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Association Between Postoperative Albumin-Corrected Anion Gap (ACAG) and 28-Day Mortality Risk in the Intensive Care Unit (ICU) After Cardiac Surgery: A Retrospective Study Based on Two Large Databases, Medical Information Mart for Intensive Care IV (MIMIC-IV) and eICU Collaborative Research Database (eICU-CRD)

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Abstract

Background

The 28-day mortality rate after cardiac surgery can reach 2%–22%, and existing scoring systems have limited efficacy in early risk identification. Albumin-Corrected Anion Gap (ACAG) can reflect signals of metabolic disorders; however, its predictive value in the acute postoperative period and its cross-center generalizability remain unclear.

Methods

This multicenter retrospective large cohort study used MIMIC-IV v3.1 as the study cohort and eICU as an independent external validation cohort. Kaplan-Meier survival curves, Cox nested models, restricted cubic spline (RCS), and C-index were used to evaluate the association between postoperative ACAG and 28-day mortality risk in the ICU and model discrimination.

Results

The MIMIC cohort included 2,206 patients (276 deaths, 12.5%) and the eICU cohort included 2,409 patients (831 deaths, 34.5%). After adjustment for confounders, ACAG was an independent risk factor for death in both cohorts (MIMIC: hazard ratio [HR] = 1.132, 95% confidence interval [CI]: 1.099–1.167; eICU: HR = 1.037, 95% CI: 1.024–1.052; both $P < 0.001$). Only the highest quartile group showed a significantly increased risk of death (eICU Q4 vs Q1: HR = 1.54, 95% CI: 1.24–1.93). RCS showed that ACAG was linearly positively associated with mortality risk (nonlinear $P = 0.401$). The C-index in MIMIC and eICU was 0.822 and 0.700, respectively.

Conclusion

Higher postoperative ACAG was significantly positively associated with 28-day all-cause mortality in the ICU after cardiac surgery. The risk of death was highest in the highest quartile group (ACAG > 20 mmol/L), and this threshold can serve as a clinical high-risk warning threshold.

1 Introduction

Globally, cardiovascular disease remains the leading cause of death, causing approximately 18.6 million deaths in 2019 [1]; cardiac surgery is an important treatment for end-stage cardiovascular disease [2, 3], but postoperative in-hospital mortality in patients is still 3%–5% [4], and most deaths occur in the early postoperative period [5, 6]. Although perioperative management techniques have continued to improve [7], existing disease severity scores still have limitations in identifying early postoperative high-risk patients: although Acute Physiology and Chronic Health Evaluation IV (APACHE IV) is the only general

ICU score validated in patients after cardiac surgery, it contains numerous variables and imposes a heavy data collection burden, limiting its clinical operability; although the Sequential Organ Failure Assessment (SOFA) score is simpler, its discrimination ability in the cardiac surgery population is lower than that of APACHE IV [8]. In particular, before metabolic disorders are fully reflected in composite scores, there is an urgent clinical need for more sensitive individualized risk stratification tools. An ideal early prognostic marker should be immediately available, low-cost, and simple to calculate, and should provide information independent of traditional prognostic factors [9]. Anion Gap (AG) is a classic laboratory indicator reflecting metabolic acidosis and has also been used for risk stratification in patients after cardiac surgery [10, 11]; elevated postoperative AG is associated with increased short- and long-term mortality risk, but it has limitations. Among unmeasured anions, serum albumin is a major component, and approximately 30% of patients after cardiac surgery develop hypoalbuminemia [12], which significantly underestimates the true value of AG [13, 14]. Therefore, how to rapidly and accurately identify high-risk patients in the early postoperative period remains a core challenge in ICU clinical practice [15]. With further research, some scholars found that Albumin-Corrected Anion Gap (ACAG), by correcting for the influence of serum albumin, can to some extent more accurately reflect the true burden of unmeasured anions in the body (such as lactate, ketone bodies, uremic toxins, etc.) [16]. At the same time, it has been demonstrated to be independently associated with short-term mortality risk in various ICU populations, including acute myocardial infarction and cardiac arrest [17, 18, 19]. Therefore, investigating the association between ACAG and 28-day mortality risk in critically ill patients after cardiac surgery has important clinical significance.

Recently, a study based on the MIMIC-IV database reported that preoperative ACAG could independently predict 28-day postoperative mortality in patients undergoing cardiac surgery (HR = 1.049, 95% CI: 1.024–1.075) and proposed ACAG > 20 mmol/L as a high-risk threshold [20]. However, preoperative ACAG mainly reflects compensatory changes under chronic comorbid conditions, whereas factors such as systemic inflammatory response, hemodynamic fluctuations, and tissue hypoperfusion induced by cardiopulmonary bypass (CPB) after cardiac surgery can lead to acute metabolic disorders such as lactate accumulation and a sharp decrease in albumin [21, 22, 23, 24, 25]; their pathophysiological characteristics are fundamentally different from the preoperative chronic compensatory state [20, 26]. At present, whether ACAG in the acute postoperative period still has independent prognostic value and whether it can be generalized to multicenter populations remain to be systematically evaluated.

Based on this, we used two large critical care databases, MIMIC-IV and eICU, to evaluate for the first time at the multicenter level the predictive performance of early postoperative ACAG for 28-day mortality risk. This study aimed to verify: (1) whether postoperative ACAG is an independent determinant of death; (2) whether ACAG > 20 mmol/L can serve as a cross-center high-risk warning threshold; and (3) whether ACAG can provide additional incremental value to existing critical illness scoring systems. We hope that the results of this study will provide ICU physicians with a simple, immediate bedside risk stratification tool.

2 Methods

2.1 Data Sources and Study Population

This study used two publicly available critical care databases. Medical Information Mart for Intensive Care IV (MIMIC-IV, v3.1) is a publicly available electronic health record dataset derived from the electronic health record system of Beth Israel Deaconess Medical Center (BIDMC), containing clinical data of patients admitted to the ICU at this center between 2008 and 2022. The dataset covers patient measurements, physician orders, diagnoses, procedures, treatments, and de-identified free-text clinical notes. The eICU Collaborative Research Database (eICU-CRD, v2.0) is a publicly available multicenter critical care database containing high-granularity data from more than 200,000 ICU admissions across 208 hospitals in the United States between 2014 and 2015. The database has been de-identified and includes vital sign measurements, care plan documentation, disease severity scores, diagnostic information, and treatment information. One author of this study completed the required training course for the database and obtained approval to extract raw data from the database (certification number: 12111381).

Study population: Inclusion criteria: (1) age ≥ 18 years; (2) undergoing cardiac surgery (Supplementary S1); (3) first ICU admission, with only the first ICU admission selected for patients with multiple ICU admissions; (4) available measurements of anion gap and serum albumin within 24 hours after ICU admission; and (5) complete survival time and outcome information. Exclusion criteria: (1) death before ICU admission; (2) complete missingness of key variables (ACAG or outcome); and (3) age < 18 years. The detailed inclusion and exclusion flowcharts for the two cohorts are provided in Supplementary S1.

2.2 Data Extraction and Variable Selection

Structured Query Language (SQL) was used in pgAdmin v9.7 to extract clinical and laboratory parameters of patients, and R 4.2.0 software was used for data cleaning after data extraction. Based on previous studies and clinical practice [17], the following variables were extracted from the two databases: (1) demographic characteristics: age, gender, and height; (2) laboratory results: anion gap, serum albumin, white blood cell count (WBC), hemoglobin, and blood urea nitrogen (BUN); (3) vital signs: heart rate (vitalhr), systolic blood pressure (vitalnbps), diastolic blood pressure (vitalnbpd), peripheral oxygen saturation (spo2), and body temperature (temperature); (4) disease severity scores: Sequential Organ Failure Assessment (SOFA) score (sofa) and Acute Physiology and Chronic Health Evaluation (APACHE) score (regarding disease severity scoring, the built-in APACHE versions differ between the two databases: MIMIC-IV provides the APACHE III score, whereas eICU-CRD provides the APACHE IV score. Although both are validated ICU disease severity scoring tools, their scoring items and weights differ. Therefore, we used the APACHE score built into each database separately in the two cohorts, and simultaneously included the SOFA score (which has a unified definition in both databases) in all multivariable models as a cross-database unified disease severity adjustment indicator to mitigate the potential bias caused by differences in APACHE versions); (5) interventions: mechanical ventilation (ventilation); and (6) outcome information: ICU mortality status (status) and ICU length of stay (icu_day). For the above laboratory indicators and vital signs, all recorded values within 24 hours after ICU

admission were averaged. Based on the above variables, the primary exposure variable ACAG was calculated from anion gap and serum albumin: ACAG (mmol/L) = anion gap (mmol/L) + 2.5 × (4.4 − serum albumin [g/dL]) [2, 11, 27]. The correction coefficient 2.5 reflects the degree to which AG is underestimated for every 1 g/dL decrease in albumin [11].

Outcome and Exposure Variables: The primary outcome was defined as 28-day all-cause mortality in the ICU [9]. Survival time (icu_day) was defined as the smaller of the actual ICU length of stay and 28 days; values exceeding 28 days were censored at 28 days. Records with ICU length of stay ≤ 0 were excluded.

2.3 Data Processing and Statistical Analysis

For candidate variables, the missing proportion of each variable was first calculated. Variables with a missing rate exceeding 30% were removed. For retained variables with a missing proportion < 30%, Multiple Imputation by Chained Equations (MICE) with Predictive Mean Matching (PMM) was used to generate five complete datasets [28]. The imputation model included all candidate covariates and the ACAG exposure variable. All subsequent analyses were performed on the pooled estimates from the five imputed datasets. Imputation was performed using the “mice” package in R software. The overall population was divided into four groups according to ACAG quartiles. Continuous variables were expressed as mean ± standard deviation for normally distributed data or median (interquartile range [IQR]) for non-normally distributed data, and categorical variables were expressed as frequencies (percentages). Between-group differences were compared using one-way analysis of variance (ANOVA) for normally distributed continuous variables, the Kruskal-Wallis rank sum test for non-normally distributed variables, and the χ^2 test or Fisher’s exact test for categorical variables. To assess multicollinearity among continuous variables, the Variance Inflation Factor (VIF) was calculated for each candidate continuous variable. VIF > 10 indicated severe collinearity, and VIF > 5 indicated moderate collinearity [29]. Variables with severe collinearity were not included in subsequent multivariable Cox regression models. VIF testing was performed separately in the five imputed datasets, and pooled estimates were reported.

2.4 Kaplan-Meier Survival Analysis

Kaplan-Meier curves were used to plot survival curves for different ACAG quartile groups, and the Log-rank test was used to compare survival differences between groups [30]. By visualizing the temporal trends in survival probability among groups with different ACAG levels, the discriminatory ability of ACAG for 28-day ICU mortality risk was preliminarily evaluated.

2.5 Association Analysis Between ACAG and 28-Day Mortality Risk

First, univariable Cox regression analysis was performed for each candidate variable to evaluate its individual association with 28-day ICU mortality risk. Subsequently, an unadjusted model and five nested models with stepwise adjustment for covariates (six models in total) were constructed to evaluate the robustness of the independent effect of ACAG [31]: (1) Unadjusted model: ACAG; (2) Model 1 (adjusted

for demographic characteristics): ACAG + age + gender + height; (3) Model 2 (adjusted for demographic characteristics and clinical interventions): ACAG + age + gender + height + mechanical ventilation; (4) Model 3 (adjusted for demographic characteristics, clinical interventions, and disease severity): ACAG + age + gender + height + mechanical ventilation + SOFA score + APACHE score; (5) Model 4 (adjusted for demographic characteristics, clinical interventions, disease severity, and laboratory indicators): ACAG + age + gender + height + mechanical ventilation + SOFA score + APACHE score + WBC + hemoglobin + BUN; (6) Model 5 (fully adjusted model): ACAG + age + gender + height + mechanical ventilation + SOFA score + APACHE score + WBC + hemoglobin + BUN + heart rate + systolic blood pressure + diastolic blood pressure + oxygen saturation + body temperature. The proportional hazards assumption of Cox regression was tested using Schoenfeld residuals.

2.6 ACAG Quartile Analysis

To further clarify the clinical high-risk cutoff for increased mortality risk associated with ACAG levels, ACAG was converted from a continuous variable to a quartile categorical variable in the main model for analysis. Using the lowest quartile group (Q1) as the reference, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each quartile group (Q2, Q3, and Q4) to identify the ACAG range at which risk began to increase significantly.

2.7 Nonlinear Association Test

In the fully adjusted model (Model 5), a restricted cubic spline (RCS) function with four knots was used to test whether there was a nonlinear association between ACAG and 28-day mortality risk. Knot positions were placed at the 5th, 35th, 65th, and 95th percentiles of the ACAG distribution [32]. The median ACAG value was used as the reference (HR = 1). The Wald test was used to evaluate the statistical significance of the overall association and the nonlinear component.

2.8 Subgroup Analysis and Interaction

Three subgroups were prespecified: (1) age (≤ 65 years vs. > 65 years); (2) gender (female vs. male); and (3) mechanical ventilation (no vs. yes). Within each subgroup, the HR and 95% CI of ACAG were evaluated in the fully adjusted model. Interactions between subgroups were statistically tested using the Wald test.

2.9 Model Discrimination Assessment and External Validation

Model discrimination was assessed using Harrell's C-index and time-dependent receiver operating characteristic (ROC) curves [33]. First, the fully adjusted model (Model 5, including ACAG and covariates such as age, gender, height, mechanical ventilation, SOFA score, APACHE score, WBC, hemoglobin, BUN, heart rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, and body temperature) was fitted in the MIMIC cohort, and Harrell's C-index of this model was calculated to quantify its overall discriminatory ability for ranking 28-day survival time in the ICU; the C-index ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination), with higher values indicating stronger discriminatory

ability. Meanwhile, time-dependent ROC curves were used to evaluate the predictive accuracy of the model at day 7 and day 14 of follow-up, and the time-dependent area under the curve (AUC) and its 95% CI were calculated [34]. Subsequently, using a “direct model application” strategy [35], the fully adjusted model (Model 5) fitted in the MIMIC cohort was directly applied to the eICU validation cohort; the C-index and time-dependent AUCs at day 7 and day 14 were calculated in the eICU cohort and compared with the corresponding metrics in the MIMIC cohort to evaluate the external generalizability of the model. All analyses were completed in R 4.2.0, in which the C-index was calculated using the concordance function in the survival package, and time-dependent ROC was implemented using the timeROC package.

2.10 Sensitivity Analysis

To evaluate the potential threat of unmeasured confounders to the conclusions of this study, the E-value method was used for sensitivity analysis. The E-value was used to quantify the minimum strength of association (on the risk ratio scale) that an unmeasured confounder would need to have with both ACAG and the outcome to completely eliminate the observed ACAG–mortality association (i.e., to reduce the HR to 1). A larger E-value indicates that the conclusion is more robust to unmeasured confounding. E-values were calculated based on the point estimate and the lower limit of the 95% CI in the fully adjusted model (Model 5).

3 Results

3.1 Study Population and Baseline Characteristics

During the data preprocessing stage, variables with a missing rate exceeding 30% (such as aspartate aminotransferase [AST]) were removed, and the remaining variables with a missing proportion < 30% were imputed using multiple imputation. The VIF test showed that none of the collected continuous variables had obvious collinearity (VIF < 5). The complete VIF results are presented in the Supplementary Table. This study ultimately included 2,206 patients in the MIMIC-IV cohort and 2,409 patients in the eICU cohort. The mean age of the MIMIC cohort was 68.3 ± 13.8 years, 64.7% (1,428/2,206) were male, and the mean ACAG was 16.7 ± 4.1 mmol/L; the mean age of the eICU cohort was 62.7 ± 15.7 years, 57.8% (1,393/2,409) were male, and the median ACAG was 17.0 mmol/L (IQR: 13.75–20.62). The disease severity of the eICU validation cohort was higher than that of the MIMIC discovery cohort. The median SOFA score of eICU patients was 8 (IQR: 5–10), whereas that of MIMIC was 5.0 ± 3.7; the median APACHE score in eICU was 102 (IQR: 74–125), whereas that in MIMIC was 44.9 ± 20.8; the proportion of mechanical ventilation was 59.6% in eICU and 83.7% in MIMIC. In terms of crude mortality, the 28-day ICU mortality rate was 34.5% (831/2,409) in the eICU cohort and 12.5% (276/2,206) in the MIMIC cohort. After grouping by ACAG quartiles, it was observed within both cohorts that as ACAG quartiles increased, SOFA score, APACHE score, WBC, BUN, and heart rate all significantly increased, whereas hemoglobin, blood pressure, and SpO_2 all significantly decreased (all between-group P < 0.001). In the MIMIC cohort, the SOFA score was 3.6 ± 2.8 in the Q1 group and increased to 7.4 ± 4.1 in the Q4 group; the APACHE III score was 34.7 ± 14.6 in the Q1 group and increased to 60.1 ± 23.9 in the Q4 group. In the eICU cohort,

the median SOFA score was 6 (IQR: 4–8) in the Q1 group and increased to 10 (IQR: 8–12) in the Q4 group; the median APACHE IV score was 82 (IQR: 56–106) in the Q1 group and increased to 120 (IQR: 96–140) in the Q4 group. The ACAG quartile cutoffs were as follows: in the MIMIC cohort, Q1 ≤ 14 mmol/L, Q2 14–16 mmol/L, Q3 16–18.75 mmol/L, and Q4 > 18.75 mmol/L; in the eICU cohort, Q1 ≤ 13.75 mmol/L, Q2 13.75–17 mmol/L, Q3 17–20.62 mmol/L, and Q4 > 20.62 mmol/L. The above baseline characteristics are detailed in Table 1.

3.2 Correlation Analysis of Each Variable with the Outcome

Univariable Cox regression analysis showed that ACAG, as a continuous variable, was significantly positively associated with 28-day ICU mortality risk in both cohorts. In the MIMIC cohort, each 1-unit increase in ACAG was associated with an 18.6% increase in mortality risk (HR = 1.186, 95% CI: 1.160–1.212, P < 0.001). In the eICU cohort, ACAG also showed a significant positive association, but with a slightly smaller effect size (HR = 1.064, 95% CI: 1.052–1.076, P < 0.001). In addition to ACAG, age, SOFA score, APACHE score, WBC, heart rate, systolic blood pressure, and SpO_2 were all significantly associated with the outcome in univariable analysis in both cohorts (P < 0.05); BUN was significantly associated in the MIMIC cohort but did not reach statistical significance in the eICU cohort (HR = 1.003, 95% CI: 1.000–1.005, P = 0.074). Hemoglobin was a significant protective factor in the MIMIC cohort (HR = 0.899), but did not reach statistical significance in the eICU cohort (HR = 1.006, P = 0.653); body temperature was not statistically significant in the MIMIC cohort (P = 0.327), but was a significant protective factor in the eICU cohort (HR = 0.838, P < 0.001).

3.3 Multivariable Cox Regression—Independent Predictive Effect of ACAG

Across the six models with different combinations of adjusted covariates, ACAG remained an independent risk factor for 28-day ICU mortality. In the unadjusted model, each 1-unit increase in ACAG was associated with an 18.6% increase in mortality risk in the MIMIC cohort (HR = 1.186, 95% CI: 1.160–1.212, P < 0.001) and a 6.4% increase in the eICU cohort (HR = 1.064, 95% CI: 1.052–1.076, P < 0.001). After adjustment for age, gender, and height (Model 1), the HRs for ACAG in the two cohorts were 1.191 (95% CI: 1.165–1.217) and 1.067 (95% CI: 1.055–1.079), respectively, both P < 0.001. After further adjustment for mechanical ventilation (Model 2), the HRs were 1.193 (1.167–1.220) and 1.066 (1.054–1.079), respectively, with little change. After inclusion of SOFA and APACHE scores (Model 3), the HR decreased to 1.154 (1.123–1.185) in the MIMIC cohort and to 1.040 (1.027–1.053) in the eICU cohort, suggesting that disease severity could partially explain the effect of ACAG. After further inclusion of laboratory indicators (Model 4: WBC, hemoglobin, BUN), the HR was 1.150 (1.118–1.183) in the MIMIC cohort and 1.045 (1.032–1.059) in the eICU cohort, with a further reduction in change. In the final fully adjusted model (Model 5, which further included heart rate, systolic blood pressure, diastolic blood pressure, SpO_2, and body temperature on the basis of Model 4), the HR was 1.132 (1.099–1.167) in the MIMIC cohort, indicating that after adjustment for all confounders, each 1-unit increase in ACAG was associated with a 13.2% increase in mortality risk; the HR in the eICU cohort was 1.037 (1.024–1.052), indicating a 3.7% increase in mortality risk, both P < 0.001. In the fully adjusted MIMIC model (Model 5),

other independently significant predictors included: age (HR = 1.02, 95% CI: 1.01–1.03, P < 0.001), APACHE III (HR = 1.02, 95% CI: 1.01–1.03, P < 0.001), SOFA score (HR = 0.96, 95% CI: 0.91–1.00, P = 0.047), SpO_2 (HR = 0.94, 95% CI: 0.92–0.97, P < 0.001), and mechanical ventilation (HR = 0.37, 95% CI: 0.25–0.54, P < 0.001). In the fully adjusted eICU model (Model 5), ACAG was one of the most robust independent predictors (HR = 1.04, 95% CI: 1.02–1.05, P < 0.001). Other independently significant variables included: age (HR = 1.01, 95% CI: 1.01–1.02, P < 0.001), heart rate (HR = 1.01, 95% CI: 1.01–1.02, P < 0.001), APACHE (HR = 1.01, 95% CI: 1.00–1.01, P < 0.001), SOFA (HR = 1.03, 95% CI: 1.00–1.05, P = 0.032), hemoglobin (HR = 1.03, 95% CI: 1.00–1.07, P = 0.048), SpO_2 (HR = 0.98, 95% CI: 0.96–0.99, P = 0.002), and body temperature (HR = 0.84, 95% CI: 0.79–0.88, P < 0.001). These results directly confirmed that ACAG was a robust independent risk factor in both cohorts.

3.4 Association Between ACAG Quartile Stratification and 28-Day Mortality Risk

Kaplan-Meier survival curves showed that the survival probabilities of different ACAG quartile groups in both cohorts began to separate early after ICU admission. In the MIMIC cohort, the survival curve of the Q4 group (ACAG > 18.75 mmol/L) declined earliest, and the gap with the Q1–Q3 groups continued to widen over time; the curves of the Q2 and Q3 groups overlapped for most of the follow-up period, with only mild separation appearing later (Log-rank P < 0.0001). In the eICU cohort, the Q4 group (ACAG > 20.62 mmol/L) also separated earliest and continued to decline, followed by the Q3 group, while the Q1 and Q2 groups were relatively close in the early period (Log-rank P < 0.0001). The risk table showed that the Q4 group had the highest cumulative number of deaths from ICU admission to the end of follow-up, intuitively reflecting the excess mortality risk in the high ACAG group. To further quantify the above stratification differences, ACAG was converted from a continuous variable to a quartile categorical variable in the fully adjusted model (Model 5), with the lowest quartile group (Q1) as the reference. In the MIMIC cohort, the mortality risk in the Q2 group (ACAG 14–16 mmol/L) was not significantly different from that in Q1 (HR = 1.026, 95% CI: 0.586–1.795, P = 0.929), and the Q3 group (ACAG 16–18.75 mmol/L) also did not reach statistical significance (HR = 1.193, 95% CI: 0.717–1.986, P = 0.497); only the Q4 group (ACAG > 18.75 mmol/L) had a significantly increased mortality risk, which was 2.14 times that of Q1 (HR = 2.139, 95% CI: 1.292–3.542, P = 0.003). In the eICU cohort, the Q2 group (HR = 1.065, 95% CI: 0.850–1.334, P = 0.583) and Q3 group (HR = 1.207, 95% CI: 0.972–1.500, P = 0.089) showed no statistical difference compared with Q1; only the Q4 group (ACAG > 20.62 mmol/L) had a significantly increased mortality risk (HR = 1.543, 95% CI: 1.237–1.926, P < 0.001). In both cohorts, the significant increase in mortality risk was concentrated in the highest quartile range. The cutoff for Q4 was 18.75 mmol/L in the MIMIC cohort and 20.62 mmol/L in the eICU cohort. Notably, Hu et al. also reported ACAG > 20 mmol/L as a high-risk threshold in the cardiac surgery population [20], and the highest quartile cutoffs in the two cohorts of this study were close to this value. To maintain consistency with previous studies and facilitate clinical memory and application, ACAG > 20 mmol/L was rounded and used as the early postoperative high-risk warning threshold after cardiac surgery. This threshold was consistent with the significant separation of the Q4 group in the KM survival curves and with the RCS

analysis, in which the HR continued to rise after ACAG > 16 mmol/L and the 95% CI no longer crossed 1.0 when ACAG > 20 mmol/L.

3.5 Nonlinear Association Test

A restricted cubic spline (RCS) function with four knots was used to test the nonlinear association between ACAG and 28-day mortality risk in the fully adjusted model. The results showed that the P value for nonlinearity was 0.401 in both cohorts, and no statistically significant nonlinear deviation was found, indicating a linear positive association between ACAG and mortality risk. The RCS curve showed that when ACAG < 14 mmol/L, the adjusted HR was close to 1.0 (95% CI crossed 1.0); after ACAG > 16 mmol/L, the HR began to rise steadily; when ACAG reached 28 mmol/L, the HR was approximately 6.0 in the MIMIC cohort and approximately 1.6 in the eICU cohort. The shapes of the RCS curves in the two cohorts were highly consistent, establishing a cross-cohort stable linear positive association between ACAG and mortality risk.

3.6 Subgroup Analysis

Three subgroups were prespecified (age stratified by 65 years, gender, and mechanical ventilation), and the effect of ACAG and its interaction within each subgroup were evaluated in the fully adjusted model. In the age subgroup, stratification was performed using 65 years as the cutoff. In the MIMIC cohort, the ACAG effect was significantly positive in both the ≤ 65 years group (HR = 1.18, 95% CI: 1.12–1.24, P < 0.001) and the > 65 years group (HR = 1.11, 95% CI: 1.06–1.15, P < 0.001), but the between-group difference was not statistically significant (interaction P = 0.349). In the eICU cohort, the age interaction was statistically significant (interaction P = 0.030), and the ACAG effect was stronger in the > 65 years group (HR = 1.049, 95% CI: 1.030–1.069, P < 0.001) than in the ≤ 65 years group (HR = 1.025, 95% CI: 1.005–1.045, P = 0.012). In the gender subgroup, no significant interaction was found in either cohort. In the MIMIC cohort, the HR was 1.18 (95% CI: 1.12–1.25) in the female group and 1.11 (95% CI: 1.07–1.16) in the male group, with an interaction P = 0.115; in the eICU cohort, the HR was 1.04 (95% CI: 1.02–1.07) in the female group and 1.03 (95% CI: 1.02–1.05) in the male group, with an interaction P = 0.759. The prognostic value of ACAG was stable in both males and females. In the mechanical ventilation subgroup, the MIMIC cohort showed a significant interaction (P = 0.007): the ACAG effect was stronger in the non-ventilated group (HR = 1.18, 95% CI: 1.07–1.31, P = 0.001) than in the ventilated group (HR = 1.12, 95% CI: 1.09–1.16, P < 0.001). However, the eICU cohort did not find a significant interaction for ventilation status (P = 0.640): the HR was 1.03 (95% CI: 1.01–1.06, P = 0.007) in the non-ventilated group and 1.04 (95% CI: 1.02–1.06, P < 0.001) in the ventilated group. The interaction directions of age and mechanical ventilation were inconsistent between the two cohorts, suggesting that subgroup-specific conclusions found in a single center should be extrapolated with caution. Gender was the only variable without interaction in both cohorts and could be regarded as a robust negative interaction conclusion.

3.7 Model Discrimination and External Validation

In the MIMIC training set, the C-index of the fully adjusted model was 0.822, indicating excellent discrimination. When the model was directly applied to the eICU external validation cohort, the C-index

was 0.700 (SE = 0.010), indicating that the model still had moderate-to-good generalizable discrimination in a multicenter environment closer to the real world.

3.8 Sensitivity Analysis

In the MIMIC cohort, the point-estimate E-value for ACAG in the fully adjusted model (Model 5) was 1.519 (lower 95% CI E-value: 1.428), suggesting that an unmeasured confounder would need to be associated with both ACAG and 28-day mortality by approximately 1.5-fold to completely explain the observed association. In the eICU cohort, the point-estimate E-value was 1.235 (lower 95% CI E-value: 1.179), meaning that an unmeasured confounder associated with both exposure and outcome by approximately 1.2-fold would be sufficient to push the effect to null, indicating relatively limited robustness. The smaller E-value in eICU was directly related to its smaller effect size (HR = 1.037). This result suggests that the independent association of ACAG in the two cohorts was consistent in direction, but differed in effect strength and robustness to unmeasured confounding, and the association in eICU was more vulnerable to residual confounding.

4 Discussion

This study confirmed in more than 4,600 patients after cardiac surgery that early postoperative ACAG is an independent determinant of 28-day mortality in the ICU. This association remained robust in both the single-center (MIMIC) and multicenter (eICU) cohorts and exhibited a linear dose-response relationship. Notably, although the risk continued to increase with ACAG, the clinically significant excess mortality risk was mainly concentrated in patients with ACAG > 20 mmol/L. This range was highly consistent across cohorts with different disease severities. After adjustment for SOFA and APACHE scores, ACAG remained independently associated, indicating that its relationship with mortality risk was not fully explained by disease severity; however, its incremental predictive value relative to SOFA/APACHE still requires further evaluation.

Elevated postoperative ACAG reflects the overall extent of acute metabolic disorders after surgical trauma and cardiopulmonary bypass. An elevated anion gap suggests the accumulation of unmeasured anions (mainly lactate), whereas hypoalbuminemia is both a consequence of capillary leak and hemodilution and a marker of enhanced inflammatory response [13, 14, 16]. ACAG integrates these two types of information into a single indicator and retains independent predictive value after adjustment for composite scores such as SOFA and APACHE, suggesting that it captures a composite signal of metabolic acidosis and hypoalbuminemia that these scoring systems do not fully cover. This mechanistic explanation is consistent with the prognostic value of ACAG previously observed in critically ill populations such as those with acute myocardial infarction and cardiac arrest [17, 18].

Hu et al., using the same MIMIC-IV database, first reported an independent association between preoperative ACAG and 28-day postoperative mortality risk in 5,006 cardiac surgery patients [20]. Wang et al. also reached similar conclusions in the coronary artery bypass grafting (CABG) population [36]. This study made several advances on this basis. First, the measurement window of ACAG was moved

from the preoperative period to within 24 hours after postoperative ICU admission, confirming that early postoperative ACAG also has independent prognostic value and extending the applicable time window of this indicator. Second, external validation was completed in an independent multicenter eICU cohort. Notably, although the disease severity (median SOFA 8 vs 5) and mortality rate (34.5% vs 12.5%) of the eICU validation population were significantly higher than those of the MIMIC discovery population, the independent predictive effect and threshold effect of ACAG remained robust, which corroborates the cross-database validation results of ACAG in patients with cardiogenic shock reported by Wang Y et al. [36]. The effect size decreased from HR 1.132 in the MIMIC cohort to HR 1.037 in the eICU cohort, and the heterogeneity test showed $I^2 = 96.3\%$ ($P < 0.0001$), indicating that although ACAG was an independent risk factor with a consistent direction in both cohorts, the effect size differed significantly. Such attenuation is not uncommon when prognostic models are generalized from a single center to multiple centers. Possible reasons include: the eICU population had higher disease severity (median SOFA 8 vs 5) and higher mortality (34.5% vs 12.5%), and patient sources, surgical types, and perioperative management practices were more diverse; in addition, the effect size in the initial training set may have been higher than the true effect in external samples due to the “winner’s curse” phenomenon [35, 37].

One difference worth discussing is the shape of the association. Hu et al. reported a nonlinear relationship between preoperative ACAG and mortality [20], whereas this study observed a linear positive association in both cohorts. This difference may stem from the essential distinction in measurement timing: elevated preoperative ACAG reflects the long-term accumulation of chronic comorbidities, and the nonlinear superposition of multiple pathological states may lead to a complex risk-response curve; whereas elevated postoperative ACAG mainly reflects acute metabolic disorders induced by surgical trauma, and its dose-response relationship is closer to linear. Although the mathematical descriptions of the association shape differ, the analysis results of the two cohorts consistently indicated that the significant increase in mortality risk was concentrated in the highest quartile range, jointly pointing to ACAG > 20 mmol/L as a clinical high-risk warning threshold. It should be noted that, under a linear relationship, this threshold reflects the point at which risk continuously accumulates with increasing ACAG until reaching statistical significance, rather than a physiological inflection point of abrupt increase. This consensus on the high-risk range across studies and time windows provides a practical reference for clinical monitoring and intervention.

In the subgroup analysis, the age interaction was significant in the eICU cohort ($P = 0.030$), showing a stronger effect of ACAG in patients > 65 years; however, no significant age interaction was found in the MIMIC cohort ($P = 0.349$). The interaction with mechanical ventilation status was significant only in MIMIC ($P = 0.007$) and disappeared in eICU ($P = 0.640$). This inconsistency between cohorts may be related to differences in population characteristics and clinical practice between the two cohorts, and it also suggests that the modifying effect of age on the prognostic effect of ACAG is not yet robust. Gender was the only variable for which no interaction was found in either cohort.

Among the extracted variables, age, SOFA score, and APACHE score, as recognized prognostic factors, remained independently associated with mortality risk after adjustment. WBC, hemoglobin, BUN, heart rate, and SpO_2 were all significantly associated with mortality risk in univariable analysis, but after adjustment for disease severity indicators such as SOFA and APACHE, their independent effects were no longer significant or were markedly attenuated, indicating that the effects of these variables on prognosis may be confounded by disease severity. Body temperature did not reach statistical significance in the MIMIC cohort but was a significant protective factor in the eICU cohort; this difference may be related to differences in the time window of temperature measurement and the baseline disease spectrum between the two cohorts. ACAG maintained independent predictive value beyond these variables, further indicating that the metabolic disorder information it carries cannot be fully covered by the above variables.

From a clinical application perspective, ACAG requires only one blood gas analysis and routine biochemical tests and can be calculated within 1–2 hours after ICU admission, without additional equipment or cost.

This study has several limitations. The retrospective design cannot completely exclude the influence of unmeasured confounders, such as surgical details including cardiopulmonary bypass time, intraoperative minimum temperature, and transfusion volume; part of the postoperative ACAG elevation may merely be an accompanying manifestation of the severity of perioperative injury. Only the average ACAG measurement within 24 hours after ICU admission was used, and its dynamic trajectory could not be evaluated; continuous monitoring of the direction of ACAG change may have stronger prognostic value than the average value. MIMIC used the APACHE III score whereas eICU used the APACHE IV score; differences in scoring items and weights may introduce some bias, which we partially addressed by simultaneously adjusting for the SOFA score. Moreover, the heterogeneity test showed a high I^2 for the ACAG effect size between the two cohorts, suggesting that the effect strength may be influenced by differences in population characteristics and clinical practice; future studies are needed to further validate the optimal risk stratification threshold of ACAG in more diverse populations. In addition, E-value analysis showed that the association had moderate robustness to unmeasured confounding in the MIMIC cohort (E = 1.52), but limited robustness in the eICU cohort (E = 1.24), suggesting that the independent robustness of this association in multicenter populations still needs to be verified in future studies incorporating more complete perioperative variables.

5 Conclusion

ACAG measured within 24 hours after postoperative ICU admission is an independent risk factor for 28-day ICU mortality after cardiac surgery, and this association remained robust in the multicenter eICU cohort. ACAG > 20 mmol/L can serve as a clinical warning threshold for identifying high-risk patients. As an immediately available and low-cost composite metabolic indicator, ACAG is expected to serve as an effective supplement to existing disease severity scores and play a substantial clinical role in early risk stratification after cardiac surgery.

Declarations

Availability of data and material

The present study utilized publicly available data sets. The relevant data from the MIMIC-IV v3.1 database are available on Physionet (https://physionet.org/content/mimiciv/3.1/),.

Ethics approval and consent to participate

Not applicable.

Clinical trial number: Not applicable.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Competing interests

The authors declare that they have no competing interests.

Approved for publication

All authors have reviewed and approved the final version of the manuscript.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

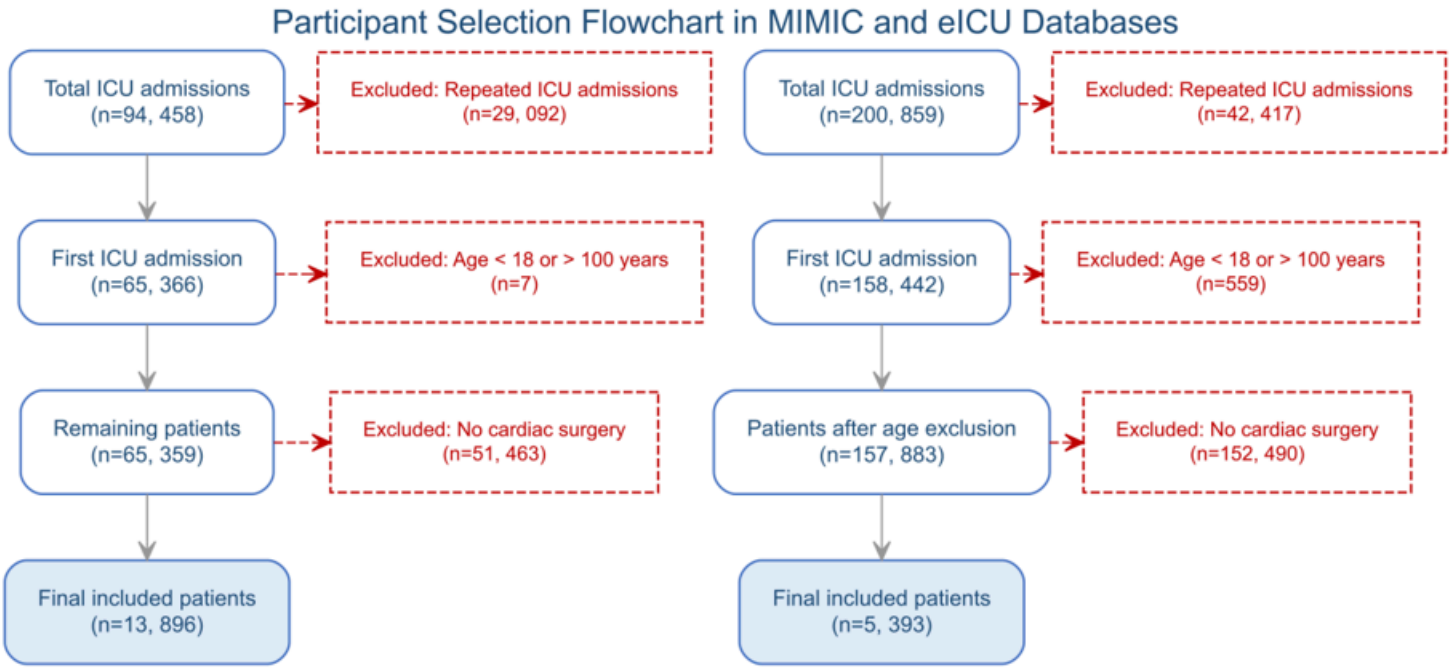


Figure 1

Two-column participant selection flowchart for the MIMIC and eICU cohorts.

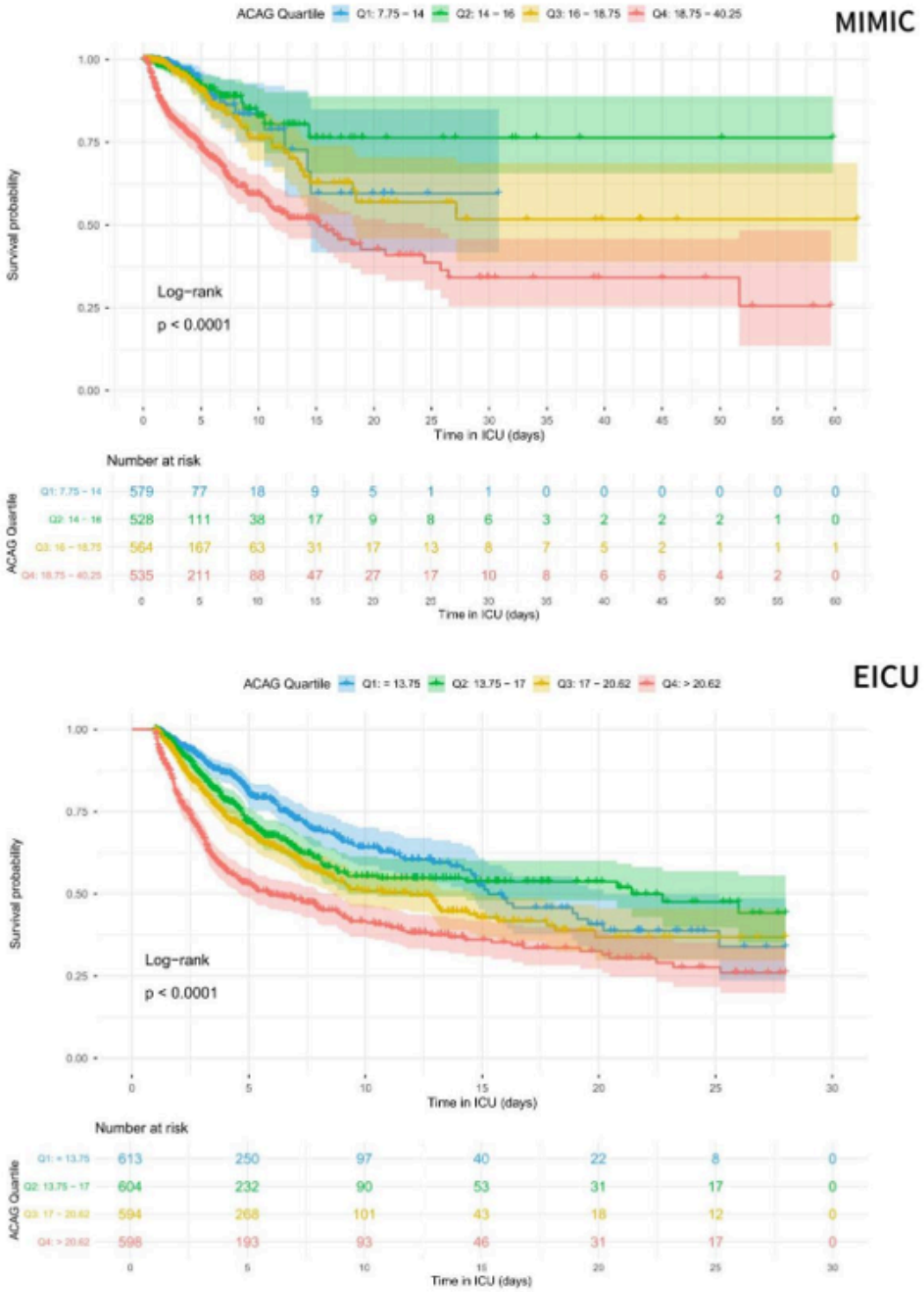


Figure 2

Kaplan-Meier survival curves for the MIMIC and eICU cohorts.

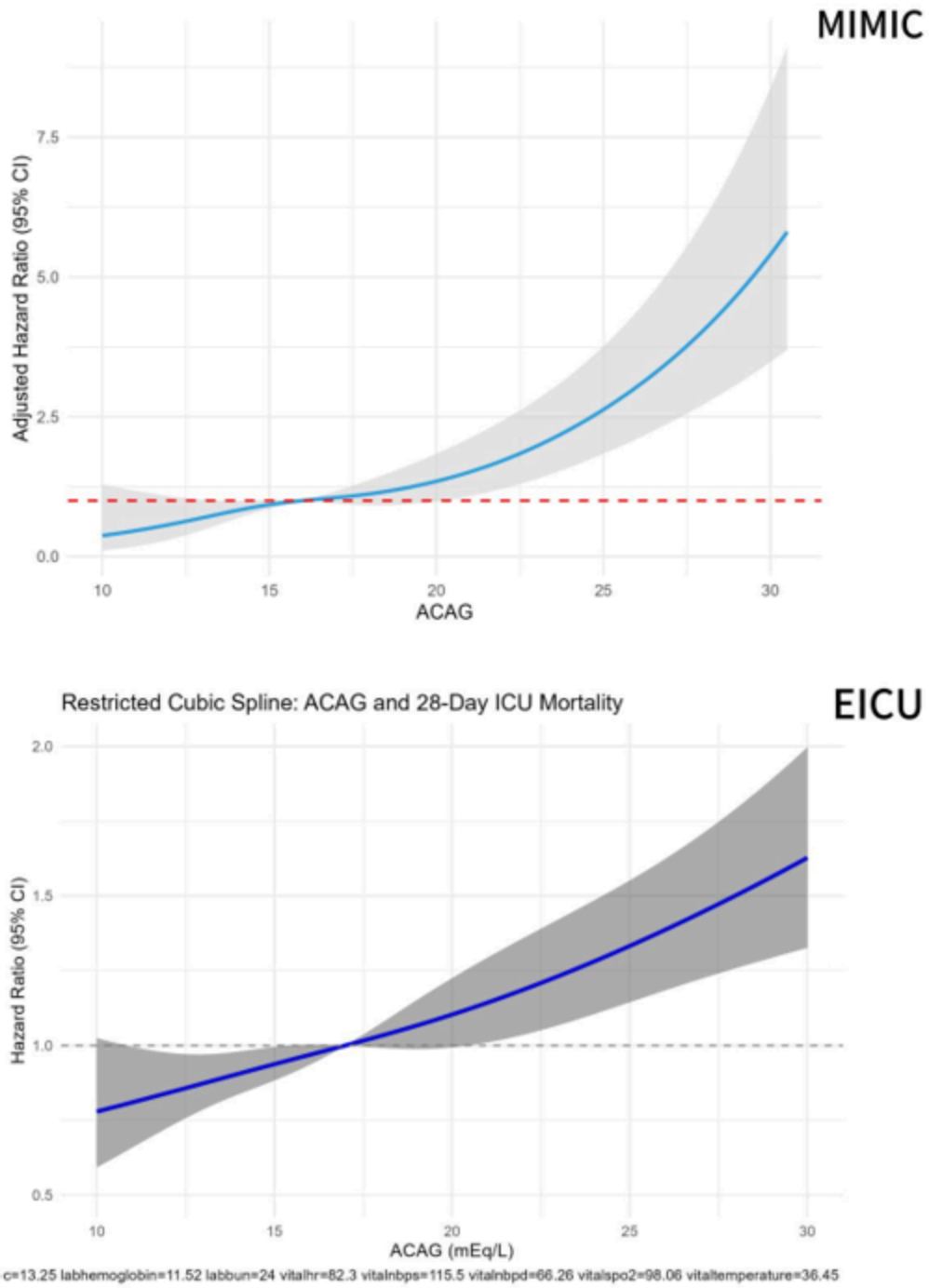


Figure 3

Restricted cubic spline (RCS) curves for the MIMIC and eICU cohorts.

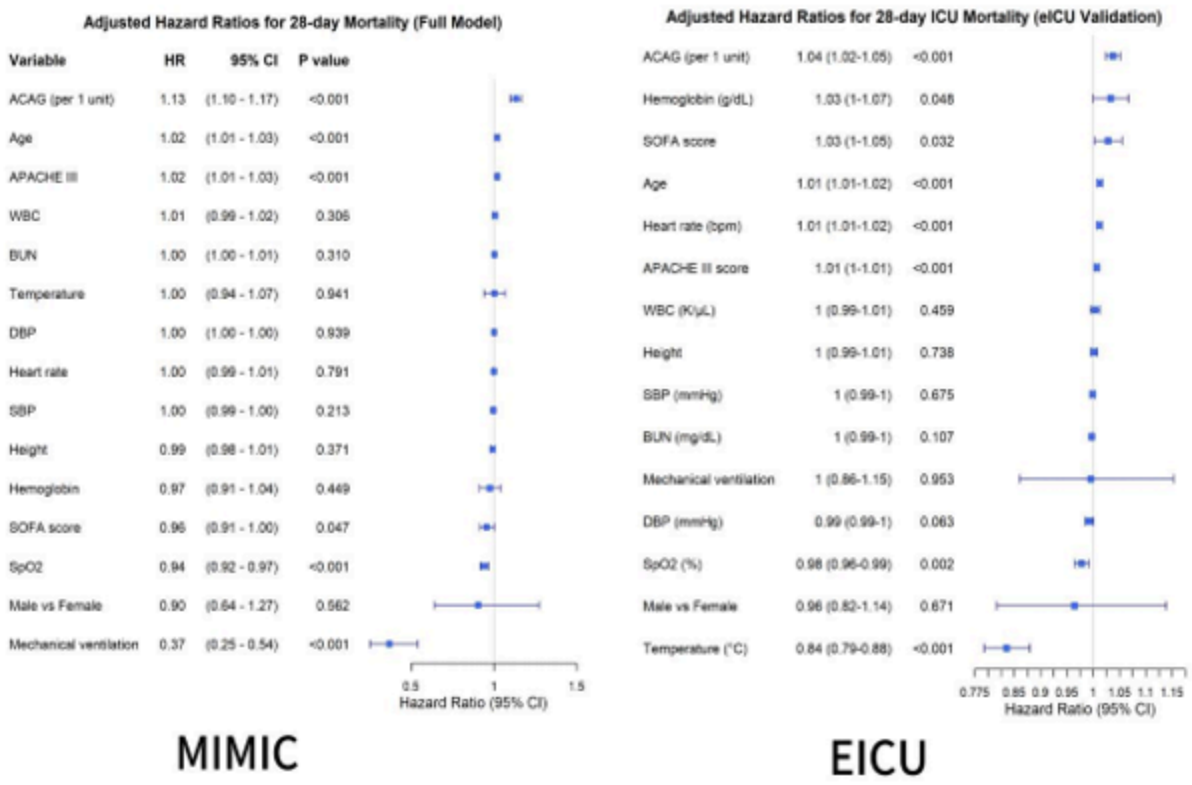


Figure 4

Main forest plot for the MIMIC and eICU cohorts.

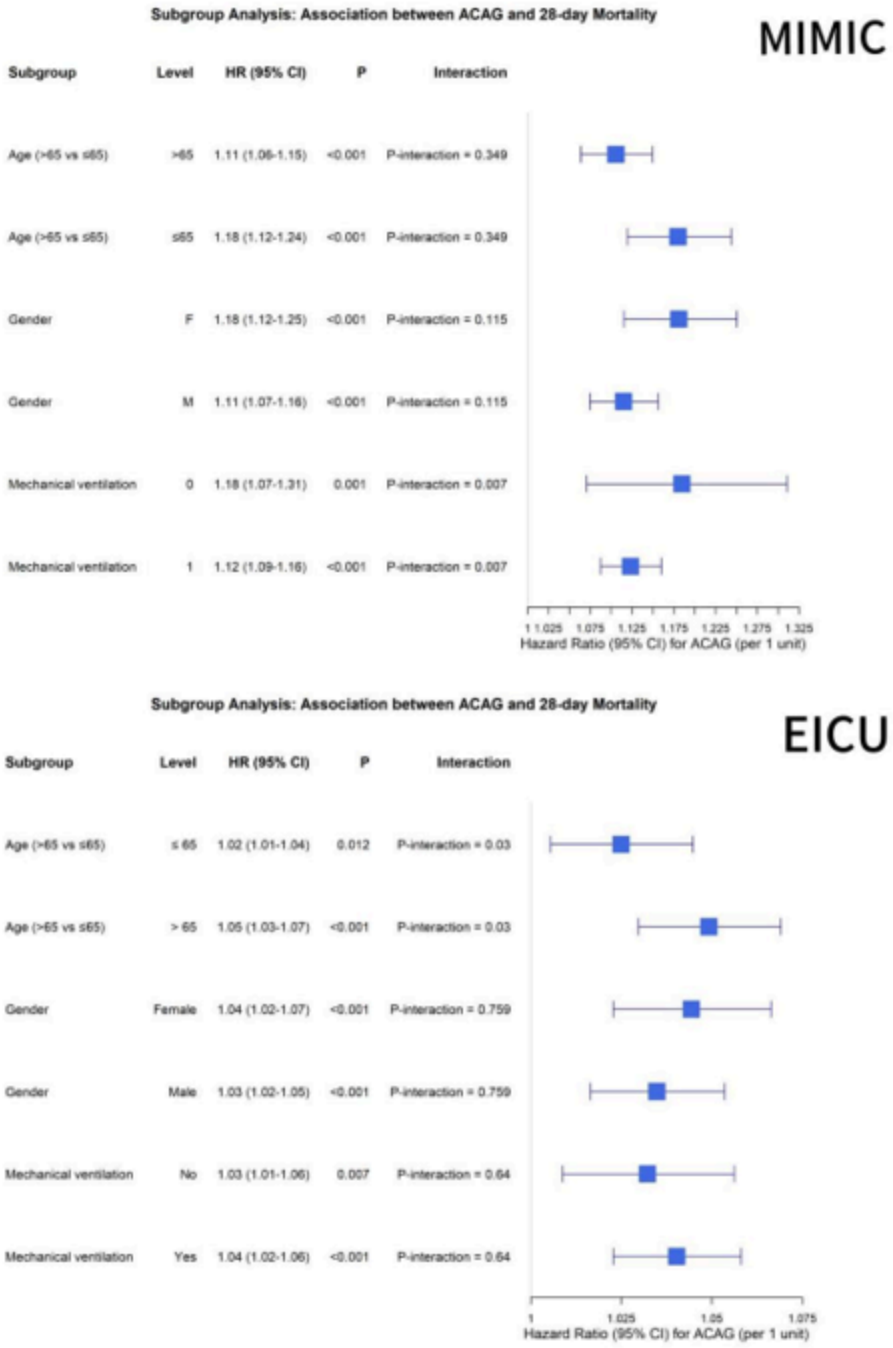


Figure 5

Subgroup forest plot for the MIMIC and eICU cohorts.

Supplementary Files

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- Table1.docx