International Journal of Chronic Obstructive Pulmonary Disease

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ORIGINAL RESEARCH

Prognostic Value of the Albumin Corrected Anion Gap in ICU Patients with Chronic Obstructive Pulmonary Disease and Sepsis: A MIMIC-IV Cohort Study

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Purpose: Chronic obstructive pulmonary disease (COPD) patients are at increased risk of sepsis, a condition associated with high mortality. The anion gap (AG) is commonly used to assess acid–base disturbances, but its reliability declines in hypoalbuminemia. The albumin-corrected anion gap (ACAG) may provide greater accuracy, yet its prognostic value in COPD patients with sepsis, defined according to Sepsis-3 criteria, remains unclear.

Patients and Methods: This retrospective cohort study analyzed 2072 ICU patients with COPD and sepsis from the Medical Information Mart for Intensive Care IV (MIMIC-IV). Cox regression models evaluated the association between ACAG and mortality, Kaplan–Meier curves illustrated survival differences, restricted cubic splines examined nonlinear relationships, and subgroup analyses assessed consistency across strata. Receiver operating characteristic (ROC) curves compared the predictive performance of ACAG, AG, and serum albumin.

Results: Elevated ACAG was independently associated with both short- and long-term mortality. In fully adjusted models, each 1 mmol/L increase in ACAG was linked to higher risk of 28-day mortality (HR 1.064, 95% CI 1.042–1.086, $P < 0.001$) and 365-day mortality (HR 1.065, 95% CI 1.043–1.087, $P < 0.001$). A threshold effect was observed at ≥19.25 mmol/L, above which mortality risk increased markedly (28-day HR 1.336, 95% CI 1.126–1.586, P = 0.001; 365-day HR 1.429, 95% CI 1.208–1.691, $P < 0.001$). Kaplan–Meier survival analysis confirmed significant differences (log-rank $P < 0.0001$), and ROC analysis demonstrated that ACAG provided superior discrimination compared with AG and albumin for both 28-day (AUC = 0.734) and 365-day mortality (AUC = 0.696). Associations were consistent across clinical subgroups without significant interactions.

Conclusion: Elevated ACAG was an independent predictor of 28-day and 365-day all-cause mortality in critically ill patients with COPD and sepsis. An inflection point of approximately 19.25 mmol/L identified a clinically meaningful threshold for risk stratification. As a simple and widely accessible parameter, ACAG may facilitate threshold-based triage and individualized management in this high-risk population, though external validation in multicenter prospective cohorts is warranted.

Keywords: COPD, sepsis, ACAG, mortality, ICU, MIMIC-IV

Introduction

Chronic obstructive pulmonary disease (COPD) represents a prevalent long-term respiratory disorder, marked by ongoing respiratory complaints and a gradual decline in airflow capacity. Data from the Global Burden of Disease Study indicate that, in 2020, COPD affected around 384 million individuals globally, resulting in an estimated 3.2 million deaths—equivalent to 6% of all global fatalities—making it the third most common cause of death worldwide.[1,2] These statistics underscore the considerable strain COPD imposes on public health systems, manifesting through extensive medical

Received: 23 June 2025
Accepted: 26 October 2025
Published: 10 December 2025

resource consumption and profound socioeconomic repercussions. Individuals diagnosed with COPD frequently experience sustained systemic inflammation and compromised lung function, which contribute to continuous states of hypoxemia and hypercapnia. Such physiological disturbances weaken host immune defenses and disrupt mucociliary clearance, thereby markedly increasing vulnerability to infectious agents.[3] Among the numerous complications associated with COPD, sepsis has been identified as both highly prevalent and particularly severe in affected individuals.[4] According to the Sepsis-3 consensus, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, operationalized as a ≥2-point increase in the Sequential Organ Failure Assessment (SOFA) score.[5] It continues to be a predominant contributor to both death and severe illness within intensive care units, with an estimated 49 million incident cases and over 11 million associated deaths reported globally each year—accounting for close to 20% of worldwide deaths.[6] Genetic analyses based on Mendelian randomization indicate that genetically predicted COPD severity, as derived from genome-wide association study (GWAS) data, increases sepsis risk by about 14.3% for each standard deviation.[7] Furthermore, individuals with COPD who progress to sepsis demonstrate markedly elevated mortality rates when compared with the broader population of sepsis patients.[8,9]

The anion gap (AG) is a commonly applied biochemical parameter in medical practice, primarily used to assess acid–base balance and to identify metabolic acidosis. Beyond its utility in diagnosis, AG has also been associated with disease severity and prognostic outcomes in patients with critical illness.[10] Nonetheless, hypoalbuminemia is frequently encountered in intensive care units (ICUs), and given that albumin constitutes a significant unmeasured plasma anion, reduced albumin concentrations can yield deceptively low AG readings, potentially obscuring metabolic abnormalities and complicating diagnostic accuracy.[11] In addition, critically ill patients with sepsis often accumulate unmeasured anions such as lactate and organic acids, further distorting the conventional AG. Mitochondrial dysfunction, which is a central mechanism in sepsis pathophysiology and is frequently aggravated in COPD due to chronic hypoxemia and systemic inflammation, promotes anaerobic metabolism and excess lactate production. These pathophysiologic changes intensify the burden of unmeasured anions and exacerbate acid–base disturbances.[12–14] To address this drawback, the albumin-corrected anion gap (ACAG) was developed, calculated as $\mathrm{ACAG(mmol/L)} = [4.4 - \mathrm{albumin(g/dL)}] \times 2.5 + \mathrm{AG(mmol/L)}$, which adjusts for serum albumin concentration and provides a more accurate estimate of the unmeasured anion burden. Recent studies suggest that the ACAG functions as a reliable prognostic indicator in multiple severe clinical conditions, including sepsis, acute kidney injury, and heart failure. It may provide enhanced predictive performance over traditional anion gap metrics, particularly in patients with hypoalbuminemia.[15,16] Among individuals with COPD, hypoalbuminemia is a frequent finding, attributed to persistent inflammation and nutritional deficits, implying that ACAG could possess enhanced prognostic relevance over AG or serum albumin when considered independently. While prior investigations have examined the relationship between ACAG and clinical outcomes in either COPD or sepsis populations, its prognostic significance in patients concurrently affected by both conditions remains inadequately elucidated.[15,17]

Accordingly, this study aimed to evaluate the prognostic significance of ACAG in critically ill patients with concurrent COPD and sepsis, based on the MIMIC-IV database. While ACAG has been examined in COPD and sepsis populations separately, its predictive value in this combined phenotype remains unexplored. We therefore sought to determine whether ACAG independently predicts 28- and 365-day all-cause mortality and to assess its potential as a practical biomarker for early risk stratification in this clinically vulnerable group.

Materials and Methods

Data Source

This study employed a retrospective cohort design with longitudinal follow-up, utilizing patient-level data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1), a database curated by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. The MIMIC-IV database is publicly available and contains comprehensive, de-identified clinical data for 76,540 adult ICU encounters recorded at Beth Israel Deaconess Medical Center (Boston, MA, USA) between 2008 and 2022.[18] To ensure patient privacy, all identifiable health information was thoroughly anonymized. Database access was authorized for the author (Baiquan Zhang, Certification ID: 69002811) following successful completion of the mandated training on data usage compliance.

According to the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (February 18, 2023, China), Article 32 stipulates that research using legally obtained public data, data generated without interfering with public behavior, or anonymized information is exempt from ethics review. Consistent with these provisions, this study was exempt from institutional ethical approval. The data use protocol and ethical guidelines were strictly followed, and the study was conducted solely for scientific research purposes. This article adheres to the STROBE guidelines for observational studies, with full details provided in Supplementary Table 1.[19]

Study Participants

Identification of patients with COPD was conducted using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM diagnostic codes, following criteria established in prior literature and verified through publicly available coding systems (https://www.findacode.com/). The specific diagnostic codes used to define COPD cases are listed in Supplementary Table 2. Sepsis was defined according to the Sepsis-3 criteria, requiring documented infection along with a SOFA score ≥2.[5,20] The SOFA scoring system quantifies organ dysfunction across six physiological systems—respiratory, coagulation, hepatic, cardiovascular, neurological, and renal—with each domain graded on a scale from 0 to 4 points.[21] Given the prominent role of sepsis as a leading contributor to ICU admissions and hospital mortality, especially among individuals with COPD, this study focused explicitly on COPD patients admitted to the ICU with a concurrent sepsis diagnosis. The exclusion parameters included: (1) age below 18 or above 90 years; (2) absence of AG or serum albumin measurements; (3) multiple ICU or hospital admissions; and (4) ICU length of stay less than 24 hours.

Variable Extraction

Data extraction and preprocessing were performed utilizing PostgreSQL (v17.1.11) in conjunction with Navicat Premium (v17) as the database management and query tools. Guided by clinical relevance, a wide array of variables was extracted, encompassing patient demographics, physiological measurements, biochemical markers, comorbid conditions, clinical scoring indices, therapeutic procedures, and outcome indicators. Demographic characteristics specifically comprised age and gender. Vital parameters documented within the initial 24 hours post-ICU admission included heart rate, respiratory rate, oxygen saturation (SpO_2), systolic arterial pressure, and diastolic arterial pressure. Laboratory data encompassed measurements of albumin, albumin-corrected ACAG, AG, prothrombin time (PT), serum glucose, electrolytes (potassium, sodium, chloride), lactate, serum creatinine, hemoglobin, platelet count, red cell distribution width (RDW), blood urea nitrogen (BUN), white blood cell count (WBC), arterial blood gases (PaO_2 and $PaCO_2$), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum bicarbonate, and blood pH. Documented clinical interventions comprised administration of vasopressors, initiation of mechanical ventilation, employment of continuous renal replacement therapy (CRRT), and usage of systemic glucocorticoids. Comorbid conditions were ascertained via ICD-9 and ICD-10 coding systems, and encompassed malignancies, ischemic heart disease, hepatic cirrhosis, congestive heart failure, acute kidney injury, arterial hypertension, and diabetes mellitus. The severity of the clinical condition was evaluated through established scoring systems including the SOFA, Simplified Acute Physiology Score II (SAPS II), Oxford Acute Severity of Illness Score (OASIS), and the Charlson Comorbidity Index (CCI). Information regarding in-hospital mortality, defined as death occurring during the recorded length of stay (LOS), was also collected.

All laboratory measurements and severity scoring indices were collected during the first 24 hours after ICU admission. For variables measured more than once within this period, the average of all day-one recordings was used for subsequent analysis. Variables exhibiting greater than 20% missingness were omitted from analysis, whereas those with less than 20% missing data underwent imputation using the missForest technique, a machine learning-based method employing random forests for multiple imputation. ACAG was computed using the formula:$\mathrm{ACAG(mmol/L)} = [4.4 - \mathrm{albumin(g/dL)}] \times 2.5 + \mathrm{AG(mmol/L)}$.[22,23] An inflection point at 19.25 mmol/L, beyond which mortality risk rose markedly, was used to define high and low ACAG groups. The number and percentage of missing values for each variable are summarized in Supplementary Table 3.

The primary outcome was defined as all-cause mortality occurring within 28 days post-ICU admission, a widely accepted marker for evaluating short-term prognosis in critically ill cohorts. The secondary endpoint was defined as 365-day mortality, enabling evaluation of the long-term predictive utility of ACAG.

Statistical Analysis

The distribution of continuous variables was evaluated for normality utilizing the Kolmogorov–Smirnov statistical test. Variables conforming to a normal distribution were expressed as mean ± SD and compared using independent t-tests. In contrast, those with non-normal distributions were summarized as medians with interquartile range (IQR) and analyzed through the Mann–Whitney *U*-test. Categorical variables were presented as counts and percentages, with intergroup comparisons performed using the chi-square or Fisher's exact test based on sample size and distribution criteria. Baseline variables were contrasted between survivor and non-survivor cohorts to determine potential predictors for inclusion in subsequent multivariable analyses.

To address multicollinearity and improve model parsimony, LASSO regression with 10-fold cross-validation was employed for variable selection. The optimal penalty parameter (Lambda_min) was chosen based on minimal cross-validated deviance. Clinically important variables, such as the SOFA score, were included in the final model despite being excluded by LASSO, owing to their established prognostic significance and potential collinearity with other selected variables. To further assess potential multicollinearity among the covariates included in Model 3, variance inflation factors (VIFs) were calculated, and the results are provided in Supplementary Table 4. To investigate the association between ACAG and all-cause mortality at 28 days (as the primary outcome) and 365 days (as the secondary outcome), multivariable Cox regression models were developed. A set of three hierarchical regression models was constructed based on clinical significance and patient baseline characteristics: Model 1 included only ACAG as the independent variable; Model 2 incorporated demographic variables (age and sex); and Model 3 extended adjustments to include comorbidities (hypertension, acute kidney injury, liver cirrhosis, and malignancy), hematologic and biochemical markers (lactate, creatinine, RDW, WBC, PaO_2), vital signs (heart rate, SpO_2, PT), therapeutic interventions (CRRT, glucocorticoid administration, and vasopressor support), as well as disease severity indices (SOFA, OASIS, CCI, and SAPS II). To explore potential non-linear associations between ACAG and mortality outcomes, multivariable modeling was supplemented with a restricted cubic spline (RCS) approach incorporating four knots. Cumulative survival across ACAG-defined strata at both 28-day and 365-day intervals was visualized through Kaplan-Meier survival plots, with intergroup differences evaluated via the Log rank test. The predictive accuracy of ACAG for 28-day mortality was assessed through receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) serving as the discriminative metric; results were benchmarked against uncorrected AG and serum albumin levels.[24] Stratified subgroup analyses were performed to evaluate 28-day mortality within categories defined by age, sex, diabetes status, hypertension, malignancy, CRRT treatment, and severity scores (SOFA, SAPS II, OASIS), with interaction terms incorporated to investigate potential effect modification. Furthermore, the Boruta feature selection algorithm, grounded in random forest classification, was applied as a model-independent method to validate the robustness and quantify the predictive relevance of ACAG within the broader set of candidate variables. A Cox-based nomogram predicted 28-day survival, validated with 500 bootstraps, calibration plots, and decision curve analysis.

All statistical procedures were conducted using R software (v4.2.2), with a two-tailed p-value below 0.05 deemed statistically significant.

Results

Baseline Characteristics

A total of 2072 patients with concurrent diagnoses of COPD and sepsis were identified and extracted from the MIMIC-IV database (Figure 1). The cohort had a median age of 71 years (IQR: 63–79), and 55.2% were male. Table 1 summarizes baseline characteristics stratified by ACAG levels using the cutoff of 19.25 mmol/L. Compared to patients with ACAG <19.25 mmol/L, those in the high-ACAG group (≥19.25 mmol/L) were slightly older and presented with more severe illness, as indicated by higher SOFA, SAPS II, OASIS, and CCI scores (all $p < 0.001$). Laboratory results showed that patients with elevated ACAG had significantly higher WBC, lactate, creatinine, BUN, RDW, ALT, AST, and glucose, while albumin and bicarbonate were notably lower (all $p < 0.001$). Electrolyte disturbances, including lower chloride and modestly higher potassium, were also more pronounced in the high-ACAG group. Furthermore, comorbidities such as acute kidney injury, diabetes, liver cirrhosis, and ischemic heart disease were more common among patients

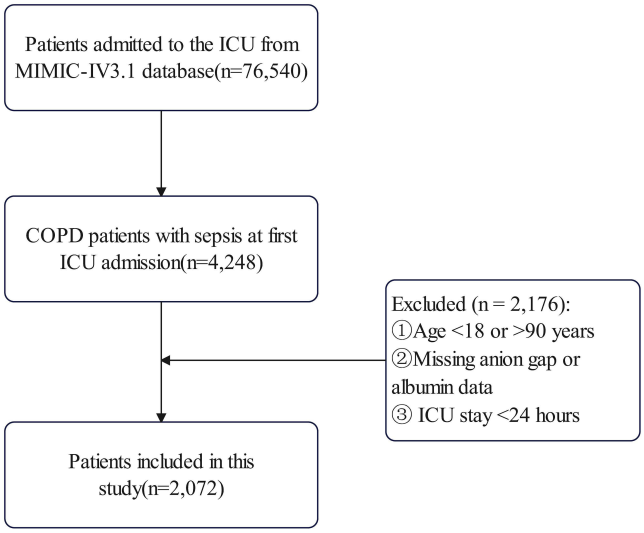

Figure 1 Flowchart of patient inclusion. A total of 76,540 ICU admissions were screened from the MIMIC-IV v3.1 database. After applying inclusion and exclusion criteria, 2072 patients with COPD and sepsis were included in the final analysis.
Abbreviations: COPD, chronic obstructive pulmonary disease; MIMIC-IV, medical information mart for intensive care IV; ICU, intensive care unit.

with high ACAG, while hypertension was less prevalent. In terms of interventions, high-ACAG patients were more likely to receive CRRT and vasopressors ($p < 0.001$ for both). Notably, hospital length of stay was shorter in the high-ACAG group, although ICU stay did not differ significantly between groups.

Table 1 Baseline Characteristics of Patients Stratified by ACAG Level

Characteristic	Overall, N = 2072	ACAG < 19.25, N = 1320	ACAG ≥ 19.25, N = 752	p-value
Age, year	71.00 (63.00–79.00)	71.00 (63.00–79.00)	72.00 (64.00–79.00)	0.040
Gender, male	1144.00 (55.21%)	715.00 (54.17%)	429.00 (57.05%)	0.205
SOFA	6.00 (4.00–9.00)	6.00 (4.00–8.00)	7.00 (5.00–10.00)	<0.001
SAPS II	42.00 (35.00–51.00)	40.00 (33.00–49.00)	45.50 (38.00–56.00)	<0.001
OASIS	36.00 (30.00–42.00)	35.00 (29.50–41.00)	37.00 (31.00–44.00)	<0.001
CCI	7.00 (5.00–9.00)	6.00 (5.00–8.00)	7.00 (5.00–9.00)	<0.001
Monitoring parameters				
RR, breaths/min	20.00 (16.00–24.00)	19.00 (16.00–24.00)	20.00 (16.00–25.00)	0.035
HR, Bpm	90.00 (78.00–106.00)	88.00 (76.00–103.00)	94.00 (82.00–110.00)	<0.001
SBP, mmHg	117.00 (101.00–137.00)	118.00 (102.00–138.00)	117.00 (100.00–134.00)	0.132
DBP, mmHg	65.00 (55.00–77.00)	65.00 (55.00–78.00)	65.00 (55.00–77.00)	0.282
SpO2, %	97.00 (94.00–100.00)	97.00 (94.00–100.00)	97.00 (94.00–100.00)	0.050
Laboratory tests				
Hemoglobin, g/dL	10.30 (8.80–11.90)	10.30 (8.80–11.90)	10.25 (8.80–11.90)	0.689
WBC, K/uL	12.10 (8.20–17.30)	11.50 (8.00–16.20)	13.20 (8.70–18.80)	<0.001
Platelets, K/uL	191.00 (131.00–265.00)	192.00 (136.00–264.00)	189.00 (124.00–269.00)	0.177
RDW, %	15.20 (14.10–16.90)	15.10 (14.00–16.70)	15.60 (14.50–17.30)	<0.001
Lactate, mg/dL	1.60 (1.20–2.40)	1.60 (1.10–2.10)	1.90 (1.40–3.25)	<0.001
Creatinine, ng/dL	1.20 (0.80–1.80)	1.00 (0.70–1.50)	1.55 (1.00–2.60)	<0.001
BUN, mg/dL	26.00 (17.00–42.00)	23.00 (15.00–36.00)	32.00 (19.00–51.00)	<0.001
ALT, U/L	26.00 (15.00–56.00)	26.00 (15.00–45.00)	30.00 (17.00–84.50)	<0.001
AST, U/L	38.00 (22.00–87.00)	36.00 (21.00–68.00)	46.00 (25.00–137.50)	<0.001
PaO2, mmHg	82.00 (54.00–136.00)	82.00 (58.00–145.50)	80.00 (49.00–117.50)	<0.001

(*Continued*)

Table 1 (Continued).

Characteristic	Overall, N = 2072	ACAG < 19.25, N = 1320	ACAG ≥ 19.25, N = 752	p-value
PaCO2, mmHg	45.00 (39.00–54.00)	45.00 (40.00–55.00)	43.00 (37.00–52.00)	<0.001
PH	7.34 (7.27–7.40)	7.34 (7.29–7.41)	7.33 (7.25–7.38)	<0.001
PT, s	14.40 (12.70–17.30)	14.40 (12.70–16.90)	14.65 (12.80–18.05)	0.002
Glucose, mg/dL	132.00 (107.00–174.00)	129.00 (105.00–164.00)	144.00 (111.00–192.50)	<0.001
Albumin, g/dL	2.90 (2.50–3.30)	3.00 (2.60–3.40)	2.80 (2.40–3.20)	<0.001
ACAG, mmol/L	17.75 (15.50–20.50)	16.25 (14.50–17.75)	21.50 (20.25–23.75)	<0.001
Anion Gap, mmol/L	14.00 (12.00–17.00)	12.00 (11.00–14.00)	18.00 (16.00–20.00)	<0.001
K, mmol/L	4.30 (3.80–4.80)	4.20 (3.80–4.70)	4.30 (3.80–4.90)	0.032
Na, mmol/L	139.00 (135.00–142.00)	139.00 (135.00–142.00)	138.00 (135.00–141.00)	0.058
Cl, mmol/L	103.00 (99.00–107.00)	103.00 (100.00–108.00)	102.00 (98.00–106.00)	<0.001
Bicarbonate, mmol/L	23.00 (20.00–26.00)	24.00 (21.00–28.00)	20.00 (17.00–24.00)	<0.001
Comorbidities				
Diabetes	694.00 (33.49%)	397.00 (30.08%)	297.00 (39.49%)	<0.001
Hypertension	791.00 (38.18%)	544.00 (41.21%)	247.00 (32.85%)	<0.001
Acute kidney injury	1181.00 (57.00%)	666.00 (50.45%)	515.00 (68.48%)	<0.001
Malignant tumors	402.00 (19.40%)	256.00 (19.39%)	146.00 (19.41%)	0.991
Heart failure	931.00 (44.93%)	573.00 (43.41%)	358.00 (47.61%)	0.065
Liver cirrhosis	240.00 (11.58%)	131.00 (9.92%)	109.00 (14.49%)	0.002
Ischemic heart disease	914.00 (44.11%)	554.00 (41.97%)	360.00 (47.87%)	0.009
Intervention				
Mechanical ventilation	1144.00 (55.21%)	715.00 (54.17%)	429.00 (57.05%)	0.205
CRRT	219.00 (10.57%)	93.00 (7.05%)	126.00 (16.76%)	<0.001
Vasopressors use	1415.00 (68.29%)	850.00 (64.39%)	565.00 (75.13%)	<0.001
Glucocorticoids use	839.00 (40.49%)	528.00 (40.00%)	311.00 (41.36%)	0.545
Outcomes				
LOS hospital, day	11.37 (6.29–19.70)	11.75 (6.65–19.87)	10.84 (5.78–19.14)	0.046
LOS ICU, day	4.43 (2.28–8.89)	4.46 (2.24–8.76)	4.39 (2.36–8.98)	0.709

Note: Values are expressed as the median (Interquartile range) or n (%).

Abbreviations: SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; OASIS, oxford acute severity of illness score; CCI, charlson comorbidity index; RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, oxygen saturation; WBC, white blood cell count; RDW, red cell distribution width; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; pH, potential of hydrogen; PT, prothrombin time; ACAG, albumin corrected anion gap; CRRT, continuous renal replacement therapy; LOS, length of stay.

Cox Regression of ACAG and 28-Day and 365-Day Mortality

To evaluate the association between ACAG and all-cause mortality, multivariable Cox regression analyses were performed. Variables directly involved in the calculation of ACAG—namely AG, serum albumin, sodium, potassium, chloride, and bicarbonate—were excluded to avoid multicollinearity. Among the remaining candidate variables that were significantly associated with survival status ($P < 0.05$; Supplementary Table 5), LASSO regression with 10-fold cross-validation was applied. As shown in Supplementary Figure 1A, the LASSO coefficient profiles shrink toward zero with increasing regularization. The optimal penalty parameter (Lambda_min) was selected based on the minimum cross-validated deviance (Supplementary Figure 1B), resulting in 20 predictors with non-zero coefficients. Clinically important variables, such as the SOFA score, were retained in the final model despite exclusion by LASSO, due to their established prognostic value and potential collinearity. Multivariable Cox regression revealed a strong and consistent correlation between higher ACAG values and elevated all-cause mortality among individuals with concurrent COPD and sepsis. When analyzed as a continuous independent variable, ACAG consistently demonstrated prognostic significance for both 28-day and 365-day mortality across all levels of model adjustment. Under full adjustment conditions in Model 3, a one-unit increment in ACAG was linked to a 6.4% rise in the hazard of 28-day mortality (HR = 1.064, 95% CI: 1.042–1.086, $P < 0.001$), and a 6.5% escalation in the likelihood of death within 365 days (HR = 1.065, 95% CI: 1.043–1.087, $P <$

0.001). Moreover, stratifying ACAG levels at a threshold of 19.25 mmol/L revealed that individuals in the elevated ACAG category (≥19.25 mmol/L) faced markedly higher mortality rates relative to those with values below this cutoff (<19.25 mmol/L). After comprehensive adjustment in Model 3, elevated ACAG (≥19.25 mmol/L) was independently associated with a 33.6% higher hazard of death within 28 days (HR = 1.336, 95% CI: 1.126–1.586, P = 0.001) and a 42.9% greater risk of 1-year mortality (HR = 1.429, 95% CI: 1.208–1.691, $P < 0.001$; Table 2).

Survival Analysis

Kaplan-Meier survival curves demonstrated that individuals with COPD and sepsis presenting with higher ACAG values (≥19.25 mmol/L) exhibited markedly reduced survival probabilities relative to those with lower ACAG measurements (<19.25 mmol/L). This disparity in survival outcomes was evident across both short-term (28-day; Figure 2A) and long-term (365-day; Figure 2B) follow-up periods, with highly significant differences confirmed by Log rank tests ($P < 0.0001$ for both time points).

The Detection of Nonlinear Relationships

The RCS model identified a statistically significant nonlinear relationship between ACAG levels and all-cause mortality risk. As shown in Figure 3A and B, there was a notable inflection point at approximately 19.25 mmol/L, beyond which the hazard of death increased sharply. This threshold was therefore adopted to stratify patients into high and low ACAG groups for subsequent analyses.

The curvilinear association was statistically confirmed for both short-term (28-day) mortality (Figure 3A; p for nonlinearity = 0.006) and long-term (365-day) mortality (Figure 3B; p for nonlinearity = 0.025).

ROC Curve Analysis of ACAG, AG, and Albumin

To assess the predictive capacity of ACAG for both short-term (28-day) and long-term (365-day) mortality, ROC curve analyses were performed, with comparative evaluation against its constituent metrics—AG and albumin. As depicted in Figure 4A, ACAG achieved the highest AUC value of 0.734 (95% CI: 0.710–0.758) for predicting 28-day mortality, demonstrating superior discrimination compared to AG (AUC = 0.709, 95% CI: 0.684–0.733) and serum albumin (AUC = 0.649, 95% CI: 0.623–0.676). Similarly, for 365-day mortality (Figure 4B), ACAG continued to demonstrate the highest predictive accuracy with an AUC of 0.696 (95% CI: 0.671–0.721), outperforming AG (AUC = 0.691, 95% CI: 0.666–0.716) and albumin (AUC = 0.595, 95% CI: 0.568–0.623), albeit with a modest decline in discriminative performance relative to the short-term analysis. The results suggest that ACAG holds potential as a prognostically informative biomarker for assessing both early and late mortality risks in individuals with COPD and sepsis, with superior predictive performance compared to conventional AG.

Table 2 Multivariable Cox Regression Analysis of ACAG and 28-Day and 365-Day Mortality in Patients

	Variable	Model I HR (95% CI)	P-value	Model II HR (95% CI)	P-value	Model III HR (95% CI)	P-value
28-day mortality	ACAG	1.094 (1.078–1.111)	<0.001	1.094 (1.078–1.111)	<0.001	1.064 (1.042–1.086)	<0.001
	Grouped ACAG						
	<19.25	Ref		Ref		Ref	
	≥19.25	1.834 (1.561–2.154)	<0.001	1.807 (1.538–2.123)	<0.001	1.336 (1.126–1.586)	0.001
365-day mortality	ACAG	1.097 (1.081–1.113)	<0.001	1.096 (1.080–1.113)	<0.001	1.065 (1.043–1.087)	<0.001
	Grouped ACAG						
	<19.25	Ref		Ref		Ref	
	≥19.25	1.964 (1.675–2.302)	<0.001	1.936 (1.651–2.270)	<0.001	1.429 (1.208–1.691)	<0.001

Notes: Model I: Unadjusted; Model II: Adjusted for age and gender; Model III: Adjusted for age, gender, CCI, SAPS II, SOFA, OASIS, hypertension, acute kidney injury, liver cirrhosis, malignancy, WBC, RDW, PT, lactate, creatinine, PaO_2, SpO_2, heart rate, CRRT, vasopressor use, and glucocorticoid use.

Abbreviations: ACAG, albumin corrected anion gap; CCI, charlson comorbidity index; SAPS II, simplified acute physiology score II; SOFA, sequential organ failure assessment; OASIS, oxford acute severity of illness score; WBC, white blood cell count; RDW, red cell distribution width; PT, prothrombin time; PaO_2, partial pressure of oxygen; SpO_2, oxygen saturation; CRRT, continuous renal replacement therapy.

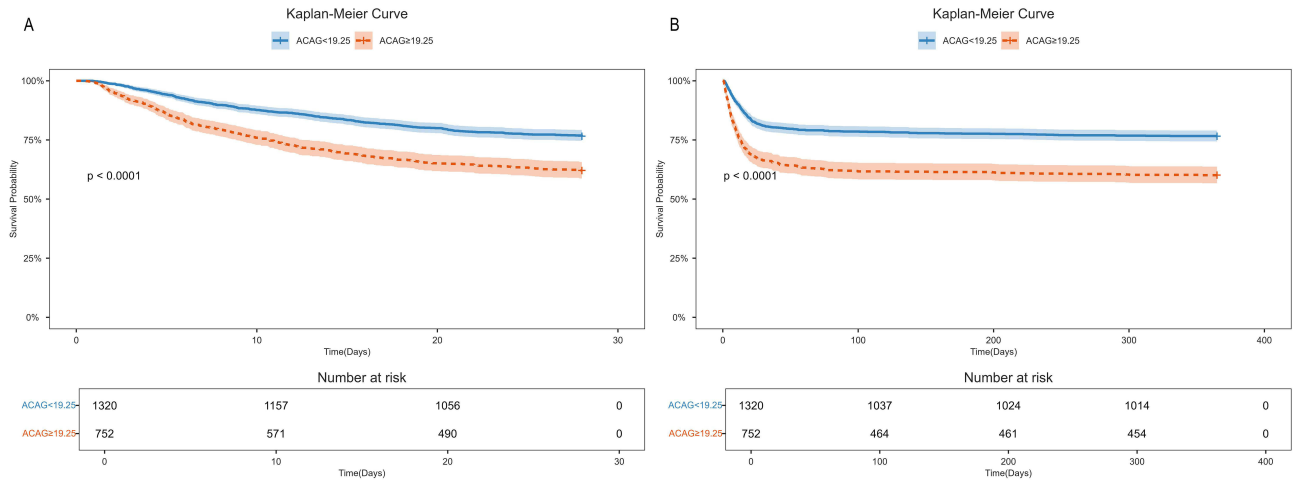

Figure 2 Kaplan–Meier curves by ACAG level in COPD with sepsis. (**A**) 28-day mortality; (**B**) 365-day mortality. Patients with ACAG ≥19.25 mmol/L showed significantly lower survival than those with ACAG <19.25 mmol/L (both log-rank $P < 0.0001$).
Abbreviations: COPD, chronic obstructive pulmonary disease; ACAG, albumin corrected anion gap.

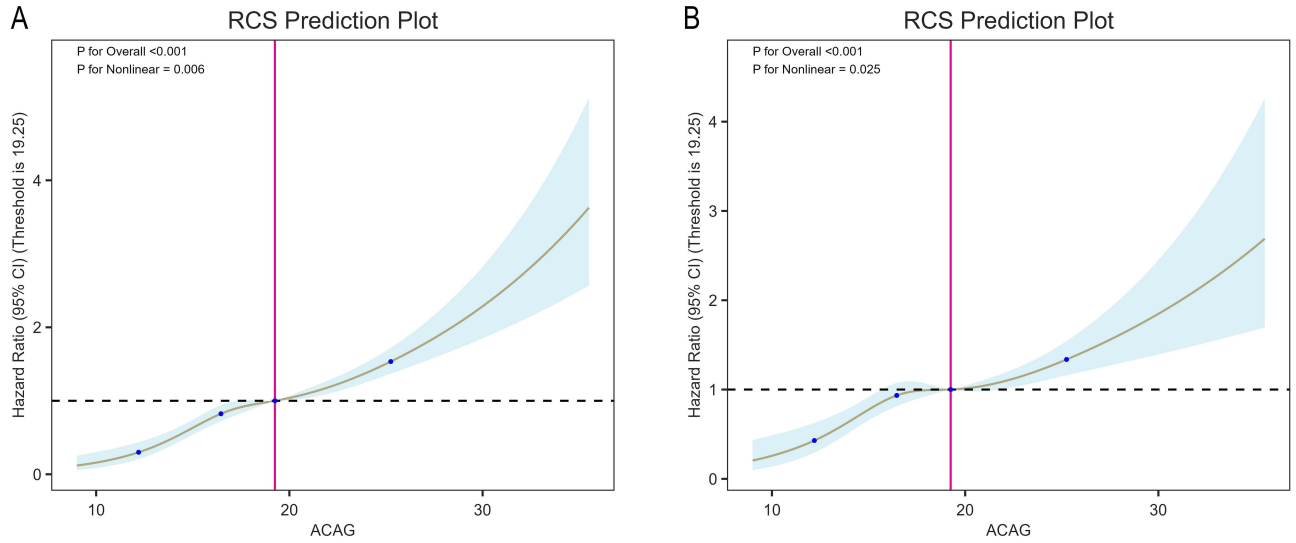

Figure 3 RCS analysis of the non-linear association between ACAG and mortality risk in COPD patients with sepsis. (**A**) 28-day mortality (P for overall association < 0.001; P for non-linearity = 0.012); (**B**) 365-day mortality (P for overall association < 0.001; P for non-linearity = 0.008). A clear inflection point was observed at 19.25 mmol/L in both models, beyond which mortality risk increased sharply.
Abbreviations: RCS, restricted cubic spline; COPD, chronic obstructive pulmonary disease; ACAG, albumin corrected anion gap.

Subgroup Analysis

Subgroup analyses showed that the association between elevated ACAG levels (≥19.25 mmol/L) and 28-day all-cause mortality was consistent across clinical subgroups (Figure 5). No significant interactions were observed across age, sex, diabetes, hypertension, malignancy, or disease severity scores (SOFA, SAPS II, OASIS), indicating that this association was not modified by these factors (all P for interaction > 0.05).

Development and Validation of a Prognostic Nomogram

A nomogram for predicting 28-day survival was constructed based on the multivariable Cox regression model (Supplementary Figure 2). When internally validated with 500 bootstrap resamples, the model achieved a bootstrap-corrected C-index of 0.715, indicating acceptable discriminative ability. The calibration curve demonstrated good agreement between predicted and observed 28-day survival probabilities (Supplementary Figure 3). Decision curve

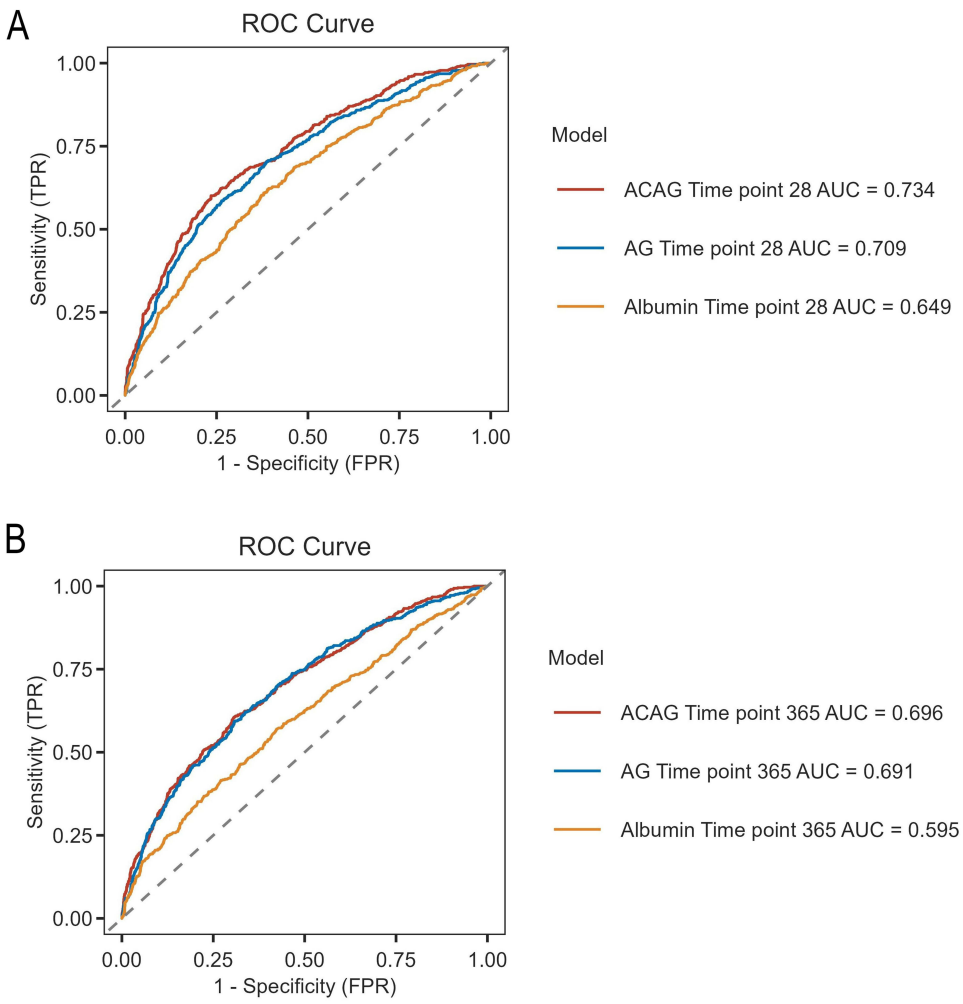

Figure 4 ROC curves comparing the predictive performance of ACAG, AG, and albumin for mortality in COPD patients with sepsis. (**A**) 28-day mortality: ACAG (AUC = 0.710, 95% CI: 0.682–0.739), AG (AUC = 0.642, 95% CI: 0.612–0.672), albumin (AUC = 0.615, 95% CI: 0.586–0.645); (**B**) 365-day mortality: ACAG (AUC = 0.693, 95% CI: 0.667–0.720), AG (AUC = 0.633, 95% CI: 0.605–0.662), albumin (AUC = 0.609, 95% CI: 0.581–0.637). ACAG demonstrated superior predictive accuracy compared to AG and albumin at both time points.

Abbreviations: ROC, receiver operating characteristic; ACAG, albumin corrected anion gap; AG, anion gap; COPD, chronic obstructive pulmonary disease; AUC, area under the curve; CI, confidence interval.

analysis further indicated that the model provided net clinical benefit across a wide range of threshold probabilities (Supplementary Figure 4), supporting its potential clinical applicability in patients with COPD and sepsis.

Relative Importance of Predictors for 28-Day Mortality as Determined by the Boruta Algorithm

To evaluate the robustness and predictive relevance of ACAG for 28-day mortality in individuals concurrently diagnosed with COPD and sepsis, we applied the Boruta feature selection algorithm. As illustrated in Supplementary Figure 5, ACAG was recognized as an important determinant of 28-day mortality and was definitively categorized as a "Confirmed" feature by the Boruta selection framework.

Discussion

Based on a large retrospective cohort extracted from the MIMIC-IV database, we identified that higher ACAG concentrations were independently associated with increased risks of 28-day and 365-day all-cause mortality among critically ill patients suffering from both COPD and sepsis. This study aims to assess the prognostic relevance of the

Subgroup	<19.25	≥19.25	Hazard Ratio (95% CI)	P value	P for interaction
Overall	309/1,320 (23.4)	285/752 (37.9)	1.40 (1.18, 1.67)	<0.001	
Age					0.127
<65	69/389 (17.7)	70/196 (35.7)	1.62 (1.12, 2.34)	0.011	
≥65	240/931 (25.8)	215/556 (38.7)	1.35 (1.11, 1.64)	0.003	
Gender					0.264
Female	147/605 (24.3)	115/323 (35.6)	1.24 (0.95, 1.62)	0.113	
Male	162/715 (22.7)	170/429 (39.6)	1.55 (1.23, 1.96)	<0.001	
Hypertension					0.553
No	200/776 (25.8)	200/505 (39.6)	1.32 (1.07, 1.63)	0.009	
Yes	109/544 (20.0)	85/247 (34.4)	1.53 (1.13, 2.08)	0.006	
Diabetes					0.468
No	224/923 (24.3)	184/455 (40.4)	1.36 (1.10, 1.68)	0.004	
Yes	85/397 (21.4)	101/297 (34.0)	1.47 (1.08, 2.00)	0.015	
Malignant Cancer					0.31
No	240/1,064 (22.6)	222/606 (36.6)	1.35 (1.11, 1.65)	0.003	
Yes	69/256 (27.0)	63/146 (43.2)	1.65 (1.15, 2.37)	0.007	
CRRT					0.693
No	265/1,227 (21.6)	210/626 (33.5)	1.34 (1.10, 1.64)	0.004	
Yes	44/93 (47.3)	75/126 (59.5)	1.89 (1.25, 2.86)	0.002	
SOFA					0.065
<5	95/485 (19.6)	34/152 (22.4)	1.00 (0.66, 1.52)	0.999	
≥5	214/835 (25.6)	251/600 (41.8)	1.54 (1.26, 1.87)	<0.001	
SAPS II					0.208
<35	59/397 (14.9)	18/109 (16.5)	1.04 (0.59, 1.82)	0.891	
≥35	250/923 (27.1)	267/643 (41.5)	1.44 (1.19, 1.73)	<0.001	
OASIS					0.629
<34	100/568 (17.6)	67/239 (28.0)	1.44 (1.03, 2.01)	0.034	
≥34	209/752 (27.8)	218/513 (42.5)	1.37 (1.12, 1.68)	0.002	

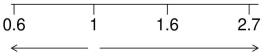

Figure 5 Subgroup analyses of the association between high ACAG levels (≥19.25 mmol/L) and 28-day all-cause mortality. The effect was consistent across subgroups defined by age (<65 vs ≥65 years), sex, diabetes, hypertension, malignant cancer, CRRT, and disease severity scores including SOFA (<6 vs ≥6), SAPS II (<41 vs ≥41), and OASIS (<35 vs ≥35). No significant interactions were observed in any subgroup (all P for interaction > 0.05).

Abbreviations: ACAG, albumin corrected anion gap; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; OASIS, oxford acute severity of illness score; CRRT, continuous renal replacement therapy.

ACAG in patients concurrently suffering from COPD and sepsis—a clinically fragile group marked by high mortality, persistent inflammation, and prevalent hypoalbuminemia—within a context that has not been extensively examined in prior studies. Importantly, multivariable Cox regression analysis confirmed that an increased ACAG (≥19.25 mmol/L) independently predicted both early and late mortality, maintaining statistical significance after adjustment for demographic characteristics, disease severity, existing comorbidities, and applied treatments. Kaplan-Meier survival curves further substantiated these results, showing significantly lower survival probabilities in patients presenting with elevated ACAG levels. Additionally, restricted cubic spline modeling identified a nonlinear association, indicating a pronounced increase in mortality risk when ACAG surpasses the threshold of approximately 19.25 mmol/L. Collectively, these results underscore the clinical utility of ACAG as a threshold-dependent risk indicator, with potential application in ICU risk stratification strategies. Of particular note, ACAG demonstrated superior prognostic performance compared to conventional markers such as AG and serum albumin in predicting both 28-day and 365-day outcomes, underscoring its enhanced predictive value in this vulnerable patient cohort.

The results of our study are consistent with earlier research demonstrating a positive relationship between increased ACAG concentrations and poor clinical outcomes across diverse critically ill cohorts. For instance, Wang et al reported that ACAG independently predicted 28-day mortality in ICU patients diagnosed with asthma and outperformed the traditional, uncorrected AG in terms of prognostic accuracy.[25] Zhang et al observed that in patients with acute pancreatitis, an ACAG level exceeding 19.03 mmol/L within the first 24 hours of ICU admission was independently

linked to elevated in-hospital mortality.[26] Among individuals with sepsis-associated acute kidney injury, Wu et al demonstrated that ACAG values exceeding 20 mmol/L were independently predictive of increased mortality and showed superior prognostic performance relative to both AG and serum albumin.[27] Likewise, Pan et al reported that in sepsis patients complicated by liver cirrhosis, elevated ACAG levels were notably linked to 28-day mortality, providing superior stratification capability relative to traditional anion gap indices.[28] Sheng et al further demonstrated that increased ACAG concentrations were positively correlated with in-hospital mortality among patients experiencing acute myocardial infarction, with ACAG exhibiting enhanced prognostic performance compared to AG and albumin.[29] Moreover, Giri et al identified a significant association between higher ACAG values and elevated mortality risk in ICU-admitted patients suffering from COPD.[15] In another study, Hu et al concluded that ACAG independently predicted mortality in ICU patients with sepsis, and outperformed AG and albumin when evaluated as individual predictors.[17]

Individuals with COPD frequently exhibit sustained systemic inflammation and recurrent infectious episodes, both of which can disrupt protein synthesis and accelerate catabolism, culminating in hypoalbuminemia.[30,31] Hypoalbuminemia not only serves as a marker of nutritional deficiency but also alters plasma anion distribution and contributes to disturbances in acid–base equilibrium. Additionally, systemic inflammatory responses may facilitate the buildup of unmeasured anions, intensifying metabolic acidosis and significantly increasing the AG.[16] COPD is further defined by progressive decline in pulmonary function and compromised alveolar gas exchange. Affected patients commonly exhibit chronic hypoxemia and hypercapnia, conditions that weaken immune defenses and hinder mucociliary function, thereby heightening infection risk. During sepsis, systemic inflammatory response syndrome induces microvascular dysfunction and mitochondrial damage, thereby promoting anaerobic metabolic pathways and lactic acid buildup, both of which exacerbate AG elevation.[32] In this physiological context, standard AG calculations may fail to accurately reflect the severity of metabolic disturbances, as hypoalbuminemia confounds the assessment. The ACAG, which adjusts for serum albumin concentration, provides a more precise evaluation of latent acid–base imbalances and the load of non-measured anions. Furthermore, an increased ACAG may act as a surrogate indicator of mitochondrial impairment and cellular metabolic instability, both pivotal mechanisms in the onset and progression of organ dysfunction during sepsis.

The clinical relevance of our findings warrants particular attention. First, ACAG represents a cost-effective and easily accessible biomarker, derivable from standard laboratory measurements. Its demonstrated prognostic value in the COPD–sepsis population suggests potential utility for early risk stratification and may inform the need for intensified clinical surveillance or therapeutic interventions. Second, the results highlight the critical need to account for serum albumin concentrations when evaluating AG values in ICU patients, particularly in the setting of hypoalbuminemia. Future prospective investigations are warranted to determine whether ACAG-guided clinical management strategies can translate into improved outcomes for patients with concomitant COPD and sepsis.[14,33]

Although this study benefits from a large sample size and rigorous statistical methodology, several limitations should be acknowledged. First, the retrospective design restricts the ability to draw definitive causal inferences, and residual confounding cannot be entirely excluded. Second, the single-center nature of the MIMIC-IV database may limit external validity and generalizability, underscoring the need for confirmation in multicenter prospective studies. Third, ACAG was measured only once within the first 24 hours of ICU admission, without accounting for potential temporal changes. Finally, COPD was identified based on ICD diagnostic codes rather than direct clinical assessments. Pulmonary function test results, such as a post-bronchodilator FEV_1/FVC ratio below 0.70, and standardized symptom scores, including the COPD Assessment Test (CAT), were not available, limiting the precision of COPD characterization.

Conclusion

In this large retrospective cohort of critically ill patients with concurrent COPD and sepsis, elevated ACAG was independently associated with increased 28-day and 365-day all-cause mortality. An inflection point of approximately 19.25 mmol/L was identified as a clinically meaningful threshold, above which mortality risk rose sharply. This threshold-based approach highlights the potential of ACAG for early risk stratification and triage in a population characterized by high mortality and prevalent hypoalbuminemia, with possible integration into existing ICU assessment frameworks. While ACAG consistently outperformed serum albumin and demonstrated modest but stable advantages over the conventional anion gap for long-term outcomes, its overall predictive performance across both short- and long-

term horizons underscores its clinical value. Future multicenter and prospective studies are warranted to validate these findings, assess external generalizability, and further refine decision thresholds for clinical practice.

Abbreviations

COPD, chronic obstructive pulmonary disease; AG, anion gap; MIMIC-IV, medical information mart for intensive care IV; ROC, receiver operating characteristic; AUC, area under the curve; ICU, intensive care unit; CI, confidence interval; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; OASIS, oxford acute severity of illness score; CCI, charlson comorbidity index; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, oxygen saturation; WBC, white blood cell count; RDW, red cell distribution width; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; pH, potential of hydrogen; PT, prothrombin time; ACAG, albumin-corrected anion gap; CRRT, continuous renal replacement therapy; LOS, length of stay; SD, standard deviation; RCS, restricted cubic spline; LASSO, least absolute shrinkage and selection operator.

Data Sharing Statement

In this study, data were obtained from the MIMIC-IV database, an open-access critical care database. Access to the database is granted upon completion of the required data use agreement and certification exam, available at: https://physionet.org/content/mimiciv/3.1/.

Ethics Approval and Informed Consent

The research involving human participants was reviewed and approved by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. In accordance with national legislation and institutional policies, written informed consent was not required for this study.

Acknowledgments

We sincerely express our gratitude to all individuals and organizations that have made contributions to the construction and improvement of the MIMIC database.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China Youth Fund Project (No.82100048) and the Medical Science and Technology Research Project of Henan Province (LHGJ20200363).

Disclosure

The authors affirm that there are no competing interests on their part.

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