Prognostic Value of Inflammation Parameters in Patients With Non-ST Elevation Acute Coronary Syndromes

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Abstract

Inflammation parameters can predict the severity of coronary artery disease and predict long-term mortality. However, there is no study in which these parameters were evaluated together. We compared the prognostic values of inflammation parameters in predicting long-term mortality in patients with non-ST elevation acute coronary syndrome (NSTE-ACS). Consecutive patients with NSTE-ACS (n = 170) were included in the study. Monocyte/high-density lipoprotein cholesterol (HDL-C) ratio (MHR), lymphocyte/monocyte ratio (LMR), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), total cholesterol/HDL-C ratio (TC/HDL-C), triglyceride /HDL-C ratio (TG/HDL-C), total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index, and ischemia-modified albumin (IMA) were measured. Total antioxidant status and TOS variables were significant independent predictors of mortality. When 1.17 value is taken as a cutoff point of TAS values, the sensitivity (70.0%) and specificity (77.39%) values calculated for this value indicate that TAS variable has a predictive value on mortality. Monocyte/high-density lipoprotein cholesterol ratio, LMR, NLR, PLR, TC/HDL-C, TG/HDL-C, TOS, and IMA levels could not be used alone in the diagnosis, severity assessment, and predicting future mortality of NSTE-ACS. Only TAS levels had a predictive value on mortality.

Keywords

non-ST acute coronary syndrome, mortality, oxidative stress, total antioxidant status, inflammation

Introduction

Although there has been a significant improvement in medical and interventional treatments in the last 20 years, mortality rates related to acute coronary syndrome (ACS) have not changed much in the long run.[1,2]

In studies conducted, parameters such as monocyte/high-density lipoprotein cholesterol (HDL-C) ratio (MHR), lymphocyte/monocyte ratio (LMR), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), total cholesterol (TC)/HDL-C ratio (TC/HDL-C), and triglyceride (TG)/HDL-C ratio (TG/HDL-C) have been shown to be associated with inflammation. It has been suggested that these parameters are associated with the presence and severity of coronary artery disease (CAD) and may predict future coronary events and mortality.[3-11]

Total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), and ischemia-modified albumin (IMA) are oxidative stress parameters. It has been shown that oxidative stress has an important role in the pathogenesis of atherosclerosis and CAD, and high oxidant levels reflect disease severity and vascular damage.[12-16]

In this study, we aimed to compare the prognostic values of new inflammation parameters associated with CAD in predicting long-term mortality.

Methods

Study Design and Patient Selection

The study was conducted in the cardiology clinic between January 2019 and June 2019. Our study was designed prospectively and included 170 patients diagnosed with non-ST elevation ACS (NSTE-ACS); 19% (n = 33) of patients underwent medical treatment. 81% (n = 137) underwent coronary angiography.

Patients who were admitted to the emergency department with chest pain and diagnosed as NSTE-ACS according to clinical, electrocardiographic, and laboratory evaluations were included in the study. Those with acute or chronic infection, autoimmune disease, chronic kidney failure, severe heart valve disease, and malignancy were excluded from the study.

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Demographic data of the patients such as age and sex were recorded. A detailed physical examination of all patients was performed, and these patients were interrogated for chronic diseases such as peripheral artery disease, hypertension, and diabetes.

After the patients were discharged, information was obtained from them, their relatives, and the hospital records (eg, by telephone). The patient group with 1-year follow-up was divided into 2 groups as with mortality and no mortality.

Either a written or an oral-witnessed informed consent was obtained from all of the participating patients provided at the emergency service. Our study was performed by complying with the principals by the Declaration of Helsinki and was approved by the local ethics committee (Ahi Evran University Faculty of Medicine Clinical Research Ethics Committee, Ethics Committee Resolution no: 2019-18/182).

Blood Sample Collection

Venous blood samples were obtained from an antecubital vein into routine biochemistry tubes containing K2EDTA. Biochemistry tubes were centrifuged at 3000 rpm for 10 minutes after waiting for 30 minutes for clotting. Serums were divided into aliquots. Complete blood and routine biochemistry parameters were measured immediately. Serums separated into aliquots were stored at −80 °C until analysis of oxidative stress parameters.

Measuring Inflammation Parameters

Complete blood count was measured on an auto-analyzer (Sysmex XN-1000, Sysmex Company); TG, TC, and HDL-C levels were measured on a routine biochemistry auto-analyzer (Cobas 8000, Roche Diagnostic Corp).

The MHR, LMR, NLR, PLR, TC/HDL-C, and TG/HDL-C values were calculated by dividing the parameters and multiplying by 100.

The TAS, TOS, and IMA levels were measured with Rel Assay brand commercial kits (Assay Kit Rel Diagnostics) using an auto-analyzer (Cobas c501, Roche Diagnostic Corp). The results are given in mmol Trolox equivalent/L, µmol H_2O_2 equivalent/L, and absorbance units, respectively.

Oxidative stress index, which is an indicator of the degree of oxidative stress, was calculated according to the formula given below. The results are expressed as "arbitrary unit" (AU).

$$OSI(AU) = (TOS \text{ [µmol } H_2O_2 \text{ equivalent/L]}$$
$$/TAS \text{ [mmol Trolox equivalent/L]}) \times 100.$$

Statistical Analysis

Statistical analysis was carried out using a Statistical Package for Social Sciences version 21.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0, IBM Corp). Normality assumption was tested by the Kolmogorov-Smirnov and Shapiro-Wilk tests. For univariate analysis of the variables in the study, chi-square, Fisher exact, Mann-Whitney U, and independent t test were used depending on the type of variable and the state of assumptions. Explanatory statistics for variables are given as mean $\pm$ standard deviation and median (interquartile ranges at the 25th and 75th percentiles). The effects of the variables included in the study in predicting mortality were analyzed using logistic regression analysis. A receiver-operating characteristic (ROC) curve analysis was used to determine whether the variables that make a significant contribution to the model as a result of the logistic regression analysis have a diagnostic value. In all statistical analyzes, situations with a $P < .05$ were interpreted as significant.

Results

Of the 170 patients included in the study, 76.5% were male and 23.5% were female. Men's mortality rate was 7.7% and women's mortality rate was 30.0%. Inhospital mortality rate was 4.6%. Demographic, clinical, and biochemical data are shown in Table 1 and inflammation and oxidative stress indices are shown in Table 2. There was no significant difference with regard to age ($P = .095$) and other comorbid factors such as diabetes mellitus ($P = .668$), hypertension ($P = .843$), CAD ($P = .608$), hyperlipidemia ($P = .939$), and smoking ($P = .705$) between the mortality and no mortality groups. As a result of univariate analysis, a significant difference was found between the 2 groups in terms of gender, TAS, TOS, glomerular filtration rate, low-density lipoprotein (LDL), albumin, and C-reactive protein (CRP). The TAS value was lower in the mortality group (1.17 ± 0.15) than in the nonmortality group (1.31 ± 0.09; $P = .000$). The TOS value was higher in the mortality group ($P = .017$). Glomerular filtration rate was lower in the mortality group ($P = .041$). Low-density lipoprotein cholesterol value was also higher in the mortality group ($P < .05$). Albumin value was lower in the mortality group ($P = .026$). The CRP value in the mortality group was higher than in the nonmortality group ($P = .004$).

Logistic regression analysis was performed for all the variables in the study. The percentage correct value of the logistic regression model created by reducing the variable with the backward elimination method was found to be 89.4%. Hosmer-Lemeshow test results are used in deciding about the model fit. The instances that have a $P > .05$ refer to the models that have high prediction value. Since the P value belonging to Hosmer and Lemeshow test score ($X^2 = 2.671$, $P > .05$) is greater than .05 in the study, it shows that the model is quite effective in predicting the mortality. The coefficients of the best model obtained as a result of logistic regression analysis are given in Table 3. According to the logistic regression analysis results, TAS and TOS variables are statistically significant independent variables in predicting the mortality ($P < .05$). The effects of OSI and LMR variables in the logistic regression model on mortality estimation were nonsignificant ($P > .05$).

The ROC analysis was carried out to determine whether there is a diagnostic cutoff value that determines the mortality risk of the independent variables entered in the model as a result of logistic regression analysis. When the ROC curve of TAS shown

Table 1. Comparison of the Demographic, Clinical, and Biochemical Characteristics of Mortality and Nonmortality Groups.

	Nonmortality	Mortality	P
Age, years	61.5 ± 10.6	68.09 ± 18.7	.095
Sex (male/female)	120 (92.3%)/28 (70.0%)	10 (7.7%)/12 (30.0%)	.002
Diabetes mellitus (yes/no), n (%)	98 (86%)/50 (89.3%)	16 (14.0%)/6 (10.7%)	.668
Coronary artery disease (yes/no), n (%)	126 (86.3%)/22 (91.7%)	20 (13.7%)/2 (8.3)	.608
Hypertension (yes/no), n (%)	76 (86.36%)/72 (87.80%)	12 (13.64)/10 (12.20%)	.843
Hyperlipidemia (yes/no), n (%)	106 (86.9%)/42 (87.5%)	16 (13.1)/6 (12.5%)	.939
Smoking (no/yes), n (%)	64 (84.2%)/84 (89.4%)	12 (15.8)/10 (10.6%)	.705
Glucose, mg/dL	128 ± 65	155 ± 87	.237
Glomerular filtration rate, %	82 ± 19	68 ± 37	.041
Triglyceride, mg/dL	157 (106-215)	198 (136-305)	.141
Total cholesterol, mg/dL	170 ± 42	199 ± 71	.052
Low-density lipoprotein, mg/dL	94 ± 35	123.2 ± 67.5	.026
High-density lipoprotein, mg/dL	41 ± 10	43 ± 14	.662
Calcium, mg/dL	9.3 ± 0.51	9.2 ± 1.2	.735
Albumin, g/dL	4.0 ± 0.4	3.6 ± 0.6	.006
White blood cell count, $10^3/\mu L$	9.32 ± 2.92	11.65 ± 7.19	.055
Hemoglobin, g/dL	13.9 ± 1.7	12.8 ± 2.	.086
Platelet count, $10^3/\mu L$	258.95 ± 83.54	297.18 ± 147.92	.210
Neutrophil count, $10^3/\mu L$	5.17 (4.06-7.57)	7.96 (4.33-18.63)	.480
Lymphocyte count, $10^3/\mu L$)	2.19 (1.67-2.74)	1.59 (0.62-2.43)	.136
Monocyte count, ($10^3/\mu L$	0.71 (0.59-0.93)	0.91 (0.47-1.43)	.484
C-reactive protein, mg/dL	0.41 (0.20-0.94)	1.96 (0.66-9.06)	.004
hsTroponin T, ng/L	3286 9756	3980 4107	.714
CKMB, ng/mL	49.4 61.4	52.8 69.6	.821

Abbreviations: CKMB, creatine kinase myocardial isoenzyme; hsTroponin T, high-sensitivity troponin T.

Table 2. Inflammation and Oxidative Stress Indices Among Patients With Mortality and Nonmortality Groups.

	Nonmortality	Mortality	P
Total antioxidant status, mmol Trolox equivalent/L	1.31 ± 0.09	1.17 ± 0.15	.000
Total oxidant status, $\mu mol\ H_2O_2$ equivalent/L	6.03 (3.94-8.88)	9.33 (6.83-13.62)	.017
Oxidative stress index, AU	494.7 (338.0-719.25)	670.0 (488.0-1121.0)	.091
Ischemia-modified albumin, ABSUs	40.22 ± 4.58	38.81 ± 3.12	.328
Monocyte to HDL-C ratio	0.01 (0.01-0.02)	0.01 (0.01-0.03)	.596
Lymphocyte to monocyte ratio	0.33 (0.24-0.46)	0.30 (0.22-2.14)	.819
Neutrophil to lymphocyte ratio	2.54 (1.65-4.09)	2.65 (1.82-16.90)	.317
Platelet to lymphocyte ratio	114.29 (79.0-160.45)	141.67 (111.0-176.83)	.129
TC to HDL-C ratio	4.24 ± 1.16	4.74 ± 1.53	.205
TG to HDL-C ratio	3.98 (2.76-5.91)	4.86 (2.82-5.95)	.301

Abbreviations: AU, arbitrary unit; ABSUs, absorbance units; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 3. Results of Logistic Regression Analysis.

			95% CI for Exp(B)	
Variables	β	Sig	Lower	Upper
Total antioxidant status, mmol Trolox equivalent/L	4.283	0.003	2.527	6.275
Total oxidant status, $\mu mol\ H_2O_2$ equivalent/L	−1.473	0.044	0.051	1.026
Oxidative stress index, AU	0.019	0.054	1.000	1.040
Lymphocyte to monocyte ratio	1.565	0.085	0.804	8.470

in Figure 1 is examined, the area under the curve (AUC) is statistically significant (AUC: 0.805, CI%: 0.670-0.941, P = .002). In Figure 1, when 1.17 is taken as a cutoff point for TAS values, the sensitivity (70.0%) and specificity (77.39%) values indicate that TAS variable has a predictive value on mortality. The TOS variable, which in the logistic regression model has a significant effect, has no diagnostic value since the area under the ROC curve is nonsignificant ($P > .05$).

Discussion

As far as we know, this study is the first to compare the prognostic values of inflammatory parameters in predicting long-
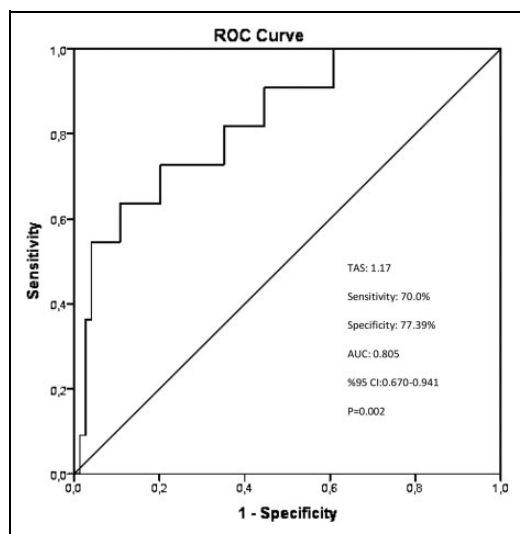
Figure 1. The receiver–operating characteristic (ROC) curve of total antioxidant status for predicting mortality.

term mortality in ACS. Among these parameters studied separately in the literature, only the TAS value significantly predicted long-term mortality.

Besides accurate and early diagnosis of ACS, it is important to be able to predict the severity of CAD. The severity of CAD is an indicator of cardiovascular mortality and can play a decisive role in the treatment approach. Therefore, recent studies have focused on biochemistry and blood count parameters, which are easy to measure, and can also predict the severity of the disease.

The atherosclerosis process is a chronic inflammatory process, and monocytes, neutrophils, and lymphocytes are the main cells of this process. It is known that while the number of monocytes and neutrophils increases, lymphocyte counts decrease in this process.[17]

A large-scale study suggested that MHR may be a marker of atherosclerotic load and found a linear relationship between MHR levels and ischemic stroke.[18] Çicek et al suggested that MHR is an independent and important variable in short- and long-term mortality.[19] Saskin et al claimed that preoperative MHR values were associated with postoperative atrial fibrillation and mortality.[20] In the formation of atherosclerotic plaque, activated circulating monocytes interact with the damaged endothelium and are taken into the intima and turned into macrophages. Macrophages form foam cells by taking LDL and other lipids oxidized with phagocytosis.[21] Therefore, the number of circulating monocytes is directly related to the development and severity of the atherosclerotic plaque. On the other hand, HDL-C has antithrombotic, anti-inflammatory, and antioxidant effects. In this way, it prevents migration of macrophages and removes cholesterol from these cells, thereby protects the endothelium. Therefore, the MHR alone can be effective in predicting the severity of atherosclerosis and cardiovascular events better than the number of monocytes or HDL-C level alone. In our study, we did

not find a significant difference in MHR rates between the groups with and without mortality.

Fan et al claimed that high levels of monocyte lymphocyte ratio may be an independent indicator of long-term cardiovascular complications in patients with non-ST-elevation myocardial infarction (NSTEMI).[22] Cai et al have shown that decreased LMR levels are independently associated with long-term mortality.[23] It is known that the lymphocyte counts decrease in ACS due to stress-related cortisol release.[24] Due to the increase in the number of monocytes and the decrease in the number of lymphocytes, the rate of LMR may be proportional to the severity of the disease. In our study, although the LMR values were lower in the mortality group, there was no significant difference between the groups.

Cho et al suggested that NLR is effective in predicting 6-month mortality in patients with primary percutaneous coronary intervention with ST elevation and myocardial infarction and may be an independent risk factor in CAD.[8] Çicek et al also showed that the NLR is a potential prognostic marker.[3] Neutrophils migrate to the ischemic area after myocardial damage caused by acute myocardial infarction. They cause damage by various inflammatory mediators and cytokines that they secrete. An increase in the NLR is due to the increasing neutrophil count and decreasing lymphocyte count as expected after a CAD event. However, we only found a nonsignificant increase in NLR in our study.

Nikolsky et al have shown that an increased PLR is associated with increased major cardiovascular complications.[25] Azab et al found that increased PLR values are important independent indicators of long-term survival in patients admitting to hospital with NSTEMI.[26] Increased platelet count and activity play a critical role in the initiation and progression of atherosclerosis. In our study, although PLR values were higher in the mortality group, they were not significantly different.

In a prospective evaluation by Onat et al, it was concluded that the TC/HDL-C ratio was the only significant independent lipid variable in predicting future coronary death and events.[10] In another study, the serum TG/HDL-C ratio was the best laboratory indicator of the presence of coronary atherosclerotic lesions.[11] The increase in serum TG and TC levels alone is sufficient for the development of atherosclerosis, even in the absence of other known risk factors.[27] However, in our study, both TC/HDL-C and TG/HDL-C were higher in the mortality group but were not statistically significant.

Studies in the literature with oxidative stress parameters such as TAS, TOS, OSI, and IMA showed that there is a strong relationship between the presence of CAD and oxidative stress. Demirbağ et al reported that TAS and TOS were significantly lower in patients with CAD than in a control group.[28] Aksoy et al showed that oxidative stress contributes significantly to the severity of CAD among young smokers, and high OSI and TOS levels reflect disease severity and vascular damage.[12] Sezen et al suggested that oxidative stress may play a role in the pathogenesis of coronary artery ectasia and found high TOS and OSI values.[13] During the ACS, the inflammatory cascade is activated due to the ischemic process. With systemic

inflammation, superoxide anion, hydrogen peroxide, and chlorinated oxidants are produced with active myeloperoxidase activity from circulating active neutrophils, and free oxygen radicals (FOR) are released into the circulation.[29] This causes the oxidant and antioxidant defense mechanism to shift toward oxidants. Therefore, it is expected that TOS and OSI levels will increase and TAS levels will decrease in the CAD process. In our study, we found that TAS levels were significantly low and TOS levels were significantly higher in the mortality group. Although there was a significant increase in OSI levels, it was not statistically significant. As a result of the ROC analysis, the cutoff value was 1.17 (sensitivity 70.0% and specificity 77.39%) for TAS as an indicator of mortality. This result shows us that TAS levels <1.17 may provide important information about mortality to clinicians on admission.

It has been shown that IMA, which is formed by the damage of the N-terminal region of postischemia, is directly related to the amount of FORs formed and increases with ischemia.[30] Some studies suggest that IMA predicts the severity of myocardial ischemia in patients with ACS and can provide clinical significance for early diagnosis of ACS and helps the physicians in deciding the treatment strategy.[14,15] On the other hand, Demir et al claimed that IMA was insufficient in the diagnosis of ACS.[16] In our study, we did not find a significant difference in the IMA levels between mortality groups; our findings were similar to the results of Demir et al.[16]

Our study had some limitations. It was not sufficiently large in terms of the number of patients, and the number of patients in the 1-year mortality group was small. The fact that our study is single centered may also limit its applicability to the general population.

As a result, MHR, LMR, NLR, PLR, TC/HDL-C, TG/HDL-C, TOS, and IMA levels are not sufficient markers that can be used alone in the diagnosis, severity assessment, and predicting future mortality of ACS. We found that only TAS levels had a diagnostic value on mortality. We believe that this parameter, which can be routinely measured on auto analyzers today, helps physicians to evaluate the patient better on admission and to help plan the treatment.

Authors' Note

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