Alkaline Phosphatase-to-Albumin Ratio as a Novel Predictor of Long-Term Adverse Outcomes in Coronary Artery Disease Patients Who underwent PCI

Running title: AAR and outcomes after PCI

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Abstract

Background: Alkaline phosphatase (ALP) and albumin (ALB) have been shown to be associated with coronary artery disease (CAD), and it has been reported that alkaline phosphatase-to-albumin ratio (AAR) is associated with the liver damage and poorer prognosis of patients with digestive system malignancy. Moreover, several
previous studies showed that there was a higher incidence of malignancy in CAD patients. However, to our knowledge, the relationship between AAR and long-term adverse outcomes in CAD patients after undergoing percutaneous coronary intervention (PCI) has not been investigated. Therefore, we aim to access the relation between AAR and long-term adverse outcomes in post-PCI patients with CAD.

**Methods:** 3378 post-PCI patients with CAD were enrolled in the retrospective CORFCHD-ZZ study from January 2013 to December 2017. The median duration of follow-up was 37.59 ± 22.24 months. The primary endpoint was long-term mortality including all-cause mortality (ACM) and cardiac mortality (CM). The secondary endpoints were major adverse cardiac events (MACEs) and major adverse cardiac and cerebrovascular events (MACCEs).

**Results:** Kaplan-Meier analyses showed that an increased AAR was positively correlated with incidences of long-term ACM (log-rank, P=0.014), CM (log-rank, P=0.011), MACEs (log-rank, P=0.013) and MACCEs (log-rank, P=0.006). Multivariate Cox regression analyses showed that the elevated AAR was an independent predictor of long-term ACM (adjusted HR=1.488 [1.031-2.149], P=0.034), CM (adjusted HR=1.837 [1.141-2.959], P=0.012), MACEs (adjusted HR=1.257 [1.018-1.551], P=0.033) and MACCEs (adjusted HR=1.237 [1.029-1.486], P=0.024).

**Conclusions:** An elevated AAR is a novel independent predictor of long-term adverse outcomes in CAD patients following PCI.

**Keywords:** Alkaline phosphatase-to-albumin ratio; Coronary artery disease; Percutaneous coronary intervention; Long-term adverse outcomes

**Introduction**
Coronary artery disease (CAD) has been a major cause of mortality, and researches on CAD have drawn intense attention worldwide. Previous studies demonstrated that several biomarkers were significantly associated with the pathogenesis of CAD: inflammatory response such as high-sensitive C-reactive protein (hsCRP) and interleukin-6 (IL-6); lipid metabolism such as triglyceride-rich
lipoprotein-cholesterol (TRL-C)\textsuperscript{[4]} and low-density lipoprotein cholesterol (LDL-C)\textsuperscript{[5]}, hypercoagulability such as D-dimer\textsuperscript{[6]} and fibrin degradation products (FDP)\textsuperscript{[7]}, atherosclerosis such as myeloperoxidase (MPO)\textsuperscript{[8]}, coronary artery calcium (CAC)\textsuperscript{[9]} and phosphorus\textsuperscript{[10]}. Alkaline phosphatase (ALP) has enzyme catalytic function that induces the hydrolysis of organic pyrophosphate\textsuperscript{[11]}, and plays an important role in modulating inflammation process, mineral metabolism and vascular calcification\textsuperscript{[12]}. Recently, some studies suggested a significant association between ALP and the pathogenesis of CAD\textsuperscript{[12,13]}. Furthermore, ALP has been reported to predict the mortality, myocardial infarction, or stent thrombosis in CAD patients following PCI\textsuperscript{[11]} which is a useful therapy to treat CAD that evidently improved the prognosis of CAD patients\textsuperscript{[14,15]}. In addition, a low albumin (ALB) level has been also considered as a powerful biomarker to reflect the onset\textsuperscript{[16]}, progress and adverse outcomes\textsuperscript{[17,18]} of CAD. Pu N et al. reported that alkaline phosphatase-to-albumin ratio (AAR) was associated with the liver damage and poorer prognosis of patients with digestive system malignancy\textsuperscript{[19]}. Moreover, several previous studies showed that there was a higher incidence of malignancy in patients with CAD\textsuperscript{[20-22]}. However, it is unknown whether AAR is associated with adverse prognosis in CAD patients. To the best of our knowledge, there is no previous study investigating the relation between AAR and long-term adverse outcomes in post-PCI patients with CAD. Considering that ALP and ALB are involved in the onset, development and prognosis of CAD, it may be feasible to evaluate the potential value of AAR as a biomarker in predicting the adverse outcomes of CAD patients. Therefore, in our study, we aim to assess the relation between AAR and long-term adverse outcomes in CAD patients after undergoing PCI.

**Methods**

**Study Population and Design**

In our study, all of the patients were from the Clinical Outcomes and Risk Factors of Patients with Coronary Heart Disease after PCI (CORFCHD-ZZ) study, which was a large, retrospective cohort study including 3561 CAD patients following PCI from the
First Affiliated Hospital of Zhengzhou University from January 2013 to December 2017 and its data were obtained from case records and follow-ups. The details of the CORFCHD-ZZ study could be browsed on http://www.chictr.org.cn (registration number: ChiCTR1800019699). A total of 3561 patients were initially enrolled; 183 patients were subsequently excluded due to unavailable baseline ALP or ALB data. Finally, there were 3378 eligible patients in our study. The inclusion criteria for eligibility in the current analysis were as follows: (1) patients aged at least 18 years; (2) at least one instance of coronary artery stenosis ≥50% confirmed by coronary angiography; (3) at least one clinical phenotype of coronary heart disease: stable angina or acute coronary syndrome; and (4) an indispensable and objective check for evidence of myocardial ischemia: positive stress test, FFR <0.80 or OCT or IVUS examination suggesting unstable plaque. Patients with the following baseline characteristics were excluded: (1) younger than 18 or older than 80; (2) severe valvular heart disease; (3) severe congenital heart disease; (4) hyperthyroidism, anemia or other high-powered heart disease; (5) pulmonary heart disease; (6) hypertrophic obstructive cardiomyopathy; (7) liver dysfunction (defined as alanine aminotransferase or total bilirubin greater than 3 times the normal upper limit); (8) renal insufficiency (defined as serum creatinine greater than 1.5 times the normal upper limit); or (9) conditions with a high-risk of bleeding, such as thrombocytopenia, blood diseases and other diseases. A flowchart of the study design was shown in Figure 1.

**Demographic, Clinical and Laboratory Characteristics**

All of the data were collected from the case records of inpatients at the First Affiliated Hospital of Zhengzhou University including the demographic, clinical and laboratory data. We recorded gender, age, family history of CAD, medications, hypertension, diabetes, smoking, alcohol consumption, systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) as the demographic and clinical data. The definitions of CAD, hypertension, diabetes, smoking and alcohol consumption were described previously[23]. In addition, we collected the laboratory data including
plasma and biochemical parameters such as the levels of blood urea nitrogen (BUN), creatinine (Cr), glucose (GLU), uric acid (UA), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), albumin (ALB), left ventricular ejection fraction (LVEF), pro-brain natriuretic peptide (Pro-BNP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP). All blood samples were collected through a standard venipuncture technique before performing coronary angiography after at least 12 h of fasting.

**Endpoints and Follow-Up**

The primary endpoint was long-term mortality, including ACM and CM. The secondary endpoints were the composite of major adverse cardiac events (MACEs) defined as cardiac death, heart failure, bleeding events and readmission, and the composite of major adverse cardiac and cerebrovascular events (MACCEs) defined as MACEs combined with stroke. All endpoints were described previously\(^ {23}\).

The mean duration of follow-up time was 37.59±22.24 months. All investigators underwent standard training on the following: (1) methods of follow-up: telephone interviews or office visits; (2) content of follow-up: complying with medical advice, the onset of endpoints and so on. The follow-up was conducted according to the above uniform criterion.

**Statistical Analysis**

All analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, Illinois, United States). Continuous variables were presented as the mean ± standard error and compared using t-tests (for data complying with a normal distribution) or Mann–Whitney U-tests (for data complying with a nonnormal distribution). Categorical variables were presented as frequencies and percentages and compared using the chi-square test. Receiver operating characteristic (ROC) curve was performed to
determine the cut-off value of AAR (<1.77 and ≥1.77). The cumulative incidences of long-term outcomes were evaluated using the Kaplan-Meier method and compared using the log-rank test. Collinearity analysis was performed to evaluate whether there was collinearity among univariables with statistical differences before conducting multivariate analysis. Multivariate Cox proportional hazards regression models were conducted to evaluate the predictive performance of AAR to long-term outcomes. All P-values <0.05 were assumed to be significant.

**Results**

**Baseline Characteristics**

In our study, the ROC curve showed that the cut-off value of AAR was 1.77, which divided a total of 3378 CAD patients after undergoing PCI into two groups: the lower group (AAR <1.77, n=1676) and the higher group (AAR ≥1.77, n=1702). As shown in **table 1**, we found that several variables were significantly different between the two groups, such as gender, alcohol consumption, age, DBP, BUN, UA, GLU, TC, HDL-C, LDL-C, ALB, LVEF, Pro-BNP, ALT, AST, GGT and ALP (all P<0.05). However, there were no significant differences in the following variables between the two groups: family history; hypertension; diabetes; smoking; aspirin; ticagrelor or clopidogrel; β-blocker; ACEI or ARB; Statins; SBP; HR; Cr and TG (all P≥0.05).

**Outcomes**

As shown in **table 2**, the incidence of ACM, CM, MACCEs and MACEs in lower AAR group were 3.0% (n=51), 1.7% (n=29), 10.2% (n=171) and 13.4% (n=225), respectively, and that in higher AAR group were 4.5% (n=76), 2.9% (n=50), 12.2% (n=208) and 15.8% (n=269). As shown in **Figure 2**, Kaplan–Meier analyses were performed to evaluate the cumulative incidences of long-term outcomes in both groups, and showed that an elevated AAR was significantly associated with long-term ACM (log-rank, P=0.014), CM (log-rank, P=0.011), MACEs (log-rank, P=0.013) and MACCEs (log-rank, P=0.006). Collinearity analysis was conducted to evaluate whether there was collinearity (VIF>2 indicating obvious collinearity) among
univariables with statistical differences before performing multivariate analysis; as shown in table 3, the analysis showed that there was obvious collinearity between TC (VIF: 3.957) and LDL-C (VIF: 3.803). However, there was no collinearity among remaining univariables after excluding TC. And then, multivariate Cox proportional hazards regression models were conducted to evaluate whether there was a significant correlation between the AAR and long-term outcomes; the models were adjusted for confounders including gender, age, alcohol consumption, BUN, UA, HDL-C and LDL-C. Patients in the higher AAR group had an increased long-term ACM (adjusted HR=1.488 [1.031-2.149], \( P=0.034 \)), CM (adjusted HR=1.837 [1.141-2.959], \( P=0.012 \)), MACEs (adjusted HR=1.257 [1.018-1.551], \( P=0.033 \)) and MACCEs (adjusted HR=1.237 [1.029-1.486], \( P=0.024 \)) incidence, compared to patients in the lower AAR group after being adjusted for the abovementioned confounders (table 4). Therefore, the increased AAR was an independent predictor of long-term adverse outcomes in CAD patients after undergoing PCI. In addition, all adjusted confounders of long-term ACM, CM, MACEs and MACCEs were shown in table S1, table S2, table S3 and table S4.

Discussion

To the best of our knowledge, this is the first study on evaluating the prognostic value of AAR to long-term outcomes in CAD patients. In our study, we found that an increased AAR was an independent predictor of long-term adverse outcomes in CAD patients following PCI after being adjusted for several confounders including gender, age, alcohol consumption, BUN, UA, HDL-C and LDL-C. Moreover, our study had a large sample (3378 enrolled patients) which improved the statistical power and made the results more credible.

Since CAD has been a major cause of mortality\(^1\), a large number of biomarkers, such as hsCRP\(^2\), LDL-C\(^5\), D-dimer\(^6\), CAC\(^9\) and ALB\(^{16-18}\), were investigated whether there was a significant relation with CAD, and the results suggested that these typical biomarkers had powerful predictive performance to poor prognosis of CAD. Furthermore, recent studies demonstrated that several emerging novel biomarkers...
were considered as independent predictors of long-term outcomes in post-PCI patient with CAD such as ALP\textsuperscript{[11,13]}, plasma mannose\textsuperscript{[24]}, liver miRNAs\textsuperscript{[25]}, cysteine-rich angiogenic inducer 61 (Cyr61)\textsuperscript{[26]} and Amyloid-\(\beta\) (1-40)\textsuperscript{[27]}. In a retrospective study, Pu N et al. found that AAR was associated with the liver damage and poorer prognosis of patients with digestive system malignancy and an elevated AAR reflected the increase of tumor site and several serum biochemical indexes levels\textsuperscript{[19]}. With the rapid development of tumor detection and anti-tumor therapy, there was a higher prevalence of malignancy in patients with CAD\textsuperscript{[20-22]}, such as the BleeMACS study\textsuperscript{[20]} sub-analysis demonstrated a non-negligible prevalence with a higher incidence of death, re-infarction and bleeding in a CAD subpopulation with malignancy compared to the overall CAD population. Similarly, CAD patients with malignancy were at higher risk of in-hospital and long-term mortality as compared to non-malignancy patients in another previous study\textsuperscript{[22]} which showed the related mechanisms were endothelial dysfunction, increased expression of pro-inflammatory cytokines, oxidative stress and platelet activity. Moreover, AAR was also demonstrated as a novel inflammatory marker of poor prognosis in patients with malignancy\textsuperscript{[19]} In addition, both ALP and ALB were involved in the onset, development and prognosis of CAD. Based on these previous findings, we logically hypothesized that AAR would be an effective predictor for adverse outcomes in CAD patients who undergo PCI.

ALP could be activated by oxidative stress, and its increase was also associated with oxidative stress\textsuperscript{[28]}. Oxidative stress, a risk factor for CAD, powerfully reflected the initiation of atherosclerosis, and NADPH oxidases were able to produce reactive oxygen species\textsuperscript{[29]} which was harmful to DNA, lipids, and proteins\textsuperscript{[19]}. Similarly, in a recent review enrolling more than 1000 studies\textsuperscript{[30]}, Tejero J et al. found that dysregulated production of reactive oxygen species (ROS) or reactive nitrogen species (RNS), such as NO, lead to oxidative stress and in turn induced the onset and development of CAD, and they interpreted particularly the related mechanisms of lots of signaling molecules such as Tyr657, heme-depleted sGC and NOXs. It is well-known that several mechanisms are involved in the pathogenesis of CAD such as
inflammatory response\textsuperscript{[3,7]}, metabolic disturbance\textsuperscript{[4,5]} and atherosclerosis\textsuperscript{[9]}. Furthermore, an elevated ALP level played an important role in contributing to inflammation process, inducing abnormal mineral metabolism and accelerating the initiation of atherosclerosis, and then leading to the onset of CAD\textsuperscript{[12]}. In addition, ALP was independently associated with the adverse outcomes in CAD patients from Iran, such as stroke and all-cause mortality\textsuperscript{[31]}. A similar study also showed that ALP was a powerful predictor of mortality, myocardial infarction, or stent thrombosis in CAD patients following PCI\textsuperscript{[11]}. On the contrary, ALB was considered as a protective factor for cardiac function\textsuperscript{[32]} and its decrease was positively associated with the incidence and long-term mortality of CAD\textsuperscript{[16,33]}. A low ALB level could attenuate fibrinolysis, decrease antioxidant capacity, disrupt endothelial functions, activate inflammatory process, increase blood viscosity and the risk of atherothrombosis, leading to adverse cardiovascular events\textsuperscript{[34]}. Furthermore, a recent study reported that autophagy may be considered as a related mechanism on how a low ALB level induced the onset of cardiovascular events in CAD patients: a reduced serum ALB level was able to induce autophagy; excessive autophagy contributed to the death of pancreatic beta cells leading to impaired glucose tolerance, and it could impair myocardial cells leading to reduced cardiac function; therefore, a low ALB level increased the incidence of cardiovascular events\textsuperscript{[35]}. More recently, H. Wada et al. demonstrated that a low ALB level was an independent predictor of long-term mortality in CAD patients without chronic kidney disease after undergoing PCI\textsuperscript{[36]}. Considering that increased ALP and reduced ALB levels in serum were significantly associated with the pathogenesis of CAD and contributed to the initiation, progress and prognosis of CAD, plus our findings from a cohort study with a large sample, thus we thought that AAR may be a reasonable and feasible biomarker to predict long-term adverse outcomes in post-PCI patients with CAD.

**Study Limitations**

First, there were some unavailable baseline ALP and ALB data from a few patients in our study, and the removal of these patients contributed to the reduction of study
sample size. Second, we didn’t take atrial fibrillation into consideration in the exclusion criteria. Third, it was not considered whether fracture healing, some bone diseases and corticosteroids had some influences on AAR. Fourth, we only collected the baseline data, so it was unknown whether dynamic change of these variables affected the endpoints. Fifth, our study was a single, retrospective study and only evaluate the relation between AAR and long-term adverse outcomes in post-PCI patients with CAD from China, thus the findings still need to be further demonstrated in other populations.

Conclusions
An elevated AAR is a novel independent predictor of long-term adverse outcomes in CAD patients after undergoing PCI, such as mortality, MACEs and MACCEs, and it is worth utilizing in clinical practice.

Declarations

Ethics statement
This study protocol was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University, and was in line with the Declaration of Helsinki. Due to the retrospective design of the study, the need to obtain informed consent from eligible patients was waived by the ethics committee. The authors were accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors' Contributions
(I) Conception and design: XYD and YYZ; (II) Administrative support: JYZ; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: QQG, JCZ, MDC, FHS, ZYL, KW, LZJ, LF, XTY, YB, ZLZ and RJZ; (V) Data analysis and interpretation: XYD and YYZ; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors

Competing interests
None
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Data Availability Statement

The data will not be shared, because the identified participant information is included in the data.

Consent for Publication:

Written informed consent for publication was obtained from each author, and there are no other persons who satisfy the criteria for authorship but are not listed.

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Figure Legends

Figure 1. A flowchart of the study design. Abbreviation: CAD, Coronary artery disease; PCI, Percutaneous coronary intervention; AAR, Alkaline phosphatase-to-albumin ratio; ALP, Alkaline phosphatase; ALB, Albumin; ACM, All-cause mortality; CM, Cardiac mortality; MACEs, Major adverse cardiac events; MACCEs, Major adverse cardiac and cerebrovascular events.

Figure 2. Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of all-cause mortality (ACM), cardiac mortality (CM), major adverse cardiac events (MACEs) and major adverse cardiac and cerebrovascular events (MACCEs). Abbreviation: AAR, Alkaline phosphatase-to-albumin ratio.
Fig. 1

3561 CAD patients after undergoing PCI from the CORFCHD-ZZ study (registration number: ChiCTR1800019699)

183 CAD patients after undergoing PCI eliminated due to the unavailable ALP or ALB data

3378 CAD patients after undergoing PCI selected ultimately

AAR < 1.77 (n=1676)  AAR ≥ 1.77 (n=1702)

Follow-up for median 37.59 ± 22.24 months

Primary endpoint: Long-term mortality including ACM and CM
Secondary endpoints: MACEs, MACCEs
Fig. 2

Cum incidence of events vs. follow-up (m) for ACM and CM, with log rank P-values for each group comparison.

ACM
- AAR group
  - lower group
  - higher group
  - lower group-censored
  - higher group-censored
  Log rank P=0.014

CM
- AAR group
  - lower group
  - higher group
  - lower group-censored
  - higher group-censored
  Log rank P=0.011

MACE
- AAR group
  - lower group
  - higher group
  - lower group-censored
  - higher group-censored
  Log rank P=0.013

MACCE
- AAR group
  - lower group
  - higher group
  - lower group-censored
  - higher group-censored
  Log rank P=0.006
Table 1: Baseline characteristics of patients

| Variables                          | AAR < 1.77 | AAR ≥ 1.77 | χ² or t or MWU | P-Value |
|-----------------------------------|------------|------------|----------------|---------|
| Family history, n (%)             | 327(19.7)  | 308(18.2)  | 1.148          | 0.284   |
| Gender, Male, n (%)               | 1212(72.3) | 1115(65.5) | 18.239         | <0.001  |
| Hypertension, n (%)               | 955(57.0)  | 922(54.2)  | 2.699          | 0.100   |
| Diabetes, n (%)                   | 403(24.0)  | 390(22.9)  | 0.601          | 0.438   |
| Smoking, n (%)                    | 526(31.4)  | 502(29.5)  | 1.424          | 0.233   |
| Alcohol consumption, n (%)        | 298(17.8)  | 251(14.7)  | 5.708          | **0.017** |
| Aspirin, n(%)                     | 1676(100)  | 1702(100)  |                |         |
| Ticagrelor or Clopidogrel, n(%)   | 1676(100)  | 1702(100)  |                |         |
| β- blocker, n (%)                 | 1184(93.9) | 1217(93.0) | 0.889          | 0.346   |
| ACEI or ARB, n (%)                | 697(41.6)  | 727(42.7)  | 0.440          | 0.507   |
| Statins, n (%)                    | 1671(99.7) | 1692(99.4) | 1.598          | 0.206   |
| Age, years                        | 62.59±10.87| 63.94±10.38| -3.695         | <0.001  |
| SBP, mm Hg                        | 133.00±17.11| 132.80±18.49| 0.317          | 0.751   |
| DBP, mm Hg                        | 79.56±11.12| 78.75±11.12| 0.644          | 0.035   |
| Heart rate, bpm                   | 74.42±22.73| 74.77±11.45| -0.567         | 0.571   |
| BUN, mmol/L                       | 5.52±3.11  | 5.82±4.94  | -2.098         | 0.036   |
| Cr, umol/L                        | 71.87±19.97| 73.60±45.69| -1.423         | 0.155   |
| UA, mmol/L                        | 301.97±83.17| 295.85±88.33| 2.063          | **0.039** |
| GLU, mmol/L                       | 5.46±1.68  | 5.82±2.54  | -4.777         | <0.001  |
| TG, mmol/L                        | 1.65±1.15  | 1.68±1.10  | 0.738          | 0.458   |
| TC, mmol/L                        | 3.84±0.99  | 3.96±1.05  | -3.369         | **0.001** |
| HDL-C, mmol/L                     | 1.05±0.27  | 1.03±0.31  | 2.066          | **0.039** |
| LDL-C, mmol/L                     | 2.33±0.82  | 2.46±0.87  | -4.200         | <0.001  |
| ALB, g/L                          | 41.87±4.30| 39.77±4.53| 13.877         | **<0.001** |
| LVEF, %                           | 60.77±6.95| 59.81±7.56| 3.477          | 0.001   |
| Pro-BNP, pg/mL                    | 238.00(101.25-594.50) | 313.00(139.00-823.15) | -6.002 | <0.001 |
| ALT, U/L                          | 23.00(15.00-38.00) | 26.00(17.00-45.00) | -5.578 | <0.001 |
| AST, U/L                          | 21.00(17.00-30.00) | 22.00(17.00-38.00) | -5.382 | <0.001 |
| GGT, U/L                          | 23.00(16.00-35.00) | 29.00(18.00-48.325) | -9.019 | <0.001 |
| ALP, U/L                          | 61.00(54.00-67.95) | 86.00(77.00-98.00) | -45.970 | <0.001 |

Abbreviation: AAR, alkaline phosphatase-to-albumin ratio; MWU: Mann–Whitney U-tests; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; GLU, glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. ALB, albumin; LVEF, left ventricular ejection fraction; Pro-BNP, pro-brain natriuretic peptide; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP,
alkaline phosphatase; Note: The boldfaced *P*-Values are statistically different.
Table 2: Outcomes comparison between both groups on log-rank test

| Outcomes      | AAR < 1.77 | AAR ≥ 1.77 | χ²  | P-Value |
|---------------|------------|------------|-----|---------|
| ACM, n (%)    | 51(3.0)    | 76(4.5)    | 6.038 | 0.014   |
| CM, n(%)      | 29(1.7)    | 50(2.9)    | 6.502 | 0.011   |
| MACEs, n (%)  | 171(10.2)  | 208(12.2)  | 6.138 | 0.013   |
| MACCEs, n (%) | 225(13.4)  | 269(15.8)  | 7.420 | 0.006   |

Abbreviation: AAR, alkaline phosphatase-to-albumin ratio; ACM, all-cause mortality; CM, cardiac mortality; MACEs, major adverse cardiovascular events; MACCEs, major adverse cardiovascular and cerebrovascular events. Note: The boldfaced P-Values are statistically different.
Table 3: Collinearity analysis for confounders

| Variables             | B    | SE   | Beta  | T     | P-Value | TOL  | VIF  |
|-----------------------|------|------|-------|-------|---------|------|------|
| Constant              | -0.148 | 0.030 | -4.977 | <0.001 |         |      |      |
| Gender                | -0.010 | 0.008 | -0.024 | -1.249 | 0.212   | 0.795 | 1.258 |
| Age                   | 0.003 | 0.000 | 0.154 | 8.620  | <0.001  | 0.938 | 1.067 |
| Alcohol consumption   | 0.009 | 0.009 | 0.018 | 0.986  | 0.324   | 0.908 | 1.101 |
| BUN                   | 0.003 | 0.001 | 0.062 | 3.541  | <0.001  | 0.971 | 1.030 |
| UA                    | 6.469E-5 | 0.000 | 0.029 | 1.574  | 0.116   | 0.891 | 1.122 |
| TC                    | 0.013 | 0.006 | 0.068 | 1.960  | 0.050   | 0.253 | 3.957 |
| HDL-C                 | -0.026 | 0.012 | -0.040 | -2.149 | 0.032   | 0.866 | 1.155 |
| LDL-C                 | -0.016 | 0.008 | -0.071 | -2.107 | 0.035   | 0.263 | 3.803 |

Abbreviation: BUN, blood urea nitrogen; UA, uric acid; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Note: The boldfaced VIF indicates that there is obvious collinearity between TC and LDL-C.
Table 4: Incidence of outcomes on multivariate Cox proportional hazards regression models

| Outcomes   | HR(95% CI)       | P-Value | Adjusted HR(95% CI)\(^a\) | P-Value |
|------------|------------------|---------|----------------------------|---------|
| ACM        | 1.554(1.090-2.216) | 0.015   | 1.488(1.031-2.149)         | 0.034   |
| CM         | 1.797(1.137-2.841) | 0.012   | 1.837(1.141-2.959)         | 0.012   |
| MACEs      | 1.290(1.053-1.579) | 0.014   | 1.257(1.018-1.551)         | 0.033   |
| MACCEs     | 1.277(1.070-1.525) | 0.007   | 1.237(1.029-1.486)         | 0.024   |

Abbreviation: ACM, all-cause mortality; CM, cardiac mortality; MACEs, major adverse cardiovascular events; MACCEs, major adverse cardiovascular and cerebrovascular events. Note: The boldfaced P-Values are statistically different.

\(^a\)Adjusted for gender, age, alcohol consumption, blood urea nitrogen, uric acid, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol.
Table S1: Cox regression analysis results for long-term ACM

| Variables            | B    | SE   | Wald   | P-Value | HR   | 95%CI          |
|----------------------|------|------|--------|---------|------|----------------|
| Gender               | -0.255 | 0.227 | 1.258  | 0.262   | 0.775| 0.496-1.210    |
| Age                  | 0.072 | 0.010 | 55.258 | <0.001  | 1.075| 1.054-1.095    |
| Alcohol consumption  | 0.258 | 0.244 | 1.118  | 0.290   | 1.295| 0.802-2.090    |
| BUN                  | 0.048 | 0.012 | 15.732 | <0.001  | 1.049| 1.024-1.074    |
| UA                   | 0.001 | 0.001 | 1.703  | 0.192   | 1.001| 0.999-1.003    |
| HDL-C                | -0.529 | 0.368 | 2.067  | 0.150   | 0.589| 0.286-1.212    |
| LDL-C                | -0.057 | 0.111 | 0.267  | 0.606   | 0.944| 0.759-1.174    |
| AAR                  | 0.398 | 0.187 | 4.503  | **0.034** | 1.488| 1.031-2.149    |

Abbreviation: ACM, all-cause mortality; BUN, blood urea nitrogen; UA, uric acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AAR, alkaline phosphatase to albumin ratio. Note: The boldfaced P-Values are statistically different.
Table S2: Cox regression analysis results for long-term CM

| Variables          | B    | SE   | Wald  | P-Value | HR   | 95%CI       |
|--------------------|------|------|-------|---------|------|-------------|
| Gender             | -0.681 | 0.318 | 4.582 | **0.032** | 0.506 | 0.271-0.944 |
| Age                | 0.068 | 0.012 | 31.764 | <**0.001** | 1.070 | 1.045-1.095 |
| Alcohol consumption| 0.011 | 0.316 | 0.001 | 0.971   | 1.011 | 0.544-1.879 |
| BUN                | 0.049 | 0.013 | 13.979 | <**0.001** | 1.050 | 1.024-1.078 |
| UA                 | 0.002 | 0.001 | 3.610 | 0.057   | 1.002 | 1.000-1.005 |
| HDL-C              | -0.911 | 0.487 | 3.500 | 0.061   | 0.402 | 0.155-1.044 |
| LDL-C              | -0.044 | 0.142 | 0.097 | 0.755   | 0.957 | 0.725-1.263 |
| AAR                | 0.608 | 0.243 | 6.258 | **0.012** | 1.837 | 1.141-2.959 |

Abbreviation: CM, cardiac mortality; BUN, blood urea nitrogen; UA, uric acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AAR, alkaline phosphatase to albumin ratio. Note: The boldfaced P-Values are statistically different.
Table S3: Cox regression analysis results for MACEs

| Variables         | B    | SE   | Wald | P-Value | HR   | 95%CI   |
|-------------------|------|------|------|---------|------|---------|
| Gender            | -0.099 | 0.132 | 0.565 | 0.452 | 0.906 | 0.700-1.172 |
| Age               | 0.007 | 0.005 | 1.652 | 0.199 | 1.007 | 0.996-1.017 |
| Alcohol consumption | -0.016 | 0.146 | 0.012 | 0.912 | 0.984 | 0.738-1.311 |
| BUN               | 0.019 | 0.010 | 3.764 | 0.052 | 1.019 | 1.000-1.039 |
| UA                | 0.000 | 0.001 | 0.369 | 0.544 | 1.000 | 0.999-1.002 |
| HDL-C             | -0.368 | 0.215 | 2.940 | 0.086 | 0.692 | 0.454-1.054 |
| LDL-C             | 0.097 | 0.062 | 2.451 | 0.117 | 1.102 | 0.976-1.244 |
| AAR               | 0.228 | 0.107 | 4.534 | **0.033** | 1.257 | 1.018-1.551 |

Abbreviation: MACEs, major adverse cardiovascular events; BUN, blood urea nitrogen; UA, uric acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AAR, alkaline phosphatase to albumin ratio. Note: The boldfaced P-Values are statistically different.
Table S4: Cox regression analysis results for MACCEs

| Variables          | B    | SE  | Wald | P-Value | HR    | 95%CI       |
|-------------------|------|-----|------|---------|-------|-------------|
| Gender            | -0.058 | 0.113 | 0.264 | 0.608  | 0.943  | 0.756-1.178 |
| Age               | 0.010 | 0.005 | 5.075 | **0.024** | 1.010  | 1.001-1.020 |
| Alcohol consumption | -0.098 | 0.133 | 0.540 | 0.463  | 0.907  | 0.699-1.177 |
| BUN               | 0.018 | 0.009 | 4.234 | **0.040** | 1.018  | 1.001-1.036 |
| UA                | 0.000 | 0.001 | 0.604 | 0.437  | 1.000  | 0.999-1.002 |
| HDL-C             | -0.243 | 0.184 | 1.759 | 0.185  | 0.784  | 0.547-1.123 |
| LDL-C             | 0.097 | 0.054 | 3.204 | 0.073  | 1.102  | 0.991-1.225 |
| AAR               | 0.212 | 0.094 | 5.126 | **0.024** | 1.237  | 1.029-1.486 |

Abbreviation: MACCEs, major adverse cardiovascular and cerebrovascular events; BUN, blood urea nitrogen; UA, uric acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AAR, alkaline phosphatase to albumin ratio. Note: The boldfaced P-Values are statistically different.