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# The Association between hs-CRP Levels with GRACE Score in Acute Coronary Syndrome Patients in H. Adam Malik Medan Central General Hospital

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## ABSTRACT

**Objective**: Acute coronary syndrome (ACS) describes a wide range of myocardial ischemia, which is always associated with the rupture of atherosclerotic plaques in coronary arteries. CRP has been shown to be a risk predictor of ACS. GRACE score has been associated with predicting early and late death in ACS patients. Therefore, this study aim to investigate the association between high sensitivity C-reactive protein (hs-CRP) levels with GRACE score in ACS patients.
**Methods**: This study was a retrospective analytic study. The study population was acute coronary syndrome patients in central general hospital of H. Adam Malik, Medan city and 51 patients who met the inclusion and exclusion criteria. Data analysis was calculated using univariate and bivariate analysis. A correlation test was carried out using Spearman correlation test to determine the association between hs-CRP levels with GRACE score in ACS patients.
**Results**: There were 51 samples included in the study. There was a significant difference ($p = 0.005$) in the mean hs-CRP levels in UAP, NSTEMI, and STEMI subjects. In contrast, there was no significant difference in GRACE score among the three ACS diagnoses. For the association of hs-CRP levels with GRACE score in all subjects, the Spearman correlation test showed a significant correlation between hs-CRP levels with GRACE score ($p < 0.001$) with a correlation coefficient (r) of 0.588.
**Conclusion**: There was a significant association between serum hs-CRP levels with GRACE score and the higher hs-CRP levels, followed by a higher GRACE score.

***Keywords***: Acute coronary syndrome, GRACE score, hs-CRP

## INTRODUCTION

Cardiovascular diseases are a cluster of heart and vascular diseases, including coronary heart disease (CHD), coronary artery disease, and acute coronary syndrome. Although clinicians often use CAD and ACS terms interchangeably, as with coronary heart disease, the two are not synonymous. ACS is a subcategory of CAD, while CHD occurs due to CAD. On the other hand, CAD is marked by atherosclerosis in the coronary artery and may be asymptomatic, while ACS is almost always symptomatic, such as unstable angina, and often associated with myocardial infarction. [1]

Acute coronary syndrome (ACS) describes a wide range of myocardial ischemia, which is always associated with the rupture of atherosclerotic plaques in coronary arteries, including unstable angina pectoris (UAP), non-ST elevated myocardial infarction (NSTEMI), or ST elevated myocardial infarction (STEMI).

The ACCESS investigator group reported that of 46% ACS that occurred in the developing countries, 54% were NSTEMI/UAP.[2] In the United States of

America, the average age for ACS is 68 years old. Male is found to be more prevalent than female in developing ACS with a ratio of 3:2. The incidence of ACS in the US is more than 780.000 and 70% of that number consists of NSTEMI. In 2010, there were 625.000 patients discharged from the hospital in the US with a diagnosis of ACS. GRACE study found that approximately 30% of ACS patients had STEMI, while 70% had NSTEMI. The average age of patients with first myocardial infarct (MI) is 65 years old in males and 72 years old in females. [3]

An accurate diagnosis and early risk stratification are crucial in implementing therapy and predicting prognosis in ACS patients. After the myocardial infarction, patients are at a higher risk of recurrent episodes, even though early revascularization and adequate poly-pharmacotherapy have been carried out. Recently, the focus has been on inflammation marker's potential role as a risk predictor of ACS. For example, the C-reactive protein (CRP) and white blood cell (WBC). In the last decade, an association between the role of inflammation mechanisms in the pathogenesis of atherosclerosis has been known. CRP has been shown to be a risk predictor for ACS. A study showed that a 0.4% mortality rate in patients with normal CRP had increased to 5.8% in patients with elevated CRP levels. CRP may also activate the complement system in the atherosclerotic coronary artery intima. Therefore, the activation of complement is involved in MI pathogenesis. Moreover, many studies had suggested the role of Interleukin-1α and Interleukin-6 in ACS. Luo et al. and Hamzah and Turki from Iraq reported increased serum IL-6 levels in ACS patients. [4; 5]

Various risk classification systems have been used to assess the risk and prognosis of MI patients, including the Global Registry of Acute Coronary Events (GRACE) risk score.[6] High-sensitivity C-reactive protein (hs-CRP) is significantly associated with poor prognosis in NSTEMI patients, regardless of the GRACE risk score, although not in STEMI patients. [7] hs-CRP concentration is associated with coronary events in patients, with an approximately 2-fold increase in patients with hs-CRP levels of >3,6 mg / L. [5]

GRACE score is associated with predicting early and late death in ACS patients; however, the association between hs-CRP levels with GRACE score is still unknown. This study aimed to describe the association between hs-CRP level with GRACE score in ACS patients. Therefore, it is expected that GRACE score can be used to determine the prognosis of ACS patients.

## MATERIALS AND METHODS

This study was a retrospective analysis. The study population was acute coronary syndrome patients treated in the RSUP H. Adam Malik Medan. The study was conducted from June 2020 – April 2021. The subjects were selected by calculating the correlation analytic sample size formula, and 51 subjects met the inclusion and exclusion criteria. The Hospital Ethics Committees have approved this study, and each subject had signed informed consent.

### STATISTICAL METHODS

The inclusion criteria for this study were acute coronary syndrome patients aged ≥18 years old diagnosed by history taking, physical examination, ECG, and cardiac enzyme test. The exclusion criteria were stable angina patients, history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), patients with chronic liver disease, severe infection or sepsis, malignancy, autoimmune disease, history of trauma, burn injuries, and prior surgeries. The variables in this study included age, gender, smoking status, familial history, hypertension, diabetes mellitus, hyperlipidemia, acute coronary syndrome (ACS), high-sensitive C-reactive protein (hs-CRP), Troponin I, creatinine levels, and GRACE score.

Univariate and bivariate analyses were carried out. A correlation test was carried out using the Spearman correlation test to determine the association of hs-CRP level with GRACE score in ACS patients. Data analysis was carried out using the SPSS program (Statistical Package for Service Solution).

## RESULTS

**Table 1. Characteristics of ACS patients**

| Characteristics | n = 51 |
|---|---|
| **Gender, n (%)** | |
| Male | 40 (78,4) |
| Female | 11 (21,6) |
| Age, mean (SD), years | 57,63 (9,97) |
| **Smoking status, n (%)** | |
| Yes | 36 (70,6) |
| No | 15 (29,4) |
| **Familial History, n (%)** | |
| Yes | 16 (31,4) |
| No | 35 (68,6) |
| **Hypertension, n (%)** | |
| Yes | 35 (68,6) |
| No | 16 (31,4) |
| **Diabetes Mellitus, n (%)** | |
| Yes | 29 (56,9) |
| No | 22 (43,1) |
| **Hyperlipidemia, n (%)** | |
| Yes | 28 (54,9) |
| No | 23 (45,1) |
| **ACS Diagnosis, n (%)** | |
| UAP | 6 (11,8) |
| NSTEMI | 14 (27,5) |
| STEMI | 31 (60,8) |

A total of 51 acute coronary syndrome (ACS) patients treated in RSUP H. Adam Malik Medan who met the inclusion criteria were included in the study. The study subject's characteristics are shown in Table 1.

Table 2 showed the laboratory results, including complete blood count, cardiac enzyme, lipid profile, random blood sugar level, and renal function.

**Table 2. Laboratory Characteristics**

| Laboratory Characteristics | |
|---|---|
| **Laboratory** | |
| **Complete Blood Workup** | |
| Hemoglobin (gr/dl)^ | 12.87 ± 1.83 |
| Leukocyte (/µl)^ | 9729.81 ± 2689.22 |
| Platelet (µl)^ | 257,980.39 ± 65538.53 |
| **Carbohydrate Metabolism** | |
| Random Blood Glucose (mg/dl)* | 161 (80 – 417) |
| **Renal Function** | |
| Urea Level(mg/dl)* | 32 (13 – 218) |
| Creatinine Level (mg/dl)* | 1.10 (0.62 – 6.96) |
| **Lipid Profile** | |
| Total Cholesterol (mg/dl)^ | 172,65 ± 44,21 |
| LDL (mg/dl)^ | 125,02 ± 39,12 |
| HDL (mg/dl)* | 32 (18 – 70) |
| Triglyceride (mg/dl)* | 121 (67 – 326) |
| **Cardiac Enzyme** | |
| Troponin I (ng/ml)* | 6,50 (0,03 – 30,20) |
| CKMB (U/L)* | 64 (16 – 744) |

^ *Data was normally distributed, shown in mean ± SD*
** Data was not normally distributed, shown in median (minimum – maximum)*

Table 3 showed the mean and median of overall laboratory characteristics based on ACS diagnosis. We found a significant difference between the mean leukocyte levels in UAP, NSTEMI, and STEMI subjects. Similar results were also found in cardiac enzyme, where a significant difference was found in the mean of Troponin I and CKMB levels in UAP, NSTEMI, and STEMI subjects.

**Table 3. Laboratory Characteristics Based on Diagnosis**

| Laboratory Characteristics | UAP | NSTEMI | STEMI | P |
|---|---|---|---|---|
| **Laboratory** | | | | |
| **Complete Blood Workup** | | | | |
| Hemoglobin (gr/dl)^ | 13,08 ± 1,65 | 12,63 ± 1,80 | 12,93 ± 1,92 | 0,845* |
| Leukocyte (/µl)^ | 6.840,07 ± 4.024,63 | 9.565 ± 2.410,13 | 10.363,55 ± 2.176,85 | 0,010* |
| Platelet (µl)^ | 262.333,33 ± 69.712,74 | 260.714,29 ± 63.093,86 | 255.903,23 ± 67.912,37 | 0,961* |
| **Carbohydrate Metabolism** | | | | |
| Random Blood Glucose (mg/dl)* | 130 (89 – 229) | 164,50 (101-372) | 176 (80 – 417) | 0,363^ |
| **Renal Function** | | | | |
| Urea Level(mg/dl)* | 29 (13 – 64) | 33 (15 – 218) | 32 (17 – 146) | 0,740^ |
| Creatinine Level (mg/dl)* | 0,80 (0,64 – 2,32) | 1,12 (0,64 – 4,09) | 1,15 (0,62 – 6,96) | 0,209^ |
| **Lipid Profile** | | | | |
| Total Cholesterol (mg/dl)^ | 175,17 ± 15,99 | 165,50 ± 46,21 | 175,39 ± 47,51 | 0,784* |
| LDL (mg/dl)^ | 119,67 ± 18,03 | 126,71 ± 39,68 | 125,29 ± 42,52 | 0,935* |
| HDL (mg/dl)* | 34,50 (25 – 51) | 33 (19 – 48) | 32 (18 – 70) | 0,614^ |
| Triglyceride (mg/dl)* | 118 (67 – 275) | 119 (70 – 225) | 125 (72 – 326) | 0,490^ |
| **Cardiac Enzyme** | | | | |
| Troponin I (ng/ml)* | 0,03 (0,03 – 0,28) | 1,85 (0,12 – 15,20) | 9,96 (0,19 – 30,20) | 0,000^ |
| CKMB (U/L)* | 27 (16 – 40) | 51 (20 – 98) | 120 (23 – 744) | 0,000^ |

** ANOVA*
*^ Kruskal Wallis*

Table 4 showed the median of hs-CRP level, which was 5.10 mg/L with the lowest 0.20 mg/L and highest 23.60 mg/L. GRACE score results showed a mean of 108.67 (SD = 24.90).

**Table 4. Characteristics of Hs-CRP and GRACE Score**

| **Parameter** | |
|---|---|
| Hs-CRP (mg/L) | 5,10 (0,20 – 23,60) |
| GRACE Score | 108,67 (24,90) |

Table 5 showed the characteristics of hs-CRP and GRACE score based on ACS diagnosis. We found a significant difference in the mean hs-CRP levels in UAP, NSTEMI, and STEMI subjects. Conversely, for the GRACE score, there was no significant difference between the three ACS diagnoses.

**Table 5. Characteristics of hs-CRP and GRACE Score Based on Diagnosis**

| | **UAP** | **NSTEMI** | **STEMI** | **P** |
|---|---|---|---|---|
| Hs-CRP (mg/L) | 1,58 ± 2,03 | 4,92 ± 4,95 | 7,54 ± 5,86 | 0,005^ |
| GRACE Score | 91,33 ± 21,61 | 112,21 ± 26,26 | 110,42 ± 24,23 | 0,190* |

** ANOVA*
*^ Kruskal Wallis*

**Table 5. Spearman Association/Correlation between Hs-CRP Levels and GRACE score.**

| | | **n** | **GRACE score** | |
|---|---|---|---|---|
| | | | **r** | **P** |
| **Hs-CRP** | All subjects | 51 | 0,588 | <0,001 |
| | Male | 40 | 0,580 | <0,001 |
| | Female | 11 | 0,534 | 0,090 |
| | UAP | 6 | 0,812 | 0,05 |
| | NSTEMI | 14 | 0,465 | 0,094 |
| | STEMI | 31 | 0,517 | 0,003 |

The association of hs-CRP and GRACE score is shown in Figure 1. Correlation analysis for all subjects using the Spearman Correlation test showed a significant correlation between Hs-CRP level with GRACE score ($p < 0.001$) with a correlation coefficient (r) of 0.588. The correlation result showed a moderate and positive correlation between hs-CRP levels and GRACE score, indicating that the higher hs-CRP level, followed by an increase of GRACE score.

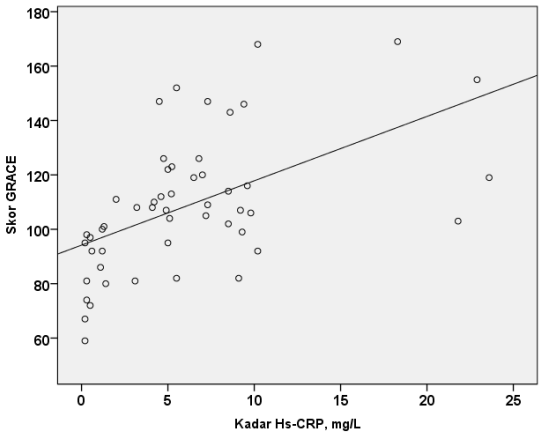


**Figure 1. Scatterplot graph of the correlation of hs-CRP levels with grace score in all subjects.**

The association of hs-CRP with GRACE score in male subjects as shown in Figure 2. Correlation analysis for 40 male subjects also showed a significant correlation between hs-CRP levels with GRACE score ($p < 0.001$) with a correlation coefficient (r) of 0.580. The correlation result showed a moderate and positive correlation between hs-CRP levels and GRACE score in male subjects, indicating that a higher hs-CRP level, followed by an increase of GRACE score.

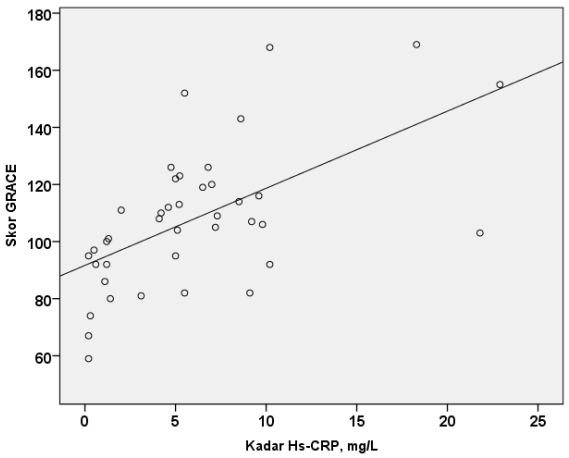


**Figure 2. Scatterplot graph of the correlation of hs-CRP levels with grace score in male subjects.**

We found no significant correlation between Hs-CRP levels with GRACE score in 11 female subjects ($p = 0.090$), 14 NSTEMI subjects ($p = 0.094$), and 6 UAP subjects ($p = 0.05$). The association of hs-CRP levels with GRACE score in SEMI subjects as shown in Figure 3. Correlation analysis in 31 STEMI subjects showed a

significant correlation between hs-CRP levels with GRACE score (p = 0.003) with a correlation coefficient (r) of 0.517. The correlation result showed a moderate and positive correlation between hs-CRP levels and GRACE score in STEMI subject, indicating that higher hs-CRP levels, followed by increased GRACE score.

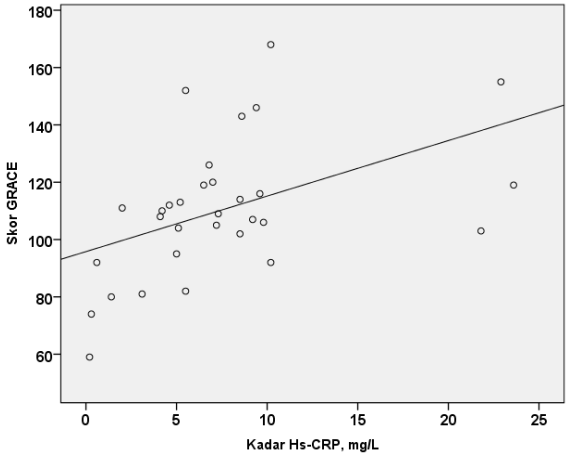


**Figure 3. Scatterplot graph of the correlation of hs-CRP levels with grace score in stemi subjects.**

## DISCUSSION

In our study, most ACS subjects were male, namely 40 subjects (78.4%) with a mean age of 57.63 years old. A study by Gonzalez-Pacheco et al. also reported that most ACS patients were male, namely 79.2% with a mean age of 60 years old. Males are reported to be more susceptible to the atherosclerosis process, presumably due to the role of estrogen hormone, which might prevent the formation of atherosclerotic plaque. Estrogen also plays a role in atherosclerotic plaque stabilization. Therefore, the atherosclerotic plaque in females is less prone to rupture compared to males. Atherosclerotic plaque in females is also reported to undergo erosion more often than rupture; therefore, the symptoms of ACS are felt more slowly. [8] Theoretically, age >55 is a non-modifiable risk factor for ACS. [9]

Based on the risk factor of ACS, this study found 36 (70.6%) subjects with smoking status, 29 (56.9%) subjects with DM, 35 (68.6%) subjects with a history of hypertension, 28 (54.9%) subjects with a history of hyperlipidemia and 16 (31.4%) subjects with a familial history of ACS. Smoking, hypertension, DM, history of hyperlipidemia, and familial history of ACS are the risk factors of ACS. [10] A previous study by Ralapanawa et al. (2019) reported 42.3% ACS patients with a smoking status, 29.3% patients with DM, 44.7%p patients with hypertension, and 41.0% patients with a familial history of ACS. [2]

In this study, we found 31 (60.8%) subjects with STEMI, 14 (27.5%) subjects with NSTEMI, and 6 (11.8%) subjects with UAP. The ACCESS investigator group had reported that of 46% ACS cases in the developing countries, most was classified as STEMI, namely 51.38%, followed by NSTEMI, namely 37.88%, and UAP with 10.75%. [11]

Based on laboratory results, the median value of Troponin I in this study was 6.5 ng/mL, and the median value for CKMB was 64 U/L. Our result was similar to Tscherny et al. (2019), which reported the median Troponin I value of 9 ng/mL and CKMB of 53 U/L. [12] The mean cholesterol level in the study was 172.65 mg/dl, LDL 125.02 mg/dl, HDL 33.29 mg/dl, and triglyceride 134.47 mg/dl. Other studies also reported lipid profile results in ACS patients, in which the mean total cholesterol was 4.96 mmol/L, LDL 3.18 mmol/L, triglyceride 1.3 mmol/L, and HDL 1.16 mmol/L.[13]

The mean GRACE score in our study was 108.67, and the mean hs-CRP level was 6.12 mg/L. Roubin (2013) reported a similar result, in which the mean GRACE score was 99.3. Based on the mean GRACE score, most subjects had a moderate risk of mortality and recurrent ACS. [14] A study by Chang (2018) reported that the mean hs-CRP level was 9.61 mg/L.[15] In a cohort study, Tong et al. (2018) found that hs-CRP is a significant predictor to myocardial infarction, which plays a crucial role in the inflammation process and pathophysiology of coronary heart disease. [16] In the study, the hs-CRP level of ≥3 mg/L had a 5.6 times risk of

acute myocardial infarction (p value < 0.0001) and had a greater ACS presentation compared to patients with a hs-CRP level of < 3 mg/L.

Based on the correlation analysis, there was a significant correlation between hs-CRP level with GRACE score (p < 0.001) with a correlation coefficient (r = 0.580) that showed a moderate and positive correlation between the hs-CRP level and GRACE score. This finding indicated that a higher hs-CRP level would be followed by an increased GRACE score. Our result is similar to previous studies, which showed a correlation between the hs-CRP level and GRACE score with a correlation coefficient (r) of 0.651. This result indicated the degree of inflammation evaluated based on the increased hs-CRP level, which would be more severe in patients with a high GRACE score. [6] The combination between the hs-CRP level and GRACE score would even improve the mortality risk stratification in ACS patients. [17] The inflammatory response in ACS occurs due to the myocardial necrosis process. [14] Other studies also reported that an increased hs-CRP level, as an inflammatory response, would correlate with the severity of atherosclerotic plaque and the number of affected vessels. [18] The limitation of our study was that we did not consider the number of vessels affected with atherosclerotic plaque. Other than the severity of atherosclerotic plaque, the increased hs-CRP level would also be determined by the number of affected vessels with atherosclerotic plaque.

## CONCLUSION

In summary, there was a significant association between serum hs-CRP levels with GRACE score and higher hs-CRP levels, followed by a higher GRACE score.

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**Conflict of Interest:** There is no conflict of interests.

**Ethical Approval:** Approved

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