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The High-Sensitivity C-Reactive Protein to Prealbumin Ratio Predicts Adverse Cardiovascular Events after ST-Elevation Myocardial Infarction

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ABSTRACT

Background: This study evaluated the association of the high-sensitivity C-reactive protein to prealbumin ratio (CPR) with adverse cardiovascular events after ST-elevation myocardial infarction (STEMI) in patients undergoing primary percutaneous coronary intervention (PCI).

Methods: The study included 682 patients who presented with STEMI and were treated with primary PCI. Patients were divided into 2 groups: high CPR (CPR ≥0.02) and low CPR (CPR <0.02). The primary endpoint of the study was the occurrence of major adverse cardiovascular events (MACE), defined as cardiovascular mortality or admission due to recurrent AMI or heart failure. Multivariate Cox regression models were used to assess the prognostic value of CPR on MACE in patients with STEMI.

Results: During a median follow-up of 18 months, the accumulated incidence rate of MACE was significantly higher in the high-CPR group than in the low-CPR group (38.7% versus 12.0%, $P < .01$). Multivariate analysis revealed that CPR was an independent predictor for increased risk of MACE (hazard ratio = 3.27, 95% confidence interval [CI] 2.14 to 4.49, $P < .01$). Receiver operating characteristic (ROC) curve analysis showed that the area under the ROC curve for predicting the diagnosis of MACE was higher for CPR (0.82, 95% CI 0.77 to 0.87) than hs-CRP (0.70, 95% CI 0.65 to 0.75).

Conclusion: CPR was independently associated with MACE and can be used for risk stratification in patients with STEMI.

INTRODUCTION

ST-elevation myocardial infarction (STEMI) commonly occurs when thrombus formation results in complete occlusion of a major epicardial coronary vessel [Kotecha 2016]. It poses a large financial and resource-directed burden on health systems, with high incidence rates in developed countries and increasing rates in the developing world [Dind 2017].

Inflammation is considered to play a substantial role in the pathophysiological process of cardiac remodeling and results in short- and long-term adverse events after STEMI [Li 2019]. Even with immediate percutaneous coronary revascularization (PCI), a large number of patients remain at risk for early electrical/mechanical complications and subsequent major adverse cardiac events (MACE) from myocardial stunning, adverse left ventricular remodeling, culprit lesion restenosis, and de novo coronary stenosis [Perers 2005]. Early detection and diagnosis are of great importance to prevent the progression of STEMI and improve patients' prognosis and survival rate [Lozano 2012]. Increased high-sensitivity C-reactive protein (hs-CRP) and decreased prealbumin concentrations, as biomarkers for systemic inflammation, were found to be predictors of adverse cardiovascular events. Recently, the hs-CRP to prealbumin ratio (CPR) was indicated to be more sensitive and specific for evaluating the systemic inflammatory state compared with the predictive value of either marker alone. CPR is reported to be associated with coronary artery disease (CAD) severity in patients with acute coronary syndrome (ACS) and stable angina pectoris [Cagdas 2019; Karabag 2018]. However, the correlation between CPR and MACE in patients with STEMI is rarely reported.

The aim of the present study was to evaluate the association of CPR with adverse cardiovascular events after STEMI in patients undergoing PCI.

METHODS

Patients

From July 2016 to June 2017, adult patients (≥18 years) with STEMI and treated with primary PCI in our hospital were enrolled in this study. The diagnosis of STEMI was determined according to the third universal definition of myocardial infarction and the Chinese STEMI diagnosis and treatment guidelines [Thygesen 2012; China Society of Cardiology of Chinese Medical Association 2015]. Exclusion criteria were as follows: history of malignancy, severe hepatic disease, estimated glomerular filtration rate <15 mL/kg/m^2, chronic heart failure, presence of inflammatory disease, >24 h between infarction and hospital admission, use of corticosteroid therapy, or recent use of nonsteroidal anti-inflammatory drugs (NSAIDs).

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All procedures involving human participants were performed in accordance with the ethical standards of the Institutional Review Board of our hospital and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all participants in the study.

Data Collection

Venous blood samples were instantly collected on admission to the hospital. Clinical data of patients included in the study were obtained by attending physicians on admission. Medical history and the existence of risk factors (eg, hypertension, diabetes mellitus, and smoking status) were recorded. Blood biochemical profiles including hs-CRP and prealbumin levels, blood glucose, low density lipoprotein (LDL) cholesterol, and hepatic and renal function were evaluated. CPR was calculated as the ratio of hs-CRP to prealbumin. The median CPR (0.02) was set as the cutoff value, and patients were divided into a high-CPR group (CPR ≥0.02) and a low-CPR group (CPR <0.02).

Study Endpoints

The primary endpoint of the study was the occurrence of MACE, defined as all-cause death, nonfatal stroke, and nonfatal myocardial infarction. Clinical follow-up information about the end points was obtained by reviewing the hospital database and by making telephone calls to all patients or their families, and these data were verified by reviewing medical records. Follow-up was completed in all patients.

Statistical Analysis

Continuous variables with normal distribution are presented as means ± standard deviation (SD) and compared with the use of Student's *t* test. All categorical variables were summarized and expressed as proportions and compared with the use of χ^2 test or Fisher's exact test, as appropriate. Cumulative endpoint event survival curves were determined by the Kaplan–Meier method, and event curves of disparate outcomes were compared by using the log-rank test. The Cox proportional hazard regression model was used to assess the prognostic value of CPR on endpoints in patients with STEMI. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of CPR and hs-CRP. All tests were 2-sided, and a *P* value <0.05 was considered significant. All statistical analyses were performed with the SPSS statistical software program package (SPSS version 20.0 for Windows; IBM Corp., Armonk, NY).

RESULTS

Patients' characteristics are presented in Table 1. A total of 682 patients with STEMI were categorized into 2 groups according to median value of CPR. It is shown that patients with higher CPR levels were older ($P < .01$) and more likely to experience CAD ($P < .01$). The high-CPR group had higher hs-CRP levers and lower prealbumin levels (both $P < .01$). CPR levels were positively associated with most laboratory measurements, including neutrophil/lymphocyte ratio, hemoglobin, platelets, leukocytes, glucose, estimated glomerular filtration rate (eGFR), glutamic oxaloacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT) (all $P < .01$).

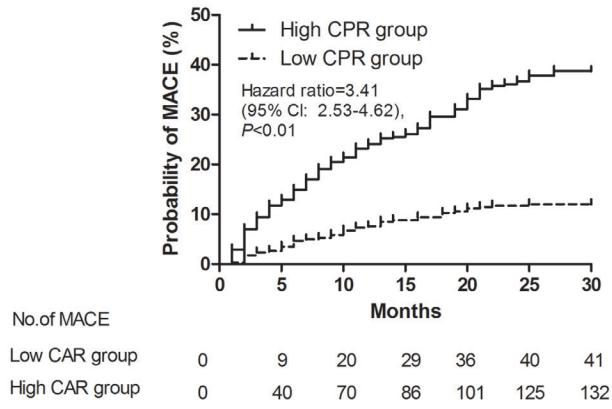

Figure 1. Kaplan–Meier curves for MACEs according to CPR values in patients with STEMI.

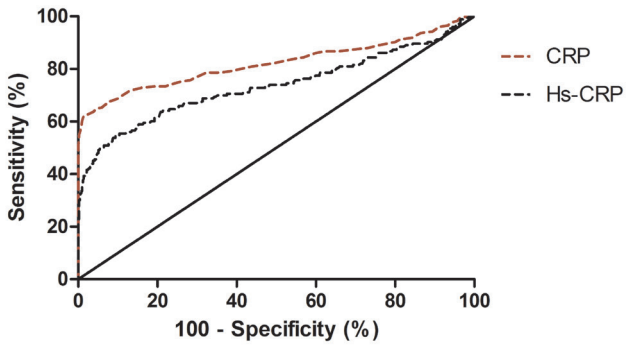

Figure 2. ROC curve analysis for assessing the diagnostic value of MACE in patients with STEMI.

The median length of follow-up was 18 months. The proportion of MACE was higher in the high-CPR group than in the low-CPR group (38.7% versus 12.0%, $P < .01$). Kaplan–Meier curves (Figure 1) and log-rank tests (Table 2) showed that the low-CPR group was associated with a higher risk of MACE (hazard ratio [HR] = 3.41, 95% confidence interval [CI] 2.53 to 4.62, $P < .01$) (Figure 1).

Multivariate Cox proportional hazard regression was performed to explore the association of CPR levels with the risk of MACE in patients with STEMI (Table 2). After adjusting for demographic variables (age, sex, and body mass index [BMI]), medical history, laboratory measurements, and treatments, CPR levels were positively associated with the risk of MACE (HR = 3.27, 95% CI 2.14 to 4.49, $P < .01$).

ROC analysis was performed to assess whether CRP could better predict adverse clinical outcomes. As shown in Figure 2, the area under the ROC curve (AUC) for predicting the diagnosis of MACE was higher for CPR (0.82, 95% CI 0.77 to 0.87) than hs-CRP (0.70, 95% CI 0.65 to 0.75).

Table 1. Patients' Characteristics According to CPR Level

Characteristic	Low CPR (n = 341)	High CPR (n = 341)	*P* Value
Demographics			
Age (y)	63.2 ± 9.7	65.8 ± 10.2	<.01
Male sex	156 (45.7)	162 (47.5)	.65
BMI (kg/m^2)	23.9 ± 2.1	24.6 ± 2.8	<.01
Current smoker	80 (23.5)	91 (26.7)	.33
Heart rate (bpm)	73 ± 13	76 ± 15	.01
Medical history			
Hypertension	213 (62.5)	222 (65.1)	.52
Diabetes mellitus	76 (22.3)	89 (26.1)	.25
Previous CAD	41 (12.0)	78 (22.9)	<.01
Laboratory measurements			
CPR	0.01 ± 0.01	0.05 ± 0.03	<.01
hs-CRP (mg/L)	0.11 ± 0.06	0.85 ± 0.71	<.01
Prealbumin (g/L)	19.0 ± 4.6	16.5 ± 4.2	<.01
Neutrophil/lymphocyte ratio	5.7 ± 2.1	6.2 ± 2.0	<.01
Hemoglobin (g/dL)	13.3 ± 1.7	12.5 ± 1.6	<.01
Platelets (×103/μL)	223.7 ± 58.1	227.0 ± 56.2	.45
Leukocytes (×103/μL)	6.4 ± 1.5	7.3 ± 1.7	<.01
Glucose (mg/dL)	99.2 ± 21.3	110.2 ± 24.2	<.01
eGFR (mL/min/1.73 m^2)	86.4 ± 26.5	79.8 ± 25.2	<.01
GOT (U/L)	22.0 ± 6.2	24.0 ± 7.3	<.01
GPT (U/L)	18.0 ± 4.0	21.0 ± 5.1	<.01
LDL cholesterol (mg/dL)	103.5 ± 31.6	101.2 ± 30.7	.34
Treatment			
Antiplatelet	328 (96.2)	332 (97.4)	.39
β Blocker	212 (62.2)	203 (59.5)	.48
ACEI/ARB	149 (43.7)	171 (50.1)	.09
Statin	159 (46.6)	141 (41.3)	.16

Data are mean ± SD or n (%).

ACE indicates angiotensin converting enzyme; ARB, angiotensin II receptor blocker.

DISCUSSION

Even with current technical advances in early diagnosis and treatments, such as PCI, patients with STEMI remain at high risk for death, and many have poor prognoses (eg, severe ventricular arrhythmia, cardiogenic shock, or cardiac rupture) [Kojima 2013]. Thus, early identification of patients with a higher risk of poor prognosis is necessary. The present study indicated that a higher CPR level was associated with an increased risk of MACE and all-cause mortality in patients with STEMI, after adjusting for potential confounding factors.

It is well known that STEMI is an acute blockage of the coronary artery in atherosclerotic lesions. As a mediator of inflammation, hs-CRP exerts a direct effect on the progression of atherosclerosis. Studies have demonstrated that hs-CRP elevation increases the levels of reactive oxygen species, improves the uptake of oxidized LDL, induces endothelial dysfunction and apoptosis, leads to the proliferation of vascular smooth muscle cells, and increases the risk of plaque rupture [Luc 2003; Thiele 2018; Wang 2003]. It has been reported that elevated hs-CRP levels were associated with increased risk of adverse cardiovascular outcomes in patients with different CAD phenotypes [Aguilar 2006; Gach 2007].

Table 2. Multivariate Cox Regression Analysis for Assessing the Association of CPR and MACE

Factor	Hazard Ratio	95% CI	*P* Value
Demographics			
Age (y)	1.07	1.01 to 1.24	.02
Male sex	1.20	0.87 to 1.51	.47
BMI (kg/m^2)	1.22	0.95 to 1.53	.08
Current smoker	1.46	0.81 to 1.82	.36
Heart rate (bpm)	1.10	0.94 to 1.37	.39
Medical history			
Hypertension	1.27	0.71 to 2.02	.58
Diabetes mellitus	1.49	0.92 to 2.21	.15
Previous CAD	3.88	2.18 to 5.03	<.01
Laboratory measurements			
CPR	3.27	2.14 to 4.49	<.01
hs-CRP (mg/L)	2.19	1.45 to 3.32	<.01
Prealbumin (g/L)	1.69	1.17 to 2.29	<.01
Neutrophil/lymphocyte ratio	1.81	1.22 to 3.01	<.01
Hemoglobin (g/dL)	1.22	0.77 to 1.49	.18
Platelets (×103/μL)	0.99	0.97 to 1.01	.11
Leukocytes (×103/μL)	1.33	0.67 to 1.71	.38
Glucose (mg/dL)	1.08	0.99 to 1.20	.07
eGFR (mL/min/1.73 m2)	0.98	0.95 to 1.04	.36
GOT (U/L)	1.04	0.76 to 1.32	.27
GPT (U/L)	1.25	0.88 to 1.62	.31
LDL cholesterol (mg/dL)	0.96	0.84 to 1.13	.26

Inflammation can induce malnutrition, which may exert a negative effect on the management of inflammation [Li 2017]. Prealbumin as a parameter in the evaluation of nourishment state was suppressed in an inflammatory environment [Kalantar-Zadeh 2008]. Low levels of prealbumin in malnourished patients may parallel vitamin C deficiency [Zhang 2011], which may link with adverse cardiac events, since vitamin C plays a key role in antioxidant and anti-inflammatory processes [Sahyoun 1996]. Decreased levels of prealbumin could increase free thyroxine, which is associated with adverse outcomes in patients with acute myocardial infarction [Friberg 2001]. Accumulating evidence has shown that hypoalbuminemia is associated with an increased risk for atherosclerosis and adverse outcomes [Wang 2019].

Related studies have shown that the presence of a systematic inflammatory response and malnutrition are responsible for poor prognosis in patients with CAD [Raposeiras Roubin 2020]. CPR reveals the balance between hs-CRP and prealbumin in the body and assesses inflammatory and nutritional status of a patient's condition, which are closely associated with atherosclerosis. CPR has been demonstrated to be superior to either hs-CRP or prealbumin alone in predicting prognosis in patients with acute medical conditions and cancers [Fairclough 2009; Feng 2019]. The current study is the first to demonstrate that CPR is an independent predictor for MACE and all-cause mortality in patients with STEMI.

Some limitations should be considered. First, the present study was the evaluation of CPR levels only once, at admission. Serial measurements are required to determine the optimum timing of blood collection for predicting prognosis. In addition, this was a single-center study with a relatively small sample size; therefore, multicenter studies with larger sample sizes are needed to validate our findings. Moreover, we captured data during a median follow-up of only 18 months; it is expected that the disease progression will be followed up and analyses will be updated in the future.

In conclusion, elevated CPR levels were associated with increased risk of MACE and all-cause mortality in patients with STEMI. As a parameter that is widely available to clinicians, CPR may represent an inexpensive tool to identify patients who are at high risk for MACE after STEMI.

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