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Association of albumin-corrected anion gap with severe consciousness disorders and outcomes in ischemic stroke: a retrospective MIMIC analysis

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The relationship between albumin-corrected anion gap (ACAG) and severe disorder of consciousness (SDOC), in-hospital mortality, and long-term mortality in patients with ischemic stroke (IS) remains unclear. This study investigates the association of ACAG with SDOC and other outcomes in IS using data from the MIMIC-IV database. A total of 2,379 IS patients were included, with a demographic breakdown showing 51% were male and an SDOC incidence of 16.4%. Analysis through Cox proportional hazards models indicated that ACAG is significantly associated with the risks of both SDOC and mortality. Additionally, restricted cubic spline(RCS) analysis suggested a nearly linear relationship between increasing ACAG levels and the incidence of SDOC. Kaplan-Meier curves demonstrated significant differences in the incidence rates of SDOC, in-hospital mortality, and long-term mortality across varying ACAG levels. The findings suggest that ACAG serves as an independent predictor for SDOC, in-hospital mortality, and long-term mortality in IS patients. Nonetheless, further prospective studies are needed to confirm these causal relationships.

Keywords Ischemic stroke, Albumin-corrected anion gap, Severe disorder of consciousness, Mortality

Abbreviations

IS	Ischemic stroke
SDOC	Severe disorder of consciousness
AG	anion gap
ACAG	Albumin-corrected AG
MIMIC-IV	Medical information mart for intensive care-IV
GCS	Glasgow coma scale
SQL	structured query language
BMI	body mass index
ALB	albumin
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CK	creatine kinase
CKMB	creatine kinase isoenzyme
SCR	serum creatinine
GLU	glucose
HB	hemoglobin
HBA1C	hemoglobin A1c
TBIL	total bilirubin
TC	total cholesterol
TG	triglycerides

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WBC	white blood cell count
HBP	hypertension
DM	diabetes mellitus
HL	hyperlipidemia
AF	atrial fibrillation
CAD	coronary artery disease
CKD	chronic kidney disease
RF	respiratory failure
HF	heart failure
SOFA	sequential organ failure assessment
OASIS	oxford acute severity of illness score
SAPSII	simplified acute physiology score II
APS III	acute physiology score III
IQR	interquartile range
LOS	length of stay
aSAH	aneurysmal subarachnoid hemorrhage
ICU	intensive care unit

Stroke is the second leading cause of death and the third leading cause of disability, with annual direct and indirect costs exceeding $891 billion worldwide[1]. Ischemic stroke (IS) accounts for 87% of all stroke cases[2]. Severe disorder of consciousness (SDOC) is a common clinical presentation in IS patients, resulting in higher in-hospital mortality and poorer discharge outcomes[3]. Few studies have investigated the incidence of SDOC in IS. Current research reported that the triglyceride glucose index and glycemic variability are predictors for cerebrovascular disease with SDOC[3,4] and measures associated with blood glucose metabolism. Therefore, further exploration of risk factors is needed for predicting SDOC in stroke patients. Accurate prediction of IS patient outcomes, especially the occurrence of SDOC, remains a key challenge in clinical practice.

Serum anion gap (AG) is a clinical measure of acid-base homeostasis that can be easily and quickly obtained. Increased AG usually indicates metabolic acidosis, which is often associated with poor prognosis in various acute and chronic conditions[5–7]. Albumin-corrected AG (ACAG) is a modified measure that accounts for the effect of serum albumin level on AG and provides a more accurately reflection of the metabolic status of patients[8–10]. ACAG has been strongly associated with short- and long-term mortality across various diseases[8,10,11], and is a valuable clinical biochemical marker that offers crucial information for the prognostic assessment of these conditions[12,13].

The relationship between ACAG level and the incidence of SDOC and outcomes of IS patients is currently unknown. Therefore, this study aims to examine the association of ACAG with SDOC and outcomes of IS patients using the MIMIC-IV database in order to assist clinicians in the early detection and treatment of high-risk patients.

Methods

Study population

The data used in this study originated from The Medical Information Mart for Intensive Care-IV (MIMIC-IV) 2.2 database developed by the Laboratory for Computational Physiology of Massachusetts Institute of Technology. MIMIC-IV is a publicly available clinical database sourced from the detailed records of 431,231 hospital admissions at the Beth Israel Deaconess Medical Center between 2008 and 2019. Patient identifiers have been removed to protect their privacy, and therefore, patient consent and ethical approval were not required. After completing relevant training, author Ying Chen (ID: 62685292) was given access to the database.

Study population inclusion criteria: Patients diagnosed with IS according to ICD-9 or ICD-10. Exclusion criteria were: (a) age $\geq$ 18 years; (b) lack of AG and albumin test data; (c) presence of SDOC [Glasgow Coma Scale (GCS) $\leq$ 8] before admission; for patients with multiple hospitalizations, only data from the first hospitalization were used.

Patient characteristics

Relevant medical information was extracted from the MIMIC-IV database using Structured Query Language (SQL). These information included demographics (age, sex race, body mass index (BMI), marital status), laboratory data [albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatine kinase (CK), creatine kinase isoenzyme (CKMB), chloride ion, serum creatinine (SCR), blood glucose (GLU), hemoglobin (HB), glycated hemoglobin A1c (HBA1C), bicarbonate (HCO3), potassium ion (Potassium), lymphocytes, sodium ion (Sodium), neutrophils (Neutrophil), platelets (Platelet), total bilirubin (TBIL), total cholesterol (TC), triglycerides (TG), white blood cell count (WBC)], prior comorbidities [hypertension (HBP), diabetes mellitus (DM), hyperlipidemia (HL), anemia, cancer, atrial fibrillation (AF), coronary artery disease (CAD), chronic kidney disease (CKD), respiratory failure (RF), heart failure (HF), alcohol use, and tobacco use identified according to ICD-9 or ICD-10], disease severity [Sequential Organ Failure Assessment (SOFA), Oxford Acute Severity of Illness Score (OASIS), Simplified Acute Physiology Score II (SAPSII), Acute Physiology Score III(APS III)], and medication use (use of antiplatelet and anticoagulant agents prior to onset of DOC.)

AG and ACAG levels were calculated by: AG (mmol/L) = (sodium + potassium) - (chloride + bicarbonate)[14], and ACAG (mmol/L) = [4.4-{albumin (g/dL)}] *2.5 + AG[15].

Handling of missing data: For variables with less than 20% missing data, missing values were imputed using the multiple imputation method based on a random forest model. Variables with > 20% missing data were classified based on the reference range or median of the data provided in the database and included as dummy variables in the analysis.

Outcome measures

The primary outcome measure was the incidence of SDOC, defined by GCS score ≤ 8, during hospitalization. Secondary outcome measures were in-hospital and long-term mortality.

Statistical analysis

Continuous variables with a normal distribution are expressed as mean (standard deviation (SD)) and compared using the *t*-test. Continuous variables without normal distribution are expressed as median (interquartile range (IQR)) and compared using the Mann-Whitney U test. Categorical variables are presented as frequency and percentage (%) and compared between groups using the Pearson chi-square test or Fisher's exact test. The Cox proportional hazards models were used to assess the association between ACAG level and the risks of primary and secondary outcomes, while correcting for multiple confounding factors (Model 1: unadjusted; Model 2: adjusted for age, sex, BMI and race; Model 3: To prevent multiple collinearity, variables with a variance inflation factor ≥ 5 were excluded, and variables from Model 2 and marital status, ALT, AST, CK, CKMB, Chloride, SCR, GLU, HB, HBA1C, Neutrophil, Platelet, TC, WBC, AF, Alcohol use, Anemia, Cancer, CHD, CKD, DM, HF, HBP, HL, RF, Tobacco use, Anticoagulant drugs, Antiplatelets drugs, APSIII, and SAPS II were included). Subsequently, the potential nonlinear relationship between ACAG level and outcomes was explored using restricted cubic spline (RCS). Subgroup analyses were also performed to explore the relationship between ACAG and outcomes in different patient populations. All data were analyzed using R4.4.1, and a $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 2379 patients with IS were included in this study, and the patient selection process is shown in Fig. 1. The median age was 71 years, and there were 51% males and 64% white people. The median length of stay (LOS) was 6 days, and SOC occurred in 389 patients (16.4%). ALT, SCR, GLU, neutrophils, and ACAG levels were higher in the SDOC group than in the non-SDOC group. In addition, the SDOC group had significantly higher number of patients with AF, anemia, RF, and neutrophil > 8.6k/μL than the non-SDOC group ($P < 0.001$). Patients with GCS > 8 had a notably higher rate of antiplatelet and anticoagulant medication use than those with GCS ≤ 8($P < 0.001$), (Table 1). Stratification of patients according to ACAG levels revealed that the incidence of SDOC (GCS ≤ 8; $P < 0.001$), in-hospital mortality ($P < 0.001$), and long-term mortality ($P < 0.001$) were gradually increased as ACAG levels. The prevalence of anemia, CHD, HF, and RF, as well as GLU, leukocytes, and various disease severity scores were significantly higher in the top ACAG levels than in the other groups (all $P < 0.001$) (Table 2).

Cox proportional hazard analysis

When ACAG was handled as a continuous variable, ACAG was significantly positively correlated with SDOC (model1 HR = 1.055; 95% CI: 1.035–1.077; model2 HR = 1.049; 95% CI: 1.027–1.071; model3 HR = 1.032; 95% CI: 1.012–1.053) and long-term mortality (model1 HR = 1.082; 95% CI: 1.070–1.096; model2 HR = 1.094; 95% CI: 1.080–1.109; model3 HR = 1.065; 95% CI; 1.044–1.087). These associations remained significant after inclusion of confounders (Table 3).

When ACAG was handled as a categorical variable, the incidence of SDOC and long-term mortality were significantly higher in the top ACAG quartile group compared to the lower quartile group, and the association remained significant after the inclusion of confounders (SDOC: model1 HR = 1.782, 95% CI: 1.339–2.372; model2 HR = 1.825; 95% CI: 1.273–2.618; model3 HR = 1.382; 95% CI: 1.129–1.692; Long-term mortality: model1 HR = 3.184, 95%CI: 2.603–3.896, model2 HR = 3.295; 95%CI: 2.676–4.058, model3 HR = 2.087, 95%CI: 1.637–2.660) (Table 3).

Kaplan–Meier survival curve analysis

Cumulative incidence curves of SDOC (GCS ≤ 8) and survival curves for in-hospital mortality and long-term mortality were plotted for each ACAG group. The results showed that the incidence of SDOC, in-hospital mortality, and long-term mortality were significantly different among the four ACAG groups ($P < 0.0001$) (Fig. 2).

Non-linear association between ACAG and outcomes

The RCS was plotted to explore the potential nonlinear relationship between ACAG and outcomes. The data showed that the increase in ACAG levels was approximately linearly proportional to SDOC and in-hospital mortality (nonlinear $P > 0.05$) and nonlinearly proportional to long-term mortality (nonlinear $P < 0.001$) (Fig. 3).

Subgroup analyses

Subgroup analysis of ACAG and SDOC indicated that age (≤ 70 years, > 70 years), DM (presence, absence), CKD (absence), and CHD (presence, absence) were significantly associated with SDOC ($P < 0.05$). The HR values were stable across different subgroups, with no interaction between ACAG and each subgroup (Fig. 4a).

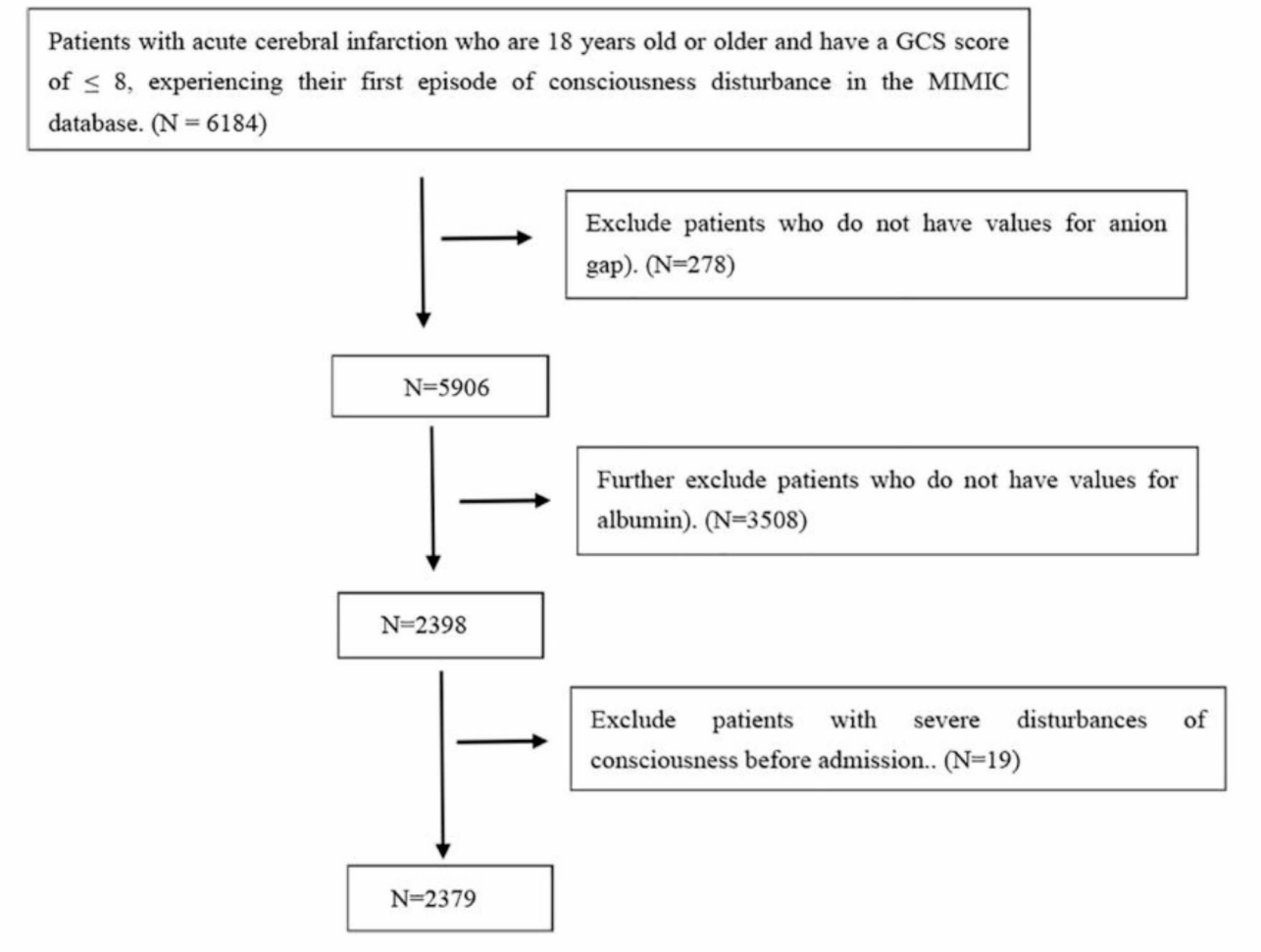

Fig. 1. Flow chart of patient selection.

Similarly, subgroup analysis of ACAG and in-hospital mortality revealed that age (≤70 years, >70 years), DM (presence, absence), CHD (presence, absence), and CKD (absence) were significantly associated with in-hospital mortality. The HR values remained stable across different subgroups, with no interaction between ACAG and each subgroup (Fig. 4b). Furthermore, subgroup analysis of ACAG and long-term mortality revealed that each subgroup was significantly associated with outcomes with stable HR values. Interaction was observed between the age and DM subgroups ($P < 0.05$) (Fig. 4c).

Discussion

This is a retrospective cohort study based on the IS population from the MIMIC-IV database. This is the first study to demonstrate that ACAG levels are associated with increased risk of SDOC and higher in-hospital and long-term mortality in patients with cerebral infarction. Our results also revealed that ACAG is approximately linearly associated with SDOC and in-hospital mortality but not with long-term mortality.

Although revascularization reduces mortality and disability in IS patients[16,17], IS remains an important cause of death and disability worldwide[18]. Therefore, early detection and early management are critical for the outcomes of high-risk patients. ACAG is a corrected form of AG that accounts for the effect of serum albumin levels on AG values[8]. ACAG holds potential clinical value for assessing the severity and outcomes of patients with trauma, sepsis, liver failure, and acute myocardial infarction, as it effectively reflects both hypoalbuminemia and metabolic acidosis[7,10,19,20]. Metabolic acidosis may exacerbate kidney injury by reducing renal blood flow and increasing the release of inflammatory mediators. Higher ACAG levels have been shown to be associated with an increased risk of acute renal failure in ICU patients[21]. ACAG is also an effective prognostic marker for patients with aneurysmal subarachnoid hemorrhage (aSAH). aSAH can cause acidosis through multiple mechanisms, including brain hypoxia, accumulation of acidic metabolites, and electrolyte disturbances such as hypokalemia and hypocalcemia[22]. ACAG has been proposed as a novel and reliable predictor for non-alcoholic fatty liver disease (NAFLD), especially in patients with central obesity. Previous study showed that ACAG may promote the development of NAFLD by contributing to lipotoxicity and glucotoxicity[23]. In IS patients, lactate may accumulate due to inadequate tissue perfusion and impaired aerobic metabolism, thereby increasing AG and ACAG levels[24].

Characteristic	Overal, $n = 2379$[1]	GCS > 8,$n = 1990$[1]	GCS ≤ 8,$n = 389$[1]	p-value[2]
Hospital mortality	275 (12%)	128 (6.4%)	147 (38%)	<0.001***
In-hospital follow-up time, days	6 [3–13]	5 [3–10]	16 [8–27]	<0.001***
Long-term mortality	845 (36%)	608 (31%)	237 (61%)	<0.001***
Long-term follow-up time, days	19 [4-187]	17 [4-206]	23 [9–82]	0.008**
Age, years	71 [59–81]	71 [60–81]	69 [58–82]	0.11
Gender				0.8
Female	1,175 (49%)	981 (49%)	194 (50%)	
Male	1,204 (51%)	1,009 (51%)	195 (50%)	
BMI, kg/m^2				<0.001***
Normal	302 (13%)	252 (13%)	50 (13%)	
Obese	649 (27%)	502 (25%)	147 (38%)	
Overweight	358 (15%)	303 (15%)	55 (14%)	
Underweight	29 (1.2%)	22 (1.1%)	7 (1.8%)	
Missing	1,041 (44%)	911 (46%)	130 (33%)	
Marital status				<0.001***
Divorced	162 (6.8%)	143 (7.2%)	19 (4.9%)	
Married	1,037 (44%)	894 (45%)	143 (37%)	
Single	594 (25%)	498 (25%)	96 (25%)	
Widowed	345 (15%)	294 (15%)	51 (13%)	
Missing	241 (10%)	161 (8.1%)	80 (21%)	
Race				<0.001***
Asian	65 (2.7%)	54 (2.7%)	11 (2.8%)	
Black	317 (13%)	273 (14%)	44 (11%)	
Other	472 (20%)	352 (18%)	120 (31%)	
White	1,525 (64%)	1,311 (66%)	214 (55%)	
ALB, g/dl	3.70 [3.30-4.00]	3.70 [3.30-4.00]	3.30 [2.80–3.80]	<0.001***
ALT, iu/l	20 [14–33]	19 [13–31]	28 [17–54]	<0.001***
AST, iu/L	24 [18–40]	23 [18–35]	39 [24–85]	<0.001***
BUN, mg/dl	18 [13–25]	17 [13–24]	20 [14–31]	<0.001***
CK, iu/l				<0.001***
<47	214 (9.0%)	185 (9.3%)	29 (7.5%)	
47–322	896 (38%)	772 (39%)	124 (32%)	
>322	256 (11%)	167 (8.4%)	89 (23%)	
Missing	1,013 (43%)	866 (44%)	147 (38%)	
CKMB, ng/mL				<0.001***
<3.0	468 (20%)	421 (21%)	47 (12%)	
3.0–10.0	630 (26%)	522 (26%)	108 (28%)	
>10.0	165 (6.9%)	91 (4.6%)	74 (19%)	
Missing	1,116 (47%)	956 (48%)	160 (41%)	
Chloride, mEq/L	103 [100–106]	103 [100–106]	104 [100–108]	<0.001***
SCR, mg/dL	0.90 [0.70–1.20]	0.90 [0.70–1.20]	1.10 [0.70–1.50]	<0.001***
GLU, mg/dL	114 [96–150]	111 [95–141]	135 [107–186]	<0.001***
HB, g/dL	12.20 [10.55–13.60]	12.30 [10.70–13.70]	11.50 [10.00-12.90]	<0.001***
HBA1C,%				<0.001***
<6.5	1,199 (50%)	1,076 (54%)	123 (32%)	≥
≥6.5	429 (18%)	376 (19%)	53 (14%)	
Missing	751 (32%)	538 (27%)	213 (55%)	
HCO3,mEq/L	24 [22–26]	25 [22–27]	23 [19–25]	<0.001***
Potassium, mEq/L	4.00 [3.80–4.40]	4.00 [3.80–4.40]	4.00 [3.70–4.50]	0.4
Lymphocyte, k/uL				0.020*
<1.2	262 (11%)	207 (10%)	55 (14%)	
1.2–1.7	157 (6.6%)	133 (6.7%)	24 (6.2%)	
>1.7	205 (8.6%)	184 (9.2%)	21 (5.4%)	
Missing	1,755 (74%)	1,466 (74%)	289 (74%)	
Sodium, mEq/L	140 [137–142]	140 [137–142]	139 [137–142]	0.8
Continued				

Characteristic	Overal, $n = 2379$[1]	GCS > 8,$n = 1990$[1]	GCS ≤ 8,$n = 389$[1]	p-value[2]
Neutrophil, k/uL				<0.001***
<1.6	22 (0.9%)	19 (1.0%)	3 (0.8%)	
1.6–6.1	249 (10%)	228 (11%)	21 (5.4%)	
6.1–8.6	145 (6.1%)	123 (6.2%)	22 (5.7%)	
>8.6	208 (8.7%)	154 (7.7%)	54 (14%)	
Missing	1,755 (74%)	1,466 (74%)	289 (74%)	
Platelet, k/uL	212 [165–268]	216 [168–269]	198 [144–264]	<0.001***
TBIL, mg/dL	0.56 [0.40–0.80]	0.50 [0.40–0.80]	0.60 [0.40-1.00]	<0.001***
TC, mg/dL				<0.001***
<144	516 (22%)	455 (23%)	61 (16%)	
144–199	692 (29%)	637 (32%)	55 (14%)	
>199	378 (16%)	356 (18%)	22 (5.7%)	
Missing	793 (33%)	542 (27%)	251 (65%)	
TG, mg/dL				<0.001***
<87	522 (22%)	469 (24%)	53 (14%)	
87–149	672 (28%)	626 (31%)	46 (12%)	
>149	424 (18%)	367 (18%)	57 (15%)	
Missing	761 (32%)	528 (27%)	233 (60%)	
WBC, k/uL	8.6 [6.5–11.6]	8.3 [6.4–11.1]	10.6 [7.7–15.5]	<0.001***
AF	481 (20%)	368 (18%)	113 (29%)	<0.001***
Alcohol use	47 (2.0%)	37 (1.9%)	10 (2.6%)	0.4
Anemia	613 (26%)	443 (22%)	170 (44%)	<0.001***
Cancer	264 (11%)	226 (11%)	38 (9.8%)	0.4
CHD	697 (29%)	552 (28%)	145 (37%)	<0.001***
CKD	212 (8.9%)	167 (8.4%)	45 (12%)	0.044*
DM	804 (34%)	668 (34%)	136 (35%)	0.6
HF	504 (21%)	385 (19%)	119 (31%)	<0.001***
HBP	1,270 (53%)	1,084 (54%)	186 (48%)	0.016*
HL	687 (29%)	601 (30%)	86 (22%)	0.001**
RF	421 (18%)	202 (10%)	219 (56%)	<0.001***
Tobacco use	164 (6.9%)	132 (6.6%)	32 (8.2%)	0.3
Anticoagulant drugs	2,047 (86%)	1,784 (90%)	263 (68%)	<0.001***
Antiplatelet drugs	1,649 (69%)	1,480 (74%)	169 (43%)	<0.001***
APSIII				<0.001***
<39	658 (28%)	562 (28%)	96 (25%)	
≥39	672 (28%)	379 (19%)	293 (75%)	
Missing	1,049 (44%)	1,049 (53%)	0 (0%)	
SOFA				<0.001***
<1	579 (24%)	450 (23%)	129 (33%)	
≥1	726 (31%)	490 (25%)	236 (61%)	
Missing	1,074 (45%)	1,050 (53%)	24 (6.2%)	
OASIS				<0.001***
<31	616 (26%)	524 (26%)	92 (24%)	
≥31	714 (30%)	417 (21%)	297 (76%)	
Missing	1,049 (44%)	1,049 (53%)	0 (0%)	
SAPSII				<0.001***
<33	589 (25%)	521 (26%)	68 (17%)	
≥33	605 (25%)	406 (20%)	199 (51%)	
Missing	1,185 (50%)	1,063 (53%)	122 (31%)	
AG, mEq/L	15.9 [13.5–18.2]	15.8 [13.4–18.0]	16.4 [13.9–19.1]	<0.001***
ACAG, mEq/L	17.9 [15.3–20.2]	17.7 [15.2–19.9]	19.1 [16.2–22.3]	<0.001***
ACAG quartiles				<0.001***
Q1	601 (25%)	533 (27%)	68 (17%)	
Q2	605 (25%)	524 (26%)	81 (21%)	
Q3	578 (24%)	498 (25%)	80 (21%)	
Q4	595 (25%)	435 (22%)	160 (41%)	

Table 1. Baseline characteristics of the GCS > 8 and GCS ≤ 8 groups. BMI (body mass index), ALB(album), ALT(alanine aminotransferase), AST(aspartate aminotransferase), BUN (blood urea nitrogen), CK(creatine kinase), CKMB(creatine kinase lsoenzyme MB), SCR (serum creatinine), GLU(glucose), HB(hemoglobin), HbA1c (hemoglobin a1c), TBIL(Total Bilirubin), TC (total cholesterol), TG (triglyceride), WBC((white blood cell), AF(Atrial Fibrillation), CHD(coronary heart disease), CKD(chronic kidney disease), DM(diabetes, HF(heart failure), HBP(high blood pressure), HL(hyperlipidemia), RF(respiratory failure), APSIII (acute physiology score III), SOFA (sequential organ failure assessment), OASIS, SAPSII(simplified acute physiological score II), AG(anion gap), ACAG(Albumin Corrected Anion Gap). [1]n (%); Median [25-75%].[2]*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Characteristic	Overall $N = 2,379$[1]	Q1 $N = 601$[1]	Q2 $N = 605$[1]	Q3 $N = 578$[1]	Q4 $N = 595$[1]	p-value[2]
Hospital mortality	275 (12%)	39 (6.5%)	45 (7.4%)	63 (11%)	128 (22%)	<0.001***
In-hospital follow-up time, days	6 [3–13]	5 [3–9]	5 [3–11]	7 [3–12]	9 [5–18]	<0.001***
Long-term mortality	845 (36%)	153 (25%)	181 (30%)	206 (36%)	305 (51%)	<0.001***
Long-term follow-up time, days	19 [4-187]	19 [3-433]	21 [4-259]	15 [5-121]	20 [6–97]	0.3
GCS ≤ 8	389 (16%)	68 (11%)	81 (13%)	80 (14%)	160 (27%)	<0.001***
Follow-up time for gcs ≤ 8,days	5 [3–10]	4 [2–7]	4 [3–8]	6 [3–10]	6 [3–14]	<0.001***
Age, years	71 [59–81]	70 [58–80]	70 [60–81]	72 [61–81]	71 [60–83]	0.14
Gender						0.7
Female	1,175 (49%)	285 (47%)	299 (49%)	295 (51%)	296 (50%)	
Male	1,204 (51%)	316 (53%)	306 (51%)	283 (49%)	299 (50%)	
BMI, k/m^2						<0.001***
Normal	302 (13%)	50 (8.3%)	65 (11%)	103 (18%)	84 (14%)	
Obese	649 (27%)	136 (23%)	174 (29%)	157 (27%)	182 (31%)	
Overweight	358 (15%)	73 (12%)	82 (14%)	97 (17%)	106 (18%)	
Underweight	29 (1.2%)	4 (0.7%)	6 (1.0%)	8 (1.4%)	11 (1.8%)	
Missing	1,041 (44%)	338 (56%)	278 (46%)	213 (37%)	212 (36%)	
Marital status						<0.001***
Divorced	162 (6.8%)	43 (7.2%)	37 (6.1%)	35 (6.1%)	47 (7.9%)	
Married	1,037 (44%)	296 (49%)	278 (46%)	251 (43%)	212 (36%)	
Single	594 (25%)	144 (24%)	153 (25%)	147 (25%)	150 (25%)	
Widowed	345 (15%)	88 (15%)	92 (15%)	77 (13%)	88 (15%)	
Missing	241 (10%)	30 (5.0%)	45 (7.4%)	68 (12%)	98 (16%)	
Race						<0.001***
Asian	65 (2.7%)	12 (2.0%)	18 (3.0%)	16 (2.8%)	19 (3.2%)	
Black	317 (13%)	75 (12%)	77 (13%)	88 (15%)	77 (13%)	
Other	472 (20%)	81 (13%)	118 (20%)	122 (21%)	151 (25%)	
White	1,525 (64%)	433 (72%)	392 (65%)	352 (61%)	348 (58%)	
ALB, g/dl	3.70 [3.30-4.00]	3.90 [3.60–4.20]	3.80 [3.40-4.00]	3.65 [3.23-4.00]	3.30 [2.80–3.80]	<0.001***
ALT, iu/l	20 [14–33]	20 [14–30]	19 [14–30]	19 [13–32]	23 [14–49]	<0.001***
AST, iu/L	24 [18–40]	23 [18–33]	23 [18–35]	24 [18–38]	33 [20–70]	<0.001***
BUN, mg/dl	18 [13–25]	16 [12–21]	17 [12–23]	17 [13–24]	23 [16–40]	<0.001***
CK, iu/l						<0.001***
<47	214 (9.0%)	41 (6.8%)	58 (9.6%)	64 (11%)	51 (8.6%)	
47–322	896 (38%)	232 (39%)	245 (40%)	228 (39%)	191 (32%)	
>322	256 (11%)	38 (6.3%)	56 (9.3%)	50 (8.7%)	112 (19%)	
Missing	1,013 (43%)	290 (48%)	246 (41%)	236 (41%)	241 (41%)	
CKMB, ng/mL						<0.001***
<3.0	468 (20%)	114 (19%)	135 (22%)	129 (22%)	90 (15%)	
3.0–10.0	630 (26%)	161 (27%)	169 (28%)	136 (24%)	164 (28%)	
>10.0	165 (6.9%)	16 (2.7%)	30 (5.0%)	33 (5.7%)	86 (14%)	
Missing	1,116 (47%)	310 (52%)	271 (45%)	280 (48%)	255 (43%)	
Chloride, mEq/L	103 [100–106]	105 [102–107]	104 [101–106]	103 [100–106]	102 [98–105]	<0.001***
SCR, mg/dL	0.90 [0.70–1.20]	0.90 [0.70–1.10]	0.90 [0.70–1.10]	0.90 [0.70–1.20]	1.20 [0.80–1.90]	<0.001***
GLU, mg/dL	114 [96–150]	105 [94–128]	112 [96–142]	117 [97–150]	129 [99–187]	<0.001***

Characteristic	Overall $N=2,379$[1]	Q1 $N=601$[1]	Q2 $N=605$[1]	Q3 $N=578$[1]	Q4 $N=595$[1]	p-value[2]
HB, g/dL	12.20 [10.55–13.60]	12.70 [11.30–13.90]	12.30 [10.80–13.60]	12.10 [10.60–13.40]	11.20 [9.40–13.20]	<0.001***
HBA1C,%						<0.001***
<6.5	1,199 (50%)	363 (60%)	316 (52%)	296 (51%)	224 (38%)	
≥6.5	429 (18%)	91 (15%)	113 (19%)	119 (21%)	106 (18%)	
Missing	751 (32%)	147 (24%)	176 (29%)	163 (28%)	265 (45%)	
HCO3,mEq/L	24 [22–26]	27 [25–28]	25 [23–26]	24 [22–26]	21 [19–24]	<0.001***
Potassium, mEq/L	4.00 [3.80–4.40]	4.00 [3.70–4.20]	4.00 [3.70–4.30]	4.10 [3.80–4.40]	4.30 [3.80–4.70]	<0.001***
Lymphocyte, k/uL						<0.001***
<1.2	262 (11%)	12 (2.0%)	39 (6.4%)	67 (12%)	144 (24%)	
1.2–1.7	157 (6.6%)	14 (2.3%)	41 (6.8%)	48 (8.3%)	54 (9.1%)	
Continued						
>1.7	205 (8.6%)	19 (3.2%)	51 (8.4%)	79 (14%)	56 (9.4%)	
Missing	1,755 (74%)	556 (93%)	474 (78%)	384 (66%)	341 (57%)	
Sodium, mEq/L	140 [137–142]	140 [138–141]	139 [137–141]	140 [137–142]	139 [137–142]	0.5
Neutrophil, k/uL						<0.001***
<1.6	22 (0.9%)	7 (1.2%)	3 (0.5%)	7 (1.2%)	5 (0.8%)	
1.6–6.1	249 (10%)	23 (3.8%)	66 (11%)	83 (14%)	77 (13%)	
6.1–8.6	145 (6.1%)	12 (2.0%)	37 (6.1%)	50 (8.7%)	46 (7.7%)	
>8.6	208 (8.7%)	3 (0.5%)	25 (4.1%)	54 (9.3%)	126 (21%)	
Missing	1,755 (74%)	556 (93%)	474 (78%)	384 (66%)	341 (57%)	
Platelet, k/uL	212 [165–268]	215 [175–265]	212 [166–268]	211 [164–268]	211 [154–275]	0.4
TBIL, mg/dL	0.56 [0.40–0.80]	0.50 [0.40–0.70]	0.60 [0.40–0.80]	0.58 [0.40–0.80]	0.60 [0.40-1.00]	0.010**
TC, mg/dL						<0.001***
<144	516 (22%)	120 (20%)	131 (22%)	136 (24%)	129 (22%)	
144–199	692 (29%)	211 (35%)	204 (34%)	151 (26%)	126 (21%)	
>199	378 (16%)	120 (20%)	92 (15%)	107 (19%)	59 (9.9%)	
Missing	793 (33%)	150 (25%)	178 (29%)	184 (32%)	281 (47%)	
TG, mg/dL						<0.001***
<87	522 (22%)	153 (25%)	147 (24%)	130 (22%)	92 (15%)	
87–149	672 (28%)	192 (32%)	181 (30%)	159 (28%)	140 (24%)	
>149	424 (18%)	102 (17%)	109 (18%)	110 (19%)	103 (17%)	
Missing	761 (32%)	154 (26%)	168 (28%)	179 (31%)	260 (44%)	
WBC, k/uL	8.6 [6.5–11.6]	7.5 [5.9–9.8]	8.3 [6.4–10.8]	9.0 [6.9–12.1]	10.6 [7.5–14.9]	<0.001***
AF	481 (20%)	135 (22%)	139 (23%)	96 (17%)	111 (19%)	0.016*
Alcohol use	47 (2.0%)	13 (2.2%)	18 (3.0%)	11 (1.9%)	5 (0.8%)	0.066
Anemia	613 (26%)	104 (17%)	123 (20%)	145 (25%)	241 (41%)	<0.001***
Cancer	264 (11%)	49 (8.2%)	60 (9.9%)	75 (13%)	80 (13%)	0.009**
CHD	697 (29%)	155 (26%)	149 (25%)	162 (28%)	231 (39%)	<0.001***
CKD	212 (8.9%)	56 (9.3%)	57 (9.4%)	49 (8.5%)	50 (8.4%)	0.9
DM	804 (34%)	146 (24%)	194 (32%)	213 (37%)	251 (42%)	<0.001***
HF	504 (21%)	81 (13%)	105 (17%)	122 (21%)	196 (33%)	<0.001***
HBP	1,270 (53%)	359 (60%)	357 (59%)	305 (53%)	249 (42%)	<0.001***
HL	687 (29%)	271 (45%)	200 (33%)	116 (20%)	100 (17%)	<0.001***
RF	421 (18%)	61 (10%)	74 (12%)	90 (16%)	196 (33%)	<0.001***
Tobacco use	164 (6.9%)	70 (12%)	46 (7.6%)	23 (4.0%)	25 (4.2%)	<0.001***
Anticoagulant drugs	2,047 (86%)	498 (83%)	530 (88%)	522 (90%)	497 (84%)	<0.001***
Antiplatelet drugs	1,649 (69%)	411 (68%)	440 (73%)	414 (72%)	384 (65%)	0.010**
apsiii						<0.001***
<39	658 (28%)	147 (24%)	180 (30%)	198 (34%)	133 (22%)	
≥39	672 (28%)	91 (15%)	120 (20%)	158 (27%)	303 (51%)	
Missing	1,049 (44%)	363 (60%)	305 (50%)	222 (38%)	159 (27%)	
sofa_24hours						<0.001***
<1	579 (24%)	117 (19%)	144 (24%)	153 (26%)	165 (28%)	
≥1	726 (31%)	111 (18%)	153 (25%)	197 (34%)	265 (45%)	
Missing	1,074 (45%)	373 (62%)	308 (51%)	228 (39%)	165 (28%)	

Characteristic	Overall $N=2,379$[1]	Q1 $N=601$[1]	Q2 $N=605$[1]	Q3 $N=578$[1]	Q4 $N=595$[1]	p-value[2]
oasis						<0.001***
<31	616 (26%)	133 (22%)	171 (28%)	174 (30%)	138 (23%)	
≥31	714 (30%)	105 (17%)	129 (21%)	182 (31%)	298 (50%)	
Missing	1,049 (44%)	363 (60%)	305 (50%)	222 (38%)	159 (27%)	
sapsii						<0.001***
<33	589 (25%)	129 (21%)	170 (28%)	178 (31%)	112 (19%)	
≥33	605 (25%)	83 (14%)	101 (17%)	144 (25%)	277 (47%)	
Missing	1,185 (50%)	389 (65%)	334 (55%)	256 (44%)	206 (35%)	
AG, mEq/L	15.9 [13.5–18.2]	12.3 [11.4–13.3]	14.9 [14.0-15.9]	17.1 [16.1–18.0]	20.1 [18.5–21.7]	<0.001***
ACAG, mEq/L	17.9 [15.3–20.2]	13.9 [12.8–14.6]	16.7 [16.0-17.4]	19.0 [18.4–19.6]	22.3 [21.2–24.5]	<0.001***

Table 2. Baseline characteristics according to ACAG index quartiles. BMI (body mass index), ALB(album), ALT(alanine aminotransferase), AST(aspartate aminotransferas), BUN (blood urea nitrogen), CK(creatine kinase), CKMB(creatine kinase lsoenzyme MB), SCR (serum creatinine), GLU(glucose), HB(hemoglobin), HbA1c (hemoglobin a1c), TBIL(Total Bilirubin), TC (total cholesterol), TG (triglyceride), WBC((white blood cell), AF(Atrial Fibrillation), CHD(coronary heart disease), CKD(chronic kidney disease), DM(diabetes, HF(heart failure), HBP(high blood pressure), HL(hyperlipidemia), RF(respiratory failure), APSIII (acute physiology score III), SOFA (sequential organ failure assessment), OASIS, SAPSII(simplified acute physiological score II), AG(anion gap), ACAG(Albumin Corrected Anion Gap). [1]n (%); Median [25-75%].[2]*$p<0.05$; **$p<0.01$; ***$p<0.001$. [a]ACAG index: Q1:<15.300; Q2: 15.300–17.850; Q3: 17.850–20.175; Q4: >20.175.

Outcomes	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
GCS < = 8						
ACAG	1.055(1.035, 1.077)	<0.001	1.049(1.027, 1.071)	<0.001	1.032(1.012, 1.053)	0.002
ACAG Quartile[a]	p for trend < 0.001		p for trend = 0.004		p for trend = 0.048	
Q1, $N=601$	Ref		Ref		Ref	
Q2, $N=605$	1.07(0.775, 1.478)	0.7	0.87(0.564, 1.341)	0.002	1.046(0.819, 1.337)	0.7
Q3, $N=578$	1.015(0.734, 1.403)	>0.9	1.257(0.843, 1.875)	<0.001	0.958(0.749, 1.226)	0.7
Q4, $N=595$	1.782(1.339, 2.372)	<0.001	1.825(1.273, 2.618)	<0.001	1.382(1.129, 1.692)	0.002
In-hospital mortality						
ACAG	1.047(1.026, 1.069)	<0.001	1.05(1.026, 1.074)	<0.001	1.03(0.997, 1.064)	0.071
ACAG Quartile[a]	p for trend < 0.001		p for trend = 0.004		p for trend = 0.042	
Q1, $N=601$	Ref		Ref		Ref	
Q2, $N=605$	0.87(0.564, 1.341)	0.5	0.834(0.541, 1.288)	0.4	0.924(0.591, 1.445)	0.7
Q3, $N=578$	1.257(0.843, 1.875)	0.3	1.131(0.756, 1.691)	0.6	1.291(0.836, 1.996)	0.2
Q4, $N=595$	1.825(1.273, 2.618)	0.001	1.603(1.114, 2.308)	0.011	1.437(0.940, 2.197)	0.094
long-term mortality						
ACAG	1.082(1.070, 1.096)	<0.001	1.094(1.080, 1.109)	<0.001	1.065(1.044, 1.087)	<0.001
ACAG Quartile[a]	p for trend < 0.001		p for trend < 0.001		p for trend < 0.001	
Q1, $N=601$	Ref		Ref		Ref	
Q2, $N=605$	1.423(1.144, 1.770)	0.002	1.474(1.182, 1.839)	<0.001	1.451(1.156, 1.821)	0.001
Q3, $N=578$	2.101(1.697, 2.602)	<0.001	2.07(1.663, 2.575)	<0.001	1.967(1.555, 2.489)	<0.001
Q4, $N=595$	3.184(2.603, 3.896)	<0.001	3.295(2.676, 4.058)	<0.001	2.087(1.637, 2.660)	<0.001

Table 3. Cox proportional hazard ratios (HR). Model 1 was unadjusted. Model 2 was adjusted for gender, age, race, BMI. Model 3 was adjusted for the variables in model 2 and further adjusted for Marital status, ALT, CK, CKMB, SCR, GLU, HB, HBA1C, Neutrophil, Platelet, TC, WBC, AF, Alcohol use, Anemia, Cancer, CHD, CKD, DM, HF, HBP, HL, RF, Tobacco use, Anticoagulant drugs, Antiplatelet drugs, APSIII, SAPS II. [a]ACAG Quartile: Q1:<15.300; Q2: 15.300–17.850; Q3: 17.850–20.175; Q4: >20.175. HR(Hazard Ratio), CI (Confidence Interval).

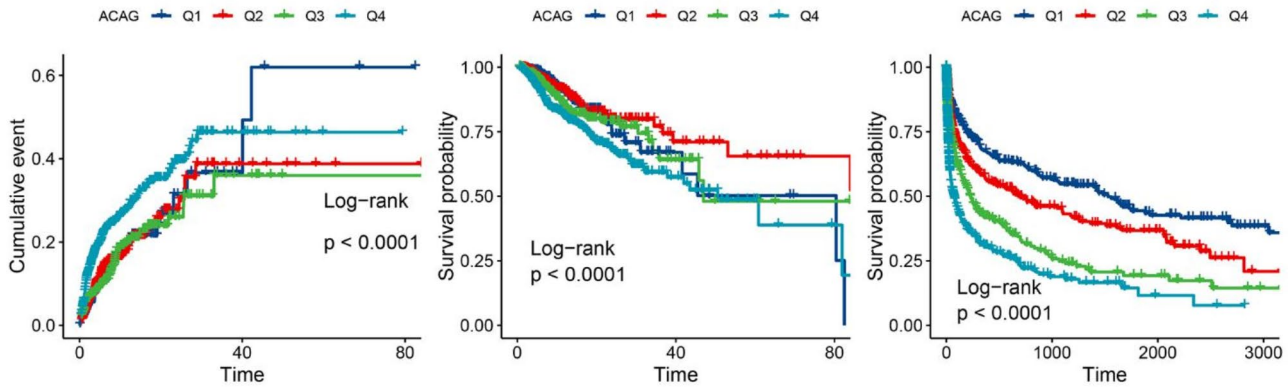

Fig. 2. Cumulative event and survival incidence curves (ACAG index: Q1:<15.300; Q2: 15.300–17.850; Q3: 17.850–20.175; Q4: >20.175). a: Cumulative event incidence curves for incidence of SDOC (GCS ≤ 8). b: Survival curve for the in-hospital mortality of the entire study population. c: Survival curves for the long-term mortality of the entire study population.

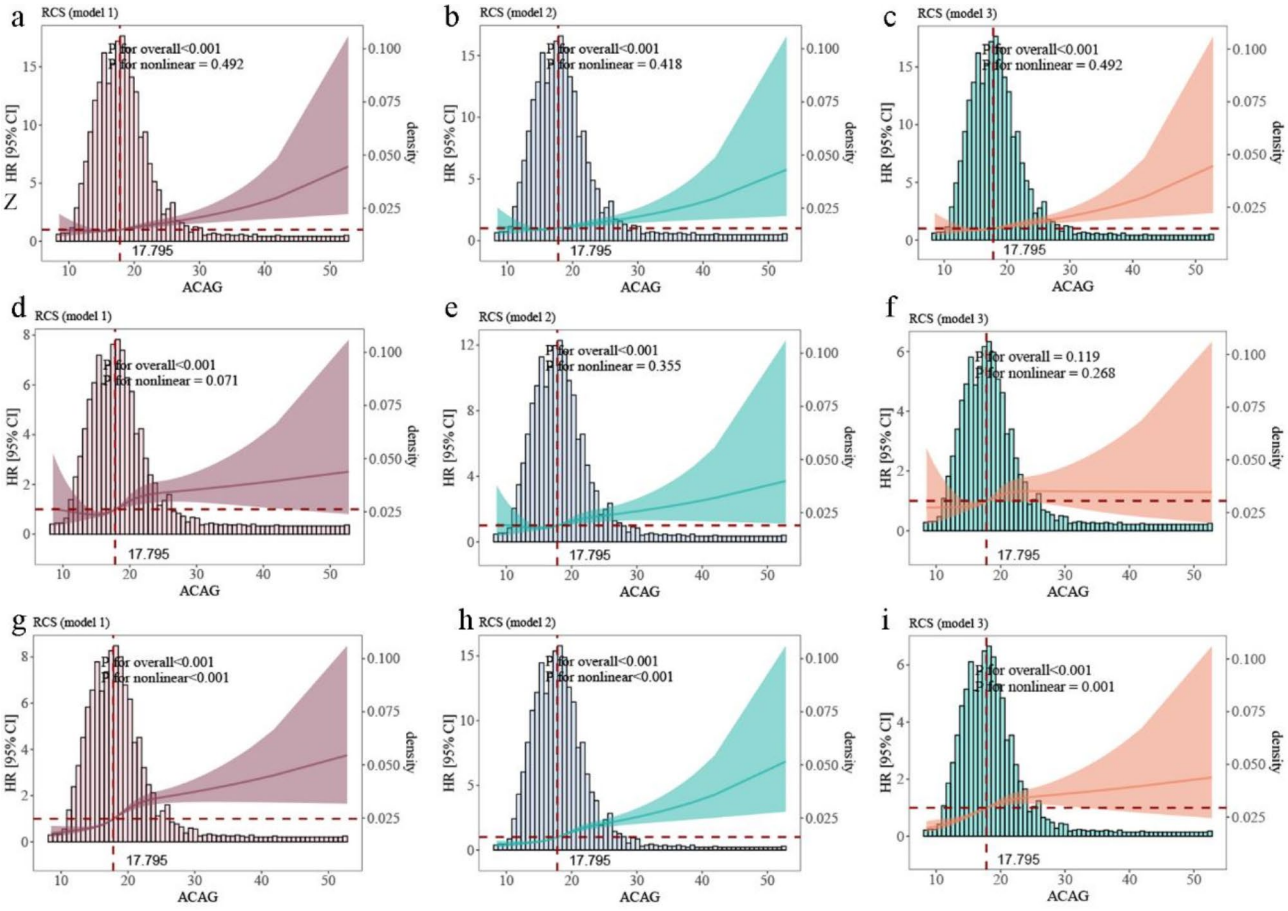

Fig. 3. RCS curves for the HR and distribution of ACAG index. (**a**–**c**) SDOC (GCS ≤ 8) cumulative incidence curves for Model 1, Model 2, and Model 3. (**d**–**f**) In-hospital mortality survival curves and histograms for Model 1, Model 2, and Model 3. (**g**–**i**) Long-term mortality survival curves and histograms for Model 1, Model 2, and Model 3. Model 1 was unadjusted. Model 2 was adjusted for gender, age, race, and BMI. Model 3 was adjusted for the variables in model 2 and further adjusted for marital status, ALT, CK, CKMB, Chloride, SCR, GLU, HB, HBA1C, Neutrophil, Platelet, TC, WBC, AF, Alcohol use, Anemia, Cancer, CHD, CKD, DM, HF, HBP, HL, RF, Tobacco use, Anticoagulant drugs, Antiplatelet drugs, APSIII, and SAPS II.

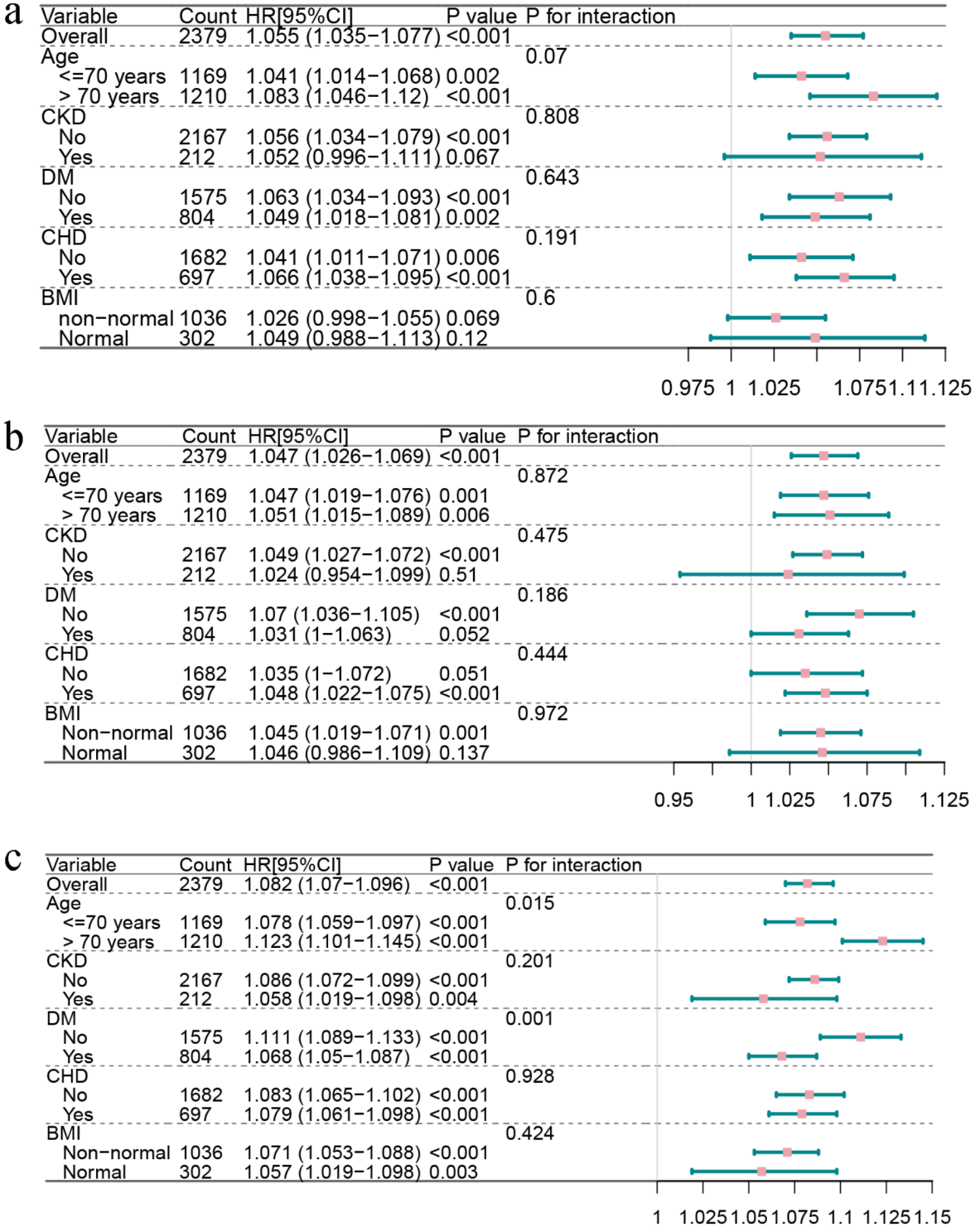

Fig. 4. Forest plots. (**a**) forest plot of HRs for SDOC in different subgroups. (**b**) forest plot of HRs for in-hospital mortality in different subgroups. (**c**) forest plots of HRs for long-term mortality in different subgroups. CKD (chronic kidney disease), BMI (body mass index), DM (diabetes mellitus), CHD (coronary heart disease), CI (confidence interval), HR (hazard ratio).

DOC is prevalent in acute IS (AIS) patients and strongly associated with poor clinical outcomes. Patients with DOC exhibit higher in-hospital mortality, are less likely to go home or engage in rehabilitation, and are less likely to walk independently at discharge[3]. In addition, DOC has been found to be useful in predicting short-term (28-day) mortality in AIS patients[25]. Patients with cardiovascular diseases admitted to the intensive care unit (ICU) are more likely to develop SDOC and more complex conditions, as well as experience higher mortality rates[26].

Studies have shown that the triglyceride glucose index and glycemic variability can predict the occurrence of DOC in cerebrovascular diseases. However, blood glucose is greatly affected by diet, and the frequency and timing of blood glucose measurement may vary from patient to patient, which consequently affect the assessment of blood glucose[4,27]. There are currently very limited data on the relationship between ACAG and the occurrence and prognosis of DOC in IS. In this study, the incidence of SDOC was 16.4% in IS patients, and the in-hospital mortality and long-term mortality were 38% and up to 61% in IS patients with SDOC, respectively. We found that the SDOC group had higher ACAG values than the non-SDOC group (19.1 [16.2–22.3] vs. 17.7 [15.2–19.9]). Moreover, the top ACAG quartile group had significantly higher risks of SDOC, in-hospital mortality, and long-term mortality compared to the lower quartile group. Collectively, these findings indicate that ACAG monitoring is favorable for the early detection and management of SDOC and for reducing mortality in IS patients.

This study proposes ACAG as a potential predictor for SDOC, in-hospital mortality, and long-term death in ischemic stroke. However, several limitations should be noted. First, despite an optimized study design, this study could not identify a definite causality between the parameters, thus warranting a large-cohort prospective study. Second, the database was sourced from the United States, where the majority of the population is white, limiting the generalizability of the data to other populations. Last, due to limitations in the database, imaging data, family history, and long-term use of antihypertensives may affect the outcomes of DOC.

Conclusion

ACAG is an important predictor for SDOC and outcomes of IS patients. Although ACAG is a promising novel risk stratification tool, its effectiveness and generalizability need to be further confirmed by subsequent prospective studies.

Data availability

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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Author contributions
All authors contributed to the study conception and design. Writing - original draft preparation: Ying Chen; Writing - review and editing: Lan Chu; Conceptualization: Ying Chen; Methodology: Ying Chen; Formal analysis and investigation: MingYao, You; Resources: Lan Chu; Supervision: MingYao, You, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
The data used in this study originated from The Medical Information Mart for Intensive Care-IV (MIMIC-IV) 2.2 database developed by the Laboratory for Computational Physiology of Massachusetts Institute of Technology. Patient identifiers have been removed to protect their privacy, and therefore, patient consent and ethical approval were not required.All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Additional information
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