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An Investigation of the Relationship Between C-reactive Protein /Albumin Ratio and Microvascular Angina

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Abstract

Objective: *This study aimed to investigate the correlation between serum C-reactive protein/albumin ratio (CRP/ALB, CAR) and microvascular angina (MVA), and to assess the predictive value of serum CAR in relation to MVA.*

Methods: *A total of 70 patients diagnosed with MVA,admitted to the Department of Cardiovascular Medicine at the Second Affiliated Hospital of Dalian Medical University between September 2022 and December 2023 were included in the observation group. Additionally,68 patients with normal or minimal (< 50%) stenosis on coronary angiography, negative ECG exercise test and normal coronary blood flow were randomly selected as the control group using a random number table method. Serum CRP, ALB and other relevant indexes were measured in both groups, with CAR calculated. Logistic regression analysis, Pearson correlation analysis, and receiver operating characteristic (ROC) curve analysis were conducted to identify independent risk factors for microvascular angina.*

Results: *Compared the MVA and control group, there were significant differences in CRP and CAR ($P < 0.05$). High serum CAR levels (OR=2.122, 95%CI, 0.609, 3.390, $P<0.001$) and high serum CRP levels (OR=1.057, 95%CI, 0.640, 1.745, $P<0.001$) were identified as independent risk factors for MVA, with the risk of MVA increasing with higher CAR and CRP levels. The ROC curve analysis revealed an AUC of 0.771 (95%CI: 0.686-0.842), with a serum CAR cut-off value of 12.02 ng/mL for predicting MVA, demonstrating a sensitivity of 68.4% and specificity of 97.1%.*

Conclusions: *Serum CAR levels serve as an independent risk factor for MVA and offer valuable predictive information for MVA diagnosis. Monitoring serum CAR levels could aid in the early identification of clinical MVA patients.*

Keywords: C-reactive Protein, Albumin, C-Reactive Protein/Albumin Ratio, Microvascular Angina Pectoris

Introduction

Microvascular angina (MVA) is a clinical syndrome characterized by acute and chronic myocardial ischemia caused by structural and functional abnormalities in precoronary arterioles, arterioles and capillaries, which can result from atherosclerotic or non-atherosclerotic factors [1]. In recent years, more and more studies have shown that patients with MVA face a higher risk of major cardiovascular events such as heart failure and acute coronary syndrome. Therefore, prompt identification and intervention for MVA patients are crucial. Current diagnostic methods for MVA includeinvasive techniques like coronary angiography and intra-coronary Doppler flow conductance wire, as well as non-invasive approaches like cardiac magnetic resonance imaging, positron emission computed tomography, and single photon emission computed tomography [2]. However, these methods are limited in their widespread use due to technical complexity and cost. Therefore, a simple, non-invasive and reliable MVA serological index is urgently needed in clinic. Research indicates that the pathogenesis of MVA is closely linked to inflammatory response and coronary microvessel dysfunction [3]. C-reactive protein (CRP), a marker of acute phase inflammation, plays a role in the diagnosis and prognosis of coronary heart disease (CHD) [4]. High-sensitivity CRP (hsCRP) is more sensitive in detection compared to CRP. Inflammation often leads to de-

creased levels of albumin (ALB), a negative phase product of the body's inflammatory response, which is inversely related to the occurrence of cardiovascular diseases [5]. Therefore, the C-reactive protein to albumin ratio (CAR)) can provide a more accurate reflection of the inflammatory state in coronary heart disease.Both CRP and ALB levels can be measured through a simple blood test, saving time and reducing costs. Currently, there is limited research on the relationship between CAR and Microvascular Angina (MVA). Therefore, this study aims to assess the diagnostic value of CAR in MVA by analyzing CRP and ALB levels in the serum of MVA patients. The findings of this study may offer valuable insights for diagnosing MVA patients. The report is as follows.

Materials and Methods

General Information

This study included 70 patients diagnosed with Microvascular Angina (MVA) who were admitted to the cardiovascular department of the Second Affiliated Hospital of Dalian Medical University between September 2022 and December 2023.The observation group,consisted of 33 females and 37 males, with an average age of 58.78±9.27 years. Additionally, 68 patients with normal or mild coronary artery stenosis < 50% based on coronary angiography and negative exercise treadmill tests, were randomly selected as the control group. This group comprised 33 women and 35 men, with an average age of 60.62±10.11 years. The research program was approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University.

Diagnostic criteria for MVA were based on the 2018 International Coronary Vasomotion Disorders International Study Group and COVADIS guidelines.The criteria[6] include: (1) Symptoms of myocardial ischemia such as angina pectoris or shortness of breath; (2) Coronary angiography showing normal or narrow coronary arteries < 50%; (3)Positive electrocardiogram exercise test or exercise treadmill test; (4)Slow blood flow in coronary arteries: at least one coronary artery with corrected TIMI (Thrombolysis In Myocardial Infarction) blood flow frame number > 27 frames (images collected at a rate of 30 frames per second) [7]. Inclusion criteria consist of: (1) Patients aged 37-85 years old admitted to hospital for chest pain for coronary angiography or coronary CT examination; (2) Clear mental status, normal communication ability, and absence of serious neuropsychiatric diseases; (3) Meeting the diagnosis of MVA.

Exclusion criteria for MVA encompass: (1)Patients with a history of acute myocardial infarction, coronary stent implantation, coronary artery bypass sugery or other revascularization procedures;(2)Patients with hypertensive heart disease, rheumatic heart disease, cardiomyopathy, heart failure, aortic dissection or other organic heart diseases; (3)Serious liver and kidney dysfunction; (4) Suspected non-cardiogenic chest pain due to pleural or intercostal neuralgia; (5)Uncontrolled,symptomatic or hemodynamic arrhythmias;(6)Presence of active inflammation (immune-related diseases, respiratory infections, etc.); (7)Diagnosis of malignant tumors.

Methods

Data Collection

Clinical data of patients upon admission were collected, including age, gender, Body Mass Index (BMI), history of hypertension, history of diabetes, and smoking status. Early morning fasting vein blood samples (from either the primary vein or median vein) were obtained after admission to assess liver function,measuring parameters such as albumin (ALB), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Additionally,low density lipoprotein (LDL-C), homocysteine (HCY), C-reactive protein (CRP) and serum creatinine (sCr) were analyzed using an automatic biochemical analyzer (Beckman, USA), with the calculation of the CAR index. The Left ventricular ejection fraction (LVEF) were measured through Siemens color Doppler ultrasound (G603, probe frequency 3~4 MHz).

Grouping of Patients

Patients were grouped based on coronary angiography findings, with the experimental group (n=64) comprising individuals showing no significant abnormalities in coronary angiography or <50% stenosis, but positive results in exercise plate test or 12-lead holter electrocardiogram (ST segment downslope or horizontal depression ≥0.1mv). Conversely, the control group (n=68) consisted of patients with less than 50% vascular stenosis or no notable abnormalities, and negative results in treadmill exercise test or holter electrocardiogram.

Statistical Processing

IBM SPSS 26.0 software package was used for data analysis. The Shapiro-Wilk test was initially used to assess the normal distribution of the measurement data. Measurement data that adhered to a normal distribution were represented as x±s and compared using a group t-test. For measurement data that did not follow a normal distribution, they were represented as M (P25, P75) and compared using the Mann-Whitney U test. Counting data were presented as [number of cases (%)] and compared using the Chi-square test. Multivariate Logistic regression was utilized for multivariate screening. Additionally, the predictive value of CAR to MVA was evaluated using receiver operating characteristic (ROC) curve and area under the curve (AUC) to determine the optimal cutoff value. Statistical significance was considered when $P < 0.05$.

Conclusions

General Data Comparison

Between the two groups showed no significant differences in gender, age, BMI, history of hypertension, history of diabetes, and smoking history ($P > 0.05$). See Table 1.

Comparison of Laboratory Data

Between the two groups showed no statistical significance in AST, ALT, ALB, sCr, LDL-C, HDL-C and LVEF ($P > 0.05$). However,significant differences were observed in HCY ($P <0.001$), CRP ($P =0.005$) and CAR ($P <0.001$) in the MVA group compared with the control group. See Table 1.

Comparison of Serum CAR Level

When comparing the serum CAR level between the MVA group and the control group using a t-test, it was found that the serum CAR level in the MVA group (12.37±4.25) was significantly higher than that in the control group (8.54±2.24) ($P < 0.001$). See Table 1.

Table 1: Comparison of Clinical Data and Laboratory Indicators Between the Two Groups

Clinical indexes	MVA Group(n=64)	Non-MVA Group(n=68)	t/z/x2	P
Age(x±s)	57.66±10.02	60.62±10.11	-1.727	0.086
Gender (%)	37(52.9)	35(51.5)	0.027	0.871
Smoking (%)	34(48.6)	24(35.3)	2.496	0.114
Hypertension (%)	37(52.9)	39(57.4)	0.282	0.596
Diabetes (%)	17(24.3)	21(30.9)	0.752	0.386
BMI(x±s)	25.16±2.91	25.25±2.96	-0.714	0.862
LDL-C [mmol/L, M (Q1, Q3)]	2.94(2.28,3.42)	2.75(2.24,3.23)	-0.488	0.626
HDL-C [mmol/L, M (Q1, Q3)]	1.31(1.04,1.60)	1.22(1.11,1.32)	-0.914	0.361
AST [U/L, M (Q1, Q3)]	22.56(16,28)	22.74(18,26)	-0.781	0.435
ALT [U/L, M (Q1, Q3)]	23.89(15,26.25)	23.03(16,25.75)	-0.200	0.841
Scr[mg/dl, M(Q1, Q3)]	67.36(55.32,77.97)	66.92(51.94,83.31)	-0.635	0.526
LVEF [%, M (Q1, Q3)]	60(58,62)	60(61,59)	-1.308	0.191
HCY(μmol/L,x±s)	5.13±1.69	3.57±0.87	6.733	<0.001
CRP (mg/dl,x±s)	41.74±3.13	42.18±3.42	-0.765	0.446
ALB(g/l,x±s)	12.37±4.25	8.54±2.24	6.540	<0.001
CAR×100(x±s)	57.66±10.02	60.62±10.11	-1.727	0.086

BMI: body mass index, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, AST:aspartate aminotransferase, ALT: alanine aminotransferase, Scr: serum creatinine, LVEF: left ventricular ejection fraction, CRP: C-reactive protein, ALB: Albumin, CAR: C-reactive protein/albumin ratio.

Logistic Regression Analysis of MVA Risk Factors

Included CRP, CAR and other statistically significant variables as independent variables, with the diagnosis of MVA as the dependent variable (assigned 0= control group, 1=MVA group). The results indicated that high serum CAR level (OR=2.122, 95%CI, 0.609, 3.390, P<0.001), and high serum CRP level (OR=1.057, 95%CI, 0.640, 1.745, P<0.001) were independent risk factors for MVA, with the risk increasing with higher serum CAR and CRP concentrations. See Table 2.

Table 2: Multivariate Logistic Regression Analysis of MVA Risk Factors

Variables	β	OR	95%CI	P
CRP	0.056	1.057	0.640~1.745	<0.001
CAR*100	0.752	2.122	0.609~3.390	<0.001

CRP: C-reactive protein, CAR: C-reactive protein/albumin ratio.

Prediction of MVA by Serum CAR and CRP

Serum CAR and CRP were evaluated as clinical indicators for predicting MVA by drawing ROC curve. The results showed that the AUC of serum CAR was 0.771, with a 95% confidence interval of 0.686 ~ 0.847. The best cut-off value of serum CAR for predicting MVA was 12.02 ng/mL, achieving a sensitivity of 68.4%, and specificity of 97.1%. the AUC of serum CRP was 0.745, with a 95% confidence interval of 0.694 ~ 0.848. The best cut-off value of serum CRP for predicting MVA was 5.05 ng/mL, achieving a sensitivity of 52.9%, and specificity of 93.5%. In summary, CAR was a better predictor of microvascular angina (MVA), and the difference was statistically significant.See Table 3, Figure 1.

Table 3 ROC Curve Analysis Results of Serum CAR Prediction of MVA

Variables	Cut Off	Sensibility %	Specificity %	AUC	95%CI
CRP	5.05mg/dl	52.9	93.5	0.745	0.694~0.848
CAR	12.02ng/mL	68.4	97.1	0.771	0.686~0.847

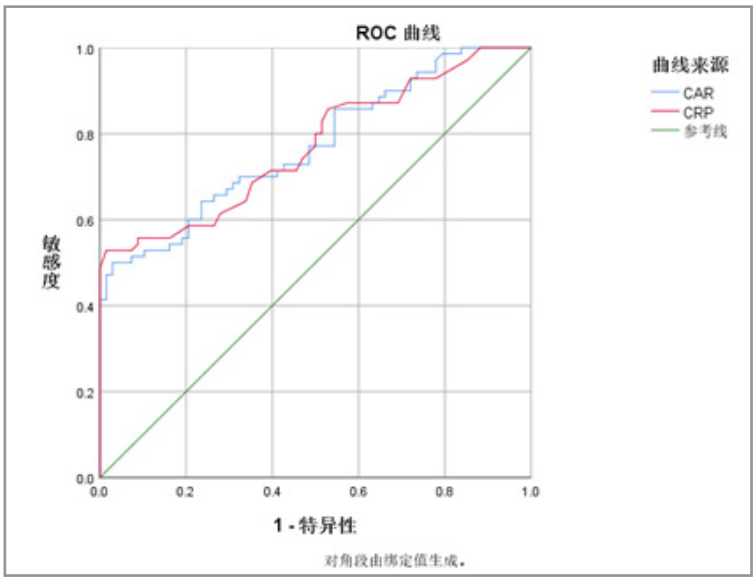

Figure 1: ROC curve of patients with microvascular angina diagnosed by serum CAR and CRP

Discussion

As we all know, coronary heart disease is a prevalent cardiovascular condition characterized by inflammation playing a key role in its pathogenesis, progression, and exacerbation, ultimately leading to vascular inflammation, plaque rupture, and thrombosis, posing a serious threat to patients' lives. One manifestation of coronary heart disease is Microvascular Angina (MVA), defined as myocardial ischemia in the absence of abnormal findings on coronary angiography. The diagnostic criteria for MVA include symptoms of myocardial ischemia, reduced coronary flow reserve or microvessel spasm, and documented myocardial ischemia not attributable to obstructive coronary heart disease, but rather to functional or structural abnormalities in the coronary microcirculation [8]. The diagnosis of MVA often requires multiple coronary angiographies, imposing a significant medical burden on patients and significantly impacting their quality of life. According to the National Heart, Lung, and Blood Institute, MVA patients have a poor prognosis, with MVA serving as a reliable independent predictor of adverse cardiovascular events [2]. Therefore, early screening and intervention for MVA are crucial. This study demonstrates that the C-reactive protein to albumin ratio (CAR) is an independent predictor of MVA diagnosis, offering a positive predictive value for MVA diagnosis and opening up new possibilities for intervention therapy. This discovery contributes to the expanded use of CAR in the assessment of coronary artery disease.

Research has identified various factors and mechanisms contributing to MVA, including vascular endothelial dysfunction, inflammatory responses, hemorheological abnormalities, and cardiac autonomic nervous dysfunction, all of which underlie the abnormal coronary microcirculation seen in MVA [9].

Recent studies have indicated that abnormal vascular endothelial function is a primary contributor to coronary microcirculation diseases,with inflammation playing a crucial role in endothelial function impairment, such as CRP and HCY have been shown to promote the activation and dysfunction of vascular endothelial cells,ultimately leading to abnormal microcirculation function. Specifically, CRP has been linked to damage in the complement system activation, inhibition of fibrinolysis, increased collagen degradation, and potential transformation of LDL-C into foam cells within macrophages [10-12]. Additionally, CRP has been found to directly impact the vasomotor function of human endothelium-derived blood vessels and elicit a pro-inflammatory response in vascular endothelial cells, thus contributing significantly to the pathogenesis of CHD. Moreover, studies have demonstrated that decreased serum albumin levels are associated with the chronic nature of diseases and indicative of an inflammatory state [13-14]. Lower albumin levels have been correlated with increased blood viscosity, impaired endothelial function, heightened platelet activation and aggregation, as well as elevated synthesis of key mediators of platelet-derived coronary artery stenosis.

The combination of CRP and ALB as positive and negative factors respectively in the inflammatory response results in a Composite Index of Cardiovascular Risk (CAR) that amplifies the predictive power compared to individual indicators, providing a more accurate reflection of inflammation activity. Research by Xia Mengyuan et al. has shown that CAR serves as an independent risk factor for coronary artery disease in postmenopausal women, with a CAR value >0.16 demonstrating a sensitivity of 68.3% and a specificity of 74.4% for multi-vessel coronary artery disease [15]. Furthermore, Karabain et al. concluded that CAR outperformed CRP and ALB in predicting coronary artery disease, serving as an independent predictor for individuals with moderate to high coronary artery disease risk [16].

The results of the study revealed that the serum CAR level in the MVA group was significantly higher compared to the control group, and with a statistically significant difference (12.37±4.25 vs 8.54±2.24, $P < 0.001$). Multivariate logistic regression analysis indicted that the serum CAR level was an independent risk

factor for MVA (OR=2.416, 95%CI: 2.234-2.624, P<0.001), suggesting a potential close relationship between CAR and the occurrence and progression of MVA. Furthermore, ROC curve and AUC analysis demonstrated that serum CAR had a good predictive value for MVA, providing strong positive predictive value for MVA diagnosis (AUC=0.762, 95%CI: 0.681 ~ 0.843), with an optimal cut-off value of 12.02 ng/mL, sensitivity of 68.4%, and specificity of 97.1%.

In conclusion, CAR plays a significant role in the development of MVA, and serum CAR level shows promise as a diagnostic indicator for MVA. However, the study has limitations that need to be acknowledged: Firstly, it was a single-center case-control study with subjects from the same hospital and period, potentially introducing selection bias; Secondly, the small sample size and limited geographical scope may reduce the generalizability of the findings. Therefore, further multi-center and large-sample studies are necessary to strengthen the evidence on the association between serum CAR and MVA. Additionally, the data on CRP and ALB were based on a single blood test prior to coronary angiography, without continuous monitoring. Future research should investigate whether CAR levels change post-coronary angiography and its implications.

In summary, CAR elevation serves as an independent predictor of MVA, surpassing CRP in predictive accuracy, and could be a promising, cost-effective parameter for MVA diagnosis.

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