Original Article

Correlation between serum cartilage oligomeric matrix protein and major adverse cardiovascular events within 30 days in patients with acute coronary syndrome

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Background: We studied the correlation between cartilage oligomeric matrix protein (COMP) and major adverse cardiovascular events in patients with acute coronary syndrome (ACS) within 30 days.

Methods: This study included 170 ACS patients who were hospitalized in the Second Affiliated Hospital of Nantong University from August 2017 to April 2019. Serum COMP level was measured at baseline. The enrolled patients were followed up for 30 days and grouped according to the occurrence of major adverse cardiovascular events (MACE) during follow-up. Among the 170 patients, 23 patients had MACE during hospitalization (MACE group), and 147 patients had no MACE (no MACE group).

Results: The serum COMP levels in the MACE group were significantly higher than those of the non-MACE group [84.85 (51.55, 141.75) *vs.* 20.65 (9.11, 46.31) ng/mL, respectively, P<0.05]. The area under the receiver operating characteristic (ROC) curve for COMP in predicting the occurrence of MACE within 30 days was 0.839, with a cutoff level of 39.9 ng/mL [95% confidence interval (CI): 0.774–0.890], 86.96% sensitivity, and 72.79% specificity (P<0.0001). Multivariate logistic regression analysis showed that serum COMP could be used as an independent predictor of MACE within 30 days in ACS patients [odds ratio (OR): 1.024, 95% CI: 1.0133–1.0349, P=0.0001].

Conclusions: Serum COMP is associated with the short-term prognosis of ACS patients. High serum COMP levels can be used as a predictor of MACE within 30 days in ACS patients.

Keywords: Cartilage oligomeric matrix protein (COMP); acute coronary syndrome (ACS); 30 days; major adverse cardiovascular events; correlation

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Introduction

Cartilage oligomeric matrix protein (COMP) is a matricellular protein found in musculoskeletal tissue. It has been widely used as a biomarker for the monitoring and prognosis of osteoarthritis and rheumatoid arthritis (1,2). Studies have shown that COMP can stimulate the proliferation of chondrocytes, inhibit blood coagulation, and increase the tension of tendons (3,4). Riessen *et al.* (5) detected COMP in the blood vessels of healthy individuals as well as atherosclerosis and restenosis patients and found that COMP was mainly expressed around vascular smooth muscle cells (VSMCs). Some studies have found that a decrease in COMP concentration in the vascular smooth muscle extracellular matrix (ECM) can promote

intimal hyperplasia and vascular stenosis (6,7). Previous studies have confirmed the correlation between COMP and coronary artery calcification in patients with end-stage renal disease patients and coronary heart disease patients (8,9). To date, there have been no studies on the correlation between COMP and prognosis in patients with acute coronary syndrome (ACS). ACS patients are predisposed to MACE, such as unscheduled coronary revascularization, stroke, recurrent angina pain, non-fatal re-infarction, re-hospitalization for cardiovascular-related illness, and all-cause death, which significantly affects their prognosis. We therefore aimed to investigate whether COMP can be used as a predictive marker of major adverse cardiovascular events (MACE) within 30 days in ACS patients. We present the following article in accordance with the STARD reporting checklist (available at http://dx.doi.org/10.21037/atm-21-333).

Methods

Ethics and informed consent

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of The Affiliated Hospital 2 of Nantong University, Nantong (IRB number: 2019KN104). Written informed consent was obtained from the patient.

Study population

A total of 170 ACS patients who were hospitalized in the department of cardiovascular medicine of the Second Affiliated Hospital of Nantong University from August 2017 to April 2019 were included in this study (123 males and 47 females; mean age, 65.85±12.90 years). All patients met the diagnostic criteria for ACS (10,11).

Data collection

The baseline information of the patients, such as gender, age, smoking history and previous history of cardiovascular and cerebrovascular diseases. were recorded on admission. Immediate revascularization included immediate percutaneous coronary intervention and coronary artery bypass grafting. The levels of troponin I (TnI), high sensitivity C-reactive protein (hs-CRP) and N-terminal brain natriuretic peptide (NT-proBNP) were measured immediately after admission. All the other measurements such as High-density lipoprotein cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C), triglycerides, total cholesterol and serum creatinine were performed on the second day of hospitalization, after fasting. Serum COMP levels were determined by sandwich ELISA with a commercially available kit (Cloud; Clone Corp, SEB197Hu, Wuhan, China).

Follow-up

The research endpoint in this study was the occurrence of MACE. The main adverse cardiovascular events were defined as (12,13): unscheduled coronary revascularization, stroke, recurrent angina pain, non-fatal re-infarction, re-hospitalization for cardiovascular-related illness, and all-cause death. Patients were followed-up in the outpatient ward or by telephone.

Statistical analysis

Continuous variables with a normal distribution are presented as mean ± standard deviation, whereas continuous variables with a skewed distribution are presented as median (25th percentile – 75th percentile). The enumeration data are presented as percentage or frequency. The independent samples *t*-test, the Mann-Whitney U test, and the χ^2 test were used to compare the measurement and enumeration data of the different groups. Receiver operating characteristic (ROC) analysis was used to help identify the predictive value of COMP for MACE in patients with a final diagnosis of ACS. Univariate and multivariate logistic analyses were used to evaluate the relationship between variables and MACE. Factors with statistical significance in the univariate regression analysis were entered into a final forward stepwise multivariate logistic regression model. Data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL) and MedCalc (version 11.2.1; MedCalc, Maria-kerke, Belgium). Statistical significance was defined as P value <0.05.

Results

Baseline characteristics

Among the 170 patients, 23 patients had MACE during hospitalization, and 147 patients had no MACE. The serum COMP levels in the MACE group were significantly higher than those of the non-MACE group [84.85 (51.55, 141.75) *vs*. 20.65 (9.11, 46.31) ng/mL, respectively,

Table 1 Comparison of the general clinical information between the two groups

	MACE group (n=23)	Non-MACE group (n=147)	P value
Age, years	73.35±10.62	64.68±12.85	0.002
Female, n (%)	8 (34.8)	39 (26.5)	0.411
Type II diabetes, n (%)	6 (26.1)	36 (24.5)	0.869
Hypertension, n (%)	17 (73.9)	107 (72.7)	0.910
Hyperlipidemia, n (%)	6 (26.1)	35 (23.8)	0.812
Current smokers, n (%)	9 (39.1)	70 (47.6)	0.448
Stroke, n (%)	6 (26.1)	35 (23.8)	0.812
Previous myocardial infarction, n (%)	7 (30.4)	30 (20.4)	0.279
BMI (kg/m^2), mean ± SD	23.97±2.27	24.62±3.09	0.336
Heart rate (min^{-1})	87.17±29.17	81.07±15.93	0.337
Systolic blood pressure (mmHg), mean ± SD	121.47±26.63	136.24±24.24	0.008
diastolic blood pressure (mmHg), mean ± SD	73.61±14.70	81.84±16.87	0.028
Triglycerides (mmol/L), mean ± SD	1.73±1.10	2.20±1.11	0.369
Total cholesterol (mmol/L), mean ± SD	4.21±0.90	4.41±1.13	0.367
HDL-C (mmol/L), mean ± SD	1.27±0.39	1.23±0.36	0.536
LDL-C (mmol/L), mean ± SD	2.53±0.65	2.81±1.06	0.159
COMP (IQR) (ng/mL)	84.85 (51.55, 141.75)	20.65 (9.11, 46.31)	0.000
Troponin I (IQR) (μg/L)	3.20 (0.81, 26.30)	1.75 (0.08, 8.53)	0.006
Hs-CRP (IQR)	29.75 (10.11, 70.28)	6.59 (3.34, 19.66)	0.000
NT-proBNP (IQR) (pg/mL)	5,808 (3,200, 23,597)	936 (326, 2,371)	0.000
Serum creatinine, median (IQR) (μmol/L)	104 (76, 117)	72 (60, 89)	0.000
LVEF (%)	54.17±9.90	59.69±8.85	0.007
Immediate revascularization, n (%)	16 (69.6)	16 (11.6)	0.000
In hospital medications, n (%)			
Aspirin	22 (95.7)	144 (97.9)	0.444
Clopidogrel/ticagrelor	22 (95.7)	144 (97.9)	0.444
Beta-blockers	14 (60.9)	110 (74.8)	0.161
ACEI or ARB	17 (73.9)	113 (76.9)	0.452
Statin	22 (95.6)	137 (91.1)	0.696

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro brain natriuretic peptide; Hs-CRP, high sensitivity C-reactive protein.

P<0.05]. Other baseline data between the two groups were analyzed and showed that some serological indicators, such as serum creatinine level, TnI level, NT-proBNP level, and hypersensitivity C-reactive protein (CRP) level were significantly higher in the MACE group than in the non-MACE group (P<0.05), whereas immediate revascularization, systolic blood pressure, diastolic blood pressure, and left ventricular ejection fraction (LVEF) were lower in the MACE group compared to the non-MACE group (P<0.05; *Table 1*).

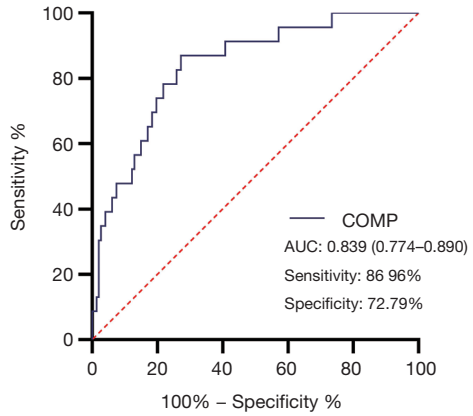

Figure 1 The ROC area under the curve (AUC) in predicting MACE. ROC, receiver operating characteristic; MACE, major adverse cardiovascular events.

Table 2 Results of Logistic analyses for 30-day MACE

	OR	95% CI	P value
COMP	1.0240	1.0133–1.0349	0.0001
Hs-CRP	1.0189	1.0053–1.0325	0.0061
Troponin I	1.0448	1.0028–1.0884	0.036
Immediate revascularization	4.7751	1.1044–20.6473	0.0001

MACE, major adverse cardiovascular events; COMP, cartilage oligomeric matrix protein; Hs-CRP, high sensitivity C-reactive protein.

ROC analysis

The area under the ROC curve of serum COMP for predicting MACE within 30 days was 0.839, with a cut-off level of 39.9 ng/mL [95% confidence interval (CI): 0.774–0.890], sensitivity of 86.96%, and specificity of 72.79% (P<0.0001; *Figure 1*).

Predicting clinical outcome

Multivariate analysis used the variables associated with the outcome in the univariate analysis at a P value of <0.1. Forward stepwise multivariate analyses showed that the significant variables for inclusion were age, systolic blood pressure and diastolic blood pressure on admission, immediate revascularization, COMP level, hs-CRP, NT-proBNP, serum creatinine and LVEF. In the multivariate analysis model, COMP level was significantly associated with MACE within 30 days in ACS patients (odds ratio (OR): 1.024, 95% CI: 1.0133–1.0349, P=0.0001). The other independent factors were CRP (OR: 1.0189, 95% CI: 1.0053–1.0325, P=0.0061), TnI (OR: 1.0448, 95% CI: 1.0028–1.0884, P=0.036), and immediate revascularization (OR: 4.7751, 95% CI: 1.1044–20.6473, P=0.0001; *Table 2*).

Discussion

COMP is a pentamer ECM glycoprotein, originally isolated from cartilage, which can stimulate chondrocyte proliferation and cartilage formation (14). Subsequently, many studies have confirmed that COMP is also expressed in synovium, skin ECM superstructure, myocardial cells, VSMCs, breast cancer cells, and activated platelets, amongst others (15-18). COMP can also inhibit intimal hyperplasia and prevent atherosclerosis (7,19). This study aimed to explore whether COMP can be used as a marker to predict the short-term prognosis of ACS patients.

ACS includes acute ST segment and non-ST segment elevation myocardial infarction and unstable angina pectoris. ACS is a group of clinical syndromes caused by complete or incomplete coronary artery occlusion induced by the rupture of vulnerable plaques, platelet aggregation, and thrombosis. Collagen is a key component of atherosclerotic plaques, and its ability to enhance the fiber cap may be a decisive factor in stabilizing vulnerable lesions (20). COMP has been confirmed to be involved in the assembly of collagen fibers (21). At the same time, researchers have also detected COMP expression around VSMCs in both human and animal models of atherosclerosis, as COMP is secreted by VSMCs (5,22). At present, the proliferation and migration of VSMCs are considered to be key factors affecting intimal thickening and restenosis in atherosclerosis (23-25). It has been found that COMP is degraded by a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS). When the concentration of COMP in the ECM of VSMCs decreases, VSMCs change from a normal contractile phenotype to a synthetic phenotype, and can migrate to the vascular intima, thus promoting intimal hyperplasia and vascular stenosis. At the same time, the concentration of COMP in peripheral serum increases (6,7,26).

Wang *et al.* found that compared to the control group, the serum COMP concentration in patients with coronary heart disease was significantly higher. The degree of coronary artery calcification was also independently correlated with serum COMP concentration (9). Our study also confirmed that the serum COMP concentration of ACS patients with a

MACE within 30 days was significantly higher than that of patients without a MACE. Furthermore, our results suggest that a high serum COMP level can be used as a predictor of MACE within 30 days in ACS patients (OR: 1.024, 95% CI: 1.0133–1.0349, P=0.0001). Some studies have found that COMP can inhibit the phenotypic switch of VSMCs. COMP overexpression may inhibit vascular calcification in the aortic ring. Bone morphogenetic protein 2 (BMP-2) is also a key factor that can accelerate the VSMC phenotype switch, and COMP can directly block this process by binding to BMP-2 using its C-terminal to compete with the BMP-2 receptor (19). Svensson *et al.* found that COMP gene knockout mice developed dilated cardiomyopathy (DCM) within 3 to 5 months (27). Huang *et al.* found that COMP was expressed in the myocardial ECM, and the expression of COMP in the left ventricular tissue of patients with end-stage DCM was significantly decreased. A possible underlying mechanism is that the stable binding of COMP with integrin β1 is fundamental to maintaining cardiac function. The downregulation of COMP expression will promote the expression of matrix metalloproteinase 9 (MMP-9) and reduce the expression of integrin β1, which inhibits the signal transduction in cardiomyocytes and may have adverse effects on these cells (17).

The above findings suggest that COMP plays a positive and important role in the inhibition of intimal hyperplasia, atherosclerosis, vascular calcification, and the maintenance of myocardial cell function and stability. Therefore, we speculate that when COMP is degraded excessively in the ECM, the concentration of COMP in peripheral blood will increase, and at the same time, the positive effects of COMP will be weakened. This may indirectly explain why ACS patients with high serum COMP have more short-term adverse cardiovascular events. However, the exact mechanism requires further study.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-333

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-21-333

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-333).The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of The Affiliated Hospital 2 of Nantong University, Nantong (IRB number: 2019KN104). Written informed consent was obtained from the patient.

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