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Predictive value of high sensitivity C-reactive protein in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention

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Aims To evaluate the predictive value of high sensitivity (hs) C-reactive protein levels on long-term survival in patients with ST-elevation myocardial infarction (STEMI) treated with primary PCI.

Methods and results We conducted a retrospective analysis of 758 STEMI patients (from January 2003 to December 2005), with STEMI onset <12 h and hs-C-reactive protein determination on admission.
Patients were classified into four groups [I (hs-C-reactive protein <0.48 mg/dL), II (hs-C-reactive protein ≥ 0.48 to <1.2 mg/dL), III (hs-C-reactive protein ≥ 1.2 to <3.1 mg/dL), IV (hs-C-reactive protein ≥ 3.1 mg/dL)] according to quartiles of hs-C-reactive protein serum level. The IV quartile hs-C-reactive protein group had a higher incidence of in-hospital mortality and cumulative adverse events. At a mean follow-up of 724 ± 376 days (range 0–1393), the IV quartile hs-C-reactive protein group showed lower estimated survival, lower estimated myocardial infarction-free survival and lower estimated event-free survival. At multivariable analysis hs-C-reactive protein appeared to be an independent predictor of long-term mortality (HR: 1.04, 95% CI: 1.01–1.07, $P = 0.003$), long-term mortality and re-infarction (HR: 1.03, 95% CI: 1.01–1.06, $P = 0.008$) and adverse events (HR: 1.03, 95% CI: 1.01–1.05, $P = 0.03$).

Conclusion Evaluation of hs-C-reactive protein on admission in STEMI patients undergoing primary PCI allows reliable risk stratification of these patients.

Keywords Myocardial infarction • Angioplasty • Transluminal • Percutaneous coronary • High-sensitivity C-reactive protein

Introduction

Inflammation has been documented to play an important role in the pathogenesis of atherosclerosis.[1] In particular, several studies have shown that C-reactive protein, an acute-phase reactant that is synthesized and secreted in the liver 6 h after an acute inflammatory stimulus, takes part directly in the atherosclerotic process and represents one of the most important predictors of vascular death in several clinical settings.[2–4] It is well known that myocardial necrosis is an established cause of the acute-phase response.[5] In patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary interventions (PCI), the prognostic role of serum C-reactive protein is not well known.[6–8] The aims of the present study were, therefore, to

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ascertain the long-term predictive value of high sensitivity C-reactive protein (hs-C-reactive protein) serum concentrations in STEMI patients undergoing primary PCI in a 'real world' setting.

Methods

Setting

This observational cohort study was performed at the Institute of Cardiology of the S. Orsola-Malpighi hospital of the University of Bologna (Italy) during the period 2003–2005.

As previously reported, the Bologna STEMI registry[9] was a prospectively collected registry to evaluate the quality of care and outcome during the establishment of a provincial network system for STEMI treatment in the Italian province of Bologna (3702 km^2). Systematic use of PCI for STEMI patients began in January 2003 in the context of the PRIMA RER project set up by the *Emilia-Romagna Region*.

Study design and selection criteria

This study was based on a prospectively assembled database dedicated to the contribution of the S. Orsola-Malpighi hospital to the PRIMA RER project. This database contains demographic information and comprehensive clinical, ECG, laboratory and procedural data; institutional follow-up data are systematically updated. The study period comprises the years 2003–2005. The present analysis regards all 985 patients directly referred to primary PCI at the S. Orsola-Malpighi intervention laboratory due to STEMI within 12 h of self-reported onset of symptoms [patients pre-treated with thrombolysis (rescue or facilitated PCI) were excluded]. For the purposes of this study, we excluded patients in whom hs-C-reactive protein was not determined on admission (220), patients with ongoing inflammatory disease or patients with malignant or infective disorders (7). Informed consent for PCI, participation in the study protocol, and anonymous publication of scientific data was systematically sought whenever possible; in line with national practice; patients in a coma or cardiogenic shock were treated and are anonymously reported in the study. No patient was excluded due to lack of informed consent. Patients were classified into four groups [I (hs-C-reactive protein $<$ 0.48 mg/dL), II (hs-C-reactive protein $\geq$ 0.48 to $<$1.2 mg/dL), III (hs-C-reactive protein $\geq$ 1.2 to $<$3.1 mg/dL), IV (hs-C-reactive protein $\geq$ 3.1 mg/dL)] according to quartiles of hs-C-reactive protein serum level.

Study end-point

The aim of the study was to evaluate the correlation between serum hs-C-reactive protein levels and long-term clinical outcome in STEMI patients treated with primary PCI.

STEMI diagnosis and PCI protocol

STEMI was defined as significant ST-elevation (in two adjacent leads and $\geq$0.1 mV in leads I–III, aVF, aVL, V4–V6 and $\geq$0.2 mV in leads V1–V3), as recorded in a pre-hospital ECG, or the first ECG obtained at the hospital of admission.[10] PCI was performed within 12 h of the self-reported onset of symptoms. Before PCI execution, all patients received aspirin (250 mg i.v.) and heparin (5000 IU i.v.) and the use of platelet glycoprotein IIb/IIIa agents, β-adrenergic blocking agents and nitrates was strongly encouraged. Heparin administration was continued for 24 h after PCI in any patient who did not receive Gp IIb/IIIa inhibitors. After PCI, ticlopidine or clopidogrel was administered to patients receiving stents. Venous blood samples for determination of total creatine phosphokinase (CK) and the MB isoenzyme were collected on admission, and 8, 16, 24, and 48 h after PCI (and on clinical indication) as well as serial 12-lead ECGs.

Angiographic analysis and definitions

Quantitative coronary angiography was analysed by experienced site investigators who were blinded to all data apart from the coronary angiogram. Differences were resolved by group discussion. Culprit vessel thrombolysis in myocardial infarction (TIMI) flow grades was assessed before and after the PCI procedure.[11] Cardiogenic shock was defined as a persistent systolic blood pressure $<$90 mmHg (as recorded in the catheterization laboratory before PCI or implantation of the aortic balloon pump) that was unresponsive to i.v. fluid administration or that required vasopressor agents to maintain systolic pressure $\geq$90 mmHg, secondary to left or right ventricular dysfunction. Treatment delay was defined as the time interval (minutes) between the onset of symptoms and the first balloon dilatation. No left ventriculograms were performed at the time of the angiography. However, all patients received two-dimensional echocardiographic evaluations within the first 24 h after PCI to assess the left (LVEF) and right ventricular ejection fractions and to exclude any mechanical complications. The 'Gp IIb/IIIa agents facilitated' PCI procedure was defined as the pre-intervention laboratory (pre-hospital, pre-transfer or in emergency department) administration of such drugs. Recurrent (Q-wave and non-Q-wave) myocardial infarction (MI) was defined as occurrence of prolonged chest pain with an increase in the CK-MB fraction above the normal limit and development (or absence) of new abnormal Q-waves. Target vessel revascularization (TVR) was defined as a coronary artery bypass grafting, or PCI performed in the culprit vessel. Stent thrombosis was defined as an angiographic thrombus within the stented vessel (documented by a clinically driven angiography).

Determination of high sensitivity C-reactive protein

Blood samples were obtained once the patient had been admitted to the intensive care unit (immediately after the primary PCI ending). Hs-C-reactive protein was measured by the high-sensitivity nephelometric method (Dade Behring: Newark, DE). Fibrinogen was measured with the Clauss method (Sysmex Corp). Leucocyte count was determined with an automated counter (ADVIA 120, Hematology System).

Data collection for in-hospital and long-term mortality

Mortality data at the intervention hospitals were available from the main database, which also provided systematic information on discharges and transfers of patients to local hospitals. Data regarding early mortality at patients' local hospitals were systematically collected by telephone. Long-term outcome was obtained directly and independently from the Emilia-Romagna Regional Health Agency through the analysis of the Hospital Discharge Records and the Municipal Civil Registries. Hospital records were reviewed for additional information whenever deemed necessary. The vital status at follow-up was obtained in 99.7% of the patients.

Statistical analysis

For data analysis hs-C-reactive protein values were divided into four groups according to the quartile values. Categorical data were expressed as numbers (percentages), continuous variables as

median (25–75th percentiles). For group comparisons, analysis of Kruscal–Wallis was used for continuous variables and the χ^2-square test for categorical variables. Correlations between variables were determined by Spearman's rank correlation test. Estimated long-term event-free survivals (from all-cause death, death/MI, death/MI/TVR) of the four hs-C-reactive protein groups were assessed by the Kaplan–Meier method. The obtained curves were compared using the Log-rank test. Logistic regression analysis was performed to determine predictors of in-hospital all-cause mortality. The following 22 variables (potential confounders) were inserted in the multivariable models: age (continuous variable), male gender, hs-C-reactive protein (continuous variable), diabetes, previous myocardial infarction, anterior myocardial infarction site, cardiogenic shock, post-PCI LVEF $\leq$ 35%, Killip class $\geq$ 2, heart rate (continuous variable), multivessel disease, IIb/IIIa agents administration, left anterior descending coronary artery/left main trunk culprit vessel, pain-to-balloon time (continuous variable), pre-PCI TIMI 0–1 flow, post-PCI TIMI 3 flow, creatinine at admission (continuous variable), glucose at admission (continuous variable), leucocyte counts at admission (continuous variable), fibrinogen at admission (continuous variable), haemoglobin at admission (continuous variable), peak levels of CK_{MB} (continuous variable). Model discrimination was assessed with the c-statistic, and model calibration was assessed with the Hosmer–Lemeshow statistic. Cox proportional-hazard regression analysis was used to verify the long-term independent predictive value of hs-C-reactive protein concerning all-cause mortality, all-cause mortality/MI and all-cause mortality/MI/TVR. To adjust for possible confounding factors, all the above reported variables were included in the multivariable models.

To test the stability of the logistic regression model and of the Cox proportional regression models, boostrap investigations (500 bootstrap samples) were carried out. Statistical analyses were performed using SPSS for Windows, release 13.0 (SPSS Inc., Chicago, IL) and using (boostrap analysis) Stata Statistical Software: Release 9.2 (College Station, TX: StataCorp LP). All *P*-values refer to two-tailed tests of significance; $P < 0.05$ was considered significant.

Table 1 Clinical characteristics and laboratory findings of the patients stratified by hs-C-reactive protein quartiles

	Hs-C-reactive protein I quartile (<0.48 mg/dL) (*n* = 189)	Hs-C-reactive protein II quartile (≥0.48 to <1.2 mg/dL) (*n* = 189)	Hs-C-reactive protein III quartile (≥1.2 to <3.1 mg/dL) (*n* = 191)	Hs-C-reactive protein IV quartile (≥3.1 mg/dL) (*n* = 189)	*P*-value
Age (years)	65 (56–76)	64 (57–77)	70 (61–78)	73 (64–81)	<0.001
Male sex	143 (76)	120 (64)	135 (71)	136 (72)	0.091
History of smoking	127 (67)	127 (67)	119 (62)	110 (58)	0.268
Hypercholesterolemia[a]	76 (40)	83 (44)	86 (45)	70 (37)	0.508
Diabetes[b]	25 (13)	26 (14)	38 (20)	48 (25)	<0.001
Hypertension	101 (53)	117 (62)	115 (60)	116 (61)	0.412
Family history of CVA	80 (42)	69 (37)	73 (38)	54 (29)	0.061
Prior myocardial infarction	23 (12)	40 (21)	31 (16)	35 (19)	0.158
Prior CABG	8 (4)	1 (0.5)	9 (5)	4 (2)	0.072
Prior PCI	13 (7)	20 (11)	16 (8)	21 (11)	0.618
Anterior myocardial infarction	88 (47)	98 (52)	114 (60)	112 (59)	0.036
Post-PCI LVEF	47 (40–55)	40 (36–55)	43 (35–50)	40 (30–47)	<0.001
Post-PCI LVEF ≤ 35%	18 (10)	25 (13)	35 (18)	62 (33)	<0.001
Heart rate (b.p.m.)	72 (63–86)	74 (63–89)	79 (65–92)	84 (70–96)	<0.001
Systolic pressure (mmHg)	125 (110–140)	130 (110–151)	125 (108–145)	123 (98–144)	0.076
Killip class ≥ 2	16 (9)	30 (16)	35 (18)	68 (36)	<0.001
Cardiogenic shock	13 (7)	21 (11)	18 (9)	36 (19)	<0.001
$Creatinine_{admission}$ (mg/dL)	1 (0.8–1.2)	1 (0.8–1.1)	1 (0.9–1.2)	1.1 (0.9–1.4)	<0.001
$Glucose_{admission}$ (mg/dL)	126 (110–160)	124 (108–153)	135 (115–165)	143 (115–210)	<0.001
$Haemoglobin_{admission}$ (g/dL)	13 (12–15)	14 (12–15)	13 (12–14)	13 (12–14)	0.773
Creatinine $kinase_{MB\ peak}$ (U/L)	117 (48–247)	125 (48–255)	143 (57–303)	138 (52–324)	0.233
WBC $counts_{admission}$ ($\times 10^3$/mL)	10.6 (8.2–12.7)	10.8 (8.5–12.3)	10.9 (8.7–13.4)	12.1 (10.1–15.8)	<0.001
Hs-C-reactive $protein_{admission}$ (mg/dL)	0.32 (0.31–0.34)	0.74 (0.62–0.95)	1.8 (1.4–2.2)	6.8 (4.4–12.2)	<0.001
$Fibrinogen_{admission}$ (mg/dL)	315 (283–364)	355 (310–391)	405 (362–437)	472 (431–537)	<0.001
Pain-to-balloon time (min)	195 (127–293)	173 (125–285)	175 (127–273)	236 (156–540)	<0.001
Door-to-balloon time (min)	69 (52–97)	65 (50–93)	75 (56–101)	77 (52–110)	0.062

Data are presented as frequencies (percentages) for categorical variables and medians (25th—75th percentiles) for continuous variables. Hs, high sensitivity; CVA, cardiovascular accident; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; WBC, white blood cell.
[a]Total cholesterol > 200 mg/dL or patients on anti-hypercholesterolemic therapy.
[b]History of diabetes before hospital admission.

Results

The 758 consecutive STEMI patients treated with primary PCI who underwent PCI at the S. Orsola-Malpighi intervention laboratory between January 2003 and December 2005 and satisfied the eligibility criteria (see Methods section) were included in the present analysis. *Table 1* lists the baseline clinical characteristics and reperfusion times of the eligible patients divided according to hs-C-reactive protein quartiles. As expected, several clinically relevant characteristics (i.e. age, diabetic status, anterior myocardial infarction site, post-PCI left ventricular ejection fraction, Killip class, heart rate, etc.) proved to be more severe in the higher hs-C-reactive protein quartiles groups (from I to IV). Moreover, leucocyte counts, fibrinogen, creatinine and glucose serum levels on admission showed significantly higher values from I to IV hs-C-reactive protein quartiles groups. Of note, as depicted in *Table 2*, patients in the higher hs-C-reactive protein quartiles disclosed a worse post-PCI culprit vessel epicardial perfusion grade. As reported in *Figure 1* (A, B, C), hs-C-reactive protein serum concentrations were correlated with post-PCI TIMI flow ($r = -0.151$), and with LVEF ($r = -0.120$). Although these correlations were statistically significant ($P < 0.001$), they were very weak ($r < 0.2$). Notably, no significant correlation was shown between $CK_{MB\ peak}$ values and hs-C-reactive protein values ($r = 0.065$).

In-hospital clinical events and predictors of in-hospital mortality

Table 3 summarizes in-hospital clinical adverse events according to hs-C-reactive protein quartiles. The IV hs-C-reactive protein quartile group showed a higher incidence of in-hospital all-cause mortality ($P < 0.001$) and adverse cumulative events ($P < 0.001$). No difference was observed among the four hs-C-reactive protein groups regarding the in-hospital occurrence of recurrent MI, TVR, stroke or major bleeding.

To evaluate the independent predictive power of hs-C-reactive protein on in-hospital mortality, the 22 clinical-angiographic and procedural variables listed in the 'Statistical analysis' of the Methods section were entered into a multivariable logistic regression model. The multivariable analysis showed hs-C-reactive protein as an independent predictor of in-hospital all-cause mortality (OR: 1.06, 95% CI: 1.002–1.119, $P = 0.04$) along with age (OR: 1.07, 95% CI: 1.033–1.112, $P < 0.001$), post-PCI LVEF $\leq$ 35% (OR: 4.98, 95% CI: 2.044–12.141, $P < 0.001$) and glucose at admission (OR: 1.009, 95% CI: 1.003–1.114, $P = 0.02$).

Table 2 Angiographic and procedural characteristics of the patients stratified by hs-C-reactive protein quartiles

	Hs-C-reactive protein I quartile (<0.48 mg/dL) (*n* = 189)	Hs-C-reactive protein II quartile (≥0.48 to <1.2 mg/dL) (*n* = 189)	Hs-C-reactive protein III quartile (≥1.2 to <3.1 mg/dL) (*n* = 191)	Hs-C-reactive protein IV quartile (≥3.1 mg/dL) (*n* = 189)	*P*-value
Infarct vessel					
Left anterior descending	95 (50)	102 (54)	107 (56)	106 (56)	
Circumflex	18 (10)	19 (10)	27 (14)	30 (16)	
Right	74 (39)	64 (34)	55 (29)	44 (23)	<0.001
Left main	1 (0.5)	4 (2)	1 (0.5)	8 (4)	
CABG	1 (0.5)	0	1 (0.5)	1 (0.5)	
Proximal disease	82 (43)	89 (47)	89 (47)	76 (40)	0.687
Multivessel disease	80 (42)	99 (52)	92 (48)	109 (58)	0.029
Stent implantation	182 (96)	177 (93)	174 (91)	173 (92)	0.225
Drug eluting stent implantation	14 (7)	10 (6)	7 (4)	5 (3)	0.190
Aortic balloon pump	19 (10)	15 (8)	26 (14)	35 (18)	0.014
Pre-PCI TIMI 0–1 flow	146 (77)	131 (69)	140 (73)	138 (73)	0.523
Post-PCI TIMI 3 flow	177 (94)	173 (92)	166 (87)	153 (81)	<0.001
Reference diameter (mm)	3 (2.5–3)	3 (2.5–3)	3 (2.5–3)	3 (2.5–3)	0.780
B-blocker therapy	85 (45)	86 (46)	81 (42)	70 (37)	0.487
Platelet Gp IIb/IIIa inhibitors	173 (92)	159 (89)	162 (85)	130 (69)	<0.001
Abciximab	156 (90)	135 (85)	141 (87)	114 (88)	0.740
Tirofiban	17 (10)	24 (15)	21 (13)	16 (12)	
Platelet Gp IIb/IIIa inhibitor-facilitated PCI	51 (27)	44 (23)	54 (28)	42 (22)	0.639

Data are presented as frequencies (percentages) for categorical variables and as medians (25th–75th percentiles) for continuous variables. Hs, high-sensitivity; TIMI, thrombolysis in myocardial infarction; Gp, glycoprotein.

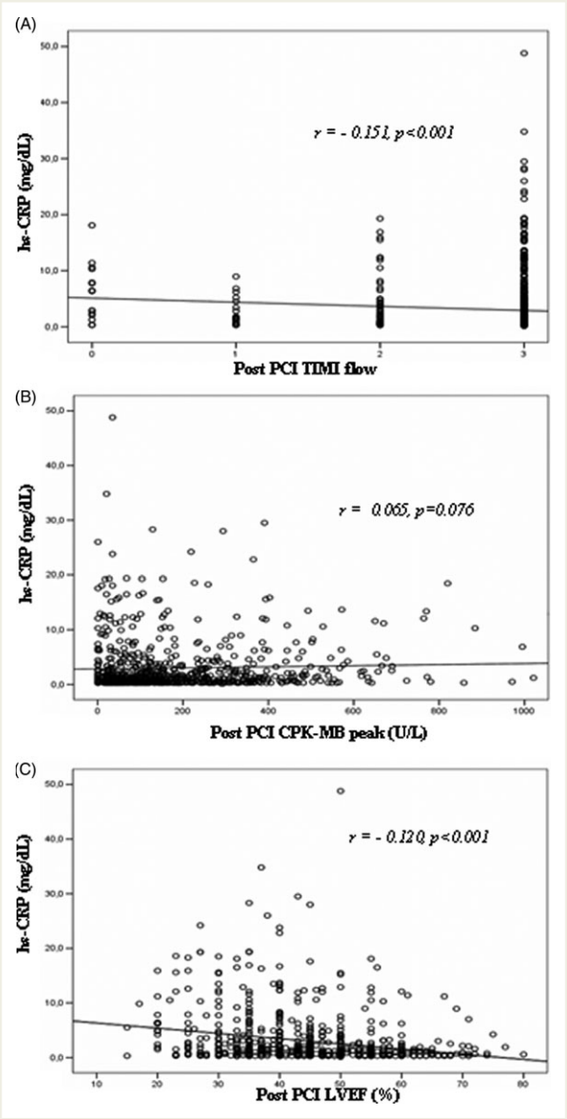

Figure 1 Bivariate correlation between hs-C-reactive protein serum concentrations and post-PCI TIMI flow (*A*), CK_{peak} values (*B*), and LVEF (*C*)

The predictive accuracy of the model correlated well with the observed events (93% of correct classification, c-statistics = 0.91, Hosmer–Lemeshow goodness-of-fit $P = 0.94$. To test the stability of the logistic regression model we performed a bootstrap investigation (500 replications) using the same 22 variables tested in the original model. The significant variables in the bootstrap model were those selected in the original analysis and no other significant variable was identified.

Long-term outcome

During a mean follow-up of 724 ± 376 days (range 0–1393), all-cause mortality occurred in 131 patients (17%). *Figure 2* reports Kaplan–Meier long-term survival curves of the four study groups. The I hs-C-reactive protein quartile showed a significantly better survival rate than the other three groups (at 2-year 95% vs. 85% II quartile, vs. 84% III quartile, vs. 68% IV quartile, $P < 0.0001$). Notably, no relevant differences could be observed between the II and III quartile whilst the II and III hs-C-reactive protein quartiles showed better survival when compared with the highest hs-C-reactive protein quartile. *Figures 3* and *4* depict Kaplan–Meier long-term death/MI-free and event-free (death/MI/TVR) survival curves according to the four groups of hs-C-reactive protein. Again, the first hs-C-reactive protein quartile was associated with better clinical outcome (significant higher survival free from non-fatal MI and from non-fatal MI/TVR) than the other three hs-C-reactive protein quartiles. Cox multivariable regression analyses were performed to evaluate independent predictors of long-term outcome (*Tables 4–6*). After adjusting for the confounding effect of baseline and procedural variables (the variables listed in the 'Statistical analysis' of the Methods section), hs-C-reactive protein independently predicted long-term all-cause mortality (HR = 1.04, 95% CI = 1.01–1.07, $P = 0.003$) (*Table 4*), all-cause mortality/MI (HR = 1.03, 95% CI = 1.01–1.06, $P = 0.008$) (*Table 5*) and all-cause mortality/MI/TVR (HR = 1.03, 95% CI = 1.01–1.05, $P = 0.03$) (*Table 6*). Of note, leucocyte counts or fibrinogen serum concentrations did not show any significant adjusted correlation with long-term outcome. As reported in *Table 4*, age, post-PCI LVEF ≤ 35%, heart rate, no GpIIb/IIIa administration, pain-to-balloon time, glucose serum concentration at admission, CPK_{MB} peak and left main or left anterior descending coronary artery as culprit vessel in association with hs-C-reactive protein emerged as independent predictors of long-term all-cause mortality. To test the stability of the Cox proportional hazards regression model we performed a bootstrap investigation (500 replications) using the same 22 variables tested in the original model. The significant variables in the bootstrap model were those selected in the original analysis [with the exception of no GpIIb/IIIa administration ($P = 0.06$) and pain-to-balloon time ($P = 0.07$) that nevertheless demonstrated a strong trend towards statistical significance], with confidence intervals slightly larger than those obtained from the original model. No other significant variable was identified.

Discussion

This study provides evidence that patients with STEMI treated by primary PCI with high hs-C-reactive protein serum concentrations are at high risk of in-hospital and long-term events. Previous studies indicate that high C-reactive protein values are independent risk factors for cardiovascular morbidity and mortality in healthy persons as well as in patients with unstable angina pectoris or severe peripheral vascular disease.[2–4] However, in the setting of STEMI and primary PCI, the C-reactive protein predictive role is not so well established.[6–8] In patients with STEMI treated by thrombolysis[12] an inflammatory state (high leucocyte counts) has been associated with reduced myocardial perfusion and thrombo-resistance. At the same time, C-reactive protein, a well-known acute phase reactant synthesized by the liver when stimulated by cytokines, may play a direct role in promoting the inflammatory component of atherosclerosis[13] and can contribute to

Table 3 **In-hospital clinical adverse events**

	Hs-C-reactive protein I quartile (<0.48 mg/dL) (*n* = 189)	Hs-C-reactive protein II quartile (≥0.48 to <1.2 mg/dL) (*n* = 189)	Hs-C-reactive protein III quartile (≥1.2 to <3.1 mg/dL) (*n* = 191)	Hs-C-reactive protein IV quartile (≥3.1 mg/dL) (*n* = 189)	*P*-value
All-cause mortality	3 (2)	7 (4)	10 (5)	31 (16)	<0.001
Recurrent myocardial infarction	1 (0.5)	0	1 (0.5)	3 (2)	0.376
Target vessel revascularization	2 (1)	2 (1)	2 (1)	2 (1)	1
Stent acute/sub-acute thrombosis	2 (100)	1 (50)	2 (100)	2 (100)	0.446
Stroke	1 (0.5)	3 (1.6)	2 (1)	2 (1)	1
Major bleeding[a]	3 (2)	2 (1)	4 (2)	7 (4)	0.418
Adverse events[b]	7 (4)	13 (7)	16 (8)	39 (22)	<0.001

Data are presented as frequencies (percentages). Hs, high-sensitivity.
[a]Defined as occurrence of intracranial or retroperitoneal bleeding or clinical signs of haemorrhage (including imaging) associated with a drop in haemoglobin of >5 g/dL.
[b]Defined as occurrence of any of the following events: death, new myocardial infarction, target vessel revascularization, stroke, major bleeding.

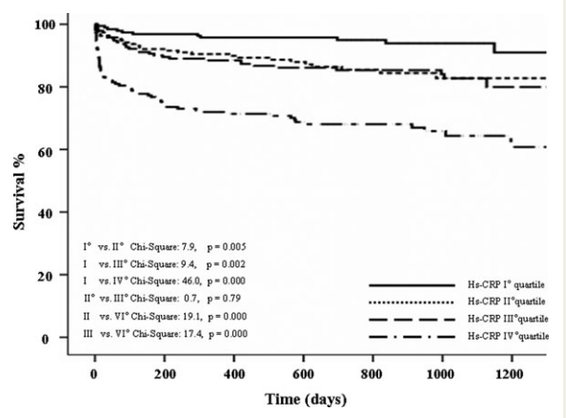

Figure 2 Kaplan–Meier curves depict estimated long-term survival according to hs-C-reactive protein quartiles

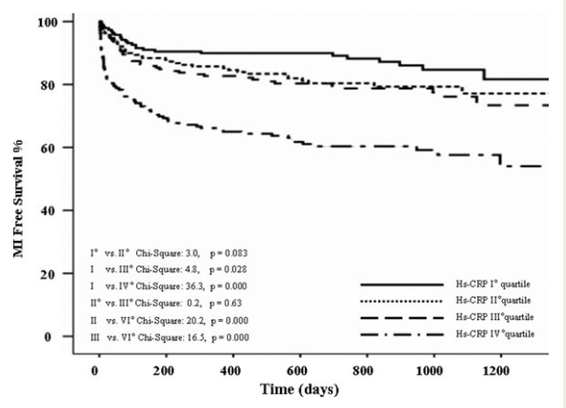

Figure 3 Kaplan–Meier curves depict estimated long-term MI-free survival according to hs-C-reactive protein quartiles

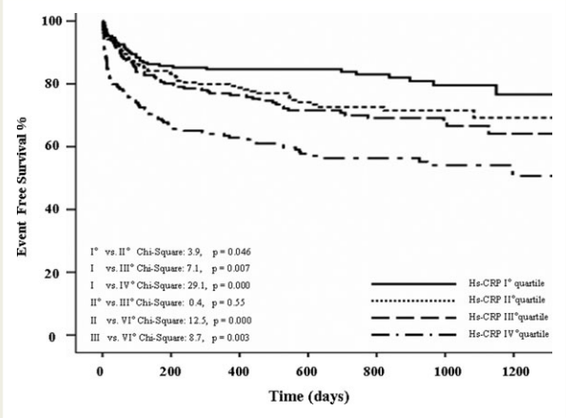

Figure 4 Kaplan–Meier curves depict estimated long-term event-free (from all-cause mortality/MI/TVR) survival according to hs-C-reactive protein quartiles

thrombus formation by inducing monocytes to express tissue factor, a potent procoagulant.[14] In patients with STEMI elevated C-reactive protein levels are related to the presence of ruptured plaques[15] and in this setting hs-C-reactive protein values may be elevated due to the underlying inflammatory process of the atherosclerotic plaque and/or the inflammatory response following myocardial necrosis.[5] Notably, previous studies suggested that C-reactive protein levels within 6 h after the STEMI onset mostly reflect the vulnerability of coronary lesions.[16] In our study, in which the median pain-to-balloon time was about 3 h, only weak relationships were found between hs-C-reactive protein levels and laboratory or instrumental parameters correlated with myocardial damage (i.e. LVEF, CPK_{MB} peak, post-PCI TIMI flow) (*Figure 1*) supporting the hypothesis that in this study hs-C-reactive protein levels were mainly related to a pre-existent inflammatory (coronary) status. Patients in the higher quartile (hs-C-reactive

Table 4 Cox regression analysis of long-term mortality in the overall study population

Variables	HR	95% CI	*P*-value
Age (years)	1.07	1.04–1.09	<0.001
Hs-C-reactive protein (mg/dL)	1.04	1.01–1.07	0.003
Post-PCI LVEF ≤ 35%	1.71	1.09–2.68	0.02
Heart rate (b.p.m.)	1.02	1.01–1.03	0.001
No IIb/IIIa agents administration	1.54	1.01–2.36	0.04
Pain-to-balloon time (min)	1.03	1.01–1.04	0.04
$Glucose_{admission}$ (mg/dL)	1.01	1.004–1.009	<0.001
$CPK_{MB\ peak}$ (U/L)	1.001	1.001–1.002	<0.001
Left main or left anterior descending coronary artery (culprit vessel)	2.38	1.22–4.65	0.01

Only variables reaching $P < 0.05$ at multivariable analysis are listed in the table. HR, hazard ratio; CI, confidence intervals.

Table 5 Cox regression analysis of long-term mortality and re-infarction in the overall study population

Variables	HR	95% CI	*P*-value
Age (years)	1.04	1.03–1.06	<0.001
Hs-C-reactive protein (mg/dL)	1.03	1.01–1.06	0.008
Anterior myocardial infarction	1.79	1.03–3.11	0.037
Post-PCI LVEF ≤ 35%	1.50	1.02–2.21	0.04
Heart rate (b.p.m.)	1.02	1.01–1.03	<0.001
Post-PCI TIMI 3 flow	0.56	0.38–0.84	0.005
Pain-to-balloon time (min)	1.01	1.01–1.02	0.02
$Glucose_{admission}$ (mg/dL)	1.01	1.002–1.006	<0.001
$CPK_{MB\ peak}$ (U/L)	1.001	1.000–1.001	0.001
$Haemoglobin_{admission}$ (g/dL)	0.88	0.81–0.97	0.01
Left main or left anterior descending coronary artery (culprit vessel)	2.46	1.41–4.29	0.001

Only variables reaching $P < 0.05$ at multivariable analysis are listed in the table. HR, hazard ratio; CI, confidence intervals.

protein levels >3.1 mg/dL) showed about 40 min longer pain-to-balloon time. We cannot exclude the possibility that this delay could have influenced hs-C-reactive protein values. However, considering that their median pain-to-balloon time was 236 min (well below the 6 h required by the liver to begin synthesis of C-reactive protein after myocardial infarction), we think that also in the patients included in the IV quartile hs-C-reactive protein values were mainly determined by a higher pre-existent inflammatory state.

Hs-C-reactive protein levels were strongly associated with in-hospital and long-term mortality, providing evidence that C-reactive protein values measured on admission can be considered as a very useful marker for the patient's mortality risk stratification. Furthermore, in agreement with what was recently reported in a small sample size study,[16] in our larger STEMI population (758 patients) treated by primary PCI we confirmed that, after adjustment for known confounders, hs-C-reactive protein values were an independent predictor of in-hospital outcome together with more well-known predictors such as age, post-PCI LVEF, cardiogenic shock, CPK_{MB} peak levels, and glucose serum concentrations at admission, suggesting a direct relationship between hs-C-reactive protein levels and PCI effectiveness in STEMI patients.

Table 6 Cox regression analysis of long-term adverse events in the overall study population

Variables	HR	95% CI	*P*-value
Age (years)	1.04	1.02–1.05	<0.001
Hs-C-reactive protein (mg/dL)	1.03	1.01–1.05	0.03
Cardiogenic shock	1.81	1.03–3.21	0.04
Post-PCI LVEF ≤ 35%	1.75	1.08–1.88	0.02
Heart rate (b.p.m.)	1.01	1.01–1.02	<0.001
Pain-to-balloon time (min)	1.01	1.01–1.02	0.04
$Glucose_{admission}$ (mg/dL)	1.04	1.001–1.005	0.004
$CPK_{MB\ peak}$ (U/L)	1.001	1.000–1.001	0.025
$Haemoglobin_{admission}$ (g/dL)	0.89	0.83–0.97	0.006
Left main or left anterior descending coronary artery (culprit vessel)	2.21	1.36–3.58	0.001

Only variables reaching $P < 0.05$ at multivariable analysis are listed in the table. HR, hazard ratio; CI, confidence intervals.

Notably the present report provides evidence of a close relationship between C-reactive protein value at admission and long-term outcome. In our STEMI patients the risk of death or death/MI or death/MI/TVR within the following 2 years was about six times higher when the hs-C-reactive protein values at admission exceeded 3 mg/L. On the contrary, low hs-C-reactive protein values (<0.48 mg/dL) were associated with a very favourable outcome (predicted 2-year mortality = 5%). Patients in the highest hs-C-reactive protein quartile depicted an unfavourable clinical profile (older age, more depressed left ventricular ejection fraction, higher incidence of cardiogenic shock, higher creatinine and glucose values). It is well known that C-reactive protein increases with age and in patients with renal insufficiency,[17,18] factors that highly influence the survival of STEMI patients. These findings alone could explain the worse clinical long-term outcome observed in patients with high hs-C-reactive protein values. However, after adjusting for all these confounding factors, the association between hs-C-reactive protein and mortality, mortality/MI and mortality/MI/TVR still remained significant, suggesting that at long-term follow-up hs-C-reactive protein could provide independent predictive power, reinforcing evidence that hs-C-reactive protein is not just a marker but most probably a direct mediator of cardiovascular events. This finding seems discordant with previous studies conducted in STEMI patients undergoing primary PCI or thrombolytic therapy in which the association between C-reactive protein values determined shortly after admission and risk of dying at follow-up was largely explained by other baseline clinical variables.[6–8] Several factors such as study population sample size, timing of C-reactive

protein determination, type of C-reactive protein assay (normal vs. high-sensitive), type of reperfusion strategy (PCI vs. thrombolysis) and IIb/IIIa agent treatment could explain this discrepancy. Notably, as reported by Dibra *et al*.,[19] a reperfusion strategy of stenting and administration of abciximab in patients with STEMI could dampen the relationship between C-reactive protein and myocardial damage. The attenuated rise in levels of circulating inflammatory markers after PCI due to the anti-inflammatory properties possessed by abciximab could explain this effect.[20] Most of our patients (84%) were treated with Gp IIb/IIIa agents (74% with abciximab) and this pharmacological strategy could obviously have reduced the C-reactive protein spillover due to myocardial necrosis in our data. It is worth noting that probably because of this IIb/IIIa agent specific effect and the early determination of C-reactive protein (79% within 6 h from symptom onset) in our data, no or only a weak correlation was found between hs-C-reactive protein levels and markers of myocardial damage, thus making C-reactive protein levels correlate more to a pre-existent heightened inflammatory vascular state.

Study limitations

Although not immune from hidden confounding factors and other sources of bias typical of observational studies, this large single centre analysis helps fill out the picture gained from previous published studies. In our study patients with high hs-C-reactive protein values on admission were overall at a higher risk when compared with those with low C-reactive protein levels (older, higher prevalence of diabetes, low LVEF, $\geq$2 Killip class, anterior infarction site, CPK_{MB} release). These confounding factors obviously contributed extensively to the close correlation observed between high hs-C-reactive protein values and in-hospital and long-term clinical outcome. To overcome these noticeable limitations we tried to control for known prognostic factors by means of statistical adjustment (multivariable regression analyses and bootstrap validation of the stability of the multivariable models). However, since the use of adjustment cannot address the problem for unknown or unmeasurable prognostic factors and considering that no type of statistical adjustment can completely overcome the pitfalls of non-randomized comparisons,[21] our results should be interpreted with caution. Due to missing admission hs-C-reactive protein values, 220 patients (220/985, 22%), were excluded from the study. Although this was not a small number of patients, we do not think that the study results were altered because the in-hospital mortality of these patients was similar to that of the 758 patients included in the analysis (7.7% vs. 6.7%, $P = 0.724$). Finally, this study has insufficient power to address the end-point of mortality. For this reason, at long-term follow-up we also tested the association between on admission C-reactive protein values and combined clinical end-point such as death/MI and death/MI/TVR. Although our data showed a close association between C-reactive protein levels and clinical outcome, we think that larger studies are needed to confirm our observations.

Conclusions

This study indicates that patients with STEMI treated by primary PCI with high hs-C-reactive protein serum concentrations are at a high risk of in-hospital and long-term events. Although hs-C-reactive protein high values were associated with a more severe clinical patients profile, potentially negatively influencing survival, our data support the hypothesis that hs-C-reactive protein levels at admission independently predict in-hospital and long-term clinical outcome. Further larger studies are needed to confirm our observations.

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Conflict of interest: none declared.

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Oedema in acute myocardial infarction

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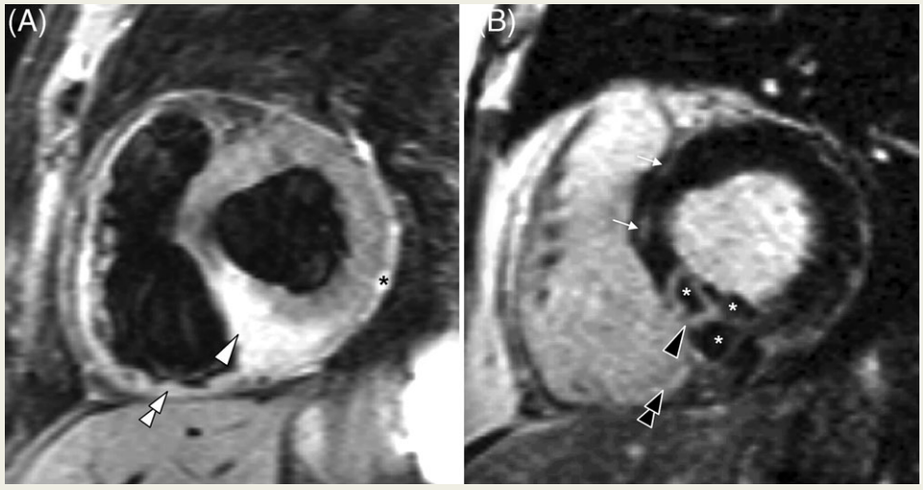

A 61-year-old man presented with inferior ST-segment elevation acute myocardial infarction and underwent prompt thrombolysis. Subsequent invasive coronary angiography revealed an occluded right coronary and no significant epicardial stenosis in the left coronary system. Cardiovascular magnetic resonance (CMR) with a T2-weighted sequence showed a large well-demarcated area of high signal intensity (bright signal) consistent with myocardial oedema of the basal inferior wall (Panel A, single white arrowhead), of the pericardium (Panel A, black asterisk), and of the right ventricle (Panel A, double white arrowhead). Imaging with an inversion recovery T1-weighted sequence 10 min after intravenous gadolinium showed enhancement indicating transmural inferior myocardial infarction (Panel B, single black arrowhead) with a complex pattern of microvascular obstruction (Panel B, white asterisks) and right ventricular myocardial infarction (Panel B, double black arrowhead). The limited bright signal observed in the mid-wall anteroseptum (Panel B, white arrows) represents the membranous portion of the interventricular septum.

The clinical course of the patient was subsequently uneventful and he was discharged with medical therapy after 1 week. CMR is unique in depicting the intramyocardial tissue characteristics of acute infarction.

Panel A. Myocardial oedema of the basal inferior wall.

Panel B. Transmural inferior myocardial infarction with a complex pattern of microvascular obstruction.