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Original Article

The Potential Role of Serum Procalcitonin and Coronary Angiographic Findings in Patients With Acute Coronary Syndromes Evaluated by the SYNTAX Score

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ABSTRACT

Background: Inflammation is crucial to the pathophysiology of atherosclerosis and adverse cardiac events. We aimed to investigate serum procalcitonin levels and SYNTAX scores in subgroups of patients with acute coronary syndromes (ACSs).

Methods: This cross-sectional study recruited patients admitted for ACSs and categorized them into 3 groups: ST-elevation myocardial infarction (STEMI), non–ST-elevation myocardial infarction (NSTEMI), and unstable angina. Serum procalcitonin and C-reactive protein were measured. The study population underwent percutaneous coronary intervention; then, SYNTAX scores were analyzed.

Results: The STEMI (64.86%) and NSTEMI (46.86%) groups were more likely to have positive procalcitonin than the unstable angina group (11.11%) (P =0.002). The mean procalcitonin level was significantly higher in the STEMI group (0.95 ± 0.47) than in the NSTEMI (0.62 ± 0.30) and unstable angina (0.05 ± 0.30) groups (P =0.001). SYNTAX scores were statistically significant in the 3 groups (P =0.004). Multivariate regression analysis indicated significant relationships between procalcitonin levels and ACS subgroups (β = -0.28, P =0.001), triple-vessel disease (β =0.07, P = 0.010), all-cause in-hospital mortality (β = 0.68, P =0.003), and the SYNTAX score (β = 0.72, P =0.004).

Conclusions: Serum procalcitonin may be associated with coronary artery disease severity measured with the SYNTAX score. Future studies should evaluate the prognostic accuracy of procalcitonin levels in patients with ACSs. ***(Iranian Heart Journal 2023; 24(3): 77-84)***

KEYWORDS: Procalcitonin, Coronary artery disease, STEMI, Proinflammatory cytokines, Myocardial infarction

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Acute coronary syndromes (ACSs), consisting of ST-elevation myocardial infarction (STEMI), non–ST-elevation myocardial infarction (NSTEMI), and unstable angina, continue to be one of the leading causes of mortality and morbidity worldwide despite the developments in medical science for their

early diagnosis and management. [1] ACSs are caused primarily by atherosclerosis, which is the buildup of plaque around the inner walls of arteries. [2]

Currently, inflammation is considered to play a key role in the pathophysiology of atherosclerosis and adverse cardiac events. [3] For instance, although C-reactive protein (CRP) levels rise in response to a variety of nonspecific inflammatory conditions, there is growing evidence that high-sensitivity CRP (hs-CRP) can be a predictive biomarker for cardiovascular risk assessment. [4]

Another inflammatory biomarker implicated in atherosclerosis is procalcitonin. Procalcitonin is the precursor of calcitonin and is produced primarily by medullary thyroid C-cells in response to hypercalcemia. Moreover, other sources like peripheral blood mononuclear cells, lymphocytes, monocytes, and macrophages of the liver are regarded as other procalcitonin secretors. [5] High levels of procalcitonin are found in severe bacterial infections and sepsis; nonetheless, procalcitonin also presents in non-bacterial inflammation like trauma, cardiothoracic or abdominal surgery, and cardiogenic shock. [6] Previous studies have investigated the possible relationship between ACSs and procalcitonin, but the results are contradictory. While multiple studies have indicated elevated levels of serum procalcitonin in patients with ACSs, [7-9] others have shown that serum procalcitonin levels are not related to ACSs. [10,11] The current study aimed to investigate serum procalcitonin levels and SYNTAX (SYNergy between percutaneous coronary intervention [PCI] With Taxus and coronary artery bypass surgery [CABG]) scores in subgroups of patients with ACSs.

METHODS

The present cross-sectional study was conducted in Dr Shariati Hospital, affiliated with Tehran University of Medical Sciences, Iran, from January 2020 through December 2021. The sample size was calculated via the following formula

$$N = (Z\ 1-\alpha/2)2 \times P\ (1-P)/d2$$

by considering a level of confidence of 95% (z =1.96), a 10% margin of error, a d (precision) of 0.06, and a P (expected prevalence) of 0.3, resulting in a desired sample size of 81. A dropout rate of 30% was estimated, and 105 patients were included in the study. However, 10 patients refused to enroll in the study.

A simple random sampling method was utilized. Eligible patients were those who were admitted for ACSs by expert cardiologists based on Harrison's guidelines [12] and were older than 18 years. Patients who did not consent to participate and those with a history of inflammatory, immunological, and/or infectious diseases were excluded. Infective processes were excluded from all the participants by clinical examinations and microbiological tests, such as blood and urine cultures. Individuals who did not meet the exclusion criteria were included and categorized into 3 groups: STEMI, NSTEMI, and unstable angina. Venous blood samples were taken for procalcitonin and other laboratory tests on the first day of admission. Electrocardiography was performed for the entire study population on admission. All the patients underwent PCI via the standard femoral approach. Each coronary artery was depicted on at least 2 separate planes. Two highly experienced interventional cardiologists, blinded to other clinical and laboratory data, analyzed the SYNTAX score. [13] Finally, in-hospital and 30-day outcomes were assessed.

Data Collection

Patients were identified with a numerical code to ensure anonymity. The collected

clinical information included demographic data, personal history, previous interventional catheterization and/or heart surgery, kidney or lung disease, laboratory test data (biochemistry, hemograms, inflammatory parameters, kidney function, lipid panels, and cardiac biomarker), and echocardiographic findings. The collected information was recorded in a Microsoft Excel spreadsheet and subsequently imported and processed in IBM SPSS, version 22.

Statistical Analysis

The normality of data distribution was assessed both visually and with the Kolmogorov-Smirnov normality test. Categorical variables were compared using the χ^2 or Fisher exact test for variables with low anticipated values and expressed as frequencies and percentages. Continuous variables were compared using the Kruskal-Wallis test. The categorical variables were presented as numbers (percentages), and continuous variables were presented as mean ± standard deviation. A *P* value of less than 0.05 was considered statistically significant. Regression analysis was performed to explore the association between procalcitonin and other variables in patients with ACSs. All the statistical analyses were performed with SPSS, version 22.

Ethics

All the experimental protocols involved in the current study were approved by the Ethics Committee of Tehran University of Medical Sciences (ID: IR.TUMS.THC.REC.1399.047). Written informed consent was obtained from the entire study population before enrollment. All the patients were candidates for PCI during the study.

RESULTS

Ninety-five patients, composed of 37 women and 58 men, with a diagnosis of ACSs were enrolled. The patients were divided into 3 groups: 37 patients (38.94%) in the STEMI group, 31 patients (32.63%) in the NSTEMI group, and 27 patients (28.42%) in the unstable angina group. Baseline characteristics, clinical manifestations, and laboratory findings were compared between the STEMI, NSTEMI, and unstable angina groups.

Table 1 presents the baseline characteristics of the studied patients. No statistically significant differences existed between the 3 groups concerning age (*P* =0.712), sex (*P* =0.061), a history of diabetes mellitus (*P* =0.743), hyperlipidemia (*P* =0.369), and a history of previous PCI (*P* =0.166). However, the 3 groups were different from each other in terms of blood pressure (*P* =0.016), the mean fasting blood sugar value (*P* =0.023), cholesterol (*P* =0.001), low-density lipoprotein (*P* =0.012), troponin I (*P* =0.001), the erythrocyte sedimentation rate (ESR) (*P* =0.001), and CRP (*P* =0.003). The status of cigarette smoking (*P* =0.590) and opium use (*P* =0.261) was not different between the 3 groups.

The STEMI (64.86%) and NSTEMI (46.86%) groups were more likely to have positive procalcitonin than the unstable angina group (11.11%) (*P* =0.002). The mean procalcitonin value in the STEMI group (0.95 ± 0.47) was significantly higher than that in the NSTEMI group (0.62 ±0.30) and the unstable angina group (0.05 ± 0.30) (*P* =0.001).

Moreover, the SYNTAX score was statistically significant in the 3 groups (*P* =0.004). Considering an optimal cutoff of 34, [14] the proportion of patients who had SYNTAX scores equal to or greater than 33 was higher in the STEMI group (45.94%) than in the NSTEMI (9.67%) and unstable angina (7.40%) groups.

In the 30-day follow-up duration, 3 deaths occurred in the STEMI group, and 1 death occurred in the NSTEMI group. Additionally, acute lung edema was reported in 2 patients

in the STEMI group, 3 in the NSTEMI group, and 3 in the unstable angina group.

As depicted in Table 2, the univariate linear regression modeling of the procalcitonin level showed that ACS subgroups, triple-vessel disease, all-cause in-hospital mortality, and the SYNTAX score were the best predictors.

After adjustments for relevant confounding factors, such as age, sex, hypertension, diabetes mellitus, and hyperlipidemia, multivariate regression analysis indicated significant relationships between procalcitonin levels and ACS subgroups ($\beta = -0.28$, $P = 0.001$), triple-vessel disease ($\beta = 0.07$, $P = 0.010$), all-cause in-hospital mortality ($\beta = 0.68$, $P = 0.003$), and the SYNTAX score ($\beta = 0.72$, $P = 0.004$).

Table 1: Demographic, clinical, and laboratory findings in the enrolled patients

Parameter	STEMI	NSTEMI	UA	*P* value
Age	63.7 ± 9.4	63.4 ± 8.8	62.2 ± 8.7	0.712
Sex				0.061
male	22 (59.45%)	21 (67.74%)	15 (55.55%)	
female	15 (40.54%)	10 (32.25%)	12 (44.44%)	
History				
Diabetes mellitus	14 (37.83%)	11 (35.48%)	8 (29.62%)	0.743
Hypertension	28 (75.67%)	19 (61.29%)	13 (48.14%)	0.016
Hyperlipidemia	20 (54.05%)	14 (45.16%)	12 (44.44%)	0.369
Angiography history	9 (24.32%)	7 (22.58%)	5 (18.51%)	0.166
Cigarette smoking	23 (62.16%)	20 (64.51%)	18 (66.66%)	0.590
Opium use	6 (16.21%)	7 (22.58%)	4 (14.81%)	0.261
Laboratory Findings				
FBS	193 ± 84	154 ± 59	144 ± 73	0.023
Creatinine	1.3 ± 0.3	1.1 ± 0.2	1.1 ± 0.4	0.472
BUN	33.57 ± 12.27	31.63 ± 11.70	31.99 ± 10.83	0.508
TG	164.8 ± 55.7	152 ± 75.2	157.8 ± 8.4	0.994
Cholesterol	224.6 ± 111.3	187.2 ± 90.3	173.8 ± 48.8	0.001
LDL	123.4 ± 39	104.5 ± 42.2	105.3 ± 36.9	0.012
HDL	32.1 ± 6.8	34.4 ± 11.7	32.9 ± 7.1	0.525
Troponin I	4.3 ± 2.7	2.1 ± 1.8	0.06 ± 0.08	0.001
ESR	22.4 ± 12.5	16.35 ± 10.20	5.3 ± 2.9	0.001
CRP	25.5 ± 7.9	12.7 ± 6.3	8.1 ± 4.0	0.003
Procalcitonin	0.95 ± 0.47	0.62 ± 0.30	0.05 ± 0.03	0.001
Positive procalcitonin	24 (64.86%)	19 (46.86%)	3 (11.11%)	0.002
TVD	14 (37.83%)	11 (35.48%)	5 (18.51%)	0.039
Syntax Score				0.004
33 ≤	17 (45.94%)	3 (9.67%)	2 (7.40%)	
< 33	20 (54.05%)	28 (90.32%)	25 (92.59%)	

UA, Unstable angina; STEMI, ST-elevation myocardial infarction; NSTEMI, Non–ST-elevation myocardial infarction; FBS, Fasting blood sugar; BUN, Blood urea nitrogen; TG, Triglyceride; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; TVD, Triple-vessel disease

Table 2: Regression analysis of factors related to the procalcitonin level

Variable	R^2	F	β	95% CI for β	T	*P* value
	Univariate Regression					
ACS subgroup	0.42	145.83	1.10	1.08 – 1.24	14.78	0.001
TVD	0.12	24.19	0.22	0.07 – 0.31	4.84	0.001
All-cause in-hospital mortality	0.31	85.07	0.54	0.43 –0.67	9.18	0.001
SYNTAX score	0.33	79.12	0.61	0.51 – 0.72	8.32	0.004
Troponin	0.13	23.72	0.18	0.13 –6.72	3.51	0.412
ESR	0.09	24.39	0.19	0.10 –1.28	3.22	0.329
CRP	0.14	28.13	0.33	0.55 – 3.16	3.50	0.119
Cholesterol	0.19	42.12	0.42	0.14 –1.80	1.66	0.271
LDL	0.10	39.13	0.18	0.03 – 1.26	0.49	0.475
	Multivariate Regression					
ACS subgroup	-	-	-0.28	-0.59 – 0.11	-9.70	0.001
TVD	-	-	0.07	0.02 – 0.16	2.52	0.010
All-cause in-hospital mortality	-	-	0.68	0.27 – 0.93	8.92	0.003
SYNTAX score	-	-	0.72	0.54 –0.86	7.78	0.004

ACS, Acute coronary syndrome; TVD, Triple-vessel disease; LDL, Low-density lipoprotein

DISCUSSION

In our study on patients with ACSs, we detected high levels of inflammatory biomarkers, namely CRP, ESR, and procalcitonin, in the STEMI group compared with the NSTEMI and unstable angina groups. A greater proportion of the patients with STEMI (45.94%) had high SYNTAX scores compared with the patients with NSTEMI (9.67%) and unstable angina (7.40%). Moreover, we found a strong correlation between procalcitonin levels and ACS subgroups, triple-vessel disease, SYNTAX scores, and all-cause mortality during hospitalization.

Ertem et al [9] reported a relationship between the SYNTAX score and the serum procalcitonin concentration and suggested that serum procalcitonin could be a predictor of high SYNTAX scores, independent of ACS subgroups. Nevertheless, they failed to demonstrate the relationship between procalcitonin levels and SYNTAX scores in different subgroups of patients (STEMI, NSTEMI, and unstable angina). Kurtul et al [14] found that procalcitonin (OR, 3.021), current smoking (OR, 2.237), hs-CRP (OR, 1.119), and triglyceride (OR, 1.005) were independent predictors of high SYNTAX scores (≥ 23).

Remarkably, there is accumulating evidence that associates procalcitonin with the prognosis of cardiovascular diseases. [14,15] In a prior study, high levels of serum procalcitonin within 48 hours post-admission were observed in patients with ACSs who died during a 6-month follow-up period. [16] In another investigation, circulating procalcitonin levels were significantly increased in patients with STEMI who developed cardiogenic shock compared with patients with STEMI or unstable angina. However, the degree of myocardial ischemia is better reflected by CRP than by procalcitonin. [17] A study on 2131 patients with coronary artery disease indicated that after 3.6 years of follow-up, procalcitonin had a good predictive value. Procalcitonin levels were significantly higher in patients with acute coronary disease and patients who died because of cardiovascular disease than in patients with stable angina. The results of a previous study showed that on Cox regression analysis, high procalcitonin levels were related to cardiovascular mortality (HR, 1.34; 95% CI, 1.08 to 1.65; *P* =0.0070). [18]

These results differ from those of a prospective cohort study on patients with STEMI that found no significant correlations between serum procalcitonin concentrations and infarct size, microvascular obstruction, and intramyocardial hemorrhage evaluated by cardiac magnetic resonance imaging. [19]

In addition to ACSs, Sharma et al [20] concluded that procalcitonin (cutoff =0.62) was a predictor of in-hospital mortality in patients with STEMI complicated with cardiogenic shock according to univariate analysis (AUC, 0.676, *P* =0.002); however, it was not an independent predictor in multivariate analysis. Increased procalcitonin levels in cardiogenic shock might be related to the inflammatory response and the release of different cytokines like interleukin-6, tumor necrosis factor-α, and soluble tumor necrosis factor receptors. [21]

The possible mechanism that describes the role of inflammation in ACSs is that some molecules (eg, inflammatory cytokines, proteases, radicals, coagulation factors) are produced by activated T cells, mast cells, and macrophages at the sites of plaque rupture. These molecules can weaken fibrous caps and transform stable plaques into a destabilized structure that can easily rupture. These events can subsequently induce the rupture of atherosclerotic plaques and exacerbate coronary thrombosis and ischemia. [22]

Altogether, some limitations restrict the generalizability of our findings. One of the notable limitations of the current study is that it was a single-center study with a small sample size, impairing our ability to generate conclusive results. Still, the results relatively conform to other similar studies. Additionally, we did not measure procalcitonin levels serially from the hospitalization day to correct possible variability since procalcitonin tends to peak within 6 and 24 hours of inflammatory stimuli. As a result, these limitations and controversial previous information cannot elucidate the clinical significance of procalcitonin as a clinical predictive or prognostic biomarker.

Future multicenter studies with more participants, longer follow-up durations, and serial procalcitonin monitoring are required to clarify the established relationship between ACSs and procalcitonin levels.

CONCLUSIONS

In the current study, we found that serum procalcitonin was associated with coronary artery disease severity measured by the SYNTAX score. More patients with STEMI had higher SYNTAX scores than patients with NSTEMI and those with unstable angina Triple-vessel disease, ACS subgroups, and in-hospital mortality were significantly correlated with procalcitonin levels. Future studies may evaluate the prognostic accuracy of procalcitonin levels in patients with ACSs.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval

All the procedures performed in the current study were in accordance with the guidelines stipulated in the Declaration of Helsinki and approved by the Ethics Committee of Tran University of Medical Sciences (TUMS) (No. IR.TUMS.MEDICINE.REC.1399.1292). All the participants or their legal guardians were asked to provide written informed consent before data collection.

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