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Acute-phase inflammatory markers during myocardial infarction: association with mortality and modes of death after 7 years of follow-up

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Background **The relationship between acute-phase inflammatory markers in the setting of acute myocardial infarction (AMI) and long-term outcomes is largely unexplored.**

Objectives **The aim of the study was to investigate the predictive power of acute-phase inflammatory markers following AMI for short-term and long-term mortality separately and modes of death.**

Methods **In 220 unselected patients with AMI [median age 67 (interquartile range 60–74) years, women 26%], blood neutrophil granulocytes, erythrocyte sedimentation rate, C-reactive protein, and α1-acid glycoprotein were measured 1, 3 and 7 days after admission. All patients completed 7 years of follow-up. Endpoints were 1-year (short-term) and 2- to 7-year (long-term) mortality and modes of death, classified as nonsudden cardiovascular, sudden, and noncardiovascular death.**

Results **The short-term mortality rate was 18%. The long-term mortality rate was 26%. The short-term mortality risk was higher in patients in whom the markers were in the upper tertile. Fully adjusted hazard ratios (and 95% confidence interval) were 3.2 (1.4–7.9), 3.5 (1.7–7.9), 3.5 (1.6–8.6), and 6.1 (2.3–19.1) for neutrophil granulocyte, erythrocyte sedimentation rate, C-reactive protein, and α1-acid glycoprotein, respectively. The excess mortality was chiefly due to nonsudden cardiovascular mortality [fully adjusted hazard ratios were 4.6 (1.7–14.7), 4.7 (1.9–13.7), 5.9 (2.0–21.3) and 5.5 (2.0–17.6), respectively], whereas no association was found with sudden death or noncardiovascular modes of death. In the long term, the association with mortality and modes of death was no longer significant.**

Conclusion **The acute-phase inflammatory markers tested following AMI are independently and concordantly associated with short-term mortality and their prediction is associated only with nonsudden cardiovascular modes of death. These markers are not associated with long-term mortality.** *J Cardiovasc Med* **10:000–000 © 2009 Italian Federation of Cardiology.**

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Keywords: α1-acid glycoprotein, C-reactive protein, inflammatory markers, long-term mortality, myocardial infarction, prognosis, short-term mortality

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Introduction

A number of inflammatory markers acting during acute myocardial infarction (AMI) have been linked to adverse outcomes [1–3]. Of these, C-reactive protein (CRP), an acute-phase reactant that is a component of the primitive innate immune system, is by far the most widely studied [4].

Although most investigations have consistently shown that acute-phase inflammatory markers are associated with early adverse outcomes, studies dealing with long-term prognosis have yielded controversial results [5–9]. Studies performed in subgroups of AMI patients who underwent primary percutaneous transluminal coronary angioplasty showed that admission CRP was independently associated with both in-hospital and long-term global mortality [6,8]. In contrast, negative results were observed by others. Nikfardjam *et al.* [7], in a retrospective evaluation, found that the association between admission CRP and outcomes was largely explained by other baseline clinical variables and, after data adjustment, CRP's predicting power was found to be weakened and nonsignificant. Accordingly, Zebrack *et al.* [9] did not find association between predischarge CRP measurements and death/nonfatal AMI in unselected AMI patients. However, it should be pointed out that in the latter study, the lack of prognostic power could be due to the delayed time of CRP measurement after AMI, when the acute inflammatory process is almost extinguished.

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Furthermore, the association between inflammatory markers and modes of death is largely unknown.

In the present study, we prospectively evaluated an unselected sample of AMI patients and followed them for 7 years. Our aim was to discern whether there was an association between four widely used acute-phase inflammatory markers and overall mortality and modes of death. Survival analysis was performed separately for short-term (within 1 year of follow-up) and long-term (2–7 years) events.

Methods

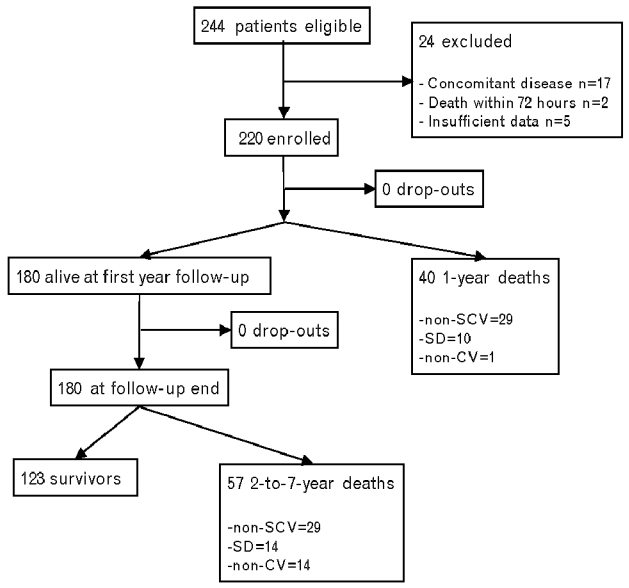
Patients

The present prospective study included 244 consecutive unselected patients admitted with definite AMI to the intensive care units of two general hospitals in north-east Italy from 3 October 1996 to 19 January 1998 (Fig. 1). Twenty-two patients with concomitant inflammatory process, neoplastic disease or incomplete data collection were excluded, as were two patients who died within 72 h of admission (Fig. 1). Thus, the present analysis was performed on 220 patients. The patients were interviewed by a physician who completed a standard record form covering details of past medical history. All of the patients gave their informed consent and the study was approved by the hospitals' ethics committees.

Measurements

All of the baseline clinical and laboratory data were obtained during the first week of hospitalization. In 21 patients, data were not available for the 7th day because of early discharge or death. The criteria for AMI diagnosis were described in detail in a previous report [7]. Blood pressure and heart rate were measured between 07.00 and 08.00 hours, and the mean of three recordings was used. The presence and degree of heart failure was assessed according to the Killip classification [10]. Left ventricular ejection fraction was assessed by two-dimensional echocardiography between the 3rd and 7th day after enrollment according to Simpson's method. Left ventricular ejection fraction was missing for 26 patients who underwent echocardiography after discharge from the intensive care units or for whom the echocardiographic images were technically unsatisfactory. The records were examined by two physicians who had no knowledge of patient clinical data.

Fig. 1



Flow diagram of progress of the patients during short-term and long-term follow-up. Non-CV, noncardiovascular; non-SCV, nonsudden cardiovascular; SD, sudden death.

Inflammatory marker measurement

Venous blood was drawn on the 1st, 3rd and 7th days for measurement of blood levels of neutrophil granulocytes, erythrocyte sedimentation rate (ESR), CRP, and α1-acid glycoprotein (α1-AGP). Neutrophil granulocyte and ESR were measured by means of a standard technique and were expressed as a number/1000 per blood millilitre and as mm of sedimentation in the first hour, respectively. Aliquots of venous blood samples were put on ice and centrifuged within 20 min at 4°C, and the plasma was stored at −20°C (storage time less than 1 month) until assayed for CRP and α1-AGP levels by the nephelometric method (Beckman Instruments, Fullerton, California, USA); both were expressed as mg/l [11].

Follow-up

At assigned time points, 1, 3, 5 and 7 years after recruitment (with 1 week of tolerance forward), each patient was called for a clinical check-up. For patients who had died, all of the available data relevant to the cause of death were collected by means of specific inquiries. For those who died during a hospital stay, the date and cause of death were obtained from public administration and hospital records (including post-mortem reports when available). For those who did not die in a hospital, data were obtained from the family doctor and the death certificate. None of the patients were lost to follow-up, the duration of which was exactly 7 years for all of the patients.

Endpoints

Primary endpoints were overall 7-year mortality, 1-year mortality (we refer to this as short-term mortality) and 2–7-year mortality (long-term mortality). The secondary endpoint was modes of death. Modes of death were classified as nonsudden cardiovascular (non-SCV), sudden, and noncardiovascular death. Sudden death was defined as out-of-hospital, witnessed cardiac arrest or death within 1 h of the onset of acute symptoms or unexpected, unwitnessed death (e.g. during sleep) in patients who were known to have been well in the previous 24 h [12]. All of the deaths were classified by two doctors blinded with regard to baseline information.

Statistical analysis

Statistical analyses were made using the Systat 12 (2008, Chicago, Illinois, USA) and JMP 4.0 for Windows (SAS Institute, 2000, Cary, North Carolina, USA). Comparisons among groups were made by Student's *t*-test or by analysis of variance (ANOVA), with an overall between-group repeated measure ANOVA and Tukey post-hoc tests, wherein data from all three days of observation were simultaneously assessed for continuous variables. Skewed variables were log transformed before analysis. Pearson χ^2 test was used for categorical variables. Survival analysis was performed using Cox proportional regression models, and hazard ratios were derived from the regression coefficients. Survival curves were constructed by the Kaplan–Meier method and compared by log-rank test. The association between variables and modes of death was tested by means of mutivariable polynomial logistic regression. Possible interactions between medications and atrial fibrillation/atrial flutter for mortality were tested in the polynomial regression models. Data are presented as median and interquartiles for continuous measures and as proportion for categorical variables. All *P* values are two-tailed and statistical significance was established as *P* value less than 0.05.

Results

The clinical characteristics of the AMI patients, according to tertiles of CRP on the 3rd day of admission (peak value), are shown in Table 1. Patients' age, sex and risk factor prevalence were similar across tertiles of CRP, though those in the upper tertile had a less-frequent history of angina or previous myocardial infarction. Patients in the upper tertile had longer prehospital time delays, higher creatinine kinase-MB isoenzyme (CK-MB) peak and more-frequent Q-wave AMI, slightly higher heart rates, and more-frequent heart failure. Left ventricular ejection fraction was slightly lower. The other clinical characteristics were similar in the three subgroups. Medications were not significantly different, but the use of angiotensin-converting enzyme (ACE) inhibitors was more frequent in the upper tertile.

In Table 2, inflammatory marker levels in the entire sample, 1, 3 and 7 days after admission are reported; all markers had significant trend changes during the acute phase of myocardial infarction. The four markers were closely correlated with each other. On the 3rd day, log-data, neutrophil granulocyte Pearson *r* coefficient was 0.21 vs. ESR, 0.48 vs. CRP, and 0.46 vs. α1-AGP; ESR $r = 0.49$ vs. CRP and 0.43 vs. α1-AGP; and CRP $r = 0.67$ vs. α1-AGP. Similar correlations were found for 1st and 7th-day data.

Inflammatory markers and mortality

After 7 years of follow-up, 97 (44%) patients had died, 58 (26%) from non-SCV causes, 24 (11%) from sudden death, and 15 (7%) from noncardiovascular causes. Short-term and long-term mortality rates are shown in Fig. 2. The values of the inflammatory markers were significantly higher in those patients who died during the first year of follow-up than in the survivors (repeated measure $P < 0.0001$ for all), whereas marker differences in the patients who died in the long-term were only marginally significant or not significant when compared with survivors (repeated measure $P = 0.05$ for neutrophil

Table 1 Clinical characteristics of patients with acute myocardial infarction according to tertiles of C-reactive protein on the 3rd day (peak value) of admission

Patient characteristics	First tertile ($n = 74$)	Second tertile ($n = 73$)	Third tertile ($n = 73$)	*P*
Age (in years)	67 (57–73)	67 (59–75)	70 (63–76)	0.25
Women	24	27	26	0.91
BMI (in kg/m^2)	25.6 (24.0–29.3)	25.9 (24.3–28.1)	26.6 (24.2–29.7)	0.11
Current smokers	43	37	31	0.33
Hypertension	49	41	52	0.39
Diabetes mellitus	20	26	30	0.38
History of angina	22	8	11	0.04
Previous myocardial infarction	27	11	11	0.01
Time to CCU[a] (in min)	160 (104–300)	150 (120–300)	285 (132–600)	0.0001
CK-MB peak (in IU/l)	91 (55–180)	172 (95–289)	175 (93–320)	<0.0001
Systolic blood pressure (in mmHg)	123 (112–136)	121 (109–130)	122 (110–132)	0.61
Diastolic blood pressure (in mmHg)	72 (65–82)	75 (66–84)	75 (68–83)	0.62
Heart rate in bpm (range)	68 (60–80)	70 (60–80)	75 (63–84)	0.06
Total cholesterol (in mg/dl) (range)	218 (181–246)	212 (176–237)	197 (171–237)	0.14
Plasma creatinine (mg/dl)	0.95 (0.86–1.10)	0.94 (0.85–1.07)	1.02 (0.87–1.23)	0.13
Q wave AMI	58	70	86	0.001
Heart failure (1st week)	34	34	49	0.09
Left ventricular ejection fraction (%) ($n = 194$)	52 (44–62)	50(41–60)	46 (38–56)	0.08
Thrombolysis	50	53	40	0.22
Antiplatelets	99	94	94	0.34
Anticoagulants	100	100	99	0.36
β-Blockers	53	55	40	0.14
ACE inhibitors	30	33	49	0.03
Statins	9	3	4	0.16

ACE, angiotensins-converting enzyme; AMI, acute myocardial infarction; CCU, coronary care unit; CK-MB, creatinine kinase-MB isoenzyme. [a] Time from onset of symptoms to arrival at coronary care unit. Values are median and interquartile ranges or percentage.

Table 2 Inflammatory marker levels during acute myocardial infarction in 220 patients

Inflammatory marker	1st day	3rd day	7th day	*P* value per trend
Neutrophils (× ml/1000)	7.5 (5.7–10.0)	5.0 (4.0–6.9)	3.9 (2.9–5.1)	<0.0001
Erythrocyte sedimentation rate (mm/h)	12 (6–22)	26 (13–49)	34 (22–68)	<0.0001
C-reactive protein (mg/l)	6.5 (3.3–22.3)	37.0 (12.7–83.5)	11.6 (5.0–36.1)	<0.0001
α-1 Acid glycoprotein (mg/l)	90 (76–111)	108 (90–132)	116 (94–141)	<0.0001

granulocyte, $P=0.05$ for ESR, $P=0.06$ for CRP, and $P=0.37$ for α1-AGP).

As mortality trends across the three measurements of each marker were similar, in the present paper only 3rd-day data are provided. At the univariable level, overall 7-year mortality rate was higher in the upper tertile for all markers. Figure 3a shows the Kaplan–Meier curves for overall mortality by α1-AGP tertiles (we chose to show this marker because it had the highest hazard ratio at multivariable analysis), and similar trends were observed also for the other three markers. However, although short-term mortality rate was strongly higher in the upper tertile, in the long-term period, the differences across tertiles were no longer significant (Fig. 2).

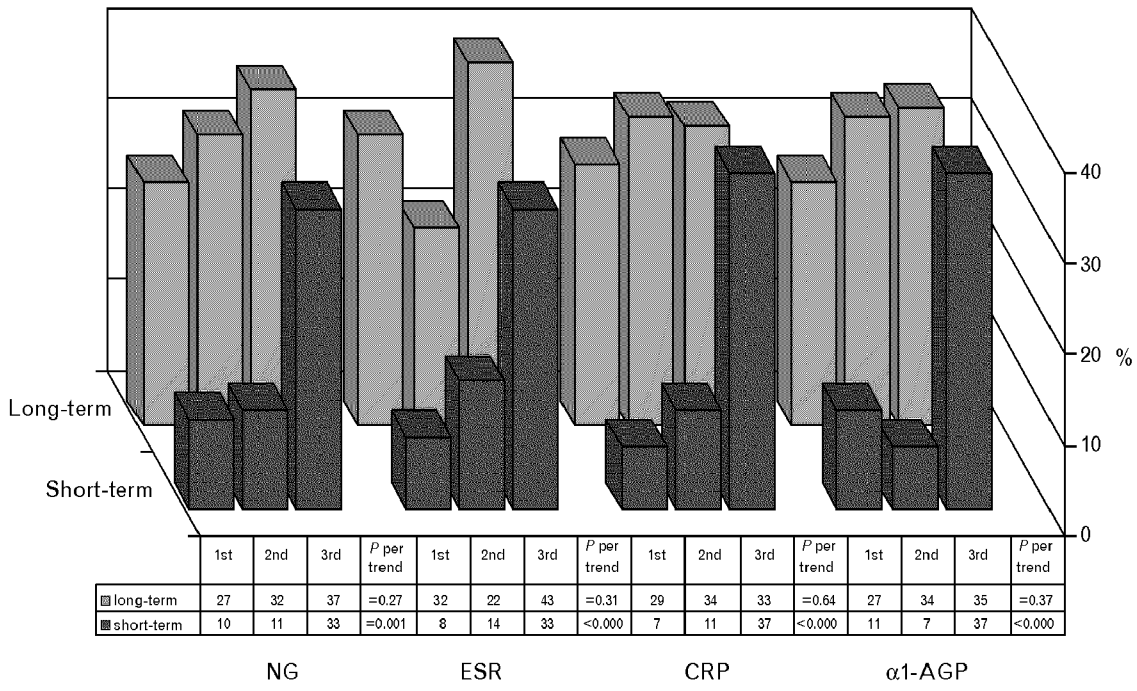
Survival analysis of all-cause mortality

Of the 18 clinical variables significantly associated with 7-year overall mortality at the univariable level, or believed to be of prognostic relevance (reported in Table 3), six were independently associated with global mortality and were considered to be the parsimonious model to test with the inflammatory markers (Table 3).

Univariable Cox analysis showed that patients in the upper tertile of all inflammatory marker levels had an increased risk of overall 7-year mortality (data not shown). When short-term and long-term periods were examined separately, inflammatory markers were found to be associated with short-term outcomes, but not with long-term outcomes (except ESR, which was associated also with long-term mortality; Table 4). After adjusting for the six confounding variables reported in Table 3, we found that all of the markers were independently associated with overall 7-year mortality; again, however, the association was significant only for short-term and not for long-term mortality (Table 5). Inclusion of left ventricular ejection fraction in the multivariable models did not modify the results.

We obtained similar results censoring the patients who had died within 1 year rather than excluding them from the survival analysis (data not shown). The same analysis using the 1st or 7th-day data yielded similar results (data not shown). Using continuous variable values instead of tertiles gave virtually identical associations with outcomes (data not shown).

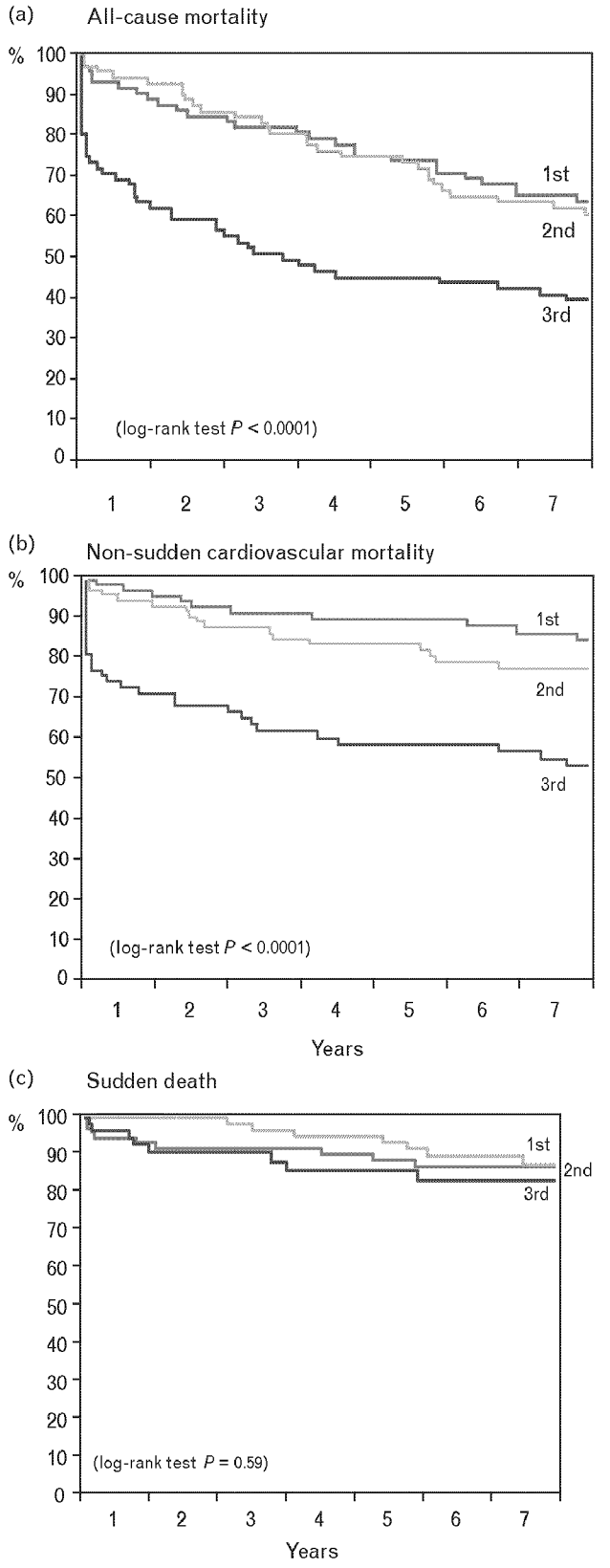
Fig. 2



	NG				ESR				CRP				α1-AGP			
	1st	2nd	3rd	*P* per trend	1st	2nd	3rd	*P* per trend	1st	2nd	3rd	*P* per trend	1st	2nd	3rd	*P* per trend
long-term	27	32	37	=0.27	32	22	43	=0.31	29	34	33	=0.64	27	34	35	=0.37
short-term	10	11	33	=0.001	8	14	33	<0.000	7	11	37	<0.000	11	7	37	<0.000

Association of short-term and long-term all-cause mortality rate with tertiles of inflammatory markers measured 3 days after admission. α1-AGP, α1-acid glycoprotein; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NG, neutrophil granulocytes.

Fig. 3



Kaplan–Meier estimates of probability of (a) overall, (b) nonsudden cardiovascular, and (c) sudden death through 7-year follow-up in the patients, stratified by tertiles of α1-acid glycoprotein measured on the 3rd day after admission.

Table 3 Adjusted hazard ratios for all-cause mortality in the parsimonious multivariable models

	Short-term mortality HR (95% CI)	Long-term mortality HR (95% CI)
All-cause mortality		
Age	3.4 (1.5–8.6)	2.9 (1.6–5.3)
Diabetes (yes/no)	2.1 (1.1–4.0)	1.8 (1.0–3.3)
Heart failure (first week) (yes/no)	3.2 (1.5–7.3)	1.1 (0.6–1.9)
Time to coronary care unit	1.4 (0.6–3.1)	1.8 (1.1–3.5)
Creatinine	2.3 (1.1–6.0)	1.2 (0.7–2.4)
Previous myocardial infarction (yes/no)	0.7 (0.3–1.5)	2.4 (1.2–4.6)

For continuous variables, upper vs. lower tertile HR. The 18 clinical variables significantly associated with overall mortality at the univariable level or believed to be of prognostic relevance (from which the parsimonious model was drawn) were age, sex, BMI, sedentary lifestyle, current smoking, history of hypertension, presence of diabetes, previous myocardial infarction, history of angina, prehospital time delay, non-ST elevation myocardial infarction, creatinine kinase-MB isoenzyme (CK-MB peak), creatinine, Killip class, systolic blood pressure, heart rate, atrial fibrillation and tachyarrhythmias. CI, confidence interval; HR, hazard ratio.

Survival analysis of modes of death

At univariable level, neutrophil granulocyte, ESR, CRP, and α1-AGP were associated with non-SCV mortality, whereas no association was found with sudden death or noncardiovascular mortality. Figure 3b and c report the Kaplan–Meier curves for α1-AGP across 7 years of follow-up for non-SCV mortality and sudden death, respectively. After full adjustment, all of the markers remained significantly associated only with non-SCV mortality (Table 5). Indeed, for non-SCV mortality, the association was significant only in the short-term period (Tables 4 and 5). Finally, we analyzed the possibility of interaction between inflammatory markers and the variables of the parsimonious Cox model (reported in Table 3) and medications (reported in Table 1). We did not find an interaction between the inflammatory markers and these variables at either univariable or multivariable level (data not shown).

Discussion

The present prospective study shows that acute-phase inflammatory markers, following AMI, are associated

Table 4 Unadjusted hazard ratios for all-cause mortality and nonsudden cardiovascular mortality, based on inflammatory markers measured on the 3rd day after hospitalization

	Short-term mortality HR (95% CI)	Long-term mortality HR (95% CI)
All-cause mortality		
Neutrophils	3.7 (1.7–8.7)	1.2 (0.6–2.2)
Erythrocyte sedimentation rate	2.9 (1.4–6.3)	2.3 (1.2–4.6)
C-reactive protein	4.0 (1.9–9.4)	1.0 (0.5–1.9)
α-1 Acid glycoprotein	6.7 (2.8–19.7)	1.1 (0.6–2.0)
Nonsudden CV mortality		
Neutrophils	4.8 (1.9–14.4)	1.3 (0.5–2.9)
Erythrocyte sedimentation rate	3.9 (1.7–10.7)	1.5 (0.6–3.6)
C-reactive protein	6.3 (2.4–21.6)	1.4 (0.5–3.6)
α-1 Acid glycoprotein	5.1 (2.1–15.2)	1.6 (0.7–3.6)

Hazard ratios are for the highest vs. the lowest tertile. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Table 5 Hazard ratios for all-cause mortality and nonsudden cardiovascular mortality in fully adjusted multivariable models, based on inflammatory markers measured on the 3rd day after hospitalization

	Short-term mortality HR (95% CI)	Long-term mortality HR (95% CI)
All-cause mortality		
Neutrophils	3.2 (1.4–7.9)	1.3 (0.7–2.6)
Erythrocyte sedimentation rate	3.5 (1.7–7.9)	1.8 (0.9–3.7)
C-reactive protein	3.5 (1.6–8.6)	0.8 (0.4–1.7)
α-1 Acid glycoprotein	6.1 (2.3–19.1)	1.2 (0.6–2.4)
Nonsudden CV mortality		
Neutrophils	4.6 (1.7–14.7)	1.6 (0.6–3.9)
Erythrocyte sedimentation rate	4.7 (1.9–13.7)	1.2 (0.5–3.0)
C-reactive protein	5.9 (2.0–21.3)	1.4 (0.5–3.9)
α-1 Acid glycoprotein	5.5 (2.0–17.6)	1.8 (0.7–4.6)

Hazard ratios are for the highest vs. the lowest tertile. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

with short-term, but not with long-term mortality. Furthermore, all of the markers were associated with non-SCV death, whereas no associations were found with either sudden death or noncardiovascular mortality. The prediction of outcomes was independent of important baseline clinical variables and medications.

It is noteworthy that neutrophil granulocyte, ESR, CRP, and α1-AGP all show concordant association with both time of death and modes of death. This concordance strengthens the idea that the inflammatory process accompanying AMI is associated only with non-SCV adverse outcomes occurring within a relatively short time after AMI.

The inflammatory response accompanying AMI is a complex, highly orchestrated process involving a number of acute-phase proteins, modulators and intercellular signaling molecules [4]. A body of evidence supports a central role for inflammation in all phases of the atherosclerotic process. Inflammatory pathways are implicated in early atherogenesis, the progression of lesions and thrombotic complications of the disease [13].

Short-term and long-term prognosis

In the setting of AMI, a number of inflammatory markers have been consistently linked with short-term prognosis, whereas results regarding long-term prognosis are discordant [2,5–9,14,15]. This is a crucial issue when using these markers in the risk stratification of AMI patients. Unlike other important predictive variables, such as age, presence of diabetes and left ventricular ejection fraction, which are independently associated with both short-term and long-term outcome after AMI, the inflammatory response to AMI, heralded by the acute-phase inflammatory markers, appears to carry prognostic information only in the short-term period [16–19].

The mechanism underlying this observation is unknown; however, our data support the hypothesis that the lack of association with long-term mortality is not due to the weight of the other variables used in the multivariable survival analyses, as even at univariable level, inflammatory markers were not associated with long-term mortality. The mechanistic basis of the CRP–atherosclerosis connection may lie in the ability of CRP to directly modulate the production of endothelium-derived vasoactive factors. It has been shown that CRP can profoundly downregulate the production of nitric oxide, the central 'controller' of cardiovascular homeostasis [20,21]. Nevertheless, there are still very few data regarding the link between the acute inflammatory process and coronary artery disease progression over time, and this issue remains largely to be elucidated [22].

Inflammatory markers and modes of death

Our study shows that the ability of inflammatory markers to predict mortality relates to only non-SCV mortality, whereas no association was found with sudden death or noncardiovascular death. Inflammatory markers can be viewed as a proxy for the intensity of the inflammatory reaction caused by the ischemic insult occurring during AMI [20]. Indeed, these markers were significantly associated with lower thrombolysis in myocardial infarction (TIMI) flow grades and more extensive coronary atherosclerosis, suggesting that inflammatory markers only predict deaths due to the progression of atherosclerotic disease [21]. We did not find an association with sudden death. To our knowledge, this is the first study showing a net difference in the relationship between inflammatory markers and non-SCV mortality and sudden death, because most studies consider total cardiovascular mortality, irrespective of whether it is sudden or not.

Limitations of the study

The main limitation of the present study is the relatively low number of patients enrolled and it could be speculated that the lack of association between inflammatory markers and long-term mortality can be due to underpower of the study, chiefly for the low rate of sudden death. Further confirmatory studies with larger cohorts of patients would be warranted. However, our data showed that all-cause short-term mortality, even including fewer events than long-term mortality (40 vs. 52 overall deaths), was strongly associated with outcome. Accordingly, also non-SCV mortality, which had the same figures in the short-term and long-term, showed a significant difference in the association with inflammatory markers in the two periods. Indeed, our study at least demonstrates a strong difference in predictive power of the inflammatory markers over time.

In conclusion, the present study shows that the acute-phase inflammatory markers tested following AMI are independently and concordantly associated with short-term, but not with long-term mortality. The excess of mortality predicted is chiefly associated with non-SCV

mortality, whereas these markers failed to predict sudden death and noncardiovascular death.

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