Does high-sensitivity C-reactive protein add prognostic value to the TIMI-Risk Score in individuals with non-ST elevation acute coronary syndromes?

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Abstract

Background: C-reactive protein (CRP) measured at hospital arrival of patients with non-ST elevation acute coronary syndromes (ACS) may add prognostic information to the TIMI-Risk Score.
Methods: Eighty-six consecutive patients admitted with unstable angina or non-ST-elevation acute myocardial infarction and symptoms onset within the prior 48 h were included. Recurrent cardiovascular events during hospitalization were defined as non-fatal myocardial infarction or death. Serum CRP was measured immediately at hospital arrival and its prognostic value in relation to in-hospital cardiovascular events was tested by the area under the ROC curve and adjusted for TIMI risk predictors by logistic regression analysis. In addition, a CRP modified TIMI-Risk score was created by adding 2 points if CRP greater than the cut-off proposed by the ROC curve analysis. The accuracy of this new score was compared with the usual TIMI-Risk Score.
Results: A significant predictive value of CRP in relation to in-hospital cardiovascular events was indicated by an area under the ROC curve of 0.80 (95% CI=0.66 to 0.93, $p=0.009$). C-reactive protein cut-off point of best prognostic performance was 7.2 mg/l. In the multivariate analysis, increased CRP (>7.2 mg/l) remained a significant predictor of events after adjustment for TIMI risk predictors (OR=14; 95% CI=1.6–121; $p=0.018$). The area under the ROC curve for the TIMI-Risk Score was 0.87 (95% CI=0.76–0.99, $p=0.001$). The addition of CRP to the TIMI-Risk Score improved its prognostic value (area under the ROC curve=0.93; 95% CI=0.87–0.99, $p<0.001$). The additional value of the new score is demonstrated by a higher specificity (86% vs. 63%, $p<0.001$) and positive predictive value (39% vs. 19%) in relation to the TIMI-Risk Score.
Conclusions: CRP measured at admission of patients with non-ST-elevation acute coronary syndromes adds prognostic information to the TIMI-Risk Score. Additionally, the incorporation of this variable into the TIMI-Risk Score calculation is an effective manner to utilize CRP for risk stratification.
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Keywords: TIMI-Risk Score; C-reactive protein; Acute myocardial infarction; Unstable angina

1. Introduction

Acute coronary syndromes (ACS) are characterized by enhanced inflammatory response which contributes to the risk of recurrent cardiovascular events [1]. Accordingly, studies of patients with non-ST-elevation ACS show an independent association between plasma level of C-reactive protein (CRP) and subsequent in-hospital coronary events [2,3]. In order to translate this statistical evidence into clinical practice, a better understanding of the clinical relevance of CRP is mandatory: how much a measurement of CRP should influence physician's impression about patient risk status?

Several independent predictors have been combined into a TIMI-Risk Score, which has been validated and extensively

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used in patients with non-ST-elevation ACS [4]. Thus, it is important to know to what extent CRP improves risk stratification defined by the TIMI-Risk Score. Recently, Foussas et al. demonstrated that CRP predicts cardiovascular events within any level of the TIMI-Risk Score [5]. Based on that, we hypothesized that incorporating CRP into the TIMI-Risk enhances this score's ability to predict events. In order to test this novel hypothesis, we calculated the TIMI-Risk Score and measured CRP at admission of 86 individuals with non-ST-elevation ACS. Based on hospital outcome, the independent prognostic value of CRP was evaluated and a TIMI-Risk Score modified by the level of plasma CRP was tested as a risk predictor.

2. Methods

2.1. Patient population

Patients admitted to the coronary care unit of Portuguese Hospital due to unstable angina pectoris or non-ST elevation acute myocardial infarction from December 2000 to March 2002 were considered candidates for the study. Inclusion criteria were defined as onset of chest discomfort in the prior 48 h in patients with positive troponin (troponin I$>$1.0 ng/ml or troponin T$>$0.1 ng/ml) and/or electrocardiographic changes consisting of transient ST-segment depression ($\geq$0.05 mV) or T wave inversion ($\geq$0.1 mV). Positive troponin patients had their index event defined as acute myocardial infarction and the remaining subjects were labeled as unstable angina. Patients with left bundle-branch block, pacemaker rhythm, ST-segment elevation acute myocardial infarction, acute inflammatory illness, or secondary conditions that could precipitate angina (anemia, arrhythmias, fever) were not included in this study. Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institution's human research ethic committee.

2.2. Laboratory assays and study protocol

A blood sample to measure CRP was drawn immediately at hospital arrival, targeting the least possible time delay from symptoms onset. Cardiovascular events during hospitalization were defined as the composite of death or nonfatal acute myocardial infarction. Myocardial infarction as an endpoint was defined as either a new Q-wave or troponin elevation during hospitalization despite negative troponin on the first day. For patients with infarction at study entry, a new peak of mass CK-MB (above the normal limit) was required for diagnosis of reinfarction. High-sensitivity CRP was measured using a commercially available immuno-enzymatic nephelometric method (Dade-Behring, Newark, Delaware, USA) with a precision limit of 0.3 mg/l and variation coefficient of 7.6% [6]. Troponin I (Diagnostics Products Corp., Los Angeles, CA) and troponin T (Roche Diagnostics, Indianapolis, IN) were measured by chemiluminescence immunoassay.

2.3. Data analysis and statistical methods

First, the predictive value of CRP and TIMI-Risk Score were tested by the area under the receiver operator characteristic (ROC) curve. The null hypothesis of no prediction would be rejected if the 95% confidence interval of this area included values $>$0.5. Based on this analysis, the best cut-off points were identified and used for calculation of sensitivity, specificity and predictive values of cardiovascular events. Incidences of recurrent events during hospitalization were compared between the groups defined by the cut-off points, using χ^2 test, with Yates correction when applicable or Fisher's exact test.

Second, multivariate analysis by logistic regression was performed in order to evaluate whether CRP is an independent predictor of in-hospital events, after correction for the TIMI-Risk variables or potential confounder variables. C-reactive protein entered this analysis as a categorical variable, defined as increased when higher than the cut-off established by the ROC analysis. Logistic regression was performed in a stepwise fashion and variables with $p<0.15$ in the first model were considered significant. In the second model, only those with $p<0.05$ were defined as significant.

Third, a new score (TIMI-Risk-CRP Score) was obtained by adding 2 points if CRP was higher than its cut-off. Elevated CRP added 2 points to the score because its odds ratio was 2 times higher than other variables' odds ratio. The area under the ROC curve was used to evaluate accuracy of the new score. Sensitivity and specificity of this score was compared with TIMI-Risk Score by McNemar's test. Predictive values were also reported.

C-reactive protein values were not normally distributed and were reported as the median and interquartile range. C-reactive protein was compared between groups by Wilcoxon's Rank Sum test. Scores were reported as median and interquartile range. Baseline categorical characteristics were compared between patients with CRP below or above its cut-off point by the χ^2 test, with Yates correction when applicable or Fisher's exact test. Numerical variables were compared by Student's *t* test or Wilcoxon's rank-sum test. Statistical significance was defined as a $p<0.05$. SPSS statistical software (ver. 9.0, SPSS Inc., Chicago IL) was used for data analysis.

3. Results

3.1. Population characteristics

Eighty-six individuals were studied, aged 65$\pm$11 y, 48 men, 49 with acute myocardial infarction and 37 with unstable angina pectoris. Based on TIMI-Risk Score (median=3, interquartile range=2–4), the population had an intermediate risk for developing in-hospital cardiovascular events. Accordingly, incidence of events during hospitalization was 8% (7 individuals: 4 died from coronary causes and 3 had non-fatal, non-ST elevation myocardial infarction). Median of CRP was 5 mg/l, with interquartile range of 1.8–16 mg/l. Time from onset of qualifying symptoms to blood sample collection to CRP measurement had a median of 5.5 h (interquartile range=2.6–11 h).
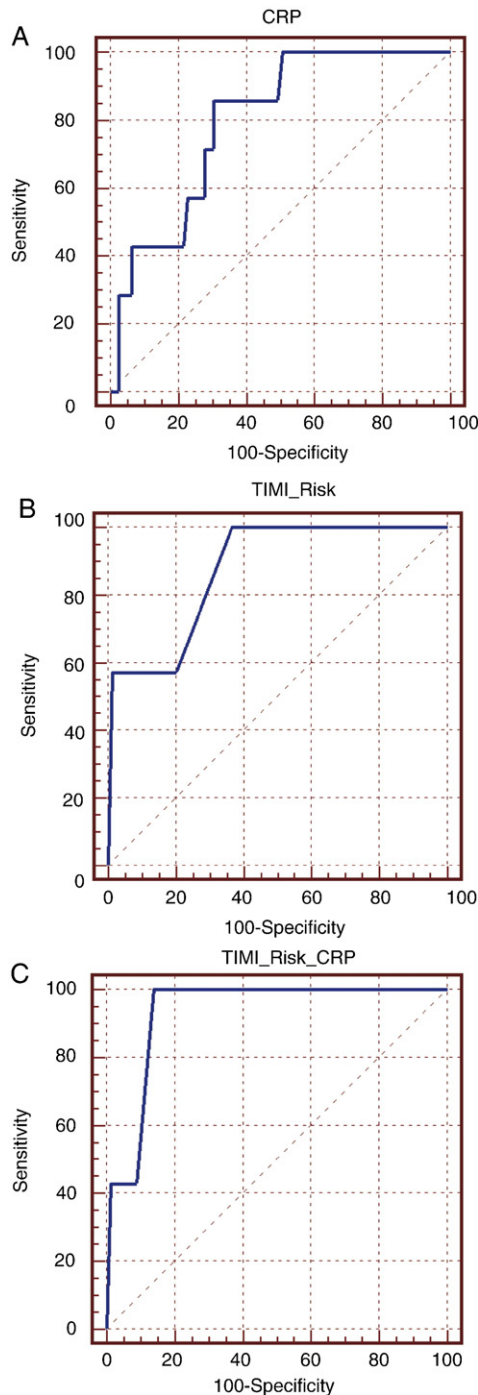
Fig. 1. Receiver operator characteristics curves of C-reactive protein (CRP — Panel A), TIMI-Risk Score (Panel B) and TIMI-Risk-CRP Score (Panel C).

3.2. Predictive value of C-reactive protein

The median of CRP at admission was higher among patients with recurrent events during hospitalization in relation to those free of events (15.9 vs. 4.7 mg/l, $p=0.009$). A significant predictive value of CRP in relation to clinical events was indicated by an area under the ROC curve of 0.80 (95% CI 0.66 to 0.93, $p=0.009$) — Fig. 1, Panel A. The cut-off point of best

Table 1
Accuracy of C-reactive protein, TIMI-Risk Score and TIMI-Risk-CRP Score in relation to in-hospital events

	AU ROC	95% CI	P value	Sensitivity	Specificity	PPV	NPV
C-reactive protein	0.80	0.66–0.93	0.009	100%	70%	20%	98%
TIMI-Risk Score	0.87	0.76–0.99	0.001	100%	63%	19%	100%
TIMI-Risk-CRP Score	0.93	0.87–0.99	<0.001	100%	86%	39%	100%

AU ROC: area under receiver operator characteristic curve. PPV: positive predictive value; NPV: negative predictive value. Sensitivities, specificities and predicted values are obtained from the cut-off points of best performance in the ROC curve.

performance by this analysis was 7.2 mg/l. This cut-off had a sensitivity of 86% for prediction of future events, which provided a negative predictive value of 98%. The specificity was 70%, implying in a positive predictive value of 20% — Table 1. In line with that, there was a higher incidence of combined events in those with CRP >7.2 mg/l (20 vs. 2%, $p=0.003$). This difference resulted from increased incidences of both in-hospital death (10 vs. 2%, $p=0.09$) and nonfatal myocardial infarction (10% vs. 0%, $p=0.02$).

3.3. Independent predictive value of CRP

The comparison between the 2 groups defined by CRP cut-off (7.2 mg/l) showed similar clinical characteristics and hospital treatment, except for the use of beta-blockers, that was more

Table 2
Baseline characteristics and treatment of the 2 groups defined by CRP cut-off point

	CRP ≤ 7.2 mg/l	CRP > 7.2 mg/l	p
Sample size	56	30	
Baseline characteristics			
Age (y)	64±12	66±11	0.32
Men	29 (52%)	19 (63%)	0.30
Diabetes	20 (36%)	11 (37%)	0.93
Smokers	4 (7%)	5 (17%)	0.17
Systemic hypertension	40 (71%)	19 (63%)	0.44
Total cholesterol (mg/dl)	198±42	204±47	0.52
Chronic use of aspirin	20 (36%)	15 (50%)	0.20
Previous myocardial infarction	11 (20%)	9 (30%)	0.28
ST-segment depression	21 (38%)	18 (60%)	0.045
Positive troponin	27 (48%)	22 (73%)	0.03
Treatment during hospitalization			
Aspirin	55 (98%)	28 (93%)	0.24
Clopidogrel	44 (79%)	23 (77%)	0.84
Tirofiban	8 (14%)	8 (27%)	0.16
Enoxaparin	53 (95%)	28 (93%)	0.81
Nitrates	47 (84%)	28 (93%)	0.21
Beta-blockers	53 (95%)	22 (73%)	0.005
Statins	32 (57%)	15 (50%)	0.53
Coronary angioplasty	13 (23%)	6 (20%)	0.73
Coronary bypass surgery	3 (5.4%)	1 (3.3%)	0.67

CRP: C-reactive protein.

prevalent among those with CRP ≤ 7.2 mg/l — Table 2. Thus, as a potential confounder variable, "use of beta-blockers" entered the multivariate analysis, among all TIMI-Risk variables and "increased CRP" (>7.2 mg/l) as potential predictive factors of in-hospital events. In this analysis, only increased CRP remained a significant independent predictor (OR = 14; 95% CI = 1.6–121; $p = 0.018$). Table 3 depicts the performance of each covariate in the logistic regression analysis.

3.4. Predictive value of TIMI-Risk Score

The area under the TIMI-Risk ROC curve in relation to in-hospital coronary events was 0.87 (95% CI = 0.76–0.99, $p = 0.001$), indicating that the score obtained at admission accurately predicted events during hospitalization — Fig. 1, Panel B. According to this analysis, the cut-off point of best performance was 3, implying on a sensitivity of 100% for prediction of future events by CRP, which provided a negative predictive value of 100%. On the other hand, the specificity was 63%, with a positive predictive value of 19% — Table 1. When the sample was divided into 2 groups defined by this point, all events took place in individuals with TIMI-Risk > 3 and those with TIMI-Risk ≤ 3 were free of adverse outcome (19 vs. 0%, $p = 0.001$). Similar trends of in-hospital death (11 vs. 0%, $p = 0.016$) and nonfatal myocardial infarction (8 vs. 0%, $p = 0.038$) resulted in this difference of combined endpoints.

3.5. Predictive value of TIMI-Risk-CRP Score

The modified TIMI-Risk Score was calculated by adding 2 points if CRP > 7.2 mg/l. C-reactive protein was conferred 2 points because its odds ratio was 2 times the value of the other variables' odds ratio. The addition of CRP to the TIMI-Risk Score improved its accuracy, with an area under the ROC curve of 0.93 (95% CI = 0.87–0.99, $p < 0.001$) — Table 1. By this analysis, the cut-off with best performance was 5. Based on this, the additional value of this new score in relation to the usual TIMI-Risk Score is demonstrated by a higher specificity (86 vs. 63%, $p < 0.001$), providing an improved positive predictive
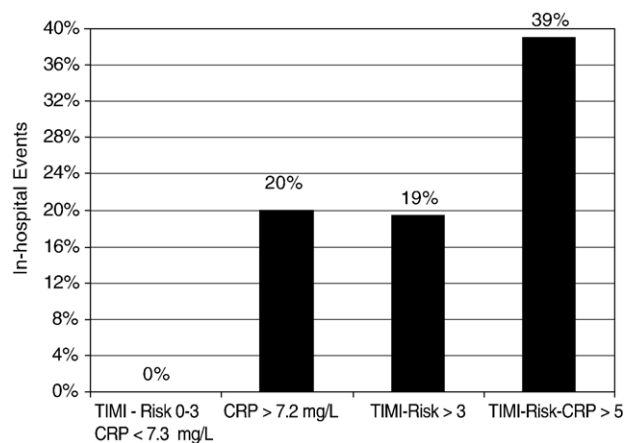
Table 3
Multivariate analysis of TIMI-Risk variables, C-reactive protein and the use of beta-blocker as predictive variables of in-hospital events

Multivariate analysis		
Predictor variable	OR (95% CI)	P
Age ≥ 65 y	9.4 (0.8–112)	0.08
CAD risk factors ≥ 3	7.0 (0.94–52)	0.06
Prior CAD	0.31 (0.01–15)	0.55
Use of aspirin	5.4 (0.20–144)	0.32
ST-depression	$38 * 10^2$ (0–$1.1 * 10^{49}$)	0.83
Positive troponin	6.5 (0.30–142)	0.23
Severe symptoms	4.2 (0.4–45)	0.23
Beta-blocker	0.95 (0.02–53)	0.98
Increased CRP	14 (1.6–121)	0.018

CAD risk factors: hypertension, diabetes, current smoking, hypercholesterolemia, family history of premature CAD; CRP: C-reactive protein; CAD: coronary artery disease; OR: odds ratio; CI: confidence interval. Multivariate analysis was performed by stepwise logistic regression. Depicted results are taken from the final model of each variable.

Fig. 2. Positive predictive value of C-reactive protein (CRP) >7.2 mg/l, TIMI-Risk Score >3 and TIMI-Risk-CRP Score >5.

value (39 vs. 19% — Fig. 2), with the same sensitivity (100%) and negative predictive value (100%) — Table 1, Fig. 2.

4. Discussion

The present study demonstrated that CRP provides prognostic information related to hospital outcomes of patients with non-ST-segment elevation ACS, independent of TIMI-Risk Score predictors. In addition, we suggested that taking CRP as a factor in TIMI-Risk calculation improves the accuracy of this score in predicting in-hospital cardiovascular events. The first observation is based on the results obtained from multivariate analysis, in which CRP was the strongest predictor of in-hospital death and myocardial infarction, after adjustment for all TIMI-Risk variables and potential confounder variables. The second conclusion relies on the main limitation of risk scores in general, a low positive predictive value (most patients classified as high risk will not develop an event during hospital stay). After the addition of CRP, the positive predictive value of the TIMI-Risk Score increased by 20% in absolute terms.

In concordance with our results, previous studies recognized CRP as an independent risk predictor for recurrent events in patients with ACS [1–3,7–14]. The GUSTO-IV cohort was the largest to evaluate this issue, showing that CRP in the fourth quartile (>10 mg/l) was associated with a greater chance of in-hospital death, after adjustment for troponin and other risk predictors [2]. However, none of these studies evaluated the additional value of CRP to the overall clinical evaluation provided by the TIMI-Risk Score. Most recently, Foussas et al. demonstrated that CRP predicts events within each risk category defined by the TIMI-Risk Score [5]. In line with that, our study is the second to evaluate CRP in relation to the TIMI-Risk Score. Furthermore, we tested the approach of incorporating CRP into this score, showing promising results. Other secondary characteristics support the novelty of the present study: first, Foussas et al. tested CRP in a high-risk population, whose enter criteria included either ST-segment depression or positive troponin. This was responsible for a 72% prevalence of ST-segment depression and 87% of positive troponin in that study. On the other hand, we

studied a moderate risk population, with 45% of ST depression and 57% of positive troponin. Second, they evaluated combined end-points, including a soft event defined by recurrent ischemia. We considered only hard events, such as death or non-fatal myocardial infarction.

Risk stratification is designed to err on the safe side, avoiding underestimation of the chance of developing an undesired event. Thus, the prediction focuses on sensitivity and often lacks specificity. Consequently, even those classified as high risk by the TIMI-Risk Score have a greater chance to remain free of a recurrent event [4]. Whether it is recommended to include a new marker in the routine evaluation of ACS patients is a matter of how much improvement of specificity is obtained, because sensitivity is already good. Based on this rational, we tested the Score modified by CRP. The TIMI-Risk-CRP Score demonstrated improvement in the ROC curve, by enhanced specificity, which provided an increment in its positive predictive value from 19 to 39%. Considering the intermediate risk of our population, 20% is a substantial increment of the positive predictive value. However, it is worth to note that the positive predictive value remains <50% (half-chance), meaning that further improvement is necessary by the addition of new independent variables to the score.

Regarding the mechanisms implicated on the prediction of cardiovascular events by CRP, it can be related to either a direct or indirect effect of this protein. During ACS a substantial increase in plasma CRP takes place as part of the acute phase reaction [15]. In these circumstances, the high concentrations of CPR may be not only a marker, but a risk factor for mortality, because CRP activates complement which may cause myocardial damage, predisposing to heart failure or arrhythmias [16]. On the other hand, the association between recurrent ischemia and CRP may indirectly be driven by a causal relationship between inflammation and atherosclerotic plaque vulnerability to rupture, with CRP being only a marker of plaque characteristics [17,18].

The major limitation of our study is the sample size, which merits consideration in 3 situations: first, we estimated CRP cut-off point in order to evaluate the performance of this inflammatory marker as a categorical variable. As a data analysis approach, it was useful. However, this cut-off cannot be considered validated for clinical practice, because an accurate and precise estimation is impaired by our small sample size. According to the current literature, the CRP cut-off point for patients with non-ST-segment elevation ACS should be 10 mg/l [2,14]. Second, established risk predictors, such as age, troponin and ST-segment depression, did not reach statistical significance in the multivariate analysis. The reason for that was probably the reduction of the statistical power related to the small sample population. Thus, it should not be seen as evidence against previously well-defined predictors. Third, based on the fact that CRP's odds ratio was double the magnitude of the other variables, we attributed 2 points in the score if CRP was increased. But larger studies are necessary to definitely determine the weight CRP should have in the TIMI-Risk-CRP Score calculation.

In conclusion, CRP measured at admission of patients with non-ST-elevation acute coronary syndromes adds prognostic information to the TIMI-Risk Score. Additionally, the incorporation of this variable into the TIMI-Risk Score calculation is an effective manner to utilize CRP for risk stratification.

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