Cytokine 115 (2019) 84–88

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Relationship between interleukin-17A and isolated coronary ectasia

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ARTICLE INFO

Keywords:
Atherosclerosis
Coronary artery ectasia
Interleukin-17A
Red cell distribution width
Fibrinogen

ABSTRACT

The aim of this study was to evaluate serum interleukin (IL)-17A levels in patients with coronary artery ectasia (CAE), the relationship between IL and 17A and CAE, and to determine the relationship between the severity of coronary ectasia and the level of IL-17A. In total, 41 patients (19 female and 22 male) with ischemic symptoms whose non-invasive cardiac tests were positive for myocardial ischemia, and in whom coronary artery ectasia were detected after coronary angiography, and 45 patients (32 female and 13 male) with normal coronary arteries were included in this study. Echocardiographic assessments were performed. Serum IL-17A levels of all patients were evaluated using an enzyme-linked immunosorbent assay. IL-17A levels of the group with isolated coronary artery ectasia were significantly higher compared with the control group (4.86 ± 3.24 and 1.37 ± 1.56 ng/ml, respectively; $p < 0.001$). There was no correlation between the levels of IL-17A and the extension of the CAE, but IL-17A levels were high in both groups. CAE patients have significantly increased levels of IL-17A, fibrinogen, and RDW compared to patients with normal coronary arteries. It was demonstrated that increased levels of IL-17A were associated with ectasia formation in CAE patients.

1. Introduction

Coronary artery ectasia (CAE) is a variant type of coronary artery disease characterised by abnormal dilatation of coronary arteries. CAE is defined angiographically as an abnormal dilatation of epicardial coronary arteries with a luminal diameter 1.5 times or wider than that of an adjacent normal segment. In an angiographic series its frequency is changed between 0.3% and 5.3% [1].

Atherosclerosis plays the most important role in etiology at approximately 50% [2]. It is thought that abnormal luminal dilatation that does not resist vascular stress is due to weakening of the media layer of atherosclerotic coronary arteries. Obstructive coronary artery disease and CAE have common mechanisms of pathogenesis [3]. There is evidence that inflammatory cytokines, activation of matrix metalloproteinases, and plaque inflammation are increased in the media and adventitia layers of the ectatic segment of the coronary arteries with diffuse chronic inflammatory cell infiltration [4].

In terms of etiology, other factors involved in CAE are congenital coronary abnormalities (20–30%), systemic inflammatory diseases (10–20%), and connective tissue diseases (10–20%) [5]. In addition, other, rare causes include bacterial and mycotic infections, herbicides, exposure to nitrite products, and trauma [6].

Interleukin (IL)-17 is a member of the cytokine family that has a role regulating T cell response to inflammation. Six IL-17 ligands have been defined: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F [7]. IL-17A is the major determinant. IL-17 is primarily secreted by T cells but also by macrophages, dendritic cells, and natural killers. It induces production of proinflammatory cytokines, chemokines, adhesive molecules, and growth factors. It also plays a role in defending cells against bacteria and fungi. It has been shown in vivo that T helper cells have a role in the pathogenesis of some autoimmune diseases, including asthma, systemic lupus erythematosus, and inflammatory bowel disease [8].

In this study, we evaluated serum levels of IL-17A in patients with isolated CAE and compared them with a control group. We also analysed the relationship between CAE and IL-17A levels in terms of the severity and extension of ectasia.

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https://doi.org/10.1016/j.cyto.2018.11.015
Received 6 February 2018; Received in revised form 4 September 2018; Accepted 13 November 2018
Available online 20 November 2018

2. Materials and methods

2.1. Research course

This study was performed at the Bakirkoy Dr. Sadi Konuk Training and Research Hospital. The aim of this study was to evaluate the serum levels of IL-17A in patients with isolated CAE as well as the relationship between IL and 17A levels and the severity of CAE. The study was approved by the hospital's ethics committee and supported by the hospital's education planning committee.

2.2. Patient selection

Between January 2015 and February 2016, we performed coronary angiography on 3516 patients and identified 57 patients with CAE. Overall, 41 patients with CAE according to their coronary angiography who met the inclusion criteria were included in the study. 45 subjects with normal coronary arteries according to their coronary angiography were included in the study as control group. Inclusion criteria for the study were to sign an informed consent form and be older than age 18. All the patients had undergone coronary angiography electively. To identify the subjects undergoing elective angiography, we excluded patients with emergent or urgent indications for coronary angiography (acute coronary syndromes, acute myocardial infarction, or cardiogenic shock) and coronary angiography performed in consideration of transplantation, valvular surgery, or other preoperative evaluation, cardiomyopathy/heart failure, and congenital heart disease evaluations.

Quantitative coronary measurements were obtained by the analysis of digital data during coronary angiography for all participants. To determine the actual width of the coronary artery lumen, a calibration was conducted using the catheter diameter. To identify the segment as ectatic, at least two measurements were taken at the proximal, mid and distal segments of the coronary arteries in patients with normal coronary angiography and in patients who were considered to have an ectatic coronary segment. If the diameter of the artery segment was ≥ 1.5 times wider than the mean artery diameter of patients with normal coronary angiography, it was accepted as ectatic and the patient was included in the isolated CAE group. Patients with no or less than 20% of the coronary plaque were included in the normal coronary group. Markis score was used for CAE classification as previously described [9]. In decreasing order of severity, diffuse ectasia of 2 or 3 vessels was classified as type 1, diffuse disease in 1 vessel and localized disease in another vessel as type 2, diffuse ectasia in only 1 vessel as type 3, and localized or segmental ectasia as type 4.

Hypertension was considered present if systolic blood pressure was > 140 mmHg and/or diastolic blood pressure was > 90 mmHg or the patient was taking antihypertensive medication. Diabetes mellitus (DM) was defined as fasting blood glucose level > 126 mg/dL or current diet or medication to lower blood glucose. Cigarette smoking was defined as > 10 cigarettes/day at the time of diagnosis. Family history criterion was defined as the presence of coronary artery disease in men before 55 years old and in women before 65 years old in the first degree relatives. Alcohol abuse or dependence was defined based on DSM-IV criteria [10].

Exclusion criteria were accepted as not signing the informed consent form, hypo- or hyperthyroid status, congestive heart failure, atrial fibrillation and all rhythms except sinus, renal dysfunction, creatinine > 1.5 mg/dL, congenital heart disease, myocarditis, pericarditis, cardiomyopathy, critical valvular heart disease, neoplastic disease, chronic inflammation, active infection, chronic hepatic disease, connective tissue disease, iatrogenic ectasia, coronary ectasia with a critical lesion, autoimmune diseases, pregnancy, mental retardation, psychotic disorders, and dementia, delirium, and other amnestic disorders.

2.3. Laboratory assessments

Blood samples were drawn without stasis at 7 to 8 AM after 20 min of supine rest, following fasting 12 h. Total plasma cholesterol, triglyceride and high-density lipoprotein cholesterol were measured by an enzymatic colorimetric method using an autoanalyzer (AU5800 AU analyser, Beckman Coulter, Inc., USA). Low-density lipoprotein levels were calculated by the Friedewald formula. The blood glucose was measured by glucose oxidase method. We analysed the blood samples of both groups using an automatic blood counter immediately. Haematological parameters, including haemoglobin (Hb), white blood cell count, and platelet count were analysed by LH 780 analyser (Beckman Coulter Inc, Miami, Florida). High-sensitive C reactive protein (HsCRP) was measured by using an ultra-high sensitive latex-based immunoassay method (Cobas integra, Roche Diagnostics, Mannheim, Germany). Citrated plasma was analysed for fibrinogen using the ACL-top coagulation analyser (Instrumentation Laboratory) based on the Clauss method using the BCS analyser (Multifibren U, Siemens Healthcare, Marburg, Germany) [11]. The measurement range was between 80 and 1200 mg/dL, and the expected values were between 180 and 350 mg/dL.

2.3.1. Evaluating serum IL-17A levels

All blood samples except IL-17a were studied on the same day. Just before the coronary angiography, venous blood samples (2 cc) were collected in an EDTA and the plasma thus obtained after centrifugation (at 4000 rpm for 10 min at 25 °C) was stored at −80 °C for the subsequent analysis of the IL-17A. After all samples had been collected for IL-17A testing, frozen serum samples were brought to room temperature. An enzyme-linked immunosorbent assay kit (ab193732-IL-17 pig ELISA kit, abcam, Cambridge, United Kingdom) was used to analyse IL-17A, which was placed in wells covered with IL-17A monoclonal antibodies and incubated. Then, IL-17A antibodies marked with biotin were added to the aggregate with streptavidin-horseradish peroxidase, which formed an immune complex. After incubation, unbound enzyme was removed by washing, and substrates A and B were added. Solution was correlated with the concentrations of IL-17A. Intraassay and interassay coefficient of variation (CV) values were calculated at < 10% and < 12%, respectively. IL-17A results were presented as ng/ml.

2.4. Echocardiography and coronary angiography assessments

All procedures were performed with transthoracic echocardiogram to complete the exclusion criteria using a GE Healthcare Vivid S5 device and 2.5–3.5 MHz transducers. Selective left and right coronary angiography (Axiom Artis, Siemens Healthcare, Germany) was performed on all patients with a femoral approach and the Judkins technique after 8–12 h fasting. Angiographic views were analysed by two expert interventional cardiologists.

2.5. Statistical analyses

All tests were performed in the 20.0 SPSS for Windows (SPSS Inc., Chicago, Illinois, USA). Categorical variables are presented as counts and percentages. Continuous variables were evaluated for normal distribution assumption using the Kolmogorov-Smirnov and Shapiro-Wilks tests and were reported as mean plus standard deviation or median with interquartile range. To compare the two groups, the Student *t*-test was used for numerical variants with a normal distribution and the Mann–Whitney *U* test was used for numerical variants without a normal distribution. To compare more than two groups, one-way analysis of variance (ANOVA) was used for parameters with a normal distribution and Kruskal-Wallis variance analysis was used for parameters without a normal distribution. To compare median IL-17A levels of multiple groups created with respect to the severity of CAE, one-way ANOVA was used because all groups had a normal distribution. The frequency

of categorical variants such as age, gender, smoking, diabetes mellitus, hypertension, hyperlipidaemia, and family history was determined cross-sectionally in the control and ectasia groups. Differences were assessed using chi-squared or Fisher tests. Correlation parameters and statistical meaningfulness for relations between variants of which at least one did not have a normal distribution were calculated with the Spearman test. Univariate and multivariate binary logistic regression analysis were performed to investigate independent correlates of LVH or/and proteinuria. Variables with a p value < 0.10 in univariate analysis were included in the multivariate regression analysis. Diagnostic poverty of IL-17A and fibrinogen levels with acute phase reactance (leucocyte and high-sensitivity C-reactive protein [HsCRP]), which exhibited significant discrepancy in the ectasia group with respect to the control group, was shown using receiver operator characteristics (ROC) curve analysis with area under the curve (AUC) ± standard error and a 95% confidence interval (CI). P values were accepted as meaningful when they were below 0.05.

3. Results

In total, 86 patients were included in the study, with 41 (47.6%) in the CAE group and 45 (52.4%) in the control group. The median age was 58.0 ± 8.9 in patient group and 58.0 ± 8.1 in control group. Gender ratios were similar between groups. Clinical features of subjects in both groups are summarised in Table 1.

Serum levels of IL-17A in patients with CAE were significantly higher than those of the control group (Table 2). Moreover, in the ectasia group, fibrinogen, red blood cell distribution width (RDW), and levels were statistically higher and leucocyte and lymphocyte levels were lower. Laboratory parameters of both groups are summarised in Table 2.

When coronary angiograms were examined and Markis score was calculated, Markis type 1 was the majority and observed in 43.9% of the ectasia group (Table 3). IL-17A levels did not differ with respect to ectasia severity (type 1–4) (Table 3). Additionally, RDW and fibrinogen also did not have any relationship with the ectasia severity.

According to the results of the correlation analysis evaluating the relationship between serum levels of IL-17A and other parameters, serum levels of IL-17A have a positive correlation with fibrinogen ($p < 0.001$, Rho:0.377) and RDW ($p < 0.009$, Rho:0.282). There was no correlation with the other parameters. Advanced analysis was performed evaluating patients who had normal fibrinogen levels because both fibrinogen and IL-17A levels were significantly higher and had a positive correlation in the ectasia group. While fibrinogen levels were normal, serum levels of IL-17A in ectasia patients were higher than in the control group (4.16 ± 3.38 vs 1.47 ± 1.57 ng/ml, respectively, $p < 0.001$).

Table 1
Baseline demographic and clinical characteristics in ectasia and control groups.

Variables	Patient group (n:41)	Control group (n:45)	P
Age (years)	58.0 ± 8.9	58.0 ± 8.1	0.783**
Male n (%)	22(53.7)	21(46.7)	0.085
Smoke n (%)	11(26.8)	12(26.7)	0.988
Alcohol n (%)	0(0)	2(4.4)	0.491*
DM n (%)	10(24.4)	7(15.6)	0.302
HT n (%)	26(63.4)	22(48.9)	0.176
HPL n (%)	12(29.3)	20(44.4)	0.142
Family history n (%)	1(2.4)	0 (0)	0.470*
BMI (kg/m^2)	29.4 ± 3.96	31.2 ± 6.11	0.148**

Abbreviations: DM: diabetes mellitus, HT: hypertension, HPL: hyperlipidaemia BMI: body mass index.
Variables were presented means ± standard deviation and n (%).
Bolded data indicate statistical significance.
* Chi square test-Fisher test.
** Student *t* test was used.

Table 2
Comparing of serum IL-17A levels and other laboratory parameters between at ectasia and control group.

Variables	Patient group (median ± SD)	Control group (median ± SD)	P
IL-17A (ng/mL)	4.86 (3.41–5.87)	1.38 (0.88–2.66)	**< 0.001****
Fibrinogen (mg/dL)	337.0 ± 75.48	305.0 ± 35.87	**0.006***
HsCRP (mg/dL)	2.9 (1.0–7.3)	2.3 (0.78–5.15)	0.141**
Glucose (FBG) mg/dL	98.0 (87.5–114.0)	97.0 (90.5–114.0)	0.835**
Total cholesterol (mg/dL)	198.0 ± 37.1	194.0 ± 41.8	0.913*
Triglyceride (mg/dL)	143.0 ± 74.0	152.0 ± 79.8	0.679*
LDL (mg/dL)	125.0 ± 32.5	120.6 ± 37.1	0.822*
ALT (U/L)	20.0 (15.5–30.5)	16.0 (13.5–25.0)	0.061**
HTC (%)	40.6 ± 4.0	40.1 ± 5.2	0.647*
RDW (%)	13.7 ± 1.4	12.3 ± 1.36	**0.001***
Leucocyte (1/mm^3)	7200 ± 1660	8490 ± 2380	**0.045***
Neutrophil (1/mm^3)	4197 ± 1239	4615 ± 1579	0.215*
Lymphocyte (1/mm^3)	2100 ± 770	2740 ± 900	**0.021***
Monocyte (1/mm^3)	590 ± 160	570 ± 180	0.788*

Abbreviations: IL-17A İnterleukin-17A, HsCRP: high-sensitivity C-reactive protein, Hb: haemoglobin, FBG: Fasting blood glucose, HbA1C: glycosylated haemoglobin, LDL: low density lipoprotein, ALT: alanine amino transaminase, HTC: haematocrit, RDW: red cell distribution width, SD: standard deviation.
Variables were presented as means ± standard deviation, or median (25th-75th percentile).
Bolded data indicate statistical significance.
* Student *t* test used for normally distributed parameters.
** Mann-Whitney *U* test used for not normally distributed parameters.

Univariate and multivariate binary logistic regression analysis were performed to investigate independent correlates of CAE and other parameters. In the multivariate model, IL-17A was the only parameter significantly associated with coronary ectasia (Table 4).

In terms of CAE, the ROC analysis demonstrated that the diagnostic power of IL-17A was greater than that of fibrinogen and RDW (Fig. 1). According to the ROC curve, when the cut off value for IL-17A was accepted as 2.88 ng/mL, it was found that the sensitivity, specificity, and positive and negative predictive values of IL-17A were 85, 84, 81, and 86%, respectively.

4. Discussion

Our study evaluated the relationship between IL and 17A and coronary ectasia comparing with the patients who have normal coronary artery. We included 41 patients with coronary ectasia and 45 patients with normal coronary artery, and examined CAE caused by atherosclerosis only excluding patients who had ectasia caused by iatrogenic, autoimmune, or inflammatory disease. The most important result of our study was that IL-17A levels in coronary ectasia patients were significantly higher than in the control group. There was a positive correlation between IL and 17A levels and fibrinogen and RDW in CAE patients. When multivariate analysis was performed, it was observed that only IL-17A was independently associated with the presence of CAE. In ROC analyses, the diagnostic power of IL-7A was greater than those of fibrinogen and RDW, and IL-17A had an acceptable sensitivity and specificity values. When we analysed subgroups based on the number of affected vessels and Markis score, there was no association between IL and 17A and Markis score.

Several etiologic factors have been proposed to contribute to CAE formation. However, the exact pathophysiologic mechanisms underlying this clinical entity have not been clearly elucidated yet. Numerous pathologic data have demonstrated destruction of the vascular media with elastin degeneration [12], whilst the functional loss of the musculoelastic components of the coronary artery media is being considered as the fundamental aspect in the pathogenesis of CAE [13].

At present, there is an accumulating amount of evidence supporting the prominent position of inflammation in the pathophysiology of CAE

Table 3
Relationship of IL-17A, fibrinogen, and RDW levels with coronary ectasia extension (Markis score).

Markis score	Patient number (%)	IL-17A (mean ± SD)	P	Fibrinogen	P	RDW	P
Type 1	18(43.9)	4.42 ± 1.43	0.760*	328.4 ± 65.9	0.342*	13.5 ± 1.5	0.606*
Type 2	6(14.6)	5.24 ± 1.96		333.2 ± 76.4		13.3 ± 0.6	
Type 3	8(19.5)	5.05 ± 3.25		386.3 ± 68.9		14.3 ± 1.1	
Type 4	9(22)	3.96 ± 5.7		340.4 ± 95.1		13.7 ± 1.9	
Total	41(1 0 0)	4.86 ± 3.24		341.1 ± 75.5		13.8 ± 1.4	

Abbreviations: IL-17A: interleukin 17A; RDW: red cell distribution width.
* The parameters were compared with One-Way Anova analysis.

Table 4
Independent correlated parameters with coronary ectasia.

Variables	Univariate analysis-OR (95% CI)	P*	Multivariate analysis-OR (95% CI)	P*
Gender	0.35 (0.144–0.854)	**0.021**	0.29 (0.044–1.958)	0.206
HsCRP	1.09 (0.994–1.195)	**0.067**	1.11 (0.931–1.318)	0.249
Fibrinogen	1.01 (1.003–1.020)	**0.007**	1.01 (0.986–1.015)	0.965
Leucocyte	1.01 (0.996–1.003)	**0.052**	1.01 (0.999–1.010	0.983
RDW	1.71 (1.216–2.403)	**0.002**	1.33 (0.728–2.443)	0.350
Lymphocyte	0.54 (0.312–0.926)	**0.025**	0.30 (0.091–0.997)	0.049
Creatinine	7.97 (0.795–79.821)	**0.078**	2.11 (1.160–84.574)	0.764
IL-17A	2.53 (1.731–3.686)	< **0.001**	3.03 (1.792–5.122)	< **0.001**

Abbreviations: HsCRP: high-sensitivity C-reactive protein; RDW: red cell distribution width; IL-17A: interleukin 17A.
Bolded data indicate statistical significance.
* Binary logistic regression analysis was used.

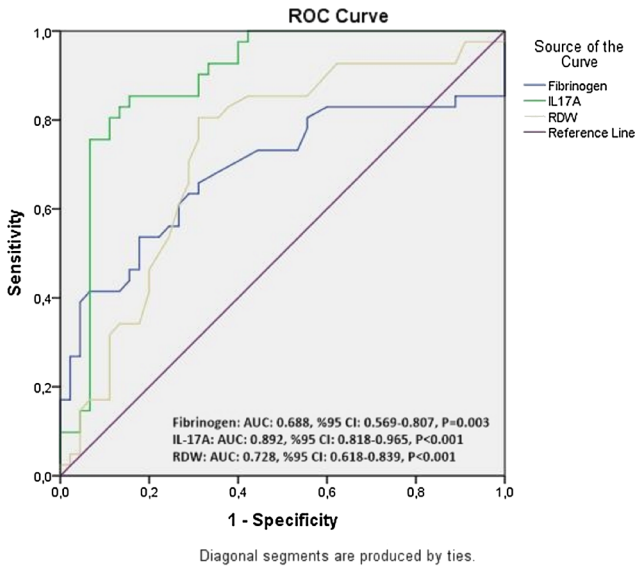

Fig. 1. ROC curve which shows diagnostic power of IL-17A, fibrinogen, and RDW in terms of coronary ectasia.

[14]. It has been demonstrated that the Th-2 secreted cytokine IL-6 enhances the up regulation and activation of matrix metalloproteinases (MMPs), which can subsequently lead to degradation of extracellular matrix, destruction of the arterial wall and eventually in the dilatation of the arteries [15]. Actually, recent studies have revealed significantly increased levels of serum IL-6, MMPs, IL-1b, TNFα, IL-10 in patients with CAE [14,16–18]. In another study, IL-4 and IL-6 levels were higher in CAE patients, while IL-2 levels were lower. Furthermore, high levels of IL-4 and low levels of IL-2 were strongly associated with CAE in the multivariate analysis [19]. Besides these Th1/Th2 cytokines, IL-17 was found to promote atherosclerotic lesion development and to be related the onset of coronary artery disease (CAD) [20,21]. Additionally, IL-17 was identified as an independent predictor of increased severity of CAD) [22]. Based on all these data, we aimed to investigate the clinical significance of IL-17A in CAE patients and to investigate its relationship with CAE width and severity. Thus, in our study, we evaluated the serum levels of IL-17A which had not been fully investigated in CAE. Our results showed that IL-17A levels were significantly higher in CAE patients than in controls.

The results of the studies in which HsCRP, neutrophil, and leukocyte levels were investigated in CAE patients are controversial. It was shown in previous studies that HsCRP was higher in CAE patients compare with control patients [14,22]. Otherwise, in several previous studies, in parallel with our study, HsCRP was not higher in CAE patients than in controls [18,23,24]. There are studies in which the neutrophil values were not significantly associated with CAE. Moreover, there are studies in which the neutrophil values were lower than in CAE patients compare with controls, as it was observed in our study [18,23]. Although this finding was unexpected in our study and was in contradiction with previous studies, this may be due to the smaller number of the study population. In addition values of leucocyte and neutrophil were in normal limits.

Fibrinogen is a proinflammatory member of the coagulation cascade [11]. There are several study in which fibrinogen was evaluated in CAE patients. In some studies, fibrinogen was found to be significantly higher in CAE patients than in the control patients [25]. Otherwise, significant results were not observed in some studies [23]. In our study, fibrinogen was increased in CAE patients compare with control patients who had normal coronary arteries. But this relationship was not observed in multivariate analysis. RDW is another parameter which was significantly higher in CAE patients in our study in accordance with the previous studies [26–28].

Markis score is used to measure the extent and severity of coronary ectasia. Our results are similar to those of Markis et al., and Type 1 was the type most seen in the Markis classification. Significant correlations between inflammatory activation and extension of CAE have been reported in several previous studies [17,26]. In contradiction with these studies, our study did not show any correlation between inflammatory parameters (IL-17A, fibrinogen and RDW) and extension of CAE.

There are some limitations of our study. The small number of patients is the most important limitation. Besides the inflammatory parameters IL-17A, fibrinogen, RDW, HsCRP investigated in the study, some other cytokines not involved might also associate with the disease severity in CAE patients. More cytokines should be examined in order to confirm our results and establish a secure hypothesis about the exact alterations of inflammatory mediators in CAE. In addition, IL-17A could not be compared with other cytokines, like IL-6 and interferon, because of budget failure. Moreover, patients and control group were evaluated only with conventional angiography. Other screening methods that exhaustively show the coronary artery wall like intravascular ultrasound and optical coherence tomography were not used. Finally, this is a cross-sectional study, with the lack of follow-up data. Therefore, further prospective studies are needed to verify the efficacy of the serum cytokine on CAE.

5. Conclusions

Our findings showed that patients with CAE have significantly increased levels of IL-17A, fibrinogen, and RDW compared to patients with normal coronary arteries. IL-17A had a positive correlation with fibrinogen and RDW. We also demonstrated that increased levels of IL-17A were associated with ectasia formation in CAE patients. Additionally, there was no a relationship between inflammatory mediators and extension of CAE in our study. Our findings suggest that further prospective studies focus on the dependent relationship between IL and 17A and CAE.

Conflicts of interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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