**Prognostic Value of Tumor Necrosis Factor-Alpha in Patients With ST-Segment Elevation Acute Myocardial Infarction**

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**Introduction and objectives.** Tumor necrosis factor-alpha (TNFα) is implicated in a variety of inflammatory processes, including cardiovascular disease. Little is known about the prognostic value of TNFα in patients with ST-segment elevation myocardial infarction (STEMI). The aim of this study was to determine the prognostic value of TNFα in this clinical setting at 6-month follow-up.  

**Methods.** The levels of TNFα, C-reactive protein (CRP), interleukin 6, and type 1 soluble intercellular adhesion molecules measured within the first 10 h of symptom onset and at 48 h in 74 consecutive patients admitted with STEMI. The relationships between these levels and the incidence of ischemic events (ie, angina, reinfarction, and death), heart failure (HF), or both (ie, all cardiovascular events) were studied.  

**Results.** Overall, TNFα levels were significantly higher in patients who had an ischemic event or HF than in those who did not (P<0.02 for both). At 48 h, the adjusted odds ratios of those in the highest TNFα quartile (2.92 pg/mL) for the development of ischemic events, HF, and all cardiovascular events combined were 13.1, 9.59, and 9.75, respectively. A TNFα level of 2.04 pg/mL at 48 h had a sensitivity of 78% and a specificity of 72.5% in predicting a cardiovascular event of any form. The CRP level, but not the TNFα level, at admission was found to be an independent predictor of the development of a cardiovascular event.  

**Conclusions.** In patients with STEMI, the plasma TNFα level 48 h after symptom onset and the CRP level at admission were independent predictors of cardiovascular events.  

**Key words:** Myocardial infarction. Prognosis. Inflammation. Interleukins. Tumor necrosis factor alpha.

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**Valor pronóstico del factor de necrosis tumoral alfa en pacientes con infarto agudo de miocardio con elevación del segmento ST**

**Introducción y objetivos.** Entre la variedad de procesos inflamatorios que implican al factor de necrosis tumoral alfa (TNFα), se encuentra la enfermedad cardiovascular. Su valor pronóstico en el infarto agudo de miocardio con elevación del segmento ST (IAMEST) es poco conocido. Este estudio trata de determinar el valor pronóstico del TNFα en este marco clínico tras 6 meses de seguimiento.  

**Métodos.** Se midieron las concentraciones de TNFα, proteína C-reactiva (PCR), interleucina 6 y moléculas solubles de adhesión celular tipo 1 en las primeras 10 h tras el inicio de los síntomas y tras 48 h en 74 pacientes con IAMEST. Se correlacionaron sus valores con la incidencia de eventos isquémicos (angina, reinfarto y muerte), insuficiencia cardíaca o ambos (eventos cardiovasculares).  

**Resultados.** Los valores de TNFα fueron significativamente mayores en pacientes con eventos isquémicos o insuficiencia cardíaca que en aquellos sin eventos (p < 0,02 para todos). A las 48 h, las odds ratio (OR) ajustadas para el último cuartil de TNFα (2,92 pg/ml) eran OR = 13,1; OR = 9,59 y OR = 9,75 para el desarrollo de eventos isquémicos, insuficiencia cardíaca y eventos cardiovasculares combinados, respectivamente. La concentración de TNFα a las 48 h de 2,04 pg/ml tuvo una sensibilidad del 78% y una especificidad del 72,5% en la predicción conjunta de dichos eventos. Al ingreso, la PCR, pero no el TNFα, mostró valor predictivo independiente en el desarrollo de eventos cardiovasculares.  

**Conclusiones.** En pacientes con IAMEST, la concentración plasmática de TNFα a las 48 h y la PCR al ingre-
so son predictores independientes de eventos cardiovasculares.

**Palabras clave:** Infarto de miocardio. Pronóstico. Inflamación. Interleucinas. Factor de necrosis tumoral alfa.

### ABBREVIATIONS

- CRP: C-reactive protein
- IL-6: interleukin 6
- LVEF: left ventricular ejection fraction
- PCI: percutaneous coronary intervention
- sICAM-1: soluble intercellular adhesion molecule-1
- TNFα: tumor necrosis factor alpha

### INTRODUCTION

Inflammation plays a key role in the pathogenesis of atherosclerosis, and is involved, on the one hand, in the genesis, development, rupture, and repair of atherosclerotic plaque and, on the other, in post-reperfusion damage, remodeling, and scarring of myocardial tissue. It is also known that an exacerbated inflammatory state plays a role in the development and progression of heart failure.

Tumor necrosis factor alpha (TNFα) is an inflammatory cytokine synthesized in various blood, endothelial and smooth muscle cells, and in cardiac myocytes. The ubiquity and function of its 2 receptors provide it with the capacity to modulate a diversity of inflammatory processes which are strongly involved in acute coronary syndrome (ACS) and in the development of heart failure due to its negative inotropic action, among others. Several lines of research have indicated that it is an independent predictor of mortality in patients with heart failure and advanced functional class, as well as in the chronic phase of myocardial infarction (MI). The synthesis of TNFα increases in the myocardium during acute myocardial ischemia and, although it is known that its concentrations in blood increase rapidly, little information is available concerning its prognostic value.

The aim of the study was to determine if early concentrations of TNFα, at admission and 48 h, together with those of C-reactive protein (CRP), interleukin 6 (IL-6) and soluble intercellular adhesion molecule-1 (sICAM-1) were predictors of ischemic events or heart failure in patients with ST segment elevation myocardial infarction (STEMI) during 6-month follow-up.

### METHODS

#### Patients

Between June 2001 and January 2003, 74 consecutive patients admitted to a single center were enrolled in the study. They were aged between 36 and 86 years old, and were diagnosed with STEMI (prolonged precordial pain for more than 30 min accompanied by persistent ECG ST-segment elevation ≥1 mm in at least 2 contiguous limb leads or ≥2 mm in at least 2 precordial leads, together with double the upper limit of creatine kinase and increased concentrations of CK-MB or troponin I). The study was approved by the hospital’s ethics committee and all the participants gave signed informed consent.

Patients were excluded if more than 10 h had passed since pain onset, they were undergoing statin therapy, had undergone a previous infarction, were in cardiogenic shock at admission or if they presented some infectious disease, immune disease, or neoplasm. Five patients under study presented chronic ischemic heart disease, although none had undergone previous revascularization. Echocardiographic study was conducted between the fourth and sixth day after admission and at 6 months. The control group consisted of 38 subjects adjusted for age and sex (63 [11] years; 28 men) and none presented acute disease, chronic disease, or were under medication; their case history, physical exploration and ECG were normal at the time of inclusion.

#### Blood Analysis

A venous blood sample was taken from the 74 patients at admission (within the first 10 h after symptom onset) and at 48 h, and a single sample from the control group. The serum was frozen at ~80°C for later analysis. The concentrations of TNFα, IL-6, and sICAM-1 were measured using ELISA kits according to the manufacturer’s instructions (R&D Systems, Minneapolis, USA) as well as CRP concentrations (Generic Assays, Dahlewitz, Germany). The sensitivities and intrasample variation and intersample variation of TNFα, IL-6, sICAM-1, and CRP were 0.12 pg/mL, <8.8%, and <12.6%; 0.7 pg/mL, <4.2%, and <6.4%; 0.35 ng/mL, 4.8%, and 10.1%; 0.56 mg/L, 5.7%, and 13.6%, respectively. Concentrations of TNFα were also determined at discharge (seventh day). Events were allocated by the researchers who were blinded to the results of the blood analysis.

#### Cardiovascular Events

The cardiovascular events were divided into 2 groups: ischemic events (angina, reinfarction, and death) and heart failure. Cardiovascular events refers to the set of combined ischemic and heart failure events, in which case the first one that occurred was recorded if both were present. Angina was defined as oppressive precordial pain associated with electrocardiographic changes occurring at admission or follow-up, excluding inducible angina during risk stratification tests. Infarction was defined at follow-up as prolonged clinical angina with...
an increase of double or more than double the upper limit of CK and concomitant CK-MB or troponin I elevation. Death was classified in all cases as death of cardiac origin (as no other cause of death occurred during the study period). The ischemic events that occurred during coronary intervention were not recorded as clinical events. Finally, heart failure was diagnosed if the patient presented Killip class II-IV.

**Statistical Analysis**

Continuous variables were expressed as mean and standard deviation and discrete variables as percentages. Non-normally distributed variables were expressed as interquartile range (IQR), represented as the difference between the 25th and 75th percentiles. The Student t test was used to compare the means between continuous variables and the Mann-Whitney test for nonparametric variables. The Friedman test was used to study TNFα samples. Percentages were compared using the χ² test. Correlations were analyzed using the Pearson correlation test for normal distributions or the Spearman ρ for nonparametric variables. The area under the receiver-operating characteristic (ROC) curve was constructed to compare the sensitivity and specificity of a given TNFα value to predict events. A multivariate binary logistic regression analysis was conducted; the dependent variable was the incidence of cardiovascular events and the independent variables (with logarithmic transformation) were those with P<.05 in the univariate analysis plus the body mass index (BMI), due to its known association with the inflammatory state, and white blood cell count at admission. The severity of coronary disease was excluded from this analysis as this datum was not available for all patients. To better understand the data, 2 models were used in the analysis; one using continuous variables and another regarding their presence within the fourth quartile. All analyses were 2-tailed and a P-value <.05 was considered significant. The statistical analysis was conducted using the SPSS statistical package (version 10.05, SPSS, Chicago, Ill., USA).

The sample size was calculated setting alpha risk at .05, beta risk at .20 in a 2-tailed test, a cardiovascular event rate in the group with TNFα below the fourth quartile (28%), and a relative risk of events in the group with TNFα within the fourth quartile (2.5), assuming a 5% loss of patients during follow-up. The calculation was performed using GRANMO 5.0 for Windows software (Barcelona, Spain).

**RESULTS**

Table 1 shows the characteristics of the study population and the patients with cardiovascular events and those without events. At admission, 58 (78%) patients underwent primary percutaneous coronary intervention, and TIMI III flow was obtained in all cases. Primary PCI was not performed in 16 patients; of these, coronary angiography indicated ischemia in 10 and revascularization after the acute phase.

During 6-month follow-up, 31 (41.9%) patients had a cardiovascular event (21 at admission and 10 new events during follow-up); 22 (29.7%) had an ischemic event; of these, there were 9 (12.2%) deaths, always of cardiac origin (5 during hospitalization, although not in the first 48 h), and there was 3 reinfarctions (4%) and 10 cases of angina (13.5%); 19 (25.7%) presented heart failure during hospitalization (61% of the women and 14.3% of the men), 9 (12.2%) were in Killip class II, 8 (10.8%) in Killip class III, and 2 (2.7%) cases of Killip class IV developed after admission; 7 continued in NYHA functional class II, but there were no new cases of heart failure during follow-up.

Table 2 shows the concentrations of cytokines (TNFα and IL-6), sICAM-1, and CRP in the control group and patients. These values were higher in the patients than in the control group for all the variables under study except in the case of TNFα at admission. Its concentrations on the seventh day were 2.52 (1.81-3.40) pg/mL. These concentrations were different in the 3 study samples (Friedman test, P<.001), the highest levels being recorded on the seventh day.

With the exception of sICAM-1 concentrations, all levels were greater in patients with cardiovascular events than in those without events, as shown in Table 3 and, more specifically, in Table 4, which shows the concentrations of these parameters according to the cardiovascular event. As shown, TNFα concentrations were greater in the patients with ischemic events or heart failure both at admission and at 48 h. Specifically, TNFα concentrations were analyzed in the group of 9 patients who died. At admission, these values were not significantly greater in this group compared to those in the surviving patients (2.74 [1.1-3.78] pg/mL and 1.64 [0.79-2.16] pg/mL, respectively; P=.11). Nevertheless, at 48 h, TNFα concentrations were indeed significantly greater in the patients who died than in surviving patients (3.69 [2.61-4.39] and 1.87 [1.33-2.47] pg/mL; P=.002) with a univariate risk of death 4.5 (95% confidence interval [CI], 2.41-8.73; P<.0001) if TNFα values were in the fourth quartile (>2.92 pg/mL).

In a multivariate analysis (adjusted for age, sex, diabetes, blood pressure, smoking, creatinine, white blood cell count, BMI, previous treatment with acetylsalicylic acid, left ventricular ejection fraction (LVEF), and CRP, TNFα, and IL-6 concentrations at admission and 48 h), only TNFα concentrations at 48 h and CRP concentrations at admission were independent predictors of ischemic events, heart failure, or both (Table 5). The white blood cell count at admission was a predictor of ischemic events, and LVEF, diabetes, and female sex were clinical predictors of heart failure. Table 6 shows that only CRP concentrations at admission and...
TABLE 1. Characteristics of the Population and the Patients With or Without Cardiovascular Events

<table>
<thead>
<tr>
<th>Variables</th>
<th>All Variables (n=74)</th>
<th>Cardiovascular Events (n=31)</th>
<th>Without Cardiovascular Events (n=43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>65 (11)</td>
<td>70 (7)</td>
<td>62 (11)</td>
<td>.001</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>56 (76)</td>
<td>20 (64)</td>
<td>36 (84)</td>
<td>.05</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>23 (31)</td>
<td>15 (48)</td>
<td>8 (19)</td>
<td>.006</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>31 (42)</td>
<td>16 (52)</td>
<td>15 (35)</td>
<td>.15</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>33 (45)</td>
<td>7 (22)</td>
<td>26 (60)</td>
<td>.002</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>18 (24)</td>
<td>5 (16)</td>
<td>13 (30)</td>
<td>.17</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27 (3)</td>
<td>27 (4)</td>
<td>28 (3)</td>
<td>.63</td>
</tr>
<tr>
<td>Previous ischemic heart disease, n (%)</td>
<td>5 (6.8)</td>
<td>3 (9.3)</td>
<td>2 (4.8)</td>
<td>.64</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>23 (31)</td>
<td>15 (48)</td>
<td>8 (19)</td>
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</tr>
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<td>5 (6.8)</td>
<td>3 (9.3)</td>
<td>2 (4.8)</td>
<td>.64</td>
</tr>
</tbody>
</table>

Previous medication, n (%)

- Acetylsalicylic acid: 13 (17.5) vs. 9 (29); P = .035
- Beta-blockers: 3 (4) vs. 1 (3.2); P = .15
- ACE inhibitors: 14 (18.9) vs. 9 (29); P = .08

Table 1: Comparison of characteristics between patients with and without cardiovascular events.

TABLE 2. Cytokine, sICAM-1, and CRP Concentrations in the Control Group and Study Population (Median and Interquartile Range)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (n=38)</th>
<th>Patients (n=74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα, at admission, pg/mL</td>
<td>1.51 (.97-1.84)</td>
<td>1.72 (.92-2.25)</td>
<td>.271</td>
</tr>
<tr>
<td>TNFα, at 48 h, pg/mL</td>
<td>2.02 (1.39-2.92)</td>
<td>2.02 (1.39-2.92)</td>
<td>.01</td>
</tr>
<tr>
<td>IL-6, at admission, pg/mL</td>
<td>.92 (.03-7.9)</td>
<td>10.9 (6-18.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IL-6, at 48 h, pg/mL</td>
<td>18.4 (9.7-36.54)</td>
<td>24.3 (20.2-31.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CRP, at admission, mg/L</td>
<td>1.6 (.7-2.5)</td>
<td>2.4 (1.3-6)</td>
<td>.04</td>
</tr>
<tr>
<td>CRP, at 48 h, mg/L</td>
<td>24.3 (20.2-31.6)</td>
<td>27.9 (23.3-323.4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

sICAM-1 indicates type-1 soluble intercellular adhesion molecule; IL-6, interleukin 6; CRP, C-reactive protein; TNFα, tumor necrosis factor alpha.

*Compared using nonparametric tests.
TNFα concentrations at 48 h were significantly elevated in the patients who had cardiovascular events during admission and follow-up.

Receiver operating characteristic analysis of TNFα concentrations at admission and 48 h showed a greater area under the curve (95% CI) in the sample taken at 48 h than that at admission (80 [68.7-89.6] and 67.7 [55.2-80.1]). A cutoff value for TNFα of 2.04 pg/mL at 48 h had a sensitivity of 78% and a specificity of 72.5% in predicting cardiovascular events at follow-up (Figure 1). If the cutoff value was 2.92 pg/mL, corresponding to the beginning of the last quartile, specificity was 93% although diagnostic sensitivity was lost (53.8%). Figure 2 shows the distribution of TNFα concentrations at 48 h in relation to whether there were cardiovascular events or not.
The TNFα concentrations recorded at 48 h were significantly negatively correlated with LVEF ($ρ$=–0.416; $P<.001$); this correlation was maintained at 6 months among the 65 surviving patients ($ρ$=–0.256; $P=.039$). In addition, there was a positive correlation between TNFα concentrations and IL-6, sICAM-1, and CRP concentrations at admission ($ρ=0.269$, $P=.02$; $ρ=0.444$, $P<.001$; and $ρ=0.286$, $P=.01$, respectively), and after 48 h ($ρ=0.309$, $P=.007$; $ρ=0.163$, $P=.1$; and $ρ=0.418$, $P=.001$, respectively).

**DISCUSSION**

Tumor necrosis factor alpha is an inflammatory cytokine present in the peripheral blood of patients with chronic ischemic heart disease and ACS. Its negative inotropic action and the association between its concentrations and the grade of heart failure are well known. It is synthesized not only in the inflammatory cells of the arterial wall and circulating blood, in the infarction area and its vicinity, but also in healthy myocardium, which indicates that it is involved in some way in cardiac remodeling after MI. It has also been directly associated with myocardial damage after ischemia/reperfusion, oxidative stress in patients with STEMI, myocardial rupture and chronic ventricular dysfunction, apoptosis, and peripheral endothelial dysfunction. Taking these data into account, the prognostic value of TNFα concentrations measured at admission and 48 h was analyzed in a group of patients with STEMI using a sample extraction protocol that had not been studied previously.
The main finding of the study is that TNFα concentrations 48 h after symptom onset in patients with STEMI is an independent predictor of cardiovascular events at 6-month follow-up. There was also a negative correlation with LVEF and a positive correlation with other inflammatory markers of recognized prognostic value. These results were obtained in a population with a number of events that, although apparently high, are very similar in terms of percentages to those found in other studies.9,10

The results show that TNFα concentrations were greater in the patients than in the control group at 48 h and at 7 days, but not at admission. There could be 2 reasons for this: the early extraction of the first sample, in the first 10 h of pain onset, which is in line with experimental data that show gradual TNFα synthesis from the onset of ischemia or necrosis;1 and the low incidence of heart failure2 (predominantly Killip class III) plus the exclusion of patients in cardiogenic shock at admission. This information, together with the lack of predictive value of TNFα concentrations at admission in the patients who died, suggests that such an early sample is unlikely to be of prognostic use. Another study also reports similar results3 regarding the limited predictive value of TNFα concentrations at admission. There is a later increase in its concentrations, which may be of prognostic value; this increase may indicate that TNFα is associated with postinfarction ventricular remodeling. However, although data are available on the potential role of TNFα in remodeling,5,12 it remains to be clarified whether its concentrations are simply a marker or if it has a key role in promoting remodeling. In this regard, it is interesting to consider the possibility that apoptosis may be core to postinfarction remodeling17 and that soluble TNFα receptor levels may correlate with apoptosis in patients with dilated cardiomyopathy.15

The prognostic value of TNFα has been studied in patients with heart failure and coronary heart disease. Several studies on heart failure have identified it either as an independent predictor of mortality4 or have strongly suggested this role.18 In patients with chronic coronary heart disease, the CARE (Cholesterol And Recurrent Events) study reported an almost 3-fold increase in events if TNFα concentrations 9 months postinfarction were in the 95th percentile. Interestingly, the mean and median TNFα values in this study (2.7 pg/mL and 2.5 pg/mL, respectively) are similar to those obtained in our series at day 7 (2.77 pg/mL and 2.52 pg/mL, respectively). This may indicate that “chronic” TNFα plasma concentrations could already be measured 7 days postinfarction; however, no samples were taken after this point in time. In the acute phase of STEMI, increased TNFα concentrations were associated with heart failure, arrhythmias and major alterations in left ventricular wall motion and perfusion measured by thallium scintigraphy in a study with 50 patients.18 In another study,4 TNFα receptor-I values at admission, but not TNFα itself, were independent predictors of death and heart failure in a group of patients with ACS (151 with STEMI). However, TNFα values were not analyzed later, unlike in the present study. The prognostic value of TNFα receptor-I has also been reported in patients with chronic heart failure.5,7

In our series, the values of the 2 samples of TNFα, CRP, and IL-6 were greater in the patients who had cardiovascular events than those who did not. The multivariate analysis showed that TNFα concentrations at 48 h were independent predictors of ischemic events and heart failure. As mentioned above, another study9 found that TNFα concentrations at admission are not independent predictors of death and heart failure; in contrast, CRP concentrations at admission are in fact predictors of these events, as described in the literature.20 The white blood cell count at admission is also an independent predictor of ischemic events when its values are in the fourth quartile (>13 300); similar data have been reported in other series of patients with STEMI.21 The clinical variables female sex, diabetes, and LVEF were predictors of heart failure, but not of ischemic events; these variables have already been identified as indicators of poor prognosis.22,23 At admission and 48 h, IL-6 concentrations were not independent predictors of events despite its known predictive value in patients with non-ST-segment elevation acute coronary syndrome.24 Thus, in line with these results, a practical strategy in the use of biomarkers in this population may be the early measurement of CRP concentrations and TNFα concentrations at 48 h.

The ROC curves for TNFα indicate a greater area under the curve for samples taken at 48 h; at this time the sensitivity and specificity in predicting cardiovascular events are moderate (around 75%) if the cutoff point is set at 2.04 pg/mL. Nevertheless, greater TNFα concentrations, corresponding to the beginning of the fourth quartile (2.92 pg/mL), are of greater clinical interest, since they have high specificity (93%), thereby reducing the number of false positives at diagnosis. Similar results have been reported for TNFα receptor type-1 at admission in patients with STEMI.9 In addition, our results are in line with those for markers of hemodynamic stress, such as B-type natriuretic peptide (BNP) in patients with STEMI. In one study,25 the relative risk for the last quartile of BNP of death, reinfarction and heart failure, and ROC curves (sensitivity 75% and specificity for a cutoff point of 40 pg/mL) are very similar to the results for TNFα in our series. Further studies should clarify with greater accuracy the prognostic value of the two groups of biomarkers.

Finally, it is difficult to define the significance of increased TNFα concentrations in this population. In the context of predicting heart failure, TNFα concentrations at 48 h could be a reflection of myocardial...
damage in the ischemic territory and cardiac remodeling, as indicated by its negative correlation with LVEF and the findings of several lines of research. As a predictor of ischemic events, similar to high CRP concentrations, it may reflect a concomitant exacerbated inflammatory state and positively correlate with other markers (IL-6, CRP and sICAM-1), all of which are involved in the inflammatory cascade and that pathophysiologically induce the development and progression of atherosclerotic disease.

**Limitations**

Our results, and in particular the multivariate analysis, should be interpreted with caution due to the sample size. On the other hand, although multivessel disease was a predictor of events in the univariate analysis, the fact of not knowing the coronary anatomy of all the patients hinders understanding the association between multivessel disease, biomarkers, and cardiovascular events. Nevertheless, a multivariate analysis that only included these patients (n=67) showed that multivessel disease is another predictor of ischemic events and total cardiovascular events (P<.001).

**CONCLUSIONS**

In the patients with STEMI, our results indicate that peripheral blood TNFα concentrations 48 h from pain onset, together CRP concentrations at admission, are independent predictors of ischemic events and heart failure at 6-month follow-up. At this time, TNFα concentrations correlate with LVEF and other inflammatory markers with known prognostic value.

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