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Impact of admission-blood-glucose-to-albumin ratio on all-cause mortality and renal prognosis in critical patients with coronary artery disease: insights from the MIMIC-IV database

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ABSTRACT

BACKGROUND Blood glucose and serum albumin have been associated with cardiovascular disease prognosis, but the impact of admission-blood-glucose-to-albumin ratio (AAR) on adverse outcomes in critical ill coronary artery disease (CAD) patients was not investigated.

METHODS Patients diagnosed with CAD were non-consecutively selected from the MIMIC-IV database and categorized into quartiles based on their AAR. The primary outcome was 1-year mortality, and secondary endpoints were in-hospital mortality, acute kidney injury (AKI), and renal replacement therapy (RRT). A restricted cubic splines model and Cox proportional hazard models assessed the association between AAR and adverse outcomes in CAD patients. Kaplan-Meier survival analysis determined differences in endpoints across subgroups.

RESULTS A total of 8360 patients were included. There were 726 patients (8.7%) died in the hospital and 1944 patients (23%) died at 1 year. The incidence of AKI and RRT was 63% and 4.3%, respectively. High AAR was markedly associated with in-hospital mortality (HR = 1.587, $P = 0.003$), 1-year mortality (HR = 1.502, $P < 0.001$), AKI incidence (HR = 1.579, $P < 0.001$), and RRT (HR = 1.640, $P < 0.016$) in CAD patients in the completely adjusted Cox proportional hazard model. Kaplan-Meier survival analysis noted substantial differences in all endpoints based on AAR quartiles. Stratified analysis and interaction test demonstrated stable correlations between AAR and outcomes.

CONCLUSIONS The results highlight that AAR may be a potential indicator for assessing in-hospital mortality, 1-year mortality, and adverse renal prognosis in critical CAD patients.

Coronary artery disease (CAD) continues to be the primary contributor to morbidity and mortality on a global scale, despite the widespread utilization of coronary revascularization procedures and optimal medication therapies.[1,2]

Previous research has established a link between glycemic abnormalities and unfavorable cardiovascular outcomes in CAD patients, particularly in those with hyperglycemia.[3,4] Hyperglycemia could result in endothelial dysfunction, overproduction of inflammatory mediators, and oxidative stress, thus accelerating atherosclerotic progression.[5–8] Furthermore, hyperglycemia could also elevate the cardiovascular risk by impairing cardiovascular neuroendocrine and cellular metabolism.[9]

Albumin, the most abundant circulatory protein, participates in metabolite transport, antioxidative activities, me-

tabolic and vascular functions, and anticoagulant effects.[10] These physiological functions of albumin are more vital in critically ill patients.[11,12] Additionally, the decrease in plasma albumin levels directly correlates with systematic inflammation and poor nutritional status. Hypoalbuminemia amplifies systemic vulnerability by impairing anti-inflammatory, antioxidant, and anticoagulant functions. Albumin deficiency elevates acute-phase reactants, reduces heparin-like anticoagulant activity, and promotes platelet aggregation, fostering a prothrombotic state.[13,14] Extensive research has demonstrated low albumin is a recognized risk factor for cardiovascular disease. Acute kidney injury (AKI) is a prevalent complication of CAD patients. AKI incidence in acute myocardial infarction (AMI) patients ranges from 5.2% to 59%.[15] Previous articles have identified that hyperglycemia on admission and serum albumin serve as useful prognostic indicators for mortality and AKI in AMI patients.[16–21] The potential mechanisms between hyperglycemia, serum albumin, and AKI may involve endothelial dysfunction, oxidative stress, and inflammation, similar to those of CAD.[18,19,22–26]

Admission-blood-glucose-to-albumin ratio (AAR), combining the pathophysiology function of blood glucose and albumin, demonstrates a strong correlation with in-hospital mortality and major adverse cardiac events (MACEs) in AMI patients with ST-segment elevation myocardial infarction.[27] However, there remains a dearth of evidence regarding the correlation between AAR and the mortality and renal prognosis of CAD patients in critical status. Thereby, this retrospective cohort study was conducted to illustrate the predictive role of AAR in in-hospital and 1-year mortality, AKI, and renal replacement therapy (RRT) in critically ill CAD patients.

METHODS

Data Source

This was a retrospective observational study, with the data obtained from the publicly available Medical Information Mart for Intensive Care IV (MIMIC-IV) database (https://mimic.mit.edu). The database encompasses clinical data of more than 190,000 distinct patient admissions at Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA) from 2008 to 2019.[28] To access this database, author Yong HONG completed the National Institutes of Health training program on the protection of human research participants, obtained Collaborative Institutional Training Initiative certification, and secured the necessary permissions to utilize the MIMIC-IV database.

Study Population

19,344 patients non-consecutively admitted to the intensive care unit (ICU) and diagnosed with CAD by the International Classification of Diseases (ICD)-9 codes (410.xx–414.xx) and the ICD-10 codes (I20.x–I22.x, and I25.x) were retrospectively selected from the MIMIC-IV database. For patients with multiple ICU admissions, only data from the initial hospitalization were analyzed. To maintain data integrity, individuals under the age of 18 years (n = 0), without AKI data within 48 h of ICU admission (n = 12), and missing documentation on glucose (n = 1454) and albumin levels (n = 9518) were excluded. Subsequently, 8360 patients were enrolled and stratified into four cohorts based on the quartiles of AAR measured on the initial day of their ICU admission. The flowchart of patient inclusion is displayed in supplemental material, Figure 1S.

Study Endpoints

The primary endpoint was 1-year mortality, and secondary endpoints included in-hospital mortality, AKI incidence, and requirement for RRT. Death information came from state or hospital death records. All patients were followed up for at least 1 year. AKI was defined under the Kidney Disease: Improving Global Outcomes guidelines, including a rise in serum creatinine (SCr) to ≥ 1.5 times the baseline value within the prior 7 days; or an increase in SCr ≥ 0.3 mg/dL within 48 h; or urine volume < 0.5 mL/kg per h within 6 h or more.[29] The minimum SCr value within 7 days at admission served as the baseline SCr.[30,31]

Data Extraction and Definitions

PostgresSQL 13.7.2 and Navicat Premium 16 were utilized for data extraction using the Structured Query Language, encompassing: (1) demographic information [gender, age, race, and body mass index (BMI)]; (2) vital signs [heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP)]; (3) severity at admission (Systemic Inflammatory Response Syndrome score, Simplified acute physiological score II, Sequential Organ Failure Assessment score, and Acute physiology score III); (4) comorbidities [atrial fibrillation (AF), AMI, AKI, coronary artery bypass grafting (CABG), heart failure (HF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), hypertension, and percutaneous coronary intervention (PCI)]; (5) medication details [statin,

aspirin, clopidogrel, rivaroxaban, warfarin, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker, beta-blocker, calcium channel blocker (CCB), loop diuretics (including furosemide and torsemide), and insulin]; and (6) laboratory tests [red blood cell, white blood cell (WBC), platelets, neutrophils, lymphocytes, hemoglobin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, hemoglobin A1c (HbA1c), blood urea nitrogen, urine creatinine (UCr), SCr, troponin T (TnT), creatine kinase-MB (CK-MB), N-terminal pro-B-type natriuretic peptide (NT-proBNP), pH, partial pressure of O_2, partial pressure of CO_2, potassium, and sodium] within the initial 24 h of ICU admission.

The AAR was calculated as follow: admission blood glucose (mg/dL)/albumin (g/L).[27] AAR quartile Q1: AAR ≤ 2.82, Q2: 2.82 < AAR ≤ 3.63, Q3: 3.63 < AAR ≤ 5.07, and Q4: AAR > 5.07.

The comorbidities were defined using the ICD-9 code and ICD-10 code. The follow-up period was from the admission date to the date of endpoints of interest.

Missing data were handled through multiple imputation using the "missForest" R package, which employs a random forest-based algorithm with 100 decision trees per iteration (ntree = 100) and a maximum of 10 cycles (maxiter = 10). Comparative analysis revealed no statistically significant differences between pre- and post-imputation data in the study cohort, as detailed in supplemental material, Table 3S. For variables exceeding 25% missingness (SBP, DBP, BMI, neutrophils, TC, TG, HDL-C, LDL-C, HbA1c, UCr, TnT, CK-MB, NT-proBNP, pH, partial pressure of O_2, and partial pressure of CO_2), we implemented dummy variable conversion instead of direct imputation to mitigate potential bias introduced by high-dimensional missing patterns.

Statistical Analysis

Continuous variables were presented as mean ± SD or medians (interquartile range). Pairwise comparisons were done by the Mann-Whitney *U* test or the Student's *t*-test according to the data's nature. Categorical variables were depicted as counts (percentages) and analyzed using the Fisher's exact probability test or the Pearson's chi-squared test between groups.

Kaplan-Meier curves were plotted for time-to-event outcomes (1-year mortality, in-hospital mortality) and cumulative incidence of AKI and RRT across AAR quartiles, with between-group differences assessed by log-rank tests.

The Cox proportional hazard models were employed to estimate hazard ratio (HR) with 95% CI for the associations between the AAR and clinical outcomes, including 1-year mortality, in-hospital mortality, AKI incidence, and RRT requirement. The Cox proportional hazard model was adjusted for various variables. Model 1 was unadjusted, while Model 2 adjusted for gender, age, race, and BMI. Based on Model 2, Model 3 further adjusted for Acute physiology score III, Simplified acute physiological score II, Sequential Organ Failure Assessment score, Systemic Inflammatory Response Syndrome score, SBP, DBP, heart rate, AF, AMI, HF, hypertension, CKD, DM, PCI, CABG, WBC, platelets, hemoglobin, TC, TG, HDL-C, LDL-C, SCr, TnT, CK-MB, NT-proBNP, aspirin, clopidogrel, ACEI, angiotensin II receptor blocker, CCB, statin, loop diuretic, insulin, and RRT. To prevent overadjustment bias, RRT was excluded from Model 3 when analyzing RRT as an outcome. AAR was analyzed both as a continuous variable and a categorical variable stratified into quartiles, with the lowest quartile serving as the reference group across all models.

A restricted cubic spline (RCS) model with 3 degrees of freedom (4 knots) was employed to investigate the dose-response relationships between AAR and clinical outcomes, including 1-year mortality, in-hospital mortality, AKI incidence, and requirement for RRT, while adjusting for potential confounding variables.

Subgroup analyses were implemented to ascertain the consistency of AAR prognostic value, including subgroups by age (< 75 years, ≥ 75 years), gender (female, male), and specific comorbidities like obesity, AMI, DM, HF, CKD, hypertension, AF, PCI, CABG, and insulin. Likelihood ratio tests appraised the links between AAR and stratified variables.

Data analyses were all done using R statistical software (R Foundation for Statistical Computing, Boston, MA, USA). A two-sided *P*-value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 8360 critical CAD patients were enrolled, with a median age of 71 (62–80) years and 5534 patients (66%) were males. The median AAR was 3.63 (2.82–5.08). The 1-year mortality was 23%, while in-hospital mortality, AKI incidence, and RRT were 8.7%, 63%, and 4.3%, respectively.

Supplemental material, Table 1S lists the baseline characteristics of patients categorized by AAR quartiles [quartile Q1: AAR ≤ 2.82 (n = 2093), Q2: 2.82 < AAR ≤ 3.63 (n = 2089), Q3: 3.63 < AAR ≤ 5.07 (n = 2089), and Q4: AAR > 5.07 (n = 2089)]. The median AAR of the four groups was 2.44 (2.21–2.64), 3.19 (3.00–3.39), 4.21 (3.89–4.58), and 6.69 (5.74–8.77), respectively. The Q4 (AAR > 5.07) group manifested the highest severity of illness scores, the fastest heart rate upon admission, lowest incidence of CABG, highest incidences of HF, AMI, COPD, PCI, and DM, higher levels of WBC, ALT, AST, SCr, glucose, potassium, and lowest levels of red blood cell, hemoglobin, albumin, and sodium. Moreover, the Q4 (AAR > 5.07) group showed more abnormal blood gas analyses, decreased usage of statins, beta-blocker, rivaroxaban, and warfarin, and increased usage of insulin and clopidogrel (all P < 0.05). Furthermore, the Q4 (AAR > 5.07) group had highest proportions of patients with TG > 149 mg/dL, HbA1c percentage > 6.4%, UCr > 132.6 mg/dL, TnT > 0.01 ng/mL, CK-MB > 10 ng/mL, NT-proBNP > 229 pg/mL, HDL-C < 45 mg/dL, neutrophil percentage > 71%, and lymphocyte percentage < 18% (all P < 0.05). Finally, higher AAR was correlated with a progressive rise in 1-year mortality (12% *vs.* 20% *vs.* 27% *vs.* 34%), in-hospital mortality (2.8% *vs.* 5.5% *vs.* 9.6% *vs.* 17%), AKI incidence (53% *vs.* 60% *vs.* 64% *vs.* 73%), and the need for RRT (1.7% *vs.* 2.2% *vs.* 4.1% *vs.* 9.2%) (all P < 0.001).

Table 1 presents the baseline characteristics for comparisons between 1-year survivors and non-survivors. The 1-year non-survivors group revealed an older age, a higher proportion of females, higher scores of illness severity at admission, higher incidences of AF, AMI, HF, COPD, CKD, and PCI, and decreased usage of statins, aspirin, rivaroxaban, warfarin, ACEI, beta-blocker, CCB, loop diuretics, and insulin. Regarding laboratory tests, 1-year non-survivors exhibited higher levels of WBC, ALT, AST, glucose, blood urea nitrogen, SCr, potassium, CK-MB, and NT-proBNP, but lower albumin levels (all P < 0.05). Besides, 1-year non-survivors had higher proportions of patients with TG > 149 ng/dL, UCr > 132.6 mg/dL, neutrophil percentage > 71%, CK-MB > 10 ng/mL, NT-proBNP > 229 pg/mL, lymphocytes percentage < 18% (all P < 0.001). They also displayed substantially higher AAR [4.3 (3.26–6.06) *vs.* 3.45 (2.72–4.78), P < 0.001] and higher AKI incidence (59% *vs.* 74%, P < 0.001) and requirement for RRT (2.2% *vs.* 11%, P < 0.001) than the survivor group. Furthermore, supplemental material, Table 2S presents the baseline characteristics for comparisons between the AKI and non-AKI.

Primary Endpoint

Kaplan-Meier survival analysis denoted significantly varied 1-year mortality across the groups. Patients with an elevated AAR exhibited an increased risk of 1-year mortality (log-rank P < 0.0001) (Figure 1A).

Taking AAR as a continuous variable, Cox proportional hazard model showed a notable association between the risk of 1-year mortality and AAR in both Model 1 (HR = 1.057, 95% CI: 1.049–1.066, P < 0.001) and Model 3 (HR = 1.016, 95% CI: 1.005–1.027, P = 0.005).

Taking AAR as a categorical variable, the highest quartile (Q4: AAR > 5.07) of AAR showcased a notable link to the risk of 1-year mortality in both Model 1 [Q1 (AAR ≤ 2.82) *vs.* Q2 (2.82 < AAR ≤ 3.63): HR = 1.414, 95% CI: 1.210–1.651, P < 0.001; Q3 (3.63 < AAR ≤ 5.07): HR = 1.777, 95% CI: 1.534–2.060, P < 0.001; Q4 (AAR > 5.07): HR = 2.279, 95% CI: 1.977–2.628, P < 0.001] and Model 3 [Q1 (AAR ≤ 2.82) *vs.* Q2 (2.82 < AAR ≤ 3.63): HR = 1.236, 95% CI: 1.055–1.448, P = 0.009; Q3 (3.63 < AAR ≤ 5.07): HR = 1.290, 95% CI: 1.108–1.503, P < 0.001; Q4 (AAR > 5.07): HR = 1.502, 95% CI: 1.285–1.757, P < 0.001].

The RCS model elicited a nonlinear relationship between AAR and the risk of 1-year mortality in both Model 1 ($P_{non\text{-}linear}$ < 0.0001) and Model 3 ($P_{non\text{-}linear}$ = 0.0001) (supplemental material, Figure 2S A–C).

A risk stratification analysis of AAR [Q3 (3.63 < AAR ≤ 5.07) + Q4 (AAR > 5.07) *vs.* Q1 (AAR ≤ 2.82) + Q2 (2.82 < AAR ≤ 3.63)] was conducted for primary endpoint in subgroups, including gender, age, obesity, AMI, DM, HF, CKD, hypertension, AF, PCI, CABG, and insulin (Figure 3). The AAR displayed a marked association with an intensified risk of 1-year mortality in subgroups of age ≤ 75 years (HR = 1.908, 95% CI: 1.650–2.207), female (HR = 1.666, 95% CI: 1.437–1.933), AMI (HR = 1.599, 95% CI: 1.367–1.871), no DM (HR = 1.977, 95% CI: 1.760–2.219), no HF (HR = 1.896, 95% CI: 1.654–2.172), no CKD (HR = 1.834, 95% CI: 1.634–2.060), no hypertension (HR = 1.935, 95% CI: 1.602–2.337), no AF (HR = 1.726, 95% CI: 1.518–1.961), PCI (HR = 1.930, 95% CI: 1.285–2.900), no CABG (HR = 1.644, 95% CI: 1.494–1.808), and using insulin (HR = 1.741, 95% CI: 1.535–1.975) (all P < 0.001). There were interactions between variables and AAR in obesity, DM, HF, and CKD subgroup analyses ($P_{interaction}$ < 0.05).

Secondary Endpoint

Based on AAR quartiles, Kaplan-Meier survival analysis analyzed in-hospital mortality (Figure 1B) and cum-

Table 1 Baseline characteristics of 1-year survivors and non-survivors.

Characteristic	Overall (*n* = 8360)	Survivors (*n* = 6416)	Non-survivors (*n* = 1944)	*P*-value
Male	5534 (66%)	4368 (68%)	1166 (60%)	< 0.001
Age, yrs	71 (62–80)	69 (61–78)	77 (68–85)	< 0.001
Race				0.002
White	5518 (66%)	4245 (66%)	1273 (65%)	
Black	530 (6.3%)	434 (6.8%)	96 (4.9%)	
Asian	179 (2.1%)	144 (2.2%)	35 (1.8%)	
Others	2133 (26%)	1593 (25%)	540 (28%)	
Body mass index, kg/m^2				< 0.001
Underweight	120 (1.4%)	86 (1.3%)	34 (1.7%)	
Normal	898 (11%)	730 (11%)	168 (8.6%)	
Overweight	1927 (23%)	1661 (26%)	266 (14%)	
Obesity	1753 (21%)	1561 (24%)	192 (9.9%)	
Missing	3662 (44%)	2378 (37%)	1284 (66%)	
Acute physiology score III	40 (31–52)	38 (30–48)	50 (39–67)	< 0.001
Simplified acute physiological score II	37 (31–44)	35 (31–41)	42 (36–52)	< 0.001
Sequential Organ Failure Assessment score	5.0 (3.0–7.0)	4.0 (3.0–6.0)	6.0 (4.0–9.0)	< 0.001
Systemic Inflammatory Response Syndrome score				< 0.001
0	66 (0.8%)	53 (0.8%)	13 (0.7%)	
1	726 (8.7%)	581 (9.1%)	145 (7.5%)	
2	2622 (31%)	2042 (32%)	580 (30%)	
3	3841 (46%)	2977 (46%)	864 (44%)	
4	1105 (13%)	763 (12%)	342 (18%)	
Vital signs				
Systolic blood pressure, mmHg				< 0.001
< 90	41 (0.5%)	29 (0.5%)	12 (0.6%)	
> 140	1262 (15%)	1132 (18%)	130 (6.7%)	
90–140	3697 (44%)	3262 (51%)	435 (22%)	
Missing	3360 (40%)	1993 (31%)	1367 (70%)	
Diastolic blood pressure, mmHg				< 0.001
< 60	744 (8.9%)	607 (9.5%)	137 (7.0%)	
> 90	310 (3.7%)	277 (4.3%)	33 (1.7%)	
60–90	3946 (47%)	3539 (55%)	407 (21%)	
Missing	3360 (40%)	1993 (31%)	1367 (70%)	
Heart rates, beat/min	84 (77–92)	83 (76–91)	87 (78–98)	< 0.001
Comorbidities				
Atrial fibrillation	3088 (37%)	2196 (34%)	892 (46%)	< 0.001
Acute myocardial infarction	2918 (35%)	2153 (34%)	765 (39%)	< 0.001
Coronary artery bypass grafting	1080 (13%)	1014 (16%)	66 (3.4%)	< 0.001
Heart failure	3177 (38%)	2157 (34%)	1020 (52%)	< 0.001
Chronic kidney disease	2106 (25%)	1458 (23%)	648 (33%)	< 0.001
Chronic obstructive pulmonary disease	1334 (16%)	850 (13%)	484 (25%)	< 0.001
Diabetes mellitus	3282 (39%)	2520 (39%)	762 (39%)	> 0.9

Continued

Characteristic	Overall (*n* = 8360)	Survivors (*n* = 6416)	Non-survivors (*n* = 1944)	*P*-value
Hypertension	6383 (76%)	4938 (77%)	1445 (74%)	0.017
Percutaneous coronary intervention	577 (6.9%)	441 (6.9%)	136 (7.0%)	0.9
Laboratory tests				
White blood cell, K/uL	9.0 (6.8–12.5)	8.6 (6.6–11.8)	10.5 (7.5–15.1)	< 0.001
Red blood cell, K/uL	3.91 (3.36–4.43)	4.00 (3.47–4.50)	3.60 (3.10–4.13)	< 0.001
Platelets, K/uL	204 (155–258)	205 (159–257)	195 (140–264)	< 0.001
Neutrophils, %				< 0.001
< 34	90 (1.1%)	54 (0.8%)	36 (1.9%)	
> 71	4143 (50%)	3017 (47%)	1126 (58%)	
34–71	1443 (17%)	1166 (18%)	277 (14%)	
Missing	2684 (32%)	2179 (34%)	505 (26%)	
Lymphocytes, %				< 0.001
< 18	3977 (48%)	2778 (43%)	1199 (62%)	
> 42	117 (1.4%)	82 (1.3%)	35 (1.8%)	
18–42	1582 (19%)	1377 (21%)	205 (11%)	
Missing	2684 (32%)	2179 (34%)	505 (26%)	
Hemoglobin, g/dL	11.80 (10.10–13.30)	12.00 (10.40–13.60)	10.80 (9.30–12.30)	< 0.001
Alanine aminotransferase, IU/L	26 (17–49)	25 (17–45)	30 (17–68)	< 0.001
Aspartate aminotransferase, IU/L	32 (21–67)	30 (20–58)	44 (24–104)	< 0.001
Albumin, mg/dL	3.50 (3.00–4.00)	3.70 (3.20–4.00)	3.10 (2.70–3.60)	< 0.001
Total cholesterol, mg/dL				0.004
≤ 199	1329 (16%)	1012 (16%)	317 (16%)	
> 199	244 (2.9%)	209 (3.3%)	35 (1.8%)	
Missing	6787 (81%)	5195 (81%)	1592 (82%)	
Triglyceride, mg/dL				< 0.001
≤ 149	1317 (16%)	947 (15%)	370 (19%)	
> 149	675 (8.1%)	499 (7.8%)	176 (9.1%)	
Missing	6368 (76%)	4970 (77%)	1398 (72%)	
High-density lipoprotein cholesterol, mg/dL				0.1
< 45	916 (11%)	696 (11%)	220 (11%)	
> 55	289 (3.5%)	236 (3.7%)	53 (2.7%)	
45–55	292 (3.5%)	234 (3.6%)	58 (3.0%)	
Missing	6863 (82%)	5250 (82%)	1613 (83%)	
Low-density lipoprotein cholesterol, mg/dL				0.055
≤ 129	1255 (15%)	964 (15%)	291 (15%)	
> 129	178 (2.1%)	150 (2.3%)	28 (1.4%)	
Missing	6927 (83%)	5302 (83%)	1625 (84%)	
Glucose, mg/dL	124 (101–163)	122 (101–159)	130 (103–178)	< 0.001
Hemoglobin A1c percentage				< 0.001
< 5.7	1173 (14%)	1015 (16%)	158 (8.1%)	
> 6.4	1250 (15%)	1090 (17%)	160 (8.2%)	
5.7–6.4	1349 (16%)	1176 (18%)	173 (8.9%)	
Missing	4588 (55%)	3135 (49%)	1453 (75%)	

Continued

Characteristic	Overall (*n* = 8360)	Survivors (*n* = 6416)	Non-survivors (*n* = 1944)	*P*-value
Blood urea nitrogen, mg/dL	21 (15–32)	19 (15–29)	28 (19–45)	< 0.001
Serum creatinine, mg/dL	1.10 (0.80–1.50)	1.00 (0.80–1.40)	1.20 (0.90–1.90)	< 0.001
Urine creatinine, mg/dL				< 0.001
< 79.6	1037 (12%)	648 (10%)	389 (20%)	
> 132.6	396 (4.7%)	264 (4.1%)	132 (6.8%)	
79.6–132.6	565 (6.8%)	361 (5.6%)	204 (10%)	
Missing	6362 (76%)	5143 (80%)	1219 (63%)	
Troponin T, ng/mL				< 0.001
≤ 0.01	141 (1.7%)	102 (1.6%)	39 (2.0%)	
> 0.01	3297 (39%)	2186 (34%)	1111 (57%)	
Missing	4922 (59%)	4128 (64%)	794 (41%)	
Creatine kinase-MB, ng/mL				< 0.001
≤ 10	2990 (36%)	2162 (34%)	828 (43%)	
> 10	1252 (15%)	816 (13%)	436 (22%)	
Missing	4118 (49%)	3438 (54%)	680 (35%)	
N-terminal pro-B-type natriuretic peptide, pg/mL				< 0.001
≤ 229	44 (0.5%)	35 (0.5%)	9 (0.5%)	
> 229	962 (12%)	612 (9.5%)	350 (18%)	
Missing	7354 (88%)	5769 (90%)	1585 (82%)	
pH				< 0.001
< 7.35	1510 (18%)	918 (14%)	592 (30%)	
> 7.45	839 (10%)	621 (9.7%)	218 (11%)	
7.35–7.45	3568 (43%)	2884 (45%)	684 (35%)	
Missing	2443 (29%)	1993 (31%)	450 (23%)	
Partial pressure of O_2, mmHg				< 0.001
< 85	1628 (19%)	963 (15%)	665 (34%)	
> 105	3700 (44%)	3065 (48%)	635 (33%)	
85–105	435 (5.2%)	289 (4.5%)	146 (7.5%)	
Missing	2597 (31%)	2099 (33%)	498 (26%)	
Partial pressure of CO_2, mmHg				< 0.001
< 35	1039 (12%)	675 (11%)	364 (19%)	
> 45	1398 (17%)	972 (15%)	426 (22%)	
35–45	3325 (40%)	2670 (42%)	655 (34%)	
Missing	2598 (31%)	2099 (33%)	499 (26%)	
Potassium, mmol/L	4.20 (3.80–4.50)	4.10 (3.80–4.50)	4.20 (3.80–4.70)	< 0.001
Sodium, mmol/L	139.0 (136.0–141.0)	139.0 (137.0–141.0)	139.0 (135.0–141.0)	0.016
Admission-blood-glucose-to-albumin ratio	3.63 (2.82–5.08)	3.45 (2.72–4.78)	4.30 (3.26–6.06)	< 0.001
Medications				
Statin	6440 (77%)	5115 (80%)	1325 (68%)	< 0.001
Aspirin	6466 (77%)	5119 (80%)	1347 (69%)	< 0.001
Clopidogrel	1652 (20%)	1250 (19%)	402 (21%)	0.2
Rivaroxaban	125 (1.5%)	100 (1.6%)	25 (1.3%)	0.4

Continued

Characteristic	Overall (*n* = 8360)	Survivors (*n* = 6416)	Non-survivors (*n* = 1944)	*P*-value
Warfarin	1920 (23%)	1560 (24%)	360 (19%)	< 0.001
Angiotensin-converting enzyme inhibitor	2974 (36%)	2495 (39%)	479 (25%)	< 0.001
Angiotensin II receptor blocker	851 (10%)	718 (11%)	133 (6.8%)	< 0.001
Beta-blocker	6123 (73%)	4895 (76%)	1228 (63%)	< 0.001
Calcium channel blocker	2271 (27%)	1801 (28%)	470 (24%)	< 0.001
Loop diuretics	5738 (69%)	4429 (69%)	1309 (67%)	0.2
Insulin	5916 (71%)	4650 (72%)	1266 (65%)	< 0.001
Events				
In-hospital mortality	726 (8.7%)	0	726 (37%)	< 0.001
Acute kidney injury	5250 (63%)	3815 (59%)	1435 (74%)	< 0.001
Renal replacement therapy	359 (4.3%)	143 (2.2%)	216 (11%)	< 0.001

Data are presented as *n* (%) or median (interquartile range).

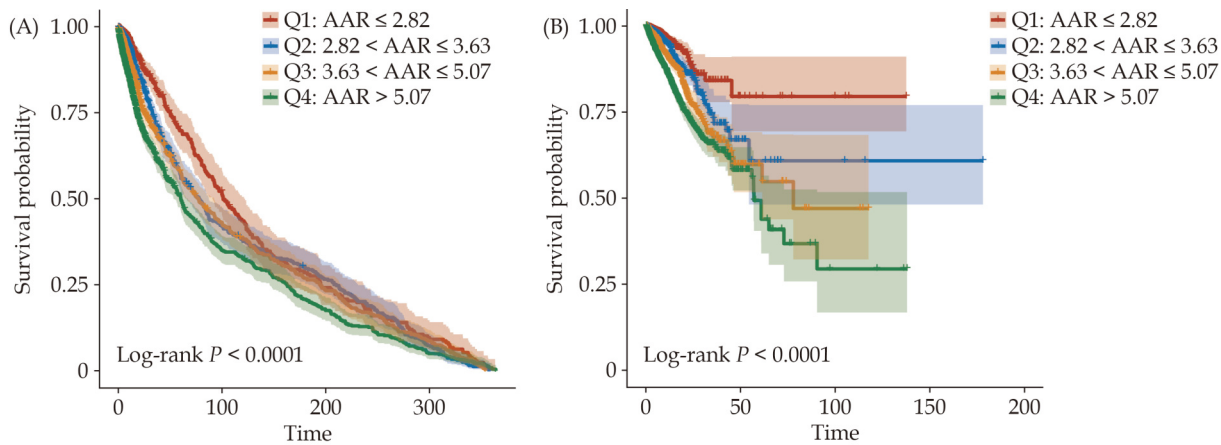

Figure 1 Kaplan-Meier survival analysis curves for 1-year mortality (A) and in-hospital mortality (B). AAR: admission-blood-glucose-to-albumin ratio.

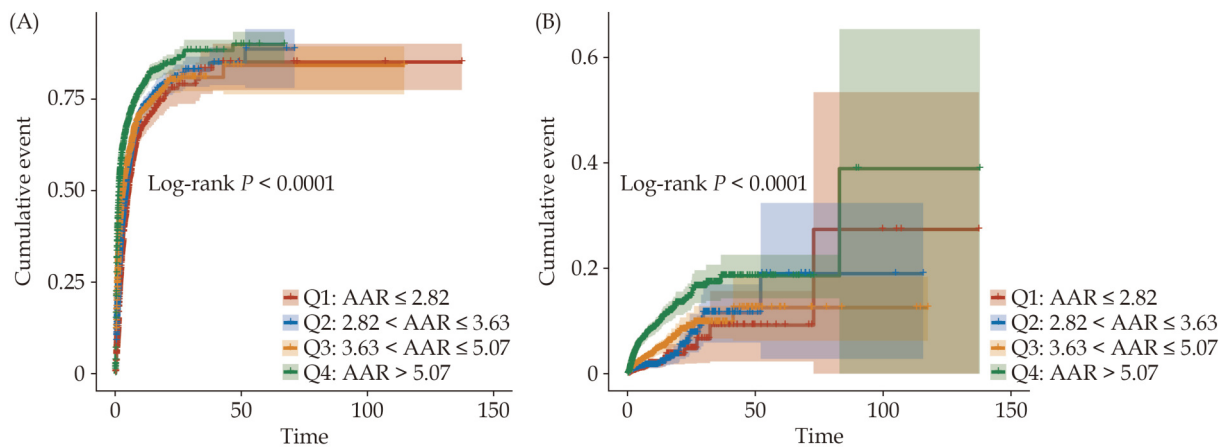

Figure 2 The cumulative event incidence curves for acute kidney injury incidence (A) and renal replacement therapy (B). AAR: admission-blood-glucose-to-albumin ratio.

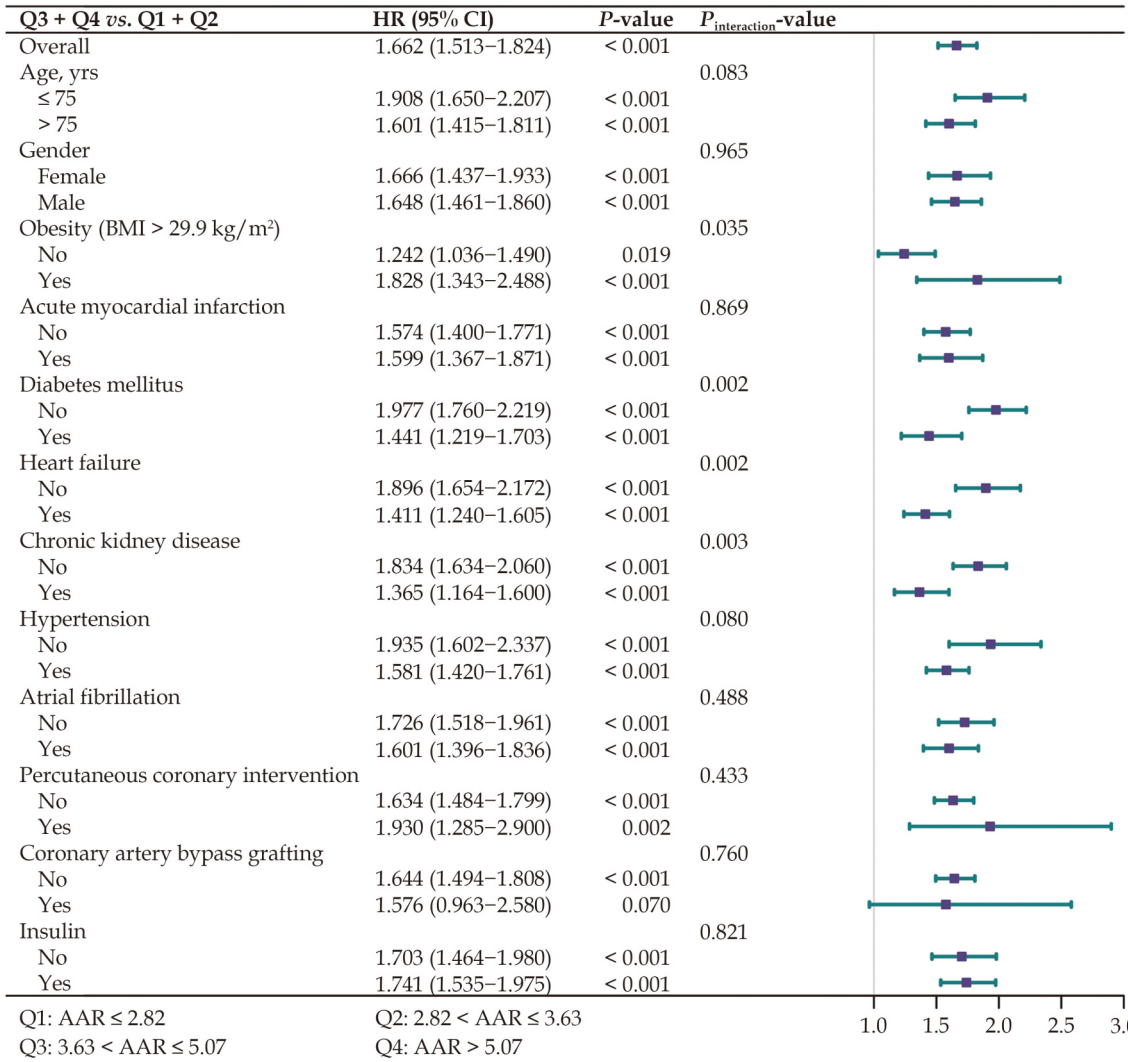

Figure 3 Forest plots for primary endpoints in various subgroups. AAR: admission-blood-glucose-to-albumin ratio.

ulative event incidence curves analyzed AKI incidence and RRT (Figure 2A & 2B), showing prominent differences in in-hospital mortality, AKI incidence, and RRT (all log-rank $P < 0.001$).

Table 2 shows the results of Cox proportional hazard analysis for the risk of in-hospital mortality, AKI incidence, and RRT in critically ill CAD patients. With AAR as a continuous variable, Cox proportional hazard analysis uncovered remarkable correlations between AAR and the risk of in-hospital mortality (HR = 1.060, 95% CI: 1.050–1.070), AKI incidence (HR = 1.059, 95% CI: 1.052–1.065), and RRT (HR = 1.067, 95% CI: 1.055–1.079) in Model 1 (all $P < 0.001$). In Model 3, AKI incidence also demonstrated a significant association with AAR (HR = 1.035, 95% CI: 1.027–1.044, $P < 0.001$), while no notable correlation was observed with the risk of in-hospital mortality (HR = 1.006, 95% CI: 0.990–1.022, $P = 0.5$) and RRT (HR = 1.01, 95% CI: 0.985–1.036, $P = 0.4$).

With AAR as a nominal variable, the highest quartile (Q4: AAR > 5.07) of AAR manifested a notable correlation with the risk of in-hospital mortality [Q1 (AAR ≤ 2.82) *vs.* Q2 (2.82 < AAR ≤ 3.63): HR = 1.69, 95% CI: 1.236–2.326; Q3 (3.63 < AAR ≤ 5.07): HR = 2.598, 95% CI: 1.938–3.482; Q4 (AAR > 5.07): HR = 3.871, 95% CI: 2.928–5.119] (all $P < 0.001$), AKI incidence [Q1 (AAR ≤ 2.82) *vs.* Q2 (2.82 < AAR ≤ 3.63): HR = 1.215, 95% CI: 1.121–1.318; Q3 (3.63 < AAR ≤ 5.07): HR = 1.368, 95% CI: 1.264–1.481; Q4 (AAR > 5.07): HR = 1.876, 95% CI: 1.737–2.027] (all $P < 0.001$), and RRT [Q1 (AAR ≤ 2.82) *vs.* Q2 (2.82 < AAR ≤ 3.63): HR = 1.201, 95% CI: 0.773–1.864, $P = 0.4$; Q3 (3.63 < AAR ≤ 5.07): HR = 2.107, 95% CI: 1.422–3.123, $P < 0.001$; Q4 (AAR > 5.07): HR = 4.406, 95% CI: 3.068–6.326, $P < 0.001$] in Model 1. In Mo-

Table 2 Cox proportional hazard models for 1-year mortality, in-hospital mortality, acute kidney injury, and renal replacement therapy.

Categories	Model 1			Model 2			Model 3		
	HR (95% CI)	*P*-value	P_{trend}-value	HR (95% CI)	*P*-value	P_{trend}-value	HR (95% CI)	*P*-value	P_{trend}-value
1-year mortality									
Continuous variable per unit	1.057 (1.049–1.066)	< 0.001		1.06 (1.052–1.069)	< 0.001		1.016 (1.005–1.027)	0.005	
Quartile			< 0.001			< 0.001			< 0.001
Q1: AAR ≤ 2.82 (*n* = 2093)	Reference			Reference			Reference		
Q2: 2.82 < AAR ≤ 3.63 (*n* = 2089)	1.414 (1.210–1.651)	< 0.001		1.407 (1.204–1.643)	< 0.001		1.236 (1.055–1.448)	0.009	
Q3: 3.63 < AAR ≤ 5.07 (*n* = 2089)	1.777 (1.534–2.060)	< 0.001		1.735 (1.497–2.011)	< 0.001		1.29 (1.108–1.503)	0.001	
Q4: AAR > 5.07 (*n* = 2089)	2.279 (1.977–2.628)	< 0.001		2.413 (2.091–2.785)	< 0.001		1.502 (1.285–1.757)	< 0.001	
In-hospital mortality									
Continuous variable per unit	1.06 (1.050–1.070)	< 0.001		1.06 (1.051–1.070)	< 0.001		1.006 (0.990–1.022)	0.5	
Quartile			< 0.001			< 0.001			0.001
Q1: AAR ≤ 2.82 (*n* = 2093)	Reference			Reference			Reference		
Q2: 2.82 < AAR ≤ 3.63 (*n* = 2089)	1.696 (1.236–2.326)	0.001		1.595 (1.163–2.188)	0.004		1.307 (0.946–1.805)	0.1	
Q3: 3.63 < AAR ≤ 5.07 (*n* = 2089)	2.598 (1.938–3.482)	< 0.001		2.47 (1.842–3.311)	< 0.001		1.537 (1.135–2.080)	0.005	
Q4: AAR > 5.07 (*n* = 2089)	3.871 (2.928–5.119)	< 0.001		3.78 (2.858–5.000)	< 0.001		1.587 (1.176–2.143)	0.003	
Acute kidney injury									
Continuous variable per unit	1.059 (1.052–1.065)	< 0.001		1.059 (1.053–1.066)	< 0.001		1.035 (1.027–1.044)	< 0.001	
Quartile			< 0.001			< 0.001			< 0.001
Q1: AAR ≤ 2.82 (*n* = 2093)	Reference			Reference			Reference		
Q2: 2.82 < AAR ≤ 3.63 (*n* = 2089)	1.215 (1.121–1.318)	< 0.001		1.215 (1.105–1.299)	< 0.001		1.21 (1.113–1.314)	< 0.001	
Q3: 3.63 < AAR ≤ 5.07 (*n* = 2089)	1.368 (1.264–1.481)	< 0.001		1.368 (1.254–1.471)	< 0.001		1.264 (1.162–1.375)	< 0.001	
Q4: AAR > 5.07 (*n* = 2089)	1.876 (1.737–2.027)	< 0.001		1.876 (1.743–2.035)	< 0.001		1.579 (1.445–1.724)	< 0.001	
Renal replacement therapy*									
Continuous variable per unit	1.067 (1.055–1.079)	< 0.001		1.062 (1.050–1.074)	< 0.001		1.01 (0.985–1.036)	0.4	
Quartile			< 0.001			< 0.001			0.012
Q1: AAR ≤ 2.82 (*n* = 2093)	Reference			Reference			Reference		
Q2: 2.82 < AAR ≤ 3.63 (*n* = 2089)	1.201 (0.773–1.864)	0.4		1.217 (0.783–1.889)	0.4		1.17 (0.745–1.836)	0.5	
Q3: 3.63 < AAR ≤ 5.07 (*n* = 2089)	2.107 (1.422–3.123)	< 0.001		2.141 (1.444–3.176)	< 0.001		1.392 (0.915–2.119)	0.12	
Q4: AAR > 5.07 (*n* = 2089)	4.406 (3.068–6.326)	< 0.001		4.333 (3.016–6.225)	< 0.001		1.64 (1.097–2.452)	0.016	

*Refers to when renal replacement therapy is used as an outcome variable, Model 3 does not adjust for renal replacement therapy. Model 1: unadjusted any variables. Model 2: adjusted for gender, age, race, and body mass index. Model 3: adjusted for variables in Model 2 plus the Acute physiology score III, Simplified acute physiological score II, Sequential Organ Failure Assessment score, Systemic Inflammatory Response Syndrome score, systolic blood pressure, diastolic blood pressure, heart rate, atrial fibrillation, acute myocardial infarction, heart failure, hypertension, chronic kidney disease, diabetes mellitus, percutaneous coronary intervention, coronary artery bypass grafting, white blood cell, platelets, hemoglobin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum creatinine, troponin T, creatine kinase-MB, N-terminal pro-B-type natriuretic peptide, aspirin, clopidogrel, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, calcium channel blocker, statin, loop diuretic, insulin, and renal replacement therapy. AAR: admission-blood-glucose-to-albumin ratio.

del 3, in-hospital mortality [Q1 (AAR ≤ 2.82) *vs.* Q2 (2.82 < AAR ≤ 3.63): HR = 1.307, 95% CI: 0.946–1.805, P = 0.1; Q3 (3.63 < AAR ≤ 5.07): HR = 1.537, 95% CI: 1.135–2.080, P = 0.005; Q4 (AAR > 5.07): HR = 1.587, 95% CI: 1.176–2.143, P = 0.003], AKI incidence [Q1 (AAR ≤ 2.82) *vs.* Q2 (2.82 < AAR ≤ 3.63): HR = 1.21, 95% CI: 1.113–1.314; Q3 (3.63 < AAR ≤ 5.07): HR = 1.264, 95% CI: 1.162–1.375; Q4 (AAR > 5.07): HR = 1.579, 95% CI: 1.445–1.724] (all P < 0.001), and RRT [Q1 (AAR ≤ 2.82) *vs.* Q2 (2.82 < AAR ≤ 3.63): HR = 1.17, 95% CI: 0.745–1.836, P = 0.5; Q3 (3.63 < AAR ≤ 5.07): HR = 1.392, 95% CI: 0.915–2.119, P < 0.12; Q4 (AAR > 5.07): HR = 1.64, 95% CI: 1.097–2.452, P < 0.016] also shown significant associations with AAR.

RCS regression model revealed a nonlinear relationship between AAR and in-hospital mortality (supplemental material, Figure 2S D–F). Supplemental material, Figure 3S A–C & D–F show AKI incidence and RRT in both Model 1 and Model 3.

Furthermore, a risk stratification analysis of AAR [Q3 (3.63 < AAR ≤ 5.07) + Q4 (AAR > 5.07) *vs.* Q1 (AAR ≤ 2.82) + Q2 (2.82 < AAR ≤ 3.63)] was conducted for secondary endpoints in various subgroups of gender, age, obesity, AMI, DM, HF, CKD, hypertension, AF, PCI, CABG, and insulin. Firstly, AAR manifested a noticeable link to an elevated risk of in-hospital mortality in subgroups of female (HR = 2.454, 95% CI: 1.847–3.261), age ≤ 75 years (HR = 2.973, 95% CI: 2.286–3.867), obesity (HR = 2.728, 95% CI: 1.362–5.461), AMI (HR = 2.246, 95% CI: 1.754–2.876), DM (HR = 1.755, 95% CI: 1.288–2.391), HF (HR = 1.703, 95% CI: 1.354–2.143), no PCI (HR = 1.717, 95% CI: 0.957–3.079), no CABG (HR = 1.502, 95% CI: 0.641–3.522), insulin (HR = 2.839, 95% CI: 2.275–3.543), and no hypertension (HR = 3.299, 95% CI: 2.203–4.726) (all P < 0.001) (supplemental material, Figure 4S). Similarly, in terms of AKI incidence, AAR demonstrated significant associations with a higher risk of AKI incidence in subgroups of female (HR = 1.547, 95% CI: 1.405–1.703), age ≤ 75 years (HR = 1.465, 95% CI: 1.367–1.571), no obesity (HR = 1.378, 95% CI: 1.251–1.519), AMI (HR = 1.450, 95% CI: 1.332–1.578), no DM (HR = 1.541, 95% CI: 1.436–1.654), no HF (HR = 1.424, 95% CI: 1.325–1.530), no hypertension (HR = 1.592, 95% CI: 1.419–1.786), PCI (HR = 1.517, 95% CI: 1.242–1.852), no CABG (HR = 1.536, 95% CI: 1.447–1.631), and no using insulin (HR = 1.738, 95% CI: 1.541–1.960) (all P < 0.001) (supplemental material, Figure 5S). Simultaneously, in the context of stratified analyses of RRT, AAR exhibited a prominent correlation with an elevated risk of RRT within similar subgroups (supplemental material, Figure 6S).

DISCUSSION

This research is the initial investigation to examine the associations of AAR with 1-year mortality, in-hospital mortality, AKI, and RRT in CAD patients. The results demonstrated that critical CAD patients with an enhanced AAR exhibited worsening prognosis, even after adjusting for potential confounders. Furthermore, this investigation introduced a convenient and reliable biomarker for predicting mortality risk and poor renal prognosis in CAD patients in ICU.

The Admission Blood Glucose, Albumin Level, AAR, CAD, and AKI

Glucose dysregulation is highly prevalent in CAD patients. A study on 4196 CAD patients showed that 31% of them had DM, 36% of acute coronary syndrome patients had glucose dysregulation, and 22% of them were newly diagnosed with DM, while among stable CAD patients, these proportions were 37% and 14%, respectively.[32] Clinical studies have elucidated the correlation between admission glucose levels and the morbidity and mortality of CAD and AKI in diverse populations. Norhammar, *et al.*[33] emphasized that elevated admission blood glucose levels served as an independent predictor for nonfatal reinfarction, hospitalization for HF, and MACEs. Similarly, Wahab, *et al.*[34] including 1664 AMI patients also revealed that higher blood glucose at admission was connected with a higher risk of in-hospital mortality and 12-month mortality. AKI was an independent risk factor for adverse outcomes in patients with AMI and non-ST-segment elevation acute coronary syndrome.[35–39] Two cohort studies by Gorelik, *et al.*[17] and Moriyama, *et al.*[20] demonstrated that hyperglycemia on admission was positively and independently linked to AKI in AMI patients. Moreover, Stolker, *et al.*[40] involving 6358 AMI patients undergoing coronary angiography, demonstrated that enhanced pre-procedural glucose levels were linked to an intensified risk of contrast-induced AKI in non-diabetic patients.

Low serum albumin has also been unraveled as an independent risk factor for CAD and AKI. In terms of CAD, a retrospective study, encompassing 743 patients, highlighted that low serum albumin was related to a high risk of all-cause mortality and MACEs.[16] Furthermore, a meta-analysis by Zhu, *et al.*[21] indicated that acute coronary syndrome patients with decreased serum albumin concentrations had a greater risk of all-cause mortality when adjusted for significant covariates. A large-scale retrospective

study by Lee, *et al*.[18] involved 1182 patients with preoperative normal renal function who underwent off-pump CABG and clarified preoperative low serum albumin as an independent risk factor for AKI. Another two small-scale single-center studies indicated that hypoalbuminemia served as an independent risk factor for AKI in patients undergoing PCI and coronary angiography.[26,41]

Furthermore, many studies have indicated the associations of serum albumin with malnutrition, glycemia control, and complications in diabetic patients. Serum albumin levels in type 2 diabetes mellitus (T2DM) patients can be diminished by impaired albumin synthesis, glycation, and albuminuria.[25,42,43] Liu, *et al*.[44] demonstrated that upregulating serum albumin levels in mice promoted glucose homeostasis and protected islet beta cells, thereby alleviating T2DM. Moreover, decreased serum albumin levels were also correlated with increases in glycated albumin and HbA1c in T2DM individuals, predicting cardiovascular events in diabetic patients.[45,46] Therefore, serum albumin levels can be used to address malnutrition and background glycemia in the general population.

AAR has recently been proposed as a novel composite index that combines the impact of admission glucose and albumin levels on the prognosis of cardiovascular diseases. An elevated AAR has been shown a strong correlation with poor clinical prognosis in AMI patients with ST-segment elevation.[27] These findings collectively emphasized the utility of AAR as a reliable and valid indicator for risk stratification of mortality and renal prognosis among critically ill CAD patients.

Potential Mechanisms Underlying the Relationship of AAR with the Prognosis of Critically Ill CAD Patients

Our findings uncovered the predictive power of AAR for mortality, AKI, and RRT in CAD patients in ICU. The potential mechanism may include that hyperglycemia and low albumin levels could result in endothelial dysfunction, inflammatory processes, oxidative stress, and accelerated atherosclerotic progression.[5–8]

Evidence suggested that hyperglycemia triggered excessive inflammatory responses by increasing circulating inflammatory cytokine concentrations, facilitated plaque destabilization, myocardial injury, and increased infarct size, thereby exacerbating adverse cardiovascular events.[19,22,47,48] Likewise, hypoalbuminemia could also promote the cytokine-driven acute-phase inflammatory response by increasing plasma levels of C-reactive protein and interleukin-6.[49]

Secondly, the elevated AAR in critically ill CAD patients may suggest a prethrombotic state.[50] Hyperglycemia could directly influence gene transcription of coagulation factors by aggravating oxidative stress and loss of the endothelial glycocalyx layer, which harbored coagulation factors and directly regulated glycation of coagulation factors, resulting in a prothrombotic shift in the coagulation system of CAD patients.[51] In addition, albumin also exerted anticoagulant and antiplatelet activities. Hypoalbuminemia may attenuate fibrinolysis.[13] Albumin displayed heparin-like activity and inhibited platelet aggregation induced by histones.[14,52]

Thirdly, the elevated AAR in critically ill CAD patients may indicate severe endothelial dysfunction. The close association between endothelial dysfunction and atherosclerosis and its risk factors is well studied, and it is a key factor for adverse event throughout the natural history of CAD.[53] Endothelial dysfunction drives atherosclerosis via diverse mechanisms, such as promoting coagulation, vasoconstriction, and impaired or pathological vascular repair.[54,55] Hyperglycemia can impair endothelial dysfunction by altering cell signaling, increasing oxidative stress, pro-inflammatory activation, and mitochondrial dysfunction.[24,56–59] All these pathophysiological changes give rise to the mortality and AKI in critically ill CAD patients.

Our results confirmed the excellent prognostic value of AAR for critically ill CAD patients. The advantages of AAR mainly include the following points. First of all, relatively stable albumin can counteract the fluctuating admission blood glucose, showing critical roles in AAR-based evaluation.[27] Secondly, in comparison to admission blood glucose and stress hyperglycemia ratio, the composite indicator AAR serves as an evaluative tool in the realms of nutrition, DM, and stress-induced hyperglycemia in critically ill CAD patients. The ability of the AAR to mirror inflammatory response, prethrombotic state, endothelial dysfunction, hyperglycemia, and malnutrition makes it a valuable tool. Moreover, the convenience and widespread use of admission blood glucose and albumin levels in the emergency department makes AAR measurement feasible in acute conditions. Regular assessment of AAR in critically ill CAD patients is crucial for enhancing risk stratification for mortality and renal outcomes, facilitating early intervention and improving prognosis. Future investigations should prioritize serial AAR measurements during hospitalization to characterize its trajectory patterns, evaluate dynamic prognostic value, and explore therapeutic adjustment thresholds. This approach may uncover critical windows for personalized intervention in high-risk CAD subgroups.

LIMITATIONS

There were some mentionable limitations of the study. Firstly, our study may be subject to selection bias inherent to hospitalized cohorts, as healthcare accessibility and socioeconomic disparities might systematically exclude vulnerable populations, potentially limiting generalizability to community-based settings. Secondly, the retrospective and observational design limited the exploration of causal relationships. Thirdly, despite multivariate adjustment and subgroup analyses, other confounders may have influenced the results. Fourthly, given inherent constraints in the MIMIC-IV database, potential confounders such as socioeconomic status, CAD subtypes, the severity of CAD and AKI, and the cause of death among study participants were not considered, potentially introducing bias. Last but not least, the analysis solely focused on the baseline AAR, overlooking any dynamic changes in AAR throughout hospitalization and ICU stay. Hence, prospective cohort studies are warranted for result validation.

CONCLUSIONS

In summary, an elevated AAR acts as a prognostic indicator and risk stratification tool for in-hospital mortality, 1-year mortality, AKI, and RRT in critically ill CAD patients. Assessing AAR can aid in decision-making and clinical management in critically ill CAD patients, especially those manifesting AMI or undergoing PCI. Further investigations are required to ascertain whether better control of AAR will enhance clinical outcomes of CAD patients with critical illness in the future.

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