Systemic Inflammatory Response Syndrome Predicts Mortality in Acute Coronary Syndrome without Congestive Heart Failure

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Introduction: High levels of inflammatory biochemical markers are associated with an increased risk among patients with acute coronary syndrome (ACS). The objective of the current study was to evaluate the prognostic significance of the systemic inflammatory response syndrome (SIRS) among ACS patients with no clinical or radiological evidence of congestive heart failure (CHF).

Methods: Consecutive patients with ACS and no clinical or radiological evidence of CHF in the emergency department (ED) were included in the study. The endpoint was hospital mortality. Categorical variables were compared by calculating proportions with 95% confidence intervals (CIs) and by using the Fisher Exact test. Continuous variables were compared by using the Wilcoxon Rank Sum test. The association of the variables with hospital mortality was assessed by using the logistic regression analysis.

Results: The study included 196 patients (60 years; female 32.6 %). Six patients (3.1 %) died in hospital and 22 patients (11.2 %) had SIRS on admission to the ED. The following variables were predictors of hospital mortality: age with an odds ratio (OR) of 1.1 (95% CI, 1-1.2) for each one additional year ($p < 0.01$), systolic arterial pressure with an OR 0.9 (95% CI, 0.9-1), diastolic arterial pressure with an OR 0.9 (95% CI, 0.8-1) for each one additional mmHg ($p < 0.01$), respiratory rate with an OR 1.5 (95% CI, 1.2-1.9) for each one additional breath per minute ($p < 0.01$), and SIRS with an OR 9 (95% CI, 1.7-47.8) (p 0.02). Because of the small number of events, it was not possible to assess the independence of these risk factors.

Conclusion: SIRS was a marker of increased risk of hospital mortality among patients with ACS and no clinical or radiological evidence of CHF. [West J Emerg Med. 2010; 11(4):373-378.]

INTRODUCTION

There is increasing evidence supporting the pathogenic role of inflammation in acute coronary syndrome (ACS).[1-4] The local inflammatory process at the coronary artery plaque may cause the release of cytokines and other inflammatory acute-phase reactants into the circulation.[5] Indeed, some evidence suggests that an independent systemic inflammatory process, apart from the local one, may also be involved in the pathogenesis of ACS.[6] Clinical manifestation of systemic inflammation is known as systemic inflammatory response syndrome (SIRS), which may be seen in infections and a variety of other conditions.[7,8] The diagnosis of SIRS is based on heart rate, respiratory rate, body temperature, and leukocyte count.[7]

Effective triaging of ACS patients is one of the main subjects of investigation in emergency medicine. One investigation line focuses on the subjacent inflammatory process as a prognostic factor. It has been demonstrated that high plasma levels of inflammatory biochemical markers are associated with an increased risk of major cardiac events in

ACS patients.[5, 9–11] However, while these biochemical markers are not routinely available in the emergency department (ED), SIRS may be easily assessed in almost every ACS patient. We hypothesized that SIRS could be a prognostic marker among ACS patients. Since tachycardia and tachypnea, two of the diagnostic criteria of SIRS, are strongly associated with congestive heart failure (CHF),[12] we excluded ACS patients with clinical or radiological evidence of CHF.

The objective of the current study was to evaluate SIRS in the ED as a predictor of hospital mortality among ACS patients with no clinical or radiological signs of CHF.

METHODS

Study design

This prospective cohort study included ACS patients consecutively admitted to the ED between February 2003 and January 2004. The study was approved by the local Institutional Research Board. The outcome was hospital mortality.

Study setting and population

The study was conducted in an urban teaching hospital with 13 ED beds. The ED sees more than 86,000 patients per year. Consecutive patients aged more than 21 years old with confirmed diagnosis of ACS were enrolled in the study. All patients provided an informed consent. Patients with clinical or radiological signs of CHF were excluded from the study.

Study protocol

Medical history, physical exam, a 12-lead electrocardiogram, leukocyte count in peripheral blood and a chest radiograph were performed in every patient. The electrocardiogram was repeated in case of recurrent symptoms. Leukocytes were counted by using an automated cell counter as per standard laboratory techniques. Each patient had two or more determinations of plasma cardiac troponin I, one of them performed at least 12 hours after the onset of the symptoms. Cardiac troponin I concentrations were measured by chemiluminescence assay, using an ACS: 180 automated analyzer (Bayer Diagnostics™) with a detection limit of 0.1 ng/ml and a cut-off value for myocardial necrosis of 0.5 ng/ml. Other diagnostic procedure and therapeutic strategies were decided by the medical team in charge of the patient. Data collection forms included medical history, clinical examination on admission to the ED and complementary tests (laboratory assays, stress test, myocardial perfusion test or coronary angiography) performed during hospitalization.

SIRS was defined by the presence of at least two of the following criteria: 1) heart rate >90 beats/minute, 2) respiratory rate >20 breaths/minute, 3) body temperature >38°C or <36°C, and 4) leukocyte blood count >12 x 10^3/mm^3 or < 4 x 10^3/mm^3.

The final diagnosis of acute myocardial infarction (AMI), unstable angina (UA), and CHF were independently assigned by two cardiologists based on the following definitions.

A final diagnosis of AMI was confirmed in the presence of two or more measurements of plasma cardiac troponin I above the cut-off value for myocardial necrosis (>0.5 ng/ml).

A final diagnosis of UA was made in the presence of at least one of the following criteria: 1) two or more determinations of plasma cardiac troponin I within the range of myocardial injury (0.1 – 0.5 ng/ml), 2) ischemic abnormalities in at least two contiguous leads on the initial electrocardiogram (transient ST-segment depression ≥0.5 mm, transient ST-segment elevation ≥1 mm, or T-wave inversion ≥2 mm), or 3) any evidence of severe coronary artery disease on complementary studies performed during hospitalization (a positive exercise stress test or cardiac perfusion test, or a coronary angiography demonstrating any severe stenosis in a major branch).

The diagnosis of CHF was based on physical exam reports (jugular venous distension, third sound, or pulmonary rales) and initial chest radiography (pulmonary edema). Echocardiography was not available in the ED.

In case of disagreement, a third cardiologist determined the final diagnosis. Inter-rater agreement was not evaluated.

Data analysis

On the basis of a previous report,[13] 120 patients were required to detect a 2.9% (95% confidence interval [CI], 0-5.9%) of hospital mortality rate among ACS patients with no CHF on admission to the hospital.

Categorical variables were reported by using proportions and continuous variables by using medians and interquartile range (IR). Categorical variables were compared by calculating proportions with 95% CIs and by using the Fisher Exact test. Continuous variables were compared by using the Wilcoxon Rank Sum test. Abnormal values for body temperature and leukocyte count draw a U-shaped curve; therefore they were analyzed as dichotomized variables ("normal"/"abnormal"). The logistic regression analysis was used to determine how factors predicted hospital mortality. The odds ratios (ORs) for in-hospital mortality and the 95% CIs were derived by using the asymptotic standard error of the estimate. Software package Excel™ version 2000 (Microsoft™ Corporation, 1999) was used for data base management and Statistix™ version 7.0 (Analytical Software™) was used for all calculations.

RESULTS

Description of the population

During the study period 255 ACS patients were evaluated in the ED. 59 (23.1%) patients had clinical or radiological signs of CHF and were excluded. The study population comprised of 196 patients (76.9%). Population characteristics

are shown in Table 1. The final diagnosis was AMI in 73 patients (37.2%) and UA in 123 patients (62.8%).

Main results

Six patients (3.1%) died in hospital. The comparison between survivors and non-survivors is shown in Table 2. The variables age, systolic and diastolic blood pressure, ST-segment elevation, and SIRS demonstrated a statistically significant difference between survivors and non-survivors. Because of the small number of events, it was not possible to assess the independence of these risk factors.[14]

22 patients (11.2%) had SIRS. The mortality rate was 13.6% (95% CI, 0-28) among patients with SIRS and 1.7% (95% CI, 0-3.7) among patients without SIRS [risk ratio (RR) 7.9, 95% CI, 1.7-36.8] ($p < 0.01$). The AMI rate was not statistically different between both groups of patients: 40.9% (95% CI, 20.3-61.3) among patients with SIRS and 36.8% (95% CI, 29.6-43.9) among patients without SIRS (RR 1.1, 95% CI, 0.6-1.9) (p 0.7).

Table 1. Baseline characteristics of 196 patients with acute coronary syndrome and no clinical or radiological signs of congestive heart failure in the emergency department.

Continuous variables	Median	IRQ
Age (years)	60	51-70
Categorical variables	**N**	**%**
Demographic data		
Female	64	32.6
Medical history		
Hypertension	124	63.3
Diabetes mellitus	21	10.7
Cigarette smoking	118	60.2
Dyslipidemia	52	26.5
Coronary artery disease	84	42.9
Chronic stable angina	49	25.0
Myocardial infarction	41	20.9
Percutaneous coronary angioplasty	20	10.2
Coronary artery bypass surgery	13	6.60
Stroke	7	3.60
Peripheral artery disease	12	6.10
Previous treatment		
Aspirin	66	33.7
Beta-blockers	64	32.6
Calcium-channel-blockers	25	12.8
Angiotensin converting enzyme inhibitors	54	27.6
Nitrates	34	17.4
Statins	9	4.60
Diuretics	14	7.10

IRQ, interquartile range

DISCUSSION

In the current study, ACS patients with SIRS on admission to the ED were at an increased risk of hospital mortality, compared with ACS patients without SIRS. SIRS was a predictor of mortality along with traditional risk factors, such as age, blood pressure, or ST-segment elevation.

Inflammation plays a central role in the development of atherosclerosis and in the process of plaque rupture in ACS.[15] Acute phase reactants of inflammation may increase in plasma, which has been shown to provide prognostic information among ACS patients.[16]

SIRS may be caused by the activation of the immune system[8] in patients with an infectious disease;[17-19] however, SIRS can develop in other non-infectious conditions, including traumatic injuries,[20,21] critical surgeries,[22,23] burns,[20] or pancreatitis.[24] To our knowledge, the current study is the first to evaluate the prevalence and prognostic significance of SIRS among ACS patients. In a previous study, Rangel-Frausto et al[25] showed that the prevalence of SIRS in a general ED was 25 to 64%. In our study, only 11.2% of patients had SIRS. However, prevalence of SIRS in our study might have been higher if patients with CHF had not been excluded because tachycardia and tachypnea are common clinical manifestations in this condition.[12] Rangel-Frausto el al [25] reported that 32 to 64% of patients with SIRS developed sepsis during hospitalization. Patients in our study did not develop any infectious disease within 72 hours after admission to the hospital; therefore, infection did not appear to have been involved in the pathogenesis of SIRS among our patients. ACS patients with SIRS were at an increased risk for hospital mortality. This finding is consistent with the findings of previous studies, which showed that SIRS was a marker of increased risk of death among patients with intestinal bleeding,[18] critical surgeries[23] and acute pancreatitis.[24]

Two of the components of SIRS, tachycardia[26-30] and high leukocyte count,[31-33] are well-known markers of risk in ACS patients.

In summary, SIRS may contribute to stratify the risk of ACS patients with no clinical or radiological signs of CHF in the ED.

LIMITATIONS

This study has important limitations. First, the standard definition of SIRS is strict and excludes patients with mild distortion of the inflammatory parameters.[34] Moreover, the biochemical markers of inflammation other than leukocytes, such as C-reactive protein, fibrinogen, interleukin-6, tumor necrosis factor α may be more accurate for establishing an inflammatory state than the measurement of non-specific clinical parameters.[8] However, the objective of this study was to evaluate the prognostic significance of classical SIRS, which may be easily determined in the ED setting.

Second, it could be hypothesized that tachypnea and tachycardia had been subtle signs of CHF, [12, 35] a marker of increased risk among ACS patients.[13, 36-39] We could not strictly evaluate this hypothesis because other complementary studies, such as echocardiography or plasma B-type natriuretic factor,[39] were not available in the ED.

Table 2. Comparison of baseline characteristics, emergency department variables and final diagnosis between non-survivors (n=6 patients) and survivors (n=190 patients).

	Non-survivors (3.1%)	Survivors (96.9%)	OR	95% CI	P
Continuous variables (median [IQR])					
Demographic data					
Age (years)	76 (67-80)	59 (51-69)	1.1	1-1.2	<0.01
Physical exam					
Systolic pressure (mmHg)	104 (93-117)	130 (118-152)	0.9	0.9-1	<0.01
Diastolic pressure (mmHg)	60 (46-68)	80 (70-86)	0.9	0.8-1	<0.01
Heart rate (beats/minute)	73 (60-107)	71 (60-80)	1	1-1.1	0.6
Respiratory rate (breaths/minute)	23 (22-28)	20 (18-21)	1.5	1.2-1.9	<0.01
Temperature (ºC)	36.1 (36-36.2)	36.2 (36-36.5)	0.1	0-9.5	0.3
Laboratory					
Leukocyte count (x 10^3/mm^3)	10.3 (7.9-13.8)	8.5 (7-11.3)	1	1-1	0.2
Categorical variables (% [95% CI])					
Demographic data					
Female	50 (18.8-81.2)	32.1 (25.9-39.1)	2.1	0.4-10.8	0.4
Medical history					
Hypertension	66.7 (30-90.3)	63.2 (56.1-70)	1.2	0.2-6.5	1
Diabetes mellitus	0*	11.1 (7.3-16.3)	0	*	0.6
Cigarette smoking	50 (18.8-81.2)	60.5 (53.4-67.2)	0.7	0.1-3.3	0.7
Dyslipidemia	0*	27.4 (21.5-34.1)	0	*	0.2
Coronary artery disease	16.7 (3-56.4)	43.7 (36.8-50.8)	0.3	0-2.2	0.2
Chronic stable angina	16.7 (3-56.4)	25.3 (19.6-31.9)	0.6	0.1-5.2	0.6
Myocardial infarction	16.7 (3-56.4)	21.1 (15.9-27.4)	0.8	0.1-6.6	1
Percutaneous coronary angioplasty	0*	10.5 (6.9-15.7)	0	*	0.6
Coronary artery bypass surgery	0*	6.8 (4-11.4)	0	*	1
Stroke	0*	3.7 (1.8-7.4)	0	*	1
Peripheral artery disease	0*	6.3 (3.7-10.7)	0	*	1
Electrocardiogram					
Left bundle complete block	16.7 (3-56.4)	3.2 (1.5-6.7)	6.1	0.6-60.9	0.2
Q waves	66.7 (30-90.3)	41.1 (34.3-48.2)	2.9	0.5-16.1	0.4
Inverted T-waves	50 (18.8-81.2)	56.8 (49.7-63.9)	0.8	0.1-3.9	1
ST-segment depression	66.7 (30-90.3)	31.1 (24.9-38)	4.4	0.8-24.9	0.09
ST-segment elevation	83.3 (43.7-97)	33.2 (26.9-40.1)	10.1	1.2-88.1	0.02
Final diagnosis					
Acute myocardial infarction	83.3 (43.7-97)	35.8 (29.3-42.8)	9	1-78.4	0.03
Systemic inflammatory response					
Systemic inflammatory response syndrome	50 (18.8-81.2)	10 (6.5-15.1)	9	1.7-47.8	0.02
Increased heart rate	33.3 (9.7-70)	10.5 (6.9-15.7)	4.3	0.7-24.7	0.1
Increased respiratory rate	83.3 (43.7-97)	24.7 (19.2-31.3)	15.2	1.7-133	<0.01
Abnormal temperature	0*	0.5 (0.1-2.9)	0*	*	1
Abnormal leukocyte count	50 (18.8-81.2)	21.6 (16.3-28)	3.6	0.7-18.7	0.1

Continuous variables are reported by using medians and interquartile ranges (IQR) and compared by using the Wilcoxon Rank Sum test. Categorical variables are reported by using percentages and 95% confidence intervals (CI) and compared by using the Fisher Exact test. The odds ratios (ORs) were calculated by using bivariate logistic regression analyses.
*Exact confidence levels were not estimated because of zero count cells.

Third, the increase in heart or respiratory rate may have been associated with fear or anxiety, [40] which are frequently triggered by pain.[41] Consequently, it is possible to speculate that persistent chest pain, an ACS risk marker, [42] rather than inflammation was the cause of tachycardia and tachypnea in our study. However, in a clinical setting, Marco et al[43] did not identify any significant association between pain score and vital signs among more than 1000 ED patients, including 80 with AMI.

Fourth, the frequency of abnormal body temperature was low in our study (only one patient), despite the fact that fever has been described as a common finding after an AMI.[44] Previous studies[45-48] reported serial body temperature determinations among AMI patients, while our study reported

only the first determination in the ED among patients across all ACS subsets. Gabriel et al[49] attributed the fever to a systemic inflammatory response, a conclusion supported by the concomitant rise of acute phase reactants.

Finally, the independence of the risk factors could not be assessed because the number of events was small.[14]

CONCLUSION

The presence of SIRS on the admission to the ED was a marker of increased risk of hospital mortality among ACS patients with no clinical or radiological evidence of CHF.

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