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Article

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Albumin-Corrected Anion Gap and Short- and Long-Term Mortality in Critically Ill Patients with Toxic Encephalopathy: A Retrospective Cohort Study

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Running title: Albumin-Corrected Anion Gap and Mortality in Toxic Encephalopathy

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Abstract

Background: Toxic encephalopathy (TE) covers a group of neurological disorders triggered by external toxins. Mortality is high, yet clinicians still lack a simple marker for early risk sorting. The albumin-corrected anion gap (ACAG) combines the anion gap with serum albumin and may summarize both metabolic and inflammatory strain. We tested whether ACAG tracks mortality in TE.

Methods: This retrospective study drew on MIMIC-IV version 3.1. Adults with TE were eligible when anion gap and albumin were available at the first ICU admission. ACAG was modeled as a continuous variable and as tertiles. Cox models estimated 28-, 90-, and 365-day all-cause mortality under stepwise adjustment. Restricted cubic splines described the dose-response pattern; Kaplan-Meier curves, subgroup analyses, and incremental prediction measures (AUC, NRI, IDI, calibration, and decision curve analysis) were also applied. E-values were calculated.

Results: Altogether 1,120 patients entered the analysis. Mean age was 63.6 ± 16.7 years and 53.3% were male. Mortality at 28, 90, and 365 days was 22.3%, 30.3%, and 38.3%. In the fully adjusted model, each 1-mmol/L rise in ACAG carried an HR of 1.05 (95% CI 1.02-1.08) at 28 days, 1.04 (1.02-1.07) at 90 days, and 1.04 (1.02-1.06) at 365 days. The top tertile also had higher mortality than the bottom tertile at all three horizons (HR 1.58, 1.61, and 1.55). E-values were 2.54, 2.60, and 2.47. The non-linearity tests were not significant (P = 0.908, 0.313, and 0.211). AUC gains were small; NRI and IDI reached significance.

Conclusions: Admission ACAG was independently linked to short- and long-term death in TE, and the pattern was close to linear. Its added predictive value was modest. These data are observational and need external confirmation.

Keywords: Toxic encephalopathy; Albumin-corrected anion gap; Mortality; Risk stratification; Cohort study

Introduction

Toxic encephalopathy (TE) arises after exposure to heavy metals, organic solvents, pesticides, carbon monoxide, drugs, or other chemicals[1]. Symptoms vary widely, from headache and confusion to seizures, coma, and death[1,2]. Some cases evolve slowly and escape notice until late, which makes early risk assessment difficult[3]. The prognosis is influenced by the type of toxin, the dose and duration of exposure, the timeliness of detoxification, and host factors such as age, comorbidity, and organ reserve. A recent MIMIC-IV analysis of TE found a U-shaped link between the glucose-potassium ratio and mortality[4], which suggests that routine metabolic indices may carry prognostic information in this group. TE still covers a clinically mixed population with uneven trajectories[5], and a simple marker that captures metabolic, inflammatory, and nutritional strain is missing.

The anion gap (AG) is calculated from routine electrolytes and reflects the balance between measured cations and unmeasured anions; clinicians use it to detect and follow metabolic acidosis[6]. Serum albumin affects the AG because albumin is the main negatively charged plasma protein. Low albumin is common in critical illness and can lower the AG, hiding a rise in unmeasured anions[7-9]. The albumin-corrected anion gap (ACAG) adds an albumin term to the AG through the Figge equation and has been proposed as a closer estimate of the true anion load[7,8]. Higher ACAG has been associated with adverse outcomes in sepsis[10], acute kidney injury requiring continuous renal replacement therapy[11], acute myocardial infarction[12], cardiac arrest[13], aneurysmal subarachnoid hemorrhage[14], and acute respiratory failure[15]. These observations suggest that ACAG may capture a general dimension of critical illness severity rather than a disease-specific process.

Several questions remain. Most prior studies examined one disease and one or two outcome windows, so short- and long-term associations are hard to compare. ACAG joins two constructs, unmeasured anions and albumin, that may carry different weight in TE, where

toxin exposure, seizures, hypoperfusion, and systemic inflammation often overlap. It is also unclear whether ACAG adds information beyond age, vital signs, Glasgow Coma Scale, hemoglobin, and glucose. TE is identified through heterogeneous ICD codes, and the prognostic value of a simple metabolic index in such a mixed group has not been established. We therefore used MIMIC-IV to test the association between admission ACAG and 28-, 90-, and 365-day all-cause mortality in TE. We also assessed the shape of that association, its consistency across subgroups, and its incremental predictive value over a basic clinical model. The design is observational, so we describe associations rather than causal effects.

Methods

Data source

This retrospective cohort used MIMIC-IV version 3.1, a public database of de-identified electronic records from ICU patients at the Beth Israel Deaconess Medical Center[16]. It contains demographic, physiological, laboratory, comorbidity, severity, and outcome data. Lei Sun obtained access after completing the required training (authorization number: 79294305). We followed the STROBE statement[17] and the TRIPOD+AI statement[18] when reporting the study.

Study population

Adults aged 18 years or older with a diagnosis of TE were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 349.82 and the Tenth Revision, Clinical Modification (ICD-10-CM) codes G92, G92.8, and G92.9. Only the first ICU admission was included. Patients were excluded if they had missing data on AG or serum albumin, an ICU stay of less than 24 h, or end-stage renal disease. The patient selection process is shown in Figure 1.

Exposure

The ACAG was calculated using the Figge equation[7,8]:

$$AG = Na^{+} - (Cl^{-} + HCO_3^{-})$$

$$ACAG = AG + 2.5 \times (4.4 - \text{serum albumin [g/dL]})$$

Normal serum albumin was set at 4.4 g/dL. For modeling, ACAG was scaled per 1-mmol/L change and also split at the tertile boundaries: 6.25-15.25 mmol/L (T1), 15.50-18.50 mmol/L (T2), and 18.75-38.50 mmol/L (T3).

Covariates

Baseline variables were extracted from the first ICU admission. Demographic variables included age and sex. Vital signs included heart rate, mean arterial pressure (MAP), respiratory rate (RR), temperature, and oxygen saturation (SpO_2). Laboratory parameters included white blood cell count (WBC), hemoglobin (Hb), red cell distribution width (RDW), platelet count (PLT), total bilirubin (TBil), serum creatinine (SCr), blood urea nitrogen (BUN), sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO_3^-), glucose, lactate (LAC), AG, albumin (ALB), and ACAG. Clinical severity was assessed using the Glasgow Coma Scale (GCS) and the Sequential Organ Failure Assessment (SOFA) score. Comorbidities, including myocardial infarction (MI), heart failure (HF), peripheral vascular disease (PVD), cardiovascular disease (CVD), chronic pulmonary disease (CPD), diabetes mellitus (DM), and liver disease (LD), were identified from ICD-9-CM and ICD-10-CM codes. ICU length of stay (LOS) and ICU mortality were also recorded.

Clinical outcomes

The primary endpoints were all-cause mortality (ACM) at 28, 90, and 365 days after ICU admission. Follow-up ran from ICU admission to death or the end of each window. ICU mortality and ICU LOS served as secondary outcomes.

Missing data

Continuous covariates with missing values were filled with the cohort mean. Table S1 gives the missing proportion for each variable. AG and albumin had no missing values in the final cohort because patients lacking either were excluded. Mean imputation was chosen because most covariates were nearly complete[19].

Statistical analysis

Continuous data are shown as mean ± SD or median (IQR), according to skewness. Counts and percentages describe categorical data. Tertile comparisons used one-way ANOVA or Kruskal-Wallis for continuous variables and chi-square or Fisher exact tests for categorical variables.

Cox proportional hazards models produced hazard ratios (HRs) and 95% confidence intervals (CIs) for ACAG and mortality. Model I controlled for age and sex. Model II added heart rate, respiratory rate, temperature, and GCS. Model III added hemoglobin and glucose. Continuous ACAG was scaled per 1-mmol/L increase. T1 served as the reference in tertile models.

Restricted cubic spline (RCS) analysis examined the dose-response curve. RCS models used the same covariates as Model III, and we report P values for the overall association and for non-linearity. Kaplan-Meier curves were drawn for the three ACAG tertiles and compared with the log-rank test.

Subgroups were defined by sex, age (<65 vs ≥65 years), MI, CVD, CPD, DM, and LD. We added interaction terms between ACAG and each subgroup variable to the Cox models and reported the interaction P values.

To evaluate the incremental predictive value of ACAG, a basic clinical model was constructed that included age, sex, heart rate, respiratory rate, temperature, GCS, hemoglobin, and glucose. ACAG was then added to this basic model. Discrimination was assessed using

the area under the receiver operating characteristic curve (AUC) with 95% CI, and AUCs were compared using the DeLong test[20]. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to quantify the improvement in risk classification and discrimination[21]. Calibration curves were plotted to compare predicted and observed mortality probabilities[22]. Decision curve analysis (DCA) was used to evaluate net benefit across a range of threshold probabilities, with treat-all and treat-none strategies as references[23].

For T3 versus T1, E-values were computed from the adjusted HR and its lower confidence limit to gauge sensitivity to unmeasured confounding[24]. An E-value is the minimum strength of association that a confounder would need with both ACAG and mortality to explain away the observed link.

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using R software (version 4.2.2) and the Free Statistics Analysis platform (version 2.4.0, Beijing Free Clinical Medical Technology Co., Ltd.)[25].

Ethics statement

The MIMIC-IV database was approved by the Institutional Review Boards of the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center. All patient data were de-identified, and the requirement for written informed consent was waived.

Results

Study population and baseline characteristics

The MIMIC-IV version 3.1 database contained 94,458 ICU admissions. We removed patients who were not on their first admission (n = 22,415) and repeat ICU stays (n = 6,677), leaving 65,366 first ICU admissions. TE was diagnosed in 3,510 patients. Further exclusions

for missing AG (n = 49) or albumin (n = 1,740), ICU stay <24 h (n = 198), and end-stage renal disease (n = 403) left 1,120 patients (Figure 1). All patients were at least 18 years old.

Participants averaged 63.6 ± 16.7 years; 597 (53.3%) were men. ACAG averaged 17.5 ± 4.6 mmol/L. T1 held 363 patients (6.25-15.25 mmol/L), T2 held 378 (15.50-18.50 mmol/L), and T3 held 379 (18.75-38.50 mmol/L). The three distributions were well separated, and every pairwise test was significant ($P < 0.001$; Figure S1).

T3 carried the highest heart rate, respiratory rate, WBC, RDW, TBil, SCr, BUN, potassium, glucose, lactate, AG, and SOFA score, while MAP, Hb, sodium, chloride, bicarbonate, and albumin were lowest (all $P < 0.05$). Age varied by tertile (60.9 ± 17.8, 65.5 ± 17.1, and 64.3 ± 14.9 years; $P < 0.001$). Men made up 49.6% of T3 and 59.5% of T1 ($P = 0.015$). Temperature, SpO_2, PLT, GCS, and prior MI, HF, PVD, CVD, CPD, or DM showed no tertile difference (all $P > 0.05$). LD was more frequent in T3 (36.9%) than in T1 (18.7%) or T2 (22.8%; $P < 0.001$).

ICU mortality climbed from 5.8% (T1) to 9.0% (T2) and 19.5% (T3; $P < 0.001$). ICU LOS also rose, with medians of 3.6, 4.1, and 5.3 days ($P < 0.001$). At 28 days, ACM was 13.8%, 22.0%, and 30.9%; at 90 days, 19.3%, 31.5%, and 39.6%; at 365 days, 25.9%, 40.5%, and 48.0% (all $P < 0.001$; Table 1).

Lactate was missing for 175 patients (15.63%). Smaller gaps were TBil (45, 4.02%), temperature (17, 1.52%), RDW (2, 0.18%), Hb (1, 0.09%), and WBC (1, 0.09%; Table S1).

Association between ACAG and all-cause mortality

In continuous analysis, a 1-mmol/L higher ACAG was associated with higher mortality at all three horizons (Table 2). For 28-day ACM, the crude HR was 1.09 (95% CI 1.06-1.11) and the fully adjusted HR was 1.05 (1.02-1.08; $P < 0.001$). The 90-day estimates were 1.07 (1.05-1.10) and 1.04 (1.02-1.07; $P = 0.001$); the 365-day estimates were 1.07

(1.05-1.09) and 1.04 (1.02-1.06; $P = 0.001$). Adjustment for age and sex, then vital signs and GCS, then hemoglobin and glucose reduced but did not remove the association.

Crude HRs for T2 and T3, with T1 as reference, were 1.68 (1.18-2.38) and 2.54 (1.83-3.54) at 28 days; 1.75 (1.30-2.35) and 2.42 (1.82-3.21) at 90 days; and 1.73 (1.33-2.23) and 2.26 (1.76-2.90) at 365 days.

Full adjustment left T2 linked to higher 90-day ACM (HR 1.43, 1.06-1.94; $P = 0.020$) and 365-day ACM (HR 1.42, 1.09-1.86; $P = 0.009$), but not 28-day ACM (HR 1.34, 0.94-1.92; $P = 0.103$). T3 remained linked to death at every horizon: 1.58 (1.12-2.23; $P = 0.010$) at 28 days, 1.61 (1.20-2.18; $P = 0.002$) at 90 days, and 1.55 (1.19-2.02; $P = 0.001$) at 365 days. E-values for T3 versus T1 were 2.54, 2.60, and 2.47; lower-limit E-values were 1.49, 1.69, and 1.67 (Figure S2).

Linearity of the association

RCS curves adjusted for Model III covariates showed a positive gradient across all three horizons (Figure 2). Overall P values were 0.008, 0.007, and 0.004 for 28-, 90-, and 365-day ACM. Non-linearity P values were 0.908, 0.313, and 0.211, so the data did not depart from a linear log-hazard relation. The adjusted HR rose across the ACAG range in each panel, and the confidence bands widened at both ends.

Kaplan-Meier survival analysis

Kaplan-Meier curves diverged by tertile at every horizon (log-rank $P < 0.0001$; Figure 3). T3 stayed lowest, with separation appearing soon after ICU entry and persisting. End-of-follow-up at-risk counts were 313, 295, and 262 at 28 days; 293, 259, and 229 at 90 days; and 269, 225, and 197 at 365 days for T1-T3.

Subgroup analyses

Subgroup analyses covered sex, age (<65 vs ≥65 years), MI, CVD, CPD, DM, and LD (Figure 4). Adjusted HRs stayed above 1.0 in every subgroup (range 1.05-1.10), and no interaction reached significance (*P* for interaction 0.287-0.955).

Incremental predictive value of ACAG

The basic model gained little discrimination when ACAG was added. AUC rose from 0.747 (0.712-0.782) to 0.759 (0.725-0.792) at 28 days (*P* = 0.032) and from 0.748 (0.717-0.779) to 0.757 (0.727-0.787) at 90 days (*P* = 0.039). At 365 days the change was 0.766 (0.737-0.794) to 0.770 (0.742-0.798; *P* = 0.174) (Table 3; Figures 5A, 6A, and 7A).

NRI and IDI reached significance at each horizon. At 28 days, NRI was 0.1760 (0.036-0.316; *P* = 0.0137) and IDI 0.0077 (0.0004-0.0149; *P* = 0.0374). At 90 days, the values were 0.1989 (0.0721-0.3256; *P* = 0.0021) and 0.0072 (0.0015-0.0130; *P* = 0.0135). At 365 days, they were 0.1779 (0.0583-0.2976; *P* = 0.0036) and 0.0076 (0.0020-0.0132; *P* = 0.0078).

Calibration curves for both models ran close to the 45° line across the observed probability range at all horizons (Figures 5B, 6B, and 7B). In DCA, the ACAG model had a small net-benefit edge over the basic model across a wide threshold range, and both models beat treat-all and treat-none over most of the clinically relevant range (Figures 5C, 6C, and 7C).

Discussion

Among 1,120 patients with TE, admission ACAG moved with 28-, 90-, and 365-day mortality. The rise was monotonic, and the log-hazard curve did not depart from linearity. T3 had higher mortality than T1 at every horizon; adjustment for demographic, physiological, and laboratory factors weakened but did not remove the estimates. E-values of 2.54, 2.60, and 2.47 imply that a confounder would need a risk ratio near 2.5 with both ACAG and death to

explain away the point estimates. Prediction gains were modest: AUC rose little, while NRI and IDI were significant.

These results agree in direction with earlier ACAG studies in critical illness. Hu et al. found an association with in-hospital mortality in sepsis and reported better performance for ACAG than for AG or albumin[10]. Zhong et al. saw higher ICU mortality among patients with acute kidney injury receiving continuous renal replacement therapy when ACAG exceeded 20 mmol/L[11]. Jian et al. described a nonlinear link with 30-day mortality after acute myocardial infarction[12]. Similar associations have been reported in cardiac arrest[13], aneurysmal subarachnoid hemorrhage[14], cardiogenic shock[26], acute respiratory failure[15], heart failure with acute kidney injury[27], sepsis-associated acute kidney injury in elderly patients[28], atrial fibrillation[29], and acute respiratory distress syndrome[30]. The consistent direction across these groups suggests that ACAG captures a broad dimension of critical illness severity. Effect sizes are not directly comparable, however, because case mix, ACAG ranges, adjustment sets, outcome windows, and analytical methods differ. Unlike some prior work, we found no evidence of nonlinearity. That may reflect differences in TE pathophysiology, the ACAG distribution, measurement timing, or limited power at the extremes. The finding means that nonlinearity was not detected; it does not prove a strictly linear biological relation.

In the same TE cohort, the glucose-potassium ratio showed a U-shaped link with mortality[4]. ACAG, by contrast, showed a graded linear pattern. The two indices are not interchangeable. The glucose-potassium ratio reflects stress hyperglycemia and potassium shifts, while ACAG reflects unmeasured anions and albumin reserve. Different shapes of association may point to different processes and argue for using more than one metabolic marker. This comparison is ecological, however, because the analyses used different exposures, adjustment models, and outcome windows.

ACAG is easy to use. It requires only electrolytes and albumin, adds no test, and is ready at ICU arrival. If other cohorts confirm the link, ACAG might help flag TE patients who need closer observation or stronger support. AUC gains were small (0.012, 0.009, and 0.004 at 28, 90, and 365 days), and the 365-day AUC difference was not significant. NRI and IDI were significant, but they can move with risk distribution, and small absolute gains do not ensure clinical value. Calibration stayed near the reference line for both models, and DCA showed only a slight net-benefit edge for ACAG. T2 and T1 also did not differ at 28 days, so no cutoff is clear. ACAG is therefore a supplementary risk marker, not a stand-alone diagnostic or prognostic tool, and treatment should not hinge on it. The data cannot show that changing ACAG would change outcomes.

ACAG blends two signals: unmeasured anions and albumin. The AG measures the gap between measured cations and anions and grows when organic acids or other unmeasured anions accumulate[6]. TE can raise the anion load through toxin-related mitochondrial injury, hypoperfusion, seizures, hyperthermia, rhabdomyolysis, renal or hepatic dysfunction, and lactate buildup[31]. Albumin is the main plasma antioxidant and scavenger and a negative acute-phase protein; low levels are common in critical illness and reflect inflammation, capillary leak, and redistribution[9] A high ACAG may therefore reflect both a larger acid load and a smaller albumin reserve. That composite nature could explain its link to death across ICU groups, but it also makes ACAG nonspecific. It marks metabolic and inflammatory burden, not TE severity itself.

Metabolic acidosis and hypoperfusion can stabilize HIF-1α and turn on NF-κB, raising inflammatory gene expression and reactive oxygen species[32,33]. Loss of mitochondrial function, ATP depletion, and calcium overload can drive necrotic, apoptotic, and necroptotic death[34]. In the brain, these events may disrupt the blood-brain barrier, worsen glutamate excitotoxicity, and injure neurons[2,35]. Albumin may counter some of this through antioxidant

and scavenging activity, oncotic support, and toxin or drug binding[9]. Low albumin may therefore mean weaker detoxification and stronger systemic inflammation. ACAG, which includes AG and albumin, might capture part of that combined burden. These ideas remain speculative. We did not measure HIF-1α, NF-κB, oxidative stress, mitochondrial function, or blood-brain barrier integrity, so the ACAG-mortality link should not be read as proof that ACAG drives these pathways.

Prediction results need a cautious reading. AUC gains were small, and the 365-day AUC comparison was not significant. NRI and IDI were significant at every horizon, but these metrics can reach significance when absolute gains are small and do not always imply clinical value. Calibration stayed near the reference line for both models, and DCA showed only a slight net-benefit edge for ACAG. ACAG may add a little prognostic information beyond routine variables, but clinical utility remains unproven. External validation, including decision-analytic and cost-effectiveness work, is needed before use.

The study has strengths. It used a large ICU database, covered three clinically relevant horizons, applied stepwise adjustment, RCS, subgroup analysis, and several performance measures, and used E-values to test sensitivity to unmeasured confounding. It also provides a rationale for further ACAG work in TE.

Limitations

Four limitations deserve attention. First, the design was retrospective and observational, so residual confounding and reverse causation cannot be ruled out, and causality cannot be inferred.

Second, all data came from one academic ICU, and TE was identified by ICD codes. Practice patterns, case mix, and coding may differ elsewhere, and the codes do not capture toxin type, exposure dose or duration, or clinical severity.

Third, ACAG was measured only at baseline, so we could not assess change over time. Mean imputation may bias estimates and understate variance, especially for lactate, which was missing in 15.63% of patients. We also did not compare ACAG with AG alone, lactate, or other acid-base markers, and we lacked data on antidotes, renal replacement therapy, albumin infusion, and organ support.

Fourth, the predictive gain was modest, the 365-day AUC comparison was not significant, and no external cohort was used. These results are hypothesis-generating and need prospective, multicenter confirmation with repeated ACAG measures and detailed toxin data.

Conclusion

In critically ill patients with TE, higher ACAG at admission was independently linked to higher 28-, 90-, and 365-day all-cause mortality, and the pattern was consistent with a linear log-hazard relation. ACAG added modest discrimination and reclassification beyond a basic clinical model. The findings are associative, not causal; prospective, multicenter studies with repeated ACAG measures and detailed toxin exposure data are needed to confirm prognostic value and clinical utility.

Declarations

Ethics approval and consent to participate

The Institutional Review Boards of the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center approved the MIMIC-IV database. Records were de-identified, and written informed consent was waived.

Consent for publication

Not applicable.

Data Availability statement

The MIMIC-IV database is publicly available through PhysioNet (https://physionet.org/content/mimiciv/3.1/). The derived datasets used in this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Lei Sun helped design the study, collected data, performed the statistical analysis, and drafted the manuscript. Ting Liu helped design the study, performed the statistical analysis, and drafted the manuscript. Yuhui Liu handled statistical analysis, data interpretation, and literature retrieval. Xianqi Yi supervised the study and critically revised the manuscript. Bing Wang designed and supervised the study and critically revised the manuscript. All authors read and approved the final version.

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Figure

Figures 1-7 and Supplementary Figures S1-S2 are provided as separate files. The legends are listed below.

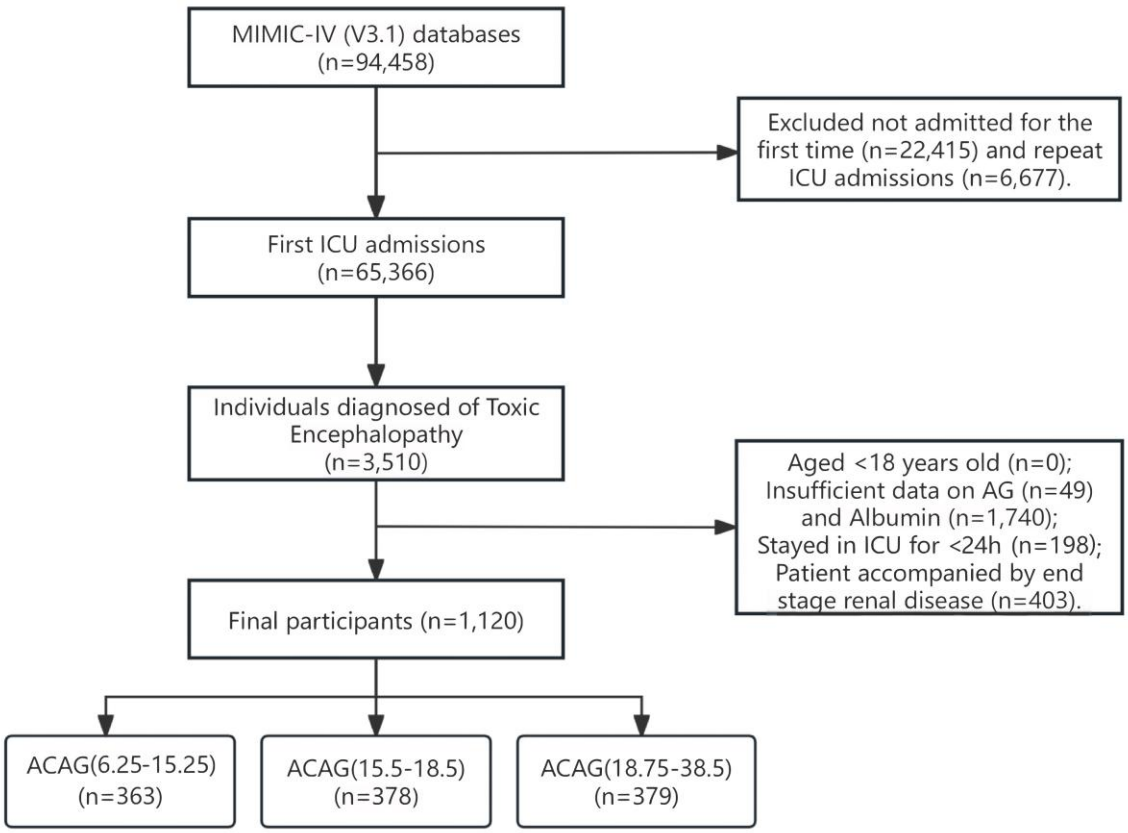


Figure 1. Flowchart of participant selection. Patients were selected from the MIMIC-IV (version 3.1) database. Of 94,458 ICU admissions, patients not admitted for the first time (n = 22,415) and repeat ICU admissions (n = 6,677) were excluded, leaving 65,366 first ICU admissions. A total of 3,510 patients with toxic encephalopathy were identified. After excluding patients with missing anion gap (n = 49) or albumin (n = 1,740), an ICU stay <24 h (n = 198), and end-stage renal disease (n = 403), 1,120 patients were included and divided into ACAG tertiles: T1 (6.25-15.25 mmol/L, n = 363), T2 (15.50-18.50 mmol/L, n = 378), and T3 (18.75-38.50 mmol/L, n = 379). Abbreviations: ACAG, albumin-corrected anion gap; ICU, intensive care unit.

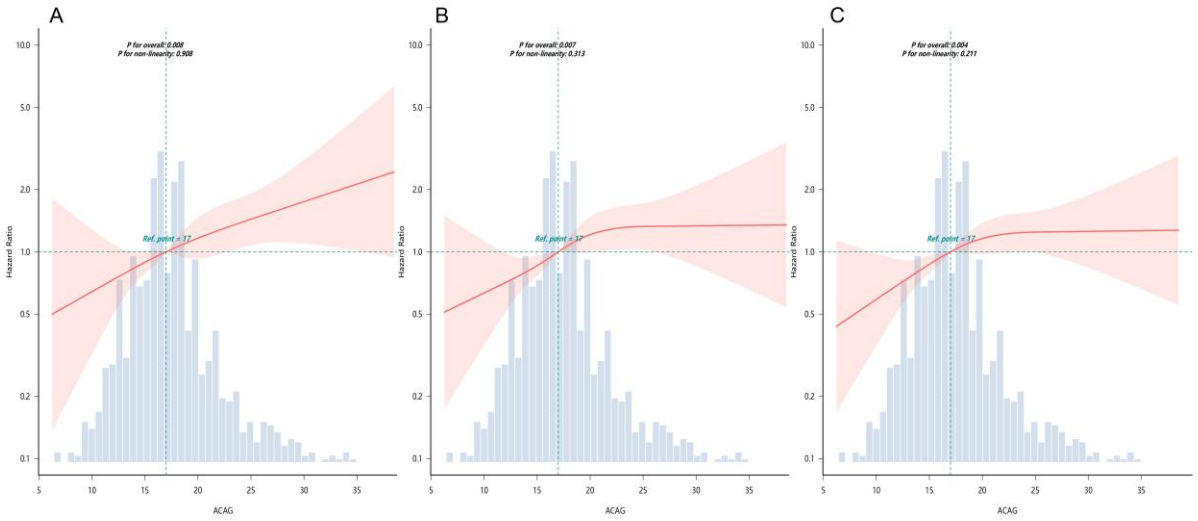


Figure 2. Restricted cubic spline curves for the association between ACAG and all-cause mortality. Panels show 28-day (A), 90-day (B), and 365-day (C) all-cause mortality. The solid red line represents the adjusted hazard ratio, and the shaded band represents the 95% confidence interval. The blue histogram shows the distribution of ACAG. The vertical dashed line indicates the reference value used in the spline model, and the horizontal dashed line indicates a hazard ratio of 1. The y-axis is on a logarithmic scale. P values for overall association and non-linearity are shown. Models were adjusted for all covariates in Model III, including age, sex, heart rate, respiratory rate, temperature, Glasgow Coma Scale, hemoglobin, and glucose. Abbreviations: ACAG, albumin-corrected anion gap; HR, hazard ratio; CI, confidence interval.

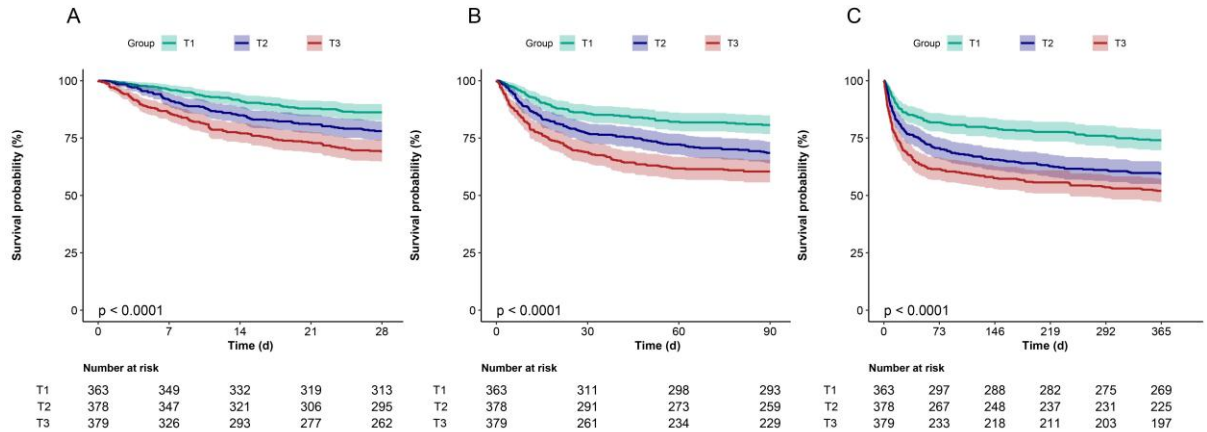


Figure 3. Kaplan-Meier survival curves according to ACAG tertile. Panels show 28-day (A), 90-day (B), and 365-day (C) all-cause mortality. Shaded bands represent 95% confidence intervals. Log-rank P values and numbers at risk are shown below each panel. T1, 6.25-15.25 mmol/L; T2, 15.50-18.50 mmol/L; T3, 18.75-38.50 mmol/L. Abbreviations: ACAG, albumin-corrected anion gap; CI, confidence interval.

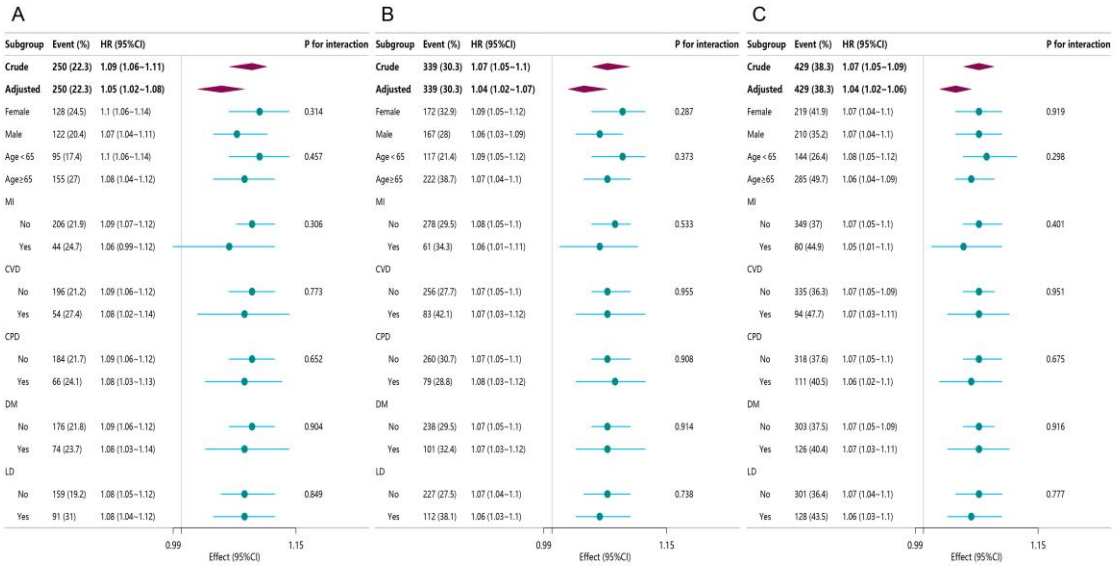


Figure 4. Subgroup analyses of the association between ACAG and all-cause mortality. Forest plots show hazard ratios per 1-mmol/L increase in ACAG for 28-day (A), 90-day (B), and 365-day (C) all-cause mortality in the overall population and in subgroups defined by sex, age, myocardial infarction, cardiovascular disease, chronic pulmonary disease, diabetes mellitus, and liver disease. Crude and adjusted hazard ratios with 95% confidence intervals are shown; P values for interaction are shown at the right of each subgroup. Models were adjusted for Model III covariates except the stratification variable. Abbreviations: ACAG, albumin-corrected anion gap; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; CVD, cardiovascular disease; CPD, chronic pulmonary disease; DM, diabetes mellitus; LD, liver disease.

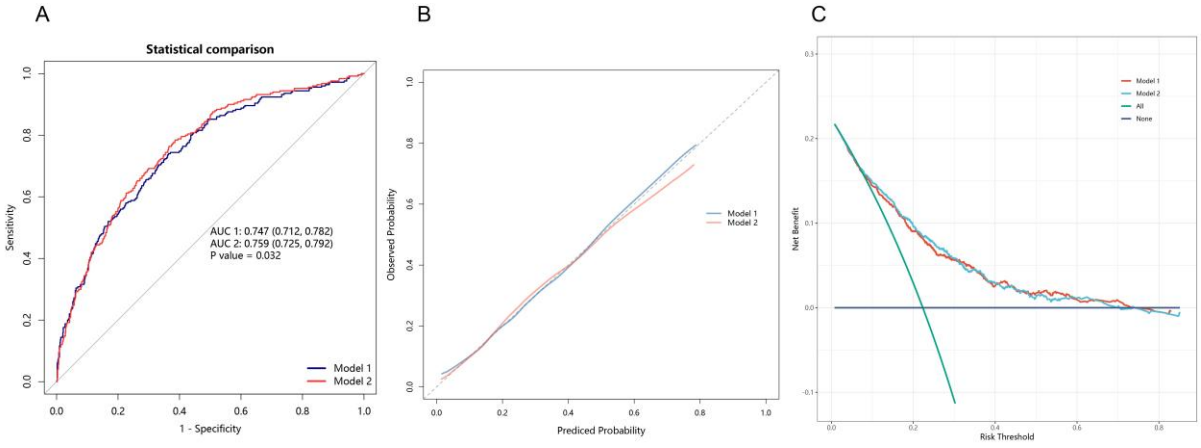


Figure 5. Incremental predictive value of ACAG for 28-day all-cause mortality. (A) Receiver operating characteristic curves for the basic model (Model 1) and the basic model plus ACAG (Model 2). AUCs with 95% confidence intervals and the P value for AUC comparison are shown. (B) Calibration

curves comparing observed and predicted probabilities. (C) Decision curve analysis; the x-axis represents the risk threshold and the y-axis represents net benefit. The green and navy lines represent the treat-all and treat-none strategies, respectively. The basic model included age, sex, heart rate, respiratory rate, temperature, Glasgow Coma Scale, hemoglobin, and glucose. Abbreviations: ACAG, albumin-corrected anion gap; AUC, area under the receiver operating characteristic curve; CI, confidence interval; DCA, decision curve analysis; GCS, Glasgow Coma Scale.

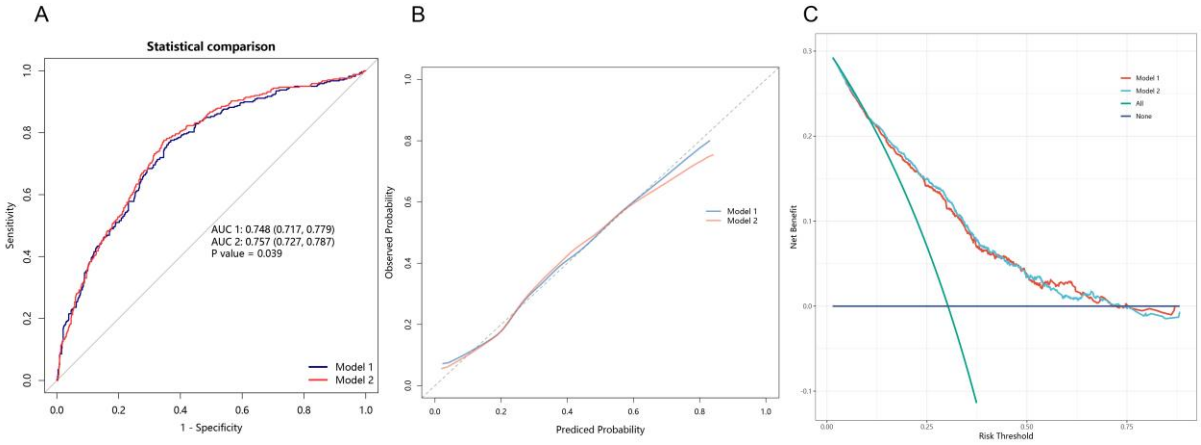


Figure 6. Incremental predictive value of ACAG for 90-day all-cause mortality. (A) Receiver operating characteristic curves for the basic model (Model 1) and the basic model plus ACAG (Model 2). AUCs with 95% confidence intervals and the P value for AUC comparison are shown. (B) Calibration curves comparing observed and predicted probabilities. (C) Decision curve analysis; the green and navy lines represent the treat-all and treat-none strategies, respectively. The basic model included age, sex, heart rate, respiratory rate, temperature, Glasgow Coma Scale, hemoglobin, and glucose. Abbreviations: ACAG, albumin-corrected anion gap; AUC, area under the receiver operating characteristic curve; CI, confidence interval; DCA, decision curve analysis; GCS, Glasgow Coma Scale.

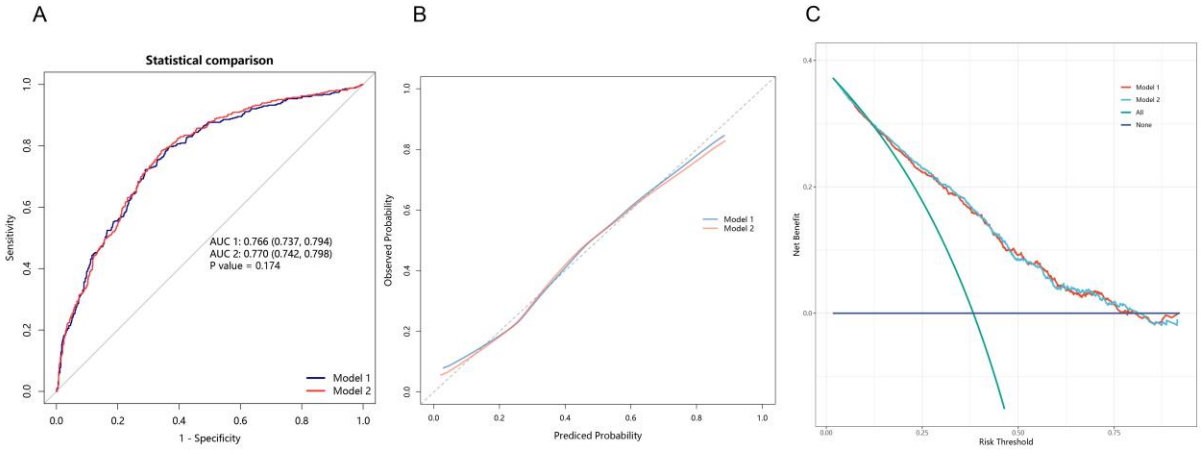


Figure 7. Incremental predictive value of ACAG for 365-day all-cause mortality. (A) Receiver operating characteristic curves for the basic model (Model 1) and the basic model plus ACAG (Model 2). AUCs with 95% confidence intervals and the P value for AUC comparison are shown. (B) Calibration curves comparing observed and predicted probabilities. (C) Decision curve analysis; the green and navy lines represent the treat-all and treat-none strategies, respectively. The basic model included age, sex, heart rate, respiratory rate, temperature, Glasgow Coma Scale, hemoglobin, and glucose. Abbreviations: ACAG, albumin-corrected anion gap; AUC, area under the receiver operating characteristic curve; CI, confidence interval; DCA, decision curve analysis; GCS, Glasgow Coma Scale.

Supplementary Figure S1. Distribution of ACAG according to ACAG tertile. Violin plots with overlaid box plots show the distribution of ACAG in T1 (6.25-15.25 mmol/L), T2 (15.50-18.50 mmol/L), and T3 (18.75-38.50 mmol/L). Pairwise P values are shown above the plots; all pairwise comparisons were significant ($P < 0.001$). Abbreviations: ACAG, albumin-corrected anion gap.

Supplementary Figure S2. E-value bias plots for the association between ACAG tertile and mortality. Panels show 28-day (A), 90-day (B), and 365-day (C) all-cause mortality for T3 versus T1. The red triangle indicates the E-value for the adjusted hazard ratio, and the gray square indicates the E-value for the lower confidence limit. The dashed curve represents the boundary for confounding strength. E-values are shown next to the symbols. Models were adjusted for Model III covariates. Abbreviations: ACAG, albumin-corrected anion gap; HR, hazard ratio; CI, confidence interval.

Tables

Table 1. Baseline characteristics of the study population according to ACAG tertile.

Variable	Total (n = 1,120)	T1 (n = 363)	T2 (n = 378)	T3 (n = 379)	*P* value
Age, years	63.6 ± 16.7	60.9 ± 17.8	65.5 ± 17.1	64.3 ± 14.9	<0.001
Male, n (%)	597 (53.3)	216 (59.5)	193 (51.1)	188 (49.6)	0.015
Vital signs					
Heart rate, beats/min	89.7 ± 16.9	85.7 ± 16.9	89.6 ± 15.6	93.5 ± 17.4	<0.001
MAP, mmHg	80.0 ± 11.2	81.0 ± 11.1	80.4 ± 10.8	78.6 ± 11.4	0.012
RR, breaths/min	20.9 ± 4.5	19.7 ± 4.1	20.7 ± 4.2	22.2 ± 4.8	<0.001
Temperature, °C	37.0 ± 0.6	37.0 ± 0.6	37.1 ± 0.6	37.0 ± 0.6	0.165
SpO_2, %	96.8 ± 2.2	96.9 ± 1.9	96.8 ± 2.1	96.6 ± 2.5	0.125
Laboratory parameters					
WBC, $\times 10^9$/L	10.7 (7.6, 15.6)	9.4 (7.1, 12.9)	10.6 (7.3, 15.5)	12.6 (8.4, 17.7)	<0.001
Hb, g/dL	10.3 ± 2.1	10.7 ± 2.2	10.2 ± 2.0	9.9 ± 2.0	<0.001
RDW, %	15.7 ± 2.8	15.1 ± 2.3	15.7 ± 2.7	16.4 ± 3.1	<0.001
PLT, $\times 10^9$/L	180.9 ± 108.4	179.0 ± 90.1	185.7 ± 102.9	177.8 ± 128.1	0.566
TBil, mg/dL	0.7 (0.4, 1.7)	0.6 (0.4, 1.0)	0.7 (0.4, 1.6)	1.1 (0.5, 3.4)	<0.001
SCr, mg/dL	1.0 (0.7, 1.6)	0.9 (0.7, 1.1)	1.0 (0.7, 1.4)	1.5 (0.9, 3.0)	<0.001
BUN, mg/dL	22.5 (13.0, 38.0)	17.0 (11.0, 26.0)	21.0 (12.0, 34.0)	34.0 (19.0, 56.0)	<0.001
Na, mmol/L	139.2 ± 6.1	139.9 ± 6.1	139.4 ± 5.9	138.3 ± 6.2	0.002
K, mmol/L	4.1 ± 0.6	4.0 ± 0.6	4.0 ± 0.6	4.2 ± 0.8	<0.001
Cl, mmol/L	104.5 ± 7.3	105.6 ± 7.4	105.1 ± 7.1	102.8 ± 7.0	<0.001
HCO_3^-, mmol/L	22.4 ± 4.8	25.1 ± 4.6	22.7 ± 3.7	19.5 ± 4.2	<0.001
Glucose, mg/dL	135.1 ± 54.3	128.0 ± 48.1	133.9 ± 54.9	143.0 ± 58.3	<0.001
Lactate, mmol/L	1.6 (1.2, 2.1)	1.4 (1.0, 1.8)	1.5 (1.2, 2.0)	1.8 (1.3, 2.9)	<0.001
AG, mmol/L	14.0 ± 4.3	10.1 ± 2.1	13.4 ± 1.6	18.3 ± 3.8	<0.001
Albumin, g/dL	3.0 ± 0.7	3.3 ± 0.6	3.0 ± 0.6	2.8 ± 0.6	<0.001
ACAG, mmol/L	17.5 ± 4.6	12.9 ± 1.8	17.0 ± 0.9	22.4 ± 3.7	<0.001
Clinical severity					
GCS	10.1 ± 4.0	10.3 ± 3.9	10.2 ± 3.9	9.8 ± 4.1	0.148
SOFA	6.8 ± 3.8	5.6 ± 3.1	6.1 ± 3.3	8.6 ± 4.2	<0.001
Comorbidities					
MI, n (%)	178 (15.9)	62 (17.1)	62 (16.4)	54 (14.2)	0.543
HF, n (%)	266 (23.8)	74 (20.4)	89 (23.5)	103 (27.2)	0.094
PVD, n (%)	85 (7.6)	25 (6.9)	27 (7.1)	33 (8.7)	0.595
CVD, n (%)	197 (17.6)	58 (16.0)	67 (17.7)	72 (19.0)	0.556
CPD, n (%)	274 (24.5)	94 (25.9)	100 (26.5)	80 (21.1)	0.172
DM, n (%)	312 (27.9)	89 (24.5)	106 (28.0)	117 (30.9)	0.155
LD, n (%)	294 (26.2)	68 (18.7)	86 (22.8)	140 (36.9)	<0.001
Outcomes					
ICU LOS, days	4.3 (2.1, 8.9)	3.6 (1.9, 7.3)	4.1 (2.0, 8.0)	5.3 (2.7, 11.1)	<0.001
ICU mortality, n (%)	129 (11.5)	21 (5.8)	34 (9.0)	74 (19.5)	<0.001
28-day ACM, n (%)	250 (22.3)	50 (13.8)	83 (22.0)	117 (30.9)	<0.001
90-day ACM, n (%)	339 (30.3)	70 (19.3)	119 (31.5)	150 (39.6)	<0.001
365-day ACM, n (%)	429 (38.3)	94 (25.9)	153 (40.5)	182 (48.0)	<0.001

Data are presented as mean ± SD, median (interquartile range), or n (%). P values are for comparisons across ACAG tertiles. Abbreviations: ACAG, albumin-corrected anion gap; MAP, mean arterial pressure; RR, respiratory rate; SpO2, oxygen saturation; WBC, white blood cell count; Hb, hemoglobin; RDW, red cell distribution width; PLT, platelet count; TBil, total bilirubin; SCr, serum creatinine; BUN, blood urea nitrogen; HCO3-, bicarbonate; AG, anion gap; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment; MI, myocardial infarction; HF, heart failure; PVD, peripheral vascular disease; CVD, cardiovascular disease; CPD, chronic pulmonary disease; DM, diabetes mellitus; LD, liver disease; ICU LOS, intensive care unit length of stay; ACM, all-cause mortality.

Table 2. Association between ACAG and 28-, 90-, and 365-day all-cause mortality.

Variable	Crude HR (95% CI)	*P* value	Model I HR (95% CI)	*P* value	Model II HR (95% CI)	*P* value	Model III HR (95% CI)	*P* value
28-day ACM								
ACAG, per 1 mmol/L	1.09 (1.06-1.11)	<0.001	1.09 (1.06-1.12)	<0.001	1.07 (1.04-1.10)	<0.001	1.05 (1.02-1.08)	<0.001
T1	Reference		Reference		Reference		Reference	
T2	1.68 (1.18-2.38)	0.004	1.56 (1.10-2.22)	0.013	1.42 (0.99-2.03)	0.055	1.34 (0.94-1.92)	0.103
T3	2.54 (1.83-3.54)	<0.001	2.41 (1.73-3.36)	<0.001	1.85 (1.31-2.62)	<0.001	1.58 (1.12-2.23)	0.010
90-day ACM								
ACAG, per 1 mmol/L	1.07 (1.05-1.10)	<0.001	1.07 (1.05-1.10)	<0.001	1.06 (1.03-1.08)	<0.001	1.04 (1.02-1.07)	0.001
T1	Reference		Reference		Reference		Reference	
T2	1.75 (1.30-2.35)	<0.001	1.59 (1.19-2.14)	0.002	1.51 (1.11-2.04)	0.009	1.43 (1.06-1.94)	0.020
T3	2.42 (1.82-3.21)	<0.001	2.26 (1.70-3.00)	<0.001	1.87 (1.39-2.53)	<0.001	1.61 (1.20-2.18)	0.002
365-day ACM								
ACAG, per 1 mmol/L	1.07 (1.05-1.09)	<0.001	1.07 (1.05-1.09)	<0.001	1.05 (1.03-1.08)	<0.001	1.04 (1.02-1.06)	0.001
T1	Reference		Reference		Reference		Reference	
T2	1.73 (1.33-2.23)	<0.001	1.57 (1.21-2.03)	0.001	1.51 (1.15-1.97)	0.003	1.42 (1.09-1.86)	0.009
T3	2.26 (1.76-2.90)	<0.001	2.10 (1.64-2.70)	<0.001	1.79 (1.38-2.34)	<0.001	1.55 (1.19-2.02)	0.001

Model I was adjusted for age and sex; Model II was adjusted for Model I covariates plus heart rate, respiratory rate, temperature, and Glasgow Coma Scale; Model III was adjusted for Model II covariates plus hemoglobin and glucose. Hazard ratios for continuous ACAG are per 1-mmol/L increase; hazard ratios for T2 and T3 are relative to T1. Abbreviations: ACAG, albumin-corrected anion gap; HR, hazard ratio; CI, confidence interval; ACM, all-cause mortality.

Table 3. Incremental predictive value of ACAG for mortality.

Model	AUC (95% CI)	*P* value	NRI (95% CI)	*P* value	IDI (95% CI)	*P* value
28-day ACM						
Basic model	0.7472 (0.7124-0.7820)	Reference	Reference		Reference	
+ ACAG	0.7587 (0.7252-0.7922)	0.032	0.1760 (0.036-0.316)	0.0137	0.0077 (0.0004-0.0149)	0.0374
90-day ACM						
Basic model	0.7480 (0.7173-0.7795)	Reference	Reference		Reference	
+ ACAG	0.7570 (0.7266-0.7874)	0.039	0.1989 (0.0721-0.3256)	0.0021	0.0072 (0.0015-0.0130)	0.0135
365-day ACM						
Basic model	0.7656 (0.7370-0.7941)	Reference	Reference		Reference	
+ ACAG	0.7704 (0.7423-0.7985)	0.174	0.1779 (0.0583-0.2976)	0.0036	0.0076 (0.0020-0.0132)	0.0078

The basic model included age, sex, heart rate, respiratory rate, temperature, Glasgow Coma Scale, hemoglobin, and glucose. Abbreviations: ACAG, albumin-corrected anion gap; AUC, area under the receiver operating characteristic curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement; ACM, all-cause mortality.

Supplementary Table S1. Missing status of covariates in the final cohort (n = 1,120).

Variable	Missing, n	Missing, %
TBil	45	4.02
Hb	1	0.09
Lac	175	15.63
RDW	2	0.18
T	17	1.52
WBC	1	0.09

Abbreviations: TBil, total bilirubin; Hb, hemoglobin; Lac, lactate; RDW, red cell distribution width; T, temperature; WBC, white blood cell count.

Abbreviations

ACAG, albumin-corrected anion gap; ACM, all-cause mortality; AG, anion gap; AUC, area under the receiver operating characteristic curve; CI, confidence interval; CPD, chronic pulmonary disease; CVD, cardiovascular disease; DCA, decision curve analysis; DM, diabetes mellitus; GCS, Glasgow Coma Scale; HF, heart failure; HR, hazard ratio; ICD, International Classification of Diseases; ICU, intensive care unit; IDI, integrated discrimination improvement; IQR, interquartile range; LD, liver disease; LOS, length of stay; MAP, mean arterial pressure; MI, myocardial infarction; MIMIC-IV, Medical Information Mart for Intensive Care IV; NRI, net reclassification improvement; PVD, peripheral vascular disease; RCS, restricted cubic spline; ROC, receiver operating characteristic; RR, respiratory rate; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; TE, toxic encephalopathy.

Supplementary Files

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