The plasma levels of mCRP is linked to cardiovascular disease in antineutrophil cytoplasmic antibody-associated vasculitis

Relationship between mCRP and cardiovascular disease in AAV

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Abstract

[Background] C-reactive protein (CRP) has 2 natural isomers, C-reactive protein pentamer (pCRP) and C-reactive protein monomer (mCRP). The levels of CRP are significantly elevated in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). mCRP not only can cause the activation of endothelial cells, platelets, leukocytes, and complements, but also have a proinflammatory structural subtype that can localise and deposit in inflammatory tissues, so it is an important mediator of a variety of clinical diseases, such as Ischemia/Reis perfusion (I/R) injury, Alzheimer's disease, age-related macular degeneration, and cardiovascular disease. Complications of myocardial infarction occurred (n=4) in 37 AAV patients we collected, so it is speculated that mCRP may be related to cardiovascular disease in patients. [Methods] Brain natriuretic peptide (BNP) and mCRP in plasma were tested by enzyme-linked immunosorbent assay (ELISA). The Acute ST-segment elevation myocardial infarction (STEMI) diagnosed by Coronary angiography and then calculated the Gensini score. Echocardiography: ejection fraction (EF%), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular mass index (LVMI). Glomerular filtration rate (eGFR) was calculated based on serum creatinine, age, and gender. [Results] The plasma levels of mCRP in AAV was significantly higher than that in healthy volunteers (P<0.001). There were 4 STEMI complications in AAV. We compared mCRP and CRP levels with STEMI complication and without STEMI complications in AAV, the plasma levels of mCRP was higher, however the plasma
levels of CRP was lower in STEMI. Plasma levels of mCRP correlated with Birmingham vasculitis activity score (BVAS), eGFR, BNP, EF%, LVEDV, LVESV, LVMI ($r=0.404, P=0.013; r=-0.341, P=0.039; r=0.349, P=0.034; r=-0.362, P=0.027; r=0.375, P=0.022; r=0.334, P=0.043; r=0.736, P<0.001$) and STEMI complications’ Gensini score ($r=0.977, P=0.023$) in AAV, however CRP didn’t correlate with BNP, EF%, LVEDV, LVESV, LVMI and Gensini score.

**[Conclusions]** The plasma levels of mCRP related to cardiovascular diseases in AAV patients.

**[Key words]** mCRP, AAV, Cardiovascular diseases, eGFR
Introduction

AAV disease is commonly characterised by a small amount of immunoglobulin deposition and segmental vascular wall necrotic inflammation. AAV patients are classified into granulomas with polyangiitis (GPA), eosinophilic granulomas with polyangiitis (EGPA), and microvascular polyangiitis (MPA) according to pathological and clinical characteristics. Target antigens for AAV diseases include protease 3 (PR3) and myeloperoxidase (MPO). Most Chinese patients with AAV are positive for MPO ANCA. MPO-ANCA is positive and can directly activate and damage glomerular endothelial cells (GEnC) in patients with AAV.

The pathogenesis of AAV is not completely clear, but ANCA and neutrophils play an important role in it. Neutrophils are activated by a series of cytokines, such as tumor necrosis factor-alpha (TNFα). When ANCA binds to Fc receptor, F(ab’)2 and antigen, neutrophils undergo respiratory burst and degranulation, releasing reactive oxygen species (ROS) and various proteases.

CRP is an acute-phase protein that is the acute inflammatory response biomarkers. During AAV disease activity and relapse, serum CRP levels can increase rapidly, and can quickly decrease during disease remission. Blood circulation human CRP consists of pCRP and tissue-related mCRP. In atherosclerosis-related experiments in mice, it was found that CRP binds to the Fc receptor CD32, while mCRP binds to another human Fc receptor subtype CD16 in neutrophils and performs the opposite function. So, FC receptor may be the key to link CRP and mCRP with AAV.
The most common pathogenesis of STEMI is atherosclerotic fragile plaque rupture and thrombus-induced cardiac muscle cell necrosis. Inflammatory reactions are also important section 18,19. CRP is directly involved in acute myocardial infarction, then mCRP obtained from the dissociation process of necrobiosis. mCRP can explain the function of CRP, while pCRP does not promote inflammation 20. In vitro tests have shown, mCRP can induce the synthesis of neutrophil-derived chemokines, stimulate the expression of monocyte integrin 21, and promote neutrophil adhesion attached to vascular endothelial cells 22.

CRP is the classical acute-phase protein named for its ability to precipitate and bind the pneumococcal C-polysaccharide. Although its blood circulation concentration is relatively low in healthy individuals, it increases sharply when tissue damage and inflammation occur 23,24. Currently, CRP can be used not only as a simple marker of inflammation but also as a very crucial and independent predictor of atherosclerotic thrombosis (including cardiovascular events) 24.

Active AAV patients have higher levels of C-reactive protein 15,25. Renal involvement is common in patients with AAV, including renal tubulointerstitial (TI) lesions 26,27. mCRP is an acute-phase protein in the form of tissues or cells and may be an antigen in the acute tubulointerstitial (ATIN) 27. Serum CRP can be decomposed into mCRP, and can induce the generation of oxygen free radicals on the surface of apoptotic and necrotic cells, resulting in inflammatory reactions 28. It was also found that mCRP is not only related to thrombosis 29 and atherosclerotic plaque rupture but also can be concentrated in localised areas after transient myocardial ischemia and related to
acute myocardial infarction (AMI)\(^{30}\). Therefore, we suspect that plasma mCRP levels are related to cardiovascular disease in AAV.

**Methods**

**Collecting plasma samples**

Plasma samples were collected from 37 patients with AAV and 20 healthy volunteers. The AAV patients diagnosed in the Department of Nephrology, Affiliated Hospital of Inner Mongolia Medical University, from October 2018 to November 2019. AAV patients all met the Chapel Hill Consensus Meeting\(^{31}\). 37 AAV patients and 20 healthy volunteers all signed informed consent. This process excludes all AAV caused by autoimmune diseases, such as IgA nephropathy, rheumatoid arthritis, Graves disease, and lupus nephritis, and does not include secondary and various acute infectious vasculitis. All patients in the group were collected 5 mL of venous blood within 24 hours of admission, separated by a centrifuge (3,000 r/min, 10 min), and the supernatant was stored in a -80 °C refrigerator for testing. Repeated freeze-thaw cycles are prohibited for this sample. Disease activity based on the BVAS in AAV patients\(^{32}\). The study was approved by the Ethics Committee of the Helsinki Declaration of Inner Mongolia Medical University.

**Detection of mCRP by ELISA**

Plasma mCRP levels were tested by ELISA using a commercial kit (Kamaishu Biotechnology Co, Shanghai, China). The 96-well microtiter plate was coated with mCRP and blocked to reduce non-specific binding. mCRP standards and samples then mixed with anti-mCRP antibodies, and the mixture added to mCRP coated plates.
Antibodies compete for binding to bound to a plate or sample. This kit uses the double antibody sandwich method to determine the level of human mCRP in the specimen. Coated microtiter plates with purified human mCRP antibodies to make solid-phase antibodies. mCRP was added to the microwells coated with monoclonal antibodies in order, and then HRP labeled mCRP antibodies bind to form an antibody-antigen complexes by enzyme-linked immunosorbent assay. After thorough washing, the substrate TMB is used to develop the color. TMB is converted into blue under the catalysis of HRP enzyme and turned into the final yellow under the action of acid. The shade of color is positively correlated with the mCRP in the sample. The absorbance (OD value) was measured with a microplate reader at a wavelength of 450 nm, and the human mCRP concentration in the sample was calculated by a standard curve.

Detection of BNP by ELISA

BNP detection using a double-antibody sandwich immunoenzyme Method, detection equipment is Unicel-TM-DXI800 (Beckman, USA) full-automatic immunoassay instrument.

Detection of circulating blood Scr, eGFR and CRP

Scr was determined by a rating method using a commercial kit (Beckman, USA). Determination of CRP by immunoturbidimetry using a commercially available kit (Goldsite, China). According to Scr, age, and gender, the eGFR of the patient is calculated. The formula is the MDRD formula adapted by Chinese experts for the Chinese. Female eGFR calculation formula.
eGFR(mL/min/1.73m²)=186×Scr-1.154×(age)-0.203×0.742×1.227 and male eGFR calculation formula eGFR(mL/min/1.73m²)=186×Scr-1.154×(age)-0.203×1.227³⁶.

Detection of EF%, LVEDV, LVESV, LVMI

The value of EF%, LVEDV, LVESV, Left ventricular end-diastolic diameter (LVIDD), Left ventricular septal end-diastolic thickness (IVSTD), Left ventricular posterior wall diastolic thickness (LVPWTD) was obtained by Echocardiography. We calculate the value of Left ventricular myocardial mass (LVM) through LVIDD, IVSTD, and LVPWTD. BSA was calculated through weight (W) and height (H).

LVM (g) =1.04 { [(LVIDD + PWTD + IVSTD)³- (LVIDD)³]-13.6}

BSA (m²) = (W⁰.⁴²⁵× H⁰.⁷²⁵) × 0.007184³⁷.

Statistical analysis

All data were statistically analyzed using SPSS19.0 statistical software package. All grouped data were tested for normality before use. The comparison of the two groups of count data conformed to the normal distribution. Independent t-tests were used. If any of the groups did not match, a non-parametric rank-sum test was used. If it met the normal distribution, it would be expressed by means ( ¯x ) ± Standard deviation (SD). Used the Shapiro-Wilk test, median and quartile range (IQR) to check the degree of dispersion of the data. Analyze the correlation between the two groups of data. If both groups met the normal distribution, used Person rank correlation, and if any group didn’t meet the normal distribution, using Spearman rank correlation. Cross-tabulation χ² test for gender comparison. P<0.05 was statistically significant.

Results
General data from AAV patients and healthy volunteers (normal control)

A total of 37 AAV patients 17 (45.9%) were female and 20 (54.1%) were male. The 4 AAV patients with STEMI complications were 2 (50.0%) male and 2 (50.0%) female, and their average age was 59.5±14.3 years. The total of 37 AAV patients' average age was 59.5±10.6 years. There were 10 (50.0%) males, and 10 (50.0%) females in the healthy volunteers and their average age was 55.3±10.7 years. Comparison of age between 37 AAV patients group and healthy volunteers (n=20, P=0.266). Comparison of sex between 37 patient groups and healthy volunteers (n=20, P=0.788). We used the same method to compare the age and gender of 4 patients with STEMI complications and 33 patients without STEMI complications in AAV patients. Therefore, both the AAV patient group and the normal control, as well as patients with STEMI complications and without STEMI complications in AAV patients, had age and sex of P>0.05, which had no statistical significance. We also analyzed relevant biochemical indicators in AAV patients (Table 1).

The plasma levels of mCRP was higher in AAV patients than in normal control

The plasma levels of mCRP in AAV patients was 244.12 (226.12, 331.725) μg/mL, and in the normal control, the plasma levels of mCRP was 170.0 (135.7, 199.3) μg/mL. We compared the plasma levels of mCRP in AAV patients and healthy volunteers (P<0.001), so statistically significant (Figure 1).

The plasma levels of mCRP was higher in STEMI complications than without STEMI complications.

We divided AAV patients with STEMI complications and without STEMI
complications groups. There were 4 STEMI complications and 33 without STEMI complications in AAV (Figure 2A). The patients with STEMI complications in AAV mCRP was 579.1±72.0 μg/mL, and the patients without STEMI complications in AAV mCRP was 240.8 (219.2, 292.1) μg/mL. We compared their plasma levels of mCRP (P=0.001). The plasma levels of mCRP in the STEMI complications group was higher than without the STEMI group (Figure 2B).

The plasma levels of mCRP was positively correlated with BVAS and Scr and negatively correlated with eGFR

BVAS in 37 AAV patients was 29.9±9.1 and BVAS in normal control was 0. Scr was 291.0 (161.5, 434.5). eGFR was Calculated by gender, age and Scr. eGFR was 17.7 (10.1, 41.0) mL/minute/1.73m² in AAV patients. eGFR was 105.1±9.4 mL/minute/1.73m² in normal control. So we analyzed the correlation between mCRP and BVAS (r=0.404, P=0.013, Figure 3A), the correlation between mCRP and eGFR(r=-0.341, P=0.039, Figure 3B).

The plasma levels of mCRP correlated with BNP, EF%, LVEDV, LVESV, LVMI and STEMI complications’ Gensini score, however CRP didn’t correlate.

The patients with STEMI complications in AAV Gensini score were 72.0±15.1. BNP levels in circulating blood were 155.7 (104.4, 204.3) pg/mL, EF (%) levels in circulating blood were 63.0±8.8 %, LVEDV was 124.2±25.3 mL, LVESV was 44.2±10.7 mL, LVMI was 86.5 (50.6, 112.6) and the 4 STEMI complications Gensini score was 72.0±15.1 in AAV patients.

We suspected that the plasma levels of mCRP might be related to the patient's heart
disease, so we analyzed the relationship among mCRP with BNP, EF%, LVEDV, LVESV, LVMI and STEMI complications’ Gensini score ( $r=0.349$, $P=0.034$ Figure 4A; $r=-0.362$, $P=0.027$ Figure 4B; $r=0.375$, $P=0.022$ Figure 4C, $r=0.334$, $P=0.043$ Figure 4D; $r=0.763$, $P<0.001$ Figure 4E; $r=0.997$, $P=0.023$ Figure 4F ), however CRP didn’t correlate with them (Table 2).

**Discussion**

More and more research has shown that CRP is pathogenic in atherosclerosis, acute myocardial infarction, cerebral infarction, and AAV disease\textsuperscript{38}. CRP is one of the biomarkers for assessing AAV disease activity. The serum CRP concentration increased during the AAV active phase and decreased rapidly with the remission of the disease\textsuperscript{15,39}. mCRP is able to bind complement factor H (FH) and is more effective than pCRP in inhibiting alternative complement\textsuperscript{40} and plays an important role in the development of AAV\textsuperscript{41,42}. PC Xu et al. MPO can inhibit the binding between CFH and mCRP, thus may inhibit the regulatory activation of alternative complements. PR3 does not bind to both pCRP and mCRP, while MPO can bind to mCRP, which will block the binding between mCRP and H factor\textsuperscript{42}. Therefore, the mechanism of mCRP and AAV disease is inseparable.

CRP can be decomposed into mCRP at high temperature, urea or acidic microenvironment\textsuperscript{43,44}. mCRP can activate platelets\textsuperscript{22}, monocytes\textsuperscript{45} and endothelial cells\textsuperscript{46}. mCRP is a key substance that promotes inflammatory response\textsuperscript{23,47}. The inflammatory response mechanism of endothelial cells is caused by the interaction of mCRP with neutrophils, macrophages, and platelets\textsuperscript{47,48}. mCRP induces IL-8, MCP-1,
E-selectin, ICAM-1, VCAM-1 and VCAM-1 in endothelial cells leading to increased adhesion of neutrophils\textsuperscript{17,49}. mCRP can bind to FH and direct FH to the damaged part of the cell\textsuperscript{50,51}, inactivate C3b, and limit the progression of inflammation\textsuperscript{40}. Therefore, we believe that the role of mCRP in the pathogenesis of AAV disease may be related to FH.

More and more reports on mCRP. In patients with lupus, the level of anti-mCRP autoantibodies is related to the degree of renal interstitial lesions\textsuperscript{52}, and mCRP has been reported as an autoantigen in interstitial nephritis-associated uveitis (TINU) syndrome\textsuperscript{53}. In AAV patients, anti-mCRP antibodies may be the cause of severe TI lesions\textsuperscript{54}.

Serum CRP levels increase due to acute infection, trauma, and inflammation\textsuperscript{55}. CRP is considered to be commonly used for the risk stratification of cardiovascular disease\textsuperscript{56,57} and is a marker of generalized atherosclerosis\textsuperscript{57,58}. CRP levels are significantly increased in cardiovascular patients without any symptoms, obvious cardiovascular disease, unstable angina pectoris, myocardial infarction, and other diseases\textsuperscript{24,59}. CRP is directly involved in the response process of acute myocardial infarction\textsuperscript{20}, Thielle et al. considered that mCRP promotes the activation of inflammation, while pCRP has no proinflammatory effect\textsuperscript{46}. In addition, Diehl EE et al. found mCRP deposition in human atherosclerotic plaque vessels\textsuperscript{60}. Similarly, studies on cardiovascular disease have found that mCRP is found in endothelial cells cultured in vitro and can promote inflammatory responses\textsuperscript{22}. In our study, 37 patients with AAV were collected and 4 patients with STEMI complications were found.
mCRP has lectin-like properties and can bind galactose-containing residues. ANCA-induced NETs can activate platelets and then promote mCRP formation on activated platelets. Then, the newly generated mCRP can further enhance thrombosis and inflammatory response during platelet activation. mCRP may be a potential link between thrombosis and inflammation in AAV. Therefore, we suspected that the occurrence of STEMI complications in patients was related to mCRP, so we did further research.

In our study, it was again proven that circulating blood levels of CRP were significantly higher in AAV patients than in healthy volunteers. We have new findings that mCRP levels are significantly increased in patients with STEMI complications, but CRP levels are not significantly increased. We then analyzed the relationship between mCRP levels and STEMI complications’ Gensini score and the relationship between mCRP levels, BNP and EF% in patients with AAV. We found that the level of mCRP is not only positively correlated with the Gensini score and BNP, but also negatively correlated with EF%.

**Conclusions**

The level of mCRP is not only related to AAV disease but also significantly related to the occurrence of cardiovascular disease in patients with AAV. Therefore, mCRP can be used as a biomarker for the plasma of cardiovascular disease in AAV.

**Abbreviations**

CRP: C-reactive protein; pCRP: C-reactive protein pentamer; mCRP: C-reactive protein monomer; ANCA: Anti-neutrophil cytoplasmic antibody; AAV:
Anti-neutrophil cytoplasmic antibody-associated vasculitis; PR3: Protease 3; MPO: Myeloperoxidase; BNP: Brain natriuretic peptide; STEMI: ST-segment elevation myocardial infarction; EF%: Ejection fraction; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; LVMI: Left ventricular mass index; AMI: Acute myocardial infarction; LVIDD: Left ventricular end-diastolic diameter; IVSTD: Left ventricular septal end-diastolic thickness; LVPWTD: Left ventricular posterior wall diastolic thickness; LVM: Left ventricular myocardial mass; GEnC: Glomerular endothelial cells; TI: Tubulointerstitial; ATIN: Acute tubulointerstitial; eGFR: Glomerular filtration rate; BVAS: Birmingham vasculitis activity score;

**Ethics approval and consent to participate**

All patients provided their informed written consent. The study was approved by the Ethics Committee of the Helsinki Declaration of Inner Mongolia Medical University.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

Two funds and Prairie supported this study. The two funds are the China Natural
Science Foundation (NO81460145) and Inner Mongolia Natural Science Foundation Project Number (2018MS08105).

Authors’ contributions
Kai-Li Wu conducted experiments, analyzed the data and drafted the manuscript. Jian Hao conceived the study and participated in the Revise manuscript and provide final approval to submit the version of the document. All authors read, and the report was approved.

Acknowledgements
The Affiliated Hospital of Inner Mongolia Medical University; Funding details are included above.

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**Figure legends**

Figure 1. We compared the plasma levels of mCRP in AAV patients (n=37) and healthy volunteers (n=20, P<0.001).

Figure 2. The plasma levels of mCRP was higher in STEMI complications than without STEMI complications in AAV.

A. The 37 AAV patients divided into 2 groups, with STEMI complications (n=4) and none of STEMI complications (n=33).

B. The plasma levels of mCRP in STEMI complications was higher than without STEMI complications in AAV.

Figure 3. The plasma levels of mCRP was compared with BVAS and eGFR in AAV.

A. The correlation of mCRP and BVAS. The plasma levels of mCRP positively correlated with BVAS (r=0.404, p=0.013). BVAS, Birmingham Vasculitis Activity Score.

B. The correlation of mCRP and eGFR. The plasma levels of mCRP negatively correlated with eGFR (r=-0.341, p=0.039). eGFR, estimated glomerular filtration rate.

Figure 4. The plasma levels of mCRP correlated with BNP, EF%, LVEDV, LVESV, LVMI and correlated with STEMI complications’ Gensini score in AAV

A. The correlation of mCRP and BNP. The plasma levels of mCR positively correlated with BNP (r=0.349, p=0.034). BNP, Brain natriuretic peptide.

B. The correlation of mCRP and EF%. The plasma levels of mCR negatively correlated with EF% (r=-0.362, p=0.027). EF%, ejection fraction.

C. The correlation of mCRP and LVEDV. The plasma levels of mCR positively
correlated with LVEVD ($r=0.375$, $p=0.022$). LVEDV, left ventricular end-diastolic volume.

D. The correlation of mCRP and LVESV. The plasma levels of mCR positively correlated with LVESV ($r=0.334$, $p=0.043$). LVESV, left ventricular end-systolic volume.

E. The correlation of mCRP and LVMI. The plasma levels of mCR positively correlated with LVMI ($r=0.736$, $p<0.001$). LVMI, left ventricular mass index.

F. The correlation of mCRP and Gensini score. The plasma levels of mCR positively correlated with STEMI complications’ Gensini score in AAV ($r=0.977$, $p=0.02$). STEMI, ST-segment elevation myocardial infarction.