Research Square

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Relationship between the albumin–corrected anion gap and prognosis among patients with intra-abdominal hypertension: a retrospective study from MIMIC-IV database

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Research Article

Keywords: Albumin-corrected anion gap, intra-abdominal hypertension, MIMIC-IV database, All-cause mortality

Posted Date: November 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11591603/v1

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Additional Declarations: No competing interests reported.

Abstract

Intra-abdominal hypertension (IAH) is common in ICU patients and associated with high mortality, but reliable prognostic markers remain lacking. This study aims to assess the prognostic value of albumin-corrected anion gap (ACAG) for 7-day all-cause mortality in ICU patients with IAH. A cohort of 617 adult ICU patients with IAH was analyzed, with ACAG levels being assessed as a predictor of 7-day mortality. Higher 7-day mortality was observed in patients with elevated ACAG, with ACAG identified as an independent risk factor for 7-day mortality (HR = 2.043, P < 0.05). ACAG demonstrated good predictive performance (AUC = 0.731), outperforming ALB and showing comparable efficacy to SOFA and AG. Subgroup analysis revealed that lower ACAG values were protective, and the interaction between ACAG and age was significant (P for interaction = 0.032), with a more pronounced prognostic value of ACAG in patients younger than 65 years. Our findings suggest that ACAG is a useful prognostic marker for 7-day mortality in IAH patients, with particular utility in younger populations.

Introduction

In 2006, the World Society of the Abdominal Compartment Syndrome (WSACS) reached a consensus on the definitions of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS), as well as the techniques for measuring intra-abdominal pressure (IAP) [1]. IAH is defined as a persistent or recurrent pathological elevation of IAP ≥ 12 mmHg [2]. The incidence of IAH in the intensive care unit ranges from 40% to 60% [3–5]. Compared with patients without IAH, the all-cause mortality rate of IAH patients is significantly higher, and the occurrence of IAH is considered an independent risk factor for the death of ICU patients [3,6]. Therefore, it is crucial to evaluate the prognosis of IAH at an early stage, but currently, there is still a lack of effective prognostic assessment indicators for IAH.

The anion gap (AG) is an important indicator associated with multiple organ dysfunction and plays a crucial role in evaluating the acid-base balance in clinical settings [7]. However, there are significant limitations in the clinical application of AG. To overcome the defect of potential false-negative results, the concept of albumin-corrected anion gap (ACAG) has been proposed in the guidelines to optimize the AG index [8,9]. In recent years, studies have confirmed that ACAG is closely associated with the development of multiple organ failure and has demonstrated important value in the prognostic assessment of critically ill conditions such as acute pancreatitis, sepsis, and acute kidney injury[10–12]. Nevertheless, there is still a lack of clinical evidence regarding the application of ACAG in IAH patients. IAH patients often have concurrent acid-base imbalance, and with the progression of the disease, it can develop into ACS, which in turn leads to multiple organ dysfunction [13]. Therefore, ACAG may be able to more accurately reflect the pathophysiological state of IAH patients and provide a new perspective for prognostic assessment.

Based on this, this study systematically screened the inpatient clinical data of patients with IAH from 2008 to 2019 in the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, aiming to

achieve two research objectives: Firstly, to deeply study the correlation between ACAG and 7-day all-cause mortality in IAH patients. Secondly, to evaluate the predictive ability of ACAG for 7-day prognosis of IAH patients.

Methods

Data source

Data were retrieved from MIMIC-IV (version 3.1), a publicly available critical care repository developed and maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. It aggregates demographic information, bedside observations, laboratory measurements, and outcome data for intensive care unit (ICU) admissions at Beth Israel Deaconess Medical Center (Boston, USA) between 2008 and 2019. Before accessing the data, one investigator completed the required training course covering 'conflict of interest' and 'research utilizing only data or samples,' and obtained access credentials under the database usage agreement (certification number: 62302397). The overall analytic framework of the present study — including cohort assembly, variable extraction, and outcome definitions — followed the workflow of a previously published MIMIC-based investigation 10, with modifications specific to the IAH population.

Ethical considerations and data privacy

Because every record in MIMIC-IV is fully de-identified and each participant is represented only by a randomly assigned coded identifier, the requirement for individual informed consent was waived by the Institutional Review Board of Beth Israel Deaconess Medical Center.

Study population

As IAH is not captured by any specific International Classification of Diseases (ICD) diagnostic code, cases were ascertained on the basis of the WSACS consensus definition 2 rather than administrative coding, in which repeated bladder pressure monitoring constitutes the cornerstone of screening. Accordingly, patients with two or more intra-abdominal pressure (IAP) readings of ≥ 12 mmHg during the ICU stay were classified as confirmed IAH cases, while those with only a single available measurement were discarded to ensure diagnostic reliability.

Eligible patients (1) were 18 years of age or older, (2) remained in the ICU for at least 24 hours, and (3) fulfilled the IAH definition described above. Individuals were excluded if they lacked repeated bladder pressure recordings, had no confirmed diagnosis of IAH, or were missing either AG or ALB values during the ICU stay. Application of these criteria yielded a final cohort of 617 patients (Fig. 1).

Data extraction

ACAG was the principal study variable and, to avoid the confounding influence of therapies initiated later in the course, was computed from the AG and ALB values obtained at the first ICU measurement. In line with the approach reported in the literature [12] ACAG was calculated as AG + 2.5 × [4.4 − ALB (g/dL)]. The data-extraction pipeline — including the candidate variable pool and the strategy for handling missing values — was adapted from a previously published MIMIC-based study 10 and implemented with Structured Query Language (SQL) in Navicat Premium (version 17.0). The following categories of information were retrieved or derived: (1) demographic characteristics; (2) comorbidities (AKI, sepsis, respiratory failure, heart failure, hypertension, diabetes, obesity, ileus, and acute pancreatitis); (3) peak laboratory measurements (RBC, WBC, RDW, PLT, Hb, HCT, creatinine, BUN, TBil, AST, ALT, glucose, PT, PTT, INR, potassium, sodium, calcium, chloride, ALB, AG, lactate, CK–MB, and pH) together with mean vital signs recorded on ICU admission (HR, SBP, DBP, MAP, RR, SpO2, and temperature); (4) treatments and interventions (mechanical ventilation, CRRT, vasoactive agents, epinephrine, and neuromuscular blockers); and (5) the SOFA score. Variables missing in more than 15% of the cohort (height, BMI, CK–MB, and lactate) were excluded to limit outcome bias, and the remaining gaps were filled by multiple imputation using the 'mice' package in R. All extracted covariates are summarized in Table 1.

Table 1
Covariates extracted from the MIMIC-IV (v 3.1).

Items	Composition
Demographic	Age, Gender, Ethnicity, Height, Weight, BMI
Vital Signs	HR, SBP, DBP, MAP, RR, SpO2, Temperature
Comorbidities	AKI, Sepsis, RF, HF, Hypertension, Diabetes, Obesity, Ileus, Acute pancreatitis
Laboratory Variables	RBC, WBC, RDW, PLT, Hb, HCT, Creatinine, BUN, TBil, AST, ALT, GLU, PT, PTT, INR, K, Na, Ca, Cl, ALB, AG, LAC, CK–MB, pH
Clinical Treatments	MV, CRRT, vasoactive drugs, epinephrine, neuromuscular blockers
Score	SOFA score
Clinical Outcomes	LOS ICU, LOS Hospital, 7-day ACM

MIMIC-IV, the Medical Information Mart for Intensive Care database; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RR, respiratory rate; SpO_2, blood oxygen saturation; AKI, acute kidney injury; RF, respiratory failure; HF, heart failure; RBC, red blood cell; WBC, white blood cell; RDW, red cell distribution width; PLT, platelet; Hb, hemoglobin; HCT, hematocrit; BUN, blood urea nitrogen; TBil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GLU, Glucose; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; K, serum potassium; Na, serum sodium; Ca, serum calcium; Cl, serum chloride; ALB, serum albumin; AG, anion gap; LAC, lactate; CK-MB, creatine kinase-MB; pH, Hydrogen Ion Concentration; MV, mechanical ventilation; CRRT, continuous renal

replacement therapy; LOS ICU, length of ICU stay; LOS Hospital, length of hospital stay; ACM, all–cause mortality.

Statistical analysis

Continuous variables were first examined for distributional normality using the Kolmogorov–Smirnov test. Normally distributed variables are reported as means with standard deviations and were compared between groups with Student's t test; skewed variables are expressed as medians with interquartile ranges [Md (P25, P75)] and were analysed with the Mann–Whitney U test. Categorical variables are summarised as counts and percentages and were compared using Pearson's χ^2 test.

The ACAG threshold was derived from the receiver operating characteristic (ROC) curve for 28-day all-cause mortality using R statistical software (version 4.3.2; R Foundation for Statistical Computing), yielding a cutoff value of 21.125. The 28-day outcome was chosen for threshold derivation because it contained the largest number of death events (n = 190 vs. 88 for 7-day mortality) and therefore provided the most stable and least overfitted threshold estimate. The cohort was subsequently dichotomised into low- and high-value ACAG groups according to this threshold (Fig. 2). In a sensitivity analysis, the cutoff value derived from the 7-day outcome (21.75) yielded essentially consistent results (7-day mortality: 25.2% vs. 6.8%; log-rank $P < 0.0001$), supporting the robustness of the dichotomisation.

Kaplan–Meier (K–M) curves were plotted to visualise survival differences between the two ACAG groups, and the log-rank test was applied for between-curve comparison. Cox proportional hazards regression was then fitted to quantify the association between ACAG and 7-day mortality. Variables with a p-value < 0.05 in the univariate models were entered into the multivariable analysis to identify independent predictors of 7-day mortality after ICU admission, and effect estimates are reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

To appraise prognostic performance, ROC analyses were performed for AG, ALB, ACAG, and the SOFA score with respect to 7-day mortality after admission, and the area under the curve (AUC), together with the corresponding sensitivity and specificity, was derived for each indicator.

Pre-specified subgroup analyses were carried out to examine whether the predictive value of ACAG for 7-day mortality was modified by clinically relevant factors, namely sex, age (< or ≥ 65 years), ethnicity (White versus other), and the presence of hypertension or diabetes. All statistical procedures were executed in SPSS version 26.0 and R version 4.3.2, and a two-sided p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 617 eligible patients were included in this study (Fig. 1). The high–value group had higher body weight, more frequent CRRT use (47.4% vs. 23.5%), and increased utilization of epinephrine and vasoactive drugs. This group was also more likely to develop RF (73.2% vs. 58.8%). Laboratory results showed significantly higher levels of BUN, calcium, creatinine, glucose, potassium, chloride, INR, PT, PTT, ALT, AST, total bilirubin and pH in the high-value group ($p < 0.001$). Additionally, the high–value group had significantly higher SOFA score (11 vs. 5). Moreover, the high–value group exhibited significantly higher 7-day ACM (24.3% vs. 6.4%, $p < 0.001$). Detailed baseline characteristics are shown in Table 2.

Table 2
Baseline characteristics in patients with IAH

Variable	Total (n = 617)	High–value group (ACAG ≥ 21.125) (n = 272)	Low–value group (ACAG<21.125) (n = 345)	χ^2/t/Z value	*P* value
Demographics					
Age, years	58 (49, 70)	58 (49, 69)	59 (49, 71)	−0.634	0.526
Gender, n (%)				2.608	0.106
Male	405 (65.6)	188 (69.1)	217 (62.9)		
Female	212 (34.4)	84 (30.9)	128 (37.1)		
Ethnicity, n (%)				0.831	0.66
White	357 (57.9)	155 (57)	202 (58.6)		
Black	35 (5.7)	18 (6.6)	17 (4.9)		
Other	225 (36.5)	99 (36.4)	126 (36.5)		
Weight, kg	85.60 (72.00, 103.00)	87.10 (75.00, 105.83)	85 (70.60, 100.45)	−2.057	0.04
Vital Signs					
HR, beats/min	98.70 ± 18.52	99.98 ± 18.24	97.69 ± 18.70	1.524	0.128
SBP, mmHg	110.06 (102.76, 120.29)	108.00 (101.78, 117.52)	112.51 (103.35, 122.61)	−3.076	0.002
DBP, mmHg	61.00 (55.10, 68.77)	60.05 (54.11, 66.94)	61.89 (56.19, 69.78)	−3.230	0.001
MAP, mmHg	76.84(71.98, 84.76)	75.36(70.79, 82.20)	77.97 (72.64, 86.64)	−3.710	<0.001
RR, times/min	21.32 (17.90, 24.70)	22.53 (18.85, 26.17)	20.39 (17.50, 23.64)	−4.901	<0.001
Temperature, °C	36.88 (36.49, 37.38)	36.81 (36.38, 37.32)	36.97 (36.56, 37.40)	−2.558	0.011
SpO_2, %	96.83 (95.14, 98.24)	96.92 (95.25, 98.27)	96.72 (95.12, 98.20)	−0.395	0.693
Clinical Treatment					
CRRT, n (%)	210 (34.0)	129 (47.4)	81 (23.5)	38.851	<0.001

Variable	Total (n = 617)	High–value group (ACAG ≥ 21.125) (n = 272)	Low–value group (ACAG<21.125) (n = 345)	χ^2/t/Z value	*P* value
Ventilation, n (%)	575 (93.2)	261 (96.0)	314 (91.0)	5.854	0.016
Vasoactive drugs, n (%)	454 (73.6)	226 (83.1)	228 (66.1)	22.615	<0.001
neuromuscular blockers, n (%)	152 (24.6)	66 (24.3)	86 (24.9)	0.036	0.85
Epinephrine, n (%)	78 (12.6)	46 (16.9)	32 (9.3)	8.031	0.005
Comorbidities					
Sepsis, n (%)	568 (92.1)	258 (94.9)	310 (89.9)	5.196	0.023
Pancreatitis, n (%)	125 (20.3)	55 (20.2)	70 (20.3)	0.000	0.983
Obesity, n (%)	85 (13.8)	39 (14.3)	46 (13.3)	0.129	0.719
RF, n (%)	402 (65.2)	199 (73.2)	203 (58.8)	13.739	<0.001
AKI, n (%)	603 (97.7)	269 (98.9)	334 (96.8)	2.983	0.084
HF, n (%)	84 (13.6)	41 (15.1)	43 (12.5)	0.881	0.348
Hypertension, n (%)	315 (51.1)	139 (51.1)	176 (51.0)	0.000	0.983
Diabetes, n (%)	168 (27.2)	79 (29.0)	89 (25.8)	0.809	0.368
Ileus, n (%)	105 (17.0)	45 (16.5)	60 (17.4)	0.077	0.781
Laboratory Indicators					
HCT, %	34.90 (30.70, 40.50)	34.80 (30.40, 40.10)	35.00 (31.00, 40.72)	−0.473	0.636
Hb, g/dL	11.60 (10.10, 13.40)	11.60 (10.10, 13.28)	11.70 (10.20, 13.50)	−0.632	0.527
PLT, 10^9/L	196.00 (128.00, 280.50)	175.50 (111.00, 277.75)	204.00 (144.00, 282.50)	−2.735	0.006
WBC, 10^9/L	15.30 (10.25, 22.25)	16.45 (10.80, 24.80)	14.40 (9.95, 20.75)	−2.531	0.011
BUN, mg/dL	29.00 (18.00, 47.00)	38.00 (23.00, 59.00)	25.00 (16.50, 38.00)	−7.268	<0.001

Variable	Total (n = 617)	High–value group (ACAG ≥ 21.125) (n = 272)	Low–value group (ACAG<21.125) (n = 345)	χ^2/t/Z value	*P* value
Ca, mmol/L	8.30 (7.70, 8.90)	8.50 (7.90, 9.20)	8.20 (7.70, 8.70)	−3.771	<0.001
Cl, mmol/L	107.00 (103.00, 112.00)	105.50 (101.00, 111.00)	108.00 (104.00, 112.50)	−4.504	<0.001
Creatinine, mg/dL	1.70 (1.10, 2.90)	2.40 (1.60, 3.78)	1.30 (0.90, 2.10)	−10.762	<0.001
GLU, mg/dL	169.00 (130.50, 227.00)	182.50 (136.00, 252.00)	159.00 (128.00, 202.50)	−3.539	<0.001
Na, mmol/L	140.00 (136.00, 143.00)	140.00 (135.00, 144.00)	140.00 (136.00, 143.00)	−0.276	0.782
K, mmol/L	4.70 (4.20, 5.40)	5.00 (4.40, 5.80)	4.50 (4.10, 5.10)	−6.126	<0.001
INR	1.60 (1.30, 2.30)	1.90 (1.40, 2.70)	1.50 (1.20, 1.90)	−6.440	<0.001
PT, s	17.80 (14.30, 23.85)	20.25 (15.30, 28.78)	16.40 (13.90, 20.25)	−6.314	<0.001
PTT, s	40.80 (31.90, 61.50)	46.10 (34.03, 68.68)	37.90 (30.90, 54.40)	−4.169	<0.001
ALT, U/L	46.00 (23.00, 173.50)	85.00 (31.25, 425.50)	33.00 (20.00, 96.00)	−6.947	<0.001
AST, U/L	109.00 (42.00, 346.50)	209.00 (68.25, 1033.50)	66.00 (34.00, 182.50)	−8.132	<0.001
TBil, mg/dL	1.50 (0.70, 4.25)	2.10 (0.90, 6.08)	1.20 (0.60, 2.90)	−5.526	<0.001
pH	7.39 (7.33, 7.45)	7.38 (7.31, 7.44)	7.40 (7.35, 7.46)	−3.865	<0.001
RDW, %	15.90 (14.60, 17.90)	16.20 (14.90, 18.48)	15.60 (14.45, 17.40)	−3.449	0.001
RBC, 10^9/L	4.27 ± 0.90	4.21 ± 0.91	4.31 ± 0.90	−1.388	0.166
Clinical Outcomes					
Sofa score	9.00 (6.00, 12.50)	11 (8, 14.75)	8 (5, 11)	−9.130	<0.001

Variable	Total (n = 617)	High–value group (ACAG ≥ 21.125) (n = 272)	Low–value group (ACAG<21.125) (n = 345)	χ^2/t/Z value	*P* value
LOS ICU, day	8.88 (4.28, 17.19)	8.58 (3.87, 14.79)	7.43 (5.08, 9.77)	–2.651	0.008
LOS hospital, day	17.57 (9.77, 27.99)	15.68 (6.45, 25.41)	18.53 (11.61, 29.34)	–3.849	<0.001
7-day ACM, n (%)	88 (14.3)	66 (24.3)	22 (6.4)	39.797	<0.001

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RR, respiratory rate; SpO_2, blood oxygen saturation; CRRT, continuous renal replacement therapy; RF, respiratory failure; AKI, acute kidney injury; HF, heart failure; HCT, hematocrit; Hb, hemoglobin; PLT, platelet; WBC, white blood cell; BUN, blood urea nitrogen; Ca, serum calcium; CI, serum chloride; GLU, Glucose; Na, serum sodium; K, serum potassium; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; pH, Hydrogen Ion Concentration; RDW, red cell distribution width; RBC, red blood cell; LOS ICU, length of ICU stay; LOS Hospital, length of hospital stay; ACM, all-cause mortality.

Correlation of ACAG with all–cause death rates

Kaplan-Meier survival curves revealed a progressively higher mortality rate in the higher ACAG group compared to the lower ACAG group at multiple time points: 7-day (6.4% vs. 24.3%, P < 0.001) (Fig. 3).

Cox regression analysis was used to assess the association between ACAG and 7-day all–cause mortality. Firstly, univariate Cox regression analysis was conducted for the variables with significant differences in the baseline analysis (Table 3), and collinear variables were excluded. The final confounding factors included: MAP, RR, temperature, CRRT, vasoactive drugs, RF, PLT, WBC, BUN, CI, creatinine, K, INR, PT, PTT, ALT, AST, TBil, pH, RDW, and SOFA score.

Table 3
Univariate Cox regression models

item	Univariate COX analysis	
	HR (95%CI)	***P* value**
Weight	1.001(0.995–1.007)	0.746
SBP	0.976(0.965–0.986)	<0.001
DBP	0.962(0.947–0.977)	<0.001
MAP	0.959(0.943–0.974)	<0.001
RR	1.062(1.032–1.092)	<0.001
Temperature	0.670(0.569–0.788)	<0.001
CRRT	0.524(0.394–0.697)	<0.001
Ventilation	0.636(0.326–1.243)	0.186
Vasoactive drug	2.703(1.774–4.117)	<0.001
Epinephrine	1.61(1.101–2.354)	0.014
Sepsis	1.813(0.928–3.54)	0.082
RF	1.794(1.287–2.501)	0.001
PLT	0.998(0.997–0.999)	0.004
WBC	1.021(1.010–1.033)	<0.001
BUN	1.010(1.006–1.014)	<0.001
Ca	1.065(0.962–1.18)	0.227
Cl	0.96(0.941–0.979)	<0.001
Creatinine	1.161(1.079–1.249)	<0.001
GLU	1.001(1.00–1.002)	0.147
K	1.280(1.122–1.461)	<0.001
INR	1.243(1.176–1.314)	<0.001
PT	1.02(1.015–1.025)	<0.001
PTT	1.005(1.002–1.009)	0.005
ALT	1.000(1.000–1.000)	0.002
AST	1.000(1.000–1.000)	<0.001
TBil	1.043(1.030–1.056)	<0.001

item	Univariate COX analysis	
	HR (95%CI)	***P* value**
pH	0.084(0.016–0.440)	0.003
RDW	1.094(1.050–1.139)	<0.001
Sofa score	1.147(1.109–1.186)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RR, respiratory rate; CRRT, continuous renal replacement therapy; RF, respiratory failure; PLT, platelet; WBC, white blood cell; BUN, blood urea nitrogen; Ca, serum calcium; CI, serum chloride; GLU, Glucose; K, serum potassium; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; pH, Hydrogen Ion Concentration; RDW, red cell distribution width.

To improve the reliability of the analysis, we performed the tests by treating ACAG as both a continuous and a binary variable. The results indicate that when ACAG is analyzed as a continuous variable, it is a significant predictor of mortality across all time intervals in the unadjusted model (Model 1) and the partially adjusted model (Model 2). However, in the fully adjusted model (Model 3), no statistical significance was observed (Table 4). Interestingly, when ACAG is treated as a categorical variable, patients in the high-ACAG group exhibited a significantly increased risk of all–cause mortality in both the short–term and long–term in the fully adjusted Model 3. The results suggest that ACAG is an independent risk factor for IAH–related mortality outcomes in the 7-day (HR = 2.043, 95% CI: 1.183–3.528, P = 0.01), models (Table 4).

Table 4
Cox proportional hazard ratios (HR) for ACM in patients with IAH

ACAG	**Model 1**		**Model 2**		**Model 3**	
7-day ACM						
ACAG (continuous)	1.090 (1.067–1.115)	<0.001	1.095 (1.071–1.121)	<0.001	1.031 (0.998–1.066)	0.064
Lower ACAG	Reference	Reference	Reference	Reference	Reference	Reference
Higher ACAG	4.266 (2.633–6.912)	<0.001	4.263 (2.629–6.910)	<0.001	2.043 (1.183–3.528)	0.01
Model 1: Unadjusted;						
Model 2: Adjusted age, gender;						

Model 3: Adjusted age, gender, MAP, RR, temperature, CRRT, vasoactive drug, RF, PLT, WBC, BUN, CI, creatinine, K, INR, PT, PTT, ALT, AST, TBil, pH, RDW, Sofa score.

MAP, mean arterial pressure; RR, respiratory rate; CRRT, continuous renal replacement therapy; RF, respiratory failure; PLT, platelet; WBC, white blood cell; BUN, blood urea nitrogen; CI, serum chloride; K, serum potassium; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; pH, Hydrogen Ion Concentration; RDW, red cell distribution width.

ROC curve analysis

After determining that ACAG was an independent predictor of IAH patients' mortality outcomes at 7-day time-points, we performed ROC curve analysis. Four indices, ACAG, SOFA, ALB, and AG, were incorporated into the analysis (Fig. 4).

At the 7-day time point, ACAG's AUC was 0.731 (95% CI: 0.676–0.785), compared with SOFA's AUC of 0.731 (95% CI: 0.675–0.787), ALB's AUC of 0.490 (95% CI: 0.426–0.555), and AG's AUC of 0.732 (95% CI: 0.677–0.787). ACAG showed comparable predictive ability to AG and SOFA, and significantly outperformed ALB, indicating it was an index with relatively high predictive efficacy (Table 5).

Table 5
Information of ROC curves in Fig. 4.

Day-mortality	variable	AUC	95%CI	Threshold	Sensitivity	Specificity
7-day-mortality	ACAG	0.731	0.676–0.785	21.625	0.716	0.647
	SOFA	0.731	0.675–0.787	11.5	0.602	0.722
	ALB	0.490	0.426–0.555	1.75	0.932	0.087
	AG	0.732	0.677–0.787	18.5	0.636	0.726

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; ACAG, albumin-corrected anion gap; AG, anion gap; ALB; albumin, SOFA, Sequential Organ Failure Assessment score; ACM, all-cause mortality. Threshold values are the Youden-optimal cutoffs for 7-day mortality; the dichotomization cutoff (21.125) was derived from 28-day mortality (see Methods).

Subgroup analyses examining the impact of ACAG on the clinical outcomes among patients suffering from IAH.

Subgroup analyses incorporated commonly - encountered clinical subgroup factors such as gender, age, race, hypertension, and diabetes. Analyses of 7-day mortality outcomes across the whole study population demonstrated that low ACAG values were protective factors for mortality outcomes, and statistical significance was achieved at each time-point (HRs all < 1, P - values all < 0.001). Further subgroup analyses indicated that ACAG did not exhibit significant interaction with the majority of

subgroup factors. Nevertheless, for the 7 - day mortality outcomes, the age subgroup showed a significant interaction with ACAG (P for interaction = 0.032), suggesting that the prognostic value of ACAG was more pronounced in patients younger than 65 years than in elderly patients (see Fig. 5 for details).

Discussion

Despite the importance of ACAG in critical care medicine, its application in IAH patients remains largely unexplored. This study represents the first attempt to evaluate ACAG as a prognostic biomarker for 7-day mortality in this patient population. The results show that when the ACAG is ≥ 21.125, the 7-day ACM of IAH patients is higher than that of IAH patients with ACAG < 21.125. Our results also indicate that ACAG is an independent predictor of 7-day death outcomes in IAH patients in the ICU.

IAH refers to the continuous increase in IAP that exceeds the compensatory function of the abdominal cavity, disrupting the normal physiological functions and causing compression and damage to multiple organs ². The impacts include the pushing of the diaphragm towards the thoracic cavity by the IAP, leading to impaired lung function; an increase in intestinal edema and ischemia; and impaired renal filtration function, etc [14]. In the intensive care unit, IAH is associated with various medical and surgical diseases, and its presence increases the mortality rate of critically ill patients [15]. Therefore, it is crucial to accurately identify patients with IAH who are at risk of poor prognosis at an early stage. This is helpful for timely implementation of effective intervention measures, thereby improving the prognosis of patients and reducing the mortality rate. Currently, the prognosis of IAH patients mostly depends on the IAP value [2]. However, the study by Bishara Bishara shows that when the IAP reaches 10–15 mmHg, it has a negative impact on the organ blood flow of rats [16]. In addition, in patients with obesity or pregnancy, the IAP value increases physiologically. Therefore, there is heterogeneity among IAH patients [17,18]. Existing studies have emphasized that in order to improve the accuracy of prognosis assessment for ICU patients, it is necessary to integrate multi-dimensional clinical indicators for comprehensive analysis [19]. As a common critical illness in the ICU, there is still much room for improvement in the prognosis assessment of IAH. In view of this, exploring the value of ACAG in predicting the prognosis of IAH patients has important clinical significance and is expected to provide a new basis for improving the comprehensive assessment system of IAH.

Unlike the traditional AG, the ACAG incorporates ALB levels during calculation, enabling more precise evaluations of acid-base balance and internal environmental homeostasis [8]. Clinical studies have demonstrated that ACAG is closely associated with the progression of metabolic acidosis, renal insufficiency, and the systemic inflammatory cascade, holding significant potential value in predicting the prognosis of critically ill patient [20–23]. Sheng's research has indicated that an ACAG level ≥ 20 mmol/L serves as an independent risk factor for short-term and long-term mortality in critically ill patients with AMI [24]. Wang's study has shown that ACAG exhibits remarkable efficacy in predicting the short-term and long-term mortality prognosis of patients with acute pancreatitis. The research data

reveal that the AUC value of ACAG is significantly higher than that of traditional evaluation indicators, including AG, ALB, systemic inflammatory response syndrome (SIRS) score, and SOFA score [10]. In addition, Gao et al. have found that when the ACAG is > 20 mmol/L, the all-cause mortality rates at 30 days and 360 days in critically ill patients with AKI increase significantly [25]. The present study further confirms that an elevated ACAG level is significantly associated with an increased ACM in patients with IAH. Previous studies have also indicated that the poor prognosis of IAH patients is closely related to the acid-base imbalance in their bodies [13]. This suggests that ACAG, as a biomarker that precisely reflects the acid-base status, may provide an important basis for prognosis assessment by revealing the potential pathophysiological disorders in IAH patients.

Subgroup analysis revealed that the prognostic value of ACAG was more pronounced in patients younger than 65 years than in elderly patients, as reflected by the significant age × ACAG interaction (P for interaction = 0.032). This discrepancy may be attributed to the altered baseline acid-base status commonly observed in elderly individuals [26]. With the decline of physiological reserve capacity in older individuals, their ability to maintain homeostasis is weakened [27]. Consequently, in elderly patients, pre-existing acid-base alterations and comorbidity-related metabolic disturbances may dilute the incremental prognostic signal conveyed by an elevated ACAG, whereas a markedly elevated ACAG in younger patients usually reflects an acute and severe derangement of acid-base homeostasis and is therefore more closely linked to early fatal outcomes.

However, the results of this study suggest that ACAG has relatively limited predictive value for medium- to long-term mortality outcomes in IAH patients. Several factors may explain these findings. First, the diverse etiologies of IAH among the study population led to substantial heterogeneity in how different forms of IAH affected ACAG, potentially diluting its predictive power. Second, ACAG may only be predictive in the early stages of the disease. As the disease progresses, other pathophysiological mechanisms, such as infection control and organ function restoration, become more critical determinants of survival outcomes. Despite these limitations, our results provide valuable insights into the application of ACAG for predicting short-term mortality in IAH patients. Future studies could focus on specific patient subgroups or combine ACAG with other biomarkers to develop more accurate prognostic models.

This study has several remarkable advantages. Firstly, the research design is rigorous. Through the prognostic evaluation at multiple time points and subgroup analysis, the predictive efficacy of ACAG is explored dynamically and comprehensively. Secondly, a multivariate Cox regression model is employed to rigorously adjust for complex confounding factors, effectively isolating the independent association between ACAG and the prognosis of IAH, thus enhancing the reliability of causal inference. Finally, as the first study focusing on the application of ACAG in patients with IAH, the results of this study fill the research gap in this field, providing an important reference for clinicians to optimize prognosis assessment strategies, and possessing strong academic and practical values.

Nevertheless, this study has certain limitations. First, as a retrospective study, its data rely on existing databases. Constrained by the data recording methods, missing or unrecorded data are inevitable. These data that could not be included in the analysis may compromise the comprehensiveness of the study results. Second, as a single-center study, the geographical distribution of the study population is relatively limited. This may prevent the findings from fully representing the characteristics of populations in different regions, potentially affecting the generalizability of the results. Finally, to ensure data reliability, individuals with missing AG and ALB values were excluded, and the inclusion criteria were strictly defined. This, to some extent, reduced the sample size and may have introduced selection bias, undermining the robustness of the study conclusions. Future research could validate the findings of this study through multi-center, prospective designs.

Conclusion

This study confirms that ACAG is closely linked to 7-day all-cause mortality in adult IAH patients in the ICU. Kaplan-Meier and Cox regression analyses show higher 7-day mortality in the high ACAG group, with ACAG serving as an independent risk factor for 7-day IAH-related mortality. ROC curve analysis demonstrates good prognostic performance for ACAG (AUC = 0.731). Subgroup analysis shows that low ACAG values are protective, and this protective association is more pronounced in patients younger than 65 years (P for interaction = 0.032). These findings suggest that ACAG can be a valuable marker for predicting 7-day prognosis of IAH patients, aiding early intervention and prognostic assessment.

Declarations

Electronic supplementary material

No supplementary information is available for this manuscript.

Author contributions

Jian Guo: Conceptualization, Methodology, Writing—Original Draft, Data Curation, Investigation, Formal Analysis, Writing—Review & Editing; Jing Wang: Conceptualization, Methodology, Writing—Original Draft, Data Curation, Investigation, Formal Analysis, Writing—Review & Editing; Xiaojie Zhang: Conceptualization, Methodology, Writing—Original Draft, Data Curation; Le Xia , Qingling Feng , Fei Wu: Data Collection, Quality Assessment;Jinqiang Zhuang: Corresponding Author, Conceptualization, Writing—Review & Editing; Min Zhu: Corresponding Author, Funding Acquisition, Writing—Review & Editing.

Funding

This study was supported by the Yangzhou City Natural Science Foundation (YZ2024189) and the 2024 Medical Research Project of the Jiangsu Provincial Health Commission (X20240058).

Availability of data and materials

The data utilized in this study were sourced from the MIMIC-IV database. For more information about the database, please visit: https://mimic.physionet.org/. One of the authors obtained authorized access to the database and was entrusted with the responsibility of extracting the data (certification number: 62302397). The datasets extracted and analyzed during this study can be made available by the corresponding author upon reasonable request.

Competing interests

The authors declared no relevant potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

For MIMIC-IV, the institutional reviews board at the Beth Israel Deaconess Medical Center granted a waiver of informed consent and approved the data sharing initiative.

Consent to Participate declaration

not applicable.

Consent for publication

not applicable.

Associated Data

This section collects any data citations, data availability statements, or supplementary materials included in this article.

Data Availability Statement

The data that support the findings of this study are available from the MIMIC-IV database, but restrictions apply to the availability of these data, which were used under license for the current research and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the holder of the database.

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Figures

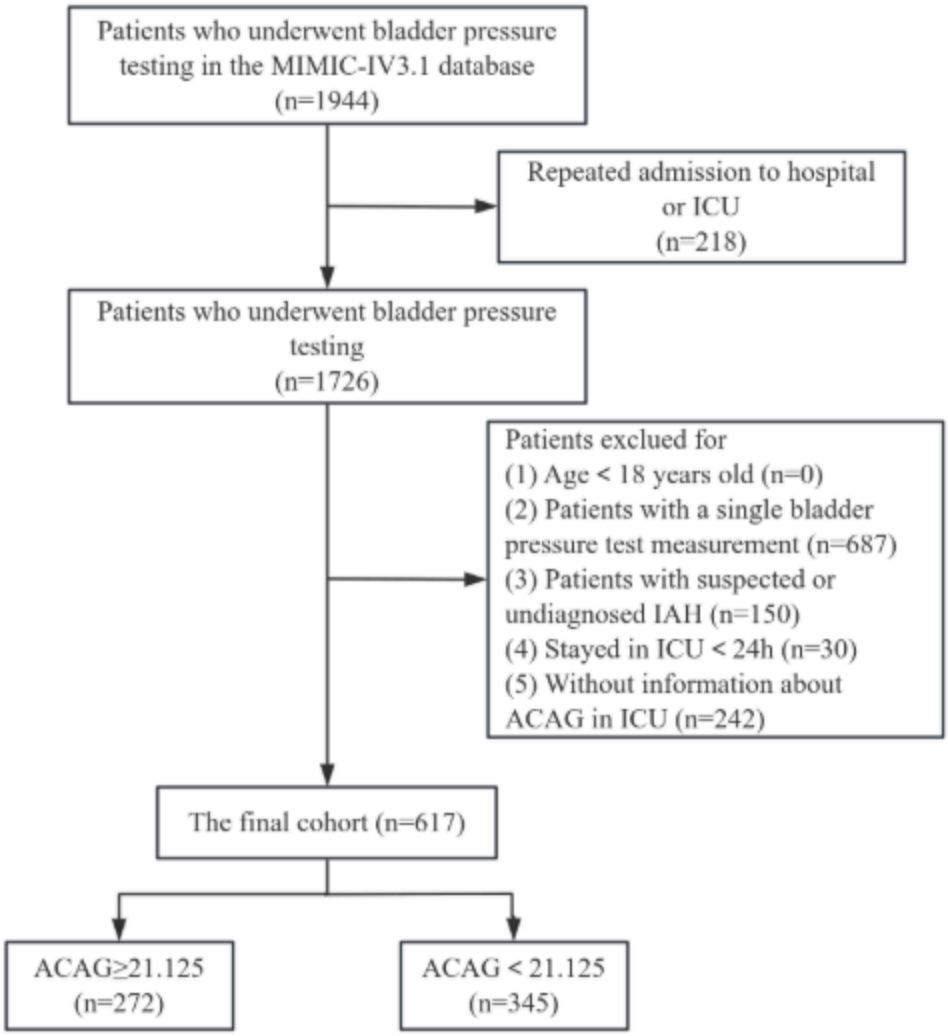

Figure 1

A flowchart for participants from the MIMIC-IV (v 3.1). MIMIC-IV, Medical Information Marketplace Intensive Care-IV; IAH, intra–abdominal hypertension; ICU, intensive care unit; ACAG, albumin-corrected anion gap.

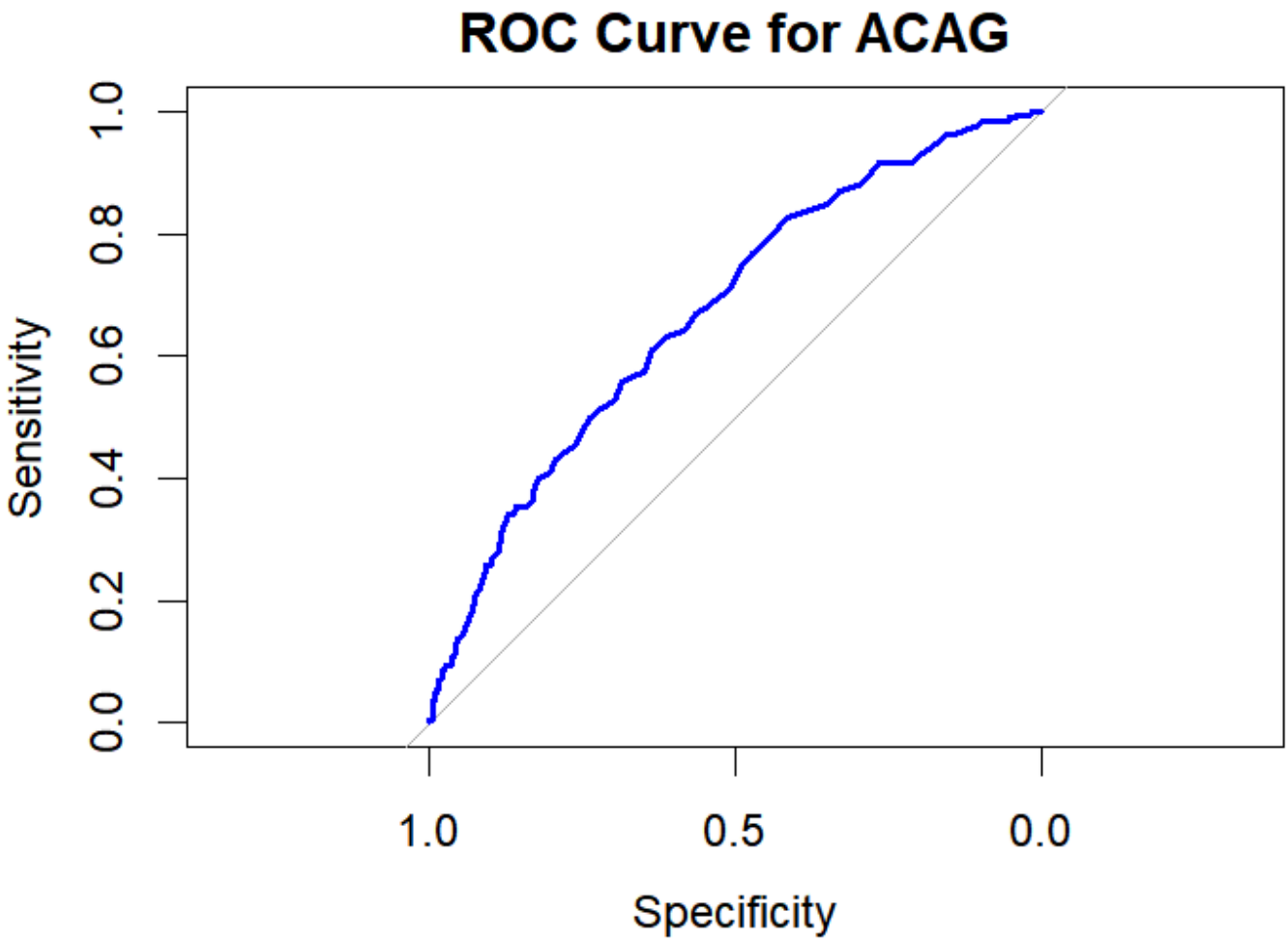

Figure 2

ROC curve for 28-day all-cause mortality, used to determine the optimal decision threshold for ACAG based on the cutoff value of 21.125.

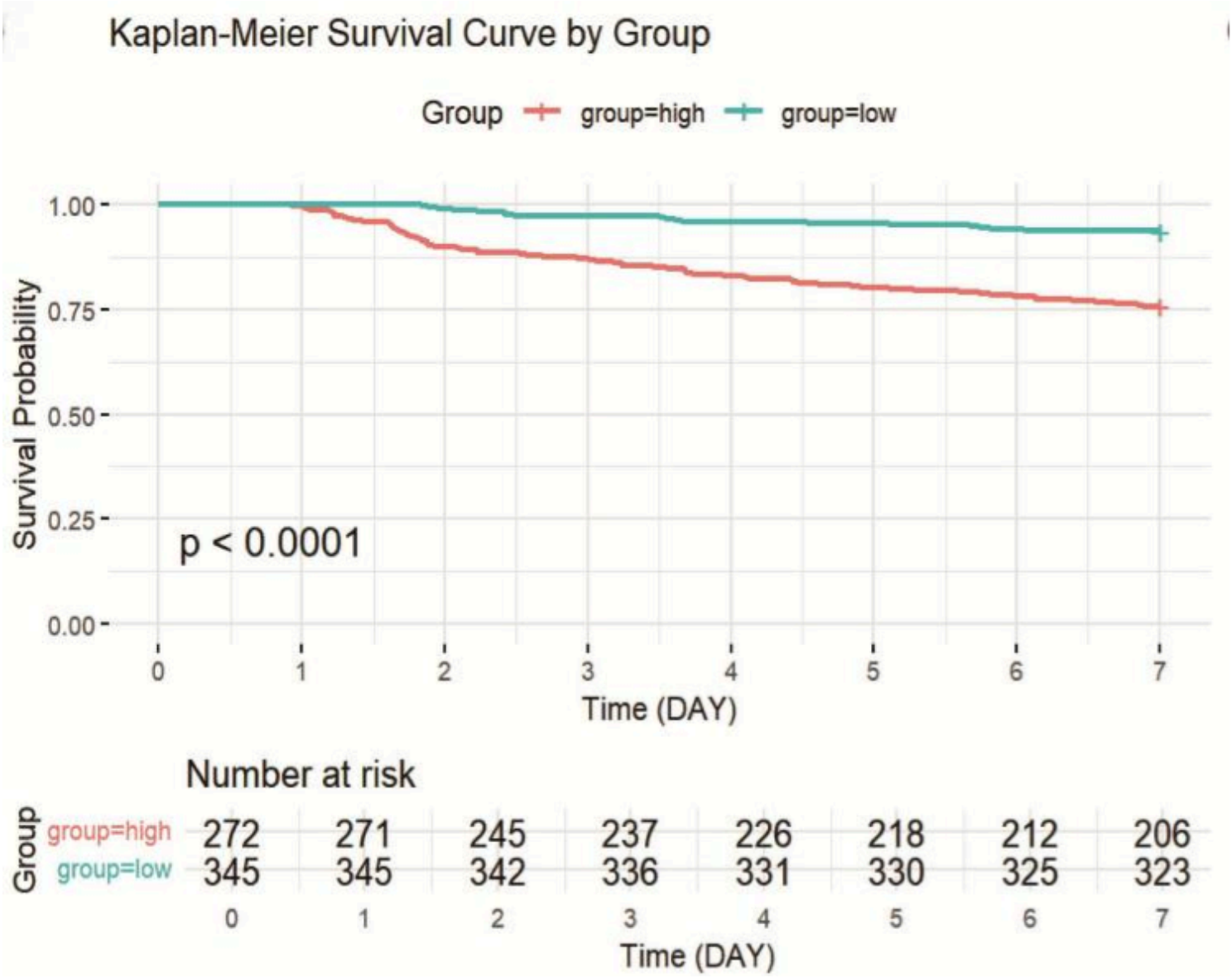

Figure 3

Kaplan-Meier survival analysis curves for 7-day all-cause mortality.

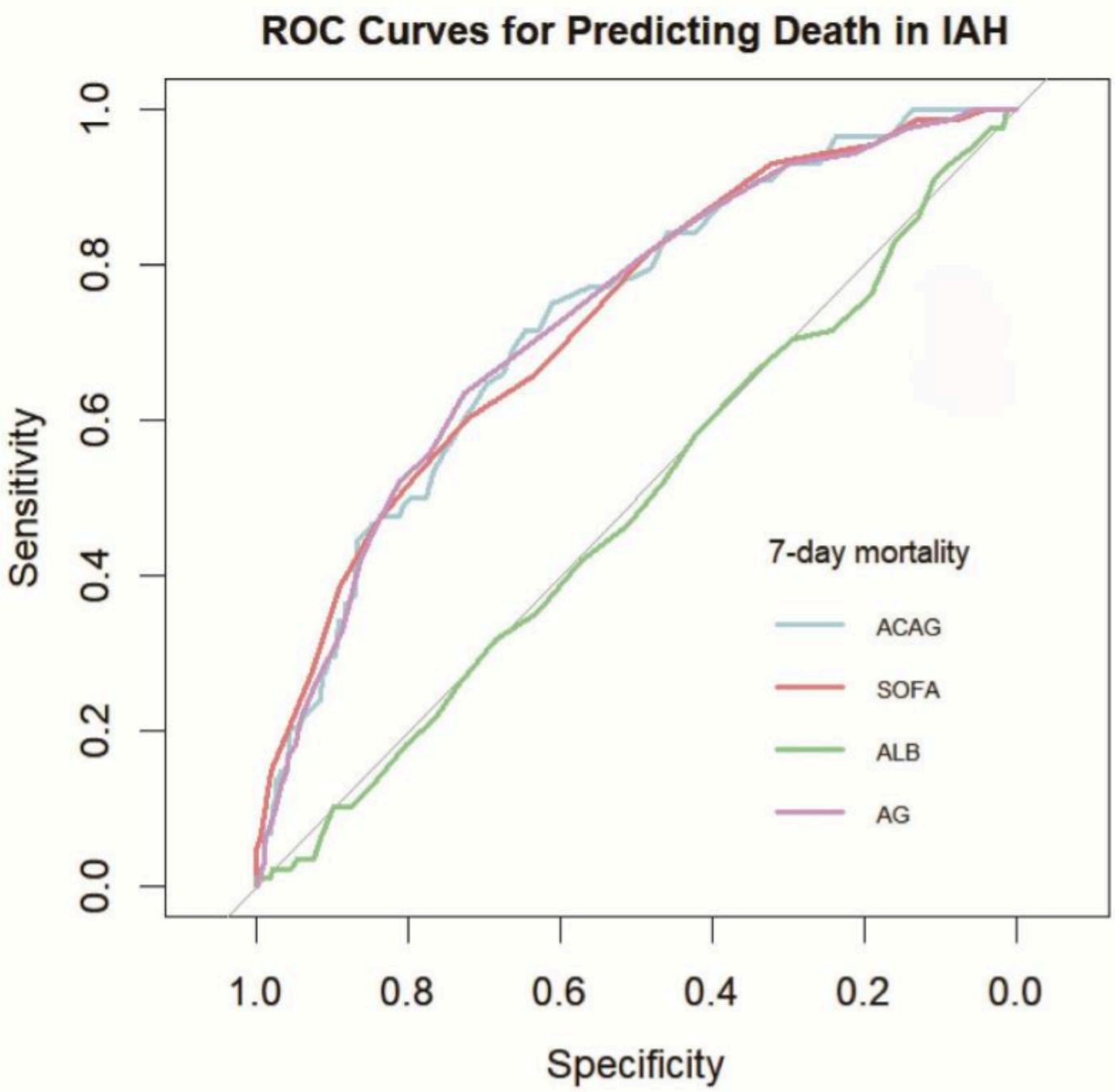

Figure 4

Receiver operating characteristic curves for 7-day all-cause mortality in patients with IAH admitted to the intensive care unit.

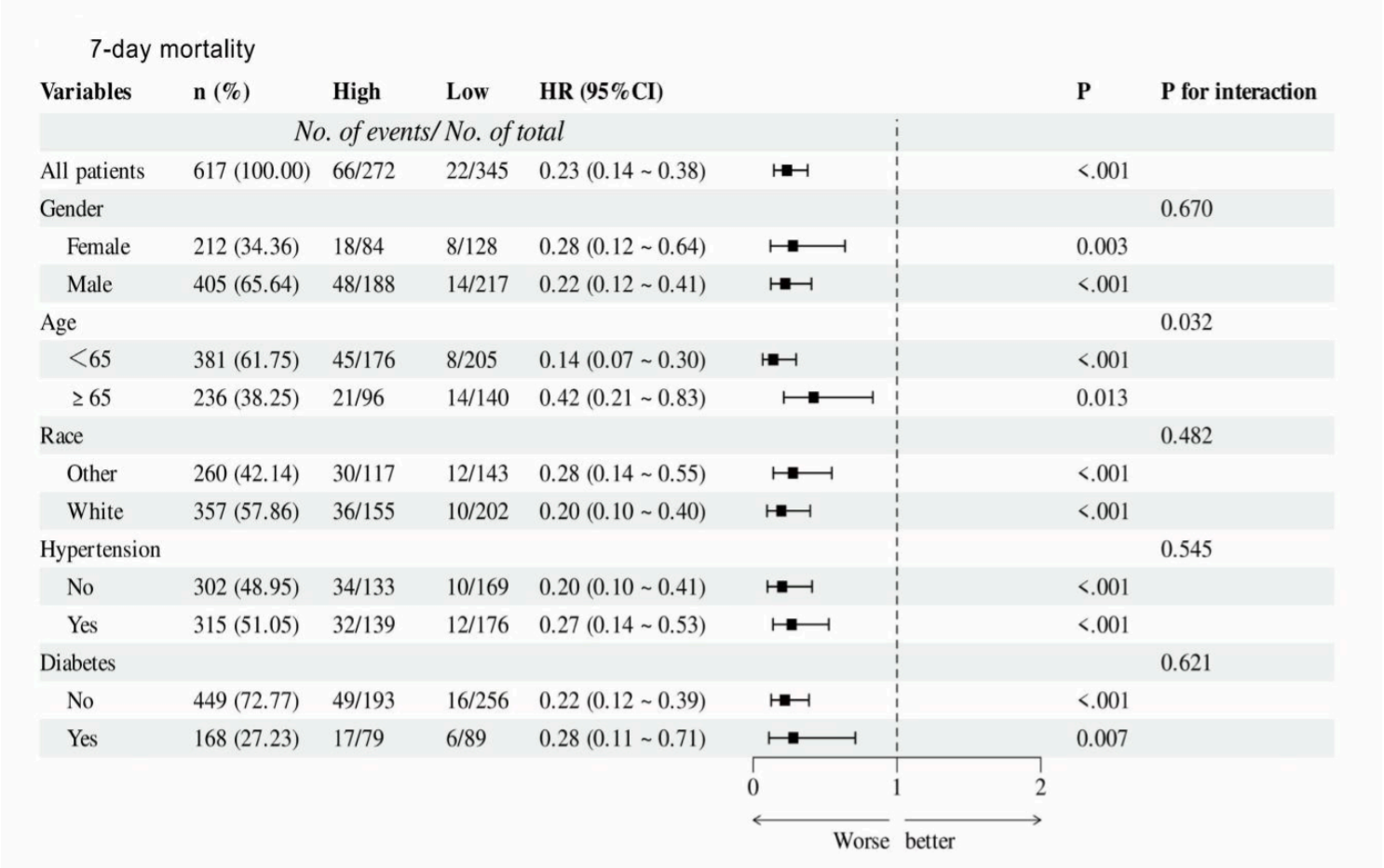

Figure 5

Forest plots presenting subgroup analyses of the associations between all - cause mortality at 7 -day intervals and ACAG among patients with intra - abdominal hypertension admitted to the intensive care unit.