The Value of Clinical Risk Factors and Inflammatory Biomarkers in Isolated Coronary Artery Ectasia: A Cross-Sectional Study From a Tertiary Center

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Abstract: Objectives. Coronary artery ectasia (CAE) is a clinical condition with uncertain etiology. Atherosclerosis is a well-known risk factor for CAE. Recently, inflammation and oxidative stress were found to be associated with CAE. The aim of this cross-sectional study was to evaluate the association of atherosclerotic risk factors and inflammatory biomarkers with isolated CAE. **Methods.** Fifty-two patients with isolated CAE and 45 patients with angiographically normal coronary arteries were retrospectively analyzed. Inflammatory biomarkers such as neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammatory index (SII), monocyte-to-high-density lipoprotein ratio (MHR), and atherogenic index of plasma (AIP) were calculated. **Results.** AIP levels were significantly higher in patients with CAE than the control group (0.55 ± 0.32 vs 0.42 ± 0.28, *P*=.04, respectively). SII, MHR, and NLR levels were similar between the groups. Multivariate logistic regression analysis revealed that male gender (Odds ratio [OR] 5.49, 95% confidence interval [CI] 1.89-15.87; *P*=.002) and hyperlipidemia (OR 3.14, 95% CI 1.13- 8.66; *P*=.02) were independent predictors of CAE. **Conclusions.** Our study showed that clinical risk factors of atherosclerosis may be more important in CAE pathogenesis than inflammatory biomarkers.

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Introduction

Coronary artery ectasia (CAE) is an uncommon but well-known congenital or acquired anatomical abnormality of the coronary arteries.[1] It is defined as diffuse or localized dilation of an epicardial coronary artery segment with a diameter of more than 1.5 times the normal coronary artery segment.[2] Previous studies showed various possible mechanisms for CAE. Congenital disorders such as Ehlers-Danlos syndrome and polycystic renal disease, many types of connective tissue diseases, and vasculitis are associated with CAE.[3-5] In addition, atherosclerosis and inflammation play a significant role in the ethiopathogenesis of CAE.[6,7] CAE is related to remodeling caused by atherosclerosis. Some prior histopathological studies showed damage of collagen and elastin, as well as accumulation of inflammatory cells, in ectatic arteries. One of the most important mechanisms for CAE is vascular inflammation, which is mainly triggered by oxidative stress.[5] CAE has been associated with a variety of clinical scenarios ranging from stable angina pectoris to myocardial infarction, and even death.[8] Therefore, it is an important clinical condition that requires strict risk modification. Determining the possible mechanism for CAE is crucial to decrease the cardiovascular risk. We hypothesized that there may be a difference between the relationship of clinical atherosclerotic risk factors and inflammatory biomarkers with CAE. Therefore, this cross-sectional study aimed to investigate the value of clinical atherosclerotic risk factors and inflammatory biomarkers in the pathogenesis of CAE based on tertiary center outcomes.

Methods

A total of 3107 consecutive patients who underwent elective coronary angiography between December 2020 and January 2022 were retrospectively analyzed in our observational and cross-sectional study. Among these patients, 52 with CAE were included in the study. Isolated CAE was defined as a localized or diffusely dilated epicardial coronary artery with a diameter of 1.5-fold or greater of a normal coronary segment. A healthy control group (n = 45) was composed of patients who had normal coronary arteries without CAE. Exclusion criteria were defined as need for urgent coronary artery bypass graft operation, end-stage renal and/or liver disease, recent infection, being on an immunosuppressive therapy, connective tissue disease, malignancy, severe frailty, and previously known systemic inflammatory disease. Of the enrolled patients, 12 were excluded due to having at least 1 of these exclusion criteria. Two patients who had missing laboratory data were excluded. Finally, 97 patients met the criteria for final analysis. The control group was composed of first-admitted patients with normal coronary arteries following patients with CAE to avoid selection bias. Our study complied with the edicts of the 1975 Declaration of Helsinki and was approved by the local medical ethical committee. Written informed consent was obtained from all patients. Demographic, clinical properties, and laboratory measurements were obtained from the electronic medical database. Age; gender; presence of hypertension (HTN), diabetes mellitus (DM), and hyperlipidemia (HL); inflammatory biomarkers such as neutrophil-to-lymphocyte ratio

Table 1. Clinical and demographic features of the study population.

	Coronary ectasia (+) (n = 52)	Coronary ectasia (-) (n = 45)	*P*-value
Age, years	62 ± 9.6	58.8 ± 12.3	.14
Male gender	36 (69.2%)	18 (40%)	.004
Diabetes mellitus	21 (40.4%)	12 (26.7%)	.16
Hypertension	35 (67.3%)	21 (46.7%)	.04
Hypercholesterolemia	20 (57.7%)	14 (31.1%)	.009
AIP	0.55 ± 0.32	0.42 ± 0.28	.04
SII	568.3 ± 376.6	572.7 ± 292.7	.95
MHR	16.4 ± 8.8	17.1 ± 13.9	.77
NLR	2.3 ± 1.2	2.5 ± 1.8	.49

AIP = atherogenic index of plasma; MHR = monocyte-to-high-density lipoprotein ratio; NLR = neutrophil-to-lymphocyte ratio; SII = systemic immune-inflammatory index

Table 2. Biochemical characteristics of the study population.

	Coronary ectasia (+) (n = 52)	Coronary ectasia (-) (n = 45)	*P*-value
Serum glucose level on admission (mg/dL)	119.1 ± 45.8	123.3 ± 67.6	.72
HbA1c (%)	6.5 ± 1.4	6.2 ± 0.9	.13
Creatinine level on admission (mg/dL)	0.91 ± 0.26	0.85 ± 0.27	.25
BUN (mg/dL)	15.7 ± 3.9	16 ± 6.7	.33
Total cholesterol (mg/dL)	186.7 ± 40.6	193.7 ± 47.2	.43
LDL-C (mg/dL)	127.3 ± 38.9	133.1 ± 39.7	.47
HDL-C (mg/dL)	40.1 ± 12.3	38.8 ± 11.1	.15
Triglycerides (mg/dL)	180.3 ± 116.8	140.6 ± 71.1	.05
Hemoglobin (gr/dL)	13.6 ± 1.8	12.9 ± 1.9	.08
Leukocyte (/mm^3)	8560 ± 2600	7877 ± 2416	.19
Lymphocyte (/mm^3)	2696 ± 1740	2268 ± 826	.14
Neutrophil (/mm^3)	4975 ± 1719	4784 ± 1843	.60
Platelet (/mm^3)	244,673 ± 68,093	250,333 ± 70,004	.69
Monocyte (/mm^3)	682.7 ± 263.9	781.8 ± 696.3	.34

BUN = blood urea nitrogen; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol

Table 3. Multivariate and univariate predictors of coronary ectasia.

	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
SII	1.01 (1.0-1.02)	.98		
AIP	4.19 (1.01-17.28)	.04		
NLR	0.91 (0.69-1.18)	.48		
MHR	0.99 (0.96-1.03)	.77		
Age	1.03 (1.0-1.07)	.14		
Male gender	3.38 (1.46-7.80)	.004	5.49 (1.89-15.87)	.002
Hypertension	2.35 (1.03-5.36)	.04		
Hyperlipidemia	3.02 (1.31-6.98)	.01	3.14 (1.13-8.66)	.02

AIP = atherogenic index of plasma; CI = confidence interval; MHR = monocyte-to-high-density lipoprotein ratio; NLR= neutrophil-to-lymphocyte ratio; OR = odds ratio; SII = systemic immune-inflammatory index

(NLR), systemic immune-inflammatory index (SII), and monocyte-to-high-density lipoprotein ratio (MHR); and atherogenic index of plasma (AIP) comprised the demographic and clinical data. Venous blood samples were obtained at hospital admission following 12 hours of fasting and included complete blood count and detailed biochemical parameters such as fasting serum glucose, HbA1c, admission creatinine, total serum cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides. NLR consisted of division of the neutrophil count by the lymphocyte count. SII was calculated by total peripheral platelet count times NLR.[9] MHR was monocyte count divided by HDL-C level. AIP was defined as log (triglyceride/HDL-C).[10] Angiographic evaluation was performed by 2 independent, experienced interventional cardiologists who were unaware of the clinical and laboratory data of the patients. The study population was divided into 2 groups according to the occurrence of CAE, which were defined as the patients with CAE group (n = 52) and the healthy control group (n = 45).

Statistical Analysis

Continuous variables were given as mean ± standard deviation, while categorical variables were presented as percentages. The Kolmogorov–Smirnov test was used for testing the normality of distributions. Student-T test or Mann Whitney U test was used for continuous variables, and chi-square test was used for categorical variables to compare the study groups. Independent predictors of isolated CAE were determined by the multivariate logistic regression analysis. Values of $P<.05$ were considered statistically significant. SPSS 22 software was used for statistical analysis.

Results

The clinical and demographic features, and laboratory information of the study groups, are shown in **Table 1** and **Table 2**, respectively. Patients with CAE had a higher prevalence of HTN, HL, and male gender. In addition, frequency of DM and age were similar between the groups. AIP levels were significantly higher in the CAE group, whereas SII, MHR, and NLR levels were similar between the groups. Whole laboratory measurements also were similar between the groups, except for triglyceride levels. Univariate and multivariate logistic regression analysis results according to CAE are shown in **Table 3**. The following variables were used in analysis: HTN, age, HL, male gender, SII, MHR, AIP, and NLR. Among these variables, male gender (OR 5.49,

95% CI 1.89-15.87; *P*=.002) and HL (OR 3.14, 95% CI 1.13-8.66; *P*=.02) were identified as independent predictors of CAE.

Discussion

In this cross-sectional study, we investigated the value of atherosclerotic risk factors and inflammatory biomarkers in the pathogenesis of isolated CAE. Our results demonstrated that male gender and HL were independently associated with CAE. However, inflammatory biomarkers did not provide significant information about the presence of CAE. CAE may be a serious clinical condition with adverse cardiovascular outcomes. Because the mortality risk of patients with CAE is similar to those with obstructive coronary artery disease (CAD), it is important to identify these patients. Different hypotheses have been proposed regarding the pathophysiology of CAE, but it is still controversial. Previous reports demonstrated a common pathophysiological mechanism between CAD and CAE.[11] Well-defined atherogenic clinical risk factors, such as HT, DM, HL, smoking, and family history, were also documented as risk factors for CAE. Two pathologies resemble, in terms of pathological findings of the lesions, the increase in frequency with age and having similar clinical presentations. A study conducted by Fariba et al[12] showed that coronary heart disease risk factors were most prevalent in patients with CAE. This may be the reason why the prevalence of clinical risk factors, such as male gender and HL, was higher in the CAE group, according to our results.

The association between atherosclerosis and CAE is well-documented.[13] AIP, which is defined as logarithm of the ratio between triglycerides and HDL-C, reflects the level of atherogenic small dense LDL-C and rapid progression of the coronary atherosclerosis. This value has been used as an index for CAD. AIP levels were significantly higher in patients with CAE than the control group, according to our results. This also shows the effect of atherosclerosis on CAE consistent with the literature. It had been previously reported that inflammation and the slowly progressing degenerative process play a crucial role in the pathogenesis of atherosclerosis and CAE.[14,15] The main change occurs in the media layer of ectatic coronary arteries. Degeneration in the media layer and an increase in metalloproteinase enzyme activity and inflammatory processes were mostly seen in the histopathological examinations of CAE cases. Various studies with different inflammatory biomarkers have shown significant association between CAE and inflammation.[16,17] The role of inflammatory modulators in determining atherosclerosis and cardiovascular risk has been emphasized in those studies. Kalaycioglu et al demonstrated a significant association between NLR and severity of isolated CAE.[18] Also, they concluded that isolated CAE may be associated more closely with severe inflammation than obstructive CAD. The reason why the inflammatory biomarkers were not found to be associated with CAE in our study may be due to the small size of our study population.

Male gender is an important risk factor for the presence of CAE.[19] A study conducted by Fariba et al[12] showed that CAE was mostly prevalent in men and those with HTN. In accordance, our results revealed that male gender was significantly predominant in the CAE group (69.2% vs 40%). The higher incidence of CAE in men may be due to the higher incidence of atherosclerosis risk factors in men and the association of CAE with atherosclerosis.

Several prior studies have also reported a significant association between hyperlipidemia and CAE. Familial hypercholesterolemia and dyslipidemia have been reported to be more common in patients with CAE.[20] Likewise, we found a high prevalence of hyperlipidemia in patients with CAE compared with the normal coronary control group. In our study, we observed that patients with CAE had an increase in clinical risk factors for atherosclerosis compared with the control group. Moreover, inflammatory biomarkers were not found to be associated with CAE. These findings hypothesize that atherogenic clinical risk factors may play a more important role in the pathogenesis of CAE. This may be because these strong, well-defined clinical risk factors are more prominent and have a predominant effect on adverse outcomes. In addition, the level of inflammatory biomarkers may differ during the clinical condition and be influenced by many different parameters.

Our study had few limitations. The small size of the study group and the cross-sectional design of the study were the main limitations. Also, data for long-term follow-up were missing. Although we found that clinical risk factors of atherosclerosis were more valuable than inflammatory biomarkers in the pathogenesis of CAE, validation of our findings in larger prospective studies is needed.

Conclusion

In conclusion, our study showed that clinical risk factors of atherosclerosis, such as HL and male gender, were independently associated with CAE. Therefore, it may be considered that these well-known clinical risk factors have a more important role in the pathogenesis of CAE compared with inflammatory biomarkers. ■

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