# Postprint: Predictive Value of C-Reactive Protein/Albumin Ratio for Long-Term Adverse Cardiovascular and Cerebrovascular Events in Patients with Type 2 Diabetes Mellitus and Acute Myocardial Infarction

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**Date:** 2024-03-27T00:00:00+00:00

## Abstract

Background Acute myocardial infarction (AMI) is one of the major threats to global public health. Although reperfusion therapy strategies are available, AMI-related major adverse cardiovascular and cerebrovascular events (MACCEs) remain a leading cause of mortality worldwide. Particularly in AMI patients with concomitant diabetes mellitus, the complexity and severity of coronary artery lesions make early detection and assessment of long-term prognosis relatively difficult. Therefore, identifying simple and readily available laboratory indicators may provide a basis for predicting MACCEs in type 2 diabetes mellitus (T2DM) patients with AMI following percutaneous coronary intervention (PCI).

Objective To investigate the predictive value of the serum C-reactive protein (CRP)/albumin (Alb) ratio (CAR) for long-term MACCEs in T2DM patients with AMI after PCI.

Methods We enrolled 1683 T2DM patients with AMI admitted to the Department of Cardiology, General Hospital of Ningxia Medical University between 2014 and 2019. General clinical data and laboratory results were collected. All patients were followed up via telephone or outpatient visits, with a median follow-up duration of 5.6 years. MACCEs were defined as all-cause death, non-fatal myocardial infarction, recurrent unstable angina, non-fatal stroke, new-onset heart failure or rehospitalization for worsening heart failure, and repeat revascularization. Patients were divided into a MACCEs group (n=508) and a non-MACCEs group (n=1175) based on whether they experienced major adverse cardiovascular events during follow-up. Univariate and multivariate Logistic regression analyses were performed to identify influencing factors of MACCEs

in T2DM patients with AMI. Kaplan-Meier survival curves were constructed, and comparisons were made using the Log-rank test. Receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive efficacy of CAR for long-term MACCEs, while net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to assess the incremental prognostic value of CAR in T2DM patients with AMI.

Results Among 1683 patients, 508 (30.18%) developed MACCEs. Multivariate Logistic regression analysis identified hypertension [OR (95%CI) = 1.994 (1.142~3.483)], coronary stent length [OR (95%CI) = 1.031 (1.002~1.062)], CRP [OR (95%CI) = 0.950 (0.915~0.986)], Alb [OR (95%CI) = 0.933 (0.880~0.989)], and CAR [OR (95%CI) = 5.582 (1.705~18.277)] as influencing factors for MACCEs in T2DM patients with AMI after PCI (P<0.05). Based on the median CAR level (0.86), patients were stratified into CAR<0.86 and CAR$ 0.86*groups.Log−ranktestresultsdemonstratedthattheMACCEsincidencewashigherintheCAR* $0.86 group compared with the CAR<0.86 group (52.68% vs. 22.92%; 2=65.65, P<0.001). ROC curve analysis revealed that the area under the curve for CAR predicting MACCEs was 0.728 (95%CI=0.702~0.754), with an optimal cutoff value of 0.576, sensitivity of 0.617, and specificity of 0.747. When added to the baseline model, CAR significantly improved the prediction of adverse cardiovascular and cerebrovascular events compared with CRP and Alb alone [C-index=0.149, P<0.01; NRI=0.377 (0.067, 0.597), P<0.05; IDI=0.166 (0.025, 0.257), P<0.05].

Conclusion CAR is an effective predictive indicator for the risk of long-term MACCEs in T2DM patients with AMI after PCI.

## Full Text

## Abstract

**Background:** Acute myocardial infarction (AMI) remains one of the leading threats to global public health. Despite available reperfusion therapies, major adverse cardio-cerebral events (MACCEs) associated with AMI continue to be a leading cause of death worldwide. This is particularly true for patients with AMI and concomitant diabetes mellitus, where coronary artery disease is more complex and severe, making early detection and prognosis of long-term outcomes for these patients challenging. Therefore, the identification of simple and accessible laboratory markers could facilitate the prediction of post-percutaneous coronary intervention (PCI) MACCEs in patients with type 2 diabetes mellitus (T2DM) and AMI.

**Objective:** To investigate the predictive value of the serum C-reactive protein (CRP)/Albumin (Alb) ratio (CAR) for long-term MACCEs following PCI in patients with T2DM and AMI.

**Methods:** A total of 1,683 patients with T2DM and AMI treated at the Cardiovascular Department of Ningxia Medical University General Hospital between

2014 and 2019 were enrolled. General clinical data and test results were collected for these patients. Follow-ups were conducted via telephone or outpatient visits, with a median follow-up period of 5.6 years. MACCEs were defined as all-cause mortality, non-fatal myocardial infarction, recurrent unstable angina, non-fatal stroke, new-onset heart failure, or rehospitalization for worsening heart failure, and revascularization. Patients were divided into the MACCEs group (508 cases) and the non-MACCEs group (1,175 cases) based on the occurrence of major adverse cardiovascular events during the follow-up period. Univariate and multivariate logistic regression analyses were performed to identify factors influencing MACCEs in patients with T2DM and AMI. Kaplan-Meier survival curves were plotted, and the Log-rank test was used for comparisons. Receiver operating characteristic (ROC) curve analysis assessed the predictive efficacy of CAR for long-term MACCEs in patients with T2DM and AMI, while the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) indices evaluated the improvement in prognostic assessment provided by CAR.

**Results:** Among the 1,683 patients, 508 (30.18%) experienced MACCEs. Multivariate logistic regression analysis indicated that hypertension [OR (95%CI) = 1.994 (1.142-3.483)], length of coronary stent implanted [OR (95%CI) = 1.031 (1.002-1.062)], CRP [OR (95%CI) = 0.950 (0.915-0.986)], Alb [OR (95%CI) = 0.933 (0.880-0.989)], and CAR [OR (95%CI) = 5.582 (1.705-18.277)] were significant predictors of post-PCI MACCEs in patients with T2DM and AMI ($P < 0.05$). Based on the median CAR level (0.86), patients were divided into two groups: CAR $< 0.86$ and CAR $\geq 0.86$. The log-rank test showed that the incidence of MACCEs was significantly higher in the CAR $\geq 0.86$ group compared to the CAR $< 0.86$ group (52.68% vs. 22.92%; $^2 = 65.65$, $P < 0.001$). The ROC curve indicated that the area under the curve (AUC) for CAR in predicting MACCEs was 0.728 (95%CI = 0.702-0.754), with an optimal cut-off value of 0.576, sensitivity of 0.617, and specificity of 0.747. Compared to baseline models, CAR significantly improved the prediction of adverse cardio-cerebral events [C-index = 0.149, $P < 0.01$; NRI = 0.377 (0.067, 0.597), $P < 0.05$; IDI = 0.166 (0.025, 0.257), $P < 0.05$].

**Conclusion:** CAR is an effective predictive marker for the risk of long-term MACCEs in patients with T2DM and AMI following PCI.

**Keywords:** Myocardial infarction; Diabetes mellitus, type 2; Major adverse cardiac and cerebral events; C-reactive protein; Albumin; Forecasting

## Introduction

Acute myocardial infarction (AMI) has been recognized as a leading cause of morbidity and mortality from cardiovascular disease worldwide [1]. The World Bank estimates that the number of AMI cases in China will increase to 23 million by 2030 [2]. Percutaneous coronary intervention (PCI) is the preferred treatment for AMI patients and can significantly reduce mortality and improve

prognosis [3]. However, some AMI patients still remain at high risk for recurrent major adverse cardio-cerebral events (MACCEs). This risk is particularly pronounced in patients with type 2 diabetes mellitus (T2DM), accounting for approximately 37% of AMI cases in China, who are classified as an extreme risk group for recurrent MACCEs [4]. Studies have shown that T2DM is associated with more complex coronary artery lesions and worse prognosis in AMI patients [5]. Therefore, early identification of residual risk factors in AMI patients with concomitant T2DM is essential for better clinical management and reduction of recurrent MACCEs incidence.

C-reactive protein (CRP) is a sensitive indicator of inflammation and a positive acute-phase reactant. Similarly, albumin (Alb), as a negative acute-phase reactant, decreases in inflammatory diseases. Consequently, the C-reactive protein/albumin ratio (CAR) is considered a more sensitive indicator reflecting the severity of inflammatory response and disease progression [6-7]. Furthermore, some studies have shown that CAR may be associated with in-stent thrombosis and in-hospital mortality in AMI patients [8]. Given that CAR is an inflammation-based prognostic indicator, and research on the relationship between CAR and long-term MACCEs in T2DM patients with AMI after PCI is limited, this study analyzed the relationship between serum CRP, Alb, and CAR with recurrent MACCEs to explore the predictive role of CAR in recurrent MACCEs.

## Methods

### Study Population

A total of 8,525 patients diagnosed with acute coronary syndrome at Ningxia Medical University General Hospital between 2014 and 2019 were initially screened. Based on inclusion and exclusion criteria, 1,863 patients with T2DM and AMI were selected, and after further screening, 1,683 patients were ultimately included in the study. The screening process is shown in [Figure 1: see original paper].

**Inclusion criteria:** Patients with elevated troponin and dynamic ST-segment or T-wave changes on electrocardiogram (with or without symptoms), diagnosed with AMI according to the "Guidelines for the Diagnosis and Treatment of ST-segment Elevation Myocardial Infarction (2019)" [9] and "Guidelines for the Diagnosis and Treatment of Non-ST-segment Elevation Myocardial Infarction (2016)" [10].

**Exclusion criteria:** (1) Absence of T2DM; (2) No PCI performed; (3) Acute infectious diseases, estimated glomerular filtration rate (eGFR) $< 30\ \mathrm{mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}}$ or chronic dialysis, severe hepatic dysfunction, malignancy, or hematological disorders; (4) Severe valvular heart disease or cardiomyopathy; (5) Incomplete clinical or follow-up data.

### Data Collection and Definitions

General clinical data were collected, including age, sex, BMI, systolic blood pressure, diastolic blood pressure, and heart rate on admission; medical history (hypertension, cerebrovascular disease, dyslipidemia, previous coronary artery disease, family history of coronary artery disease); and smoking history (defined as smoking $\geq$ 1 cigarette/day for $\geq$ 1 year and currently smoking regularly or occasionally before admission).

Admission diagnosis [ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI)], in-hospital medications [aspirin, clopidogrel, ticagrelor, $\beta$-receptor antagonists, statins, angiotensin-converting enzyme inhibitors (ACEI)], laboratory parameters [white blood cell count (WBC), lymphocyte count (LYM), monocyte count (MXD), hemoglobin, platelet count, triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), CRP, Alb, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, eGFR, glycated hemoglobin (HbA1c), fasting plasma glucose (FPG)], and angiographic data [infarct-related artery, lesion characteristics, number of stents, stent diameter, and stent length] were recorded. All data were verified using the electronic medical record system. CRP and Alb concentrations from the first blood sample during hospitalization were measured at the central laboratory of Ningxia Medical University General Hospital. CAR was calculated as the ratio of CRP to Alb.

### Follow-up and Endpoints

Patients were followed up via telephone or outpatient visits every 3 months until June 31, 2023. MACCEs were defined as all-cause death, non-fatal myocardial infarction, recurrent unstable angina, non-fatal stroke, cardiac rehospitalization (due to new-onset or worsening heart failure), and repeat revascularization. Cardiac death was defined as fatal stroke and myocardial infarction, sudden death, and other cardiac-related deaths. All-cause death was defined as death from any cause. Non-fatal stroke, including ischemic and hemorrhagic stroke, was defined as cerebral dysfunction caused by sudden blockage or rupture of a cerebral blood vessel, diagnosed based on signs of neurological dysfunction or evidence from brain imaging. Cardiac rehospitalization referred to readmission due to new-onset or worsening heart failure. Any coronary revascularization was defined as revascularization of target or non-target vessels.

### Statistical Analysis

SPSS 25.0 software was used for statistical analysis. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$) and compared between groups using independent samples t-test. Non-normally distributed continuous variables were expressed as median (P25, P75) and compared using rank-sum test. Categorical variables were expressed as frequencies

and percentages, with inter-group comparisons performed using $^2$ test. Multivariate logistic regression analysis was used to explore factors influencing MACCEs in T2DM patients with AMI. The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of CAR for MACCEs. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to assess the predictive performance of CRP, Alb, and CAR for MACCEs. A P-value $< 0.05$ was considered statistically significant.

## Results

### Baseline Characteristics

The study followed patients for 40-108 months (median 67 months). The mean age was (63.1 $\pm$ 10.8) years; 1,143 were male and 540 were female. There were 508 patients in the MACCEs group and 1,175 in the non-MACCEs group. Patients in the MACCEs group were older, had higher proportions of females, higher heart rate, higher prevalence of hypertension and cerebrovascular disease, higher rates of previous coronary artery disease, more frequent infarction of the right coronary artery (RCA), longer implanted stent length, higher WBC count, higher CRP levels, higher CAR, higher creatinine, and higher FPG levels compared to the non-MACCEs group. In contrast, they had lower diastolic blood pressure on admission, lower smoking rates, lower rates of left anterior descending artery (LAD) infarction, lower Alb levels, lower hemoglobin, lower eGFR, and lower ejection fraction (EF), with all differences being statistically significant ($P < 0.05$) (Table 1). No significant differences were observed between groups in BMI, dyslipidemia history, family history of coronary artery disease, admission diagnosis (STEMI and NSTEMI), in-hospital medications (aspirin, clopidogrel, ticagrelor, $\beta$-blockers, statins, ACEI), angiographic information (left main and left circumflex artery proportions, bifurcation lesions, calcified lesions, intra-aortic balloon pump usage, number of stents, stent diameter), LYM, MXD, platelet count, TC, TG, HDL, LDL, AST, ALT, or HbA1c (all $P > 0.05$).

### Multivariate Logistic Regression Analysis

Using the occurrence of MACCEs as the dependent variable and variables with statistical and clinical significance from Table 1 as independent variables, multivariate logistic regression analysis was performed. Variable assignments are shown in Table 2. The results showed that hypertension, stent length, CRP, Alb, and CAR were independent influencing factors for MACCEs in AMI patients ($P < 0.05$) (Table 3).

### Kaplan-Meier Survival Analysis

During the median follow-up period of 67 months, 508 patients (30.18%) experienced MACCEs [all-cause death in 236 cases (14.02%), cardiac death in 172 cases (10.21%), non-fatal myocardial infarction in 52 cases (3.09%), recurrent

unstable angina in 140 cases (8.32%), non-fatal stroke in 29 cases (1.72%), heart failure rehospitalization in 96 cases (5.70%), and repeat revascularization in 115 cases (6.83%)]. Based on the median CAR value (0.86), patients were divided into CAR $< 0.86$ and CAR $\geq 0.86$ groups. Log-rank test results showed that the MACCEs rate in the CAR $\geq 0.86$ group [201 cases (47.74%)] was significantly higher than in the CAR $< 0.86$ group, with higher incidence rates for all individual components [non-fatal myocardial infarction in 23 cases (5.46%), recurrent unstable angina in 51 cases (12.11%), all-cause death in 105 cases (24.94%), heart failure rehospitalization in 35 cases (8.31%), and non-fatal stroke in 20 cases (4.75%)] (all $P < 0.05$) (Figure 2).

### Predictive Value of CAR

Compared with CRP and Alb alone, the addition of CAR improved reclassification and discrimination beyond the baseline risk model, with NRI of 0.377 and IDI of 0.166 (both $P < 0.05$). Furthermore, after adding CAR, the C-index of the baseline risk model changed from [0.541 (0.502-0.580), $P = 0.039$] to [0.690 (0.655-0.725), $P = 0.001$] (Table 4). The ROC curve for CAR predicting MACCEs in AMI patients showed an area under the curve of 0.728 (95%CI = 0.702-0.754), with an optimal cut-off value of 0.576, sensitivity of 0.617, and specificity of 0.747 (Figure 3).

## Discussion

The most common cause of death from coronary atherosclerotic cardiovascular disease is coronary ischemia or infarction due to plaque rupture. Patients with T2DM have a 2-fold higher risk of cardiovascular death compared to non-diabetic patients [11], primarily because chronic hyperglycemia causes panvascular injury (macro- and microvascular disease) through oxidative stress and vascular inflammation, impairs collateral circulation formation, increases effective circulating blood volume and cardiac load, predisposes to heart failure, and increases mortality, severely affecting patient prognosis [12]. Studies have shown that once T2DM patients develop AMI, persistent hyperglycemia and oxidative stress can exacerbate the inflammatory response, thereby increasing the incidence of MACCEs after PCI [13]. Therefore, for STEMI patients with T2DM, besides active reperfusion therapy, attention should be paid to the patient' s inflammatory status to detect and minimize long-term MACCEs as early as possible.

This study found that among AMI patients with T2DM, those who developed long-term MACCEs were older, had higher proportions of hypertension and coronary artery disease history, and showed reduced eGFR and EF. Additionally, serum inflammatory levels (WBC count and CRP) were significantly elevated, while albumin levels were markedly decreased. CRP is an acute-phase inflammatory marker synthesized by the liver. Besides being associated with inflammatory or infectious states, its chronic elevation is associated with adverse cardiovascular risk. The CANTOS trial (Canakinumab Anti-inflammatory Throm-

bosis Outcomes Study) supports CRP as a driver of residual inflammatory risk that promotes adverse cardiovascular events [14]. The potential biological mechanisms linking CRP with MACCEs risk primarily involve the pro-atherosclerotic and pro-thrombotic effects of inflammation. CRP can increase reactive oxygen species levels in T2DM patients with AMI, increase oxidized LDL uptake, and induce vascular endothelial cell dysfunction and apoptosis [15]. Furthermore, CRP can stimulate monocytes, endothelial cells, and vascular smooth muscle cells to release tissue factor and activate the metalloproteinase system, thereby inducing a pro-thrombotic state [16]. Previous studies have shown that AMI patients with elevated CRP levels over 10 years have an increased risk of MACCEs [17]. Therefore, it is necessary to include CRP as an indicator for assessing long-term adverse cardio-cerebral event risk.

Albumin is the major protein in human serum that regulates extracellular fluid osmotic pressure and binds various chemicals. Physiological levels of serum albumin can suppress vascular cell adhesion molecule-1 expression and increase oxygen free radical scavenging, thereby reducing inflammatory response and endothelial cell apoptosis, suggesting that albumin is an anti-inflammatory and antioxidant factor [18]. ODUNCU et al. [19] reported that serum albumin levels $< 3.5$ g/dl on admission were an independent predictor of all-cause mortality at 40 months in AMI patients. Studies have shown that low albumin levels are independent predictors of heart failure and in-hospital death in AMI patients [20]. Albumin may also inhibit platelet activation and aggregation by promoting prostacyclin D2 expression and inhibiting thromboxane synthetase activity, and low albumin levels can increase blood viscosity by increasing erythrocyte lysophosphatidylcholine, leading to endothelial dysfunction [21]. Studies have shown that patients with lower serum albumin exhibit higher CRP levels, suggesting an inverse relationship between serum albumin and CRP [22]. The relationship between malnutrition, inflammation, and atherosclerosis (MIA syndrome) has been demonstrated in chronic kidney disease patients, and nutritional status and inflammation levels are significantly associated with higher morbidity and mortality in end-stage renal disease patients [23]. A recent study showed that malnutrition assessed by the Controlling Nutritional Status score and Geriatric Nutritional Risk Index is common in T2DM patients and is closely associated with adverse cardiovascular events [24]. Therefore, an indicator that can simultaneously assess inflammatory and nutritional status may play a role as a new therapeutic target in T2DM and AMI patients.

CAR is a newly introduced indicator calculated as the ratio of CRP to albumin levels and is considered a more accurate marker of inflammatory status and malnutrition than measuring CRP or albumin alone. Studies have shown that CAR is superior to CRP and albumin in predicting the severity and extent of coronary artery disease [25]. Furthermore, research has found that AMI patients with high SYNTAX scores have higher CAR than those with low SYNTAX scores, and CAR is positively correlated with the SYNTAX score, demonstrating good predictive value for coronary artery burden and adverse cardiovascular events in AMI patients [26]. The results of this study indicate that CAR has

good discriminatory ability for long-term MACCEs in T2DM patients with AMI after PCI.

### Limitations

This study has several limitations. First, as a retrospective study with an insufficient sample size, large-sample, multicenter, prospective studies should be conducted in the future. Second, only preoperative serum CRP and albumin levels were included; dynamic monitoring of CRP and albumin during follow-up and measurement of other inflammatory factors should be performed to further explore the relationship between inflammation, glucose metabolism, and MACCEs.

## Conclusion

In conclusion, serum CRP and albumin play important roles in assessing long-term MACCEs risk in T2DM patients with AMI after PCI. Elevated serum CRP/albumin ratio increases the risk of recurrent adverse cardio-cerebral events in AMI patients, and serum CAR can predict the risk of MACCEs in T2DM patients with AMI.

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*Note: Figure translations are in progress. See original paper for figures.*