

## Original Article

# Relationships among serum IL-6, TNF- $\alpha$ , CRP and coronary artery lesion in patients with acute myocardial infarction

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**Abstract:** *Background:* The inflammatory reaction is considered as an important factor in the occurrence and development of coronary artery disease. This study aimed to investigate the relationships among serum interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), C-reactive protein (CRP) and coronary artery lesion in patients with acute myocardial infarction (AMI). *Methods:* One hundred and ninety-two patients with acute ST-segment elevation myocardial infarction were enrolled. The patients were grouped according to the Gensini scores on the degree of coronary artery lesion. The serum IL-6, TNF- $\alpha$  and CRP levels were determined, and the correlations among IL-6, TNF- $\alpha$ , CRP and degree of coronary artery lesions were analyzed. *Results:* There was a positive correlation between IL-6 and Gensini score ( $r = 0.544$ ,  $P < 0.01$ ), between TNF- $\alpha$  and Gensini score ( $r = 0.216$ ,  $P < 0.01$ ) and between CRP and Gensini score ( $r = 0.468$ ,  $P < 0.01$ ). The IL-6 and CRP levels in moderate and severer group were significantly higher than those in the mild group, respectively (both  $P < 0.01$ ), and the TNF- $\alpha$  level in severer group was significantly higher than that in the moderate group ( $P < 0.01$ ). The TNF- $\alpha$  level in severer group was significantly higher than mild and moderate group, respectively (both  $P < 0.01$ ), and there was no significant difference between mild and moderate group ( $P > 0.05$ ). The TNF- $\alpha$  level was positively correlated with IL-6 level ( $r = 0.271$ ,  $P = 0.042$ ). There was no correlation between CRP and TNF- $\alpha$  or between CRP and IL-6 ( $P > 0.05$ ). *Conclusion:* IL-6, TNF- $\alpha$  and CRP are correlated with the degree of coronary artery lesion in AMI patient, and can be used as the predictors for AMI.

**Keywords:** Acute myocardial infarction, interleukin-6, tumor necrosis factor- $\alpha$ , C-reactive protein, gensini score

## Introduction

Acute myocardial infarction (AMI) is presented by the sharp reduction or interruption of coronary artery blood supply on the basis of coronary artery disease, which causes the serious and persistent acute myocardial ischemia [1]. The clinical manifestations of AMI include the persistent severe pain in back of chest, fever, increased activity of serum myocardial enzyme and electrocardiograph change, leading to the severe arrhythmia, shock, heart failure or death [2-4]. AMI is one of the most important causes of adult mortality. In China, the admission rate and long-term mortality rate of patients with AMI are 6% and 12%, respectively [5]. The risk factors of coronary artery disease include age, smoking, hypertension, hyperlipidemia, diabetes, inflammatory reaction and others [6, 7]. At present, the inflammatory reaction is consid-

ered as an important factor in the occurrence and development of coronary artery disease [8]. Studies have indicated that, interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and C-reactive protein (CRP) play important roles in the promotion of coronary artery disease [9-11]. This study observed the changes of serum IL-6, TNF- $\alpha$  and CRP level in patients with AMI, and analyzed their correlations. The objective was to provide a reference for the application of these indicators to predict AMI.

## Materials and methods

### Subjects

One hundred and ninety-two cases of patients with AMI performing coronary angiography in Beijing Tongzhou District Luhe Hospital (Beijing, China) from June 2015 to December 2015 were

**Table 1.** Grouping of patients according to Gensini score of coronary artery

Group	Gensini score	Case (n)
Mild group	0-40	73
Moderate group	41-79	77
Severer group	$\geq 80$	42

enrolled. There were 134 males and 58 females. The age of patients was 38-72 years, with average age of  $64.6 \pm 13.4$  years. All cases were in line with the diagnostic criteria of acute ST-segment elevation myocardial infarction. All patients were confirmed with AMI by emergency coronary angiography within 90 min after admission, and received the interventional therapy in emergency. All patients received the blood routine, biochemical, myocardial enzyme, chest X-ray and echocardiography (ECG) examination. The exclusion criteria were as follows: 1) the time after the onset of myocardial infarction with acute ST segment elevation was longer than 12 h, and the patients did not receive the emergency intervention treatment; 2) the patients had non-ST-elevation myocardial infarction; 3) the patients had acute/chronic inflammation, systemic immune disease or cancer; 4) the patients had combined liver and kidney dysfunction; 5) the patients were using immunosuppressive drugs. This study was approved by the ethics committee of Beijing Tongzhou District Luhe Hospital. Written informed consent was obtained from all participants.

#### Data collection

The data including gender, age, hypertension, diabetes, waistline, abdominal perimeter, body mass index (BMI), low-density lipoprotein (LDL), IL-6, TNF- $\alpha$ , CRP, ECG, ultrasound, coronary angiography and other indexes were collected.

#### Calculation of coronary artery stenosis degree and grouping

The coronary artery stenosis degree was calculated according to the diagnostic criteria of Coronary Artery Surgery Study (CASS) [12] and Gensini scoring criteria [13], which were: coronary stenosis  $\leq 25\%$ , 1 point; 25%-49%, 2 points; 50%-74%, 4 points; 75%-90%, 8 points; 91%-99%, 16 points; 100%, 32 points. For the lesion in different segments, the coronary artery was multiplied by the corresponding coefficients. The final score of coronary artery

lesion was the sum of the branch points [14]. According to the inclusion and exclusion criteria, the Gensini scores were calculated. The patients were grouped into 3 groups according to the Gensini score (**Table 1**).

#### Determination of serum IL-6, TNF- $\alpha$ and CRP level

In the second morning of the admission, 4 mL venous blood was extracted under the fasting state. The serum TNF- $\alpha$  and IL-6 levels were determined using enzyme linked immunosorbent assays [15]. The serum CRP level was determined according to the reported methods [16]. The related kits were provided by Fuzhou Maixin Biotechnology Development Co., Ltd. (Fuzhou, China).

#### Statistical analysis

All statistical analysis was carried out using SPSS17.0 software (SPSS Inc., Chicago, IL, USA). The enumeration data were presented as rate, and compared using  $\chi^2$  test. The measurement data were presented as mean  $\pm$  SD, and compared using one-way analysis of variance with LSD-t test. Spearman correlation analysis was performed on the correlations among IL-6, TNF- $\alpha$ , CRP and degree of coronary artery lesion.  $P < 0.05$  was considered as statistically significant.

## Results

#### General clinical data of patients

The general clinical data of patients were shown in **Table 2**. There was no significant difference of gender, age, hypertension, diabetes, waistline, abdominal perimeter, BMI or LDL among mild, moderate and severer groups ( $P > 0.05$ ).

#### Comparisons of serum IL-6 level among three groups

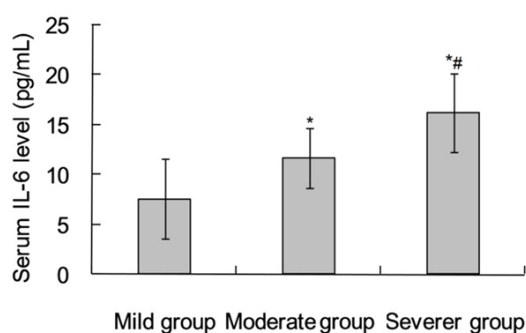
The serum IL-6 levels in mild, moderate and severer groups were  $7.57 \pm 2.06$ ,  $11.68 \pm 3.71$  and  $16.24 \pm 4.08$  pg/mL, respectively, which was increased gradually with the increase of coronary artery lesion degree. The correlation analysis showed that, the Gensini score of coronary artery lesion degree was positively correlated with the serum IL-6 level ( $r = 0.544$ ,  $P < 0.05$ ). The pairwise comparison showed that,

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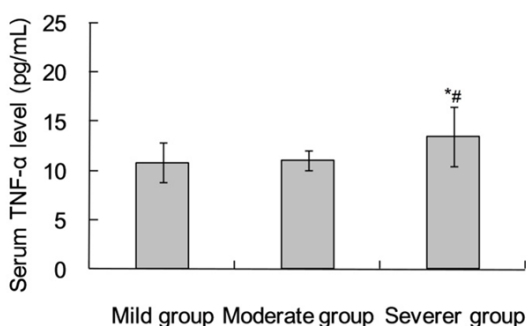
**Table 2.** General clinical data in three groups

Index	Mild group	Moderate group	Severer group
Gender (male)	78.1%	79.2%	79.6%
Age (years)	63.5 $\pm$ 13.3	63.3 $\pm$ 12.6	62.2 $\pm$ 15.1
Hypertension	46.6%	46.7%	51.2%
Diabetes	24.5%	26.3%	25.5%
Waistline (cm)	87.6 $\pm$ 10.9	88.9 $\pm$ 9.2	90.0 $\pm$ 8.9
Abdominal perimeter (cm)	90.5 $\pm$ 10.9	91.6 $\pm$ 8.9	93.5 $\pm$ 9.3
BMI (kg/m <sup>2</sup> )	24.7 $\pm$ 3.4	25.5 $\pm$ 4.5	25.7 $\pm$ 3.9
LDL (mol/L)	2.7 $\pm$ 0.71	3.0 $\pm$ 0.91	2.9 $\pm$ 0.73

BMI, body mass index; LDL, low-density lipoprotein.



**Figure 1.** Comparison of serum IL-6 level among three groups. \*P < 0.01 compared with mild group; #P < 0.01 compared with moderate group. IL-6, interleukin-6.



**Figure 2.** Comparison of serum TNF- $\alpha$  level among three groups. \*P < 0.01 compared with mild group; #P < 0.01 compared with moderate group. TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

the serum IL-6 level in moderate and severer group was significantly higher than that in mild group, respectively (both P < 0.01), and the serum IL-6 level in severer group was significantly higher than that in moderate group (P < 0.01, **Figure 1**).

### Comparisons of serum TNF- $\alpha$ level among three groups

The serum TNF- $\alpha$  level in mild, moderate and severer groups was 10.85 $\pm$ 1.82, 11.11 $\pm$ 1.36 and 13.48 $\pm$ 3.76 pg/mL, respectively, which was also increased gradually with the aggravation of coronary artery lesion. The correlation analysis showed that, the Gensini score of coronary artery lesion degree was positively correlated with the serum TNF- $\alpha$  level (r = 0.216, P < 0.05). The pairwise comparison showed that the serum TNF- $\alpha$  level in severer group was significantly higher than that in mild and moderate group, respectively (both P < 0.01), and there was no significant difference between mild and moderate group (P > 0.05, **Figure 2**).

The serum TNF- $\alpha$  level in severer group was significantly higher than that in mild and moderate group, respectively (both P < 0.01), and there was no significant difference between mild and moderate group (P > 0.05, **Figure 2**).

### Comparisons of serum CRP level among three groups

The serum CRP levels in mild, moderate and severer groups was 6.92 $\pm$ 0.76, 10.26 $\pm$ 1.55 and 18.85 $\pm$ 3.12 ng/mL, respectively, and it was also increased gradually with the aggravation of coronary artery lesion. The correlation analysis showed that, the Gensini score of coronary artery lesion degree was positively correlated with the serum CRP level (r = 0.468, P < 0.05). The pairwise comparison showed that the serum CRP level in moderate and severer group was significantly higher than that in mild group, respectively (both P < 0.01), and the serum CRP level in severer group was significantly higher than that in moderate group (P < 0.01) (**Figure 3**).

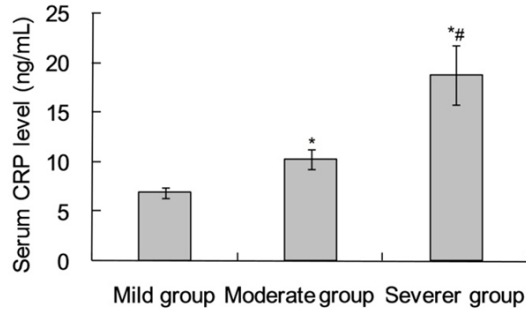
### Correlations among IL-6, TNF- $\alpha$ and CRP

The Spearman correlation analysis showed that, in AMI patients, the serum TNF- $\alpha$  level was positively correlated with the serum IL-6 level (r = 0.271, P = 0.042, **Figure 4**). There was no correlation between serum CRP level and serum TNF- $\alpha$  level or between serum CRP level and serum IL-6 level (P > 0.05).

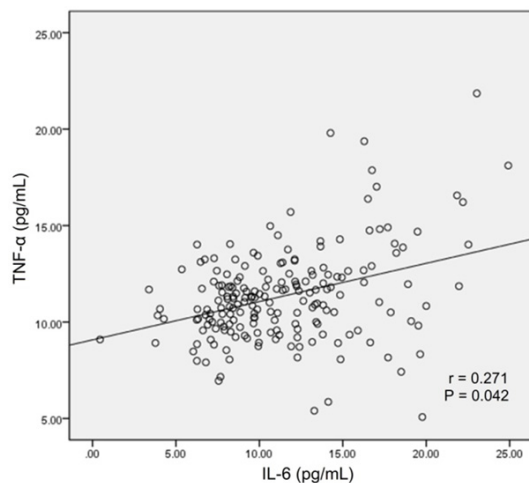
### Discussion

Inflammation plays a key role in the development of atherosclerosis [17]. Cytokines are the main inflammatory mediators, which include

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**Figure 3.** Comparison of serum CRP level among three groups. \* $P < 0.01$  compared with mild group; # $P < 0.01$  compared with moderate group. CRP, C-reactive protein.



**Figure 4.** Correlations between serum IL-6 and TNF- $\alpha$  levels in acute myocardial infarction patients.

IL-6, TNF- $\alpha$ , CRP, etc. [18-20]. Patients with AMI are in the acute stage of inflammatory reaction [21]. The early detection of high-feasible inflammatory parameters can predict the severity of coronary artery disease in AMI patients, and assess the trend of disease progression. This has great significance to improve the treatment level, decrease the mortality rate, and reduce the complications and disputes between doctors and patients. It is reported that IL-6, TNF- $\alpha$  and CRP can reflect the severity of atherosclerosis, and indirectly reflect the stability of plaque [22, 23]. However, the study of the correlations among IL-6, TNF- $\alpha$ , CRP and coronary artery lesion severity in AMI patients are rarely reported. This study has observed the changes of serum IL-6, TNF- $\alpha$  and CRP level in patients with AMI, and analyzed their correlations.

IL-6 is produced by fibroblasts, monocytes/macrophages, T-lymphocytes, B-lymphocytes, epithelial cells, keratinocytes and a variety of tumor cells. It plays a variety of biological effects through combination of IL-6R and gp130 receptor signal transduction. The complex of IL-6 can activate the T-lymphocytes in atherosclerotic plaques, which secrete the interferon, promote the vascular smooth muscle apoptosis, and improve the plaque instability, leading to the plaque rupture [24]. Results of this study showed that, the serum IL-6 level in mild, moderate and severe groups was increased gradually with the increase of coronary artery lesion degree, and the Gensini score of coronary artery lesion degree was positively correlated with serum IL-6 level ( $r = 0.544$ ,  $P < 0.05$ ). The serum IL-6 levels in moderate and severe group were significantly higher than that in mild group, respectively (both  $P < 0.01$ ), and the serum TNF- $\alpha$  level in severe group was significantly higher than that in moderate group ( $P < 0.01$ ). This suggests that, IL-6 is involved in the formation of AMI, and is correlated with the degree of coronary artery lesion. IL-6 can be used as an indicator to predict the severity of coronary artery lesion in AMI patients.

TNF- $\alpha$  is a multifunctional inflammation cytokine, and is mainly produced by monocytes and macrophages. TNF- $\alpha$  can cause the formation of inflammatory reaction, cell necrosis and neo-vascularization, and promote the production of endothelins, leading to the vascular injury. TNF- $\alpha$  is involved in the development of coronary heart disease, and its level is related to the degree of myocardial ischemia [25]. In this study, the serum levels of TNF- $\alpha$  in severe group was significantly higher than the mild and moderate group ( $P < 0.01$ ). There was no significant difference between mild and moderate group ( $P > 0.05$ ). The reason may be that the TNF- $\alpha$  concentration is affected by many factors in the plasma. In addition, different interval between disease onset and the detection will result in different results. In this study, the interval between disease onset and detection was within 24 h, and the different blood sampling time may lead to the difference of results. The correlation analysis showed that, the degree of coronary artery lesion and TNF- $\alpha$  level were positively correlated ( $r = 0.216$ ,  $P < 0.05$ ). This suggests that, TNF- $\alpha$  is involved in

the AMI, and is related to the degree of coronary artery lesion. TNF- $\alpha$  can be used to predict the severity of coronary artery lesion of AMI.

CRP is a non-specific inflammatory marker. The infection from a variety of pathogenic microorganisms, trauma and immune response can stimulate the synthesis of CRP. CRP can conversely promote the immune damage caused by complement activation. The inflammatory cells contain CRP receptors. CRP binds the receptor to activate the cells, inducing the vascular damage by direct infiltration, aggregation or indirect production of cytokines [26]. CRP can be used as a sensitive marker for evaluating the relationship between inflammation and coronary heart disease [27]. Results of this study showed that, the serum CRP level in mild, moderate and severer groups was also increased gradually with the aggravation of coronary artery lesion. The serum CRP level in moderate and severer group was significantly higher than that in mild group, respectively (both  $P < 0.01$ ), and the serum TNF- $\alpha$  level in severer group was significantly higher than that in moderate group ( $P < 0.01$ ). This indicates that, CRP is also involved in the AMI, and is related to the degree of coronary artery lesion.

In addition, results of the present study found that, in AMI patients, the serum TNF- $\alpha$  level was positively correlated with the serum IL-6 level ( $r = 0.271$ ,  $P = 0.042$ ). There was no correlation between serum CRP level and serum TNF- $\alpha$  or between serum CRP level and serum IL-6 level ( $P > 0.05$ ). In conclusion, IL-6, TNF- $\alpha$  and CRP are correlated with the degree of coronary artery lesion in AMI patient, and can be used as the predictors for AMI. This study has great significance for further application of IL-6, TNF- $\alpha$  and CRP to predicting AMI. This study still has some limitations. The sample size of this study is relatively small. Larger sample size will make the results more convincing. In our next studies, the sample size should be further increased for obtaining more satisfactory results.

#### Disclosure of conflict of interest

None.

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