C-Reactive Protein Diagnostic and Prognostic Value in Patients Presenting at the Emergency Room with Chest Pain

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OBJECTIVE
To test immediate diagnostic and prognostic values of C-reactive protein (CRP) in patients admitted to the emergency room (ER) with chest pain (CP) without ST-segment elevation on the electrocardiogram (ECG).

METHODS
From January 2002 to December 2003, 980 patients were consecutively seen in the ER with CP suggestive of acute coronary syndrome (ACS) (age = 64.9 ± 14.3, men = 55%, diabetic = 18%, normal ECG = 84%). Serial CRP, creatine kinase MB mass (CKMB-mass) and troponin I determinations were performed on admission, in addition to serial ECG. CRP measurements were standardized (s-CRP) by the upper limit of normal (ULN) of the test used (3.0 mg/L for high-sensitivity C-reactive protein [hs-CRP] and 0.1 mg/dL for titrated CRP [t-CRP]).

RESULTS
One hundred and twenty-five patients were diagnosed with acute myocardial infarction (AMI), and their s-CRP values were 1.31 ± 2.90 (median = 0.47) compared to 0.79 ± 1.39 (0.30) in no-AMI patients (p = 0.031). The s-CRP > 1.0 showed 30% sensitivity and 80% specificity, plus negative and positive predictive values of 6.1% and 96.7%, respectively, for AMI diagnosis. There were forty in-hospital cardiac events (16 deaths, 22 urgent revascularizations, and 2 acute myocardial infarction). In the first quartile of the s-CRP (< 0.10), three events were recorded, while in the fourth quartile (> 0.93) 15 events (p = 0.003) occurred. In the logistic regression model, masculine gender and s-CRP > 0.32 (odds ratio 7.6, 2.8 and 2.2, respectively) were independent predictors of cardiac events and left ventricular failure.

CONCLUSION
In patients with chest pain presenting at the emergency room, s-CRP was not a good marker of AMI, although this diagnosis is virtually excluded by a normal value; in addition, values one-third above the upper limit of normal (>1 mg/L for hs-CRP or >0.33 mg/dL for t-CRP) were predictive of in-hospital adverse cardiac events.

KEY WORDS
C-reactive protein, chest pain, in-hospital prognosis.
The C-reactive protein (CRP), an acute-phase inflammatory response marker produced in the liver and discovered in the 1930s\(^1\), is a valuable tool in evaluating some acute diseases, such as rheumatoid arthritis, acute pancreatitis, and pneumonias\(^2\). It has come to prominence in the cardiovascular field with the inflammatory hypothesis of atherosclerosis\(^3\). Its assessment adds predictive value to cholesterol measurements in determining risks of a first cardiac event in healthy men and women\(^4\). This feature is corroborated by other primary prevention studies\(^5\)\(^\text{-}^\text{11}\). Recently, CRP measurement has been recommended to evaluate global cardiovascular risk in intermediate-risk patients and as one of the clinical criteria for diagnosing metabolic syndrome\(^1\)\(^2\)\(^\text{-}^\text{14}\).

In patients with established coronary artery disease, CRP measurement has proved valuable in identifying those at higher risk of new events\(^1\)\(^5\). Patients with acute coronary syndrome (ACS) and elevated CRP level on admission have increased risk of complications both during hospitalization and after discharge\(^1\)\(^6\)\(^\text{-}^\text{17}\). However, in the medical literature, particularly in Brazil, studies evaluating the role of CRP specifically in patients admitted with chest pain (CP) in the emergency room (ER) are needed.

This prospective study was aimed at evaluating the in-hospital diagnostic and prognostic role of CRP in the admission of patients presenting at the emergency room with chest pain suggestive of myocardial ischemia without ST-segment elevation on the first electrocardiogram (ECG).

**Methods**

**Study population** - From January 1, 2002 to December 31, 2003, a total of 980 patients were consecutively seen in the ER of a private tertiary hospital with CP during the previous twelve hours, suspected ACS and no ST-segment elevation on admission ECG. These patients underwent a systematized evaluation protocol at the Chest Pain Unit and had creatine kinase MB mass (CKMB-mass) and troponin I determined on admission\(^1\)\(^8\). Subsequent serial measurements of these myocardial necrosis markers were performed according to the degree of probability of developing ACS. In the highest and lowest probability groups, CKMB was measured at hours 3 and 9 and at hour 3, respectively, and only in the highest probability group troponin I was measured at hour 9. ECG recordings followed the same systematic approach used for CKMB-mass measurement. Patients with the highest probability of developing ACS underwent echocardiogram. In the absence of myocardial necrosis or ischemia at rest, the protocol recommended that a provocative test (exercise stress test, dobutamine echocardiography or myocardial perfusion SPECT) be performed. Characteristics of the population studied are shown in Table 1. Mean age was 64.9 ± 14.3, and 54.6% of the patients were male, 18.3% were diabetic, 67% were hypertensive, 23.2% had history of myocardial infarction, and 84% had normal admission ECG. Median systolic blood pressure and heart rate were 140 mmHg and 75 bpm, respectively.

**Blood chemistry and endpoints studied** - C-reactive protein was evaluated on admission, at the same time as a blood sample was collected for measuring myocardial necrosis markers (CKMB-mass and troponin I). Two different techniques were used for these measurements: Immunochemical (Vitros Chemistry Products, Johnson & Johnson Clinical Diagnostics, Rochester, USA), titrated CRP (t-CRP), in 80% of the cases, with analytical sensitivity (AS) of 0.1 mg/dL and upper limit of normal (ULN) of 1.0 mg/dL. And immunonephelometric (Dade Behring Inc., Marburg, Germany), high-sensitivity CRP (hs-CRP), in the remaining 20%, with 0.175 mg/L AS and 3.0 mg/L ULN. Choice of the CRP technique was up to the ER doctor. It should be emphasized that the hs-CRP assay was performed at the central laboratory, thus delaying the result, which was usually available between 12 and 24 hours after blood collection. In order to perform a joint statistical analysis (t-CRP + hs-CRP), CRP results were standardized (s-CRP) through the ratio of patients’ level to the ULN of the test used. This way, an s-CRP of 0.8 (therefore here no unit is possible) represents a CRP level 20% lower than the ULN, that is, 0.8 mg/dL for t-CRP or 2.4 mg/L for hs-CRP. Likewise, an s-CRP of 1.3 (30% above the ULN) represents a t-CRP of 1.3 mg/dL or hs-CRP of 3.9 mg/L, and so on.

Both CKMB-mass and troponin I were assessed using the immunofluorescence method (Dade Behring Inc., Marburg, Germany), with 0.6 ng/mL and 0.1 ng/mL AS and 5.0 ng/mL and 1.0 ng/mL ULN, respectively.

The final non-ST-segment elevation AMI diagnosis was based on a typical rise in CKMB-mass and/or troponin I, accompanied or not by ST-segment changes on ECG, when no other cause of chest pain was found\(^1\)\(^9\). The final diagnosis of unstable angina was established when, in the absence of necrosis marker increase, chest pain was accompanied by dynamic changes of ventricular repolarization on ECG (ST-segment depression greater than 0.5 mm or T-wave inversion), myocardial ischemia on the pre-discharge provocative test, or significant coronary heart disease on coronary angiography. The presence of ACS (non-ACF) was ruled out if the provocative test was negative for myocardial ischemia after all investigation recommended for chest pain had been completed. The diagnosis of AMI was ruled out if serial measurement of myocardial necrosis markers was normal even though the patient had not undergone a provocative test.

All patients were followed up on during hospitalization, and in-hospital death (cardiovascular), AMI, and urgent myocardial revascularization (percutaneous angioplasty or heart surgery) were considered adverse cardiac events (endpoints).

This study was approved by the institution’s Research Ethics Committee.

**Statistical analysis** - Statistical analysis was performed using the SPSS package for Windows, Version 11. Data indicate mean or median with their standard deviation. The Mann-Whitney test was applied to compare proportions. A multivariate analysis using forward stepwise logistic regression was performed to check for independent variables related to the endpoint adverse cardiac events. P values < 0.05 (two-tailed) were considered statistically significant.
RESULTS

Of the 980 patients presenting with CP, 401 were diagnosed with ACS, 276 (28.2%) of whom with unstable angina and 125 (12.8%) with non-ST-segment elevation AMI. Of the remaining 579 patients, the diagnosis of ACS (non-ACF) was eliminated in 452 and that of AMI (Table 2) was eliminated in 127. Length of stay in hospital was 21 hours (median).

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Mean s-CRP of patients investigated for CP was 0.86 ± 1.68, and in 20.1% of the cases this value was above 1.0. Serum s-PCR values were 1.31 ± 2.90 (median = 0.47) in patients diagnosed with AMI and 0.79 ± 1.39 (0.30) in patients without AMI (p = 0.031, Mann-Whitney), as shown in Figure 1. In unstable angina this level was 0.75 ± 1.29 (0.28). S-CRP higher than 1.0 showed the following characteristics predictive of AMI diagnosis: 30% sensitivity, 80.4% specificity, 61% positive predictive value, and 96.7% negative predictive value; the area under the ROC curve was 0.56.

There were forty in-hospital adverse cardiac events: 16 deaths, 22 urgent revascularizations, and 2 AMI. In the first quartile of s-CRP, values lower than 0.10, there were 3 events, while in the fourth quartile of s-CRP, values higher than 0.93, there were 15 events (p = 0.003, for linear trend), as shown in Figure 2. Mean s-CRP in patients who survived compared with those who died was 0.8 ± 0.3 vs. 2.3 ± 0.6, p = 0.082.

Logistic regression analysis identified the following variables as independent predictors of in-hospital ischemic events (death, AMI, and urgent myocardial revascularization): 1) left ventricular failure, with 95% confidence interval (95% CI) and a 6.5 (3.0-14.1, p < 0.001) odds ratio, 2) masculine gender, with 3.0 (1.4-6.3, p = 0.004) OR, and 3) s-CRP above 0.32 (median), corresponding to values higher than 1 mg/L for hs-CRP or 0.33 mg/dL for t-CRP, with 2.2 OR (1.1-4.5, p = 0.029) (Figure 3).

DISCUSSION

The present study shows the usefulness of CRP measurement on admission in patients seen at the emergency department with CP suggestive of ACS and non-ST-segment elevation on baseline ECG.

The s-CRP level was significantly higher in patients diagnosed with AMI, compared with those without AMI (1.31 vs. 0.79, p = 0.031). Thus, increased s-CRP level

Table 1 – Characteristics of the population studied

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>64.9 ± 14.3</td>
</tr>
<tr>
<td>Masculine gender</td>
<td>535 (54.6)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>657 (67)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>179 (18.3)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>463 (47.2)</td>
</tr>
<tr>
<td>Smoking</td>
<td>140 (14.3)</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>227 (23.2)</td>
</tr>
<tr>
<td>LVF at admission</td>
<td>59 (6.0)</td>
</tr>
<tr>
<td>Normal/nonspecific ECG on admission</td>
<td>820 (83.7)</td>
</tr>
<tr>
<td>Hospital stay (median/hours)</td>
<td>21</td>
</tr>
<tr>
<td>Standard CRP (median ± SD)</td>
<td>0.86 ± 1.7</td>
</tr>
</tbody>
</table>

LVF- left ventricular failure; ST- standard deviation.

Table 2 – Final diagnoses of chest pain survey

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>n (%)</th>
<th>s-CRP (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>125 (12.8)</td>
<td>1.31 ± 2.90 (0.47)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>276 (28.2)</td>
<td>0.75 ± 1.29 (0.28)</td>
</tr>
<tr>
<td>Absence of ACS</td>
<td>452 (46.1)</td>
<td>0.80 ± 1.41 (0.36)</td>
</tr>
<tr>
<td>AMI exclusion</td>
<td>127 (13)</td>
<td>0.80 ± 1.52 (0.27)</td>
</tr>
</tbody>
</table>

ACS- acute coronary syndrome; AMI- acute myocardial infarction.

Fig. 1 – AMI - Acute myocardial infarction - Standardized CRP in patients with and without AMI.
on admission was a useful tool in identifying more severely ill patients with CP, data consistent with that found in the literature. Mach et al evaluated 110 patients with clinical and electrocardiographic criteria suggestive of AMI, out of a population of 201 patients admitted to the ER with chest pain, and found a significant difference between admission CRP in patients with or without final diagnosis of AMI (1.70 vs. 0.50 mg/dL, respectively; p < 0.001). Such data suggest that CRP level on admission may be an ACS marker to identify patients at higher risk of developing AMI. Higher CRP level in the group of patients with ACS compared with the other patients experiencing chest pain was also found in another study.

Although s-CRP does not serve to diagnose AMI, due to its low sensitivity and low positive predictive power (30% and 61%, respectively), its normal value virtually excludes this diagnosis, because it shows good sensitivity and excellent negative predictive value (80.4% and 96.7%, respectively). In patients admitted for CP alone, normal CRP levels build confidence for hospital discharge.

S-CRP measurement on admission proved to be an important tool in predicting adverse cardiac events during hospitalization. Therefore, patients with s-CRP > 0.93 (last quartile) had five times more in-hospital cardiac events (death, AMI, unstable angina, and urgent myocardial revascularization) than those with s-CRP < 0.10 (first quartile), fifteen vs. 3 events, p = 0.003. In other words, higher s-CRP at the initial evaluation

![Fig. 2](image-url) – Analysis of standard CRP quartiles and in-hospital adverse cardiac events (CE).

![Fig. 3](image-url) – Predictive variables for in-hospital adverse cardiac events, according to multivariate analysis; LVF - Left ventricular failure.
in patients experiencing CP points to poorer outcome during hospitalization. Published studies analyzing the short-term role of CRP, specifically during hospital stay, focused patients diagnosed with ACS (AMI and unstable angina) and found an association between CRP and inhospital outcome22,23. However, Ferreiros et al., in their study with patients admitted for unstable angina, failed to demonstrate this association24.

Multivariate analysis identified s-CRP as independently related to in-hospital adverse cardiac events, along with left ventricular failure and masculine gender. Thus, patients with chest pain and s-CRP > 0.32 (median) had 2.2-fold adverse cardiac events during hospitalization. This result is common in patients admitted with AMI, a condition in which CRP values were significantly higher in those who evolved to cardiac death, cardiac rupture or development of left ventricular aneurysm25, but not in patients with chest pain. Short-term CRP predictive value (thirty days) in patients with unstable angina and AMI has encouraged emergency physicians to require CRP measurement at hospital admission26,27. Currently, CRP measurement, specifically high-sensitivity CRP (hs-CRP), is recommended only for patients with stable coronary heart disease or ACS (class IIA, evidence level B)28.

This study has some limitations: Firstly, CRP level was measured only on admission, when it is known that its concentration peaks later later. Nonetheless, CRP serial measurement to evaluate patients with chest pain, the focus of which are myocardial necrosis markers, would hardly be justifiable. Another limitation was the use of two techniques with different sensitivity threshold to determine CRP levels, requiring a statistical device to improve data interpretation (CRP standardization). It must be noted that both techniques measure the same protein and the inflammatory phenomenon. Finally, this can be considered a small study, due to the low rate of in-hospital adverse cardiac events (4.1%), that expected in the kind of population studied, which may justify the non-statistical significance found when s-CRP level was compared among patients who survived and those who died.

In conclusion, data from this study indicate that CRP determination in evaluating patients admitted to the emergency room with chest pain may be useful to rule out AMI diagnosis, in addition to predict in-hospital adverse cardiac events, when its value is higher than one-third the normal upper limit (hs-CRP > 1 mg/L or t-CRP > 0.33 mg/dL).

Potential Conflict of Interest
No potential conflict of interest relevant to this article was reported.

References


