The Egyptian Journal of Hospital Medicine (April 2024) Vol. 95, Page 2281- 2288

Relationship between The Systemic Immune Inflammatory (SII) Index and The Severity of Isolated Coronary Artery Ectasia

Mahmoud Kamel Ahmed[1], Mahmoud Ismail Mahmoud*[2], Tamer Ezzat Ghazy[1]

[1]Department of Cardiology, Faculty of Medicine, Menoufia University, Menoufia, Egypt
[2]Department of Cardiology, Mataria Teaching Hospital, Cairo, Egypt

***Corresponding author:** Mahmoud Ismail Mahmoud, **Mobile:** (+20) 01014850408, **E-mail:** dr_mimg@yahoo.com

ABSTRACT

Background: An uncommon angiographic finding that is regarded as an unusual type of atherosclerosis is coronary artery ectasia (CAE). No much research has been done on the connection between the inflammatory process and isolated CAE. A new inflammatory measure called the Systemic Immunoinflammatory (SII) Index was utilized to predict cardiovascular outcomes in patients with coronary artery disease (CAD).

Objective: This study aimed to examine the possible association between the SII index and the presence and also the severity of isolated CAE.

Patients and methods: 169 patients from the Cardiology Department, Menoufia University and Mataria Teaching Hospital who underwent coronary angiography and revealed 143 patients with isolated CAE, and 26 patients had normal coronaries (control group). Patients with CAE were divided into 4 groups according to severity depending on Markis classification. the SII index was evaluated to all patients.

Results: SII index was higher in cases than in control group (737.9 ± 182.4 vs 290.16 ± 33.5 respectively). It also reflects the strong positive correlation between the SII index and the severity of the CAE. Post hoc test showed higher levels of SII index in type 1 vs type 2, type 2 vs type 3 and type 3 vs type 4 (907.35 ± 119.7, 680.51 ± 56.3, 470.5 ± 45.1 & 410.63 ± 37.3 respectively) (P<0.001**)**.

Conclusion: Patients with isolated CAE have a higher level of inflammation than patients with normal coronaries, and there is a positive correlation between the SII index and severity of CAE.

Keywords: Coronary artery ectasia severity, Systemic immune inflammatory index, CAD.

INTRODUCTION

In 3% to 8% of angiographic cases, CAE, dilatation of an arterial segment to a diameter at least 1.5 times that of the neighboring normal coronary artery, occurs. It may be localized or diffuse, affecting a coronary artery's whole length. In half of the instances, atherosclerosis is the cause. Ectasia and CAD are coexisting conditions in the vast majority of these individuals. Just 10%–20% of CAE have been linked to connective tissue or inflammatory diseases [(1)].

Unknown is the precise pathophysiology of CAE. Because it can manifest as myocardial ischemia or coronary syndrome, CAE is an anatomical variation or a clinical constellation of CAD. While, atherosclerosis usually results in artery lumen constriction, the mechanism behind luminal dilatation in certain atherosclerotic arteries remains unclear. The blood vessel's medial and exterior elastic membranes are expanding as a result of arterial remodeling. Luminal expansion appears to be the consequence of an enlarged and expansive remodeling of the exterior elastic membrane caused by CAE. One of the main pathophysiologies of the expansive remodeling is thought to be the enzymatic breakdown of the extracellular matrix and the thinning of the tunica media linked to severe chronic inflammation [(2)].

Similar to individuals with obstructive CAD, CAE is linked to an elevated risk of death. Additionally, it has been demonstrated that CAD risk factors such as smoking, diabetes, hypertension, and hyperlipidemia are linked to CAE [(3)].

Although any one of the three coronary arteries may be ectatic, 75% of patients only have an isolated artery affected [(4)]. The most frequent sites of the CAE are the proximal and middle segments of the right coronary artery, which are followed by the left anterior descending artery and the circumflex artery [(5-7)].

Markis classified CAE into four types: Type 1 is characterized by generalized ectasia involving 2 or 3 vessels. Type 2 consisted of diffuse ectasia in 1 vessel and distinct ectasia in another. Type 3 consisted of widespread ectasia in only one vessel. Type 4 ectasia is limited to a single vessel and can be localized or segmental [(8)].

The new inflammatory measure known as the systemic immune-inflammation index may give important insights into inflammation. The formula utilized to compute the SII index was (PLT × neutrophil/lymphocyte) [(9)].

It has been demonstrated that the SII index is a valuable marker mainly for predicting poor clinical

Received: 14/01/2024
Accepted: 13/03/2024

outcomes in individuals with inflammatory disorders and cancer [10].

Since then, research on cardiovascular disorders has been carried out, and it has been discovered that these disorders are a strong indicator of unfavorable clinical outcomes in heart failure and CAD [11, 12].

PATIENTS AND METHODS

This prospective analytical study was conducted on 169 patients who underwent coronary angiography for suspected angina pectoris in Menoufia University Hospital and Mataria Teaching Hospital and revealed 26 patients with normal coronaries (control group) and 143 patients with isolated CAE classified according to severity of ectasia into 4 groups depending on Markis classification.

Group 1 included 81 patients with type 1 ectasia, group 2 included 19 patients with type 2 ectasia, group 3 included 24 patients with type 3 ectasia, group 4 included 19 patients with type 4 ectasia, and group 5 included 26 patients with normal coronary angiogram (control).

Exclusion criteria: Patients with acute coronary syndrome, a history of systemic autoimmune or inflammatory diseases, significant hematological disorder, end-stage renal disease, severe liver disease, malignancy, acute or chronic infections, and acute illness.

METHODS

All patients were subjected to careful history taking (age, gender, special habits, autoimmune diseases, hematological diseases, malignancy and any risk factors for CAD), full clinical examination, 12 lead electrocardiography, conventional echocardiographic study (routine M-mode, two dimensional and doppler studies recorded for each participant), laboratory investigations including CBC, renal function tests, troponin, estimating the value of the systemic immune-inflammatory index (SII; Plt. count X neutrophilic count/lymphocytic count) and Elective coronary angiography (Right and left coronary angiography and assessment of the CAE severity by Markis classification [8]).

Ethical approval: Faculty of Medicine, Menoufia University 's Local Ethics Committee accepted the study's overall design, and each participant provided informed written consent. The Helsinki Declaration was adhered to at every stage of the investigation.

Statistical analysis

Using SPSS version 24.0 for Windows, data were coded, calculated, and analyzed. The sample's personal and clinical characteristics were described using descriptive statistics. Frequency tables (including numbers and percentages) were used to display the qualitative data. In the case of quantitative variables, the one sample Kolmogorov-Smirnov test was used to verify the normality of the data before it was presented using central indices and dispersion.

For normally distributed variables, the mean ± SD was used. The X^2-test was used to assess the clinical feature comparison between the patients and controls in analytical statistics. We used the independent t test and one-way Annova to examine the relationship between normally distributed continuous variables. For data that is regularly distributed, Pearson correlation is employed. When it was equal to or less than 0.05, the p-value was deemed significant.

RESULTS

The mean age of the control group was 41.6 ± 6.2 years vs 54.9 ± 9 years among cases and males represented 60% of the cases, while the percentage between males and females was equal among controls. 45.5% of the study population were diabetic, 50.2% were hypertensive and 38% were smokers with no significance between the 2 groups (Table 1).

Table (1): Comparison between cases and controls regarding demographic and clinical data

parameter	Total (169)	Cases (143)	Control (26)	Test of significance
Age		54.9 ±9	41±6.2	t-test **p<0.001***
Sex (total) Male Female	 99(58.6) 70(41.4)	 86(60) 57(40)	 13(50) 13(50)	X^2 P=0.3
DM	77(45.5)	66(46.2)	11(42.3)	X^2 P=0.7
HTN	85(50.2)	74(51.7)	11(42.3)	X^2 P=0.37
Smoking	64(38)	55(38.5)	9(34.6)	X^2 P=0.7

*: significant.

Comparing between the 4 types of ectasia regarding sex, male patients were distributed as follow: 66.3% among type 1, 8.1% in type 2, 16.3% in type 3 and 9.3% in type 4 (Table 2).

Table (2): Sex and other risk factors among the 4 groups of ectasia

	Ectasia type 1 N=81	**Ectasia type 2 N=19**	**Ectasia type 3 N=24**	**Ectasia type 4 N=19**	**Test of significance** X^2-test
Sex Male Female	 57(66.3) 24(42.1)	 7(8.1) 12(21.1)	 14(16.3) 10(17.5)	 8(9.3) 11(19.3)	**P=0.023***
DM	36(54.5)	8(12.1)	10(15.2)	12(18.2)	P=0.5
HTN	46(62.2)	11(14.9)	7(9.5)	10(13.5)	P=0.1
Smoking	39(70.9)	4(7.3)	7(12.7)	5(9.1)	P=0.053

*: significant

In comparison with control group, CAE cases showed a higher level of Hb (12.05 ± 1.08 and 12.93 ± 1.66), WBCs (5.9 ± 1.2 and 8.1 ± 1.88), platelet (180.96 ± 20.5 vs 262.7 ± 64.4), neutrophils (3.3 ± 0.73 and 5.5 ± 1.37) and cases also associated with higher levels of SII index (290.16 ± 33.5 and 737.9 ± 182.4) (Table 3).

Table (3): Comparison between cases and controls regarding the laboratory readings

Parameter	**Cases (143)**	**Control (26)**	**Test of significance** t-test
S. creatinine (mg/dL)	1.07±0.25	1.04±0.2	P=0.63
HB (g/dl)	12.93±1.66	12.05±1.08	**P=0.01***
WBCs × 10^9/L	8.1±1.88	5.9±1.2	**p<0.001***
Platelet × 10^{11}/unit	262.7±64.4	180.96±20.5	**p<0.001***
Neutrophil per microliter	5.5±1.37	3.3±0.73	**p<0.001***
Lymphocytes (µL)	2.13±0.52	2.06±0.47	P=0.823
SII index	737.9±182.4	290.16±33.5	**p<0.001***

*: significant.

Post hoc test to compare between ectasia groups showed higher levels of SII index in type 1 vs type 2, type 2 vs type 3, and type 3 vs type 4. A higher level of neutrophils was found in type 1 vs type 4. Also, a higher levels of lymphocyte was found in type 1 vs type 3 , and type 2 vs type 3. Finally, regarding **platelets levels**, we demosntrated a higher level in type 1 vs type 2, type 3, and type 4 (Table 4).

Table (4): Laboratory findings according to type of ectasia

	Type 1 (81)	**Type 2(19)**	**Type 3(24)**	**Type 4(19)**	**Test of significance** (One way Annona)
S. creatinine (mg/dl)	1.1 ±0.26	0.93±0.23	1.04±0.23	1.11±0.2	P=0.06
SII index	907.35±119.7	680.51±56.3	470.5±45.1	410.63±37.3	**P<0.001***
Lymphocytes (µL)	1.8±0.44	2.03±0.50	3.14±0.74	2.32±0.56	**P=0.013***
Neutrophils per microliter	5.8±1.42	5.33±1.28	5.22±1.30	4.67±1.22	**P=0.01***
Platelets × 10^{11}/unit	293.37±71.85	254.36±58.95	213.08±42.1	203.4±38.63	**p<0.001***
WBC × 10^9/L	8.3±1.85	7.95±1.9	8.25±1.84	7.56±1.87	P=0.44
HB (g/dl)	12.68±1.77	13.66±1.78	12.9±1.12	13.17±1.47	P=0.11

*: significant

CAE cases showed RWMA by using 2D ECHO where 36.4% of cases showed positive ischemic changes, while one of control reported ischemic changes, also significant higher mean EF among controls than in cases wasw reported (0.612 ± 0.05 vs 0.634 ± 0.04 respectively) (table 5).

Table (5): Echo findings among cases and controls

Parameter	Total	Cases (143)	Control (26)	Test of significance
RWMA[2]	52(30.8)	52(36.4)	0	FET **P<0.001***
EF[1]	mean ± SD	0.612±0.05	0.634±0.04	t-test **P=0.013***
IVSD		0.86±0.21	0.89±0.18	t-test P=0.55
LVPWD		0.86±0.2	0.88±0.17	t-test 0.73
LVEDD		4.7±0.3	4.76±0.33	t-test 0.85
LVESD		3.1±0.22	3.2±0.27	t-test 0.06
RWT		0.36±0.08	.37±0.08	t-test 0.7
LVM		63.7±20.4	64.68±16.9	t-test 0.8
EPASP		27.3±6.3	25.3±3.9	t-test 0.14
AORTA		3.5±0.22	3.37±0.2	t-test 0.2
LT.ATRIUM		3.7±0.25	3.5±0.16	t-test **<0.001***
AO/LA		0.91±0.07	0.95±0.07	t-test **0.016***
Mitral E velocity		0.66±0.1	0.66±0.09	t-test 0.9
Mitral A velocity		0.77±0.14	0.81±.0.09	t-test 0.24
E/A RATIO		0.86±0.22	0.86±0.12	t-test 0.95

*: significant; FET: Fischer exact test

CAE cases also showed dynamic ST-T changes in 43.4% of cases vs 11.5% among controls (p=0.002) (Table 6).

Table (6): ECG changes among cases and controls

	Total	**Cases (143)**	**Control (26)**	**Test of significance**
Dynamic ST-T changes	65(38.5)	62(43.4)	3(11.5)	**X^2 P=0.002***
Atrial Fibrillation	13(7.7)	10(7)	3(11.5)	FET P=0.4
Ventricular Extrasystoles	20(11.8)	18(12.6)	2(7.7)	FET P=0.7
Atrial Extrasystole	22(13)	20(14)	2(7.7)	FET P-0.5
AV block	6(3.6)	5(3.5)	1(3.9)	FET P=1
LBBB	14(8.3)	13(9.1)	1(3.8)	FET P-0.7
RBBB	23(13.6)	19(13.3)	4(15.4)	FET 0.7
Wide QRS	37(21.9)	32(22.5)	5(19)	X^2 P=0.7
LVH criteria	22(13)	19(13.5)	3(11.5)	FET P=1

*: significant

The results of the correlation analysis showed that there were a strong negative significant correlation between ectasia and SII index, a moderate positive significant correlation between ectasia and lymphocytes, and a weak negative significant correlation between ectasia and neutrophils (Table 7).

Table (7): Correlation between ectasia and other parameters

Variables	**r**	**P**
WBCs	-0.099	0.24
Neutrophil	**-0.28**	**0.001***
Lymphocytes	**0.36**	**<0.001***
SII index	**-0.88**	**<0.001***
S . creatinine	-0.11	0.17

r: correlation coefficient; *: significant

DISCUSSION

The principal objective of our study was to evaluate the relationship between the SII index and the severity of isolated CAE according to Markis classification. Some papers have investigated the association between isolated CAE and inflammatory markers [8, 13].

Our investigation found that patients with isolated CAE had considerably higher SII index values than those with normal coronaries. We also found that the greater the SII score, the more severe the coronary ectasia. Exaggerated expansive remodeling, in which both the luminal size and the exterior elastic membrane grow, is assumed to be the cause of CAE [2, 14]. Matrix metalloproteinases (MMPs) are overexpressed in CAE. The primary pathogenetic mechanism of the excessive expansive remodeling is proposed to be the enzymatic breakdown of the extracellular matrix by MMP and other lytic enzymes and the thinning of the tunica media associated with severe chronic inflammation [15].

Regarding the demographics and risk factors between controls and cases. there was no significant difference between cases and controls and between all groups of ectasia as regards HTN, DM and smoking. This findings were compatible with **Demopoulos *et al.* [4], Swaye *et al.* [16] and Yalcin *et al.* [17].** Other studies had shown results against our findings as in the study of **Pinar *et al.* [18] Kundi *et al.* [19]** and **Lam and Ho [20]** who speculated that the systemic HTN might play a role in the pathogenesis of this disease and this could be explained by the larger sample size.

Males represented 60% of the cases. This finding is compatible with **Devabhaktuni *et al.* [7], Kundi *et al.* [19], Lam and Ho [20], Cohen and O'Gara [21] Esenboğa *et al.* [22]. Sudhir *et al.* [23]** discovered a higher frequency of ectasia in families with high cholesterol levels. Interestingly, people with diabetes have a reduced risk of CAE [24, 25]. Smoking and cocaine usage were also identified as independent predictors of CAE [26].

Regarding ECG changes among cases and controls, 43.4% of cases had ST changes vs 11.5% among controls (p=0.002). This finding was compatible with **Devabhaktuni *et al.* [7].**

Regarding the laboratory readings between cases and controls, we found that there was a higher levels of Hb in cases than in controls (12.93 ± 1.66 and 12.05 ± 1.08), WBCs (8.1 ± 1.88 and 5.9 ± 1.2), platelets (262.7 ± 64.4 vs 180.96 ± 20.5), neutrophils (5.5 ± 1.37 and 3.3 ± 0.73) and SII index (737.9 ± 182.4 and 290.16 ± 33.5). In comparison between ectasia groups, higher levels of SII index and lymphocytes and neutrophils in type 1 vs type 2, type 2 vs type 3, and type 3 vs type 4. These findings are compatible with the study of **Yalcin *et al.* [17], Kundi *et al.* [19], Li *et al.* [27] and Yilmaz *et al.* [28]** but this study found that there was no significant difference in platelet count between cases and control groups.

The study of **Esenboğa *et al.* [22]** also found that patients with isolated CAE had significantly higher SII index values compared to those with obstructive CAD and normal CA. **Tosu and Biter [29]** found also that higher SII index is associated with the presence of isolated coronary ectasia but it doesn't correlate the level of SII index with the severity of ectasia. **Vrachatis *et al.* [30]** found that patients with CAE have higher levels of inflammatory biomarkers.

CONCLUSION

Patients with isolated CAE had a higher level of inflammation than patients with normal coronaries, and there was a positive correlation between the SII index and severity of CAE .

LIMITATIONS OF THE STUDY

1. Small sample size of the study.
2. We did not analyze other inflammatory markers that could provide important comprehensive information.
3. Patients with ACS and significant coronary stenosis were excluded.
4. We didn't follow up the patients to assess the value of SII index on the prognosis.
5. Speckle tracking is better than conventional echo to assess the effect of ectasia on left ventricular function.

Financial support and sponsorship: Nil
Conflict of interest: Nil

REFERENCES

1. **Hartnell G, Parnell B, Pridie R (1985):** Coronary artery ectasia: Its prevalance and clinical significance in 4993 patients. Br Heart J., 54: 392-5.
2. **Antoniadis A, Chatzizisis Y, Giannoglou G (2008):** Pathogenetic mechanisms of coronary ectasia. Int J Cardiol., 130 (3): 335-43.
3. **Saglam M, Karakaya O, Barutcu I *et al.* (2008):** Identifying cardiovascular risk factors in a patient population with coronary artery ectasia. Angiology, 58: 698–703.
4. **Demopoulos V, Olympios C, Fakiolas C *et al.* (1997):** The natural history of aneurysmal coronary artery disease. Heart, 78: 136-141
5. **Sharma S, Kaul U, Sharma S *et al.* (1990):** Coronary arteriographic profile in young and old Indian patients with ischaemic heart disease: a comparative study. Indian Heart J., 42: 365-9.
6. **Rath S, Har-Zahav Y, Battler A *et al.* (1985):** Rate of nonobstructive aneurysmatic coronary artery disease; angiographic and clinical follow up report. Am Heart J., 109: 785-91.
7. **Devabhaktuni S, Mercedes A, Diep J *et al.* (2016):** Coronary Artery Ectasia-A Review of Current Literature. Curr Cardiol Rev., 12 (4): 318–23.
8. **Markis J, Joffe C, Cohen P *et al.* (1976):** Clinical significance of coronary arterial ectasia. Am J Cardiol., 37: 217-222.
9. **Hu B, Yang X, Xu Y *et al.* (2014):** Systemic immune-inflammation index predicts prognosis of patients after

curative resection for hepatocellular carcinoma. Clin Cancer Res., 20: 6212-22.

10. **Yang R, Chang Q, Meng X *et al.* (2018):** Prognostic value of Systemic immune-inflammation index in cancer: A meta-analysis. J Cancer, 9: 3295-302.
11. **Seo M, Yamada T, Morita T *et al.* (2018):** Prognostic value of systemic immune-inflammation index in patients with chronic heart failure. Eur Heart J., 39: 70. Doi: 10.1093/eurheartj/ehy564.P589
12. **Huang J, Zhang Q, Wang R *et al.* (2019):** Systemic immuneinflammatory index predicts clinical outcomes for elderly patients with acute myocardial infarction receiving percutaneous coronary intervention. Med Sci Monit., 25: 9690-701.
13. **Sarli B, Baktir A, Saglam H *et al.* (2014):** Neutrophil-to-lymphocyte ratio is associated with severity of coronary artery ectasia. Angiology, 65 (2): 147-51.
14. **Chatzizisis Y, Coskun A, Jonas M *et al.* (2007):** Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. Journal of the American College of Cardiology, 49 (25): 2379-2393.
15. **Mason D, Kenagy R, Hasenstab D *et al.* (1999):** Matrix metalloproteinase-9 overexpression enhances vascular smooth muscle cell migration and alters remodeling in the injured rat carotid artery. Circulation Research, 85 (12): 1179-1185.
16. **Swaye P, Fisher L, Litwin P *et al.* (1983):** Aneurysmal coronary artery disease. Circulation, 67: 134–138.
17. **Yalcin A, Topuz M, Akturk I *et al.* (2015):** Is There a Correlation Between Coronary Artery Ectasia and Neutrophil–Lymphocyte Ratio? Clinical and Applied Thrombosis/Hemostasis, 21 (3): 229-234.
18. **Pinar B, Lopez P, Lozano M *et al.* (2003):** Coronary ectasia: prevalence, and clinical and angiographic characteristics. Rev Esp Cardiol., 56: 473–479.
19. **Kundi H, Gök M, Çetin M *et al.* (2016):** Relationship between platelet-to-lymphocyte ratio and the presence and severity of coronary artery ectasia. Anatol J Cardiol., 16 (11): 857-862.
20. **Lam C, Ho K (2004):** Coronary artery ectasia: a ten-year experience in a tertiary hospital in Singapore. Ann Acad Med Singap., 33 (4): 419-22.
21. **Cohen P, O'Gara P (2008):** Coronary Artery Aneurysms: A Review of the Natural History, Pathophysiology, and Management. Cardiology in Review, 16 (6): 301-304.
22. **Esenboğa K, Kurtul A, Yamantürk Y *et al.* (2022):** Comparison of systemic immune-inflammation index levels in patients with isolated coronary artery ectasia versus patients with obstructive coronary artery disease and normal coronary angiogram. Scand J Clin Lab Invest., 82 (2): 132-137.
23. **Sudhir K, Ports T, Amidon T *et al.* (1995):** Increased prevalence of coronary ectasia in heterozygous familial hypercholesterolemia. Circulation, 91 (5): 1375–1380.
24. **Baugh M, Gavrilovic J, Davies I *et al.* (2003):** Monocyte matrix metalloproteinase production in Type 2 diabetes and controls--a cross sectional study. Cardiovasc Diabetol., 2: 3. doi: 10.1186/1475-2840-2-3.
25. **Kornowski R, Mintz G, Lansky A *et al.* (1998):** Paradoxic decreases in atherosclerotic plaque mass in insulin-treated diabetic patients. Am J Cardiol., 81 (11): 1298–1304.
26. **Satran A, Bart B, Henry C *et al.* (2005):** Increased prevalence of coronary artery aneurysms among cocaine users. Circulation, 111 (19): 2424–2429.
27. **Li J, Nie S, Qian X *et al.* (2009):** Chronic inflammatory status in patients with coronary artery ectasia. Cytokine, 46 (1): 61-64.
28. **Yilmaz M, Kayançiçek H, Korkmaz H *et al.* (2020):** A new inflammatory marker: elevated eosinophil-tolymphocyte ratio associated with presence and severity of isolated coronary artery ectasia. Cardiovasc J Afr., 31 (5): 227-235.
29. **Tosu A, Biter H (2021):** Association of systemic immune-inflammation index (SII) with presence of isolated coronary artery ectasia. Arch Med Sci Atheroscler Dis., 6: 152-157.
30. **Vrachatis D, Papathanasiou K, Kazantzis D *et al.* (2022):** Inflammatory Biomarkers in Coronary Artery Ectasia: A Systematic Review and Meta-Analysis. Diagnostics, 12 (5): 1026. doi: 10.3390/diagnostics12051026.