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Diagnostic value of high sensitivity C-reactive protein in differentiating unstable angina from myocardial infarction

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Original Article

Abstract

BACKGROUND: Differentiating between unstable angina and myocardial infarction (MI) is clinically important as they require different treatments. High sensitivity C-reactive protein (hs-CRP) has recently been recognized as prognostic factor in acute coronary syndrome. Since this biomarker may indicate the prognosis of heart disease, identifying its diagnostic value will be clinically important. This study investigated the diagnostic value of the level of hs-CRP in differentiating MI from unstable angina.

METHODS: Blood samples were obtained from all patients with suspected MI or unstable angina at the time of referral. The patients were put in one of the two groups based on final diagnosis. The exclusion criteria were infectious diseases, immune system diseases, history of a recent surgery or trauma, kidney failure, liver failure, cancers, and use of anti-inflammatory drugs. Data was entered in SPSS and analyzed by independent t, Mann-Whitney U and chi-square or Fisher's exact tests. ROC curve was used to determine hs-CRP cut-off point. The sensitivity and specificity were calculated at the cut-off point.

RESULTS: Overall, 60 patients (30 patients with MI and 30 patients with unstable angina) were studied. Hs-CRP level was 3.68 ± 0.86 mg/l in patients with MI and 2.35 ± 1.30 mg/l in patients with unstable angina ($P < 0.001$). The best cut-off point for differentiating unstable angina from MI was hs-CRP levels equal to or greater than 3.27 mg/l. At this cutoff point, the sensitivity and specificity were both 77%.

CONCLUSION: Patients with MI had higher levels of hs-CRP than subjects with unstable angina. Hs-CRP levels equal to or higher than 3.27 mg/l are more likely to be associated with MI. It is recommended to test this biomarker in all patients with acute coronary syndrome.

KEYWORDS: Myocardial Infarction, Acute Coronary Syndrome, Unstable Angina, Diagnosis

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Introduction

Inflammatory marker proteins have been used as a noninvasive method to assess atherosclerosis and prognosis of patients. High sensitivity C-reactive protein (hs-CRP) is an inflammatory marker which has received great attention recently.[1-5] Many studies have evaluated the relationship between this biomarker and the incidence and prognosis of cardiovascular diseases. While some of these studies have suggested an association between hs-CRP and prognosis and mortality of patients, others have suggested opposite results.[6-10] According to a number of studies, hs-CRP concentrations more than 3 mg/l is more associated with disease outcome and may worsen the prognosis in

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patients with acute coronary syndrome (ACS).[11-13]

Research on the value of hs-CRP in the diagnosis of ACS has also reported controversial results.[14-16] However, studies in this field have had shortages and further studies are hence warranted. For instance, although it is important to differentiate unstable angina from myocardial infarction (MI) since they require distinct treatments, no study has assessed the diagnostic value of hs-CRP in differentiating between these two diseases. Considering the fact that increased levels of hs-CRP have been suggested to worsen the prognosis of cardiovascular diseases, evaluating the diagnostic value of this biomarker in distinguishing unstable angina from MI may be clinically important. Therefore, this study investigated the sensitivity and specificity of different levels of hs-CRP in differentiating MI from unstable angina.

Materials and Methods

The study protocol was first approved by ethics committee of Kurdistan University of Medical Sciences (Sanandaj, Iran). The participants were then selected from individuals with chest pain who referred to the emergency ward of Tohid Hospital (Sanandaj, Iran). Patients were only included if the diagnosis of MI or unstable angina was confirmed by a cardiologist. The subjects were selected through convenience sampling until the sample size was reached. Blood samples were obtained from all patients with suspected MI or unstable angina at the time of referral and the participants were categorized based on the final diagnosis. The exclusion criteria were having an infectious disease in the past three weeks, immune system and autoimmune diseases, a history of surgery in the past two months, a history of trauma in the past two months, chronic renal failure, hepatitis, cancers, and use of anti-inflammatory drugs. Using the formula of differences in the mean and having $\alpha = 1\%$, $\beta = 10\%$, and mean hs-CRP of 1.7 ± 09 mg/l for MI and 0.93 ± 09 mg/l for unstable angina,[15] the minimum sample size was calculated as 22 subjects in each group. We studied 30 patients in each group.

After explaining the objectives of the study to the patients, they were asked to sign the consent forms. All patients completed a questionnaire and preliminary examinations (e.g. blood pressure measurement) were conducted under standard conditions.

Data was entered in SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to assess the normal distribution of quantitative data. Quantitative data of the two groups was compared with Student's independent t-test or Mann-Whitney test. Chi-square and Fisher's exact tests were used to compare qualitative data. Receiver operating characteristic (ROC) curve was used to determine hs-CRP cutoff point. The sensitivity and specificity were calculated at the cutoff point.

Results

We studied 30 patients with MI and 30 patients with unstable angina (mean age: 59.8 ± 12.9 years). Females constituted 51.6% of the participants (n = 31). Fifteen subject (25.0%) lived in rural areas and 14 (23.3%) had a family history of MI. Overall, 38 patients (63.3%) were active smokers and 14 (23.3%) were non-active smokers. History of hypertension, diabetes, and hyperlipidemia were reported by 22 (36.6%), nine (15.0%), and 16 patients (26.7%), respectively. The two groups had no significant differences in any variables except smoking. While vomiting was significantly more prevalent in the group with MI, there was no statistically significant differences between the two groups regarding other symptoms (Table 1).

Hs-CRP level was 3.68 ± 0.86 mg/l in patients with MI and 2.35 ± 1.30 mg/l in patients with unstable angina ($P < 0.001$). The best cutoff point for differentiating unstable angina from MI was hs-CRP levels equal to or greater than 3.27 mg/l (Figure 1). At this cutoff point, the sensitivity and specificity were both 77% (Table 2) and the area under the ROC curve was calculated as 0.794 (95% confidence interval 0.68-0.91; $P < 0.001$).

Table 1. Comparison of characteristics of patients with myocardial infarction (MI) and unstable angina

Variables	MI	Unstable Angina	P
Sex			
Male	12 (40)	17 (56.7)	0.196
Female	18 (60)	13 (43.3)	
Place of residency			
Urban	21 (70.0)	24 (80.0)	0.371
Rural	9 (30.0)	6 (20.0)	
Family History of MI	7 (23.3)	7 (23.3)	1.000
Current Smoker	15 (50.0)	23 (76.7)	0.032*
Passive Smoker	8 (26.7)	6 (20.0)	0.542
Hypertension	9 (30.0)	13 (43.3)	0.284
Hyperlipidemia	5 (16.7)	11 (36.7)	0.143
Diabetes	2 (6.2)	7 (23.3)	0.145†
Chest pain	27 (90.0)	29 (96.7)	0.612†
Dyspnea	18 (60.0)	15 (50.0)	0.436
Sweating	18 (60.0)	14 (46.7)	0.301
Vomiting	18 (60.0)	8 (26.7)	0.009*
Level of education**	1 (0-4)	1 (0-4)	0.362§
Diabetes duration (year)	1 (1-1)	8 (3-20)	0.040*
Hypertension duration (year)	9 (3-15)	7 (1-21)	0.689§
Hyperlipidemia duration (year)	1 (1-12)	3 (1-16)	0.524§
Age (year)	59.9 ± 13.1	59.7 ± 12.9	0.945
Body mass index (kg/m^2)	25.7 ± 3.7	26.5 ± 3.5	0.417††
High sensitivity C-reactive protein (mg/l)	3.68 ± 0.86	2.35 ± 1.30	< 0.001††*
Chest pain duration (hour)	2.50 (0.50-80)	3.00 (0.15-24.00)	0.464§
Smoking (Packs/year)	20.50 (0.75-120.00)	19.00 (0.45-100.00)	0.721§

Values are expressed as n (%), mean (range), or mean ± SD; †: Fisher's exact test was applied; ††: Student's independent t-test was applied; §: Mann-Whitney test was applied, Other comparisons were done by chi-square test;* Statistically significant; ** 0: Illiterate; 1: Elementary school; 2: Junior high school; 3: High school; 4: College; MI: Myocardial infarction

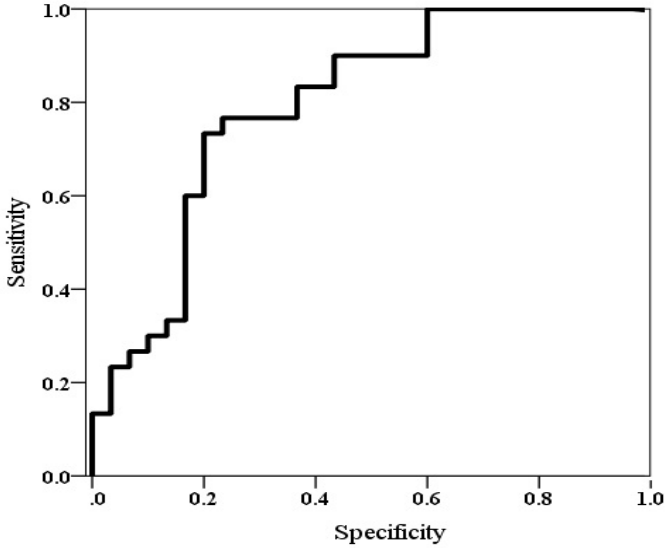

Figure 1. Receiver operating characteristic (ROC) curve to differentiate myocardial infarction from unstable angina (The area under the curve was calculated as 0.794 for 3.27 mg/l; 95% confidence interval: 0.68-0.91; P < 0.001).

Table 2. Calculating sensitivity and specificity of different high sensitivity C-reactive protein (hs-CRP) levels for differentiating myocardial infarction from unstable angina

Hs-CRP (mg/l)	Sensitivity	Specificity
0.22	1.00	0.03
0.45	1.00	0.07
0.71	1.00	0.10
0.85	1.00	0.13
0.94	1.00	0.17
1.06	1.00	0.20
1.22	1.00	0.30
1.43	1.00	0.40
1.85	0.93	0.40
2.15	0.90	0.40
2.26	0.90	0.43
2.48	0.90	0.53
2.65	0.90	0.57
2.79	0.87	0.57
2.96	0.83	0.60
2.99	0.83	0.63
3.17	0.77	0.63
3.24	0.77	0.70
3.27†	0.77	0.77
3.35	0.73	0.77
3.48	0.67	0.80
3.66	0.60	0.80
3.82	0.60	0.83
3.93	0.53	0.83
3.99	0.43	0.83
4.09	0.33	0.87
4.19	0.30	0.90
4.28	0.27	0.90
4.38	0.23	0.97
4.48	0.13	0.97
4.57	0.13	1.00
4.64	0.10	1.00
4.70	0.07	1.00
5.73	0.00	1.00

† The best diagnostic level; Hs-CRP: High sensitivity C-reactive protein

Discussion

In this study, patients in both groups had similar baseline characteristics. Hs-CRP levels were higher in patients with unstable angina than patients in those with MI. The cutoff point for differentiating between the two diseases was calculated as 3.27 mg/l. Accordingly, it seems that hs-CRP could be helpful in differentiating MI from unstable angina.

Several studies have recently shown that inflammation is one of the mechanisms of cardiovascular diseases.[4,5] Zairis et al. found that hs-CRP level is a predictor of mortality over the next five years in patients with ACS[7] and that it may be associated with MI size.[14] Tanaka et al. indicated hs-CRP level to be associated with atherosclerotic plaque rupture, i.e. higher levels were detected in subjects with greater number of ruptured atherosclerotic plaques.[17]

Most previous studies have investigated the prognostic value of hs-CRP in cardiovascular diseases and very few have assessed its diagnostic value in different heart diseases. It is very important to differentiate MI from unstable angina and also to differentiate unstable angina from stable angina since they require different treatment approaches. Thakur et al. found hs-CRP levels to be 1.70 ± 0.75 and 0.93 ± 0.35) mg/l in patients with cardiovascular disease and healthy people, respectively ($P < 0.001$).[4] Yip et al. reported levels of 2.95 mg/l in patients with MI and 1.35 mg/l in subjects with unstable angina ($P < 0.001$). They found this biomarker to be related with disease prognosis and suggested it as an indicator of the amount of attention a patient has to receive.[15] In another study, Yip et al. calculated hs-CRP levels as 2.7 and 1.4 mg/l in subjects with MI and unstable angina, respectively. The values had no relation with gender, smoking, diabetes, body mass index (BMI), or hypercholesterolemia.[18] In contrast, Diercks et al. rejected the diagnostic value of hs-CRP in differentiating acute coronary syndrome from other diseases (area under the ROC curve: 0.49).[16] Amanvermez et al. reported significantly higher level of hs-CRP in patients with MI than in those with unstable angina. While the area under the ROC curve was 0.6 in their study, unfortunately, they did not set a cutoff point.[19]

As it is seen, the mean levels of hs-CRP have been different in previous studies. This might have been caused by different sampling methods or inclusion/exclusion criteria. The higher area under the ROC curve obtained in the

present study compared to those calculated by Diercks et al.[16] and Amanvermez et al. may be justified by our careful consideration over the exclusion criteria (we eliminated conditions which could influence hs-CRP levels). Therefore, it is recommended to use hs-CRP level of 3.27 mg/l to differentiate MI from unstable angina. At this cutoff point, the sensitivity and specificity are both equal to 77%. Additionally, we calculated the sensitivity and specificity of various levels of this biomarker. This allows the physicians to choose the appropriate level and to use suitable diagnostic and treatment approaches in different situations.

Although hs-CRP levels may increase in patients affected by atherosclerosis, such increase can also be caused by the pathology of MI. This provides a means of diagnosing MI. This biomarker can be associated with higher levels of plaque rupture which is probably a reason for its high levels in patients with MI.[17] Patients with unstable angina who have higher levels of hs-CRP have also been suggested to be at greater risk of mortality and MI.[10,20]

Conclusion

Hs-CRP levels were higher in patients with MI than in those with unstable angina. Hs-CPR levels of 3.27 mg/l or higher are in favor of MI. It is recommended to assess this biomarker in all patients with ACS.

Conflict of Interests

Authors have no conflict of interests.

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