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C-Reactive Protein, Uric Acid, and Coronary Artery Ectasia in Patients with Coronary Artery Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Onur Argan
CDEF 2 Serdar Bozyel

1 Department of Cardiology, Balikesir University Medical Faculty, Balikesir, Türkiye
2 Department of Cardiology, Kocaeli City Hospital, Health Sciences University, Kocaeli, Türkiye

Corresponding Author: Onur Argan, e-mail: onur_argan@yahoo.com
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Background: Coronary artery ectasia (CAE) is frequently present with coronary artery disease (CAD). However, it is not clear why some patients with CAD progress to CAE while others do not. The pathogenesis of CAE is still poorly elucidated. C-reactive protein (CRP) and serum uric acid are well-known markers of inflammation. We aimed to investigate the possible associations among CRP, uric acid, and CAE in patients with CAD.

Material/Methods: We retrospectively evaluated data from 2400 patients undergoing coronary angiography. Seventy-four patients with CAE and CAD and 124 patients with only CAD detected on coronary angiography examination were included in this study. Univariate and multivariate logistic regression analyses were performed to evaluate the associated parameters of CAE in patients with CAD.

Results: Patients with CAE and CAD were younger than patients with only CAD (63±9.5 vs 66.1±9.4, *P*=0.028). Male sex was more prevalent in patients with CAE and CAD than in patients with only CAD (86.5% vs 74.2%; *P*=0.029). CRP and uric acid were higher in patients with CAE and CAD compared to the patients with only CAD (10.9±12.8 vs 6.6±6.4; *P*=0.004; 5.9±1.4 vs 5.2±1.5; *P*=0.002, respectively). In multivariate regression analysis, age [*P*=0.029,OR(95% CI) 0.958(0.921-0.996)], CRP [*P*=0.010,OR (95% CI) 1.058 (1.014-1.103)], and uric acid [*P*=0.002,OR (95%CI) 1.527 (1.173-1.988)] were associated with CAE in patients with CAD.

Conclusions: The CRP and uric acid levels were higher in patients with CAE and CAD compared to the patients who only had CAD. Also, CRP and uric acid were associated with CAE. These results reflect the higher-grade vascular inflammation relative to atherosclerotic involvement in the presence of concomitant CAE in patients with CAD.

Keywords: Coronary Aneurysm • Coronary Angiography • Coronary Artery Disease • Uric Acid

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Introduction

Coronary artery ectasia (CAE) has been defined as diffuse or localized lesions of the coronary arteries with a luminal dilatation exceeding 1.5 times that of the normal adjacent coronary segment [1,2]. CAE is associated with increased mortality and morbidity through mechanisms such as thrombus formation, dissection, or coronary slow flow [3].

Prevalence rates of CAE in studies performed with coronary angiography were 0.3-5.3%, and CAE was detected in 1-5% of patients with angiographically diagnosed coronary artery disease (CAD) [4,5].

Approximately 50% of CAE cases are related to atherosclerosis, whereas 20-30% are related to congenital anomalies (eg, hereditary collagen defects, hereditary hemorrhagic telangiectasia, marfan syndrome, ehlers danlos syndrome), and 20-30% are related to inflammatory and connective tissue diseases (eg, systemic lupus erythematosus, ankylosing spondylitis, rheumatoid arthritis) [6]. There is a prominent association between CAE and systemic inflammatory vasculitis (eg, Kawasaki disease, Behcet's disease, Takayasu arteritis) [7].

The main etiology of CAE is thought to be atherosclerosis [8]. Histopathological findings of CAE, such as lipid destruction, deposition, and reduction of the elastic fibers in external and internal elastic lamina, were similar in atherosclerosis [9,10]. Also, inflammation plays a critical role in all stages of atherosclerosis [11]. Postmortem histopathological results have shown that the vascular inflammation in patients with CAE is more extensive and severe than in patients with CAD [12]. According to many authors, atherosclerosis is an inflammatory disease that presents with different clinical presentations, including plaque rupture, coronary slow flow, atheromatous development, coronary microvessel dysfunction, coronary spasm, restenotic process, and myocardial ischemia [13-15]. Chronic inflammation in the vessels is associated with arterial dilatation, extensive arterial damage, and elevated inflammatory markers [16]. The underlying etiology of CAE is unclear, but studies have shown that CAE may be a form of atherosclerosis and has stronger inflammatory status than in normal coronary arteries [17,18]. Strong evidence for the association between inflammation and CAE is demonstrated by inflammatory markers [19,20]. C-reactive protein (CRP) directly contributes to the atherosclerotic process. Increasing evidence demonstrates that inflammation plays a critical role in all stages of atherosclerosis. Increased CRP, as an important marker of inflammation, is known to be associated with atherosclerotic formation and endothelial dysfunction [21,22].

The relationship between uric acid and cardiovascular diseases has been known for nearly half a century. Many studies have demostrated the relationship between uric acid and CAD, CAE, cerebrovascular disease, metabolic syndrome, hypertension, and preeclampsia [23]. Uric acid is a marker of increased xanthine oxidase activity that transforms xanthine/hypoxanthine to uric acid. It is a critical mediator of inflammatory responses and cellular damage [24]. Superoxide free radicals associated with xanthine oxidase is responsible for endothelial injury [25,26]. Also, xanthine oxidase induces formation of matrix-metalloproteinases, which may play a role in ectatic transformation of the wall through proteolysis of matrix proteins [27]. Clinical and experimental studies have demonstrated that higher uric acid levels are correlated with systemic inflammation and endothelial dysfunction [28,29]. Uric acid was also found to be associated with markers of early atherosclerosis on carotid artery intima media thickness [30]. Torzewski et al found that increased uric acid levels are an independent predictor of ischemic heart disease and cardiovascular mortality. Increased uric acid levels have been demonstrated to play a role in the pathogenesis of CAD [31].

Previous studies have investigated the role of CRP and uric acid in patients with isolated CAE (CAE without CAD), in patients with normal coronary arteries, and in patients with CAD alone, but few studies have evaluated the role of inflammation using CRP and uric acid in patients with CAE and CAD [6,11,12,19,32,33]. Current guidelines focus on anti-inflammatory therapies for CAD [16,17]. Therefore, it is important to identify subgroups of patients with CAD caused by inflammation who may benefit from anti-inflammatory therapy.

The aim of our study was to investigate the possible association between CRP and uric acid as an inflammatory marker and CAE in patients with CAD.

Material and Methods

This study was approved by the Balikesir University Clinical Research Ethics Committee according to the Declaration of Helsinki (Decision no: 2023/136; Date: 11.10.2023). Given the retrospective nature of the study, patient consent was not required.

Study Population

We retrospectively evaluated data on 2400 patients who underwent coronary angiography due to suspected CAD. The indication for coronary angiography was presenting with typical angina symptoms, suspected or positive results for ischemia in the non-invasive screening test (treadmill test, coronary computed tomography angiography, or myocardial perfusion scintigraphy) for all patients. We included 74 patients with CAE and CAD and 124 patients with only CAD.

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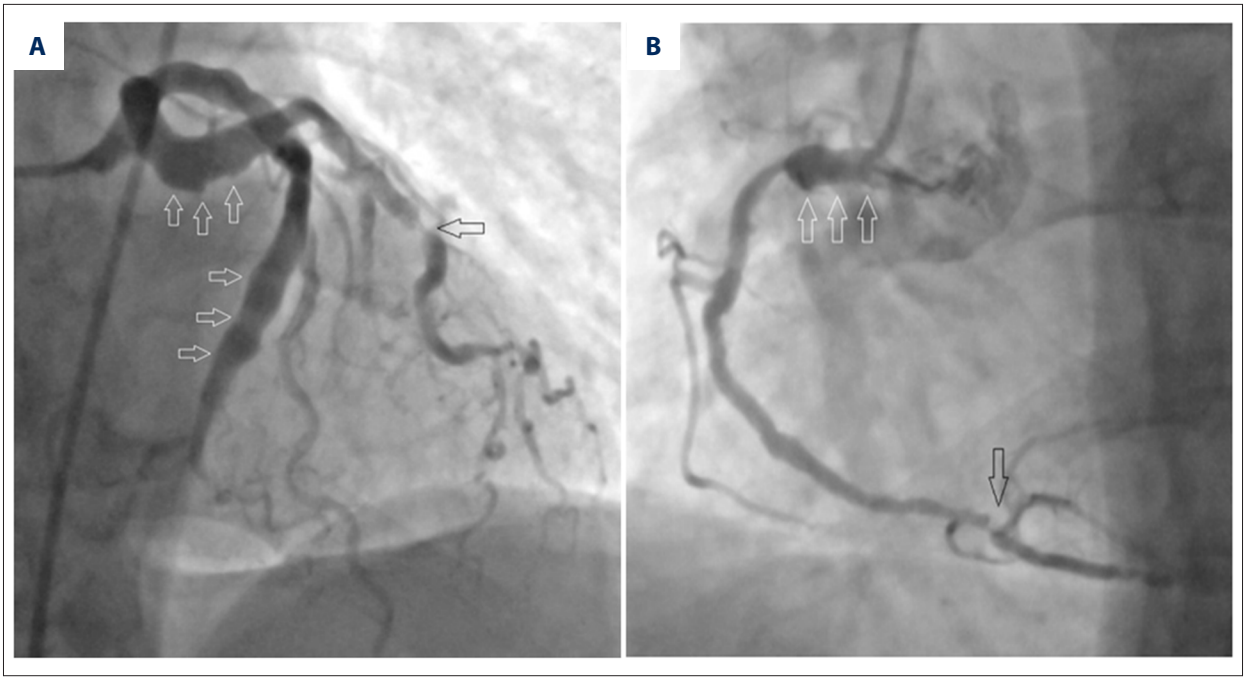

Figure 1. Right anterior oblique view of coronary angiography image showing coronary artery ectasia in the circumflex coronary artery (white arrowheads) and significant coronary artery stenosis in the same coronary artery (black arrowhead) (**A**); and right coronary artery with ectatic coronary segment and significant coronary stenosis (black arrowhead) (**B**) in a patient with coronary artery ectasia and coronary artery disease.

Exclusion Criteria

We excluded patients with acute heart failure, infection, sepsis, malignancy, autoimmune disease, iatrogenic CAE due to the previous coronary intervention, congenital heart disease, trauma or surgery within 3 month, pregnancy, or end-stage renal or liver failure.

Evaluation of Coronary Artery Ectasia and Coronary Artery Disease

Coronary angiography was performed by the Judkins technique using Judkins right and left coronary catheters with sterile precautions. This study was performed using a Siemens Healthineers Artis Zee Floor (Germany) and Philips Allura Coronary Angiography System (Holland). All of the coronary angiography examinations were evaluated retrospectively. Coronary angiography images evaluated and analyzed using the Extremepacs Pacs Software system (Version 4.3; serial 2015-001). CAE was defined as the enlargement of coronary artery by 1.5 times or more compared to normal adjacent coronary segment [12] (**Figure 1**). A normal segment was defined as a coronary artery segment without stenosis or ectasia on coronary angiography imaging. If no normal adjacent coronary segment existed, the mean diameter of the same coronary artery in the other group served as the normal value. Distribution of CAE and the number of coronary arteries involved were recorded. The severity of CAE was classified according to Markis et al classification [34], in which type I is diffuse CAE of 2 or 3 vessels, type II is diffuse CAE in 1vessel and focal dilatation in another vessel, type III is diffuse CAE of 1 vessel only, and type IV is focal CAE.

Patients with CAD were consecutively selected from among the patients who underwent coronary angiography during the study period. The coronary arteries were evaluated for the extent of the coronary lesion by diameter stenosis and extent of disease along the coronary arteries. Typical stenosis of 20% or more in at least 1 coronary artery was defined as CAD [12] (**Figure 2**). Coronary angiography is an invasive diagnostic procedure that allows visualization of the coronary artery lumen, but it cannot visualize atherosclerosis in the vascular wall. Therefore, coronary angiography can only diagnose coronary artery disease if luminal stenosis is detected. In our study, CAD was confirmed by comparing the findings of coronary angiography with the findings of coronary computed tomography angiography in patients who previously underwent coronary computed tomography angiography.

Definitions

Hypertension is defined as blood pressure levels ≥140/90 mmHg or using any antihypertensive drug [35]. Diabetes mellitus was defined as fasting blood sugar levels ≥126 mg/dl or

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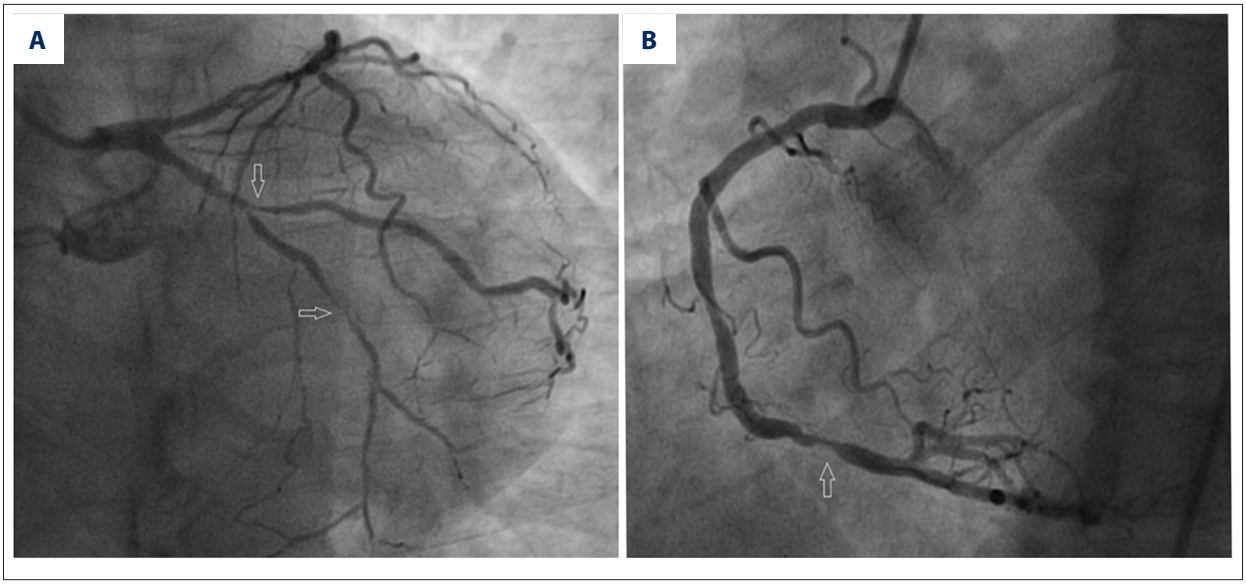

Figure 2. Right anterior oblique view of coronary angiography image showing significant coronary stenosis in the circumflex coronary artery and obtuse marginal artery (arrowheads) (**A**); and significant stenosis in the right coronary artery (arrowhead) (**B**) in a patient with coronary artery disease without coronary artery ectasia.

2-hour postprandial blood sugar levels ≥200 mg/dl or HBA1C ≥6.5, or using antidiabetic drug or insulin [36]. Smoking was defined as active tobacco use in the last 6 months [37].

Statistical Analysis

The data were analyzed using SPSS 13.0 (SPSS, Inc., IBM, Chicago, USA). The Kolmogorov-Smirnov test was performed to analyze the distribution of parameters. Continuous variables are expressed as mean±standard deviation and abnormally distributed variables are expressed as median and percentiles (25-75). Categorical variables are expressed as percentages and frequencies. Pearson and Spearman analyses were used for the correlation analysis. The chi-square test was used for categorical variables, while the *t* test and Mann-Whitney U test were used for categorical variables with normal and non-normal distributions, respectively.

Univariate and multivariate logistic regression analyses were performed to evaluate the associated parameters of CAE in patients with CAD. The variables with $P<0.1$ in the univariate analysis were incorporated into the multivariate logistic regression analysis. Age, sex, CRP, and uric acid were found to be significant in univariate logistic regression analyses. In this model, age, CRP, and uric acid were associated with CAE in patients with CAD in mutivariate logistic regression analysis. Receiver operating curve (ROC) analysis was used to calculate the required CRP and uric acid cut-off values with maximum sensitivity and specificity associated with CAE. Also, the area under the ROC curve (AUC) was calculated. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics of the Study Population

We included 74 patients with CAE and CAD and 124 patients with only CAD. The mean age of patients with CAE and CAD was 63±9.5 years and that of patients with only CAD was 66.1±9.4 years. Patients with CAE and CAD tended to be younger than patients with only CAD ($P=0.028$). Males were more prevalent in both groups, and patients with CAE and CAD were more likely to be male than patients with only CAD (86.5% vs 74.2%; $P=0.029$). BMI was similar between groups (28.4±3 vs 28.2±4.3; $P=0.853$).

Of the cardiovascular risk factors, hypertension (68.9% vs 68.9%; $P=0.149$), diabetes mellitus (41.9% vs 48.4%; $P=0.230$) and current smoker (39.2% vs 37.1%; $P=0.442$) were similar between groups.

Ejection fraction was not significantly different between groups 55 (60-65) vs 60 (55-65); $P=0.677$). **Table 1** shows a comparison of the baseline characteristics and echocardiographic parameters between patients with only CAD and patients with CAE and CAD.

Laboratory Parameters of the Study Population

Of the laboratory parameters, CRP (10.9±12.8 vs 6.6±6.4; $P=0.004$) and uric acid (5.9±1.4 v. 5.2±1.5; $P=0.002$) were higher in patients with CAE and CAD compared to the patients with only CAD. Other laboratory parameters were similar between

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Table 1. Comparison of the baseline characteristics between patients with only coronary artery disease and patients with coronary artery ectasia and coronary artery disease.

	Patients with coronary artery ectasia and coronary artery disease (n=74)	Patients with coronary artery disease without coronary artery ectasia (n=124)	P
Age (years)	63±9.5	66.1±9.4	0.028
Sex (Male/Female)	64/10 (86.5%-13.5%)	92/32 (74.2%-25.8%)	0.029
Body mass index (kg/m^2)	28.4±3	28.2±4.3	0.853
Hypertension	51 (68.9%)	75 (60.5%)	0.149
Diabetes mellitus	31 (41.9%)	60 (48.4%)	0.230
Current smoker	29 (39.2%)	46 (37.1%)	0.442
Ejection fraction (%)	55 (60-65)	60 (55-65)	0.677

Table 2. Comparison of the laboratory parameters between patients with only coronary artery disease and patients with coronary artery ectasia and coronary artery disease.

	Patients with coronary artery ectasia and coronary artery disease (n=74)	Patients with coronary artery disease without coronary artery ectasia (n=124)	P
Glucose (mg/dl)	115 (97-155)	114 (100-162)	0.429
HbA1c	6.6 (5.9-7.5)	6.1 (5.8-7.4)	0.184
Hemoglobin (g/dl)	13.2±1.9	13.5±1.5	0.190
Hematocrit (%)	39.6±4.9	40.9±4.4	0.093
Creatinine (mg/dl)	1.01 (0.86-1.1)	0.95 (0.85-1.1)	0.120
Urea (mg/dl)	34 (30-44)	34 (27-39)	0.416
eGFR (ml/min)	77 (69-91)	80.7 (66.4-90.9)	0.982
Total cholesterol (mg/dL)	183.8±54.8	182±48.5	0.825
Triglyceride (mg/dL)	175.3±82.6	160.6±76.1	0.245
LDL (mg/dL)	103.8±43.7	110.5±41.6	0.330
HDL (mg/dL)	44.8±10.6	44.1±10.1	0.665
AST (U/L)	20.4±6.9	22.6±8.4	0.081
ALT (U/L)	20.5±10.8	19.4±8.2	0.478
TSH (mIU/L)	1.22 (0.86-2.31)	1.44 (0.77-1.89)	0.926
Platelet (10^3/µL)	267.8±75.5	251.5±63	0.149
White blood cell count (10^3/µL)	8.4±2.4	7.9±6.4	0.233
C-reactive Protein (mg/dl)	10.9±2.8	6.6±6.4	0.004
Uric acid (mg/dl)	5.9±1.4	5.2±1.5	0.002

eGFR – estimated glomerular filtration rate, LDL – low-density lipoprotein; HDL – high-density lipoprotein; AST – aspartate transaminase; ALT – alanine transaminase; TSH – thyroid stimulating hormone; CRP – C-reactive protein.

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Table 3. Associated parameters of coronary artery ectasia in patients with coronary artery disease in univariate and multivariate regression analysis.

Variables	Univariate regression analysis OR (95% CI)	*P* value	Multivariate regression analysis OR (95% CI)	*P* value
Sex	2.226 (1.022-4.849)	0.044	2.048 (0.793-5.290)	0.139
Age	0.965 (0.935-0.997)	0.030	0.958 (0.921-0.996)	0.029
CRP	1.051 (1.013-1.091)	0.008	1.058 (1.014-1.103)	0.010
Uric acid	1.416 (1.123-1.786)	0.003	1.527 (1.173-1.988)	0.002

OR – odds ratio, CI – confidence interval.

groups. **Table 2** shows a comparison of the laboratory parameters between patients with only CAD and patients with CAE and CAD.

Associated Parameters of Coronary Artery Ectasia

To determine the parameters associated with CAE in patients with CAD, we used univariate and multivariate logistic regression analyses. In univariate analysis, sex [*P*=0.044, OR (95% CI) 2.226 (1.022-4.849)], age [*P*=0.030, OR (95% CI) 0.965 (0.935-0.997)], CRP [*P*=0.008, OR (95% CI) 1.051 (1.013-1.091)] and uric acid [*P*=0.003, OR (95% CI) 1.416 (1.123-1.786)] were found to be significant. Those that were significant were included in the multivariate analyses. In this model, age [*P*=0.029, OR (95% CI) 0.958 (0.921-0.996)], CRP [*P*=0.010, OR (95% CI) 1.058 (1.014-1.103)] and uric acid [*P*=0.002, OR (95% CI) 1.527 (1.173-1.988)] were associated with CAE in patients with CAD. Associated parameters of CAE in patients with CAD in univariate and multivariate regression analysis are presented in **Table 3**.

A receiver operating curve (ROC) analysis showed that a cut-off CRP >4.02 mg/dl had a sensitivity of 62% and specificity of 59% for detection of CAE (AUC=0.647, 95% CI, 0.558-0.735, *P*=0.003). A ROC analysis showed that a cut-off uric acid >5.45 mg/dl had a sensitivity of 64% and specificity of 60% for detection of CAE (AUC=0.663, 95% CI, 0.571-0.756, *P*=0.001). Evaluation of the association between CRP, uric acid, and the presence of CAE in patients with CAD in receiver operating characteristic curve (ROC) analysis is shown in **Figure 3**.

Classification and Distribution of Coronary Artery Ectasia

The ectatic segments in coronary angiography was categorized according to the Markis et al [34]. The most common pattern was type 3 (52.7%, n=39), type 1 (29.7%, n=22), type 4 (10.8%, n=8), and type 2 (6.8%, n=5), respectively. The most frequently involved coronary artery in CAE is the right coronary artery. The distribution of CAE in coronary arteries were as follows: 6 patients (8.1%) in the left main coronary artery, 32 patients (43.2%) in the left anterior descending artery,

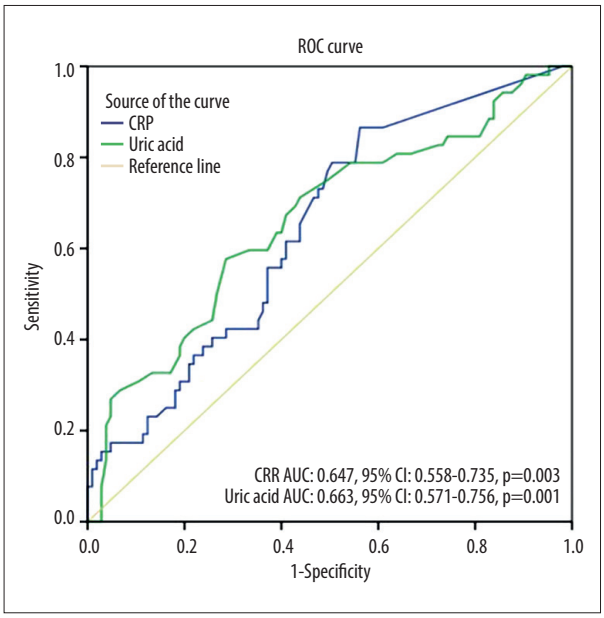

Figure 3. Evaluation of the association between C-reactive protein (CRP), uric acid, and the presence of coronary artery ectasia in patients with coronary artery disease in receiver operating characteristic (ROC) curve analysis.

33 patients (44.6%) in the circumflex artery, and 46 patients (62.2%) in the right coronary artery.

Discussion

The main finding of our study is the higher CRP and uric acid as an inflammatory marker in patients with CAE and CAD compared to the patients with only CAD. Also, CRP and uric acid were associated with CAE. The fact that CRP and uric acid levels were higher in patients with CAE and CAD reflects higher-grade vascular inflammation in patients who had both CAE and atherosclerosis than in those with atherosclerotic involvement only. Recent guidelines on CAD have included anti-inflammatory treatments [38,39]. Coronary ectasia, a subgroup of CAD,

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may benefit from anti-inflammatory treatment due to the increased inflammatory activity.

Turhan et al [19] found that hsCRP levels were significantly higher in patients with isolated CAE (CAE without CAD) compared to patients with CAD and patients with normal coronary arteries (NCA). They also found that patients with CAD had significantly higher levels of hsCRP compared to patients with NCA, and that more severe inflammation may be more involved in the etiology of CAE than in CAD. Sen et al [32] compared the uric acid levels of patients with isolated CAE (CAE without CAD), patients with CAD, and patients with NCA. They found that uric acid was not different significantly between the isolated CAE and CAD groups, but uric acid levels were significantly higher in both groups compared with the control group. Daoud et al [6] compared the serum uric acid in patients with isolated CAE (CAE without CAD), patients with CAD and patients with NCA. They showed that uric acid levels were significantly higher in patients with isolated CAE and patients with CAD compared to the control group. Tosu et compared the serum uric acid and CRP in patients with isolated CAE (CAE without CAD), patients with CAD and patients with NCA. Uric acid and CRP did not show a significant difference between CAE and CAD groups, while this values were found significantly higher in both groups compared to the control group. Additionally uric acid was independently related with CAE. They suggested that both CAE and CAD shared similar pathophysiological mechanisms [12]. Demir et al compared the uric acid levels among patients with isolated CAE (CAE without CAD), patients with CAD, and patients with NCA. A significant difference was not detected in uric acid and HsCRP between CAE and CAD groups. However, uric acid and HsCRP were higher in CAE and CAD groups than the control group. Also, uric acid and HsCRP were independently associated with CAE and CAD [11]. Parvathareddy et al investigated the hsCRP and uric acid levels in patients with isolated CAE (CAE without CAD) and patients with CAD. The inflammatory etiology of CAE was supported by the higher hsCRP and uric acid levels compared to the patients with obstructive CAD [33].

In the only study comparing uric acid between patients with CAD and patients with CAE and CAD, uric acid levels were significantly higher in patients with CAD and in patients with CAE and CAD compared to patients with isolated CAE (CAE without CAD) and patients with NCA. Although no significanct difference was noted between patients with CAD and patients with CAE and CAD in this study; uric acid were higher in patients with CAE and CAD (6.6±1.8 mg/dl) compared to patients with CAD (6.4±1.5 mg/dl) [40].

Most relevant studies have compared patients with isolated CAE (CAE without CAD) and patients with CAD, showing that inflammatory parameters were similar in patients with isolated CAE (CAE without CAD) and patients with CAD, and inflammatory parameters were higher in the isolated CAE and CAD groups compared to the patients with NCA. This suggests that inflammation, which is a well-known cause of CAD, is also associated with a similar grade of CAE.

Many studies have compared patients with isolated CAE (CAE without CAD) and patients with CAD, but few have compared inflammation parameters between patients with CAD and patients with CAE and CAD. In the only study comparing uric acid between patients with CAD and patients with CAE and CAD, uric acid were significantly higher in patients with CAD and in patients with CAE and CAD compared to the patients with isolated CAE (CAE without CAD) and patients with NCA. Although no significant difference was noted between patients with CAD and patients with CAE and CAD in this study, uric acid levels were higher in patients with CAE and CAD compared to the patients with CAD [40]. In our study, CRP and uric acid levels were higher in patients with CAE and CAD compared to patients with only CAD. Also, CRP and uric acid levels were associated with CAE in patients with CAD. These results reflect higher-grade vascular inflammation in patients with coexisting CAE and CAD than in those with CAD only. This result is also supported by the above studies. Anti-inflammatory treatments are drawing attention in the recent guidelines on CAD [38,39]. CAE, as a subgroup of CAD, may benefit from anti-inflammatory treatment due to the increased inflammatory activity.

Prevalence of CAE is 0.3-5.3% in coronary angiography reports and 1-5% among patients with angiographically diagnosed CAD [4,5]. The prevalence of CAE was 3.1% in our study population. The most common pattern was type 3 according to the Markis et al classification. This result was similar to previous studies [33,41,42]. The artery most commonly involved in CAE was the right coronary artery. These finding was consistent with previous studies [33,43].

In our study, patients with CAE and CAD tended to be younger than patients with CAD. Also, younger age was related with CAE. While similar results were found in some studies [4], age was not significantly different in others [44]. Also, there were more males (86.5%) among patients with CAE and CAD compared to the patients with CAD in our study. This difference was significant in univariate analysis but it not in multivariate analysis. Several reports show that CAE is more predominant in males, like in our study [4,45].

There were some limitations in this study. First, it was conducted on a small number of patients. Second, this was a single-center, retrospective study. Third, other inflammatory markers like ICAM-1, tumor necrosis factor-alfa, Eselectin, matrix-metalloproteinases, and interleukin-6 related with CAE were not assessed. Fourth, coronary angiography is an invasive diagnostic

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procedure that allows visualization of the coronary artery lumen, but there are some limitations of coronary angiography, including lack of visualization of the vascular wall. Therefore, angiography cannot detect the atherosclerotic plaque in patients without evidence of luminal narrowing by coronary angiography. It would be better to evaluate with intravascular imaging techniques such as intravascular ultrasound for detecting evidence of atherosclerosis. Fifth, tissue samples were not used in our study and our findings need to be supported by tissue-based prospective studies.

Conclusions

In our study, CRP and uric acid were higher in patients with CAE and CAD compared to the patients with only CAD. Also, CRP and uric acid were associated with CAE in patients with CAD. The fact that CRP and uric acid levels were higher in patients with CAE and CAD reflects higher-grade vascular inflammation in patients who have both CAE and atherosclerosis than in those with atherosclerotic involvement only. Anti-inflammatory treatments are considered in the current guidelines of CAD [38,39]. CAE, as a subgroup of coronary artery disease, may benefit from anti-inflammatory treatment due to the increased inflammatory activity. Results of this study may encourage further research into inflammation and anti-inflammatory therapies on CAE in patients with CAD. These findings need to be supported by tissue-based studies.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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