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Diagnostic value of high sensitivity C-reactive protein levels in dedifferentiation of stable angina from unstable angina

Reza Madadi[1], Katayoon Haddadian[2], Ebrahim Ghaderi[3]

1 Assistant Professor, Department of Cardiovascular, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran
2 Student of Medicine, Department of Cardiovascular, School of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran
3 Assistant Professor, Kurdistan Research Center for Social Determinants of Health, Kurdistan University of Medical Sciences, Sanandaj, Iran

Original Article

Abstract

BACKGROUND: Differentiation of stable angina from unstable angina is important because they need different approaches. Few studies have been conducted to assess the diagnostic value of high sensitive C-reactive protein (hs-CRP) in differentiating these two diseases. This study aimed to evaluate the diagnostic value of hs-CRP levels for differentiating stable angina from unstable angina.

METHODS: After signing the consent form, patients with unstable angina who referred to Tohid Hospital emergency in Sanandaj, Iran, and patients with stable angina who referred to the special clinic of the hospital were evaluated. Disease was confirmed by a cardiologist. Morning serum hs-CRP was tested using MONOBIND laboratory kit (USA). Data were analyzed by SPSS using Student's independent t-test, Mann-Whitney U, chi-square, Fisher exact test, and receiver operating characteristic curve.

RESULTS: hs-CRP levels in patients with stable angina and unstable angina were 1.6 (± 1.18) and 2.35 (± 1.30) mg/l, respectively (P = 0.025). The hs-CRP level ≥ 2.31 mg/l was the best cut-off point for differentiating stable from unstable angina. At this cut-off point, the sensitivity and specificity were 56% and 73%, respectively. Area under the curve was calculated to be 0.679 (95% confidence interval: 0.54-0.81) (P = 0.017).

CONCLUSION: hs-CRP level is helpful for differentiating patients with stable angina from those with unstable angina. It is recommended to consider the hs-CRP level of 2.31 mg/l as the best cut-off point.

KEYWORDS: Acute Coronary Syndrome, Stable Angina, Unstable Angina, Diagnostic Test, Receiver Operating Characteristic Curve

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Introduction

Inflammation is a common component of atherosclerosis and is a likely cause of rupture in atherosclerotic plaques. Inflammatory proteins have been investigated in several studies as a biomarker of atherosclerosis.

High sensitive C-reactive protein (hs-CRP) is one of the biomarkers that have been used widely.[1-5] In patients with acute coronary syndrome (ACS), hs-CRP above 3 mg/l may be associated with a worse prognosis. However, some other studies have not confirmed the association between this biomarker and prognosis of the disease.[6-13]

In addition, some studies have assessed the diagnostic value of this biomarker in diagnosis of ACSs including stable angina, unstable angina, and stroke; in some cases, it was proved as useful diagnostic tool[14-16] while other studies showed

Corresponding Author:
Katayoon Haddadian
Email: katyhad@ymail.com

contrary results.[16,17] Hence, its efficiency is controversial, and there is a need for further researches. Differentiation of stable angina from unstable angina is important because they need different treatment procedures; however, there is a controversy about the efficiency of hs-CRP for differentiating stable from unstable angina.[17-20]

Since some previous studies have shown that increased level of hs-CRP worsens the prognosis, [10,11,18,21] the assessment of diagnostic value of this biomarker for differentiating these two diseases can be clinically valuable because it can simultaneously indicate the prognosis of the disease.

It is of great importance for clinicians to determine a cut-off point for diagnostic tests. Receiver operating characteristic (ROC) curve analysis is a method for determining the cut-off point. In this method, a curve is plotted for every point of diagnostic test valve to calculate sensitivity and specificity. Hence, this curve can present the diagnostic test's efficiency for the classification of patients.[22]

Therefore, this study aimed to examine the diagnostic value of hs-CRP levels and to determine the sensitivity and specificity of different levels of this biomarker in the differentiation of stable angina and unstable angina.

Materials and Methods

Using convenience sampling, patients with unstable angina were selected among those who referred to Tohid Hospital emergency in Sanandaj, Iran, due to chest pain, and patients with stable angina were selected among those referred to the special clinic in Tohid Hospital. Stable angina and unstable angina were confirmed by a cardiologist.

This study was approved by the Ethics Committee of Kurdistan University of Medical Sciences and the purposes of the study were explained to patients and informed consents were obtained. Fasting blood samples were collected from all patients in the morning at the early time of attending the hospital. Exclusion criteria included the presence of infectious diseases in the past 3 weeks, the immune system and autoimmune disease, recent surgery in the past 2 months, a history of trauma in the past 2 months, renal failure, liver failure, cancers, and the use of anti-inflammatory drugs.

Considering differences between averages, having $\alpha = 1\%$, $\beta = 10\%$, and average hs-CRP levels of 1.7 (± 0.9) mg/l for stable angina group versus 0.93 (± 0.9) mg/l for unstable angina group, the sample size was calculated to be 22 patients in each group;[15] in this study, 30 patients were included in each group. All the patients filled a questionnaire which included their past records; in addition, to measure CRP, blood samples were tested using MONOBIND (Monobind, Inc. Lake Forest, CA, USA) laboratory kit, made in USA.

Data were entered in SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). The quantitative data in the two groups were compared using Student's independent t-test or Mann-Whitney U test, and the qualitative data were compared using chi-square and Fisher exact test. To determine the CRP cut-off point, ROC curve was used, and the specificity and sensitivity were determined at the cut-off point.

Results

A total of 60 patients, including 30 patients with stable angina and 30 patients with unstable angina were studied. From all, 24 patients (40%) were female. Mean age of patients in the stable angina and unstable angina groups were 62.1 ± 14.3 and 59.7 ± 12.9 years, respectively (P = 0.5). Among them, 16 (26.7%) patients were from rural areas and the rest were from urban areas. A total of 20 patients (33.3%) had a history of heart attack in their family. Twelve patients (20%) were smokers; 18 patients (30%) had a history of hypertension, 9 patients (15%) had a history of diabetes, and 17 patients (28%) had a history of hyperlipidemia. Apart from that blood pressure, which was higher in the unstable angina group (P = 0.024), the other variables were similar between the two groups and there was no statistically significant difference (Table 1).

Table 1. Comparison of characteristics of patients in the two groups of unstable angina and stable angina

Variables	Stable angina	Unstable angina	P
Sex			
Male, n (%)	19 (63.3)	17 (56.7)	0.790
Female, n (%)	11 (36.7)	13 (43.3)	
Residency			
Urban, n (%)	20 (66.7)	24 (80.0)	0.380
Rural, n (%)	10 (33.3)	6 (20.0)	
Family history of MI, n (%)	8 (26.7)	7 (23.3)	0.410
Current smoker, n (%)	5 (16.7)	7 (23.3)	0.740
Passive smoker, n (%)	7 (23.3)	6 (20.0)	0.754
HTN, n (%)	5 (16.7)	13 (43.3)	0.024*
Hyperlipidemia, n (%)	6 (20.0)	11 (36.7)	0.250
Diabetes, n (%)	2 (6.7)	7 (23.3)	0.140**
Age (year)	62.1 ± 14.3	59.7 ± 12.9	0.499***
BMI	26.4 ± 4.9	26.5 ± 3.5	0.991***
hs-CRP (mg/l)	1.6 ± 1.18	2.35 ± 1.3	0.025*,***
Smoking (pack/year)	5 (0.15-32)	19 (0.45-100)	0.268€

* Statistically significant;** Fisher's exact test was applied; *** Independent t-test was applied; € Mann-Whitney U test was applied; Other comparisons were done by chi-square test; MI: Myocardial infection; HTN: Hypertension; BMI: Body mass index; hs-CRP: High sensitive C-reactive protein

hs-CRP levels in patients with stable angina and unstable angina were 1.6 ± 1.18 and 2.35 ± 1.30 mg/l, respectively, and the difference was statistically significant (P = 0.025). A hs-CRP level ≥ 2.31 mg/l was the best cut-off point for differentiating stable from unstable angina. In this cut-off point, the sensitivity and specificity were 56% and 73%, respectively (Figure 1). With a level of 2.31 mg/l, the area under the curve was calculated as 0.679 (95% confidence interval = 0.54-0.81) (P = 0.017). Table 2 shows sensitivity and specificity of some hs-CRP levels for differentiating stable and unstable angina.

Discussion

In this study, the baseline characteristics of the two groups were similar. Compared with stable angina group, hs-CRP level in patients with unstable angina was higher. The best cut-off point to differentiate unstable angina from stable angina was calculated as 2.31 mg/l. Therefore, hs-CRP seems to be helpful in differentiating stable angina from unstable angina.

Differentiating stable from unstable angina is important because these two diseases need different processes and different approaches to be treated, and also there is no specific biomarker for differentiating these two. In this study, we concluded that to differentiate these two diseases we have to set a cut-off point. There are few studies that have assessed the diagnostic value of this biomarker in differentiation of stable and

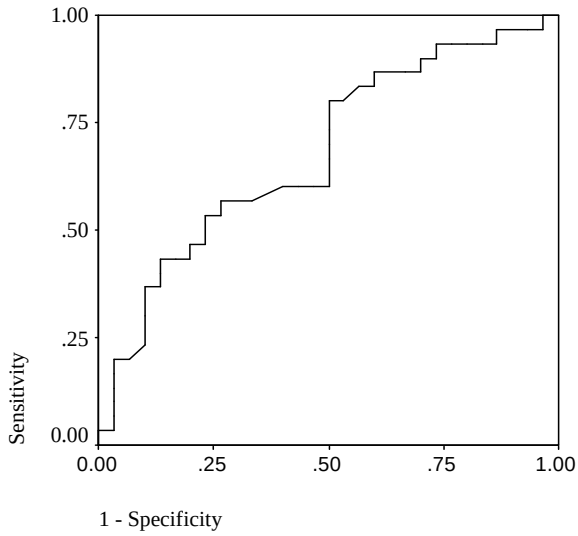

Figure 1. Receiver operating characteristic curve for differentiating unstable angina from stable angina; The area under the curve in a level of 2.31 mg/l was calculated as 0.679 (95% confidence interval = 0.54-0.81) (P = 0.017)

Table 2. Calculated sensitivity and specificity of high sensitive C-reactive protein levels for the differentiation of stable angina from unstable angina

hs-CRP (mg/l)	Sensitivity	Specificity
0.130	1.00	0.03
0.205	0.96	0.06
0.265	0.96	0.13
0.320	0.93	0.13
0.450	0.93	0.16
0.555	0.93	0.20
0.615	0.93	0.26
0.750	0.90	0.30
0.815	0.86	0.30
0.885	0.86	0.40
0.970	0.83	0.43
1.065	0.80	0.50
1.220	0.70	0.50
1.310	0.66	0.50
1.420	0.60	0.50
1.560	0.60	0.53
1.740	0.60	0.56
2.025	0.60	0.60
2.250	0.56	0.66
2.310†	0.56	0.73
2.360	0.53	0.73
2.415	0.53	0.76
2.495	0.46	0.80
2.615	0.43	0.80
2.745	0.43	0.83
2.860	0.43	0.86
3.035	0.36	0.86
3.235	0.30	0.90
3.320	0.23	0.90
3.545	0.20	0.93
3.745	0.20	0.96
3.940	0.16	0.96
4.120	0.13	0.96
4.250	0.10	0.96
4.355	0.06	0.96
4.445	0.03	0.96
4.540	0.03	1.00
5.560	0.00	1.00

† The best diagnostic level; hs-CRP: High sensitive C-reactive protein

unstable angina. One of the studies showed that the best time for taking biomarker samples from patients with stable angina was in the morning, because the biomarker was at its highest level.[21] Based on the mentioned study, the biomarker's level was associated with coronary artery disease and with increasing the severity of coronary artery disease the biomarker's level was increased too. They determined a cut-off point for differentiating patients with severe coronary atherosclerosis based on the mild one which was equal to 5.5 mg/l in the morning with sensitivity and specificity of 66.4% and 79.1%, respectively.[21] In Thakur et al.'s study[4] the hs-CRP levels in patients with coronary heart disease and in healthy subjects were reported as 1.70 ± 0.75 and 0.93 ± 0.35 mg/l, respectively, which showed a statistically significant difference ($P < 0.001$). Some other studies also showed that patients with unstable angina which had higher levels of this biomarker were at higher risk of death and heart failure.[13,18]

In the study by Diercks et al.,[17] patients with chest pain were examined for ACS, and they were also tested to measure their levels of this biomarker. They concluded that this biomarker did not have a diagnostic value in differentiating the two groups. Even so, their study was retrospective and might have had some biases. Another study by Amanvermez et al.,[20] showed that the hs-CRP level in patients with unstable angina was higher than in controls. They also concluded that this biomarker might be useful in early diagnosis of ACS.

Our study had some limitations. We did not assess the relation between this biomarker and cardiac enzymes, electrocardiography changes, and the severity of coronary artery disease. Nonetheless, they were not among the objectives of the study, but assessing them could also present broader information about the biomarker in ACS. However, based on our results, the biomarker levels of 2.31 mg/l and higher show unstable angina while the levels below 2.31 mg/l indicate stable angina. When using this biomarker, the presence of infectious and inflammatory diseases should be considered because they will interfere with the test results.

Conclusion

hs-CRP level is valuable for differentiating patients with stable angina from those with unstable

angina. It is recommended to consider the hs-CRP level of 2.31 mg/l as the best cut-off point.

Conflict of Interests

Authors have no conflict of interests.

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