The prognostic role of high-sensitivity C-reactive protein in patients with acute myocardial infarction

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J Geriatr Cardiol 2020; 17: 379–383. doi:10.11909/j.issn.1671-5411.2020.07.007

Keywords: Atrial fibrillation; Coronary artery disease; High sensitive C-reactive protein; Myocardial infarction; Prognosis

1 Introduction

Inflammation is one of the main mechanisms in the pathogenesis of atherosclerosis, and the interest to the evaluation of inflammatory biomarkers in coronary artery disease (CAD) has been increasing over the last decade.\textsuperscript{1,2} Destabilization of chronic artery plaques, which leads to acute coronary syndromes, has been associated with inflammatory status.\textsuperscript{1,3}

C-reactive protein (CRP) is a plasma protein of the pentraxins family. CRP is widely used as a general inflammatory marker since it is an acute phase protein synthesized by hepatocytes in response to proinflammatory cytokines, particularly interleukin-6.\textsuperscript{4}

Experimental studies have demonstrated that CRP might affect CAD progression through various pathways, such as activating the complement system and platelets, suppressing fibrinolysis, promoting the proliferation of smooth muscle cells, microphage polarization, and lipid deposition.\textsuperscript{5,6} Researchers have verified CRP functioning in vivo as driving inflammation, platelet aggregation, and thrombosis in transgenic mice.\textsuperscript{7}

An acute increase in high sensitivity CRP (hs-CRP) shortly after ST-elevation myocardial infarction (STEMI) reaches its peak value within 48–72 h and gradually decreases over the next several weeks to reference range < 10 mg/L.\textsuperscript{8,9} Acute hs-CRP phase levels before marked elevation of cardiac troponin I (cTnI) may make the body prime to respond to any necrotic or injured tissue.\textsuperscript{10} This evidence has been supported by De Servi, et al.\textsuperscript{11} depicting that in acute myocardial infarction (AMI) patients there is a large variability in hs-CRP levels. Thus, patients presenting with high hs-CRP titers at baseline are more hyperresponsive to circulating cTnI.\textsuperscript{11}

In clinical practice, hs-CRP has been the most studied risk factor among systemic markers of inflammation.\textsuperscript{2,3,9,10} Prospective cohort and cumulative studies have supported that relatively high levels of hs-CRP in otherwise healthy individuals is linked to an increased risk of future heart attack, stroke, sudden cardiac death, and/or peripheral arterial disease, as well as cardiac events in CAD patients with colon cancer, complications of diabetes, and obesity.\textsuperscript{12}

2 Prognosis after myocardial infarction and grading the extent of CAD

Risk scores with strong prognostic ability, particularly the Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) scores, have been broadly used with the aim of early risk stratification.\textsuperscript{13,14} The SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) score (SS) is an anatomy-based risk score that helps evaluate degree, extension, and complexity of coronary artery lesions.\textsuperscript{15} Multiple studies have convinced its use in predicting adverse events during hospitalization and in the long term.\textsuperscript{10,14,16,17} Guidelines have recommended it as a useful tool in selecting an appropriate strategy for revascularization, particularly in patients at high risk (referring to left main coronary artery lesion, multivessel lesions, and diabetes).\textsuperscript{18,19} However, the above scores do not include inflammatory markers. Addressing this issue, several studies on the predictive value of hs-CRP in AMI have been conducted.

The American Heart Association and U.S. Centers for Disease Control and Prevention define cardiovascular risk groups for hs-CRP levels as follows. Low risk: < 1.0 mg/L;
average risk: 1.0–3.0 mg/L; high risk: > 3.0 mg/L.[20] Patients with higher hs-CRP values have the highest risk of cardiovascular disease and those with lower values have less risk.[21] Specifically, individuals with high-normal hs-CRP have 1.5 to 4 times higher risk of heart attack, than subjects with low-normal hs-CRP.[20]

It seems that inflammatory markers can add prognostic information to the scoring system.[3,13,22] AMI is associated with an extensive myocardial inflammation, which leads to a systemic inflammatory response.[16,22] Interestingly, a higher level of hs-CRP has been shown a predictor of in-hospital cardiac events in AMI, independently of the GRACE risk score.[23]

In the early phase of AMI, hs-CRP may be a simple marker of the magnitude of the inflammatory response to myocardial ischemia.[16] Besides myocardial necrosis and infarct size, other kinds of tissue damage could cause a hs-CRP elevation in patients with STEMI, such as atherosclerotic mass, underlying inflammatory process, and circulating proinflammatory cytokines.[17] HS-CRP has been shown associated with hospital outcomes: death, MI, and angina. This underlines the role of this biomarker in the risk assessment of patients with acute coronary syndromes.[24]

3 HS-CRP and CAD characteristics and outcomes

Main studies showing associations between elevated level of hs-CRP and short- and long-term risks during and following AMI are presented in Table 1.

3.1 The extent of coronary atherosclerosis

Several studies have shown the value of hs-CRP in prediction of CAD severity. Liu, et al.[1] identified an independent association between hs-CRP and the number of stenotic coronary arteries (OR: 1.72, 95% CI: 1.08–2.74, \(P = 0.022\)). In other studies, the authors found that hs-CRP is the strongest predictor of SS in patients with an acute coronary syndrome, undergoing coronary angiography (OR: 1.14, 95% CI: 1.05–1.25, \(P = 0.002\)).[3] Gijbers, et al.[25] described that the severity of CAD was related to hs-CRP in both male and female patients with stable CAD; an elevated hs-CRP was associated with microvascular CAD rather than epicardial CAD. Additionally, the late microvascular obstruction size correlates with hs-CRP as determined early after AMI.[26]

3.2 Infarct size

Recently, Bouzidi, et al. showed that cTnI and hs-CRP were the best markers predicting infarct size in STEMI patients.[27] However, it should be noted that this particular study lacks a detailed description of the estimation of infarct size. Several approaches are used for measuring infarct size: blood serum markers, single-photon emission computed tomography myocardial perfusion imaging, magnetic resonance imaging, and delayed enhancement multidetector computed tomography.[28,29] The measurement of infarct size by serum markers has multiple limitations. The measurement of peak high sensitivity cTnI level allows estimating initial necrosis size, but the available data validating this marker are limited. Technetium (Tc)-99m sestamibi single-photon emission computed tomography myocardial perfusion imaging is thought the best available technique for the quantification of infarct size.[28] Magnetic resonance imaging allows estimating the final infarct size at least three months after acute coronary syndrome.[30] Recent studies have demonstrated the utility of delayed enhancement multi-detector computed tomography in determining the infarct size.[31] Although the measurement of global and regional left ventricular function by echocardiography is often used clinically in the estimation of infarct size, this approach has a number of well-known shortcomings.[29]

3.3 Cardiac arrhythmias

There is evidence that CRP represents a distinct pathophysiological pathway to developing new-onset atrial and ventricular arrhythmias in patients with AMI.[32–34] CRP has been shown independently and strongly associated with the occurrence of atrial fibrillation, as compared with peak creatine kinase-MB and LVEF.[34] The results of the TRUMP (Translational Research Investigating Underlying disparities in recovery from acute Myocardial infarction: Patients’ Health status) registry have identified hs-CRP independently associated with new in-hospital atrial fibrillation after AMI.[33]

The incidence of ventricular arrhythmia following AMI has been correlated with hs-CRP.[24] Kobayashi, et al.[32] demonstrated that CRP at the time of hospital admission in AMI patients was one of the independent predictors of in-hospital recurrent ventricular tachycardia and fibrillation.

3.4 Heart failure

Patients with AMI with higher hs-CRP levels at admission were older, had higher baseline creatinine levels, and were at increased risk of long-term development of heart failure.[35,36] The development of heart failure after STEMI is the most common complication associated with increased mortality.[28,37] A higher level of hs-CRP has been associated with a worse prognosis in patients with athero-
# Table 1. Studies showing associations between elevated level of hs-CRP and short- and long-term risks during and following acute myocardial infarction.

| Author               | Study design, country               | Population                                      | Type of risk, condition                                                                 | Key findings for associations |
|----------------------|-------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------|
| Liu, et al.¹⁳       | Prospective, observational study in a single center, China | Patients with AMI, \( n = 10,020 \)  
Age: 58.1 ± 10.1 yrs, 22.7% female | Long-term sign: predicting the number of stenotic coronary arteries  
*OR = 1.72 (95% CI: 1.08–2.74); \( P = 0.022 \) | *Adjusted OR = 1.15 (95% CI: 1.05–1.25); \( P = 0.002 \) |
| Karadeniz, et al.²⁶ | Population study, Turkey             | Patients with STEMI and NSTEMI, \( n = 321 \)  
Age: 63 ± 13 yrs, 22.7% female | Short-term risk: the strongest predictor of SS  
*OR = 1.14 (95% CI: 1.05–1.25); \( P = 0.002 \) | Correlation:  
\( r = 0.60, P < 0.0001 \) |
| Mayr, et al.²⁰       | Population study, Austria            | Patients within eight days after first STEMI with PCI, \( n = 118 \)  
Age: 55.7 ± 11.7 yrs, 16.1% female | Short-term sign: infarct size prediction (cardiac magnetic resonance)  
*Adjusted OR: 1.073 (95% CI: 1.004–1.148); \( P = 0.039 \) | |
| Yoshizaki, et al.²⁴  | Prospective observational trial, Japan | Patients with STEMI, \( n = 259 \)  
Age: 74 ± 10 yrs, 25% female | Short-term risk: atrial fibrillation  
*Adjusted OR: 1.11 (95% CI: 1.04–1.27) | *Adjusted OR: 1.122 (95% CI: 1.005–1.252); \( P = 0.040 \) |
| Kobayashi, et al.²³  | Retrospective observational study, Japan | Patients with STEMI, \( n = 6033 \)  
Age: 74 ± 10 yrs, 25% female | Short-term risk: an independent predictor of in-hospital ventricular tachycardia/fibrillation storm  
*Adjusted OR: 1.034 (95% CI: 1.004–1.064); \( P = 0.021 \) | *Adjusted OR: 1.72 (95% CI: 1.67–1.78); \( P = 0.001 \) |
| Raposeiras-Roubín, et al.²⁵ | Population study, Spain | Patients with AMI, \( n = 98 \)  
Age: 60.0 ± 13.5 yrs, 26.5% female | Short-term risk: a predictor of worse in-hospital outcomes independently of GRACE risk score  
*Adjusted OR: 1.15 (95% CI: 1.14–1.25) | |
| Bursi, et al.⁴¹      | Prospective study, USA               | Patients with STEMI and NSTEMI, \( n = 329 \)  
Age: 69 ± 16 yrs, 48% female | Long-term risk: a predictor of heart failure and death  
*For heart failure adjusted HR: 2.47 (95% CI: 1.27–4.82); \( P = 0.004 \)  
*For death Adjusted HR: 3.96 (95% CI: 1.78–8.83) | *Adjusted OR: 1.29 (95% CI: 1.23–1.36); \( P = 0.0001 \) |
| Ribeiro, et al.¹⁵     | Prospective cohort study, Brazil     | Patients with STEMI and NSTEMI, \( n = 300 \)  
Age: 59 ± 11 yrs, 30.7% female | Long-term risk: an independent predictor of 30-day mortality  
*For death Adjusted for TIMI, OR: 1.27 (95% CI: 1.07–1.51); \( P = 0.005 \)  
*For heart failure Adjusted for GRACE, OR: 1.26 (95% CI: 1.06–1.49); \( P = 0.007 \) | Higher in patients with peak > 47.5 mg/L than in below level \( P < 0.001 \) |
| Stumpf, et al.⁴⁹      | Single-center prospective observational cohort trial, Germany | Patients with STEMI and NSTEMI, \( n = 81 \)  
Age: 69 ± 11 yrs, 31% female | Long-term risk: predicting one-year total mortality and HF mortality  
*Adjusted OR = 1.15 (95% CI: 1.06 to 1.28 per unit increase), \( P = 0.0017 \) | Binary logistic regression analysis.  
*Adjusted OR = 1.15 (95% CI: 1.06 to 1.28 per unit increase), \( P = 0.0017 \) |
| Milano, et al.³⁴      | Retrospective cohort study, Brazil   | Patients admitted with STEMI, \( n = 118 \)  
Age: 60 yrs (interquartile range of 19.75 yrs)  
30.6% female | Short-term risk: predicting in-hospital mortality  
*For death adjusted HR: 1.06 to 1.28 per unit increase, \( P = 0.0017 \) | *Adjusted OR: 1.14 (95% CI: 1.05–1.25); \( P = 0.002 \) |
| Tello-Montolia, et al.³⁵ | Prospective study, Spain and UK | Non-ST ACS patients with 6-months follow-up, \( n = 358 \)  
Age: 67.4 ± 12.4 yrs  
35.8% female | Long-term risk: a predictor of adverse events (cardiovascular death, recurrent ACS, nonselective revascularization and 1.24–2.92), \( P = 0.0034 \)  
(or admission for acute heart failure) | *For unstable angina 30-day mortality prediction  
Adjusted OR: 1.28 (95% CI: 1.18–1.39); \( P = 0.0001 \) |
| Suleiman, et al.²⁶     | Prospective study, Israel            | Patients with STEMI, \( n = 448 \)  
Age: 60 ± 12 yrs; 16.1% female | Long-term risk: predicting 30-day mortality and heart failure  
*For heart failure adjusted HR: 1.27 (95% CI: 1.13–1.49); \( P = 0.001 \)  
*For death Adjusted for TIMI, OR: 1.27 (95% CI: 1.07–1.51); \( P = 0.005 \) | \*Adjusted OR: 2.19 (95% CI: 1.38–3.51) |
| Yanishi, et al.³⁷      | AMI-Kyoto registry, Japan            | Patients with STEMI, \( n = 1060 \)  
Age: 70.0 ± 12.4 yrs; 29% female | Short-term risk: predicting in-hospital mortality  
*For death adjusted HR: 1.30 (95% CI: 1.13–1.50); \( P = 0.0006 \) | *Adjusted OR: 2.19 (95% CI: 1.38–3.51) |
| Ahmed, et al.²¹       | Korea AMI registry, Korea            | Overweight/obese patients with STEMI and NSTEMI, \( n = 8174 \)  
Age: 62.7 ± 12.4 yrs; 24% female | Long-term risk: predicting all-cause mortality at 12 months  
*For death adjusted HR: 2.38 (95% CI: 1.079–5.259), \( P = 0.032 \) | \*Adjusted OR: 1.16 (95% CI: 1.05–1.28); \( P = 0.001 \) |

AMI: acute myocardial infarction; CI: confidence interval; GRACE: Global Registry of Acute Coronary Events score; HR: hazard ratio; hs-CRP: high-sensitivity C-reactive protein; NSTEMI: non ST-elevation myocardial infarction; OR: odds ratio; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction risk score; *Adjusted for age, sex, body mass index, and other confounding variables.

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thrombosis, heart failure, and arrhythmias. Few studies have reported the association between hs-CRP and heart failure after STEMI. Bursi, et al reported on the usefulness of hs-CRP at admission to predict the time course of heart failure following STEMI.

3.5 Mortality

Hs-CRP can be associated with major adverse cardiovascular events (MACE) in patients with a large anterior STEMI undergoing primary percutaneous coronary intervention (PCI). Patients in the highest hs-CRP quartile showed increased mortality rates at 30-days follow-up. There has been evidence that preprocedural hs-CRP is independently associated with MACE and all-cause death in patients with primary PCI during a median follow-up period of 6.5 years. In AMI patients after PCI with high-intensity statin treatment, baseline hs-CRP was an independent predictor for MACE at 36-month follow-up with the most prominent evidence in the first six months. This highlights the anti-inflammatory effects of statins. A peak hs-CRP value has been reported as a strong independent predictor of total mortality and heart failure-related mortality in the following year of follow up.

4 Conclusions

In patients with AMI, the level of hs-CRP may correspond to the extent of coronary artery lesion, the size of myocardial necrosis area, the risk of recurrent acute coronary syndrome, the risk of new-onset atrial fibrillation, ventricular tachycardia, heart failure decompensation/development, and death. It should be acknowledged that CRP is a marker of inflammation, and it is a non-specific sign for many acute and chronic diseases that may coexist in patients with AMI. We strongly believe that hs-CRP levels should be evaluated in future studies devoted to better prediction models of AMI outcomes.

Acknowledgement

This work was supported by the Ministry of Science and Higher Education grant (#MD-2314.2020.7). The authors declare no conflict of interest.

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