Prognostic and Diagnostic Significance of Serum High-Sensitivity C-Reactive Protein Level in Patients with Acute Idiopathic Pericarditis

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ABSTRACT: **Background:** The frequency of increased high-sensitivity C-reactive protein (hs-CRP) and the time course of evolution of their levels in patients with acute idiopathic pericarditis (AIP) are not well established.

Objective: To assess the time course of evolution of hs-CRP levels and the possible clinical significance of maximal hs-CRP levels in patients with AIP

Methods: We retrospectively reviewed the medical files of 241 patients admitted to the hospital with a diagnosis of AIP between March 2006 and March 2017. Data on demographics, time of symptom onset, laboratory and imaging findings, and outcome were collected.

Results: Data on serum hs-CRP levels were available for 225 patients (age 18–89 years, 181 men). Fever, pleural effusion, and age were independently associated with hs-CRP levels. Major cardiac complications (MCC) (death, cardiac tamponade, cardiogenic shock, large pericardial effusion, ventricular tachycardia, pericardiocentesis, or pericardiectomy) were more common in patients with hs-CRP levels above the median compared to those below (21.2% vs. 4.5%, respectively, $P < 0.001$). Hs-CRP levels were independently associated with MCC (odds ratio [OR] 1.071, 95% confidence interval [95%CI] 1.016–1.130, $P = 0.011$). Hs-CRP levels were elevated in 76.0%, 92.3% and 96.0% of the patients tested < 6 hours, 7–12 hours, and > 12 hours of symptom onset, respectively ($P = 0.003$). The frequency of elevated hs-CRP among patients tested > 24 hours was 98.1%.

Conclusions: Hs-CRP levels rise rapidly among patients with AIP. Maximal hs-CRP levels are associated with MCC. A normal hs-CRP level is rare among patients tested > 24 hours of symptom onset.

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KEY WORDS: acute idiopathic pericarditis, C-reactive protein (CRP), outcome, pericardial effusion

Acute idiopathic pericarditis (AIP) is an inflammatory syndrome. The diagnosis for AIP is based on the presence of two of the following criteria: pericarditic chest pain, pericardial friction rub, electrocardiogram changes, and new or worsening pericardial effusion [1]. However, there is no gold standard for the diagnosis and it may be difficult to confirm the diagnosis of AIP by using only clinical and non-invasive imaging findings.

C-reactive protein (CRP) is a well-known acute-phase reactant. It is synthesized rapidly in the liver, and peak plasma levels are achieved after 24–48 hours [2,3]. High-sensitivity-CRP (hs-CRP) serves as a sensitive marker of inflammation in many conditions [2-6] and is typically elevated in acute pericarditis [1,7,8]. Elevated serum CRP levels occur in many inflammatory conditions [9-11]. In patients with bacteremia, for example, the prevalence of elevated serum CRP levels was reported to be 98.4% [4]. However, Imazio et al. [7] found normal CRP values on presentation in 22% of patients with acute pericarditis tested less than 24 hours from symptom onset. They attributed this low rate of increased CRP values to initiation of treatment before the initial CRP measurement in some patients and the early arrival in others. However, these findings have not been confirmed and the value of initial CRP level for the diagnosis of AIP is unclear.

The magnitude of the rise in CRP level varies remarkably among patients with acute pericarditis [12]. In certain inflammatory conditions, peak CRP levels are influenced by the causative pathogen and severity of inflammation, and higher levels of peak CRP were associated with risk of recurrence [5,7].

The aim of this study was to assess the prevalence of increased serum hs-CRP levels according to the time from symptom onset, and the possible clinical significance of maximal serum hs-CRP levels in patients with AIP.

PATIENTS AND METHODS

The study was approved by the medical center ethics committee. This retrospective study comprised patients admitted to our medical center with a diagnosis of AIP between 1 March 2006 and 31 March 2017. All patients with a first episode of AIP were included if the diagnosis complied with current guidelines, which are the presence of two of the following: typical chest pain, friction rub, new or worsening pericardial effusion, and typical electrocardiographic changes [7]. Exclusion criteria were pericarditis of known etiology (e.g., rheumatoid arthritis, sys-

temic lupus erythematosus, familial Mediterranean fever, tuberculosis, post-myocardial injury syndrome, uremia, purulent pericarditis, or acute or recent myocardial infarction), presence of severe systemic disease or active malignancy, and pregnancy. Patients referred from other hospitals were excluded as well.

All the medical files were reviewed to extract data on presenting symptoms, demographics, physical examinations, echocardiography, electrocardiography, chest X-ray, computed tomographic chest rentgenography, nuclear magnetic resonance imaging and laboratory findings

Laboratory findings included biomarkers, initial and maximal serum hs-CRP levels, white blood cell count, and liver enzymes. Hs-CRP levels were determined using a Beckman Coulter AU 2700 analyzer (Beckman Coulter, Inc., Brea, CA, USA) or Cobas 8000 c-701 analyzer (Roche Diagnostics, Indianapolis, IN, USA), using the particle-enhanced immunoturbidimetric assay. The correlation in hs-CRP results between these instruments is excellent ($R^2 = 0.9895$). Hs-CRP levels > 0.5 mg/dl were considered elevated.

We calculated the time between the onset of pericarditis symptoms and initial hs-CRP measurement, as well as the prevalence of elevated hs-CRP levels in those patients. We also calculated the times from onset of prodromal symptoms and the initial and maximal hs-CRP measurements. The size of pericardial effusion was assessed by echocardiography and categorized semi-quantitatively as absent (score = 0), small (score = 1), moderate (score = 2), or large (score = 3) [13,14]. Left ventricular global function and regional wall motion abnormalities were assessed by echocardiography. Left ventricular systolic function was categorized as severely decreased when left ventricular ejection fraction was less than or equal to 30%. Maximal white blood cell count on the first day of admission was recorded. Patients were treated at the discretion of the attending physician. As a rule, non-steroidal anti-inflammatory agents were used as a first-line therapy unless contraindicated or when a rapid effect was desired. The following were considered major cardiac complications (MCC): death, cardiac tamponade, non-obstructive cardiogenic shock, ventricular tachycardia, pericardiocentesis, pericardiectomy, and large symptomatic pericardial effusion.

STATISTICAL ANALYSIS

Categorical variables are described as numbers and percentages. Continuous variables were evaluated for normal distributions using a histogram and Q–Q plot. Since all variables were not normally distributed, the continuous variables were reported as the median and interquartile range. The correlation between peak hs-CRP levels and continuous variables was evaluated using Spearman's correlation coefficient. The association between peak hs-CRP levels and categorical variables was evaluated using the Mann-Whitney test.

Linear regression after Ln transformation of peak hs-CRP levels was used to identify independent predictors of peak hs-CRP levels and to evaluate the hypotheses. Fisher's exact test was used to compare frequencies of elevated hs-CRP levels at different time periods from symptom onset. Logistic regression was used to evaluate the association between maximal hs-CRP and MCC while controlling for age, sex, and symptom duration. All statistical tests were two-sided. A P value < 0.05 was considered statistically significant. All statistical tests were performed using SPSS software version 24 (IBM SPSS statistics, IBM corp., Armonk, NY, USA).

RESULTS

MAXIMAL HS-CRP LEVEL AND OUTCOMES

The cohort included 241 patients (age 18–89 years; 181 men). Data on hs-CRP level were available for 225 patients. Elevated hs-CRP levels were found in 220 of the 225 patients (97.8%). The range of maximal hs-CRP levels was 0.1–39.0 mg/dl (median, 9.0 mg/dl). MCC were recorded in 29 patients: nine underwent pericardiocentesis, one had emergent pericardiectomy, one had cardiogenic shock related to myocardial involvement with left ventricular dysfunction, one had both cardiac tamponade and severe left ventricular dysfunction with cardiogenic shock persisting after pericardiocentesis, and 17 had large pericardial effusion. Twelve patients had more than one complication.

Table 1 shows the baseline characteristics and outcomes of the 225 patients with available hs-CRP levels. Of these patients, 52.4% had prodromal symptoms, 65.9% had pericardial effu-

Table 1. Baseline characteristics

	N
Median age, years (IQR range)	50.0 (33.0–63.5)
Male gender	170 (75.6%)
Prodrome*	110 (52.4%)
Fever	70 (32.0%)
Sore throat	37 (16.9%)
Diarrhea	20 (9.1%)
Myocardial involvement	70 (31.4%)
Median WBC count/μL (IQR range)	10800 (7975–13157)
Pleural effusion	67 (33.7%)
Pericardial effusion	147 (65.9%)
Tamponade	10 (4.4%)
Cardiac complications	29 (12.9%)
Median peak hs-CRP level mg/dL (IQR range)	9.95 (4.50–17.35%)
Median time from prodrome onset to admission, days (IQR range)	5.0 (3.0–14.0)
Median time from chest pain onset to admission, hours (IQR range)	24 (12–96)

*Signs and symptoms unrelated to pericarditis that could reflect a preceding or underlying disease

Hs-CRP = high-sensitivity C-reactive protein, IQR = inter-quartile range, WBC = white blood cell

sion, and 33.7% had concomitant pleural effusion. Table 2 shows the maximal hs-CRP levels according to baseline characteristics and outcomes. Fever, pericardial effusion, pleural effusion, and MCC were associated with higher hs-CRP levels. A history of prodromal symptoms or any of the specific prodromal symptoms other than fever had no significant effect on peak hs-CRP levels.

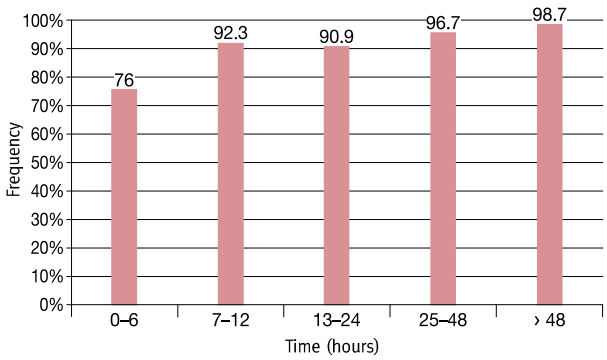
Linear regression analysis of a model that included age, gender, fever, pericardial effusion, and pleural effusion revealed that fever (75.24%, 95% confidence interval [95%CI] 34.48–128.34, $P < 0.001$), pleural effusion (114.56%, 95%CI, 59.57–188.50, $P < 0.001$), and age (one-year increment, 0.89%, 95%CI, 0.13–1.66, $P = 0.022$) were independently associated with hs-CRP level. Notably, hs-CRP levels remained normal in only one of the 147 patients (0.7%) who had pericardial effusion, as opposed to 4 out of 76 patients without effusion (5.3%, $P = 0.0471$). MCC were much more common among patients with hs-CRP levels above the median than those with lower levels (24 of 113, 21.2% vs. 5 of 112, 4.5%, $P < 0.001$). Logistic regression analysis of a model that included age, sex, symptom duration, and MCC revealed that MCC was independently associated with peak hs-CRP levels (odds ratio [OR] = 1.071 95%CI 1.016–1.130, $P = 0.011$) and age (OR for 1-year increment 1.035, 95%CI 1.003–1.067, $P = 0.032$). There were no differences in maximal hs-CRP level or rate of MCC between patients with evidence for coronary atherosclerosis on angiography (n=16) and the other patients.

Table 2. High sensitivity C-reactive protein level according to baseline characteristics and outcomes

	Without characteristic		With characteristic		*P* value
	Median	IQR	Median	IQR	
Male gender	9.60	4.50–16.57	12.14	3.75–20.30	0.267
Prodrome	8.70	3.92–15.80	9.97	4.70–18.42	0.190
Fever	7.50	3.67–14.85	15.65	8.85–22.00	‹ 0.001
Cough	9.80	4.42–16.72	14.0	5.40–28.70	0.065
Sore throat	11.25	4.65–17.70	6.80	4.00–14.80	0.201
Diarrhea	10.60	4.50–17.60	9.30	4.77–17.85	0.833
Pericardial effusion	6.20	3.07–12.33	12.40	6.00–20.00	‹ 0.001
Myocardial involvement	11.20	4.85–17.60	7.35	3.57–17.00	0.133
Pleural effusion	6.70	3.35–13.70	17.40	11.90–23.00	‹ 0.001
MCC	9.00	4.04–16.15	16.80	11.85–23.00	‹ 0.001

IQR = inter-quartile range, MCC = major cardiac complications

Figure 1. Frequency of elevated serum high sensitivity C-reactive protein levels according to the time from symptom onset



TIME COURSE OF EVOLUTION OF CRP ELEVATION

Data on the time of onset of pericarditis symptoms were available for 202 of the patients. The range of initial hs-CRP levels was 0.1–34.0 mg/dl (median 5.4 mg/dl). Elevated hs-CRP levels were found in 20 of the 25 patients (80.0%) when measured at less than or at 6 hours after the onset of pericarditis symptoms, in 24 of the 26 patients (92.3%) measured at 7–12 hours after symptom onset, and in 145 of the 151 patients (96.0%) measured more than 12 hours after symptom onset ($P = 0.003$).

Figure 1 shows the frequency of increased serum hs-CRP levels among the patients according to the time from symptom onset. The proportion of patients with elevated serum hs-CRP levels increased rapidly, and reached a plateau level after 6 hours. The difference in frequency of elevated hs-CRP level among patients tested at 0–6 hours, 6–12, and more than12 hours was statistically significant ($P = 0.003$). Hs-CRP remained normal only in 2 of the 107 patients (1.9%) tested more than 24 hours after onset of symptoms.

To examine the possible effect of prodromal disease on CRP levels, we assessed the evolution of CRP level in patients with and without prodromal symptoms. Data on prodromal symptoms were available for 197 patients. Table 3 shows the frequency of increased hs-CRP levels among the patients with and without prodromal symptoms according to the time from symptom onset. The proportion of patients with an elevated CRP level at 0–6 hours tended to be higher among patients with prodromal symptoms but the difference was not statistically significant. By contrast, the maximal CRP levels were higher in patients who were tested later after onset of prodromal symptoms. For example, patients admitted ≤ 4 days after symptom onset had a median CRP level of 8.8 mg/dl (interquartile range [IQR] 4.9–12.3), whereas those admitted more than 4 days after

Table 3. Frequency of elevated high sensitivity C-reactive protein levels according to time from symptom onset

Time, hours	All (n=202)	With prodrome (n=123)	Without prodrome (n=74)
0–6	19/25 (76.0%)	11/12 (91.7%)	7/11 (63.6%)
7–12	24/26 (92.3%)	12/13 (92.3%)	12/13 (92.3%)
13–24	40/44 (90.9%)	23/24(95.8%)	18/20 (90.0%)
25–48	29/30 (96.7%)	22/22 (100.0%)	7/8 (87.5%)
› 48	76/77 (98.7%)	52/52 (100.0%)	22/22 (100.0%)

symptom onset had a median CRP level of 12.6 mg/dl (IQR 4.5–22.9, $P = 0.044$).

DISCUSSION

To the best of our knowledge, this study is the first report that shows that maximal serum hs-CRP levels in patients with AIP are associated with the frequency of major in-hospital cardiac complications. The association was independent and strong, as a maximal hs-CRP level above the median was associated with a fivefold increase in MCC. Moreover, our results show that in patients diagnosed with AIP according to current guidelines, a normal hs-CRP level is rare. The rise in serum CRP levels in our patients was rapid, and elevated levels were found in more than 90% of patients presenting more than 6 hours after the onset of symptoms.

VALUE OF SERUM CRP LEVELS FOR THE DIAGNOSIS OF AIP

The results of this study show that CRP levels rarely remain normal in patients with AIP, which corresponds with previous observations of patients with acute pericarditis [7]. These findings suggest that elevated CRP levels are an integral part of the pathophysiological changes in acute pericarditis. It is unclear, however, whether a normal CRP level measured more than12 hours after onset of symptoms in patients with suspected AIP rules out the diagnosis.

It has been consistently reported that CRP levels remain normal in a very small minority of patients with infection, including septicemia, or inflammation [2-5]. It is unclear whether this reflects a false positive diagnosis or an impaired response of CRP production to inflammation. Therefore, it is possible that normal serum hs-CRP levels in a patient with suspected AIP who fulfills at least two of the recommended diagnostic criteria may not necessarily rule out the diagnosis of pericarditis [1]. However, the results of this study show a very low frequency of normal CRP levels among patients who present more than 12 hours after the onset of symptoms onset of AIP, and an extremely low frequency among patients presenting more than 24 hours of symptom onset. Thus, the diagnosis of acute inflammation in patients with suspected pericarditis who have a normal hs-CRP level more than 24 hours after symptom onset should be questioned. Of note, prodrome affected maximal hs-CRP levels in our patients, but did not increase the frequency of positive (elevated) hs-CRP results. These findings may support the hypothesis that serum hs-CRP level does not increase in response to inflammation in some rare cases.

DETERMINANTS OF PEAK PLASMA CRP LEVELS

Our findings show that age, pleural effusion, and fever were independently associated with maximal serum CRP levels. The associations of fever and pleural effusion with elevated CRP levels were reported previously [7] and age is known to affect basal CRP levels. Different prodromal symptoms may reflect different causative pathogens, and a relationship between peak plasma CRP levels and the underlying pathogen has been reported previously in certain infections. However, in our study none of the specific prodromal symptoms were associated with peak hs-CRP levels. The lack of association with prodrome suggests that the increase in CRP levels is related to pericarditis rather than the underlying prodromal disease, although it is still possible that patients without overt prodromal symptoms merely had a subclinical infection.

The mechanism by which pleural effusion is associated with CRP level is unclear. It has been reported previously that CRP is an independent predictor of pleural effusion in patients with pulmonary embolism [15]. The pleural effusion in these patients was associated with pulmonary infarction and a more proximal location of the pulmonary emboli. Moreover, a relationship between CRP and presence of pleural effusion has been described in children with community-acquired pneumonia [16].

PROGNOSTIC SIGNIFICANCE OF PEAK SERUM CRP LEVELS

To the best of our knowledge, this is the first report of a significant independent relationship between maximal serum CRP levels and in-hospital complications in patients with AIP. This finding is not surprising because a relationship between serum CRP levels and disease severity has been described previously in other conditions [4,5,9-11,17-19]. A relationship between maximal CRP levels and outcome has been reported in various acute disease conditions. Carrero et al. [17] reported a higher risk of death and major adverse cardiac events among patients with acute myocardial infarction and hs-CRPabove or equal to 2 mg/dl. Mani and colleagues [18] found that initial and subsequent increases in hs-CRP levels during the16 weeks following acute coronary syndrome were associated with higher risk of major adverse cardiovascular events, cardiovascular death, and all-cause death. Among patients with stroke, hs-CRP levels above10 mg/dl were found to be associated with increased hazard of all-cause mortality (OR 2.65, 95%CI 1.99-3.53) [19]. Milwidsky and co-authors [20] found that the rate of change in wide-range CRP in the first 24 hours of an acute ST-elevation myocardial infarction was independently associated with risk of 30-day mortality. Thus, our findings add to the growing body of evidence of a relationship between serum CRP levels in acute disease conditions and outcome.

Whether elevated CRP levels play a causative role in inflammation is unclear. Inflammation is a known factor in the development of atherosclerosis [21]. Epidemiologic studies have demonstrated a significant association between elevated CRP levels and the prevalence of atherosclerosis as well as the risk for events in patients with coronary artery

disease [22]. There is growing evidence showing that CRP has a direct pro-inflammatory effect and can contribute to atherosclerosis, atherothrombosis, and inflammation by activating the complement, the clotting system, and mediating LDL uptake by macrophages [20,21,23,24]. The pro-inflammatory effects of CRP may explain the association in our patients between CRP levels and pericardial effusion, pleural effusion, and MCC. Conversely, data from genetic trials show that although elevated CRP is associated with atherosclerosis, genetic variants associated with increased CRP levels are not [22,25]. Therefore, more research is necessary to clarify the possible causative role of CRP in inflammation and atherosclerosis. Nevertheless, our finding that MCC is much more common among patients with maximal CRP levels above the median may help clinicians in the risk assessment of patients with AIP.

VALUE OF THE INITIAL CRP MEASUREMENT FOR THE TRIAGE OF PATIENTS WITH SUSPECTED AIP

Our findings show that serum CRP levels increase rapidly in patients with AIP and become elevated in most of the patients who present at more than 6 hours of symptom onset, and that a normal hs-CRP level is rare among patients with AIP presenting more than 24 hours of symptom onset, whether they had or did not have a prodrome. Moreover, because most of our patients (88%) presented more than 6 hours of symptom onset, the measurement of serum hs-CRP on presentation is relevant for most patients with suspected AIP.

LIMITATIONS

Because this was not a blinded study, the role of any initial CRP result in the decision to admit the patients is unknown. Importantly, there were no readmissions for missed diagnoses of pericarditis. In addition, hs-CRP measurements were not serial and were performed at the discretion of the attending physician. Thus, higher peak CRP levels could have been missed.

CONCLUSIONS

Hs-CRP levels rise rapidly among patients with AIP. A normal hs-CRP level is rare among patients tested more than 24 hours of symptom onset. Maximal hs-CRP levels are associated with MCC.

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