	7.67 (3.34)	7.83 (3.29)	8.90 (3.56)	<0.001
APS III (mean (SD))	61.88 (28.04)	57.44 (25.72)	58.69 (26.20)	61.55 (28.71)	69.81 (29.75)	<0.001
Heart rate (mean (SD))	92.05 (22.18)	88.06 (21.28)	89.86 (20.03)	94.19 (22.88)	96.07 (23.50)	<0.001
Respiratory rate (mean (SD))	20.98 (5.49)	20.46 (5.53)	20.83 (5.24)	21.02 (5.48)	21.61 (5.67)	0.025
SpO_2 (mean (SD))	95.46 (6.09)	95.43 (6.21)	95.71 (6.59)	95.38 (5.74)	95.32 (5.79)	0.801
MBP (mean (SD))	75.63 (19.09)	77.47 (19.55)	74.98 (18.26)	74.48 (18.66)	75.60 (19.77)	0.126
WBC (mean (SD))	12.31 (6.87)	10.75 (5.76)	11.85 (6.55)	13.07 (7.52)	13.55 (7.20)	<0.001
Hemoglobin (mean (SD))	11.56 (2.49)	11.70 (2.31)	11.52 (2.37)	11.46 (2.59)	11.55 (2.66)	0.572
Platelets (mean (SD))	211.27 (100.61)	204.74 (86.37)	208.93 (108.76)	218.58 (99.32)	212.83 (106.32)	0.245
RDW (mean (SD))	16.37 (2.55)	16.11 (2.47)	16.51 (2.58)	16.26 (2.67)	16.60 (2.46)	0.025
Neutrophils (mean (SD))	75.85 (14.36)	73.79 (14.48)	76.49 (12.58)	76.90 (14.11)	76.21 (15.93)	0.009
Total protein (mean (SD))	6.41 (1.05)	6.58 (0.99)	6.37 (1.03)	6.34 (1.03)	6.36 (1.13)	0.002
Albumin (mean (SD))	3.03 (0.64)	3.26 (0.58)	3.04 (0.63)	2.94 (0.65)	2.87 (0.66)	<0.001
ALT (mean (SD))	116.08 (425.36)	77.46 (229.67)	83.91 (252.79)	99.49 (367.55)	203.32 (680.05)	<0.001
AST (mean (SD))	163.46 (611.25)	102.60 (352.22)	100.49 (313.02)	146.54 (528.68)	304.00 (983.42)	<0.001
ALP (mean (SD))	117.76 (109.39)	103.57 (90.36)	113.84 (96.82)	122.51 (124.61)	131.08 (120.30)	0.003
Total bilirubin (mean (SD))	1.18 (1.26)	0.98 (0.89)	1.10 (1.04)	1.17 (1.20)	1.45 (1.70)	<0.001
BUN (mean (SD))	38.87 (26.24)	32.48 (19.75)	36.14 (23.34)	39.94 (26.11)	46.90 (32.07)	<0.001
Creatinine (mean (SD))	2.05 (1.73)	1.48 (0.87)	1.92 (1.38)	2.07 (1.63)	2.74 (2.40)	<0.001
Sodium (mean (SD))	136.38 (5.49)	137.07 (4.87)	136.37 (5.27)	136.29 (5.68)	135.79 (6.00)	0.010
Calcium (mean (SD))	8.54 (0.93)	8.67 (0.82)	8.58 (0.85)	8.50 (0.96)	8.42 (1.07)	0.001
Chloride (mean (SD))	100.45 (6.96)	101.54 (6.17)	101.26 (6.77)	100.40 (6.91)	98.61 (7.55)	<0.001
Potassium (mean (SD))	4.36 (0.85)	4.38 (0.73)	4.31 (0.78)	4.27 (0.79)	4.50 (1.03)	<0.001
Aniongap (mean (SD))	12.38 (5.23)	6.72 (2.09)	10.25 (1.72)	13.33 (1.91)	19.19 (3.80)	<0.001
Bicarbonate (mean (SD))	24.67 (5.77)	28.15 (5.44)	25.39 (4.78)	24.08 (4.80)	21.06 (5.67)	<0.001
RRT, n (%)	144 (8.9)	20 (4.9)	30 (7.4)	37 (9.1)	57 (14.0)	<0.001
Ventilation, n (%)	977 (60.2)	272 (67.2)	235 (57.9)	235 (58.0)	235 (57.9)	0.013
Mortality, n (%)	405 (25.0)	75 (18.5)	85 (20.9)	105 (25.9)	140 (34.5)	<0.001

SD: standard deviation; COPD: chronic obstructive pulmonary disease; BMI: body mass index; SOFA: Sequential Organ Failure Assessment; APS III: Acute Physiology Score III; SpO_2: arterial oxygen saturation; MBP: mean blood pressure; WBC: white blood cell count; RDW: red cell distribution width; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; BUN: blood urea nitrogen; RRT: renal replacement therapy.

TABLE 2. Baseline characteristics of MIMIC-IV participants according to quartiles of albumin-corrected anion gap.

Characteristic	Overall (n = 4583)	Q1 (n = 1146)	Q2 (n = 1146)	Q3 (n = 1146)	Q4 (n = 1145)	*p* value
Male, n (%)	2728 (59.5)	727 (63.4)	680 (59.3)	654 (57.1)	667 (58.3)	0.012
Diabetes, n (%)	1796 (39.2)	401 (35.0)	411 (35.9)	468 (40.8)	516 (45.1)	<0.001
Hypertension, n (%)	3439 (75.0)	866 (75.6)	863 (75.3)	855 (74.6)	855 (74.7)	0.938
COPD, n (%)	878 (19.2)	219 (19.1)	236 (20.6)	219 (19.1)	204 (17.8)	0.414
Age (mean (SD))	72.28 (12.88)	72.15 (11.79)	72.25 (13.01)	73.26 (12.56)	71.47 (14.03)	0.010
BMI (mean (SD))	28.49 (6.00)	28.15 (5.84)	28.74 (6.19)	28.51 (6.04)	28.55 (5.91)	0.119
SOFA (mean (SD))	8.19 (3.67)	6.65 (2.91)	7.19 (3.26)	8.48 (3.48)	10.45 (3.77)	<0.001
APSIII (mean (SD))	58.27 (26.03)	45.15 (19.86)	51.15 (22.00)	61.97 (24.43)	74.84 (26.94)	<0.001
Heart rate (mean (SD))	86.80 (18.12)	82.21 (14.16)	84.82 (16.61)	88.31 (19.28)	91.87 (20.34)	<0.001
Respiratory rate (mean (SD))	18.38 (5.21)	16.42 (4.43)	17.54 (4.82)	18.93 (5.20)	20.64 (5.36)	<0.001
SpO_2 (mean (SD))	97.04 (4.45)	98.10 (3.39)	97.38 (4.11)	96.76 (4.45)	95.92 (5.35)	<0.001
MBP (mean (SD))	74.31 (16.56)	73.17 (15.65)	74.59 (16.35)	74.22 (16.62)	75.29 (17.51)	0.020
WBC (mean (SD))	13.47 (8.33)	12.58 (7.85)	12.83 (9.25)	13.42 (7.27)	15.05 (8.60)	<0.001
Hemoglobin (mean (SD))	10.48 (2.36)	10.04 (2.07)	10.35 (2.31)	10.65 (2.36)	10.86 (2.59)	<0.001
Platelets (mean (SD))	201.72 (104.23)	174.50 (76.82)	195.51 (88.31)	215.95 (118.20)	220.94 (120.25)	<0.001
RDW (mean (SD))	15.37 (2.33)	14.66 (1.89)	15.12 (2.11)	15.58 (2.29)	16.13 (2.71)	<0.001
Neutrophils (mean (SD))	11.20 (6.65)	10.00 (5.55)	10.36 (6.07)	11.46 (6.61)	12.99 (7.75)	<0.001
Total protein (mean (SD))	5.48 (1.03)	5.62 (1.03)	5.48 (0.99)	5.43 (1.05)	5.38 (1.05)	<0.001
Albumin (mean (SD))	3.11 (0.62)	3.23 (0.58)	3.09 (0.62)	3.05 (0.61)	3.05 (0.66)	<0.001
ALT (mean (SD))	112.69 (456.16)	66.97 (300.39)	66.04 (214.85)	83.50 (233.28)	234.35 (788.99)	<0.001
AST (mean (SD))	192.62 (837.29)	113.23 (540.84)	104.52 (264.92)	135.85 (370.52)	417.09 (1496.57)	<0.001
ALP (mean (SD))	104.38 (96.23)	82.46 (55.02)	96.01 (98.79)	107.94 (94.65)	131.15 (118.51)	<0.001
Total bilirubin (mean (SD))	1.09 (1.88)	0.81 (0.94)	0.82 (0.75)	1.14 (1.77)	1.60 (3.03)	<0.001
BUN (mean (SD))	33.34 (24.85)	22.16 (13.24)	26.68 (16.03)	34.65 (22.41)	49.87 (33.05)	<0.001
Creatinine (mean (SD))	1.73 (1.56)	1.06 (0.63)	1.28 (0.81)	1.76 (1.41)	2.81 (2.21)	<0.001
Sodium (mean (SD))	137.97 (4.93)	138.67 (3.70)	138.63 (4.20)	137.68 (5.24)	136.92 (6.03)	<0.001
Calcium (mean (SD))	8.36 (1.39)	8.42 (2.27)	8.36 (0.87)	8.34 (0.89)	8.33 (1.03)	0.466
Chloride (mean (SD))	103.40 (7.10)	106.82 (5.93)	104.87 (6.02)	102.56 (6.67)	99.37 (7.41)	<0.001
Potassium (mean (SD))	4.41 (0.85)	4.31 (0.61)	4.28 (0.76)	4.36 (0.85)	4.68 (1.05)	<0.001
Aniongap (mean (SD))	15.59 (5.16)	10.52 (1.87)	13.44 (1.70)	16.21 (1.81)	22.19 (4.78)	<0.001
Bicarbonate (mean (SD))	22.57 (4.90)	24.99 (4.09)	23.84 (3.98)	22.45 (4.24)	18.98 (5.03)	<0.001
RRT, n (%)	314 (6.9)	16 (1.4)	31 (2.7)	71 (6.2)	196 (17.1)	<0.001
Ventilation, n (%)	2949 (64.3)	791 (69.0)	723 (63.1)	707 (61.7)	728 (63.6)	0.001
Mortality, n (%)	798 (17.4)	66 (5.8)	111 (9.7)	235 (20.5)	386 (33.7)	<0.001

SD: standard deviation; COPD: chronic obstructive pulmonary disease; BMI: body mass index; SOFA: Sequential Organ Failure Assessment; APS III: Acute Physiology Score III; SpO_2: arterial oxygen saturation; MBP: mean blood pressure; WBC: white blood cell count; RDW: red cell distribution width; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; BUN: blood urea nitrogen; RRT: renal replacement therapy.

TABLE 3. Logistic models for the association between anion gap or albumin-corrected anion gap and all-cause in-hospital mortality.

ACAG or AG	Case/Total	Model 0	Model 1	Model 2	Model 3
Quartiles			Odds Ratios		
ACAG Q1	405/1622	reference	reference	reference	reference
ACAG Q2	406/1622	1.17 (0.82, 1.65)	1.20 (0.84, 1.70)	1.11 (0.78, 1.60)	1.14 (1.09, 1.18)
ACAG Q3	405/1622	1.54 (1.10, 2.16)	1.62 (1.16, 2.28)	1.47 (1.03, 2.10)	1.41 (1.36, 1.47)
ACAG Q4	406/1622	2.32 (1.68, 3.21)	2.57 (1.85, 3.58)	2.13 (1.50, 3.06)	2.29 (2.20, 2.38)
p for trend		<0.001	<0.001	<0.001	<0.001
Per ACAG quartiles increase	1622/1622	1.33 (1.20, 1.48)	1.38 (1.24, 1.50)	1.30 (1.16, 1.46)	1.22 (1.08, 1.37)
Per ACAG unit increase	1622/1622	1.07 (1.04, 1.09)	1.07 (1.05, 1.10)	1.06 (1.03, 1.08)	1.06 (1.06, 1.06)
AG Q1	405/1622	reference	reference	reference	reference
AG Q2	406/1622	1.06 (0.75, 1.49)	1.07 (0.76, 1.51)	1.13 (0.80, 1.62)	1.09 (0.76, 1.57)
AG Q3	405/1622	1.41 (1.02, 1.97)	1.42 (1.02, 1.97)	1.51 (1.07, 2.14)	1.46 (1.03, 2.08)
AG Q4	406/1622	1.86 (1.35, 2.56)	2.03 (1.47, 2.81)	2.16 (1.52, 3.09)	1.73 (1.20, 2.49)
p for trend		<0.001	<0.001	<0.001	<0.001
Per AG quartiles increase	1622/1622	1.24 (1.12, 1.38)	1.28 (1.15, 1.42)	1.30 (1.16, 1.46)	1.21 (1.08, 1.36)
Per AG unit increase	1622/1622	1.05 (1.03, 1.07)	1.06 (1.03, 1.08)	1.06 (1.03, 1.08)	1.04 (1.02, 1.07)

Model 0: anion gap or albumin-corrected anion gap without adjust; Model 1: age and gender were adjusted; Model 2: age, gender, SpO_2, neutrophils, RDW, albumin, BUN, sodium, chloride, RRT and ventilation were adjusted; Model 3: the variables in model 2 plus SOFA and APS III were adjusted.
ACAG: albumin-corrected anion gap; AG: anion gap.

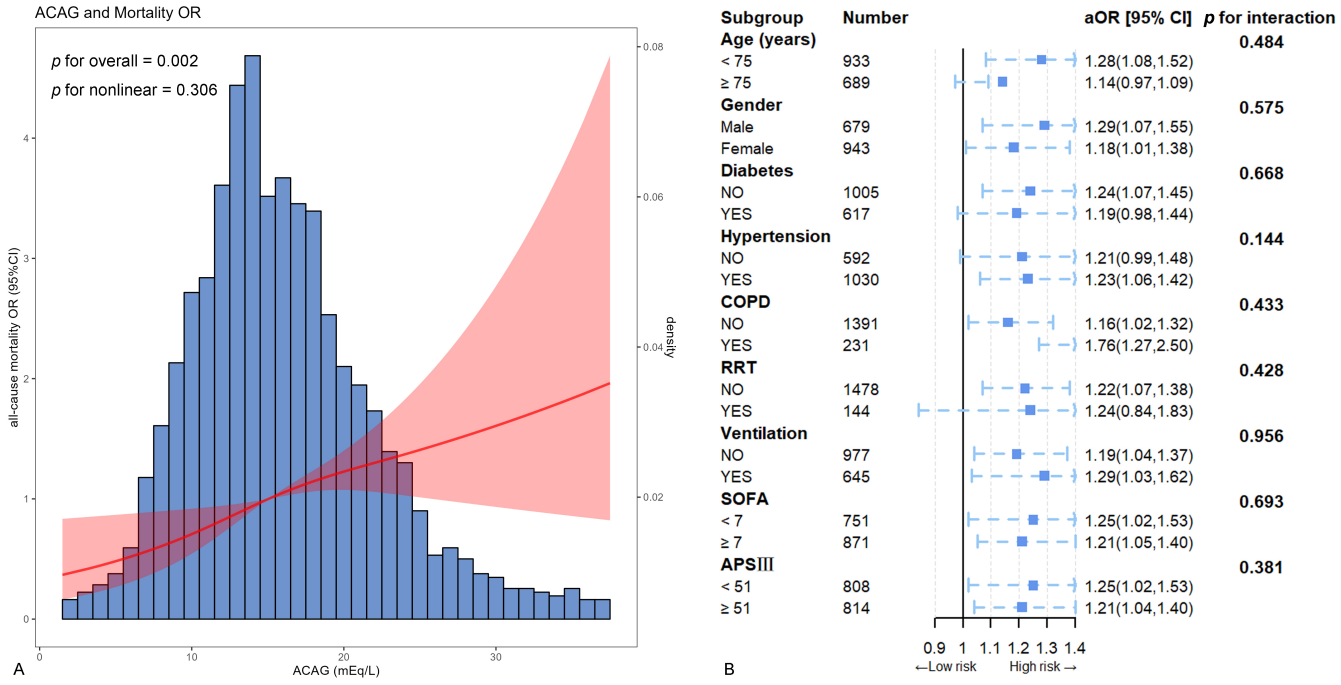

FIGURE 2. Association of ACAG with all-cause mortality: restricted cubic spline and subgroup analysis. (A) The adjusted cubic spline model illustrates the association between the ACAG and the risk of all-cause mortality. (B) Odds ratios and error bars representing 95% confidence intervals from Model 3 are presented by subgroups. Multiplicative interaction terms for each subgroup were assessed, with all subgroups showing no statistically significant differences ($p > 0.05$ for all). COPD: chronic obstructive pulmonary disease; RRT: renal replacement therapy; SOFA: the Sequential Organ Failure Assessment; APS III: Acute Physiology Score III; aOR: adjusted odds ratios; CI: confidence interval.

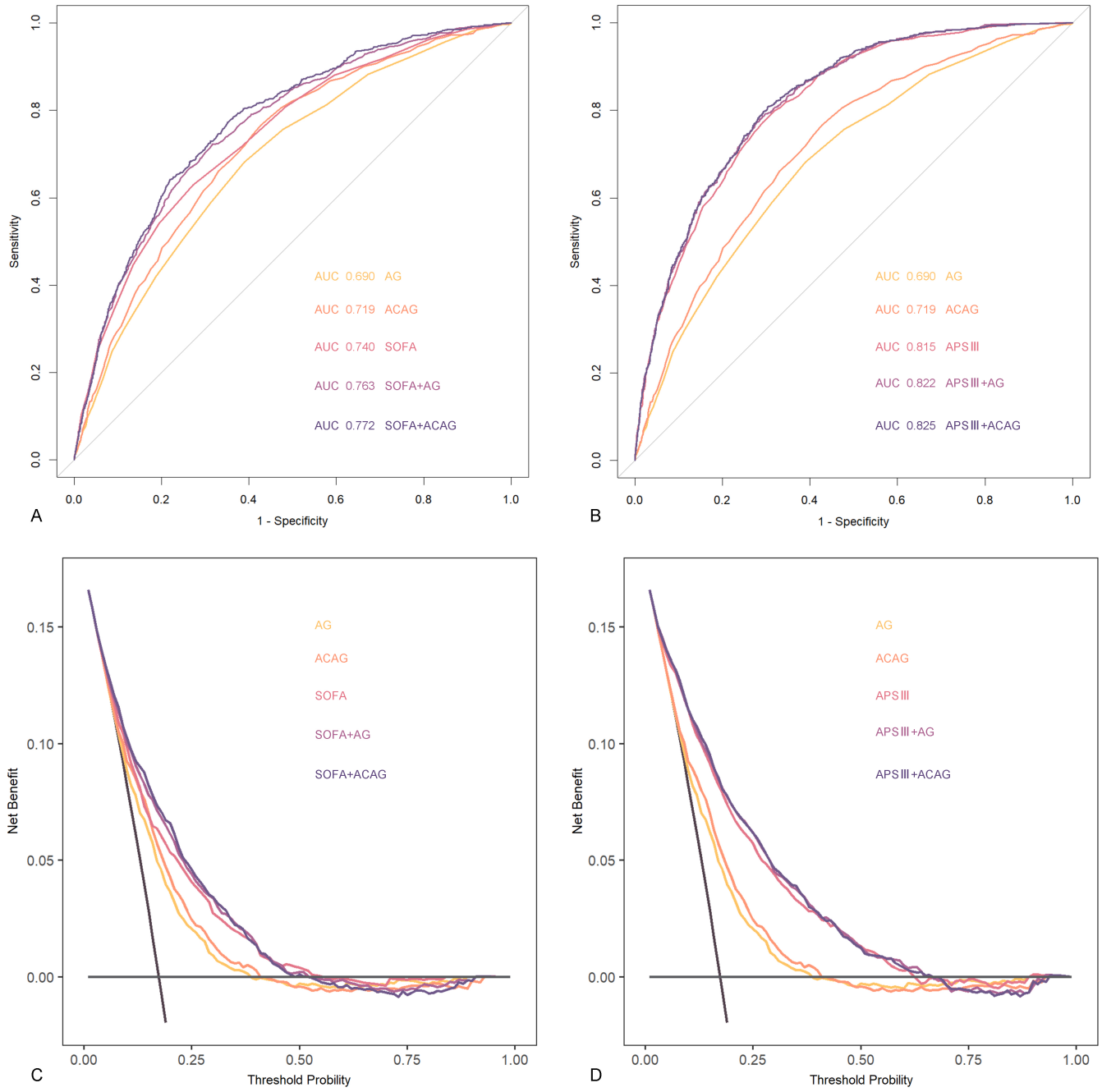

FIGURE 3. Receiver operating characteristic (ROC) curves (A,B) and clinical decision curves (C,D) for AG, ACAG, SOFA, APS III, AG or ACAG plus SOFA, and AG or ACAG plus APS III in predicting all-cause mortality. ACAG: albumin-corrected anion gap; AG: anion gap; SOFA: sequential organ failure assessment; APS III: acute physiology score III; AUC: area under the ROC curve.

4. Discussion

This study elucidated the association between ACAG and the risk of in-hospital mortality in ICU heart failure patients requiring inotropes and vasopressors, suggesting that ACAG could serve as a valuable supplement to the existing SOFA and APS III scoring systems.

Metabolic acidosis is the most common acid-base imbalance in critically ill patients, with ACAG serving as a metric for assessing metabolic acid-base status. Previous evidence has indicated that ACAG acts as a prognostic marker for adverse outcomes in patients with cardiovascular diseases and critical illnesses. Jian *et al.* [13] identified high ACAG levels as a significant risk factor for 30-day all-cause mortality in ICU patients with acute myocardial infarction, demonstrating superior accuracy compared to the anion gap, which aligns with those reported by Sheng [12]. Additionally, Wang *et al.*'s [14] study suggested that elevated ACAG levels may correlate with more severe coronary artery stenosis and heart failure, thereby increasing the risk of postoperative systemic inflammatory response, microcirculation disorder and complications. Moreover, higher ACAG levels have been closely associated

with in-hospital mortality in various diseases, including acute pancreatitis [15], asthma [16], acute renal failure [17], and sepsis [10]. Building on these investigations, the current study sought to investigate the association between ACAG levels and in-hospital mortality in ICU heart failure patients treated with inotropes and vasopressors. Notably, patients in the ICU requiring such treatment exhibited a markedly heightened risk of mortality compared to those not needing it, with observed mortality rates of 24.97% and 17.41%, respectively, in this population, contrasting with rates of 13.4% and 13.3% in all ICU heart failure patients [18]. Thus, our study held significant practical relevance in this regard. By conducting various analytical methods, including multivariate adjustment and curve fitting, all findings consistently revealed a linear relationship between ACAG levels and adverse outcomes, with the prognostic impact of ACAG surpassing that of AG and subgroup analysis results further underscoring the consistent relationship across all subgroups.

SOFA and APS III, recognized as effective tools for critical care physicians to gauge the severity of patients' conditions, are widely used in clinical practice [19]. In line with previous research, our findings underscored the prognostic value of these two scores. Importantly, the association of ACAG with all-cause in-hospital mortality risk remained independent of SOFA and APS III scores. Furthermore, the incorporation of ROC curve analysis and decision curve analysis expanded the analytical scope of the data, offering additional confirmation from an alternative perspective. These results suggest that incorporating ACAG alongside SOFA and APS III could significantly enhance the assessment of adverse outcomes, positioning ACAG as a potent adjunct to the SOFA and APS III tools. To the best of our knowledge, our study represents the first endeavor to evaluate ACAG in conjunction with SOFA and APS III. Nonetheless, acknowledging the inherent limitations of observational studies, further investigations, including randomized controlled trials, are imperative to validate the present findings.

Our study had some limitations. Firstly, being a retrospective study, inherent selection bias and regression bias were unavoidable. Nonetheless, to mitigate the influence of these biases, a sensitivity analysis was conducted on the population from an alternative center. Secondly, the absence of dynamic monitoring of ACAG, SOFA and APS III may have limited the accurate reflection of potential changes in patient's conditions and treatment circumstances, warranting further research to address this gap. Lastly, despite incorporating confounding factors in the multivariate logistic regression models, the possibility of residual and unmeasured confounders affecting the study outcomes remains.

5. Conclusions

ACAG was independently associated with the risk of in-hospital all-cause mortality in ICU heart failure patients treated with inotropes and vasopressors and could be considered an effective adjunct to the SOFA and APS III scores, with its inclusion potentially enhancing the effectiveness of the risk warning system in this patient population.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

JYW and KW—designed the study and carried them out. WK and GBF—supervised the data collection. JYW and YW—analyzed the data; interpreted the data. JYW, YW, GBF and WK—prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1888051940889116672/attachment/Supplementary%20material.docx.

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