Big Endothelin 1/Serum Uric acid Ratio as A predictor of Isolated Coronary Artery Ectasia

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Abstract
Background: Coronary artery ectasia (CAE) is the over-expansion of coronary arteries, which can cause Acute coronary syndrome (ACS); its causes and pathophysiology are under research until now.
Aim of the work: Investigate a novel laboratory predictor of isolated coronary artery ectasia in chronic stable coronary artery syndrome patients, using Big Endothelin-1(ET-1), highly sensitive CRP, and Big Endothelin 1 / serum uric acid ratios.
Methods: Within our study, we highlight the relation between Big Endothelin 1 / serum uric acid ratio as a predictor of isolated coronary artery ectasia; we measured big ET-1 and serum uric acid with enzyme-linked immunosorbent assay (ELISA) in 135 patients (CAE, n=50; CAD, n=45; normal, n=40) and assessed the connection with isolated CAE.
Results: The Big Endothelin 1/serum uric acid ratio was a significant predictor of CAE, Big Endothelin 1/serum uric acid ratio is strongly linked with CAE by multivariate analysis (OR 95%CI: 0.29 (0.14-0.61), p=0.001).
Conclusions: A higher level of Big Endothelin 1 / serum uric acid ratio was a predictor independently associated with CAE patients. These marker levels may, therefore, provide diagnostic information for CAE patients.

Keywords: Big Endothelin, serum uric acid, LDL, CAE, HDL

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Introduction

Coronary artery ectasia (CAE) is described by the abnormal dilation of a coronary artery to at least one and half times the diameter of the adjacent healthy segment, involving at least one-third of the entire arterial length. It is a variant of coronary artery disease (CAD) and can occur in 0.3-8% of coronary angiography patients and 0.22-1.4% of autopsy series. It may occur alone or in combination with stenotic lesions [1].

The presence of ecstatic segments in the coronary arteries can lead to sluggish blood flow, which can contribute to exercise-induced angina (chest pain), myocardial infarction (heart attack), and the strictness of any associated stenotic lesions (narrowing of the artery) [2]. The "ectasia" describes the coronary artery diffuse dilatation, while the "aneurysm" is related to a focal dilatation. In the context of CAE, a 1.5-2-fold normal coronary artery dilatation on angiography indicates CAE, while a dilatation larger than two-fold is classified as a coronary aneurysm[3].

Although the reported incidence of CAE may overestimate its actual frequency in the general population, it remains a form of CAD that challenges clinicians to understand its causes, natural course, and treatment options. Coronary artery ectasia (CAE) can have various underlying causes, including atherosclerosis, congenital

origins, and inflammatory and connective tissue diseases. Atherosclerosis is the most common cause, accounting for approximately 50% of cases. In many patients with CAE, it coexists with coronary artery disease (CAD), characterized by plaque build-up in the arteries [4].

Coronary artery ectasia (CAE) is associated with sluggish or turbulent blood flow due to aneurysmal segments. This can lead to an escalation of exercise-induced angina pectoris incidence (chest pain) and myocardial infarction (heart attack), unrelated to the coexisting stenotic lesions severity (narrowing of the artery). Among patients with coronary artery ectasia (CAE), those with pure ectasia, constituting approximately 15% of CAE cases, typically experience a less severe disease progression. However, it is worth noting that around 39% of these patients still display indications of prior myocardial infarction [5].

The exact pathophysiology of CAE needs to be better defined. Still, various factors have been implicated, including oxidative stress, endothelial dysfunction, enhanced platelet activity, microvascular disease, inflammation, and exaggerated positive vascular remodeling. Atherosclerotic plaques lie in a depression in the media layer of the blood vessel wall rather than projecting into the lumen. Arterial remodeling, which involves both expansion and shrinkage of the artery, is a fundamental process in coronary artery disease pathophysiology. Positive remodeling, characterized by arterial expansion, is frequently linked to unstable coronary syndromes. On the other hand, adverse remodeling, which involves arterial shrinkage, is associated with stable coronary syndromes [6].

Coronary ectasia may represent a severe form of atherosclerotic plaque growth-induced expansive vascular remodeling. The medial extracellular matrix degradation, a crucial pathological process, is induced by multiple factors. Changes in blood flow dynamics and alterations in the inflammatory and fibroproliferative responses play significant roles in the development of atherosclerosis. Inflammation has been identified as a critical factor in the pathogenesis of atherosclerosis, with its involvement from the early stages to progression and thrombotic complications[7].

It is believed to involve the destruction of the tunica media and the infiltration of inflammatory cells in the ectatic segments. Various studies have examined the relationship between inflammation and CAE, and isolated CAE patients showed higher levels of adhesion molecules, C-reactive protein (CRP) with high-sensitivity, matrix metalloproteinase, interleukin-6, and leukocytes, monocytes, and neutrophils compared to patients with obstructive CAD [8].

Specific proteins have been implicated in developing coronary ectasia and destroying the extracellular matrix. These proteins are released from neutrophils, and various environmental cues and inflammatory stimuli influence their activation. The neutrophil extracellular traps (NETs) are linked to atherothrombosis, endothelial dysfunction, atherogenesis, and experimental abdominal aortic aneurysm. Autopsy studies have confirmed that the destruction and degradation of elastic fibers in the blood vessels middle layer are the principal pathological features of coronary artery dilation [9].

Endothelin-1 (ET-1) is a highly potent and long-lasting vasoconstrictor peptide. Endothelin-1 (ET-1) synthesis is primarily regulated at the gene transcription level, producing big ET-1 as an inactive intermediate. This intermediate can be cleaved by endothelin, an enzyme converting enzyme (ECE) forming active ET-1. ET-1 exerts its physiological effects through two receptors: Endothelin receptor A (ETA) and endothelin receptor B (ETB). These receptors have different distributions and effects, suggesting that ET-1 may have separate roles in various organs [10].

Endogenous ET-1 is thought to contribute to the progression of different cardiovascular diseases. In clinical practice, ET receptor antagonists treat patients with pulmonary hypertension. Additionally, these antagonists are being investigated as potential treatment options for heart failure, cardiac hypertrophy, systemic hypertension, cerebral vasospasm, and renal diseases. ET antagonists hold promise in managing these conditions and their associated cardiovascular complications [11].

In recent years, numerous markers of inflammation have emerged as potential indicators of coronary artery ectasia (CAE) and the severity of CAE. A correlation between the CAE progression and inflammatory markers, including uric acid, high-sensitivity C-reactive protein (hs-CRP), visfatin, endocan, interleukin-6 (IL-6), liver enzymes, big endothelin-1, and white blood cells is developed [12-15].

This work aims to find a novel laboratory predictor of isolated coronary artery ectasia in chronic stable coronary artery syndrome patients, using Big Endothelin-1(ET-1), highly sensitive CRP, and Big Endothelin 1 / serum uric acid ratios.

Methods

The prospective study included 135 patients from individuals referred for coronary angiography between May 2022 and October 2022. All patients were selected from the cardiac catheterization laboratory of Minia University Hospital. Based on the results of coronary angiography, patients were divided into three equal groups (all groups are age, sex, and cardiovascular risk factors matched.

Patients' medical history, clinical examination, electrocardiogram, echocardiography with complete study and comments on Trans-thoracic echocardiographic assessment:

It was performed with The ACUSON SC2000 PRIME ultrasound system, Siemens, Germany. An echocardiographic study was done using 2D, M-mode and Doppler and tissue Doppler techniques. All members of the study population were examined in the left lateral recumbent position and will be asked to avoid deep inspiration or Valsalva maneuver. Systolic and diastolic functions of LV were assessed, LA antero-posterior diameter and aortic root (Ao) dimensions as well as LA/Ao ratio was measured in PLAX view

LV diastolic function was assessed by mitral inflow pattern in apical 4-chambers view and calculating E/A ratio. 'E' wave represents the early ventricular diastole and 'A' wave represents the atrial contraction and septal tissue Doppler velocities to estimate e`/a`, e` represents early diastolic annular velocity, a` represents annular late diastolic velocity ,pulmonary hypertension state all included. All Echocardiographic measurements were performed according to the recommendations of American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) guidelines [16]. By two blinded examiners and measurements were averaged. Complete blood count, Fasting blood glucose (FBG), Liver function test, lipid profile, High

Sensitive CRP(hsCRP), significant Endothelin-1 level (Big),serum uric acid level. The included patients were evaluated regarding age, sex, and risk factors.

Coronary angiography

Coronary angiography was performed by Retrograde catheterization of the heart. The angiograms were examined by two impartial interventional cardiologists unaware of the patient's clinical condition or laboratory test results.

Exclusion Criteria

Exclusion criteria refer to specific conditions, diseases, or medical histories that were used to exclude certain individuals from participating in the study. In this context, the exclusion criteria are as follows:

Patients with any of the following were excluded. Acute coronary syndrome, Significant valvular disease (more than mild), Heart failure, Cardiomyopathies, Significant kidney, lung, or liver disease, Systemic connective tissue diseases, Any chronic or acute inflammatory disease, Thyroid function disorder, Malignancy Pacemaker implantation, hematological disorders, history of malignancy and other chronic systemic diseases, acute or chronic infection and stroke [5-7]. All participants who were found to have any of these conditions or met any of these criteria were excluded from the study. All patients and control individuals who participated in the study gave informed consent, and the local ethics committee approved the study.

Statistical analysis:

The statistical analysis method utilized in this study involves the following steps:

The data is presented using the Median, interquartile range (IQR), number, and percent to summarize the quantitative and qualitative variables. The Mann-Whitney Test is applied for comparing quantitative data between two groups when the data is non-parametric, meaning it does not meet the assumptions of normality. The Kruskal-Wallis Test compares quantitative data among multiple groups when the data is non-parametric. The Chi-square test is used for qualitative data comparison between groups when the expected count in less than 20% of cells is less than 5. However, Fisher's Exact test is utilized if more than 20% of cells have an expected count of less than 5. The significance level is set at P value < 0.05, indicating that any result with a p-value less than 0.05 is considered statistically significant. In summary, this statistical analysis approach utilizes appropriate non-parametric tests for comparing data between groups and applies the significance level to determine statistically significant results. Median and IQR instead of mean and standard deviation are particularly suitable for non-parametric data, where extreme values or non-normal distributions can affect the results.

Sample collection and storage

Blood samples are collected from patients before coronary angiography under complete aseptic conditions; specimens clot for two hours at room temperature or overnight at 4°C before centrifugation for 20 minutes at approximately 1000xg. Serum samples were then stored in aliquots at -20°C for later use (repeated freeze/thaw cycles were avoided).

Human Endothelin 1 (EDN1) measurement

ELISA Kit is a sandwich enzyme immunoassay for the in vitro quantitative measurement of EDN1 in human serum or other biological fluids.

Results:

135 patients were included in this study. Patients were categorized into the following three groups:

- Group (A): (control group) 40 normal coronary angiography patients.
- Group (B): 50 CAE patients.
- Group (C):45 patients with only obstructive coronary artery disease.

Table 1: Demographic and baseline clinical data of different study groups

Characteristic	Total	control group (A) (n =40)	coronary artery ectasia (B) (n =50)	Obstructive coronary artery disease (C) (n =45)	P value			
					total	A Vs B	A Vs C	B Vs C
Age (month)								
Median± IQR	56.0±14	55.00±12.0	55.50±12.0	60.00±15.00	0.157	0.528	0.045*	0.252
Minimum	31	35	31	40				
Maximum	75	65	75	72				
gender								
Male	79(58.5%)	13(32.5%)	32(64.0%)	34(75.6%)	<0.001 *	<0.001*	0.003*	0.222
Female	56(41.5%)	27(67.5%)	18(36.0%)	11(24.4%)				
Diabetes								
Diabetic	55(40.7%)	20(44.4%)	14(28.0%)	21(52.5%)	0.052	0.458	0.018*	0.095
Not diabetic	80(59.3%)	25(55.6%)	36(72.0%)	19(47.5%)				
Hypertension								
Hypertensive	71(52.6%)	23(51.1%)	18(36.0%)	30(75.0%)	0.001*	0.023*	<0.001*	0.138
Not Hypertensive	64(47.4%)	22(48.9%)	32(64.0%)	10(25.0%)				
Smoking								
Smoker	56(41.5%)	20(44.4%)	24(48.0%)	12(30.0%)	0.201	0.170	0.083	0.729
Non Smoker	79(58.5%)	25(55.6%)	26(52.0%)	28(70.0%)				
Weight (Kg)								
Median± IQR	80.0±7.0	79.00±5.00	80.00±10.0	80.0± 9.0	0.561	0.482	0.287	0.684
Minimum	64	70	64	70				
Maximum	95	95	95	94				
height (cm)								
Median± IQR	169.0±5.0	165.00± 7.00	170.0±7.0	170.00±7.0	0.006*	0.013*	0.002*	0.649
Minimum	160	160	160	162				
Maximum	178	173	178	177				
BMI (Kg/m2)								
Median± IQR	27.68±3.05	27.85±4.28	27.68±2.98	27.68±2.94	0.734	0.371	0.659	0.887
Minimum	22.49	23.99	22.49	24.22				
Maximum	37.11	37.11	33.87	33.06				
Diastolic D								
• **0**	17(12.6%)	4(8.9%)	6(12.0%)	7(17.5%)	0.169	0.063	0.256	0.519
• **1**	76(56.3%)	29(64.4%)	30(60.0%)	17(42.5%)				
• **2**	40(29.6%)	10(22.2%)	14(28.0%)	16(40.0%)				
• **3**	2(1.5%)	2(4.4%)	0(0.0%)	0(0.0%)				
EF %								
Median ±IR	61.0±8.0	61.0±5.0	60.0±8.0	61.00±8.0	0.618	0.573	0.681	0.340
Minimum	30	38	30	48				
Maximum	78	70	78	77				
E velocity cm/s								
Median ±IR	69.0±17.0	67.00±16.75	69.50±17.00	69.00±13.00	0.568	0.476	0.284	0.754
Minimum	45.0	55.0	45.0	56.0				
Maximum	88.0	88.0	86.0	82.0				
A velocity cm/s								
Median ±IR	70.0±18.0	68.50±22.0	70.0±18.75	73.00±13.32	0.057	0.122	0.018*	0.366
Minimum	20.0	40.0	41.0	20.0				
Maximum	115	87.0	115.0	90.0				
E\A ratio								
Median ±IR	0.929±0.357	1.17±0.416	0.932±0.322	0.88±0.31	0.078	0.067	0.038*	0.631
Minimum	0.649	0.80	0.649	0.788				
Maximum	3.85	1.47	1.90	3.85				
TDI (Ea Cm/s)								
Median ±IR	11.0±7.0	11.00±9.0	11.00±6.0	11.00±7.00	0.961	0.928	0.947	0.739
Minimum	3	4.0	4	3.0				

Maximum	16	16.0	15	15.0				
Lt ventricle dimensions **Median ±IR** **Minimum** **Maximum**	5.0±0.60 3.80 6.10	5.00±0.80 4.0 5.80	5.0±0.50 4.20 6.10	5.00±0.50 3.80 5.90	0.833	0.512	0.968	0.717
Lt Atrium dimensions **Median ±IR** **Minimum** **Maximum**	3.70±0.40 3.0 4.90	3.80±0.375 3.20 4.20	3.65±0.625 3.00 4.90	3.70±0.35 3.00 4.70	0.280	0.455	0.080	0.524
Aorta diameter **Median ±IR** **Minimum** **Maximum**	2.80±0.50 2.0 3.50	2.80±0.40 2.50 3.30	2.70±0.60 2.00 3.50	2.70±0.50 2.10 3.50	0.359	0.157	0.397	0.544
PASP **Median ±IR** **Minimum** **Maximum**	29.0±8.0 3.4 50.0	30.0±10.8 3.4 50.0	29.00±9.0 20.0 45.0	2.800±3.0 23.0 39.0	0.551	0.699	0.343	0.382
LA/Ao **Median ±IR** **Minimum** **Maximum**	1.33±0.189 0.969 2.0	1.33±0.146 1.03 1.56	1.35±0.215 1.00 2.00	1.33±0.18 0.969 1.81	0.475	0.342	0.853	0.268

IQR: interquartile range *BMI: Body mass index*
PASP: Pulmonary artery systolic pressure *LA/Ao: Left atrium to aorta ratio*
EF%: Ejection fraction *TDI: Tissue Doppler imaging*
Data displayed as Median, interquartile range (IQR), number, and percent

Table 1 presents the demographic and baseline clinical data of different study groups, which are referred to as the control group (A), coronary artery ectasia (B), and obstructive coronary artery disease (C). The table contains various characteristics, and each characteristic is compared among the different study groups. The statistical analysis was performed using the different described in the table. The tests used include the Mann-Whitney and Kruskal-Wallis tests for non-parametric quantitative data and the chi-square test for qualitative data. The significance level was set at a p-value of less than 0.05.

The age, weight, and smoking status differences among the three groups are not statistically significant ($P > 0.05$). There is a statistically significant difference in gender distribution among the groups. The total and all pairwise comparisons show significant differences ($P < 0.001$). The presence of diabetes shows a statistically significant difference between the groups in the total comparison and the comparison between group C and the others ($P < 0.05$). The presence of hypertension exhibits a statistically significant difference between the groups in all comparisons.

All comparisons show a critically significant height difference and BMI between the groups. diastolic dysfunction levels and EF % do not offer a statistically significant difference between the groups. The E and A velocities show a statistically significant difference between group C and the others. Tissue Doppler Imaging (TDI) Ea velocity does not show a statistically significant difference between the groups. There is no statistically significant difference in left ventricle dimensions between the groups. The groups have no statistically significant difference in left atrium dimensions and aorta diameter. No statistically significant difference exists between the PASP ratio and LA/Ao groups.

The results indicate statistically significant differences in some characteristics (gender, diabetes, hypertension, height, E velocity, A velocity, E/A ratio). In contrast, other

characteristics (age, smoking, weight, BMI, Diastolic D, EF %, TDI Ea Cm/s, left ventricle dimensions, left atrium dimensions, aorta diameter, PASP, LA/Ao) do not show significant differences among the study groups.

Table 2: Laboratory data among different study groups

Characteristic	Total	Control group(A) (n =40)	Coronary artery ectasia (B) (n =50)	obstructive coronary artery disease (C) (n =45)	P value			
					Total	A Vs. B	A Vs. C	B Vs. C
Direct Bilirubin **Median± IQR** **Minimum** **Maximum**	0.10±0.10 0.00 0.80	0.10±0.10 0.0 0.80	0.10±0.10 0.02 0.80	0.10±0.10 0.10 0.20	0.346	0.589	0.438	0.138
Cholesterol **Median± IQR** **Minimum** **Maximum**	160.0±50.0 100 280	155.0±30.0 100 200	160.0±51.0 110 280	190.0±70.0 115 250	0.001*	0.104	<0.001*	0.042*
TRIG **Median± IQR** **Minimum** **Maximum**	155.0±60.0 55 290	115.0±20.0 85 165	147.50±66.0 55 290	115±63.0 85 230	0.009*	0.002*	0.150	0.137
LDL **Median± IQR** **Minimum** **Maximum**	99.0±48.0 43 188	88.0±28.0 43 127	94.50±45.0 43 188	122.0±56.0 51 173	0.001*	0.116	<0.001*	0.016*
HDL **Median± IQR** **Minimum** **Maximum**	38.0±5.0 28 60	4.0±2.0 33 45	38.0±5.0 28 60	38.0±5.0 30 55	0.027*	0.010*	0.036*	0.806
Uric Acid **Median± IQR** **Minimum** **Maximum**	5.40±2.25 2.40 11.30	3.80±0.70 2.90 5.30	6.40±0.95 4.40 11.30	5.30±1.50 2.40 9.50	<0.001*	<0.001*	<0.001*	<0.001*
HSCRP **Median± IQR** **Minimum** **Maximum**	4.05±9.90 0.10 41.0	3.10±3.40 0.10 26.50	3.60±7.93 0.20 31.0	12.0±19.60 0.30 41.0	<0.001*	0.104	<0.001*	0.001*
Big Endothelin 1 **Median± IQR** **Minimum** **Maximum**	24.0±43.0 1.0 170.0	5.50±3.0 1.0 22.0	23.0±27.75 3.50 170.0	51.0±21.50 13.0 112.50	<0.001*	<0.001*	<0.001*	<0.001*

IQR: interquartile range **HSCRP**: High-sensitivity C-reactive protein
HDL: High-density lipoprotein **LDL**: Low-density lipoprotein
Data displayed as Median and interquartile range (IQR)

The laboratory data among the different study groups (A, B, and C) show significant variations in several characteristics. Notably, cholesterol, TRIG, LDL, uric acid, HSCRP, and Big Endothelin 1 levels exhibit significant differences between the groups, indicating potential associations with the different coronary artery conditions. On the other hand, direct bilirubin and HDL levels do not show significant differences between the groups. The findings suggest that these laboratory parameters play a role in distinguishing between coronary artery ectasia and obstructive coronary artery disease. Further investigation is warranted to understand the clinical implications of these differences and their potential role in disease diagnosis and management.

In summary, Table 2 compares different characteristics between the three groups (A, B, and C). It shows that some characteristics, such as cholesterol, TRIG, LDL, HDL, uric acid, HSCRP, and Big Endothelin 1, exhibit significant differences between the groups. In contrast, others, like direct bilirubin, do not show any significant differences.

Table 3: Laboratory results for studied groups

Characteristic	Total (n =135)	Control group(A) (n =40)	Coronary artery ectasia (B) (n =50)	Obstructive coronary artery disease (C) (n =45)	P value			
					Total	A Vs. B	A Vs. C	B Vs. C
ALT/AST **Median± IQR** **Minimum** **Maximum**	1.15±0.52 0.39 2.50	1.05±0.40 0.57 1.77	1.15±0.60 0.39 2.50	1.23±0.48 0.66 2.00	0.018*	0.061	0.005*	0.334
HSCRP/serum uric acid ratio **Median± IQR** **Minimum** **Maximum**	0.99±1.75 0.03 7.55	0.88±1.04 0.03 6.97	0.52±1.06 0.03 4.77	2.07±3.22 0.05 7.55	<0.001*	0.900	<0.001*	<0.001*
Big Endothelin 1 / serum uric acid ratios **Median± IQR** **Minimum** **Maximum**	4.06±6.99 0.29 28.33	1.51±0.65 0.29 6.55	3.53±4.77 0.59 28.33	9.81±5.83 3.17 22.08	<0.001*	<0.001*	<0.001*	<0.001*
LDL/HDL ratio **Median± IQR** **Minimum** **Maximum**	2.61±1.35 0.96 5.75	2.27±0.87 1.13 3.47	2.58±1.17 0.96 5.75	3.24±1.53 1.16 4.66	<0.001*	0.022*	<0.001*	0.011*
HSCRP/Albumin ratio **Median± IQR** **Minimum** **Maximum**	0.90±2.27 0.02 11.43	0.65±0.83 0.02 7.57	0.88±1.90 0.05 6.83	2.67±4.56 0.07 11.43	<0.001*	0.118	<0.001*	0.002*

IQR: interquartile range
HSCRP: High-sensitivity C-reactive protein
ALT: Alanine aminotransferase
AST: Aspartate transaminase
HDL: High-density lipoprotein
LDL: Low-density lipoprotein

Table 3 presents various ratios and measurements in different groups (A, B, and C) and the total group. The characteristics include ALT/AST ratio, HSCRP/serum uric acid ratio, Big Endothelin 1/serum uric acid ratio, LDL/HDL ratio, and HSCRP/Albumin ratio. Table 3 shows the Median, interquartile range (IQR), minimum, and maximum values for each ratio in each group. Additionally, Table 3 provides p-values to indicate the statistical significance of the differences between the groups for each ratio.

The total group and group C have significantly higher ALT/AST ratios than group A. There are significant differences in this ratio between all groups. There are significant differences in this ratio between all groups. The total group and group C have significantly higher LDL/HDL ratios than group A. There is also a significant difference between groups A and B. There are significant differences in this ratio between all groups.

The results suggest potential associations with coronary artery ectasia and obstructive coronary artery disease. These ratios serve as valuable indicators for understanding the pathophysiology and differentiation of the two conditions. Further investigation and validation would be practical to confirm the clinical significance of these findings.

Table 4: Multivariate binary logistic regression for prediction of coronary artery ectasia

Predictors	Odds ratio	C.I 95%		P-value
		Lower	Upper	
HDL	0.95	0.51	1.78	0.879
LDL	1.21	0.73	1.99	0.460
CHOLESTEROL	0.86	0.54	1.39	0.546
TRIG	1.05	0.95	1.15	0.389
Big Endothelin 1	1.29	1.13	1.47	<0.001*
ALT/AST ratio	1.70	0.29	9.99	0.557
HSCRP/ serum uric acid ratio	0.54	0.34	0.87	0.011*
Big Endothelin 1 / serum uric acid ratio	0.29	0.14	0.61	0.001*
LDL/HDL ratio	0.09	0.00	39.55	0.438

HSCRP: High-sensitivity C-reactive protein **ALT**: Alanine aminotransferase
AST: Aspartate transaminase **HDL**: High-density lipoprotein **LDL**: Low-density lipoprotein

Table 4 presents a multivariate binary logistic regression analysis results to identify coronary artery ectasia (CAE) predictors. The odds ratio for Big Endothelin 1 is 1.29, with a 95% confidence interval ranging from 1.13 to 1.47. The p-value (<0.001) suggests that Big Endothelin 1 is significantly associated with increased odds of CAE in the studied groups. HSCRP/serum uric acid ratio and Big Endothelin 1/serum uric acid ratio have p-values below 0.05, indicating that they are significantly associated with increased odds of CAE in the studied groups.

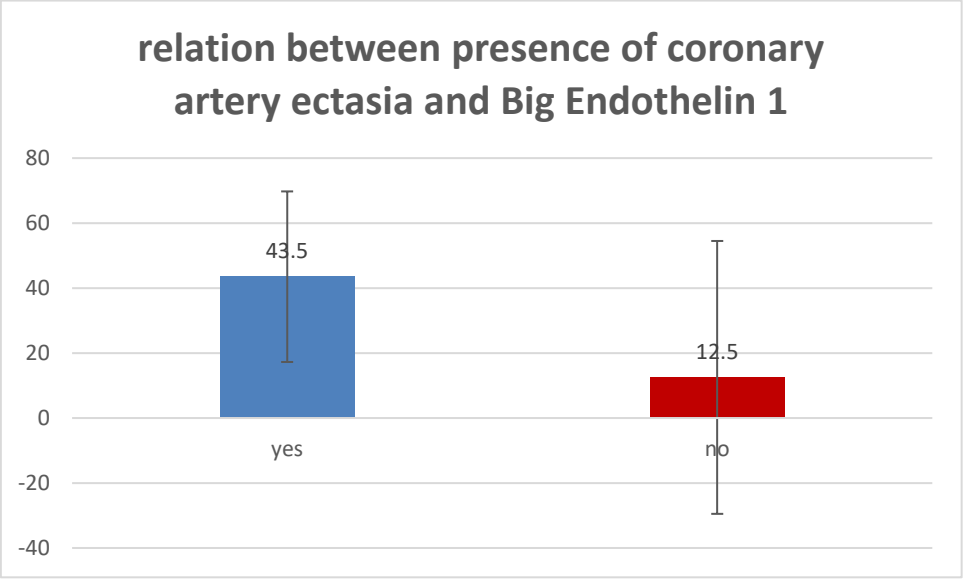

Figure 1: Relation between the presence of coronary artery ectasia and Big Endothelin 1

Table 5: ROC Curve for Big Endothelin 1 for diagnosis of coronary artery ectasia

AUC	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cut point
0.72	96.0%	51.8%	53.9%	95.7%	13.25

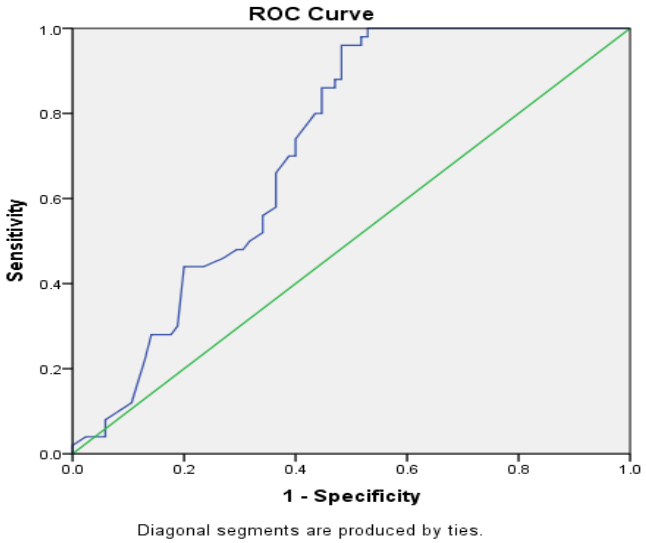

Figure 2: ROC Curve analysis of (big ET-1) revealed that a cut-off value of bigET-1>13.25 has a sensitivity of 96% and a specificity of 51% for predicting coronary ectasia.

Figure 1 illustrates the relationship between coronary artery ectasia and Big Endothelin 1 levels. Figure 1 suggests a connection between elevated levels of Big Endothelin 1 and coronary artery ectasia. Table 5 presents the receiver operating characteristic (ROC) curve analysis for Big Endothelin 1 as a diagnostic tool for coronary artery ectasia with moderate accuracy. Figure 2 further emphasizes the ROC Curve analysis of Big Endothelin 1, explicitly highlighting that a cut-off value greater than 13.25 for big ET-1 demonstrates a high sensitivity of 96% but a relatively lower specificity of 51% for predicting the presence of coronary artery ectasia. However, while the results show high sensitivity, the specificity could be improved, as indicated by Figure 3.

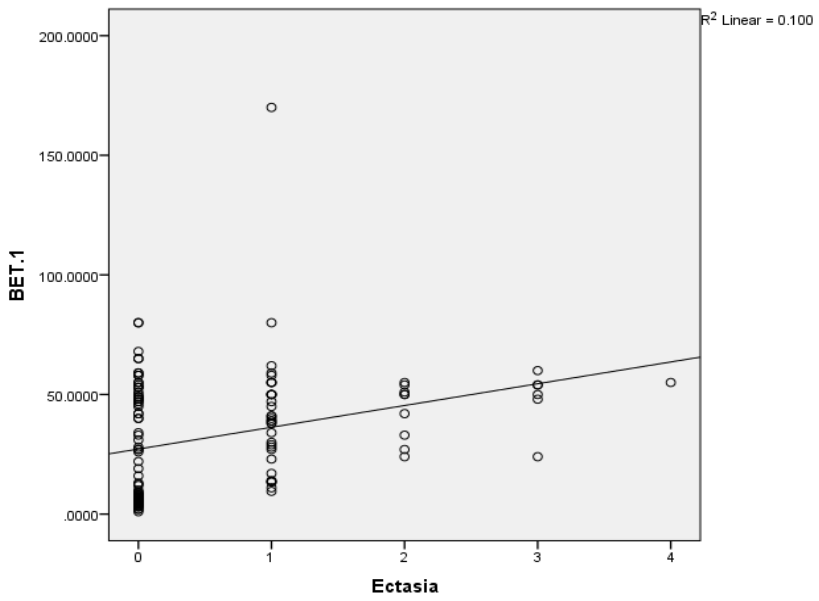

Figure 3: Correlation between the presence of coronary artery ectasia and Big Endothelin 1

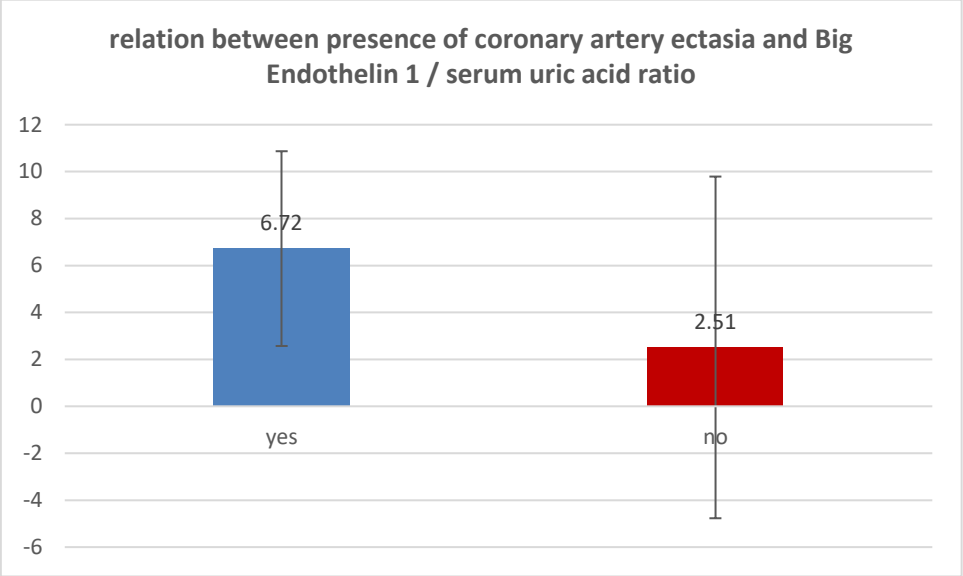

Figure 4: Relation between the presence of coronary artery ectasia and Big Endothelin 1 / serum uric acid ratio

Table 6: ROC Curve for Big Endothelin 1 / serum uric acid ratio for diagnosis of coronary artery ectasia

AUC	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cut point
0.64	90.0%	50.6%	51.7%	89.6%	2.66

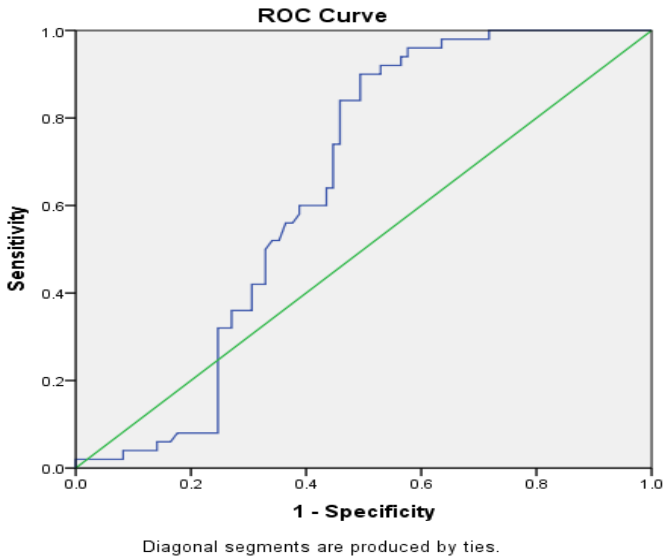

Figure 5: ROC Curve analysis of (Big ET-1/ serum uric acid ratio) revealed that a cut-off value of bigET-1>2.66 has a sensitivity of 90% and a specificity of 50% for predicting coronary ectasia

Figure 4 demonstrates the relationship between coronary artery ectasia and the Big Endothelin 1/serum uric acid ratio, indicating a potential link between these factors. Table 6 presents the ROC curve analysis for the Big Endothelin 1/serum

uric acid ratio as a diagnostic marker for coronary artery ectasia. The positive predictive value is 51.7%, and the negative predictive value is 89.6%. This cut-off point indicates that values above 2.66 might indicate coronary artery ectasia. Figure 5 emphasizes the ROC Curve analysis of the Big Endothelin 1/serum uric acid ratio.

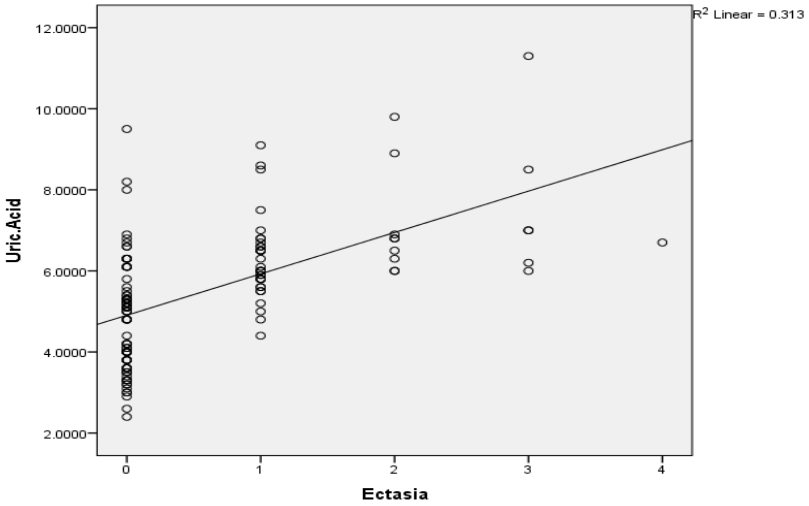

Figure 6: Correlation between the presence of coronary artery ectasia and serum uric acid

Figure 6 displays the correlation between coronary artery ectasia and serum uric acid levels, indicating that elevated serum uric acid levels could be associated with coronary artery ectasia. Figure 7 shows the correlation between coronary artery ectasia and Big ET-1/serum uric acid ratio. These results suggest that the Big Endothelin 1/serum uric acid ratio and serum uric acid levels might have some association with coronary artery ectasia.

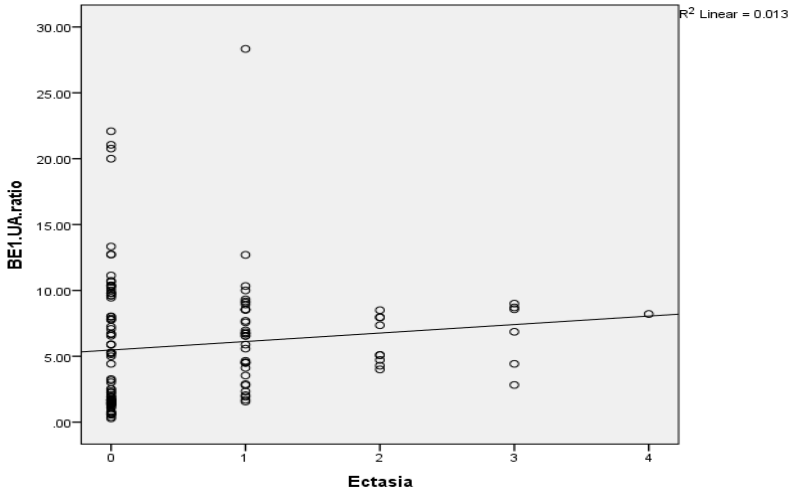

Figure 7: Correlation between the presence of coronary artery ectasia and Big ET-1/serum uric acid ratio

Table 7: ROC Curve for HSCPR /serum uric acid ratio for diagnosis of coronary artery ectasia

AUC	Sensitivity	specificity	Positive predictive value	negative predictive value	Cut point
0.36	98.0%	9.4%	38.9%	88.9%	0.0619

Table 7 presents the ROC curve analysis for the High-Sensitivity C-reactive protein (HSCPR)/serum uric acid ratio as a diagnostic tool for coronary artery ectasia. The positive predictive value is 38.9%, and the negative predictive value is 88.9%. This cut-off point suggests that values above 0.0619 might be linked to coronary artery ectasia. The results indicate that the HSCPR / serum uric acid ratio might have limited diagnostic accuracy for coronary artery ectasia.

Based on the provided data, Big Endothelin 1, HSCRP/serum uric acid ratio, and big Endothelin 1/serum uric acid ratio: These predictors show statistically significant associations with coronary artery ectasia. An increase in Big Endothelin 1, HSCRP/serum uric acid ratio, or Big Endothelin 1/serum uric acid ratio leads to higher odds of having coronary artery ectasia. The other predictors, including age, gender, diabetes, hypertension, smoking, BMI, and various laboratory measures, are not significantly associated with increased odds of CAE in the studied groups.

Discussion:

The major findings of the present study suggest a significant association between Big Endothelin-1 (ET-1), HsCRP, Serum Uric Acid levels, and isolated Coronary Artery Ectasia (CAE) compared to coronary artery disease (CAD) patients and angiographically normal controls. The study identified the following key points.

Our findings align with Wang Y, Zhang Y et al. [17], which also demonstrated a higher level of Big ET-1 in isolated coronary artery ectasia (CAE) patients compared to coronary artery disease (CAD) patients or normal controls. In both studies, Big ET-1 was identified as an independent isolated CAE predictor.

These consistent findings further support the association between Big ET-1 and CAE. Big ET-1 is known to be a vasoconstrictor released from various cells, and its higher levels in patients with isolated CAE suggest a potential role in the pathogenesis of the condition. However, the exact mechanism underlying the correlation between higher levels of ET-1 and CAE still needs to be better understood.

It is worth noting that the present study and the study by Wang Y, Zhang Y et al. [17] contribute to the existing knowledge by highlighting the significance of Big ET-1 as a potential biomarker and predictor for isolated CAE. The association between ET-1 and atherosclerosis pathogenesis may provide further insights into the development and progression of CAE. However, more research is needed to fully elucidate the underlying mechanisms and establish the clinical implications of these findings.

Our findings agree with Wang Y et al. [18], which found that an elevated level of hs-CRP (high-sensitivity C-reactive protein) was connected with a higher risk of cardiovascular events (CVs) and indicated its potential involvement in the progression of coronary artery ectasia (CAE).

The consistency in results between the two studies suggests that hs-CRP may be a significant predictor of CAE. Elevated levels of hs-CRP have been associated with inflammation and have been recognized as a marker of systemic

inflammation. The association between hs-CRP and CAE suggests that inflammation may play a role in the pathogenesis and progression of CAE.

It is crucial to emphasize that both studies provide evidence for the potential involvement of hs-CRP in CAE but to fully identify the mechanisms and the clinical implications of these findings, and additional research is needed. Understanding the role of inflammation, as indicated by elevated hs-CRP levels, may provide valuable insights into managing and treating CAE and related cardiovascular events.

The results also showed that hs-CRP and serum uric acid might be significant predictors of CAE; these results were similar to Demir Ş et al. [19] findings, which demonstrated that an elevated level of hs-CRP and serum uric acid were linked to a high risk of cardiovascular events, CRP may potentially play a role in the advancement of CAE.

Serum uric acid (UA) levels and cardiovascular disease relation have been identified for decades. Numerous studies have demonstrated the association between hyperuricemia (elevated UA levels) and coronary heart disease, cardiovascular disease, and mortality [20].

Yang Z et al. [21] observed that patients with coronary artery ectasia (CAE) had high blood uric acid levels. This finding suggests a potential link between uric acid and the pathogenesis of CAE. The study proposed that uric acid may increase oxidative stress on the endothelium, leading to endothelial dysfunction. However, the precise mechanism by which uric acid contributes to endothelial dysfunction in the context of CAE is not yet fully understood.

Laboratory and clinical research has indicated that UA levels play a role in various processes, including platelet adhesion, the generation of free radicals, and oxidative stress. These factors are known to contribute to the development and progression of cardiovascular diseases.

While the relationship between UA and cardiovascular diseases, including CAE, is established in the literature, additional investigation is required to comprehend these findings' underlying mechanisms and clinical significance. Understanding the role of UA in platelet function, oxidative stress, and endothelial dysfunction may provide valuable insights into managing and preventing cardiovascular diseases.

The Big Endothelin 1/serum uric acid ratio is a new biomarker for predicting coronary artery ectasia and has not been discussed before; it signifies a novel finding in the field. The ratio suggests that the relationship between Big Endothelin 1 and serum uric acid may be relevant in predicting coronary artery ectasia's presence or progression.

Given this new information, exploring the underlying mechanisms and potential clinical implications of the Big Endothelin 1/serum uric acid ratio in the context of coronary artery ectasia would be valuable. Further research would be necessary to validate and corroborate these findings, understand the predictive value of this ratio, and explore its potential utility in clinical practice.

Conclusion:

The present study demonstrated significant findings regarding the association of Big Endothelin 1 (ET-1) and serum uric acid levels with coronary artery ectasia (CAE). The study showed that isolated CAE patients demonstrated significantly higher Big ET-1 levels than those with coronary artery disease (CAD) or normal controls. Additionally, the study identified the Big Endothelin 1/serum uric acid ratio as a new biomarker for predicting CAE.

The results suggested that both Big ET-1 and serum uric acid levels can be involved in the pathogenesis and progression of CAE. Higher levels of Big ET-1 were associated with an increased risk of isolated CAE, while the Big Endothelin 1/serum uric acid ratio showed promise as a predictive biomarker for CAE.

These findings provide additional insights into the cardiovascular field, expanding our understanding of the potential involvement of Big ET-1 and serum uric acid in CAE.

Limitations:

While the study provides valuable insights into the association between Big Endothelin 1 (ET-1), serum uric acid levels, and coronary artery ectasia (CAE), it is essential to acknowledge some limitations:

1. Sample Size: The limited sample size may impact the findings' generalizability. A larger sample size would increase the statistical power and strengthen the study's conclusions.
2. Selection Bias: The study might have inherent selection biases, as the participants may not represent the broader population with CAE. The recruitment process and inclusion criteria must be considered to assess the potential preferences.
3. Observational Nature: The study design appears observational, meaning causality cannot be inferred. While the study establishes associations between Big ET-1, serum uric acid levels, and CAE, it does not establish a cause-and-effect relationship.
4. Cross-Sectional Design: If the study has a cross-sectional design, it only provides a snapshot of data at a single point in time. Longitudinal studies would be needed to assess the temporal relationship between Big ET-1, serum uric acid levels, and the development or progression of CAE.
5. Confounding Factors: The study may not have accounted for all potential confounding factors that could influence the association between Big ET-1, serum uric acid levels, and CAE. The provided information did not mention medication use, comorbidities, lifestyle factors, and other biomarkers.
6. Lack of Mechanistic Insights: The study needs to provide detailed mechanistic insights into how Big ET-1, serum uric acid levels, and the Big Endothelin 1/serum uric acid ratio are involved in the pathogenesis of CAE. Additional research is necessary to understand the underlying mechanisms and potential interactions.
7. Publication Bias: The provided information needs to mention details about potential publication bias, which could affect the inclusion and reporting of studies with non-significant results.

These limitations highlight areas for further investigation and the need for more

robust studies to confirm and expand upon the findings. Additional research with larger sample sizes, longitudinal designs, and consideration of confounding factors is necessary to strengthen the understanding of the relationship between Big ET-1, serum uric acid levels, and CAE.

Declarations:

Ethics approval and consent to participate: The protocol and procedures applied in this study were approved by the ethical committee of the Faculty of Medicine, Minia University. All participants provided written informed consent before being involved in the study. The steps, the aims, the potential benefits, and the hazards were all reviewed and discussed clearly with the patients and/or their relatives. All methods were carried out following relevant guidelines and regulations. Approval No.324: 5/2022

Day: 16 May 2022

Consent for publication: Not applicable.

Availability of data and materials:

The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality and informed consent. Still, they are available from the corresponding author upon reasonable request.

Competing interests: Not applicable.

Source of funding: Not applicable.

Author Contributions: All authors contributed to the study's concept and design. All authors participated in the clinical research. All authors performed material preparation, data collection, and analysis. All authors wrote the first draft of the manuscript, and all authors commented on previous versions. All authors read and approved the final manuscript.

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References

1. Giannoglou GD, Antoniadis AP, Chatzizisis YS, Damvopoulou E, Parcharidis GE, Louridas GE. Prevalence of ectasia in human coronary arteries in patients in northern Greece referred for coronary angiography. Am J Cardiol. 2006; 98(3):314-8. doi: 10.1016/j.amjcard.2006.02.034.
2. Devabhaktuni S, Mercedes A, Diep J, Ahsan C. Coronary Artery Ectasia-A Review of Current Literature. Curr Cardiol Rev. 2016;12(4):318-323. doi: 10.2174/1573403x12666160504100159
3. Hartnell GG, Parnell BM, Pridie RB. Coronary artery ectasia. Its prevalence and clinical significance in 4993 patients. Br Heart J. 1985;54(4):392-5. doi: 10.1136/hrt.54.4.392.
4. Richards GHC, Hong KL, Henein MY, Hanratty C, Boles U. Coronary Artery Ectasia: Review of the Non-Atherosclerotic Molecular and Pathophysiologic Concepts. Int J Mol Sci. 2022;23(9):5195. doi: 10.3390/ijms23095195.
5. Markis JE, Joffe CD, Cohn PF, Feen DJ, Herman MV, Gorlin R. Clinical significance of coronary arterial ectasia. Am J Cardiol. 1976;37(2):217-22. doi: 10.1016/0002-9149(76)90315-5.
6. Matsuzawa Y, Lerman A. Endothelial dysfunction and coronary artery disease: assessment, prognosis, and treatment. Coron Artery Dis. 2014;25(8):713-24. doi: 10.1097/MCA.0000000000000178.
7. Galis ZS, Sukhova GK, Kranzhöfer R, Clark S, Libby P. Macrophage foam cells from experimental atheroma constitutively produce matrix-degrading proteinases. Proc Natl Acad Sci U S A.

1995;92(2):402-6. doi: 10.1073/pnas.92.2.402.

8. Kundi H, Gök M, Çetin M, Kızıltunç E, Çiçekcioğlu H, Güven Çetin Z, Karayiğit O, Örnek E. Relationship between platelet-to-lymphocyte ratio and the presence and severity of coronary artery ectasia. Anatol J Cardiol. 2016;16(11):857-862. doi: 10.14744/AnatolJCardiol.2015.6639.
9. Huang Y, Mironova M, Lopes-Virella MF. Oxidized LDL stimulates matrix metalloproteinase-1 expression in human vascular endothelial cells. Arterioscler Thromb Vasc Biol. 1999;19(11):2640-7. doi: 10.1161/01.atv.19.11.2640.
10. Houde M, Desbiens L, D'Orléans-Juste P. Endothelin-1: Biosynthesis, Signaling and Vasoreactivity. Adv Pharmacol. 2016;77:143-75. doi: 10.1016/bs.apha.2016.05.002.
11. Eddahibi S, Raffestin B, Clozel M, Levame M, Adnot S. Protection from pulmonary hypertension with an orally active endothelin receptor antagonist in hypoxic rats. Am J Physiol. 1995;268(2 Pt 2): H828-35. doi: 10.1152/ajpheart.1995.268.2.H828.
12. Balta S, Demirkol S, Celik T, Kucuk U, Unlu M, Arslan Z, Balta I, Iyisoy A, Kocak N, Haqmal H, Yokusoglu M. Association between coronary artery ectasia and neutrophil-lymphocyte ratio. Angiology. 2013;64(8):627-32. doi: 10.1177/0003319713480424.
13. Li JJ, Nie SP, Qian XW, Zeng HS, Zhang CY. Chronic inflammatory status in patients with coronary artery ectasia. Cytokine. 2009;46(1):61-4. doi: 10.1016/j.cyto.2008.12.012.
14. Vrachatis DA, Papathanasiou KA, Kazantzis D, Sanz-Sánchez J, Giotaki SG, Raisakis K, Kaoukis A, Kossyvakis C, Deftereos G, Reimers B, Avramides D, Siasos G, Cleman M, Giannopoulos G, Lansky A, Deftereos S. Inflammatory Biomarkers in Coronary Artery Ectasia: A Systematic Review and Meta-Analysis. Diagnostics (Basel). 2022;12(5):1026. doi: 10.3390/diagnostics12051026.
15. Z. Cao , Jinyu Wang, Zuyi Weng , Xinyu Tao , Ying Xu , Xiaoqing Li , Xiao Tan , Zhengxia Liu, Chen Qu,.Metabolomic analysis of serum from pure coronary artery ectasia patients based on UPLC-QE/MS technique.Clinica Chimica Acta 534 (2022) 93–105 .
16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003.
17. Wang Y, Zhang Y, Zhu CG, Guo YL, Huang QJ, Wu NQ, Gao Y, Qing P, Liu G, Dong Q, Li JJ. Big endothelin-1 level is a useful marker for predicting the presence of isolated coronary artery ectasia. Biomarkers. 2017;22(3-4):331-336. doi: 10.1080/1354750X.2016.1265001.
18. Wang Y, Wang Y, You S, Wang H, Yin D, Dou K, Song W. Independent Prognostic Value of High-sensitivity C-reactive Protein in Patients with Coronary Artery Ectasia. Chin Med J (Engl). 2016;129(21):2582-2588. doi: 10.4103/0366-6999.192778.

19. Demir Ş, Karakoyun G, Kanadasi M. Elevated high sensitivity C-reactive protein and uric acid levels in coronary artery ectasia. Acta Biochim Pol. 2014;61(4):687-91.
20. Nagahama K, Iseki K, Inoue T, Touma T, Ikemiya Y, Takishita S. Hyperuricemia and cardiovascular risk factor clustering in a screened cohort in Okinawa, Japan. Hypertens Res. 2004;27(4):227-33. doi: 10.1291/hypres.27.227.
21. Yang Z, Yuan J, Cui J, Guan H, Qiao S. Association of the lymphocyte-to-monocyte ratio, mean diameter of coronary arteries, and uric acid level with coronary slow flow in isolated coronary artery ectasia. BMC Cardiovasc Disord. 2021;21(1):156. doi: 10.1186/s12872-021-01952-4.
22. Lang R, Badano L, Devereux R, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European. 2015; 8(3): 148–190.