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# RELATIONSHIP BETWEEN HIGH-SENSITIVITY C-REACTIVE PROTEIN (HS-CRP) SERUM LEVELS AND THE NUMBER OF CORONARY ARTERY LESION IN ACUTE CORONARY SYNDROME (ACS) PATIENT

**Nova Sipahutar*[1], Rahmad Isnanta[2], & Refli Hasan[2]**
[1]Resident Department of Internal Medicine, Faculty of Medicine, University of North Sumatra
[2]Cardiology Division Department of Internal Medicine, Faculty of Medicine, University of North Sumatra
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**Keywords:**Acute Coronary Syndrome (ACS), hs-CRP, Vessel Score, Angiography.

## Abstract

**Introduction**:Acute Coronary Syndrome (ACS) is one of the clinical manifestations of Coronary Heart Disease (CHD) that has high morbidity and mortality. Atherosclerosis is a process that underlies the occurrence of CHD. Inflammation plays an important role in the process of atherosclerosis. Some prospective studies suggest that inflammatory markers such as a high sensitivity C-Reactive Protein (hs-CRP) serum is a predictors of cardiovascular events.

**Aim**:The aim of this study was to determine the relationship of hs-CRP levels with the number of coronary artery lesions in patients with Acute Coronary Syndrome (ACS).

**Methods**:This cross-sectional study was conducted at the H. Adam Malik General Hospital in Medan from October to December 2018 to 48 ACS patients. Examination of hs-CRP levels, laboratory analysis for blood and coronary angiography was made in this study. Hs-CRP levels were divided into 2 groups based on the risk of cardiovascular events. The number of coronary artery lesions was assessed by vessel score. Furthermore, association of serum hs-CRP with vessel scores compared using Chi-Square analysis.

**Results**:From 48 research subjects, there were 16 (33.33%) people each with STEMI, NSTEMI and UAP respectively. Subjects in the group with hs-CRP≥3 mg / L as many as 15 (31.25%) people and the group with hs-CRP<3 mg / L were 33 (68.75%) people, while based on vessel scores, subjects with a Vessel score of 0, 1, 2, and 3 were as many as 10 (20.83%), 12 (25.00%), 10 (20.83%), and 16 (33.33%) people respectively. The mean hs-CRP level in patients with Vessel scores 0 was 0.510 ± 0.203 mg / L, 1 was 1.967 ± 0.729 mg / L, 2 was 2.010 ± 0.689 mg / L, and 3 was 5.388 ± 1.979 mg / L. In the Chi-Square analysis, there was a significant relationship between hs-CRP levels and vessel score ($p < 0.001$).

**Conclusion**:There was a significant relationship between hs-CRP levels and the number of coronary artery lesions in ACS patients.

## Introduction

CHD is a condition in which there is a decrease in the supply of oxygen and blood in the myocardium region due to blockage or spasm of the coronary blood vessels. This situation causes insufficient heart needs to pump blood throughout the body. The blockage of the coronary blood vessels is mostly caused by the atherosclerosis process.[1] Atherosclerosis is a chronic inflammatory process. High sensitivity-C Reactive Protein (hs-CRP) can be used to early detect an inflammatory process in CHD because it can measure CRP levels in very small quantities and is measured by a very sensitive method.[2]

Significant CHD was defined as the presence of more than 50% minimal stenosis in one coronary artery as evidenced by angiography.[3] Acute Coronary Syndrome (ACS) is one of the main clinical manifestations of CHD and one of a leading cause of death in Indonesia.[4] Relationship between high-sensitivity C-reactive protein (hs-CRP) serum levels and the number of coronary artery lesion in which evaluated from angiography in CHD patients is still debated.[5] Many studies said that the increase in hs-CRP levels is related to the severity of coronary artery stenosis but many also do not indicate a relationship. The limited data that represent the association between hs-CRP and number of coronary artery lesions in ACS patients in Indonesia become a primary reason to accomplish this study.

## Method

**Study Samples**
The study was conducted in the Cardiology Division of the Department of Internal Medicine, RSUP H. Adam Malik, Medan, North Sumatera, Indonesia. The research began with literature searches, title consultations, proposals preparation, proposal seminars, research and data analysis and preparation of reports requiring a time between October to December 2018.

**Study Design**
This study is using a cross-sectional design with the independent variable is hs-CRP and the dependent variable is the number of coronary artery lesions. Sampling technique using single proportion sample size calculation. The subjects who met the inclusion and exclusion criteria were asked to give informed consent to participate and fill in the approval letter to take part in the study.

The hs-CRP examination was performed by taking 3 ml of venous blood from the subject before they were carried out with coronary angiography. Next step, the blood is centrifuged for serum collection. Serum can be stored in the refrigerator at -30ºC before inspection. The serum was then examined by Immunoturbidimetric's latex particle-enhanced method using Roche / Hitachi ® 902 Automatic Analyzer. After gather the results, subject divided into two grups, Grup I with hs-CRP level <3 mg / L and Grup II with hs-CRP level ≥ 3 mg / L. Next step, ACS patients undergo an angiography examination. Actions and assessments of angiography results are carried out by the same cardiologist. Coronary artery stenosis lesions were assessed from the patient's angiography, evaluated and classified according to vessel score. Then after all the data was collected, data analysis and processing were then conducted.

**Statistical Analysis**
To measure the relationship between hs-CRP levels and the number of coronary arteries that undergoing stenosis, Chi-Square test was used. Data analysis using computer statistics with p value < 0.05 was considered statistically significant.

## Result

The study was attended by 48 research subjects during the period of October 2018 to December 2018 at the Cardiovascular Unit Care (CVCU) Department of Cardiology, RSUP. H. Adam Malik, Medan, North Sumatera, Indonesia. Subjects were identified as acute coronary syndrome patients who were in accordance with the inclusion and exclusion criteria. All subjects were willing to take a coronary angiography. In this study hs-CRP levels were divided into 2 groups, group I with hs-CRP levels <3 mg / L and group II with hs-CRP levels P 3 mg / L. Patients with hs-CRP level <3 mg / L were as much as 33 people (68.75%) while patients with hs-CRP level ≥ 3 mg / L were 15 people (31.25%) (Table 1). There were significant differences in leukocyte and CK-MB levels that were significant between the hs-CRP group <3 mg / l and the hs-CRP group ≥ 3 mg / l (p = 0.025 and p = 0.020). Furthermore it was seen that there were differences in the number of STEMI, NSTEMI and UAP patients that were significant between the hs-CRP group <3 mg / l and the hs-CRP group ≥ 3 mg / l (p <0.001).

***Tabel 1.Characteristics of the study subjects based on hs-CRP levels***

| Variable | hs-CRP < 3 mg/l<br>N=33 | hs-CRP ≥ 3mg/l<br>N=15 | P |
|---|---|---|---|
| Sex, (n) (%)<br>- Male<br>- Female | <br>26 (78.79)<br>7 (21.21) | <br>13 (86.67)<br>2 (13.33) | 0.700[a] |
| Age (Years), (Mean± SD) | 56.67 ± 8.45 | 53.13 ± 9.39 | 0.201[c] |
| Body mass index (kg), (Mean± SD) | 24.92 ± 3.66 | 25.57 ± 3.86 | 0.579[c] |

| | | | |
|---|---|---|---|
| Risk Factors, (n) (%) | | | |
| - Hypertension | 32 (96.97) | 14 (93.33) | 0.532[a] |
| - DM | 15 (45.45) | 7 (46.67) | 0.938[b] |
| - Dyslipidemia | 18 (54.55) | 7 (46.67) | 0.613[b] |
| - Smoking | 28 (84.85) | 13 (86.67) | 1.000[a] |
| Laboratory Results, (Mean± SD) | | | |
| - Hb (gr/dl) | 12.80 ± 1.91 | 13.07 ± 2.60 | 0.695[c] |
| - Leukocytes (/mm$^3$) | 9.317.58 ± 1.765.02 | 11.478.67 ± 3.212.11 | **0.025[c]** |
| - Platelets (/mm$^3$) | 249.180 ±57.861 | 276.130 ± 84.404 | 0.275[c] |
| - (mg/dl) | 172.39 ± 85.28 | 137.07 ± 81.03 | 0.184[c] |
| - SGOT (U/L) | 22.82 ± 6.41 | 26.87 ± 8.93 | 0.080[c] |
| - SGPT (U/L) | 22.52 ± 5.68 | 23.60 ± 6.96 | 0.570[c] |
| - Creatinine (mg/dl) | 0.94 ± 0.27 | 0.96 ± 0.27 | 0.752[c] |
| - Cholesterol Tot(mg/dl) | 189.06 ± 55.45 | 176.33 ± 34.12 | 0.336[c] |
| - LDL (mg/dl) | 123.42 ± 52.07 | 111.20 ± 35.30 | 0.348[c] |
| - HDL (mg/dl) | 32.67 ± 5.77 | 32.47 ± 9.31 | 0.928[c] |
| - Triglyceride (mg/dl) | 167.21 ± 61.92 | 141.00 ± 54.26 | 0.165[c] |
| - CKMB (U/L) | 25.76 ± 11.19 | 208.53 ± 186.86 | **0.020[c]** |
| - Troponin I (µg/L) | 1.50 ± 5.75 | 8.43 ± 9.51 | **<0.001[d]** |
| ACS Characteristics, (n) (%) | | | |
| - STEMI | 3 (9.09) | 13 (86.67) | **<0.001[b]** |
| - NSTEMI | 14 (42.42) | 2 (13.33) | |
| - UAP | 16 (48.49) | 0 (0) | |

[a]*Fisher-Exact,*[b]*Chi-Square,* [c]*Independent T-Test,* [d]*Mann-Whitney*

Hs-CRP mean in each vessel score was as follows : vessel score 0 with a total of 10 people (20.83%) had a mean of 0.510 ± 0.203, vessel score 1 with a total of 12 people (25.00%) had a mean of 1.967 ± 0.729, vessel score 2 with a total of 10 people (20.83%) had a mean of 2.010 ± 0.689, and the vessel score 3 with a total of 16 people (33.33%) had a mean of 5.388 ± 1.979 (Table 2). Based on Table 2 it can be seen that the mean hs-CRP increases with increasing vessel score.

***Tabel 2. Mean of hs-CRP based on vessel score***

| Vessel score | N (%) | Mean hs-CRP (mg/L) |
|---|---|---|
| 0 | 10(20.83) | 0.510±0.203 |
| 1 | 12(25.00) | 1.967±0.729 |
| 2 | 10(20.83) | 2.010±0.689 |
| 3 | 16(33.34) | 5.388±1.979 |

Tables 3 and 4 represent the distribution and the results of the chi-square test to analyze the relationship of hs-CRP levels with vessels score. The chi-square test results showed that there was a significant relationship between hs-CRP and vessel scores ($p < 0.001$).

***Tabel 3. Patient distribution based on hs-CRP level and vessel score***

| hs-CRP Levels | Vessel score | | | | Total |
|---|---|---|---|---|---|
| | 0 (n) | 1 (n) | 2 (n) | 3 (n) | |
| hs-CRP < 3.00 mg/l | 10 (20.83%) | 11 (22.92%) | 10 (20.83%) | 2(4.17%) | 33 (68.75%) |
| hs-CRP ≥ 3.00 mg/l | 0(0%) | 1(2.08%) | 0(0%) | 14 (29.17%) | 15 (31.25%) |
| Total | 10 (20.83%) | 12(25%) | 10 (20.83%) | 16 (33.34%) | 48 (100%) |

***Tabel 4. Results of Chi-Square Analysis of hs-CRP relationship with vessel score***

| | | Vessel Score | | p |
|---|---|---|---|---|
| | | SVD | MVD | |
| hs-CRP Levels | hs-CRP < 3 mg/L | 21 (43.75%) | 12 (25%) | <0.001 |
| | hs-CRP ≥ 3 mg/L | 1 (2.08%) | 14 (29.17%) | |
| Total | | 22 (45.83%) | 26 (54.17%) | |

**Disscusion**

Atherosclerosis is a process that underlies the occurrence of CHD and it is a multifactorial process with interrelated mechanisms. Atherosclerosis is a chronic inflammatory process. Inflammation plays an important role in every stage of atherosclerosis starting from the beginning of plaque development until plaque rupture occurs.[6]

This study shows that inflammation plays an important role in the process of atherogenesis and its various complications including CHD. Hs-CRP is an inflammatory marker that is widely used in research to predict the presence of CHD. Previous research stated that there was an association between hypertension, diabetes mellitus, dyslipidemia and smoking with hs-CRP levels.[7,8,9] However, in this study there was no significant relationship between risk factors and hs-CRP levels in both groups ($p > 0.05$). This maybe happen due to lifestyle changes and the use of antidiabetic drugs, antihypertensive and cholesterol-lowering drugs on previous occasion.[10,11,12]

In this study there were significant differences in the number of STEMI, NSTEMI and UAP patients between hs-CRP group <3 mg / l and the hs-CRP group ≥ 3 mg / l ($p <0.001$). This is consistent with the study conducted by Tong et al, where patients with hs-CRP values ≥ 3 mg / L had a greater ACS presentation compared to patients with hs-CRP values <3 mg / L (61% vs 31%, p value = 0.02) .[13] There were significant differences in the number of patients between each vessel score in both groups ($p <0.001$). The mean hs-CRP level was higher in patients with vessel scores 3 which were 5.388 ± 1.979 mg / L compared with vessel scores 0 (0.510 ± 0.203 mg / L), vessel scores 1 (1.967 ± 0.729 mg / L) and vessel scores 2 ( 2.010 ± 0.689 mg / L). This is in accordance with the study of Guruprasad et al, which found an increase in mean hs-CRP level in patients with 3VD compared with 1VD (1.9 ± 2.4 vs 1.4 ± 1.5 mg / L; $p = 0.01$) .[14]

In this study Chi-square hypothetical categorical comparative test was conducted and showed a significant relationship between hs-CRP levels and the number of coronary artery lesions assessed using a vessel score in ACS patients ($p <0.001$). This is in accordance with the research conducted by Hasnat et al, where in the study found a significant relationship between hs-CRP levels and vessel scores ($r = 0.7409$; $p = 0.01$) .[15] Similarly, the research conducted by Lidija Memon et al., Where it was found that an increase in serum hs-CRP level increased with an increase in the number of major coronary arteries undergoing stenosis ≥ 50% ($p <0.01$).[16] Tenzin Nyandak et al. show a significant correlation between hs-CRP level and the extent of coronary artery stenosis ($r = 0.316$, $p <0.004$).[17] Likewise with the study conducted by Zairis et al, where hs-CRP concentration correlates with the complexity of stenosis in ACS patients ($r = 1.8$, $p <0.001$). These results indicate that higher hs-CRP levels reflect an increase in the severity of the disease other than an indicator of the presence of ACS and further confirmation that inflammation is not only an important trigger in the mechanism of ACS associated with plaque rupture, but

also as a supporting factor for chronic atherosclerosis.[18] In the study of Arroyo et al., It was stated that hs-CRP levels correlated with the number of coronary arteries with complex stenosis (r = 0.36, p = 0.01). This can be used to identify patients with complex coronary lesions and also large intracoronary thrombosis. In addition, hs-CRP can also help to identify patients with non-complex lesions that are prone to become plaque rupture.[19] This study is a cross sectional study that cannot explain the causal relationship so that this study only looks at the relationship between the increase in serum hs-CRP and the number of coronary artery lesions in ACS patients. The use of statins and drugs which have anti-inflammatory effects such as steroids that can reduce serum hs-CRP levels should be optimally excluded so that accurate results are obtained.

## Conclusion

There was a significant relationship between hs-CRP serum levels and the number of coronary artery lesions assessed by vessel score in ACS patients ($p < 0.001$). The hs-CRP level in the group of patients with a Vessel score of 3 was higher than the group of patients with a Vessel score of 0, 1 and 2.

## Suggestion

Further research is needed with a larger sample and prospective research design to obtain a causal relationship between an increase in serum hs-CRP levels and the number of coronary artery lesions that undergo stenosis in patients with ACS.

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