The Impact of Serum Interleukin-4, Interleukin-10, Interleukin-17a, and Interleukin-22 Levels on the Development of Sporadic Ascending Aortic Aneurysms

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ABSTRACT

Introduction: Aortic aneurysms are chronic diseases associated with inflammatory/immunological mechanisms. Interleukins (ILs) with pro-inflammatory and anti-inflammatory activities are shown to be related to the development of aortic damage. In this context, this study aims to evaluate the serum IL-4, IL-10, IL-17A, and IL-22 in patients with sporadic thoracic ascending aortic aneurysms.

Patients and Methods: The population of this prospective study consisted of all consecutive patients with sporadic ascending aortic aneurysms who underwent thoracic aortic aneurysm repair between November 2019 and September 2022. In the end, 29 patients (the patient group) and 19 healthy voluntary participants without aortic pathology (the control group) were included in the study. The study's primary outcome was the differences in serum IL levels between the groups.

Results: The patient group was significantly older than the control group (p= 0.042). Significantly higher neutrophil-to-lymphocyte ratio (NLR) values were detected in the patient group (p= 0.031). The median IL-10 (p= 0.001), IL-17A (p< 0.001), and IL-4 (p< 0.001) levels were significantly lower in the patient group than in the control group. There were no significant correlations between serum IL levels and the aneurysm diameter (p> 0.05). On the other hand, there were moderate correlations between IL-10 and IL-17A (r= 0.409, p= 0.038), IL-10 and IL-22 (r= 0.464, p= 0.017), and IL-17A and IL-4 (r= 0.496, p= 0.006). NLR ≥1.95 was found to be an independent risk factor for sporadic ascending aortic aneurysms [Odds Ratio (OR)= 4.53, 95% confidence interval (CI)= 1.12-21.17, p= 0.040].

Conclusion: IL-10, IL-17A, and IL-4 were significantly lower in patients with sporadic ascending aortic aneurysms larger than 55 mm. NLR was an independent risk factor for sporadic ascending aortic aneurysms. The diameter of the aneurysm was not correlated with ILs. There were positive correlations between IL-10, IL-17A, and IL-4 levels.

Key Words: Ascending aorta; inflammation; interleukins

Serum İnterlökin-4, İnterlökin-10, İnterlökin-17a ve İnterlökin-22 Düzeylerinin Sporadik Asendan Aort Anevrizmalarinin Gelişimine Etkisi

ÖZET

Giriş: Aort anevrizmaları inflamatuvar/immünolojik mekanizmalarla ilişkili kronik hastalıklardır. Proinflamatuvar ve antiinflamatuvar aktivitelere sahip interlökinlerin (IL) aort hasarı gelişimiyle ilişkili olduğu gösterilmiştir. Bu bağlamda, bu çalışmanın amacı sporadik torasik asendan aort anevrizması olan hastalarda serum IL-4, IL-10, IL-17A ve IL-22 düzeylerinin değerlendirilmesidir.

Hastalar ve Yöntem: Bu prospektif çalışmanın popülasyonu, Kasım 2019 ile Eylül 2022 arasında torasik asendan aort anevrizması onarımı yapılan, cerrahi tedavisi yapılan ardışık hastaları içermiştir. Çalışmaya 29 hasta (hasta grubu) ve aort patolojisi olmayan 19 sağlıklı gönüllü (kontrol grubu) dahil edildi. Çalışmanın birincil sonlanımı, gruplar arasındaki serum IL seviyelerindeki farklılıklar olarak belirlendi.

Bulgular: Hasta grubundaki hastalar, kontrol grubuna göre anlamlı olarak daha yaşlıydı (p= 0.042). Ortanca IL-10 (p= 0.001), IL-17A (p< 0.001) ve IL-4 (p< 0.001) düzeyleri çalışma grubunda kontrol grubuna göre anlamlı olarak daha düşüktü. Serum IL düzeyleri ile anevrizma çapı arasında anlamlı bir ilişki yoktu (p> 0.05). IL-10 ile IL-17A (r= 0.409, p= 0.038), IL-10 ile IL-22 (r= 0.464, p= 0.017) ve IL-17A ile IL-4 (r= 0.496, p= 0.006) arasında orta düzeyde korelasyon tespit edildi. Nötrofil-lenfosit oranı (NLO) değerleri hasta grubundaki hastalarda daha yüksekti (p= 0.031). NLO değerinin ≥1.95 olması sporadik asendan aort anevrizmaları için bağımsız bir risk faktörü olarak bulundu [Odds Ratio (OR)= 4.53, %95 güven aralığı (CI)= 1.12-21.17, p= 0.040].

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Sonuç: IL-10, IL-17A ve IL-4, 55 mm'den büyük sporadik asendan aort anevrizması olan hastalarda anlamlı olarak daha düşüktü. NLO değeri, sporadik asendan çıkan aort anevrizmaları için bağımsız bir risk faktörü olarak bulundu. Anevrizma çapı ile IL düzeyleri arasında bir korelasyon yoktu. IL-10, IL-17A ve IL-4 seviyeleri arasında pozitif korelasyonlar tespit edildi.

Anahtar Kelimeler: Asendan aorta; inflamasyon; interlökinler

INTRODUCTION

The aorta can be subject to aortic dilatation/aneurysm, which, if left untreated, may cause aortic rupture and aortic dissection in the context of several diseases[1,2]. Giant cell arteritis, immunoglobulin (Ig) G4-related pathologies, Kawasaki disease, and Marfan syndrome are specific diseases that may lead to the development of aortic dilatations and aneurysms[1-6]. However, atherosclerotic pathogenesis-related sporadic aortic aneurysms constitute the most frequent etiology. Although several risk factors, including smoking, arterial hypertension, and male gender, have been defined as risk factors, aortic aneurysm is a chronic inflammatory disease[7-9]. The mechanisms that weaken the immune response might be beneficial in preventing the extent of aortic damage[8]. Nevertheless, the relationship between inflammatory/immunological mechanisms and aortic injury remains controversial[1,7,9].

Interleukins (ILs) are biologically active small peptides with different mechanisms of action, either pro- or anti-inflammatory, or immunomodulatory properties[6,8]. IL-1α, IL-1β, IL-4, IL-6, IL-10, IL-17A, IL-19, IL-22, and IL-32 are the ILs that promote, halt, or suppress the inflammatory processes[1,6-8,10-14]. It has been speculated that several ILs might potentially play a role in developing aortic aneurysms. The potentially beneficial effects of genetic and pharmacological inhibition of ILs on the progression of aortic dilatation have been studied in the literature[6]. However, some of these studies have failed to demonstrate any prominent relationship between these ILs and aortic aneurysm formation in animal and human studies, whereas others reported controversial results[15]. On the other hand, the relationship between ILs and arterial aneurysms has been demonstrated in animal studies. In contrast, the relevant human studies were contradictory and could not reveal any positive potential effect of ILs[1]. In addition, most of the experimental and clinical studies were related to the inflammatory changes in abdominal aortic aneurysms. Only a few were about non-familial thoracic ascending aneurysms[16,17], necessitating further studies to be conducted in order to clarify the regulatory function of the ILs with pro-inflammatory activity and the effect of the anti-inflammatory treatment strategies based on ILs[18].

This study was carried out to evaluate the serum levels of ILs, i.e., IL-4, IL-10, IL-17A, and IL-22, in patients with non-familial thoracic ascending aortic aneurysms in comparison with healthy control subjects, considering the limited number of studies about the impact of ILs with anti-inflammatory and pro-inflammatory properties on the development of the thoracic aneurysms.

PATIENTS and METHODS

Study Design

The population of this prospective study consisted of all consecutive patients with sporadic ascending aortic aneurysms who underwent thoracic aortic aneurysm repair between November 2019 and September 2022. The study protocol was approved by the local ethics committee (Approval date, Number: 08.05.2022 & E-10420511-050-14513). The study was carried out in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Population and Sample

Among the consecutive patients who underwent thoracic aortic aneurysm repair, the ones with non-familial sporadic thoracic aortic aneurysms diagnosed using transthoracic echocardiography (ECHO), computed tomography (CT), or magnetic resonance imaging (MRI), and an aortic diameter larger than 55 mm, which indicated surgical repair, were included in the study[19]. On the other hand, patients with familial and syndromic forms and autoimmune connective tissue disorders associated with aortic dilatation/aneurysm, active cancer, and an aortic diameter ≤55 mm were excluded from the study. In the end, 29 patients with sporadic ascending aortic aneurysms who underwent surgical repair were included in the patient group. The median diameters of the tubular ascending aorta at 2 cm above the sinotubular junction and the level of sinuses of Valsalva in the patient group were 51.0 mm (range 37.0-62.0) and 42.0 mm (range 32.0-60.0), respectively[20].

In addition, 19 healthy voluntary participants without a dilatation/aneurysm of the thoracic ascending aorta were included in the control group. The median diameter of the tubular ascending aorta in the control group was 32.4 mm (range 27.3-36.2).

Interventions

Transthoracic ECHO and CT&MRI were performed in all patients and healthy control subjects by an echocardiographer with at least 12 years of ECHO experience and a radiologist with 30 years of CT&MRI experience, respectively. Fasting

blood samples were taken from the patients in the last 48 hours before the surgical treatment for laboratory investigations. The serum samples were stored for immunological parameters per standard procedures at -80 °C until analysis. The IL measurements described in the literature used the techniques described in the literature[5,9]. The LEGENDplex™ Custom Human T Helper Cytokine Panel (version 2, ID: 741028, BioLegend, USA) was used to quantify the ILs simultaneously.

Variables

Demographic characteristics (age, gender, weight, and height) and laboratory characteristics [hemoglobin, neutrophil-to-lymphocyte ratio (NLR), creatinine, glycated hemoglobin (HbA1c), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, e-glomerular filtration rate (eGFR), and C-reactive protein (CRP)] were prospectively determined during the last admission before the surgical treatment and recorded into a predesigned worksheet. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters (kg/m^2). The patients' diameters were determined during the last ECHO examination and recorded for the ascending aorta (in cm) and the sinus of Valsalva, along with the ejection fraction (%). The ILs investigated within the scope of the study were IL-4, IL-10, IL-17A, and IL-22.

Statistical Analysis

The descriptive statistics obtained from the collected data were expressed as mean ± standard deviation values in the case of continuous variables with normal distribution, as median with minimum-maximum values in the case of continuous variables without normal distribution, and as numbers and percentages in the case of categorical variables. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to analyze the normal distribution characteristics of the numerical variables.

Pearson's Chi-squared and Fisher's exact tests were used to compare the differences between categorical variables in 2 x 2 tables.

The Mann-Whitney U test was used to compare two independent groups where numerical variables had no normal distribution.

Spearman's rho correlation coefficients were calculated to analyze the relationships between numerical variables without normal distribution.

Univariate and multivariate logistic regression analyses determined the independent risk factors for sporadic thoracic aortic aneurysm development. Statistically significant and clinically essential factors in the univariate analysis were included in the multivariate analysis.

The receiver operating characteristic (ROC) analysis using the DeLong method with the Youden index was used to determine the optimal cut-off values of NLR, IL-10, IL-17A, and IL-4 in predicting sporadic thoracic aortic aneurysm development. The area under the curve (AUC) values and the corresponding 95% confidence interval (CI) values were calculated.

Jamovi project 2.3.24.0 (Jamovi, version 2.3.24.0, 2023, retrieved from https://www.jamovi.org) and JASP 0.17.1 (Jeffreys' Amazing Statistics Program, version 0.17.1, 2023, retrieved from https://jasp-stats.org) software packages were used in the statistical analyses. The probability (p) statistics of ≤0.05 indicated statistical significance.

RESULTS

The patient group was significantly older than the control group (p= 0.042). There was no significant difference between the groups in gender and BMI values (p> 0.05) (Table 1).

Table 1. Comparison of the study and control groups in terms of demographic characteristics and clinical/laboratory findings

	Patient Group (n= 29)	Control Group (n= 19)	p
Age (year) #	62.0 (20.0-76.0)	45.0 (19.0-81.0)	**0.042***
Sex ##			
Female	8 (27.6)	10 (52.6)	0.148**
Male	21 (72.4)	9 (47.4)	
Body mass index (kg/m^2) #	27.0 (20.5-41.5)	26.0 (24.0-32.0)	0.315*
Obesity (≥30 kg/m^2), yes ##	9 (31.0)	3 (15.8)	0.316**

##: n (%), #: median (min-max)
*: Mann-Whitney U test.
**: Pearson Chi-square/Fisher's exact test.

Table 2. Laboratory parameters of the groups

	Patient group (n= 29)	Control group (n= 19)	p*
Hemoglobin, (g/dL) #	14.2 (9.9-16.1)	14.3 (10.9-17.3)	0.555
HbA1c (%) #	5.6 (5.0-6.9)	5.5 (5.3-6.3)	0.345
HDL (mg/dL) #	45.0 (30.0-119.0)	61.0 (38.0-89.0)	**0.010**
LDL (mg/dL) #	120.0 (40.0-168.0)	132.0 (61.0-195.0)	0.129
Triglycerides (mg/dL) #	112.0 (54.0-337.0)	76.0 (42.0-223.0)	0.054
CRP (mg/dL) #	0.3 (0.0-9.7)	0.1 (0.0-1.3)	**0.004**
Creatinine (mg/dL) #	0.9 (0.4-1.6)	0.8 (0.6-1.3)	0.916
eGFR (ml/min/1.73 m^2) #	95.4 (40.9-121.0)	88.0 (65.0-127.0)	0.712
Neutrophil/lymphocyte ratio#	2.2 (1.2-5.0)	1.8 (0.9-3.2)	**0.031**
Serum interleukin levels			
IL-10 (pg/mL) #	1.7 (1.5-2.1)	2.0 (1.6-3.8)	**0.001**
IL-17A (pg/mL) #	0.1 (0.1-0.2)	0.2 (0.1-0.3)	**<0.001**
IL-4 (pg/mL) #	1.7 (1.4-3.5)	2.2 (1.7-7.8)	**<0.001**
IL-22 (pg/mL) #	2.2 (1.4-4.7)	2.5 (1.5-6.3)	0.092

#: Median (min-max)
*: Mann-Whitney U test.
HbA1c: Glycosylated hemoglobin, HDL: High density lipoprotein, LDL: Low density lipoprotein, CRP: C-reactive protein, eGFR: Estimated glomerular filtration rate, IL: Interleukin.

The median ejection fraction was higher, yet not significantly, in the control group than in the patient group (62.0% vs. 60.0%) (p= 0.121).

The distribution of the laboratory characteristics by the groups is shown in Table 2. The groups had significant differences in HDL and CRP levels and NLR values. The median HDL values were higher in the patient group (61.0 mg/dL) than in the control group (45.0 mg/dL) (p= 0.010). For the patient group, the median CRP values were measured at 0.3 mg/d, whereas 0.1 mg/dL in the control group (p= 0.004). The patient group had significantly higher NLR values than the control group (for median NLR, 2.2 vs. 1.8) (p= 0.031) (Table 2).

The median IL-10 levels were significantly lower in the patient group than in the control group (1.7 pg/mL vs 2.0 pg/mL) (p= 0.001). The patient group had significantly lower median values of IL-17A (0.1 pg/mL vs. 0.2 pg/mL, p< 0.001) and IL-4 (1.7 pg/mL vs. 2.2 pg/mL, p< 0.001) than the control group. On the other hand, there was no significant difference between the groups in IL-22 levels (2.2 pg/mL vs. 2.5 pg/mL9. p= 0.292).

In predicting the development of sporadic ascending thoracic aneurysms, the ROC curve analysis revealed that optimal cut-off values of NLR, IL-10, IL-17A, and IL-4 were >1.95 (65.52% for sensitivity, 78.95% for specificity), ≤1.99 pg/mL (96.15% for sensitivity, 52.63% for specificity), ≤0.16 pg/mL (86.21% for sensitivity, 89.47% for specificity), and ≤1.92 pg/mL (79.31% for sensitivity, 88.24% for specificity), respectively (Table 3) (Figure 1). IL-17A had the highest AUC

Table 3. The receiver operating characteristics (ROC) curve analysis of the demographic and interleukin levels in predicting development of sporadic ascending aortic aneurysms

	AUC	Sensitivity	Specificity	Cut off	95% CI	p
Neutrophil/lymphocyte ratio	0.686	65.52	78.95	>1.95	0.536-0.812	**0.018**
IL-10 (pg/mL)	0.803	96.15	52.63	≤1.99	0.657-0.906	**<0.001**
IL-17A (pg/mL)	0.885	86.21	89.47	≤0.16	0.760-0.959	**<0.001**
IL-4 (pg/mL)	0.862	79.31	88.24	≤1.92	0.728-0.946	**<0.001**

AUC: Ara under the curve, CI: Confidence interval, IL: interleukin.

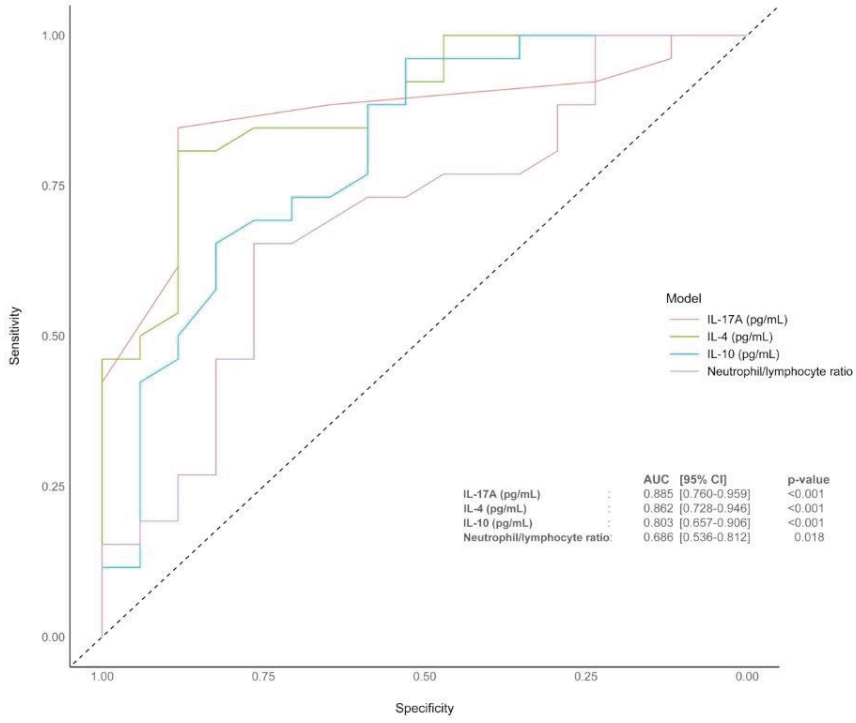

Figure 1. The receiver operating characteristics (ROC) curve analysis of ILs in predicting the development of sporadic ascending aortic aneurysms.

value (AUC= 0.085, 95% CI= 0.760-0.959, p< 0.001). IL/17A values of ≤0.16 pg/mL predicted sporadic ascending aortic aneurysms with 86.21% sensitivity and 89.47% specificity.

The results of the univariate and multivariate regression analyses on the predictive powers of the variables in predicting the development of sporadic ascending aortic aneurysms are shown in Table 4. Based on the multivariate analysis, there was

Table 4. Univariate and multivariate regression analysis in predicting the development of sporadic ascending aortic aneurysms

	Univariate		Multivariate	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Age (year)	1.05 (1.01-1.10)	**0.034**	1.04 (0.96-1.13)	0.294
Sex				
Male vs. Female	2.92 (0.88-10.19)	0.084	--	--
Obesity				
≥30 vs. <30	2.40 (0.60-12.18)	0.241	--	--
Neutrophil/lymphocyte				
>1.95 vs. ≤1.95	7.12 (2.00-30.60)	**0.004**	2.48 (0.30-20.82)	0.403
IL-10 (pg/mL)				
>1.99 vs. ≤1.99	27.78 (4.43-548.29)	**0.003**	9.46 (0.37-244.59)	0.176
IL-17A (pg/mL)				
>0.16 vs. ≤0.16	53.12 (10.54-436.53)	**<0.001**	3.70 (0.25-53.87)	0.338
IL-4 (pg/mL)				
>1.92 vs. ≤1.92	28.75 (6.09-219.07)	**<0.001**	14.67 (0.70-305.23)	0.083

OR: Odds ratio, CI: Confidence interval, IL: Interleukin.

no independent risk factor in predicting the development of sporadic ascending aortic aneurysms.

There was no significant correlation between ILs and the aneurysm diameter (p> 0.05). Nevertheless, there were moderate correlations between IL-10 and IL-17A (r= 0.409, p= 0.038), IL-10 and IL-22 (r= 0.464, p= 0.017), and IL-17A and IL-4 (r= 0.496, p= 0.006) levels.

DISCUSSION

The study indicated that serum IL-10, IL-17A, and IL-4 levels were significantly lower in patients with sporadic ascending aortic aneurysms larger than 55 mm. Even though IL-22 did not significantly differ between the patient and control groups, the significant correlations between IL-10, IL-17A, and IL-4 might indicate a compensatory anti-inflammatory status.

Previous studies reported that aortic injury, either aneurysms and/or dissection, usually lead to altered expressions and changed epigenetic regulations of several ILs, including IL-4, IL-6, IL-17, and IL-10[5,10,16,17,21-24]. Nevertheless, there were notable, controversial findings related to the IL families and their increased or decreased levels in various clinical presentations of aortic aneurysms[21,23]. We also detected that the number of studies focusing on sporadic aortic aneurysms was limited.

Malm et al. detected significantly higher IL-10 levels in patients with abdominal aortic aneurysms than in healthy control subjects[19]. Other studies reported conflicting outcomes on the plasma and tissue extract levels of IL-10[25,26]. Besides, some studies reported lower levels of anti-inflammatory ILs, including IL-10, in patients with ruptured aortic aneurysms[27]. As in this study, Liao et al. detected significantly lower IL6, IL10, and IL17A levels in patients with abdominal aortic aneurysms[28]. They also showed that IL10 was significantly correlated with aneurysm development and growth rate in the positive direction[28]. In sum, the exact role of IL-10, as an anti-inflammatory cytokine, in human aortic aneurysmatic pathologies remains obscure. Furthermore, the positive correlations found between some of the ILs analyzed in the study might suggest complex relationships between pro-inflammatory and anti-inflammatory cytokines. Counter relations between anti-inflammatory and pro-inflammatory ILs and the potentially compensatory roles of some of the ILs might lead to such controversies.

The impact of pro-inflammatory ILs, such as IL-6, IL-22, and IL-17-A, on developing aortic aneurysms has been investigated. Elevated serum levels of pro-inflammatory cytokines have been associated with aortic aneurysms[29,30]. Dawson et al. found elevated IL-6 levels within the aorta of the patients with abdominal and thoracic aortic aneurysms who underwent endovascular aneurysm repair[29]. In one experimental animal model, the authors reported a critical role of IL-17 in promoting inflammation during abdominal aortic aneurysm formation[30]. Ye et al. showed significantly higher levels of IL-22 and IL-6 in patients with acute thoracic aortic dissection than those without dissection[31]. They concluded that IL-22 might be a prognostic factor for the acute presentation of thoracic aortic aneurysms. The findings of this study contradicted the previously drawn conclusions. We found lower levels of IL-17A in patients with sporadic ascending aortic aneurysms. Besides, there were no significant differences in IL-22 levels between the patient and control groups. The compensatory mechanisms between anti-inflammatory and pro-inflammatory ILs might be essential during the development of aortic aneurysms.

The impact of ILs on aneurysm size, morphology, and growth rates has been addressed in the literature. Ahmad et al. found no significant relationship between IL-1α and the features of infrarenal abdominal aortic aneurysms[9]. Liao et al. found a weak and negative correlation between IL10 levels and maximal aortic diameters and a positive correlation between IL-17A levels and the maximal cross-sectional area of the aneurysms of 476 aortic aneurysm patients[28]. In comparison, no significant correlation was found in this study between the ILs, i.e., IL-4, IL-10, IL-17-A, and IL-22, and the diameter of the ascending thoracic aneurysms. Further large-scale studies are needed to establish the potential benefits of ILs in monitoring disease activity.

Despite the challenges in obtaining reliable data from animal models for human studies evaluating aortic aneurysms, several experimental studies that aimed to enhance anti-inflammatory and dampen pro-inflammatory pathways have been performed. In one of these studies, Adam et al. reported a reduction in the rates of aortic dissection when they transfected an IL-10 transcribing nonimmunogenic minicircle vector in a mouse model[8]. They speculated that the augmentation of systemic IL-10 expression and corresponding plasma levels led to significant reductions in the aneurysm size. IL-19, IL-32, and IL-38 were other ILs studied experimentally featuring the suppression of abdominal aortic aneurysm formation[13-15]. IL-6 infusion animal models featuring the initiation of macrophage accumulation and aortic dilatation and IL-1α disruption leading to more giant aneurysms were also performed[6,11]. IL-22 is another cytokine that reportedly increased in patients with aortic dissection[31]. In parallel, Wang et al. demonstrated the inhibition of aortic dissection via IL-22 deficiency in an experimental abdominal aortic aneurysm model[12]. In contrast, the findings of this study did not support

the impact of IL-22 on aneurysm formation. Nevertheless, future studies may reveal the potential benefits of these molecules in preventing aortic aneurysms and prolonging the time between diagnosis and the need for interventions.

The small sample size was the primary limitation of this study. On the other hand, it was essential to include only the patients with sporadic ascending thoracic aneurysms larger than 55 mm in the study to ensure the homogeneity of the sample. The age differences between the groups might be a confounding factor impacting the IL levels.

In conclusion, it was determined that the serum IL-10, IL-17A, and IL-4 levels were decreased in patients with sporadic ascending thoracic aortic aneurysms larger than 55 mm. The reduced levels of these ILs might be associated with the development of aortic aneurysms in the thoracic part of the aorta. The cytokine correlations indicate a compensatory mechanism associated with aortic aneurysm formation. Future studies are needed to further analyze the cause-and-effect relationships in the context of the development of sporadic thoracic ascending aortic aneurysms.

Ethics Committee Approval: The study protocol was approved by the local ethics committee (Approval date, Number: 08.05.2022 & E-10420511-050-14513). The study was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

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