

<Original Article>

## Study on the evaluation of serum hsCRP as predictor of the coronary artery disease by using Framingham Risk Score (FRS)

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**Summary** The study about the relationship between serum hsCRP value and the cardiovascular disease has been few in Japan and its relationship is uncertain yet. The aim of the study is to clarify the relationship between serum hsCRP value and Framingham Risk Score (FRS) as a forecast score of the coronary artery disease by using basics medical checkup data. We divided a subject into following five groups according to serum hsCRP: "Low" as 0.01-0.06 mg/dl, "Mild" as 0.07-0.11 mg/dl, "Moderate" as 0.12-0.19 mg/dl, "High" as 0.20-0.38 mg/dl, "Highest" as 0.38-1.50 mg/dl.

Results as follows: As the relationship between serum hsCRP and FRS, higher group of serum hsCRP value showed higher FRS, and "Low" and "Mild" group were significance differences with other three groups. Groups of serum hsCRP 0.12 mg/dl over showed high risk of the coronary artery disease as  $FRS \geq 6$  by logistic-regression analysis.

The result of present study suggested that serum hsCRP value was associated with a risk factor of the coronary artery disease for men and women. Serum hsCRP value showed a relationship with the FRS as well as a coronary artery disease-related factor. As known the inflammation is a new risk factor of the coronary artery disease, serum hsCRP value could be a representative test value to show episode risk of the coronary artery disease.

**Key word:** hsC-Reactive Protein, Framingham Risk Score, Basic medical examination data, Coronary artery disease

### 1. Introduction

The major cause of deaths in Japan is in order of malignant neoplasm, cardiovascular disease, and cerebrovascular disease. Cardiovascular disease accounts for about 30% of the cause of death<sup>1)</sup>.

Hypertension, lipids abnormality symptom, diabetes mellitus and obesity are known as a risk factor of the cardiovascular disease. In late years, however, inflammatory contributes for developing cardiovascular disease and it has been recognized that the inflammation is one of the risk factors of cardiovascular

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disease.

The inflammation contributes to not only arteriosclerotic progress but also destabilization of the plaque. Thus the inflammatory marker attracts attention as a predictor of the cardiovascular disease.

In an inflammatory marker, hsC-reactive protein (hsCRP) generated with liver is known as the superior inflammatory marker because it is a worldwide standardized method for measurement, no individual difference prescribed by heredity and possible to long-term conservation<sup>2)</sup>.

Large-scale epidemiologic studies such as MONICA Augsburg Study<sup>3-5)</sup>, Helsinki Heart Study<sup>6,7)</sup>, reported that the hazard ratio of the cardiovascular disease was higher in the group showing high level of serum hsCRP compared with in the low level group of serum hsCRP. The epidemiologic studies about the correlation with the risk factor of the cardiovascular disease and serum hsCRP value have been conducted in Europe and U.S.

However, the study about the relationship between serum hsCRP value and the cardiovascular disease has been few in Japan and its relationship is uncertain yet. The aim of the study is to clarify the relationship between serum hsCRP value and Framingham Risk Score (FRS) as a forecast score of the coronary artery disease by using basics medical checkup data.

## 2. Methods

### 1. Subject

The subject is 12,004 participants of the basic medical checkup performed in Habikino City, Osaka (3,759 men, 8,245 women).

8,682 (2,624 men, 6,058 women) who had basic medical checkup and satisfied following condition were analyzed.

- 1) Age: aged 40 through 74 year-old.
- 2) serum hsCRP value: less than 1.5 mg/dl.
- 3) No deficit in oneself-style diagnosis questionnaire and FRS was calculated.
- 4) There were no cerebrovascular accident, history of previous heart disorder and doubtless.

The protocol of this study was approved by the Institutional Review Board Osaka Prefecture

University.

### 2. The basic medical checkup:

The designated medical doctors in the Habikino-city conducted drawing blood and a standard medical examination. The previous medical history, a drinking situation, the smoking status were asked by oneself-style medical interview sheet.

### 3. Measurement parameter

#### 1) BMI

BMI was calculated by height and weight.

$$\text{BMI} = \text{weight (kg)} / \text{height (m)}^2.$$

#### 2) The measurement of the blood test value

The blood sampling was taken by hungry state. 5 ml was collected from an elbow vein and 2 ml was anticoagulation with K<sub>2</sub>EDTA. Then it was used for the measurement of the blood count.

The total items were 25 items such as a total white-cell count, blood platelet, total protein, alkaline phosphates, serum hsCRP value in addition to the inspection items were 11 items which were measured in the health-care service for elderly.

The serum hsCRP value was measured by high sensitive CRP by latex immuno-nephelometry.

The measurement results were accumulated and compiled into a database by Habikino City government through medical institution.

### 4. Statistical analysis

Subjects were divided by age and BMI and compared of serum hsCRP value by age and BMI differences. The seven groups divided by every 5 years old and two groups divided by BMI <25 and BMI ≥25. The association of serum hsCRP value and the coronary artery disease was analyzed using serum hsCRP evaluation method by Ridker<sup>8)</sup>.

Ridker<sup>8)</sup> evaluated using following five groups: "Low" as 0.01-0.06 mg/dl, "Mild" as 0.07-0.11 mg/dl, "Moderate" as 0.12-0.19 mg/dl, "High" as 0.20-0.38mg/dl, "Highest" as 0.38-1.50 mg/dl.

In this study, the association of serum hsCRP value and FRS was analyzed by these five groups.

The FRS (Framingham Risk Score) was calculated from age, Total cholesterol (T-Cho), HDL-choles-

terol (HDL-Cho), systolic blood pressure, high blood pressure treatment exists, whether or smoking habits based on a score list of Coronary Heart Disease (10-year risk) of Framingham Heart Study.

The statistical analysis conducted student t-test, one-way analysis of variance and logistic-regression

analysis by using Macintosh Stat view Ver. 5.0 Computer Program (SAS Institute Inc., Berkeley, USA). In addition, the significance level was  $P < 0.05$ . Serum hsCRP was not normal distribution, was performed a logarithmic transformation

Table 1 Characteristics of subject

	Total n=(8682) Mean $\pm$ S.D.	Men (n=2624) Mean $\pm$ S.D.	Women (n=6058) Mean $\pm$ S.D.
Age (year)	61.5 $\pm$ 8.4	62.6 $\pm$ 8.4	61.0 $\pm$ 8.4
Height (cm)	156.9 $\pm$ 8.0	165.2 $\pm$ 6.3	153.3 $\pm$ 5.6
Weight (kg)	57.2 $\pm$ 10.3	64.6 $\pm$ 9.7	54.0 $\pm$ 8.7
Body mass index	23.2 $\pm$ 3.4	23.6 $\pm$ 3.1	22.9 $\pm$ 3.6
Systolic blood pressure (mmHg)	129.3 $\pm$ 18.2	133.1 $\pm$ 17.9	127.7 $\pm$ 18.1
Diastolic blood pressure (mmHg)	76.0 $\pm$ 10.9	78.4 $\pm$ 11.0	74.9 $\pm$ 10.6
Total Cholesterol (mg/dl)	216.3 $\pm$ 35.5	203.3 $\pm$ 33.9	222.0 $\pm$ 34.7
HDL-Cholesterol (mg/dl)	63.0 $\pm$ 16.2	56.3 $\pm$ 15.2	65.9 $\pm$ 15.8
Triglyceride(mg/dl)	128.4 $\pm$ 82.7	150.1 $\pm$ 102.1	119.0 $\pm$ 70.7
LDL-Cholesterol (mg/dl)	127.9 $\pm$ 33.4	117.5 $\pm$ 32.6	132.5 $\pm$ 32.7
White blood cell (cells/ $\mu$ l)	5.7 $\pm$ 1.6	6.2 $\pm$ 1.7	5.5 $\pm$ 1.5
Albumin (g/dl)	4.4 $\pm$ 0.25	4.4 $\pm$ 0.28	4.4 $\pm$ 0.24
Alkaline Phosphatase (IU/L)	231.2 $\pm$ 69.4	226.1 $\pm$ 67.0	233.5 $\pm$ 70.4
$\gamma$ -glutamyl transpeptidase (IU/L)	37.0 $\pm$ 51.4	59.5 $\pm$ 76.9	27.2 $\pm$ 30.2
Serum high-sensitive C-reactive protein (mg/L)	0.13 $\pm$ 0.16	0.15 $\pm$ 0.19	0.12 $\pm$ 0.15
Hemoglobin A1c (%)	5.3 $\pm$ 0.84	5.4 $\pm$ 0.99	5.3 $\pm$ 0.77

Number of subjects: 8,682 (2,624 men, 6,058 women)

Table 2 Standard coefficient of regression between serum hsCRP value and coronary artery disease related factor

	Standard correlation coefficient	<i>p</i> value
Age	0.630	<0.001
Body mass index	0.163	<0.001
Systolic blood pressure (mmHg)	0.079	<0.001
Diastolic blood pressure (mmHg)	0.060	<0.001
Total Cholesterol (mg/dl)	-0.030	0.0057
HDL-Cholesterol (mg/dl)	-0.147	<0.001
Triglyceride(mg/dl)	0.077	<0.001
LDL-Cholesterol (mg/dl)	0.003	0.7677
White blood cell (cells/ $\mu$ l)	0.230	<0.001
Albumin (g/dl)	-0.115	<0.001
Alkaline Phosphatase (IU/L)	0.119	<0.001
$\gamma$ -glutamyl transpeptidase (IU/L)	0.099	<0.001
Hemoglobin A1c (%)	0.109	<0.001

Number of subjects: 8,682 (2,624 men, 6,058 women)

Table 3 The relationship between serum hsCRP and FRS

	Standard correlation coefficient	<i>p</i> value
FRS	0.121	<0.001
Age score	0.001	0.9335
LDL score	-0.019	0.0756
HDL score	0.145	<0.001
Blood pressure score	0.093	<0.001
Diabetes score	0.077	<0.001
Smoking score	0.060	<0.001

Table 4 Odds ratio of high-risk of the coronary artery disease (FRS  $\geq$  6) differences of each serum hsCRP groups by logistic regression analysis

Serum hsCRP group	Low (0.01-0.06 mg/dl)	Mild (0.07-0.11 mg/dl)	Moderate (0.12-0.19 mg/dl)	High (0.20-0.38 mg/dl)	Highest (0.39-1.50 mg/dl)
Subjects (n)	3178	3657	613	765	469
FRS $\geq$ 6	1791	2390	450	584	348
No adjust					
OR	Reference	1.461	2.138	2.499	2.227
95%CI	—	1.325-1.611	1.764-2.592	2.085-2.994	1.790-2.771
<i>p</i> value	—	<0.001	<0.001	<0.001	<0.001
Adjust 1					
OR	Reference	1.167	1.490	1.641	1.579
95%CI	—	1.039-1.310	1.192-1.862	1.328-2.028	1.224-2.038
<i>p</i> value	—	0.0029	0.0005	<0.001	0.0004
Adjust 2					
OR	Reference	1.130	1.298	1.442	1.429
95%CI	—	1.004-1.273	1.032-1.633	1.157-1.797	1.095-1.866
<i>p</i> value	—	0.0431	0.0258	0.0011	0.0087

Adjust 1: Sex, Age, BMI

Adjust 2: Sex, Age, BMI, TG, WBC, Alb, ALP,  $\gamma$ -GTP

### 3. Results

#### 1. Characteristics of the subject and distribution of the serum hsCRP value

The average age of analysis subjects was  $62.6 \pm 8.4$  years old of male and  $61.0 \pm 8.4$  years old of female. Characteristics of subject showed in Table 1.

Figure 1 showed distribution of the serum hsCRP value.

Median was 0.1 mg/dl (estimated median was 0.1019 mg/dl, 0.1083 mg/dl of male and 0.0992 mg/dl of female).

#### 2. The relationship between serum hsCRP value, age

and BMI

The relationship between serum hsCRP value and age showed in Figure 2. The serum hsCRP value went up when age elevated. Men showed slightly high value but the mean of serum hsCRP value of men and women was less than 0.2 mg/dl which was ceiling reference value in all age divisions.

The relationship between serum hsCRP value and BMI showed in Figure 3. The serum hsCRP value of BMI  $\geq$  25 group was higher than BMI < 25 group. There was significance difference in each age division. BMI  $\geq$  25 of 50-54 years old men showed that serum hsCRP value exceeded a ceiling reference.

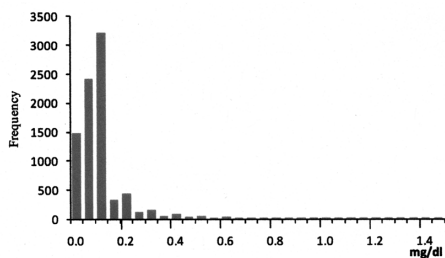


Fig. 1 Distribution of the serum hsCRP value in 12,001 participants of the basic medical checkup performed

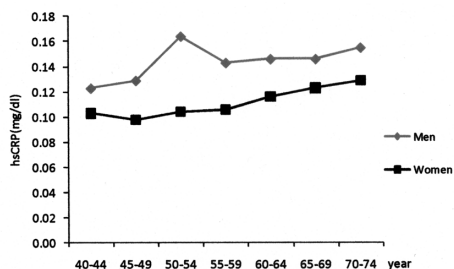


Fig. 2 The variation of mean serum hsCRP by age group

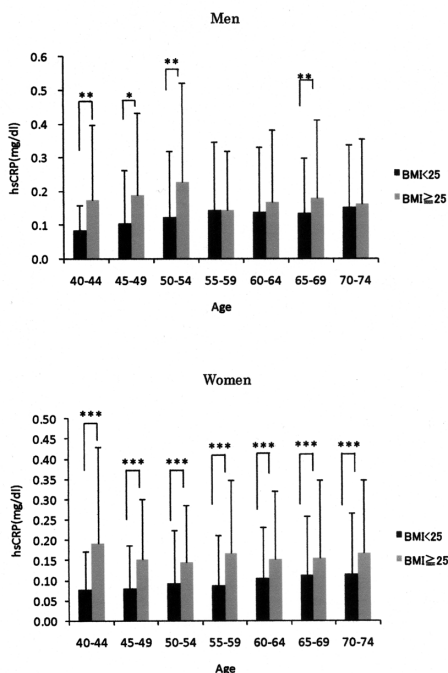


Fig. 3 Comparison between mean serum hs CRP value of BMI <25 group and BMI ≥25 by age groups.  
\*:  $P < 0.05$ , \*\*:  $P < 0.01$ ,  
\*\*\*:  $P < 0.001$ : student t-test

### 3. The relationship between serum hsCRP and coronary artery disease-related factor

Standard coefficient of regression between serum hsCRP value and coronary artery disease related factor showed in Table 2. Serum hsCRP value and age, BMI, systolic blood pressure, diastolic blood pressure, triglyceride, a total white-cell count, alkaline phosphatase, gamma glutamyl transpeptidase ( $\gamma$ -GTP), and glycosylated hemoglobin A1c (HbA1c) were

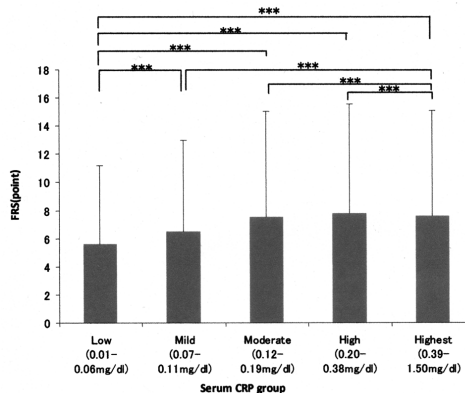


Fig. 4 The mean FRS(point) by serum hsCRP groups.  
\*\*\*:  $P < 0.001$ : One-way analysis of variance

positively correlated, and serum total cholesterol, high density lipoprotein cholesterol, albumin were negatively correlated.

### 4. The relationship between serum hsCRP value and FRS

Mean FRS of all subjects was  $6.4 \pm 3.9$ . The standard regression of serum hsCRP value and the FRS was  $r = 0.121$  ( $P < 0.001$ ) (Table 3).

Figure 4 showed the mean FRS (point) by serum hsCRP groups. Serum hsCRP value of "Low" and "Mild" groups showed significantly lower than other three groups.

Table 4 showed Odds ratio of high-risk of the coronary artery disease ( $FRS \geq 6$ ) differences of each groups by "Low" group with criteria. Other four groups showed higher value of ratio compared of "Low" group.

#### 4. Discussion

Previous study reported that hypertension, lipids abnormality symptom, diabetes mellitus and obesity were a risk factor of life-style related diseases, but there were some cases that myocardial infarction develops without these risk factors. In late years, serum hsCRP value was known a new risk factor of the cardiovascular disease.

Large-scale epidemiologic studies have reviewed the forecast efficacy for the cardiovascular disease of the serum hsCRP value in Europe and America. However, there are little studies about relationship between serum hsCRP value and the cardiovascular disease in Japan.

Therefore this study analyzed the relationship between serum hsCRP value and FRS which was the a forecast score of the coronary artery disease by using basics medical checkup.

As mean serum hsCRP value in this study was lower than these of Europe and America and the distribution distorted it in the left. Nakamura et al. reported that Japanese basic ceiling value of serum hsCRP was 0.2 mg/dl<sup>9)</sup>. In the Hisayama study, representative large scale epidemiologic studies, reported that the cutoff value of the serum hsCRP value as high risk of the coronary artery disease was 0.1 mg/dl and reporting<sup>10)</sup>.

Moreover, subjects for higher age and BMI showed higher serum hsCRP value. Yamada et al reported that men of serum hsCRP value showed higher than women. There were showed positive correlation with age, systolic blood pressure, diastolic blood pressure, serum triglyceride, BMI and negative correlation with high density lipoprotein cholesterol<sup>11)</sup>. Present study showed a similar result that there were significance negative correlation with serum high density lipoprotein cholesterol and the serum albumin. Even though previous study reported that serum hsCRP value and serum albumin showed positive correlation<sup>12)</sup>, present study showed negative correlation with serum hsCRP value and serum albumin level. The result in present study could be caused by changes of the protein synthesis pattern of stem cells from the inflammation cytokine under inflammation

state.

As the relationship between serum hsCRP and FRS, higher group of serum hsCRP value showed higher FRS and "Low" and "Mild" group were significance differences with other three groups. CRP-H group showed high risk of the coronary artery disease as  $FRS \geq 6$  by logistic-regression analysis. Otuka et al.<sup>13)</sup> reviewed that odds ratio of  $FRS \geq 6$  was 6.97 in upper quartile of serum hsCRP value compared with lower quartile for a 40-59-year-old man. Although there was difference with sex, age in this study subjects, the result showed similar in this study. The result of present study suggested that serum hsCRP value was associated with a risk factor of the coronary artery disease for man and woman. Serum hsCRP value showed a relationship with the FRS as well as a coronary artery disease-related factor. As known the inflammation is a new risk factor of the coronary artery disease, serum hsCRP value could be a representative test value to show episode risk of the coronary artery disease.

However, this study cannot mention the forecast efficacy of the coronary artery disease because the result in this study showed relationship between serum hsCRP value and the coronary artery disease by cross-sectional analysis. The future study using serum hsCRP value should consider about the personal dosage situation and percent of body fat because the statin of pharmaceutical used for lipids abnormality symptom affects inflammation suppression effect<sup>14)</sup>, Serum hsCRP -lowering effect<sup>15)</sup>, CRP production by fat cells. This study suggested that serum hsCRP value is possibility a predicted marker of the coronary artery disease. Thus, future study needs examination about the forecast efficacy of serum hsCRP value by the large scale cohort study.

In conclusion, the results of this study suggest that the measurement of the serum hsCRP value is significant for prevention of arterial sclerosis and the coronary artery disease.

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