

## **Prognostic values of high-sensitivity C-reactive protein for patients receiving percutaneous coronary intervention.**

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### **Abstract**

**This study aimed to investigate the prognostic values of high-sensitivity C-Reactive Protein (hs-CRP) for patients receiving Percutaneous Coronary Intervention (PCI). 89 patients receiving PCI from September 2010 to December 2012 were selected as the study subjects. Before PCI surgery, the serum indexes including hs-CRP, total cholesterol, high-density lipoprotein cholesterol, urea and apolipoprotein A were measured. After surgery, the patients were followed up for 3 years. The readmission and death due to cardiovascular diseases were used as the end point events. The corrections of serum indexes with the end point events were analysed. Results showed that, the level of hs-CRP was significantly correlated with cardiovascular readmission and cardiovascular death, respectively ( $P < 0.05$ ). Logistic regression analysis showed that, hs-CRP was a risk factor for cardiovascular readmission and cardiovascular death (OR was 1.874 and 6.279, respectively; 95% CI was 1.052-2.460 and 4.310-7.521, respectively). hs-CRP is a risk factor for cardiovascular readmission and cardiovascular death after PCI, and it can be used for evaluate the prognosis of patients with PCI.**

**Keywords:** C-reactive protein, Percutaneous coronary intervention, Prognosis, Readmission, Death.

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### **Introduction**

Cardiovascular Disease (CVD) is a leading cause of premature death and disability worldwide and is responsible for more than 17 million deaths annually, with approximately 80% of the disease burden in low- and middle-income countries such as China [1]. The traditional risk factors of CVD include age, hypertension, lipid abnormality, smoking and diabetes history, and the lipid abnormality is an important factor [2]. However, the traditional risk factors cannot explain all the risk factors of CVD. The cholesterol level in 40% patients with cardiovascular death is lower than the normal level [3]. At present, Percutaneous Coronary Intervention (PCI) is an effective method for treatment of coronary artery stenosis. However, the in-stent restenosis, stent-site bleeding and stroke are still the common clinical problems after PCI surgery [4]. Therefore, it is urgent to find a biomarker to predict the survival rate and the risk of CVD recurrence after PCI surgery, for providing evidence for the clinical therapy monitoring in this high-risk population.

A number of studies [5-7] have shown that the inflammation plays an important role in the occurrence and development of CVD. The occurrence of cardiovascular events can be considered as an inflammatory response in nature, and the circulating inflammatory markers can be used as predictors of CVD. High-sensitivity C-Reactive Protein (hs-CRP) is one of inflammatory markers, which is synthesized by the liver [8]. In severe infection or tissue damage, the concentration of hs-CRP

can increase to 10,000 times to normal. The low-level increased C-reactive protein is one of the important risk factors of CVD. C-reactive protein, companied with traditional risk factors and blood lipid risk factors, has become a predictive index of CVD [9]. This study collected 89 patients who underwent PCI in our hospital from September 2010 to December 2012. The hs-CRP and other cardiovascular indicators were measured before PCI surgery. The patients were followed up for 3 years, and the corrections of hs-CRP and other cardiovascular indicators with patient readmission and death due to cardiovascular diseases were analysed. The objective was to provide a reference for application of hs-CRP to predicating cardiovascular end point events in clinic.

### **Materials and Methods**

#### **Subjects**

Eighty-nine patients receiving PCI treatment in Second Department of Cardiovasology, Tangshan Gongren Hospital from September 2010 to December 2012 were enrolled in this study. There were 57 males and 32 females. The age of patients was 52-78 years ( $62.19 \pm 6.29$  years). 24 patients were complicated with diabetes, and 41 patients were complicated with hypertension. 36 patients had smoking history. The exclusion criteria were as follows: patients with PCI surgical history; patients admitted to emergency hospital due to Acute Myocardial Infarction (AMI)/Acute Coronary Syndrome (ACS); patients with acute inflammation. The inclusion criteria

were as follows: patients with surgical indications of PCI; patients were voluntary for receiving PCI surgery; patients fully understood this study, and were voluntary for joining this study. For unconscious patients, the PCI was performed with consent of the patient family. This study was approved by the ethics committee of Tangshan Gongren Hospital. Written informed consent was obtained from patients or their families.

### **Observation indexes and detection methods**

Before surgery, 5 ml of fasting venous blood was taken from the patients. After centrifugation at 1200 r/min (4°C) for 5 min, the serum was obtained, and was stored at -80°C for use. The observation indexes included hs-CRP, Total Cholesterol (TC), High-Density Lipoprotein Cholesterol (HDL-C), urea and Apolipoprotein A (Apo-A), which were measured in accordance with the reported methods [8,10].

### **Follow-up and record of end point events**

The readmission and death due to cardiovascular diseases were used as the end point events for patients receiving PCI treatment. All patients were followed up for 3 years after PCI surgery. The telephone follow-up was conducted once every six months for understand whether the end point events happened.

### **Statistical analysis**

SPSS 17.0 was used for statistical analysis. The continuous measurement data including age, hs-CRP, TC, urea, HDL-C and apo-A were presented as mean  $\pm$  SD, and were analysed using t-test. The enumeration data including smoking were represented as the number and rate (%), and were analysed using  $\chi^2$  test. The risk factors for hs-CRP predicting cardiovascular end point events were assessed by logistic regression analysis. If the data did not meet normal distribution, they were conversed by natural logarithm for calculating the Odds Ratio (OR), which were presented by 95% Confidence Interval (95% CI).  $P < 0.05$  was considered as statistically significant.

## **Results**

### **Basic data of patients with and without readmission due to cardiovascular diseases**

After 3-year follow-up, the patients were grouped according to the occurrence of cardiovascular end point events, and the data were analysed. Results showed that, there were 61 patients (68.5%) with readmission due to cardiovascular diseases and 28 patients (31.5%) without readmission. The age of patients with readmission was  $68.47 \pm 5.39$  years, which was

significantly greater than  $61.37 \pm 4.08$  years of the patients without readmission ( $P < 0.05$ ). The proportion of smoking cases and the levels of hs-CRP, urea and Apo-A in patients with readmission were significantly higher than those in the patients without readmission ( $P < 0.05$ ). There was no significant difference of TC or HDL-C level between patients with readmission and without readmission ( $P > 0.05$ ) (Table 1).

### **Basic data of patients with and without death due to cardiovascular diseases**

As shown in Table 2, there were 9 patients (10.1%) with death due to cardiovascular diseases and 80 patients (89.9%) without death. The age of patients with death was  $75.46 \pm 3.72$  years, which was significantly greater than  $67.23 \pm 4.86$  years of the patients without death ( $P < 0.05$ ). The proportion of smoking cases and the levels of urea, HDL-C, hs-CRP and Apo-A in patients with death were significantly higher than those in the patients without death. There was no significant difference of TC level between patients with death and without death ( $P > 0.05$ ) ( $P < 0.05$ ).

### **Comparison of risk factors among four intervals of hs-CRP level**

The patients were grouped according to four intervals of hs-CRP level, and the risk factors were compared. The results were shown in Table 3. In six cardiovascular end points and risk factors (readmission, death, re-obstruction, stent re-plantation, stroke and AMI/ACS), the level of hs-CRP was significantly correlated with cardiovascular readmission and cardiovascular death ( $P < 0.05$ ).

### **Multi-factor Logistics regression analysis of risk factors for cardiovascular readmission and cardiovascular death**

Using cardiovascular readmission and cardiovascular death as the dependent variables, the hs-CRP was transformed into the natural logarithm for Logistic regression analysis. As shown in Tables 4 and 5, the hs-CRP was a risk factor for cardiovascular readmission and cardiovascular death ( $P < 0.05$ ; OR was 1.874 and 6.279, respectively). Namely, when hs-CRP level was raised by one natural logarithm, the risk of cardiovascular readmission and cardiovascular death increased 1.874 and 6.279 times, respectively. In addition, all the age, smoking history and WBC were the risk factors related to cardiovascular readmission and cardiovascular death ( $P < 0.05$ ). The OR values of age, smoking history and WBC for cardiovascular readmission were 1.620, 2.672 and 2.074, respectively, and those for cardiovascular death were 5.709, 5.039 and 3.507, respectively.

**Table 1.** Basic data of patients with and without readmission due to cardiovascular diseases.

Group	Age (year)	Smoking (n, %)	TC (mmol/l)	Urea ( $\mu$ mol/l)	HDL-C (mmol/l)	hs-CRP (mg/l)	Apo-A (g/l)
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Readmission (n=28)	68.47 ± 5.39	19, 68%	4.05 ± 0.76	8.49 ± 1.36	1.13 ± 0.43	18.63 ± 4.21	1.05 ± 0.36
No readmission (n=61)	61.37 ± 4.08	10, 16%	4.13 ± 0.82	5.72 ± 2.40	1.07 ± 0.39	8.62 ± 3.59	0.96 ± 0.59
t/χ <sup>2</sup>	9.86	8.72	0.59	9.53	0.86	13.59	3.05
P	<0.05	<0.05	>0.05	<0.05	>0.05	<0.05	<0.05

TC: Total Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; hs-CRP: high-sensitivity C-Reactive Protein; Apo-A: Apolipoprotein A.

**Table 2.** Basic data of patients with and without death due to cardiovascular diseases.

Group	Age (year)	Smoking (n, %)	TC (mmol/l)	Urea (μmol/l)	HDL-C (mmol/l)	hs-CRP (mg/l)	Apo-A (g/l)
Death (n=9)	75.46 ± 3.72	6, 67%	4.27 ± 0.96	10.76 ± 2.56	1.19 ± 0.53	32.51 ± 7.62	1.07 ± 0.26
No death (n=80)	67.23 ± 4.86	12, 15%	4.13 ± 1.04	6.19 ± 0.82	1.02 ± 0.41	10.37 ± 2.66	1.01 ± 0.32
t/χ <sup>2</sup>	11.59	9.28	0.88	11.53	8.26	21.74	3.84
P	<0.05	<0.05	>0.05	<0.05	<0.05	<0.05	<0.05

TC: Total Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; Hs-CRP: High-sensitivity C-Reactive Protein; Apo-A: Apolipoprotein A.

**Table 3.** Comparison of risk factors among four intervals of hs-CRP level.

Hs-CRP (mg/l)	0-0.59	0.59-1.30	1.30-3.65	3.65-82.51	t/χ <sup>2</sup>	P
Readmission (n)	4	6	8	10	4.883	<0.05
Death (n)	1	1	3	5	3.634	<0.05
Re-obstruction (n)	4	4	5	6	0.037	>0.05
Stent re-plantation (n)	2	2	3	5	1.045	>0.05
Stroke (n)	1	4	4	2	2.004	>0.05
AMI/ACS (n)	1	3	1	2	1.029	>0.05

Hs-CRP: High-sensitivity C-Reactive Protein; AMI/ACS: Acute Myocardial Infarction/Acute Coronary Syndrome.

**Table 4.** Logistics regression analysis of risk factors for cardiovascular re-admission.

Risk factors	P	OR	95% CI
Hs-CRP	0.002	1.874	1.052-2.460
Age	0.021	1.620	1.357-4.981
Smoking	0.007	2.672	1.962-5.760
WBC	0.009	2.074	1.523-3.679

Hs-CRP: High-sensitivity C-Reactive Protein; WBC: White Blood Cell; OR: Odds Ratio; 95% CI: 95% Confidence Interval.

**Table 5.** Logistics regression analysis of risk factors for cardiovascular death.

Risk factors	P	OR	95% CI
Hs-CRP	0.000	6.279	4.310-7.521
Age	0.005	5.709	3.168-8.339
Smoking	0.003	5.039	2.560-6.703
WBC	0.004	3.507	1.479-8.347

Hs-CRP: High-sensitivity C-Reactive Protein; WBC: White Blood Cell; OR: Odds Ratio; 95% CI: 95% Confidence Interval.

## Discussion

The inflammatory response is involved in the occurrence and progression of cardiovascular events after PCI. In this process, the inflammatory markers can be used as a reliable indicator for predicting the cardiovascular events [11]. Hs-CRP is a highly sensitive index of inflammatory response. It can be used to monitor the change of cardiovascular disease and predict the disease prognosis. In addition, it can be used to forecast the risk of cardiovascular disease in sub-healthy population [12]. Therefore, hs-CRP has important clinical application value. As an important marker of acute inflammation phase of acute myocardial infarction, the increase of hs-CRP can be used as an independent predictor of postoperative prognosis of AMI. The possible mechanisms are as follows: i) hs-CRP can activate the complement system, activate endothelial cells or mediate macrophage phagocytosis of unmodified low density lipoprotein, and induce endothelial cells to produce a variety of cytokines and chemokines such as monocyte chemotaxis-1, intercellular adhesion molecule-1, vascular endothelial cell

adhesion molecule-1 and E-selection; ii) hs-CRP in the involved vessels and in obstructed cardiac muscles can attract the membrane attack complex, leading to vascular injury and plaque rupture; iii) the increase of circulating hs-CRP level can also result in torpescence of vascular endothelial dilatation, decreased production of nitric oxide and its activity, and decreased blood flow; iv) the hs-CRP can also delay the formation of fibrin by inhibiting platelet aggregation and release reaction, which leads to coagulation dysfunction. It is shown that, hs-CRP is closely related to the severity of coronary heart disease. The elevation of hs-CRP may indicate the unstable condition of coronary heart disease [13]. Hs-CRP is positively correlated with the degree and extent of coronary artery stenosis. The concentration of hs-CRP increases along with the aggravating of coronary artery disease degree and range [14].

Results of this study showed that, the levels of hs-CRP, urea and Apo-A in patients with readmission were significantly higher than those in the patients without readmission ( $P < 0.05$ ); the levels of urea, HDL-C, hs-CRP and Apo-A in patients with death were significantly higher than those in the patients without death ( $P < 0.05$ ). Logistic regression analysis showed that, hs-CRP was a risk factor for cardiovascular readmission and cardiovascular death (OR was 1.874 and 6.279, respectively; 95% CI was 1.052-2.460 and 4.310-7.521, respectively). These were consistent with the results of previous studies. Above results indicate that, for patients with elevated hs-CRP level after PCI surgery, more active anti-inflammatory and anti-heart failure treatment should be given to improve the prognosis.

It is confirmed that, the AMI patients with elevated hs-CRP level are more susceptible to complications such as heart rupture, left ventricular aneurysm and death within one year. Some studies have noted that the elevated TC, HDL-C and urea levels in patients with cardiovascular events will increase the risk of readmission and death [15,16]. This indicates that, the blood lipid level is also an important factor that affects the occurrence of cardiovascular disease in patients after PCI surgery. In addition, the results of this study found that age, smoking history and WBC, white blood cell were the risk factors of cardiovascular readmission and cardiovascular death. However, in this study, there was no significant difference of TC level between patients with readmission and without readmission ( $P > 0.05$ ), or between patients with death and without death ( $P > 0.05$ ), with no significant differences of HDL-C between patients with readmission and without readmission ( $P > 0.05$ ). This may be caused by the individual factors of patients. In addition, the sample size of this study is relatively small. In our next studies, the sample size should be further increased for obtaining more satisfactory outcomes. In conclusion, hs-CRP is an independent risk factor for predicting cardiovascular readmission and death after PCI surgery. For patients with PCI, the postoperative blood lipid level should be controlled, for avoiding the occurrence of cardiovascular events and guaranteeing the safety of the patient life.

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