# Association of Serum Prealbumin with Angiographic Severity in Patients with Acute Coronary Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF 1 Chenglong Zhang
BC 2 Pei Liu
ACDEF 1 Ke Xia
BC 1 Han Fang
BC 1 Minna Jiang
BC 1 Qiying Xie
AF 1 Zaixin Yu
AF 1 Tianlun Yang

1 Department of Cardiology, Xiangya Hospital of Central South University, Changsha, Hunan, P.R. China
2 Department of Cardiology, The 3rd Hospital of Changsha, Changsha, Hunan, P.R. China

Corresponding Author: Tianlun Yang, e-mail: tianluny@163.com
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**Background:** Serum prealbumin (PA), which is a nutritional index, has been found to be associated with severities and prognoses of various diseases. However, there are no reports about the relationship between PA and angiographic severity of coronary artery disease.

**Material/Methods:** This cross-sectional study included 867 patients with acute coronary syndrome (ACS) who underwent coronary angiography. Patients were divided into quartiles of PA and coronary artery stenosis was determined by angiographic Gensini score, the presence of high Gensini score (Gensini score ≥120), and triple-vessel disease. Multivariate linear and logistic regression analyses were performed to explore the relationship between PA and disease severity in a coronary angiogram.

**Results:** There was a significant and independent negative correlation between PA and Gensini score in multivariate linear regression (p=0.015). Logistic regression analysis revealed that crude odds ratios of triple-vessel disease and high Gensini score were 2.47 (95% CI: 1.66–3.67) and 1.83 (95% CI: 1.50–3.49), respectively, in the first quartile of PA compared with the fourth quartile and the results remained significant for high Gensini score after adjustment for confounding factors. In addition, estimated glomerular filtration rate, liver function, and high-sensitivity C-reactive protein (hs-CRP) had no interactive relationships in the above associations. Patients with lower levels of albumin or higher levels of hs-CRP or the ratio of hs-CRP to PA (hs-CRP/PA) also had more severe coronary atherosclerosis.

**Conclusions:** PA is negatively and independently associated with angiographic severity in patients with ACS, indicating for potential use in estimating the burden of coronary atherosclerosis.

**MeSH Keywords:** Acute Coronary Syndrome • Coronary Angiography • Coronary Stenosis • Prealbumin

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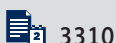
## Background

Acute coronary syndrome (ACS), defined as the spectrum of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina, is a severe presentation of cardiovascular diseases. It is one of the leading diseases with higher mortality rates across the world, including China [1]. Therefore, it is necessary to screen an effective and appropriate parameter to perform early estimation of coronary stenosis.

Serum prealbumin (PA) is a negative acute-phase reactive protein with a short half-life (about 2 days) and is synthesized mainly in the liver. It is generally used to determine nutritional status. Due to its shorter half-life, PA is more sensitive in assessing malnutrition than is albumin, whose half-life is about 20 days. Moreover, an increasing number of investigations have shown that PA is closely associated with a variety of conditions, such as postoperative complications [2], recurrence of malignant carcinoma [3], and prognosis of heart failure [4,5] and acute kidney injury [6]. In addition, investigations showed that the ratio of hs-CRP to PA (hs-CRP/PA) may be superior to either hs-CRP or PA in the assessing associations with severities and progressions of several diseases [6–8]. However, few relevant studies have focused on patients with coronary artery disease (CAD). One study showed that in patients under chronic hemodialysis, levels of serum PA were lower in patients with CAD than those without CAD [9]. Another study reported that PA was negatively correlated with atherosclerotic vascular disease (ASVD) [10]. However, the association between PA and angiographic extent of CAD has not been investigated in previous research.

Therefore, the main purpose of the present cross-sectional study was to investigate the association between serum PA and coronary artery stenosis, which was determined by Gensini score and the presence of high Gensini score (Gensini score ≥120) and triple-vessel disease in patients with ACS. We also examined whether the association of PA with coronary severity was independent of confounding factors, especially liver and renal function and inflammation status, through multivariate regression and subgroup analyses.

## Material and Methods

### Study population

We reviewed the medical records of consecutive patients from Jan 2013 to Dec 2013 who were admitted in the Department of Cardiology, Xiangya Hospital, Central South University. Patients who were diagnosed with ACS and underwent coronary angiography, including percutaneous coronary intervention (PCI), were enrolled in our study. The diagnosis of ACS is made according to clinical symptoms, angiographic reports, and other accessory examinations, and the standard of ACS diagnosis is based on diagnostic criteria of ACS in ACCF/AHA guidelines [11,12]. Exclusion criteria were: acute inflammation, known carcinoma, preexisting severe hepatic or renal diseases, and any missing information. After exclusion, a total of 867 patients were included in our final analysis (637 men, 230 women, average age 61.0±10.1 years). Since our study was retrospectively designed, written informed consent from participants could not be obtained, but our study protocol was approved by the Ethics Committee of Xiangya Hospital, Central South University.

Medical histories of patients were acquired by intern residents within 24 h after admission. Smoking status and histories of hypertension and diabetes mellitus or whether the patients were under treatment for related diseases were collected. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a mercury sphygmomanometers at least 2 times after resting 10–15 min in supine position. The means of 2 blood records were used in the study. Seated resting pulse rates were obtained by residents by palpating the radial artery for at least 30 s and pulse rates were regarded as heart rates in our study.

Fasting blood samples were taken from the median cubital vein on the next morning of admission. White blood cell count (WBC), hemoglobin, platelet count, serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), albumin, PA, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), hs-CRP, serum creatinine, and uric acid were measured in the clinical laboratory using a biochemical analyzer MODULAR PP (Roche Diagnostics GmbH, Germany). Estimated glomerular filtration rate (eGFR) was calculated using the equation of the Modification Diet for Renal Disease modified by the Chinese coefficient [13]: eGFR (ml/min/1.73 m$^2$)=186×serum creatinine (exp[−1.154])×age (exp[−0.203]) ×1.233×0.742 (if female). Then, the results were divided by 90 ml/min/1.73 m$^2$ of eGFR, which is the cut-off value of stage 1 chronic kidney disease [14]. The patients were divided into quartiles of PA (<209.9 mg/L, 209.9–253.6 mg/L, 253.6–322.8 mg/L, ≥322.8 mg/L). The patients were also classified into 3 groups by hs-CRP with cut-off values of 3 mg/L and 10 mg/L, which are widely used as cut-off values in prognosis prediction in patients with ACS, and those in the upper tertile are classified as having elevated risks of adverse outcomes [15]. The patients were also divided into tertiles of hs-CRP/PA to examine its association with coronary stenosis.

### Evaluation of the coronary artery stenosis

All patients received coronary angiographic examinations or PCI in the cardiac catheterization room after the completion

of preoperative preparation. Transradial approaches and TIG catheters were chosen for most patients, and Judkins catheters via femoral approaches were also performed, if appropriate. According to specific angiographic outcomes, at least 2 projections for each main coronary artery were recorded for analysis. The angiograms of the patients were evaluated by 2 experienced interventional cardiologists who were blinded to our study. CAD was defined if more than 50% of the lumen diameter was occluded in any of the main coronary arteries, including the left main coronary artery (LM), left anterior descending artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA). Stenosis of diagonal branch, obtuse marginal branch, and posterior branch of the left ventricle was recorded as LAD, LCX, and RCA, respectively, and LM stenosis was recorded as both LAD and LCX. Triple-vessel disease was defined if stenosis was detected in LAD, LCX, and RCA concurrently.

The severity of coronary stenosis was quantitatively evaluated using the Gensini scoring system [16], which was calculated according to stenosis severity as 1 point for <25% stenosis, 2 points for 26–50% stenosis, 4 points for 51–75% stenosis, 8 points for 76–90% stenosis, and 32 points for total occlusion. The score was then multiplied by a weight coefficient representing the importance of the position of the lesion in the coronary artery system. For example, 5 for the LM, 2.5 for the proximal region of the LAD and LCX, 1.5 for the middle region, and 1 for the distal region of the LAD and mid-distal region of the LCX. A Gensini score ≥120 (high Gensini score) was considered as advanced coronary disease and 31.4% of the subjects were in this group. The severity of coronary stenosis was reflected by Gensini score, the presence of triple-vessel disease, and high Gensini score in the present study.

### Statistical analysis

Continuous variables were examined by test of normality before analysis and are expressed as means (standard deviation, SD) or medians (range of interquartile), as appropriate. Categorical variables are presented as counts (percentage). One-way analysis of variance (ANOVA) and Kruskal-Wallis test were used for comparison among quartiles of PA. The chi-squared test was used for comparison of categorical variables among groups. Univariate regressions were performed to assess the correlations between baseline characteristics and Gensini score, and a multivariate linear regression for independent determinants of Gensini score was also performed. Multivariate logistic regressions were carried out for the association between quartiles of PA and angiographic coronary severity determined by the presence of triple-vessel disease and high Gensini score. Analyses in subgroups divided by eGFR, liver function, and hs-CRP were also performed to detect whether an interaction relationship existed. All statistical analyses were conducted using

the SPSS 19.0 software package (SPSS Inc., Chicago, IL, USA) for Windows. All statistical tests were 2-sided and a $p < 0.05$ was considered statistically significant.

## Results

A total of 867 consecutive patients with ACS were included in the final analysis. The baseline characteristics of the entire population according to quartiles of PA (<209.9 mg/L, 209.9–253.6 mg/L, 253.6–322.8 mg/L, ≥322.8 mg/L) are presented in Table 1. As shown in Table 1, patients with increased levels of PA tended to be younger and had higher levels of hemoglobin, platelet count, albumin, TC, TG, HDL-C, and uric acid; patients in the first quartile of PA had lowest levels of LDL-C but highest levels of hs-CRP; and patients in the last quartile had lowest levels of TBIL. No significant differences were detected in terms of sex, history of hypertension, diabetes mellitus, smoking status, heart rate, WBC, ALT, AST, or eGFR. Coronary angiographic descriptions of all patients are also listed in Table 1. As mentioned above, 31.4% of all subjects were classified into the high Gensini score group. Patients with decreased levels of PA had higher Gensini score and proportions of high Gensini score and triple-vessel disease (p≤0.001). In terms of specific stenosis arteries, higher levels of LM, LCX, and RCA were found in patients with lower levels of PA (p≤0.001).

Angiographic characteristics of the patients divided by hs-CRP (<3 mg/L, 3–10 mg/L, ≥10 mg/L) and tertiles of albumin (<36.4 g/L, 36.4–40.2 g/L, ≥40.2 g/L) and hs-CRP/PA (<0.0073, 0.0073–0.0277, ≥0.0277) are shown in Figure 1. Patients in the first tertile of albumin had higher levels of Gensini score (105.8±63.4 versus 87.7±55.2, p<0.001) and increased proportions of high Gensini score (36.9% versus 28.5%, p=0.032) and triple-vessel disease (67.4% versus 56.6%, p=0.008) compared to the third tertile. Patients with hs-CRP ≥10 mg/L had higher Gensini score (112.2±57.7 versus 92.8±61.0, p<0.001) and proportion of triple-vessel disease (76.7% versus 55.2%, p<0.001) compared to those with hs-CRP <3 mg/L. Patients in the third tertile of hs-CRP/PA had higher levels of Gensini score (108.1±60.3 versus 89.1±59.1, p<0.001) and elevated proportions of high Gensini score (38.1% versus 28.2%, p=0.021) and triple-vessel disease (72.8% versus 52.9%, p<0.001) compared to the first tertile.

We performed univariate analysis between baseline characteristics and Gensini score using Pearson correlation or Spearman correlation analysis, as appropriate. As shown in Table 2, male sex, diabetes mellitus, smoking, WBC, LDL-C, ALT, AST, hs-CRP, and uric acid were positively correlated with Gensini score, while hemoglobin, albumin, PA, HDL-C, and eGFR were negatively correlated with Gensini score. When all the above variables were taken into the multivariate regression model, only

**Table 1.** Baseline and angiographic characteristics of the population according to quartiles of PA.

| Variables | PA (mg/L) | | | | | | | | P value |
|---|---|---|---|---|---|---|---|---|---|
| | Q1 (217) <209.9 | | Q2 (216) 209.9–253.6 | | Q3 (217) 253.6–322.8 | | Q4 (217) ≥322.8 | | |
| **Clinical characteristics** | | | | | | | | | |
| Male, n (%) | 155 | (71.4) | 151 | (69.9) | 168 | (77.4) | 163 | (75.1) | 0.272 |
| Age, years | 63.0 | (56.0–70.0) | 62.5 | (56.0–68.0) | 61.0 | (53.0–69.0) | 60.0 | (54.0–66.0) | **0.002** |
| Hypertension, n (%) | 126 | (58.1) | 128 | (59.3) | 129 | (59.4) | 141 | (65.0) | 0.458 |
| Diabetes mellitus, n (%) | 60 | (27.6) | 62 | (28.7) | 43 | (19.8) | 55 | (25.3) | 0.145 |
| Smoking, n (%) | 117 | (53.9) | 115 | (53.2) | 116 | (53.5) | 112 | (51.6) | 0.967 |
| Heart rate, beats per min | 72.0 | (64.0–81.0) | 72.0 | (64.0–80.0) | 72.0 | (64.0–80.0) | 72.0 | (66.0–80.0) | 0.393 |
| **Laboratory examination** | | | | | | | | | |
| WBC, ×10⁹/L | 7.00 | (5.70–8.83) | 6.60 | (5.65–8.20) | 6.80 | (5.70–8.53) | 6.75 | (5.57–8.20) | 0.671 |
| Hemoglobin, g/L | 126.1 | (16.1) | 130.6 | (16.0) | 134.3 | (15.4) | 135.4 | (13.1) | **<0.001** |
| Platelet, ×10⁹/L | 161.0 | (133.8–204.0) | 175.0 | (148.0–207.0) | 177.0 | (143.8–205.0) | 182.0 | (152.8–213.5) | **0.017** |
| Albumin, g/L | 35.9 | (4.4) | 39.2 | (4.9) | 38.8 | (4.3) | 39.4 | (4.2) | **<0.001** |
| PA, mg/L | 179.0 | (146.0–194.8) | 230.3 | (221.2–241.7) | 286.4 | (269.8–303.0) | 373.8 | (345.9–412.8) | **<0.001** |
| TC, mmol/L | 3.99 | (3.36–4.67) | 4.11 | (3.46–4.94) | 4.35 | (3.71–5.06) | 4.42 | (3.75–5.36) | **<0.001** |
| TG, mmol/L | 1.30 | (0.90–1.89) | 1.41 | (1.02–1.91) | 1.48 | (1.04–2.23) | 1.56 | (1.12–2.50) | **<0.001** |
| HDL-C, mmol/L | 0.98 | (0.86–1.18) | 1.05 | (0.89–1.26) | 1.10 | (0.93–1.30) | 1.18 | (1.01–1.36) | **<0.001** |
| LDL-C, mmol/L | 2.36 | (1.85–3.00) | 2.70 | (2.01–3.45) | 2.55 | (2.01–3.27) | 2.52 | (2.03–3.29) | **0.015** |
| ALT, U/L | 27.0 | (17.5–43.1) | 26.3 | (17.9–40.8) | 27.8 | (16.3–42.6) | 24.7 | (17.3–39.2) | 0.879 |
| AST, U/L | 26.6 | (20.3–51.1) | 23.9 | (19.3–36.0) | 24.1 | (19.7–39.7) | 24.1 | (19.2–31.9) | 0.065 |
| TBIL, mmol/L | 10.4 | (7.6–15.2) | 10.1 | (7.9–14.0) | 11.0 | (8.3–13.9) | 9.4 | (7.2–12.7) | **0.024** |
| eGFR, ml/min/1.73 m² | 96.7 | (25.4) | 93.8 | (23.7) | 96.4 | (25.1) | 95.1 | (22.1) | 0.571 |
| hs-CRP, mg/L | 8.24 | (2.18–20.00) | 2.94 | (0.99–10.10) | 3.97 | (1.19–8.29) | 3.92 | (1.03–8.23) | **<0.001** |
| Uric acid, μmol/L | 312.5 | (268.0–376.4) | 338.7 | (289.3–406.7) | 334.0 | (288.0–403.5) | 360.0 | (310.9–412.9) | **<0.001** |
| **Coronary angiographic characteristics** | | | | | | | | | |
| Gensini score | 107.6 | (61.1) | 101.6 | (60.4) | 89.2 | (56.4) | 84.1 | (57.9) | **<0.001** |
| High Gensini score, n (%) | 84 | (38.7) | 75 | (34.7) | 66 | (30.4) | 47 | (21.7) | **0.001** |
| Triple-vessel disease, n (%) | 154 | (71.0) | 139 | (64.4) | 129 | (59.4) | 108 | (49.8) | **<0.001** |
| Stenosis coronary artery, n (%) | | | | | | | | | |
| LM | 35 | (16.1) | 24 | (11.1) | 18 | (8.3) | 9 | (4.1) | **<0.001** |
| LAD | 211 | (97.2) | 208 | (96.3) | 202 | (93.1) | 210 | (96.8) | 0.123 |
| LCX | 180 | (82.9) | 172 | (79.6) | 163 | (75.1) | 147 | (67.7) | **0.001** |
| RCA | 176 | (81.1) | 166 | (76.9) | 161 | (74.2) | 135 | (62.2) | **<0.001** |

Data are expressed as mean (standard deviation) or median (interquartile range) or n (%) as appropriate. PA – prealbumin; WBC – white blood cell; TC – total cholesterol; TG – triglyceride; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; ALT – alanine aminotransferase; AST – aspertate aminotransferase; TBIL – total bilirubin; eGFR – estimated glomerular filtration rate; hs-CRP – high-sensitivity C-reactive protein; LM – left main coronary artery; LAD – left anterior descending artery; LCX – left circumflex coronary artery; RCA – right coronary artery.
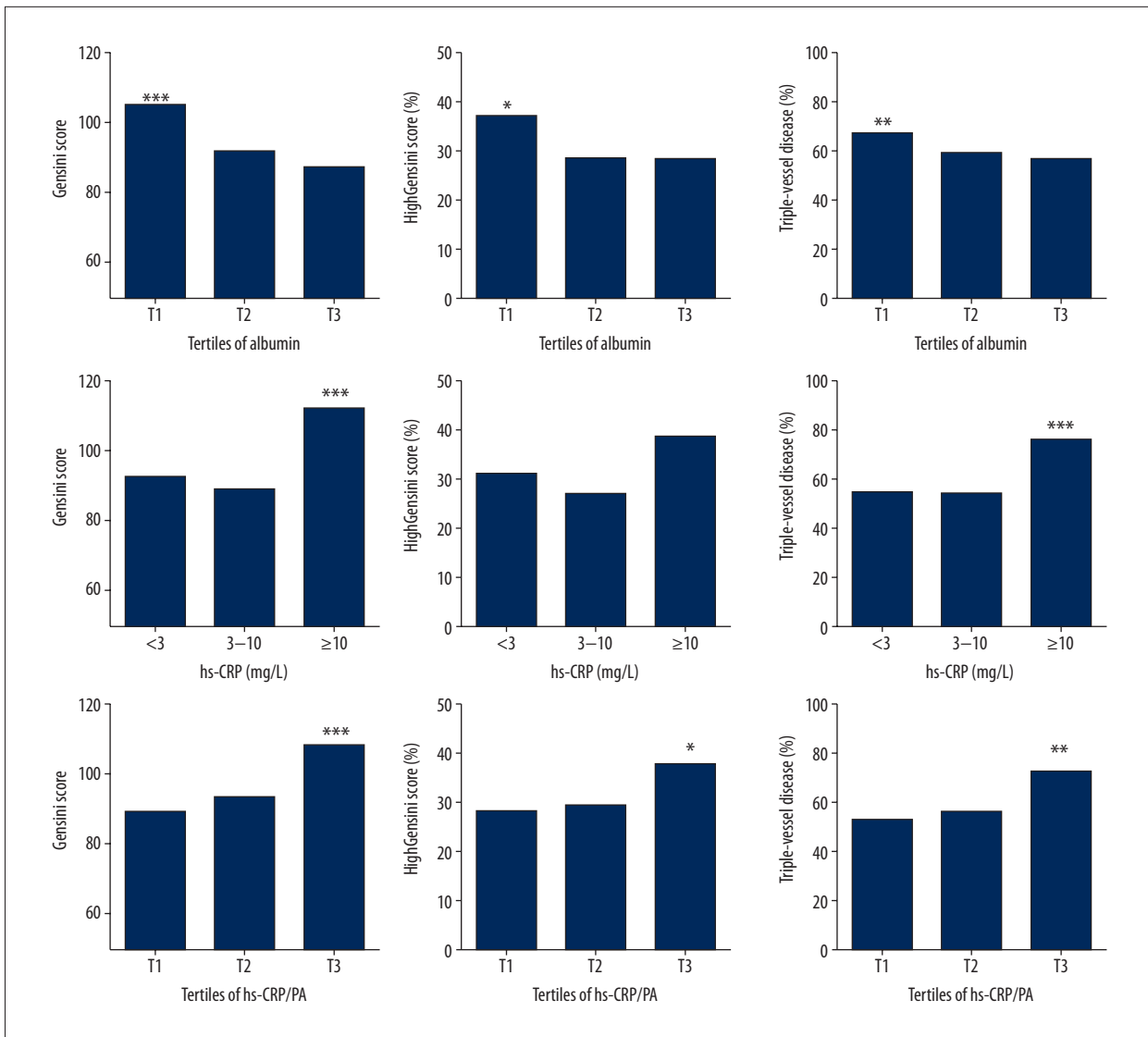
**Figure 1.** Coronary angiographic characteristics in subgroups of albumin, hs-CRP, and the ratio of hs-CRP to PA (hs-CRP/PA). * p<0.01, ** p<0.05, *** p<0.01 versus the first group for albumin and the third group for hs-CRP and hs-CRP/PA. hs-CRP – high-sensitivity C-reactive protein; PA – prealbumin.

male sex, diabetes mellitus, albumin, PA, LDL-C, and eGFR remained as independent determinants of Gensini score.

Finally, we performed multivariate logistic regression analysis to calculate the odds ratios of triple-vessel disease and high Gensini score across quartiles of PA (Tables 3, 4). The fourth quartile of PA was considered as the reference group, and sex, age, hypertension, diabetes mellitus, smoking status, heart rate, WBC, platelet, albumin, TC, TG, HDL-C, LDL-C, eGFR, liver function, and hs-CRP were included in adjusted models if the variables were not divided as subgroups. As presented in Tables 3, 4, patients with decreased quartiles of PA had elevated risks of both triple-vessel disease and high Gensini score in crude models (p for trend <0.001 for both). Results

showed that patients in the first quartile of PA had an odds ratio of 2.47 (95% confidence interval [CI]: 1.66–3.67) for triple-vessel disease and 2.28 (95% CI: 1.50–3.49) for high Gensini score in crude models. When adjusted for confounding factors, similar trends for triple-vessel disease and high Gensini score across quartiles of PA still existed (p for trend <0.043 and <0.044, respectively), although the odds ratios did not reach statistical significance for triple-vessel disease (Adjusted odds ratio: 1.64, 95% CI: 0.98–2.72, Q1 group versus Q4 group of PA). In the subgroup analysis, increased odds ratios of triple-vessel disease and high Gensini score in decreased quartiles of PA in patients with an eGFR ≥90 ml/min/1.73 m² were detected (p for trend=0.009 and 0.008, respectively), and increased odds ratios of triple-vessel disease were obtained in

**Table 2.** Univariate analysis and multivariate linear regression analysis of determinants of Gensini score.

| Variables | Univariate analysis | | Multivariate analysis | | |
|---|---|---|---|---|---|
| | Correlation coefficient | P value | Regression coefficient | 95% CI | P value |
| Male | 0.11 | 0.002 | 14.42 | 1.52, 27.32 | **0.029** |
| Diabetes mellitus | 0.10 | 0.003 | 11.04 | 1.00, 21.08 | **0.031** |
| Smoking | 0.13 | <0.001 | 8.16 | −2.13, 18.45 | 0.120 |
| Hemoglobin, g/L | −0.09 | 0.009 | −0.29 | −0.62, 0.04 | 0.082 |
| WBC, ×10$^9$/L | 0.10 | 0.005 | −0.08 | −1.83, 1.68 | 0.933 |
| Albumin, g/L | −0.14 | <0.001 | −1.34 | −2.34, −0.29 | **0.012** |
| PA, mg/L | −0.16 | <0.001 | −0.07 | −0.12, −0.01 | **0.015** |
| HDL-C, mmol/L | −0.14 | <0.001 | −10.92 | −28.06, 6.23 | 0.212 |
| LDL-C, mmol/L | 0.12 | 0.001 | 9.00 | 4.53, 13.49 | **<0.001** |
| ALT, U/L | 0.09 | 0.011 | −0.04 | −0.19, 0.12 | 0.651 |
| AST, U/L | 0.16 | <0.001 | 0.07 | −0.02, 0.15 | 0.133 |
| hs-CRP, mg/L | 0.15 | <0.001 | 0.09 | −0.26, 0.44 | 0.612 |
| eGFR, ml/min/1.73 m$^2$ | −0.11 | 0.002 | −0.24 | −0.43, −0.05 | **0.014** |
| Uric acid, μmol/L | 0.07 | 0.032 | 0.03 | −0.02, 0.08 | 0.200 |

CI – confidence interval; WBC – white blood cell; PA – prealbumin; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; ALT – alanine aminotransferase; AST – aspertate aminotransferase; hs-CRP – high-sensitivity C-reactive protein; eGFR – estimated glomerular filtration rate.

decreased quartiles of PA in patients with normal liver function (p for trend=0.037). However, interaction analysis did not reach statistical significance for the interactive relationship in eGFR, liver function, or hs-CRP with triple-vessel disease or high Gensini score (p>0.05 for all). We also defined an abnormal liver function as ALT and/or AST >80 U/L to reclassify the patients into subgroups, or by a cut-off value of 60 ml/min/1.73 m$^2$ in eGFR or 3 mg/L in hs-CRP or the median of hs-CRP (4.18 mg/L) to further explore if any interaction existed, but the results were negative.

## Discussion

The current study demonstrates that patients with ACS whose serum PA levels were lower may have more serious coronary ischemia burden determined by Gensini score and the presence of high Gensini score and triple-vessel disease. Moreover, the above associations remained significant except for triple-vessel disease, although a similar trend still existed after adjusting for possible confounding factors, including hs-CRP, albumin, and liver and renal function. To the best of our knowledge, this was the first study to evaluate the relationship between serum

PA and coronary stenosis in patients with CAD. Our results indicate that PA may have the ability to estimate coronary stenosis, but further research is needed to verify our conclusions.

PA is a negative acute-phase reactive protein with a short half-life (about 2 days), making it sensitive in detecting short-term malnutrition and assessing the effects of nutritional supplementation [17]. Because measurement of serum PA is convenient, it is generally used as a marker of determining nutritional status [18]. The synthesis of PA is mainly in the liver and its serum concentration could be influenced by several factors, such as nutritional intake, liver disease, renal dysfunction, inflammatory status, acute alcohol intoxication, prednisone therapy, and zinc deficiency [19,20]. PA was reported to be associated with severities and prognosis of a range of diseases, including cardiovascular diseases [4,5]. Our results revealed that PA was negatively and independently correlated with coronary stenosis in patients with ACS, which has not been reported in previous investigations.

The possible underlying mechanisms for PA and coronary stenosis may be as follows: Firstly, inflammation is one of the dominating elements in the pathogenesis of atherosclerosis.

**Table 3.** Odds ratios and 95% CI of triple-vessel disease according to quartiles of PA in all subjects and subgroups.

| | N | PA | | | | P for trend | P for interaction |
|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | | |
| **All subjects** | | | | | | | |
| Crude | 867 | 2.47 (1.66, 3.67) | 1.82 (1.24, 2.68) | 1.48 (1.01, 2.16) | 1.00 | **<0.001** | |
| Adjusted | 714 | 1.64 (0.98, 2.72) | 1.57 (0.97, 2.55) | 1.32 (0.83, 2.10) | 1.00 | **0.043**[a] | |
| **eGFR, ml/min/1.73 m²** | | | | | | | |
| <90 | 294 | 0.97 (0.40, 2.33) | 0.78 (0.34, 1.76) | 0.89 (0.40, 2.01) | 1.00 | 0.851[a] | 0.436 |
| ≥90 | 420 | 2.18 (1.14, 4.17) | 2.30 (1.22, 4.33) | 1.56 (0.85, 2.86) | 1.00 | **0.009**[a] | |
| **Liver function[b]** | | | | | | | |
| Normal | 478 | 1.75 (0.94, 3.24) | 1.81 (1.01, 3.25) | 1.24 (0.71, 2.18) | 1.00 | **0.037**[a] | 0.624 |
| Abnormal | 236 | 1.25 (0.47, 3.34) | 0.92 (0.35, 2.42) | 1.14 (0.46, 2.84) | 1.00 | 0.766[a] | |
| **hs-CRP, mg/L** | | | | | | | |
| <10 | 518 | 1.36 (0.76, 2.44) | 1.51 (0.87, 2.63) | 1.22 (0.72, 2.04) | 1.00 | 0.206[a] | 0.766 |
| ≥10 | 196 | 3.19 (0.94, 10.82) | 1.55 (0.49, 4.92) | 1.83 (0.54, 6.23) | 1.00 | 0.087[a] | |

[a] Adjusted for gender, age, hypertension, diabetes mellitus, smoking status, heart rate, white blood cell, platelet, albumin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, liver function, eGFR, hs-CRP, if not analyzed in subgroups. [b] Abnormal liver function was defined as ALT >40 U/L and/or AST >40 U/L. CI – confidence interval; PA – prealbumin; eGFR – estimated glomerular filtration rate; hs-CRP – high-sensitivity C-reactive protein; ALT – alanine aminotransferase; AST – aspertate aminotransferase.

**Table 4.** Odds ratios and 95% CI of high Gensini score according to quartiles of PA in all subjects and subgroups.

| | N | PA | | | | P for trend | P for interaction |
|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | | |
| **All subjects** | | | | | | | |
| Crude | 867 | 2.28 (1.50, 3.49) | 1.92 (1.25, 2.95) | 1.58 (1.02, 2.44) | 1.00 | **<0.001** | |
| Adjusted | 714 | 1.83 (1.07, 3.14) | 1.95 (1.16, 3.28) | 1.88 (1.12, 3.13) | 1.00 | **0.044**[a] | |
| **eGFR, ml/min/1.73 m²** | | | | | | | |
| <90 | 294 | 0.98 (0.42, 2.32) | 1.17 (0.52, 2.62) | 1.38 (0.62, 3.10) | 1.00 | 0.818[a] | 0.322 |
| ≥90 | 420 | 2.74 (1.34, 5.58) | 2.49 (1.23, 5.03) | 2.20 (1.10, 4.42) | 1.00 | **0.008**[a] | |
| **Liver function[b]** | | | | | | | |
| Normal | 478 | 1.85 (0.94, 3.63) | 2.07 (1.08, 3.96) | 2.38 (1.27, 4.49) | 1.00 | 0.125[a] | 0.418 |
| Abnormal | 236 | 1.47 (0.56, 3.86) | 1.49 (0.57, 3.89) | 1.07 (0.41, 2.79) | 1.00 | 0.326[a] | |
| **hs-CRP, mg/L** | | | | | | | |
| <10 | 518 | 1.55 (0.82, 2.95) | 2.13 (1.17, 3.88) | 1.61 (0.90, 2.88) | 1.00 | 0.105[a] | 0.330 |
| ≥10 | 196 | 2.20 (0.67, 7.21) | 1.23 (0.36, 4.16) | 3.41 (0.98, 11.88) | 1.00 | 0.638[a] | |

[a] Adjusted for gender, age, hypertension, diabetes mellitus, smoking status, heart rate, white blood cell, platelet, albumin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, liver function, eGFR, hs-CRP, if not analyzed in subgroups. [b] Abnormal liver function was defined as ALT >40 U/L and/or AST >40 U/L. CI – confidence interval; PA – prealbumin; eGFR – estimated glomerular filtration rate; hs-CRP – high-sensitivity C-reactive protein; ALT – alanine aminotransferase; AST – aspertate aminotransferase.

As a negative acute-phase protein, the synthesis of PA is suppressed in inflammatory status in which multiple inflammatory cytokines are involved, including interleukin-1, interleukin-6, and TNF-α, resulting in elevated generation of hs-CRP and decreased synthesis of PA by the liver [20,21], which was also demonstrated by our finding that patients located in the lowest quartile of PA had the highest levels of hs-CRP. We made adjustment for hs-CRP in the regression models and classified patients by hs-CRP in interactive analysis; however, the results inferred that the association of PA with coronary stenosis was independent of hs-CRP. Secondly, symptoms such as loss of appetite, nausea, and vomiting are reported in some patients with ACS, especially in females [22], leading to down-regulation of synthesis of PA due to decreased caloric and protein intake, and this condition may be more obvious in patients with severe coronary stenosis. Thirdly, the synthesis of PA is also decreased if liver function is damaged [19], which is not uncommon in patients with ACS due to hemodynamic changes and hypoxia injury of the liver [23]. However, we excluded those patients with existing severe liver diseases in the enrollment step, and the association between PA and coronary severity remained significant after adjustment for liver function indexes, revealing that liver dysfunction cannot fully account for the relationship between PA and coronary stenosis.

Impaired renal function is associated with not only the prevalence of CAD, but also the severity of atherosclerotic burden in patients with suspected CAD or confirmed ACS, as reflected by Gensini score and SYNTAX score [24,25], which is another scoring system used to assess coronary stenosis. In our study, multivariate regression analysis revealed that eGFR was negatively associated with Gensini score, which is in accordance with previous studies [24,25]. Further analysis indicated that decreasing risks of triple-vessel disease and high Gensini score were shown in increasing quartiles of PA in patients with eGFR ≥90 ml/min/1.73 m$^2$, but the interactive relationships were not significant. This may be because PA is degraded by the kidneys and its serum levels may increase in conditions of renal dysfunction, thus affecting the association with PA and severity of CAD.

Serum albumin is one of the classical markers determining nutritional status, and a low serum albumin level upon admission can predict in-hospital adverse outcomes in ACS [26]. Multivariate regression analysis in our study showed that albumin was independently associated with Gensini score, which is in agreement with previous studies [27–29]. However, in the logistic regression analysis, the odds ratios of high Gensini score (OR=1.17, 95% CI: 0.75–1.82, p=0.50) and triple-vessel disease (OR=0.99, 95% CI: 0.63–1.56, p=0.97) in patients in the lowest tertile of albumin were not significant compared with the highest tertile after adjusting for other factors (data not shown). This discordance may due to the discrepancies of study population and the methods of evaluating coronary stenosis, as in 1 study SYNTAX score was used for assessing coronary stenosis [28].

Hs-CRP is an indicator of systemic inflammatory response and is associated with a wide range of acute and chronic diseases, including CAD [30]. Inflammation plays a vital role in the initiation and progression of atherosclerosis [31] and numerous prospective studies have demonstrated that hs-CRP can predict future CAD risk in both males and females [30]. Our study showed that patients in the third tertile of hs-CRP had elevated Gensini score and risks of triple-vessel disease compared with the first tertile. hs-CRP was positively correlated with Gensini score in univariate analysis, but hs-CRP did not remain independently associated with Gensini score in multivariate regression analysis, which disagrees with a previous study reporting that hs-CRP was an independent determinant of Gensini score in patients with suspected CAD [29]. It is noteworthy that a multiethnic study indicated that hs-CRP is within normal range at the very onset of first STEMI in 41% of cases [32]. Therefore, whether hs-CRP is a good indicator of coronary stenosis in patients with ACS needs to be determined by further investigations.

Because the synthesis of PA is influenced by inflammation, some studies integrated inflammatory response and nutrition status with their ratio [6,7,33] to diminish their interference. It was reported that CRP/PA was strongly associated with the severity of organ dysfunction in critically ill patients [33]. In addition, another investigation inferred that CRP/PA, but not PA or CRP, was independently associated with mortality in patients with acute kidney injury [6]. In the present study, our results revealed that patients in the highest tertile of hs-CRP/PA had increased Gensini score and risks of high Gensini score and triple-vessel disease. However, the odd ratios of high Gensini score (OR=0.97, 95% CI: 0.61–1.55, p=0.89) and triple-vessel disease (OR=1.57, 95% CI: 0.98–2.52, p=0.06) in the third tertile of hs-CRP/PA did not reach statistical significance compared with the first tertile after adjusting for other factors (data not shown). Therefore, we conclude that hs-CRP/PA is not superior to PA in the evaluation of coronary stenosis.

Our study has several limitations. The cross-sectional design prevented us from determining whether a low PA level was the result of acute coronary events, or whether patients with low PA level were prone to acute coronary events. In addition, as we only included patients with ACS, the generalizability of our conclusions to other populations, such as patients with stable angina pectoris or asymptomatic coronary atherosclerosis, is unknown. The prognostic predictive ability of PA was not provided in our study because we did not record short- or long-term adverse outcomes, nor did we have sequential measurements of PA to examine the association of dynamic variation of PA with coronary stenosis.

## Conclusions

In this cross-sectional study, we concluded that serum PA is negatively and independently associated with angiographic coronary stenosis in patients with ACS, indicating that PA may be a good index for use in early assessment of atherosclerosis burden. Further research is needed to determine if PA can predict subsequent adverse outcomes in patients with CAD.

### Conflict of interest

None.

## References:

1. He J, Gu D, Wu X et al: Major causes of death among men and women in China. N Engl J Med, 2005; 353: 1124–34

2. Yu PJ, Cassiere HA, Dellis SL et al: Impact of preoperative prealbumin on outcomes after cardiac surgery. J Parenter Enteral Nutr, 2015; 39: 870–74

3. Kawai H, Ota H: Low perioperative serum prealbumin predicts early recurrence after curative pulmonary resection for non-small-cell lung cancer. World J Surg, 2012; 36: 2853–57

4. Lourenco P, Silva S, Frioes F et al: Low prealbumin is strongly associated with adverse outcome in heart failure. Heart, 2014; 100: 1780–85

5. Cabassi A, de Champlain J, Maggiore U et al: Prealbumin improves death risk prediction of BNP-added Seattle Heart Failure Model: Results from a pilot study in elderly chronic heart failure patients. Int J Cardiol, 2013; 168: 3334–39

6. Xie Q, Zhou Y, Xu Z et al: The ratio of CRP to prealbumin levels predict mortality in patients with hospital-acquired acute kidney injury. BMC Nephrol, 2011; 12: 30

7. Harriman S, Rodych N, Hayes P, Moser MA: The C-reactive protein-to-prealbumin ratio predicts fistula closure. Am J Surg, 2011; 202: 175–78

8. Esfahani A, Makhdami N, Faramarzi E et al: Prealbumin/CRP based prognostic score, a new tool for predicting metastasis in patients with inoperable gastric cancer. Gastroenterol Res Pract, 2016; 2016: 4686189

9. Yeo Y, Byun SW, Lee JY et al: Lack of association between small dense low-density lipoprotein levels and coronary artery disease in chronic hemodialysis patients. Am J Nephrol, 2009; 30: 310–14

10. Dalrymple LS, Johansen KL, Chertow GM et al: Longitudinal measures of serum albumin and prealbumin concentrations in incident dialysis patients: The comprehensive dialysis study. J Ren Nutr, 2013; 23: 91–97

11. Wright RS, Anderson JL, Adams CD et al: 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation, 2011; 123: 2022–60

12. O'Gara PT, Kushner FG, Ascheim DD et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation, 2013; 127: 529–55

13. Ma YC, Zuo L, Chen JH et al: Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol, 2006; 17: 2937–44

14. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis, 2002; 39: S1–266

15. He LP, Tang XY, Ling WH et al: Early C-reactive protein in the prediction of long-term outcomes after acute coronary syndromes: A meta-analysis of longitudinal studies. Heart, 2010; 96: 339–46

16. Gensini GG: A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol, 1983; 51: 606

17. Ingenbleek Y, Young V: Transthyretin (prealbumin) in health and disease: nutritional implications. Annu Rev Nutr, 1994; 14: 495–533

18. Shenkin A: Serum prealbumin: Is it a marker of nutritional status or of risk of malnutrition? Clin Chem, 2006; 52: 2177–79

19. Caccialanza R, Palladini G, Klersy C et al: Serum prealbumin: an independent marker of short-term energy intake in the presence of multiple-organ disease involvement. Nutrition, 2013; 29: 580–82

20. Beck FK, Rosenthal TC: Prealbumin: A marker for nutritional evaluation. Am Fam Physician, 2002; 65: 1575–78

21. Kalantar-Zadeh K, Anker SD, Horwich TB, Fonarow GC: Nutritional and anti-inflammatory interventions in chronic heart failure. Am J Cardiol, 2008; 101: 89E–103E

22. Shin JY, Martin R, Suls J: Meta-analytic evaluation of gender differences and symptom measurement strategies in acute coronary syndromes. Heart Lung, 2010; 39: 283–95

23. Lofthus DM, Stevens SR, Armstrong PW et al: Pattern of liver enzyme elevations in acute ST-elevation myocardial infarction. Coron Artery Dis, 2012; 23: 22–30

24. Duran M, Uysal OK, Gunebakmaz O et al: Glomerular filtration rate is associated with burden of coronary atherosclerosis in patients with acute coronary syndrome. Angiology, 2014; 65: 350–56

25. Kim IY, Hwang IH, Lee KN et al: Decreased renal function is an independent predictor of severity of coronary artery disease: An application of Gensini score. J Korean Med Sci, 2013; 28: 1615–21

26. Hartopo AB, Gharini PP, Setianto BY: Low serum albumin levels and in-hospital adverse outcomes in acute coronary syndrome. Int Heart J, 2010; 51: 221–26

27. Joki N, Hase H, Tanaka Y et al: Relationship between serum albumin level before initiating haemodialysis and angiographic severity of coronary atherosclerosis in end-stage renal disease patients. Nephrol Dial Transplant, 2006; 21: 1633–39

28. Kurtul A, Murat SN, Yarlioglues M et al: Usefulness of serum albumin concentration to predict high coronary SYNTAX score and in-hospital mortality in patients with acute coronary syndrome. Angiology, 2016; 67: 34–40

29. Che J, Li G, Wang W et al: Serum autoantibodies against human oxidized low-density lipoproteins are inversely associated with severity of coronary stenotic lesions calculated by Gensini score. Cardiol J, 2011; 18: 364–70

30. Rifai N, Ridker PM: High-sensitivity C-reactive protein: A novel and promising marker of coronary heart disease. Clin Chem, 2001; 47: 403–11

31. Libby P: Inflammation in atherosclerosis. Nature, 2002; 420: 868–74

32. Cristell N, Cianflone D, Durante A et al: High-sensitivity C-reactive protein is within normal levels at the very onset of first ST-segment elevation acute myocardial infarction in 41% of cases: A multiethnic case-control study. J Am Coll Cardiol, 2011; 58: 2654–61

33. Pinilla JC, Hayes P, Laverty W et al: The C-reactive protein to prealbumin ratio correlates with the severity of multiple organ dysfunction. Surgery, 1998; 124: 799–805