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Association of elevated albumin-corrected anion gap with all-cause mortality risk in atrial fibrillation: a retrospective study

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Abstract

Background Compared to the conventional anion gap, the albumin-corrected anion gap (ACAG) offers a more precise measure of acid-base imbalance, providing superior prognostic insight. However, the prognostic relevance of ACAG in individuals of atrial fibrillation (AF) remains insufficiently explored. This research seeks to evaluate the correlation between ACAG levels and mortality risk in individuals with AF.

Methods We identified individuals diagnosed with AF from the Medical Information Mart for Intensive Care (MIMIC)-IV database. Participants were categorized into quartiles based on their ACAG levels. The outcomes included 30 days and 365 days all-cause mortality. Kaplan–Meier survival curves were utilized to evaluate cumulative survival across the ACAG quartiles. We applied Cox regression and restricted cubic spline regression analyses to evaluate the correlation between ACAG levels and prognosis. Subgroup analyses and interaction assessments were applied to confirm the robustness of the findings.

Results A total of 2920 AF patients (54.93% male) were incorporated into the analysis, with 1.61% identified as having paroxysmal AF. The 30-day and 365-day mortality rates were 22.91% and 39.21%, respectively. Kaplan–Meier survival curves demonstrated that elevated ACAG levels were significantly linked to increased mortality (log-rank $P < 0.001$). In multivariate Cox proportional hazards analyses, increased ACAG independently predicted mortality at both 30 days (adjusted hazard ratio [aHR], 1.04; 95% CI, 1.02–1.05; $P < 0.01$) and 365 days (aHR, 1.03; 95% CI, 1.02–1.05; $P < 0.01$) after adjusting for potential confounders. A positive relationship between rising ACAG levels and mortality risk was showed by restricted cubic spline analysis. Subgroup analyses revealed no significant interactions (all interaction P-values > 0.05).

Conclusions In individuals with AF, higher ACAG levels are related to a greater mortality risk at 30 and 365 days. These findings suggest that ACAG may serve as a valuable prognostic marker for AF patient stratification. Incorporating ACAG into clinical decision-making could support improved therapeutic strategies and enhance patient outcomes.

Keywords Atrial fibrillation, Albumin-corrected anion gap, Intensive care unit, Mortality, Retrospective analysis

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Introduction

Atrial fibrillation (AF) constitutes the most prevalent cardiovascular disease, with a rising incidence worldwide [1]. It affects approximately 1–3% of the general population, with higher rates observed in older individuals, males, and individuals with comorbidities [2–6]. In 2019, global epidemiological data indicated approximately 59.7 million cases of AF, including 4.72 million new diagnoses that year [7]. AF is linked to a range severe serious complications, making it a key element in the global burden of cardiovascular disease [8–11]. Despite advancements in available therapies, managing AF remains challenging due to the complexity of its pathophysiology and the variability in patient responses to treatment. Identifying reliable prognostic markers is essential for preventing complications and improving outcomes in these patients.

The anion gap (AG), developed in the mid-20th century, is commonly employed to evaluate acid-base disturbances in critically ill patients. Beyond its role in metabolic assessments, AG has been associated with disease severity and clinical outcomes [12–15]. AG reflects the concentration of unmeasured anions, including serum albumin, lactate, and acetoacetate. However, low serum albumin levels, frequently observed in critically ill individuals, can lead to falsely low AG values, limiting its prognostic accuracy. To overcome this limitation, the albumin-corrected anion gap (ACAG) was introduced. ACAG provides a more accurate assessment of unmeasured anions by adjusting for fluctuations in serum albumin levels [16].

ACAG has been linked to disease risk [17] and clinical outcomes in various conditions [18–22], including sepsis, acute pancreatitis, acute myocardial infarction, heart failure, and acute kidney injury. However, its prognostic significance in AF patients remains unexplored. Given the role of metabolic imbalances in cardiovascular disease, ACAG could also serve as an important marker for adverse outcomes in AF. Investigating the relationship between ACAG levels and mortality in AF patients is essential for guiding clinical decision-making. This study assesses the correlation between ACAG and all-cause mortality at 30 and 365 days in AF patients by utilizing the Medical Information Mart for Intensive Care (MIMIC)-IV database. Our findings aim to offer meaningful insights for risk stratification and inform treatment strategies. By demonstrating the prognostic utility of ACAG, we hope to offer evidence supporting its incorporation into clinical practice to enhance patient outcomes.

Methods

Data source

This study utilized information from version 2.2 of the MIMIC-IV database, a publicly available, large-scale, and de-identified dataset that offers extensive clinical data from intensive care units (ICU) patients in Beth Israel Deaconess Medical Center in Boston, Massachusetts. This dataset provides demographic information, nursing notes, laboratory findings, medications usage, and mortality data. The first author, Jia Xu, fulfilled all eligibility requirements for accessing the database (Certification ID: 64822128) and took charge of data extraction. Since the dataset contains anonymized patient information without identifiable health data, informed consent was not required.

Participant selection

We identified 59,865 admissions with a diagnosis of AF. From these recodes, 20,797 ICU patients were selected for further analysis. Exclusion criteria were as follows: (1) younger than 18; (2) multiple hospital admissions; (3) multiple ICU admissions; (4) comorbidities such as end-stage renal disease, cirrhosis, or cancer; (5) diagnosis of AIDS; (6) ICU stays shorter than 24 h; and (7) insufficient data on AG and albumin levels. After applying these criteria, 2,920 patients were included in the final analysis, of whom 47 (1.61%) were diagnosed with paroxysmal AF. Participants were subsequently divided into quartiles according to their ACAG levels for further comparison (Fig. 1).

Data collection

Navicat Premium (version 15) was used to extract data. To minimize the impact of treatment interventions, data were gathered from the initial 24 h following ICU admission. Collected demographic data included age, sex, and race. Documented comorbidities included myocardial infarction, congestive heart failure, hypertension, diabetes, obesity, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), rheumatic disease, paraplegia, renal disease, and liver disease. Laboratory parameters included white blood cell (WBC), platelet count, hematocrit, hemoglobin, red cell distribution width (RDW), AG, albumin, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, sodium, potassium, international normalized ratio (INR), prothrombin time, and partial thromboplastin time. Vital signs included heart rate and blood pressure parameters (systolic, diastolic, and mean). Severity was assessed using Oxford Acute Severity of Illness Score (OASIS), the Sequential Organ Failure Assessment (SOFA), and the Simplified Acute Physiology Score II (SAPS II). Diagnostic and therapeutic parameters included the

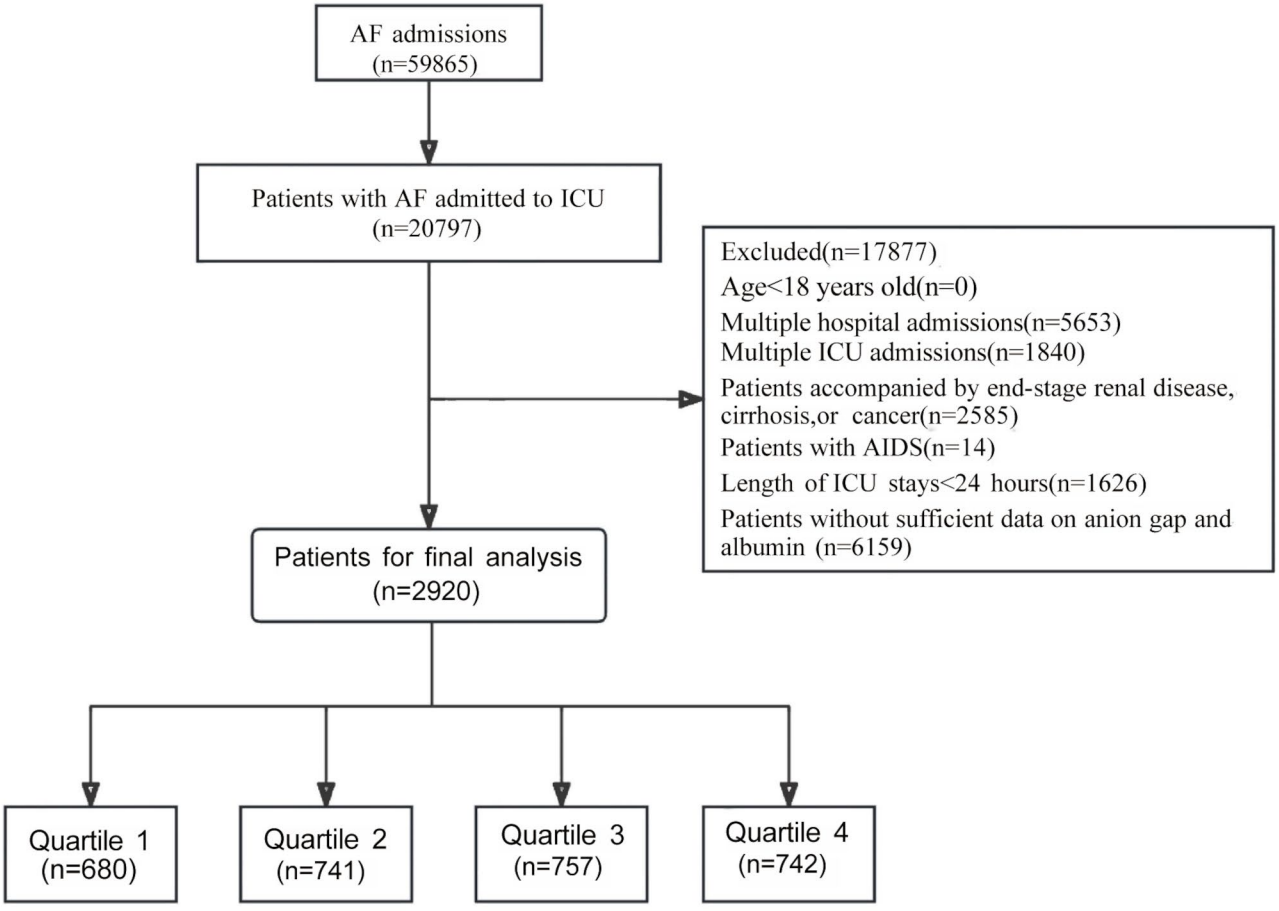

Fig. 1 The flowchart of study sample selection steps. AF, atrial fibrillation; ICU, intensive care unit; AIDS, acquired immune deficiency syndrome

use of aspirin, clopidogrel, beta-blockers, amiodarone, dabigatran, statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEI/ARB), heparin, warfarin, vasoactive drugs, intra-aortic balloon pump and coronary angiography. Length of stay was recorded for both the hospital and ICU, with clinical outcomes including mortality rates at hospital, 30 days, and 365 days. We excluded variables with more than 20% missing data to minimize bias, and used multiple imputation, performed through a random forest technique to predict missing entries [23, 24].

Clinical outcomes

The primary follow-up period began at the time of hospital admission. The main endpoint was 365-day all-cause mortality, with a secondary endpoint of 30-day all-cause mortality.

Calculation of ACAG

The AG and albumin values were directly retrieved. ACAG was calculated using the following equation: ACAG (mmol/l) = AG (mmol/l) + [4.4 -Albumin (g/dl)] *2.5 [16].

Statistical analysis

The distribution of continuous variables was assessed with the Kolmogorov-Smirnov test. Since none of the parameters followed a normal distribution, they were presented as medians with interquartile ranges (IQR) and analyzed through the Mann-Whitney U test. Categorical variables were expressed as percentages and analyzed through chi-square test. Kaplan–Meier survival curves were used to assess cumulative survival across the quartiles based on ACAG. Univariable Cox regression analysis was applied to determine the factors associated with the mortality risk. Multivariate Cox regression models served to confirm the collection between ACAG and outcomes, with adjustments made in various models. Confounding factors included those with a p-value < 0.05 in univariable analysis, along with clinically relevant and prognostically significant variables. Model 1 conducted without adjustments. Model 2 accounted for age, sex, and race. Model 3 incorporated additional variables such as heart rate, blood

pressure parameters (systolic, diastolic, and mean), acute myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, obesity, paraplegia, renal disease, liver disease, statin, beta-blockers, ACEI/ARB, heparin, warfarin. model 4 further incorporated hematocrit, hemoglobin, WBC, RDW, BUN, creatinine, sodium, potassium, glucose, INR, prothrombin time, partial thromboplastin time, SOFA, OASIS and SAPSII. Both continuous and categorical ACAG variables were analyzed, with the lowest quartile as the reference group. Trend *p*-values were computed across quartiles. Restricted cubic spline (RCS) regression with four knots was applied to assess non-linear relationships between baseline ACAG and mortality outcomes. Stratified analyses explored the prognostic value of ACAG by sex, age (< 65 or ≥ 65 years), race, diabetes, and hypertension status. Interaction effects were evaluated through likelihood ratio tests. Statistical significance was defined as a two-tailed *P*-value < 0.05. All analyses were performed using R (version 4.4.1) and SPSS (version 25.0).

Results

This study analyzed 2,920 patients diagnosed with AF, with a median age of 78 years (IQR: 69–86) (Table 1). Among them, 1,604 (54.93%) were male. The median ACAG level was 19.25 mmol/L (IQR: 16.75–22.50). Hospital mortality observed in 18.15% of patients, while the 30 days and 365 days mortality rates stood at 22.91% and 39.21%, respectively.

Baseline characteristics of participants

Individuals were divided into four quartiles: Quartile (Q) 1: 9.00-16.75mmol/L; Q2: 16.75–19.25 mmol/L; Q3:19.25–22.50 mmol/L; Q4: 22.50-51.25mmol/L (Table 1). The median ACAG values for these quartiles were 15.25 mmol/L (IQR: 14.00–16.00), 18.00 mmol/L (IQR: 17.25–18.50), 20.50 mmol/L (IQR: 19.75–21.50), and 25.25 mmol/L (IQR: 23.56–28.25), respectively. Higher quartile patients exhibited increased levels of platelets, WBC, RDW, AG, BUN, creatinine, glucose, potassium, INR, prothrombin time, partial thromboplastin time, while their albumin levels were lower(all *P*<0.05). As ACAG levels increased, the prevalence of conditions such as myocardial infarction, congestive heart failure, diabetes, obesity, renal disease, and liver disease became more common, whereas cerebrovascular disease and paraplegia were less frequently reported. Additionally, higher ACAG levels also correlated with elevated severity scores and more frequent use of amiodarone, heparin and vasoactive drugs (all *P* < 0.05). Mortality rates increased across quartiles: hospital mortality ranged from 10.59% in Q1 to 31.94% in Q4 (*P* < 0.01), 30-day mortality ranged from 14.56% in Q1 to 36.52% in Q4 (*P* < 0.01), and 365-day mortality ranged from 28.24% in Q1 to 53.91% in Q4 (*P* < 0.01).

Baseline differences between 365-day survivors and non-survivors are shown in Table 2. Non-survivors tended to be of greater age, presented with higher admission severity scores, and displayed a greater prevalence of myocardial infarct, congestive heart failure, diabetes, obesity, peripheral vascular disease, cerebrovascular disease, paraplegia, renal disease, and liver disease. Non-survivors also exhibited elevated levels of platelets, WBC, RDW, AG, BUN, creatinine, glucose, sodium, potassium, INR, prothrombin time, partial thromboplastin time, and heart rate, but lower hematocrit, hemoglobin, albumin, blood pressure. The use of statins, beta-blockers, ACEI/ARBs, heparin, and warfarin was less frequent among non-survivors. Non-survivors had notably higher ACAG levels than survivors. (20.50 vs. 18.50, *P* < 0.01).

Primary outcomes

Kaplan-Meier survival curves (Fig. 2) demonstrate that higher ACAG levels corresponded with increased risks of mortality at both 30 days and 365 days.

Univariate Cox regression analysis (Table 3) was performed using covariates with statistically significant differences (*P* < 0.05) identified in Table 2. Unadjusted analyses revealed that age, sex, myocardial infarction, congestive heart failure, obesity, peripheral vascular disease, cerebrovascular disease, paraplegia, renal disease, liver disease, hematocrit, hemoglobin, WBC, RDW, albumin, AG, ACAG, BUN, creatinine, glucose, sodium, potassium, INR, prothrombin time, partial thromboplastin time, blood pressure parameters and severity scores, as well as the use of statins, beta-blockers, ACEI/ARBs, heparin, and warfarin, were all significant predictors of prognosis in patients with AF(*P* < 0.01). Multivariate Cox regression (Table 4) confirmed the relationship between ACAG and 365-day mortality across all models: model 1: HR: 1.07 (95%CI: 1.06–1.08, *P*<0.01), model 2: HR, 1.07, (95%CI:1.06–1.08, *P*<0.01), model 3: HR:1.06 (95%CI 1.05–1.07, *P*<0.01) and model 4: HR: 1.03 (95%CI: 1.02–1.05, *P*<0.01). When ACAG was analyzed as an ordinal parameter, patients in the highest quartile exhibited a markedly increased risk of 365-day mortality compared to those in the lowest quartile: model 1: HR 2.45 (95% CI 2.06–2.91; *P*<0.01), model 2: HR 2.21 (95% CI 1.85–2.66; *P*<0.01), model 3: HR 1.93 (95% CI 1.60–2.33; *P*<0.01) and model 4: HR 1.31 (95% CI 1.05–1.61; *P* = 0.01). A similar trend was observed for 30-day mortality (Table 4).

RCS analyses shown in Fig. 3 indicated a linear link between increased ACAG and mortality outcomes at both 30 days and 365 days, with no significant

Table 1 Characteristics and outcomes of participants categorized by ACAG[a]

Variables	Overall (*N* = 2920)	Quartile 1 (*N* = 680)	Quartile 2 (*N* = 741)	Quartile 3 (*N* = 757)	Quartile 4 (*n* = 742)	*P*-value
ACAG, mmol/L	19.25 (16.75, 22.50)	15.25 (14.00,16.00)	18.00 (17.25,18.50)	20.50 (19.75,21.50)	25.25 (23.56,28.25)	< 0.01
Paroxysmal atrial fibrillation, *n* (%)	47 (1.61)	6 (0.88)	14 (1.89)	15 (1.98)	12 (1.62)	0.35
Demographic variables						
Age (years)	78.00 (69.00, 86.00)	77.00 (68.00,85.00)	80.00 (69.00,86.00)	78.00 (71.00,86.00)	77.00 (67.00,85.00)	< 0.01
Sex, male, *n*(%)	1604 (54.93)	388 (57.06)	380 (51.28)	405 (53.50)	431 (58.09)	0.03
Race, White, *n*(%)	2046 (70.07)	475 (69.85)	544 (73.41)	523 (69.09)	504 (67.92)	0.11
Comorbidities, *n*(%)						
Myocardial infarction	747 (25.58)	144 (21.18)	166 (22.40)	203 (26.82)	234 (31.54)	< 0.01
Congestive heart failure	1500 (51.37)	277 (40.74)	367 (49.53)	428 (56.54)	428 (57.68)	< 0.01
Diabetes	969 (33.18)	170 (25.00)	219 (29.55)	262 (34.61)	318 (42.86)	< 0.01
Hypertension	1154 (39.52)	278 (40.88)	333 (44.94)	296 (39.10)	247 (33.29)	< 0.01
Obesity	341 (11.68)	61 (8.97)	80 (10.80)	88 (11.62)	112 (15.09)	< 0.01
Peripheral vascular disease	446 (15.27)	94 (13.82)	124 (16.73)	101 (13.34)	127 (17.12)	0.09
Cerebrovascular disease	725 (24.83)	219 (32.21)	210 (28.34)	171 (22.59)	125 (16.85)	< 0.01
COPD	866 (29.66)	201 (29.56)	201 (27.13)	249 (32.89)	215 (28.98)	0.10
Rheumatic Disease	138 (4.73)	27 (3.97)	32 (4.32)	37 (4.89)	42 (5.66)	0.45
Paraplegia	298 (10.21)	103 (15.15)	87 (11.74)	67 (8.85)	41 (5.53)	< 0.01
Renal Disease	805 (27.57)	100 (14.71)	182 (24.56)	247 (32.63)	276 (37.20)	< 0.01
Liver Disease	178 (6.10)	19 (2.79)	35 (4.72)	36 (4.76)	88 (11.86)	< 0.01
Laboratory data						
Hematocrit, %	35.80 (31.60, 40.50)	36.90 (32.30,41.00)	35.30 (31.30,40.10)	35.50 (31.40,40.20)	36.05 (31.50,40.80)	< 0.01
Hemoglobin, g/dL	11.70 (10.20, 13.30)	12.10 (10.60,13.50)	11.60 (10.20,13.10)	11.60 (10.10,13.20)	11.70 (10.03,13.30)	< 0.01
Platelets, K/uL	211.00 (161.00, 279.00)	201.00 (158.00,251.25)	212.00 (167.00,270.00)	213.00 (163.00,284.00)	220.00 (157.25,306.00)	< 0.01
WBC, K/uL	12.90 (9.30, 18.00)	10.30 (8.00,14.10)	12.40 (9.10,16.80)	13.20 (9.50,18.30)	16.25 (11.30,22.17)	< 0.01
RDW, %	14.60 (13.70, 16.00)	14.10 (13.40,15.30)	14.40 (13.70,15.70)	14.80 (13.70,16.30)	15.00 (14.00,16.67)	< 0.01
Albumin, g/dL	3.40 (2.90, 3.80)	3.70 (3.30,4.00)	3.40 (3.00,3.80)	3.40 (2.90,3.70)	3.20 (2.70,3.60)	< 0.01
AG, mmol/L	17.00 (14.00, 20.00)	13.00 (12.00,14.00)	15.00 (14.00,16.00)	18.00 (17.00,19.00)	22.00 (20.25,25.00)	< 0.01
BUN, mg/dL	27.00 (19.00, 45.00)	21.00 (16.00,28.00)	24.00 (17.00,34.00)	29.00 (21.00,48.00)	46.00 (29.00,69.00)	< 0.01
Calcium, mg/dL	8.60 (8.20, 9.10)	8.80 (8.30,9.20)	8.60 (8.20,9.10)	8.60 (8.20,9.10)	8.50 (8.00,9.10)	< 0.01
Chloride, mEq/L	105.00 (102.00, 109.00)	106.00 (102.00,109.00)	106.00 (102.00,109.00)	105.00 (101.00,110.00)	105.00 (101.00,110.00)	0.67
Creatinine, mg/dL	1.30 (0.90, 1.90)	1.00 (0.80,1.20)	1.10 (0.80,1.50)	1.30 (1.00,1.90)	2.10 (1.40,3.10)	< 0.01
Glucose, g/dL	152.00 (121.00, 208.00)	133.00 (110.00,165.00)	146.00 (119.00,188.00)	159.00 (126.00,212.00)	189.00 (140.00,269.00)	< 0.01
Sodium, mEq/L	140.00 (138.00, 143.00)	141.00 (138.00,143.00)	140.00 (138.00,143.00)	140.00 (137.00,143.00)	140.00 (137.00,144.00)	0.19
Potassium, mEq/L	4.50 (4.10, 5.00)	4.30 (4.00,4.70)	4.40 (4.10,4.80)	4.40 (4.10,5.00)	4.90 (4.40,5.60)	< 0.01
INR	1.40 (1.20, 2.10)	1.30 (1.20,1.70)	1.40 (1.20,2.00)	1.40 (1.20,2.00)	1.60 (1.30,2.77)	< 0.01
Prothrombin time, s	15.70 (13.30, 22.40)	14.55 (12.90,18.20)	15.80 (13.20,21.60)	15.50 (13.30,21.30)	17.85 (14.30,29.80)	< 0.01
Partial thromboplastin time, s	35.40 (29.60, 54.52)	33.00 (28.80,42.50)	34.50 (29.00,49.50)	35.50 (29.30,57.20)	41.25 (31.63,70.28)	< 0.01
Vital signs						
Heart rate, beats/min	85.00 (73.00, 98.00)	79.00 (70.00,91.00)	83.00 (72.00,96.00)	87.00 (75.00,99.00)	92.00 (78.00,105.00)	< 0.01

Table 1 (continued)

Variables	Overall (*N* = 2920)	Quartile 1 (*N* = 680)	Quartile 2 (*N* = 741)	Quartile 3 (*N* = 757)	Quartile 4 (*n* = 742)	*P*-value
Systolic blood pressure, mmHg	115.00 (106.00, 128.00)	121.00 (110.00,134.00)	119.00 (108.00,131.00)	114.00 (105.00,128.00)	110.00 (102.00,118.00)	< 0.01
Diastolic blood pressure, mmHg	62.00 (55.00, 69.00)	64.00 (56.00,72.00)	63.00 (55.00,70.00)	62.00 (55.00,69.00)	60.00 (53.25,67.00)	< 0.01
Mean blood pressure, mmHg	77.00 (71.00, 85.00)	80.00 (73.00,88.00)	78.00 (71.00,85.00)	76.00 (70.00,84.00)	74.00 (68.00,81.00)	< 0.01
Clinical severity						
SOFA	5.00 (3.00, 8.00)	3.00 (2.00,5.00)	4.00 (2.00,6.00)	5.00 (3.00,8.00)	7.00 (5.00,11.00)	< 0.01
OASIS	34.00 (29.00, 40.00)	31.00 (26.00,37.00)	34.00 (28.00,39.00)	34.00 (29.00,39.00)	38.00 (32.00,46.00)	< 0.01
SAPS II	39.00 (32.00, 49.00)	34.00 (28.00,40.00)	37.00 (31.00,45.00)	40.00 (33.00,48.00)	49.00 (40.00,60.00)	< 0.01
Diagnostic and therapeutic, ***n*(%)**						
Aspirin	1246 (42.67)	301 (44.26)	303 (40.89)	337 (44.52)	305 (41.11)	0.33
Clopidogrel	218 (7.47)	45 (6.62)	47 (6.34)	63 (8.32)	63 (8.49)	0.26
Statin	1220 (41.78)	321 (47.21)	333 (44.94)	315 (41.61)	251 (33.83)	< 0.01
Beta-Blockers	1896 (64.93)	461 (67.79)	484 (65.32)	505 (66.71)	446 (60.11)	0.01
ACEI/ARB	286 (9.79)	73 (10.74)	89 (12.01)	70 (9.25)	54 (7.28)	0.02
Amiodarone	720 (24.66)	140 (20.59)	163 (22.00)	172 (22.72)	245 (33.02)	< 0.01
Dabigatran	26 (0.89)	5 (0.74)	6 (0.81)	10 (1.32)	5 (0.67)	0.53
Heparin	2263 (77.50)	473 (69.56)	561 (75.71)	597 (78.86)	632 (85.18)	< 0.01
Warfarin	568 (19.45)	128 (18.82)	163 (22.00)	139 (18.36)	138 (18.60)	0.25
Vasoactive drugs	2203(75.45)	481 (70.74)	525 (70.85)	579 (76.49)	618 (83.29)	< 0.01
Intra-aortic balloon pump	23 (0.79)	2 (0.29)	7 (0.94)	8 (1.06)	6 (0.81)	0.383
Coronary angiography	48 (1.64)	6 (0.88)	14 (1.89)	15 (1.98)	13 (1.75)	0.347
Length of stay, **days**						
Length of stay in hospital	9.00 (5.00, 14.00)	7.00 (5.00,12.00)	9.00 (6.00,14.00)	9.00 (5.00,15.00)	10.00 (6.00,17.00)	< 0.01
Length of stay in ICU	3.00 (2.00, 6.00)	3.00 (2.00,5.00)	3.00 (2.00,6.00)	3.00 (2.00,6.00)	4.00 (2.00,8.00)	< 0.01
Events, ***n*(%)**						
Hospital mortality	530 (18.15)	72 (10.59)	84 (11.34)	137 (18.10)	237 (31.94)	< 0.01
30-day mortality	669 (22.91)	99 (14.56)	124 (16.73)	175 (23.12)	271 (36.52)	< 0.01
365-day mortality	1145 (39.21)	192 (28.24)	239 (32.25)	314 (41.48)	400 (53.91)	< 0.01

[a] ACAG: Q1 (9.00-16.75), Q2 (16.75–19.25), Q3 (19.25–22.50), Q4 (22.50-51.25)

Abbreviation: ACAG, albumin-corrected anion gap; COPD, chronic pulmonary disease; WBC, white blood cell; RDW, red cell distribution width; AG, anion gap; BUN, blood urea nitrogen; SOFA, sequential organ failure assessment; OASIS, Oxford Acute Severity of Illness Score; SAPS II, simplified acute physiology score; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker

Table 2 Baseline characteristics between survivors and non-survivors at 365 days

Variables	Total (*N* = 2920)	survivors (*N* = 1775)	non-survivors (*N* = 1145)	*P*-value
ACAG, mmol/L	19.25 (16.75, 22.50)	18.50 (16.25, 21.25)	20.50 (17.75, 24.25)	< 0.01
Paroxysmal atrial fibrillation, *n* (%)	47 (1.61)	33 (1.86)	14 (1.22)	0.182
Demographic variables				
Age (years)	78.00 (69.00, 86.00)	75.00 (66.00, 83.00)	82.00 (74.00, 88.00)	< 0.01
Sex, male, *n* (%)	1604 (54.93)	1012 (57.01)	592 (51.70)	< 0.01
Race, White, *n* (%)	2046 (70.07)	1246 (70.20)	800 (69.87)	0.85
Comorbidities, ***n*(%)**				
Myocardial infarction	747 (25.58)	415 (23.38)	332 (29.00)	< 0.01
Congestive heart failure	1500 (51.37)	851 (47.94)	649 (56.68)	< 0.01
Diabetes	969 (33.18)	562 (31.66)	407 (35.55)	0.03
Hypertension	1154 (39.52)	716 (40.34)	438 (38.25)	0.26
Obesity	341 (11.68)	240 (13.52)	101 (8.82)	< 0.01
Peripheral vascular disease	446 (15.27)	242 (13.63)	204 (17.82)	< 0.01
Cerebrovascular disease	725 (24.83)	398 (22.42)	327 (28.56)	< 0.01
COPD	866 (29.66)	518 (29.18)	348 (30.39)	0.48
Rheumatic Disease	138 (4.73)	78 (4.39)	60 (5.24)	0.29
Paraplegia	298 (10.21)	162 (9.13)	136 (11.88)	0.02
Renal Disease	805 (27.57)	417 (23.49)	388 (33.89)	< 0.01
Liver Disease	178 (6.10)	84 (4.73)	94 (8.21)	< 0.01
Laboratory data				
Hematocrit, %	35.80 (31.60, 40.50)	36.20 (32.00, 40.80)	35.30 (30.90, 40.00)	< 0.01
Hemoglobin, g/dL	11.70 (10.20, 13.30)	11.90 (10.40, 13.50)	11.40 (9.90, 12.80)	< 0.01
Platelets, K/uL	211.00 (161.00, 279.00)	210.00 (162.00, 273.00)	213.00 (159.00, 288.00)	0.42
WBC, K/uL	12.90 (9.30, 18.00)	12.40 (9.10, 17.10)	13.70 (9.70, 19.20)	< 0.01
RDW, %	14.60 (13.70, 16.00)	14.30 (13.50, 15.50)	15.10 (14.00, 16.70)	< 0.01
Albumin, g/dL	3.40 (2.90, 3.80)	3.50 (3.00, 3.90)	3.30 (2.80, 3.70)	< 0.01
AG, mmol/L	17.00 (14.00, 20.00)	16.00 (14.00, 19.00)	18.00 (15.00, 21.00)	< 0.01
BUN, mg/dL	27.00 (19.00, 45.00)	24.00 (17.00, 37.50)	34.00 (23.00, 56.00)	< 0.01
Calcium, mg/dL	8.60 (8.20, 9.10)	8.70 (8.20, 9.10)	8.60 (8.10, 9.10)	0.34
Chloride, mEq/L	105.00 (102.00, 109.00)	106.00 (102.00, 109.00)	105.00 (101.00, 110.00)	0.72
Creatinine, mg/dL	1.30 (0.90, 1.90)	1.20 (0.90, 1.70)	1.50 (1.00, 2.30)	< 0.01
Glucose, g/dL	152.00 (121.00, 208.00)	147.00 (118.00, 194.00)	165.00 (126.00, 226.00)	< 0.01
Sodium, mEq/L	140.00 (138.00, 143.00)	140.00 (138.00, 143.00)	141.00 (138.00, 144.00)	< 0.01
Potassium, mEq/L	4.50 (4.10, 5.00)	4.40 (4.10, 4.90)	4.60 (4.20, 5.30)	< 0.01
INR	1.40 (1.20, 2.10)	1.40 (1.20, 1.90)	1.50 (1.20, 2.40)	< 0.01
prothrombin time, s	15.70 (13.30, 22.40)	15.30 (13.10, 20.30)	16.60 (13.70, 25.90)	< 0.01
partial thromboplastin time, s	35.40 (29.60, 54.52)	34.60 (29.50, 53.10)	37.00 (29.80, 57.20)	0.02
Vital signs				
Heart rate, beats/min	85.00 (73.00, 98.00)	84.00 (72.50, 98.00)	86.00 (74.00, 99.00)	0.05
Systolic blood pressure, mmHg	115.00 (106.00, 128.00)	117.00 (107.00, 129.00)	113.00 (104.00, 126.00)	< 0.01
Diastolic blood pressure, mmHg	62.00 (55.00, 69.00)	63.00 (56.00, 71.00)	60.00 (54.00, 68.00)	< 0.01
Mean blood pressure, mmHg	77.00 (71.00, 85.00)	78.00 (72.00, 86.00)	75.00 (69.00, 83.00)	< 0.01
Clinical severity				
SOFA	5.00 (3.00, 8.00)	4.00 (2.00, 7.00)	6.00 (4.00, 9.00)	< 0.01
OASIS	34.00 (29.00, 40.00)	33.00 (27.00, 38.00)	37.00 (32.00, 44.00)	< 0.01
SAPS II	39.00 (32.00, 49.00)	36.00 (30.00, 44.00)	45.00 (37.00, 54.00)	< 0.01
Diagnostic and therapeutic*n*(%)				
Aspirin	1246 (42.67)	759 (42.76)	487 (42.53)	0.90
Clopidogrel	218 (7.47)	121 (6.82)	97 (8.47)	0.10
Statin	1220 (41.78)	783 (44.11)	437 (38.17)	< 0.01
Beta-Blockers	1896 (64.93)	1191 (67.10)	705 (61.57)	< 0.01
ACEI/ARB	286 (9.79)	194 (10.93)	92 (8.03)	0.01
Amiodarone	720 (24.66)	428 (24.11)	292 (25.50)	0.40

Table 2 (continued)

Variables	Total (*N* = 2920)	survivors (*N* = 1775)	non-survivors (*N* = 1145)	*P*-value
Dabigatran	26 (0.89)	20 (1.13)	6 (0.52)	0.09
Heparin	2263 (77.50)	1351 (76.11)	912 (79.65)	0.03
Warfarin	568 (19.45)	389 (21.92)	179 (15.63)	< 0.01
Vasoactive drug	2203 (75.45)	1317 (74.20)	886 (77.38)	0.05
Intra-aortic balloon pump	23 (0.79)	17 (0.96)	6 (0.52)	0.196
Coronary angiography	48 (1.64)	33 (1.86)	15 (1.31)	0.255

Abbreviation: ACAG, albumin-corrected anion gap; COPD, chronic pulmonary disease; WBC, white blood cell; RDW, red cell distribution width; AG, anion gap; BUN, blood urea nitrogen; INR, international normalized ratio; SOFA, sequential organ failure assessment; OASIS, Oxford Acute Severity of Illness Score; SAPS II, simplified acute physiology score; ACEI/ARB, angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker

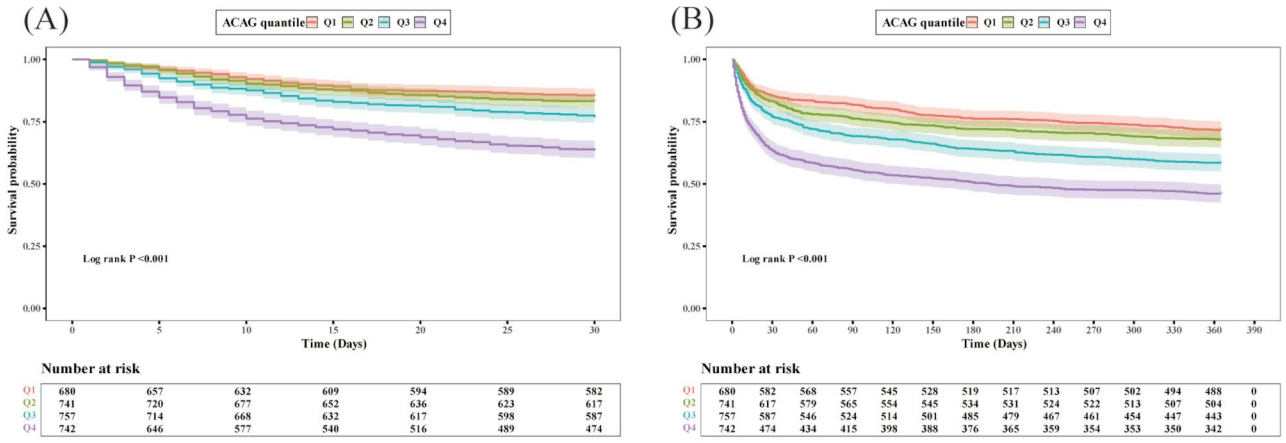

Fig. 2 Kaplan-Meier survival analysis curves for (A)30-day and (B)365-day all-cause mortality. ACAG quantile: Q1 (9.00-16.75), Q2 (16.75–19.25), Q3 (19.25–22.50), Q4 (22.50-51.25)

non-linearity detected (P for non-linearity = 0.729 and 0.503, respectively) after adjusting for relevant confounders.

Subgroup analyses

We employed subgroup analyses to investigate whether ACAG remained a significant predictor of mortality across various demographic and clinical groups (Fig. 4). Higher ACAG levels were consistently associated with 365-day mortality across all subgroups, including by sex, age (< 65 and ≥ 65 years), race, diabetes, and hypertension status (all $P < 0.05$). Similarly, ACAG significantly predicted 30-day mortality across subgroups, including males and females, individuals ≥ 65 years, and those with or without diabetes or hypertension, as well as among non-White patients (all $P < 0.05$). Interaction terms between ACAG and subgroup factors failed to achieve statistical significance.

Discussion

This is the first investigation to assess the connection between ACAG and mortality outcomes in AF, offering new insights into its prognostic value. Our analysis showed a clear, linear relationship between higher ACAG levels and increased risks of all-cause mortality at both 1 month and 1 year, even after adjusting for confounders. The robustness of these results across various statistical approaches highlights their dependability. Subgroup analyses further confirmed that ACAG remains a significant prognostic marker across diverse clinical and demographic groups, suggesting its potential as a universal risk indicator in AF patients. As a readily available biomarker, ACAG could complement traditional risk assessments, serving as a clinical decision-support tool.

The traditional AG is frequently employed to evaluate acid-base disturbances. It is defined by the gap between measured serum cations and anions. Elevated AG is often seen in conditions such as lactic acidosis, diabetic ketoacidosis, and renal failure, and has been correlates with worse outcomes in critical patients [25, 26]. However, AG is influenced by serum albumin levels, with each 1 g/L reduction in albumin lowering AG by approximately 2.3–2.5 mmol/L [27]. Hypoalbuminemia, which is prevalent in critically ill patients, including those with AF(approximately 54% in our cohort), can result in misinterpretation of AG levels, thereby impairing clinical judgment and risk stratification [28].

Table 3 Univariate COX analysis of risk factors correlated with 365-day all-cause mortality

Variables	HR (95%CI)	*P*-value
ACAG	1.07 (1.06 ~ 1.08)	< 0.01
Age (years)	1.04 (1.03 ~ 1.04)	< 0.01
Sex, male, *n* (%)	0.84 (0.74 ~ 0.94)	< 0.01
Myocardial infarction, *n* (%)	1.26 (1.11 ~ 1.43)	< 0.01
Congestive heart failure, *n* (%)	1.28 (1.14 ~ 1.43)	< 0.01
Diabetes, *n* (%)	1.13 (1.01 ~ 1.28)	0.05
Obesity, *n* (%)	0.69 (0.57 ~ 0.85)	< 0.01
Peripheral vascular disease, *n* (%)	1.24 (1.06 ~ 1.44)	< 0.01
Cerebrovascular disease, *n* (%)	1.33 (1.17 ~ 1.51)	< 0.01
Paraplegia, *n* (%)	1.30 (1.09 ~ 1.56)	< 0.01
Renal Disease, *n* (%)	1.45 (1.28 ~ 1.64)	< 0.01
Liver Disease, *n* (%)	1.58 (1.28 ~ 1.96)	< 0.01
Hematocrit, %	0.99 (0.98 ~ 0.99)	0.02
Hemoglobin, g/dL	0.94 (0.91 ~ 0.96)	< 0.01
WBC, K/uL	1.01 (1,0.01 ~ 1.02)	< 0.01
RDW, %	1.12 (1.10 ~ 1.15)	< 0.01
Albumin, g/dL	0.68 (0.62 ~ 0.75)	< 0.01
AG, mmol/L	1.06 (1.05 ~ 1.07)	< 0.01
BUN, mg/dL	1.01 (1.01 ~ 1.01)	< 0.01
Creatinine, mg/dL	1.11 (1.08 ~ 1.15)	< 0.01
Glucose, g/dL	1.01 (1.01 ~ 1.01)	< 0.01
Sodium, mEq/L	1.03 (1.01 ~ 1.04)	< 0.01
Potassium, mEq/L	1.24 (1.17 ~ 1.30)	< 0.01
INR	1.07 (1.05 ~ 1.10)	< 0.01
prothrombin time, s	1.01 (1.01 ~ 1.01)	< 0.01
Partial thromboplastin time, s	1.01 (1.01 ~ 1.01)	0.02
Systolic blood pressure, mmHg	0.99 (0.99 ~ 0.99)	< 0.01
Diastolic blood pressure, mmHg	0.98 (0.98 ~ 0.99)	< 0.01
Mean blood pressure, mmHg	0.98 (0.98 ~ 0.99)	< 0.01
SOFA	1.11 (1.09 ~ 1.12)	< 0.01
OASIS	1.06 (1.05 ~ 1.06)	< 0.01
SAPS II	1.04 (1.04 ~ 1.04)	< 0.01
Statin	0.80 (0.71 ~ 0.90)	< 0.01
Beta-Blockers	0.79 (0.70 ~ 0.89)	< 0.01
ACEI/ARB	0.73 (0.59 ~ 0.90)	< 0.01
Heparin	1.18 (1.02 ~ 1.36)	0.02
Warfarin	0.68 (0.58 ~ 0.80)	< 0.01

Abbreviation: HR, Hazard Ratio; CI, Confidence Interval; ACAG, albumin-corrected anion gap; WBC, white blood cell; RDW, red cell distribution width; AG, anion gap; BUN, blood urea nitrogen; INR, international normalized ratio; SOFA, sequential organ failure assessment; OASIS, Oxford Acute Severity of Illness Score; SAPS II, simplified acute physiology score; ACEI/ARB, angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker

ACAG, which adjusts AG for serum albumin levels, improves the sensitivity of metabolic acidosis diagnosis and offers better prognostic accuracy. It provides a more reliable marker of disease severity and outcomes in ICU patients. Previous studies have highlighted ACAG's utility in predicting mortality across various conditions. For instance, Hu et al. [18] reported that ACAG offers more reliable forecast of in-hospital mortality than either albumin or AG in patients with sepsis. Similarly, Li et al. [20]showed that elevated ACAG levels were linked to increase in-hospital mortality in individuals with acute pancreatitis. In AMI, elevated ACAG levels outperformed AG in predictive value for 30 days mortality [29], and Sheng H et al. [22] further identified increased ACAG as an important marker for forecasting long-term mortality in severe acute myocardial infarct patients. Other studies have also linked higher ACAG levels with increased ICU mortality among individuals with acute kidney injury receiving continuous renal replacement therapy [30] and demonstrated its prognostic value for 30 days and one year mortality in severe acute kidney injury patients [19]. Consistent with these findings, our study evaluated the correlation between ACAG and mortality in individuals with AF, revealing that increased ACAG independently predicts both 30 days and one year mortality. These findings highlight its potential to identify high-risk individuals and facilitate early intervention.

While the exact mechanisms linking elevated ACAG to adverse outcomes in AF remain unclear, several plausible pathways may be involved (1) Elevated ACAG may reflect disturbances in electrolytes such as sodium, potassium, calcium, and chloride, which can alter the electrophysiological properties of the atria, potentially promoting the onset and maintenance of AF, thus worsening outcomes [31]. (2) ACAG elevation is associated with chronic inflammatory responses and oxidative stress, both of which contribute to atrial fibrosis and impaired electrical activity, further promoting AF and poor prognosis [32, 33]. (3) Elevated ACAG may indicate severe acidosis, which can impair myocardial excitability and destabilize myocardial cell membranes, triggering or worsening AF. Additionally, metabolic acidosis, resulting from lactate or ketone accumulation, further exacerbates systemic inflammation and oxidative stress, thereby worsening AF prognosis [34]. (4) Increased ACAG is correlates with comorbidities such as congestive heart failure, kidney disease, and liver dysfunction in AF patients, as observed in this study. These comorbidities contributes to the poor long-term prognosis in these patients [35]. (5) Elevated ACAG may reflect underlying metabolic disturbances that exacerbate multi-organ dysfunction, ultimately affecting patient prognosis.

Our study further underscores the significant role of comorbidities in the prognosis of AF. Specifically, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, renal and liver disease, and paraplegia all contribute to adverse outcomes in AF. Myocardial infarction and congestive heart failure contribute to adverse AF outcomes through mechanisms such as heart remodeling and mutual symptom exacerbation, leading to increased morbidity and mortality. Peripheral vascular

Table 4 Cox proportional hazard ratios (HR) for all-cause mortality

Variables	Model 1		Model 2		Model 3		Model 4	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
365-day mortality								
Continues variable per unit	1.07 (1.06 ~ 1.08)	< 0.01	1.07 (1.06 ~ 1.08)	< 0.01	1.06 (1.05 ~ 1.07)	< 0.01	1.03 (1.02 ~ 1.05)	< 0.01
Quartile								
Q1 (*N* = 680)	Ref.		Ref.		Ref.		Ref.	
Q2 (*N* = 741)	1.18 (0.98 ~ 1.43)	0.09	1.08 (0.89 ~ 1.31)	0.43	1.02 (0.84 ~ 1.24)	0.81	0.96 (0.79 ~ 1.16)	0.67
Q3 (*N* = 757)	1.62 (1.35 ~ 1.93)	< 0.01	1.46 (1.22 ~ 1.76)	< 0.01	1.35 (1.12 ~ 1.62)	< 0.01	1.15 (0.95 ~ 1.40)	0.14
Q4 (*N* = 742)	2.45 (2.06 ~ 2.91)	< 0.01	2.21 (1.85 ~ 2.66)	< 0.01	1.93 (1.60 ~ 2.33)	< 0.01	1.31 (1.05 ~ 1.61)	0.01
***P*for trend**		< 0.01		< 0.01		< 0.01		< 0.01
30-day mortality								
Continues variable per unit	1.08 (1.07 ~ 1.10)	< 0.01	1.08 (1.07 ~ 1.09)	< 0.01	1.07 (1.06 ~ 1.09)	< 0.01	1.04 (1.02 ~ 1.05)	< 0.01
Quartile								
Q1 (*N* = 680)	Ref.		Ref.		Ref.		Ref	
Q2 (*N* = 741)	1.16 (0.89 ~ 1.51)	0.26	1.10 (0.84 ~ 1.43)	0.50	1.03 (0.79 ~ 1.35)	0.81	0.94 (0.71 ~ 1.23)	0.63
Q3 (*N* = 757)	1.66 (1.30 ~ 2.13)	< 0.01	1.54 (1.20 ~ 1.98)	< 0.01	1.41 (1.09 ~ 1.82)	0.01	1.16 (0.90 ~ 1.50)	0.26
Q4 (*N* = 742)	2.91 (2.31 ~ 3.67)	< 0.01	2.62 (2.06 ~ 3.35)	< 0.01	2.26 (1.76 ~ 2.91)	< 0.01	1.43 (1.08 ~ 1.89)	0.01
***P*for trend**		< 0.01		< 0.01		< 0.01		< 0.01

Model 1: unadjusted

Model 2: adjusted for age, sex, race

Model 3: adjusted for Model2 + systolic blood pressure, diastolic blood pressure; mean blood pressure, myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, obesity, paraplegia, renal disease, liver disease, statin, beta-blockers, ACEI/ARB, heparin, warfarin

Model 4: Model 3 + hematocrit, hemoglobin, WBC, RDW, BUN, creatinine, glucose, sodium, potassium, INR, prothrombin time, and partial thromboplastin time, SOFA, OASIS, SAPSII

Abbreviation: HR, Hazard Ratio; CI, Confidence Interval; ACEI/ARB, angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker; WBC, white blood cell; RDW, red cell distribution width; BUN, blood urea nitrogen; INR, international normalized ratio; SOFA, sequential organ failure assessment; OASIS, Oxford Acute Severity of Illness Score; SAPS II, simplified acute physiology score

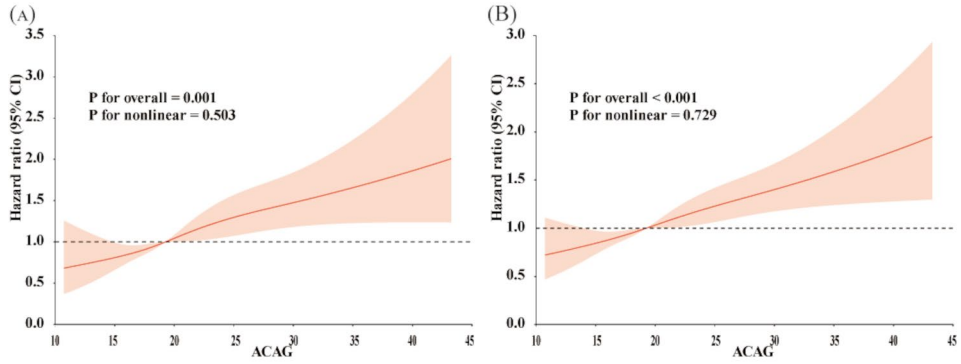

Fig. 3 Restricted cubic spline curve for (**A**) 30-day and (**B**) 365-day all-cause mortality. ACAG, albumin-corrected anion gap; CI, confidence interval

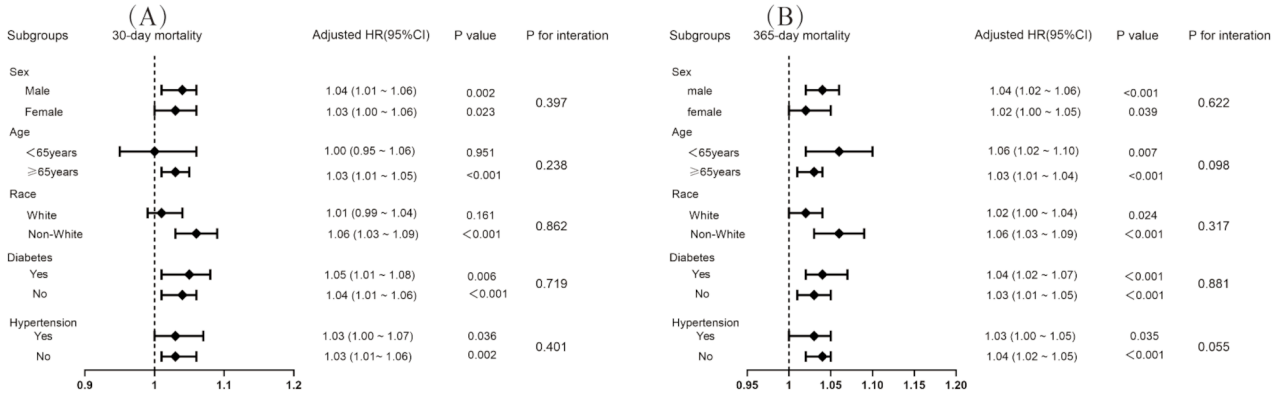

Fig. 4 Forest plots of HRs for the mortality in different subgroups. HR, hazard ratios

and cerebrovascular diseases elevate the risk of thromboembolism, while renal and liver diseases complicate the management of AF, particularly with regard to anticoagulation therapy [36]. Paraplegia further increases thromboembolic risks due to immobility. Interestingly, obesity showed a paradoxical protective effect in this cohort, possibly due to higher metabolic reserves, altered pharmacokinetics, and more frequent medical monitoring. Notably, diabetes was not identified as a significant risk factor for the long-term prognosis of AF in our study. These findings underscore the importance of considering comorbidities when managing AF to optimize treatment strategies and improve patient outcomes. Additionally, studies have demonstrated that the Atrial Fibrillation Better Care pathway improves patient outcomes across different comorbidity profiles, although the degree of risk reduction varies [37].

In clinical practice, coronary angiography, intra-aortic balloon pump, and vasoactive drugs significantly influence the prognosis of AF patients. Coronary angiography aids in diagnosing coronary artery disease and guiding interventions like percutaneous coronary intervention, which can improve outcomes in AF patients with coronary artery disease by enhancing myocardial perfusion. Intra-aortic balloon pump provides short-term hemodynamic support, stabilizing circulation in critical AF patients with acute heart failure or cardiogenic shock. Vasoactive drugs help manage acute hemodynamic instability, improving circulation and stabilizing blood pressure, but their long-term use may increase risks, such as arrhythmias or myocardial ischemia. Although no significant effects on AF prognosis were found in this study, the potential impact of these interventions on outcomes should be further explored in future research with larger or more diverse patient populations.

The strength of this study lies in its identification of ACAG as an important predictor of mortality risk in AF patients. As far as we are aware, no prior research has documented this association in this patient population. The robustness of our findings across various statistical models, combined with the use of a large dataset, enhances the reliability of our conclusions. However, several limitations should be acknowledged: First, the cohort in this study was exclusively derived from MIMIC-IV, which primarily includes critically ill ICU patients, limiting the generalizability of our findings to all AF patients. Second, despite employing multiple statistical analyses, residual confounding

cannot be entirely excluded, as certain variables—such as the timing of AF, use of advanced cardiac therapies, and specific causes of death—were not available in the database. Third, while the association between ACAG and mortality in AF patients is significant, the retrospective framework of the research restricts our ability to establish a causal relationship. Fourth, although our cohort focused on patients diagnosed with AF at discharge, AF was not always the primary reason for ICU admission, which may further limit the generalizability of our findings. Fifth, a previous study has demonstrated that peripheral artery disease is associated with adverse outcomes in AF patients [38]. However, the potential impact of peripheral artery disease on AF outcomes was not considered in the current study. Lastly, we only assessed ACAG during the initial 24 h of ICU admission and were unable to track variations during the hospital stay. Monitoring dynamic changes in ACAG during hospitalization may further enhance its role in clinical decision-making.

Conclusions

This research highlights the significance of ACAG as a valuable prognostic indicator for predicting both short- and long-term mortality in critically ill patients with AF. As an independent risk factor, ACAG can offer clinicians a valuable tool for pinpointing high-risk individuals and initiating timely interventions designed to enhance clinical outcomes. Future prospective investigations are essential to validate these results in diverse populations, particularly in outpatients or general hospital settings, and to explore the mechanisms driving the relationship between elevated ACAG and poor prognosis.

Abbreviations

AF	Atrial fibrillation
AG	Anion gap
ACAG	Albumin-corrected anion gap
MIMIC-IV	Medical Information Mart for Intensive Care IV
ICU	Intensive care unit
IQR	Interquartile range
HR	Hazard ratios
CI	Confidence intervals
COPD	Chronic pulmonary disease
WBC	White blood cell
RDW	Red cell distribution width;
BUN	Blood urea nitrogen
SOFA	Sequential organ failure assessment
OASIS	Oxford Acute Severity of Illness Score
SAPS II	Simplified acute physiology score
ACEI/ARB	Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker
RCS	Restricted cubic spline regression

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Author contributions
Jia Xu and Zhen Wang conceptualized and designed the study. Jia Xu carried out the data extraction. Jia Xu, Yun Wang, and Xinran Chen analysis data and manuscript drafting. Lan Ma and Xiaochen Wang contributed to manuscript revision. Each author has made meaningful intellectual contributions and endorsed the final manuscript prepared for submission.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study gathered information from MIMIC-IV. As the database contains de-identified patient information, privacy is safeguarded, and no further ethical approval or consent from patients was needed.

Consent for publication
Not applicable.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

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