Research Article

EJCM E Journal of Cardiovascular Medicine

EJCM 2022;10(4):160-166

DOI: 10.32596/ejcm.galenos.2022.2022-03-025

Relationship of Ascending Aortic Aneurysm with Serum Uric Acid and Blood Inflammatory Parameters

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Abstract

Objectives: Ascending aortic aneurysm (AAA) is defined as the enlargement of the aorta at the point where it exits the heart, and many pathophysiological processes play a role in its development. Studies have shown that the inflammatory process and blood uric acid levels play a role in many cardiovascular diseases. In our study, we investigated the effects of uric acid and blood inflammation parameters on the development of AAA by comparing them with the control group.

Materials and Methods: The study included 97 patients who were found to have AAA in echocardiographic examination and 100 patients without AAA. Patients with AAA were determined as group 1, and those without aneurysm were determined as group 2. The clinical and laboratory data of the patients were evaluated retrospectively through the hospital information system.

Results: In the AAA group, compared to the control group, uric acid levels (5.7±1.4 vs 3.9±0.8, p=0.001), systemic immune inflammation index (SII) [538 (330-854) vs 440 (324-578), p=0.007] and neutrophil-lymphocyte ratio (NLR) [4.7 (3.7-5.9) vs 4.1 (3.2-4.9), p=0.001] were found to be significantly higher, while the platelet-lymphocyte ratio [110 (84-170) vs 105 (82-135) p=0.186] was found to be similar. In multivariate logistic regression analysis, uric acid (p=0.001) was found to be an independent predictor of AAA.

Conclusion: In our study, we found that inflammatory parameters such as NLR and SII, and serum uric acid level were higher in patients with AAA compared in the control group. We showed that increased serum uric acid level is an independent predictor of AAA.

Keywords: Ascending aortic aneurysm, uric acid, systemic immune inflammatory index, neutrophil/lymphocyte ratio

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Received: 18.03.2022 **Accepted:** 15.10.2022

Cite this article as: Atay M, Çalışkan S, Güngören F. Relationship of Ascending Aortic Aneurysm with Serum Uric Acid and Blood Inflammatory Parameters. EJCM 2022;10(4):160-166.
DOI: 10.32596/ejcm.galenos.2022.2022-03-025

Introduction

Ascending aortic aneurysm (AAA) is one of the most common diseases of the aorta after atherosclerosis[1]. AAA, which is usually asymptomatic, is detected incidentally by imaging methods. In patients with Marfan syndrome, bicuspid aortic valve, or patients with a wide aorta on pleurography, the definitive diagnosis can be made with contrast-enhanced computed tomographic angiography (CTA) or magnetic resonance angiography[1].

Many studies have been conducted to prevent mortality and morbidity in AAA and to understand the underlying pathophysiology. Among the mechanisms suggested for the pathophysiology of AAA, it is stated that the effect of hemodynamic strength due to hypertension (HT), the chronic inflammatory process formed in the vessel wall, oxidative stress and the role of genetic predisposition[2,3]. The disruption of the balance between matrix metalloproteinases and their inhibitors plays a role in aortic wall degeneration. The increase in inflammatory cells in the aortic wall causes this imbalance to become more pronounced[2]. Another pathophysiological process is that increased oxidative stress causes damage to the vessel wall. Studies have shown that uric acid, which affects oxidative stress, plays a role in cardiovascular diseases[4].

Blood inflammation markers are increased in many diseases and are used in determining prognosis. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are frequently used as indicators of inflammation. Additionally, current studies indicate that the systemic immune inflammatory index (SII), which is a new parameter, is a good indicator of inflammation[5,6]. SII, which is an index obtained by multiplying the NLR with the platelet count, provide important prognostic information in chronic diseases. Considering the chronic inflammatory process of AAA in the vascular wall, whether there is a relationship between SII and AAA is an issue that needs to be investigated. In our study, we investigated the relationship between serum uric acid levels and NLR and PLR, which are indicators of inflammation, and between SII, a relatively new indicator and AAA.

Materials and Methods

Patient Population

Patients admitted to Bahçelievler State Hospital between January 2015 and January 2021 and diagnosed with AAA were included in the study. In the echocardiographic examination, 97 patients with an ascending aortic diameter greater than 38 mm were determined as group 1. One hundred patients with normal AAA diameters were taken as group 2 (control group). The demographic characteristics and laboratory data of the patients were retrospectively reviewed through the hospital registry system. Patients using antihypertensive medicines and patients with blood pressure values >140/90 mmHg in the last three follow-ups were considered hypertensive. We have followed up in patients using echocardiography and routine laboratory values at the time of the examination.

Patients with known liver disease, chronic renal failure (creatinine >1.5 mg/dL), hematological disease, those using thiazide diuretics, those with bicuspid aortic valve, previous cardiac and aortic surgery history, and gout disease diagnosis were excluded from the study.

Ethics committee approval was received for the study from the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (protocol number: 2021/331).

Laboratory Analysis

Hemoglobin (Hb), white blood cell (WBC), red cell distribution width (RDW), mean platelet volume (MPV), and platelet counts were measured using an automatic complete blood count device (Coulter LH 750 Hematology Analyzer, Beckman Coulter, Miami, Florida). The NLR was calculated by dividing the neutrophil count by the lymphocyte count and the PLR was calculated by dividing the platelet count by the lymphocyte count. The SII index was calculated by multiplying the NLR by the platelet count. The reference ranges for uric acid were taken as 3.5-7.2 mg/dL in male patients and 2.6-6 mg/dL in female patients.

Echocardiography

Echocardiographic measurements were performed according to recommendations of the guidelines of the American echocardiography society[7]. The ascending aortic diameter was measured in 2 dimensions using an Echocardiography device (EPIQ 7, Philips Medical Systems, Andover, MA). The diameter measured perpendicular to the aorta in the parasternal long axis view was recorded as the largest aortic diameter. Patients with an ascending aortic diameter greater than 38 mm were considered aneurysmal. 2D and M-mode were used for heart cavities and aortic diameter measurements.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) 24.0 program was used for statistical analysis. While evaluating the study data, independent sample t-test was used in the comparison of two groups of normally distributed parameters as well as descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum). Pearson chi-square test was used in the analysis of qualitative data. Receiver operating characteristic (ROC) curve test was used to calculate the sensitivity and specificity values according to the groups (cut-off). Logistic regression analysis was used to examine the effects of NLR, PLR, SII Index and uric acid value on the groups. A p-value of <0.05 was considered statistically significant.

Results

The basic demographic characteristics and laboratory parameters of the groups included in the study are presented in Table 1. The mean age of group 1 was 67.9±14 and group 2 was 65.1±12.8 (p=0.137). There was no significant difference between the two groups in terms of the presence of comorbidities such as diabetes mellitus (DM), HT, hyperlipidemia (HL), and coronary artery disease (CAD) (p>0.05). Low density lipoprotein (LDL), triglyceride, aspartate aminotransferase, alanine aminotransferase, WBC, platelet count, MPV and RDW values were similar between groups 1 and group 2 (p>0.05). High density lipoprotein (HDL) was significantly higher in group 1 [45 (37-52) vs 38 (39-75), p=0.015], while Hb value was lower (13.0±1.8 vs 13.5±1.5, p=0.034). Uric acid level (5.7±1.4 vs 3.9±0.8, p=0.001), SII index [538 (330-854) vs 440 (324-578), p=0.007] and NLR [4.7 (3.7-5.9) vs 4.1 (3.2-4.9), p=0.001] were found to be higher in the AAA group than in the control group. PLR [110 (84-170) vs 105 (82-135) p=0.186] values were similar between the two groups.

Multivariate logistic regression analysis was performed to identify the independent predictors of AAA. A model was created by including HDL, uric acid, SII index, NLR, presence of HT, presence of diabetes, presence of HL,

Table 1. Demographic and laboratory data of the patient and control groups

	Group 1	Group 2	
Male gender, n (%)	50 (51.5)	47 (47)	[a]**0.523**
Age, years	67.9±14.0	65.1±12.8	[b]**0.137**
Diabetes, n (%)	21 (21.6)	22 (22)	[a]**0.953**
Hypertension, n (%)	42 (43.3)	40 (40)	[a]**0.639**
Hyperlipidemia, n (%)	19 (19.6)	21 (21)	[a]**0.805**
CAD, n (%)	16 (16.5)	16 (16)	[a]**0.925**
LDL cholesterol, g/dL	118 (93-145)	121 (93-145.5)	[c]**0.648**
HDL cholesterol, mg/dL	45 (37-52)	38 (39-57)	[c]**0.015***
Triglyceride, mg/dL	133 (93-168)	119 (93-168)	[c]**0.412**
AST, m/L	20 (16-25)	19 (16-22)	[c]**0.223**
ALT, m/L	17 (12-24)	16 (12-21)	[c]**0.273**
WBC, x10^9/L	8.1±2.3	7.5±1.9	[b]**0.580**
Hemoglobin, g/dL	13.0±1.8	13.5±1.5	[b]**0.034***
Platelet, 10^9/L	243±78	256±65	[b]**0.200**
MPV, fL	9.7±1.4	9.9±1.1	[b]**0.666**
Uric acid, mg/dL	5.7±1.4	3.9±0.8	[b]**0.001****
RDW	13.9±1.7	13.4±1.3	[b]**0.070**
SII index	538 (330-864)	440 (324-578)	[c]**0.007****
NLR	4.7 (3.7-5.9)	4.1 (3.2-4.9)	[c]**0.001****
PLR	110 (84-170)	105 (82-135)	[c]**0.186**

*[a]Pearson chi-square, [b]Independent sample t-test, [c]Mann-Whitney U test. **p<0.01, *p<0.05*
CAD: Coronary artery disease, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, WBC: White blood cell, MPV: Mean platelet volume, RDW: Red cell distribution width, SII: Systemic immune inflammatory index, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, LDL: Low density lipoprotein, HDL: High density lipoprotein

gender, presence of CAD and Hb level in the multivariate analysis. When the table containing the coefficients in the regression model and the significance of these coefficients were examined, it was observed that uric acid and NLR were independent predictors of AAA (Table 2).

ROC curve analysis was performed to determine a cutoff value for uric acid, which was determined as an independent predictor in multivariate regression analysis. In the ROC curve analysis, the sensitivity of uric acid above 4.56 mg/dL in predicting AAA was 77.3%, and the specificity was 77% (area under the curve 0.881) (Figure 1).

Discussion

The main finding of our study is that serum uric acid level, NLR and SII are higher in patients with AAA than in the control group. Also, serum uric acid level and NLR are independent predictors of AAA development.

The incidence of AAA increases with advancing age, and it mostly shows an asymptomatic course[8,9]. The asymptomatic course of this disease, the results of which can be fatal when symptomatic, causes a delay in diagnosis[10]. Early recognition and treatment of modifiable risk factors are important in AAA, where acquired factors and genetic factors play a role in its etiology[9,10]. There is a genetic transmission in 20% of the patients, and autosomal dominant transmission is observed[10].

Oxidative stress is another mechanism implicated in the pathogenesis of AAA. Several mechanisms are proposed for the damage of oxidative stress to the vessel wall in AAA. Inflammatory cells in the aortic wall, mechanical distension, smooth muscle cells, growth factors and lipid mediators increase oxidative stress by producing reactive oxygen derivatives[11]. It has been determined that uric acid is central to oxidative stress-related cardiovascular diseases, mostly from the data obtained from epidemiological studies. The protective effects of allopurinol, which lowers serum uric acid levels, have been demonstrated in cardiovascular diseases such as ischemia-reperfusion injury, in which oxidative stress plays an important role[12].

Factors such as smooth muscle cells, mechanical distension, growth factors, and most importantly,

Table 2. Multivariate regression analysis for AAA risk factors

	Odd's ratio	95% CI For EXP(B)		Multivariate p-value
		Lower	Upper	
HDL	1,006	0.966	1,047	0.787
Uric acid	0.187	0.113	0.311	**0.000**
SII index	1,002	0.999	1,004	0.269
NLR	0.414	0.174	0.985	**0.046**
Hypertension	1,108	0.458	2,680	0.820
Diabetes	1,083	0.375	3,127	0.883
Gender	0.853	0.318	2,289	0.752
Coronary artery disease	0.888	0.226	3,495	0.866
Hyperlipidemia	0.842	0.278	2,550	0.761
Hemoglobin	1,272	0.944	1,714	0.114

NLR: Neutrophil-lymphocyte ratio, SII Systemic immune inflammatory index, LDL: Low density lipoprotein, HDL: High density lipoprotein, AAA: Ascending aortic aneurysm, CI: Confidence interval

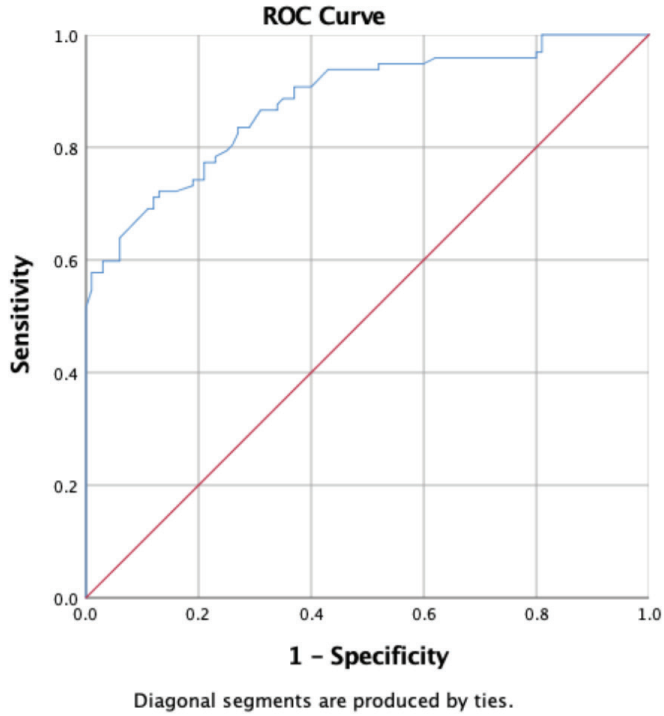

Figure 1. Evaluation of uric acid by ROC analysis
ROC: Receiver operating characteristic

inflammatory cells are thought to affect the balance between aortic wall regeneration and destruction, and AAA develops because of this imbalance[13]. Especially, recently, it has been stated that an increase in uric acid may cause vascular endothelial dysfunction by increasing oxidative stress[2,14]. Uric acid is a product of purine metabolism and is indicated as a strong indicator of cardiovascular risk and poor outcome[15]. Uric acid causes the conversion of nitric oxide (NO) to glutathione and reduces the amount of NO[16]. Considering the vasodilator effects of NO on vascular smooth muscle cells, the negative effects of increased uric acid levels in the pathogenesis of aortic aneurysms can be understood more easily. Additionally, some studies have also shown that increased serum uric acid levels result in the proliferation of vascular smooth muscle cells and have proinflammatory effects on vascular smooth muscle cells[17]. However, studies have not clearly demonstrated the relationship between AAA sensitivity and severity and uric acid increase[14]. In our study, we found that the uric acid levels were significantly higher in the group with aortic aneurysm than in the healthy group. In a study by Cai et al.[14] in patients with Behçet's disease, it was stated that serum uric acid level could be used as an independent marker for the risk and severity of AAA. Our study is consistent with the literature in this respect. Additionally, in our study, we found that a serum uric acid level above 4.56 mg/dL had a sensitivity of 77.3% and a specificity of 77% in predicting AAA. Şerefli et al.[18] found that homosyctein levels higher in coronary artery bypass patients with infrarenal AAA. In another study, the AAA diameter was found to be higher in patients with increased homocysteine values[19].

In a study by Uluganyan[10], it was observed that although male gender was found to be high in the AAA group, it did not reach statistical significance. In the same study, age, presence of DM, presence of HL, presence of CAD, HDL level, LDL level, and TG level was found to be similar between the AAA group and the healthy groups[10]. In our study, when the AAA group and the control groups were compared, age and gender were similar between the two groups. In our study, comorbid conditions such as DM, HT, and CAD, were found to be similar in both groups. In a study by Esen et al.[2], unlike our study, HT was found to be significantly higher in the AAA group. HT plays a role in the development of AAA by applying a continuous radial force to the aortic vessel wall by weakening and expanding the vessel wall[10]. The similarity found in both groups in our study may be due to the small number of patients included in the study.

HDL modulate oxidative stress as an anti-inflammatory and antioxidant, as well as regulates cholesterol flow from tissues. It shows its anti-inflammatory effect on monocytes through apolipoprotein A1, which is its main component[15]. Additionally, HDL molecules increase the release of NO synthase. In a study conducted in patients with bicuspid aortic valve, it was shown that patients with AAA had lower HDL levels than patients without aortic dilatation[20]. Also in our study, HDL level was found to be higher in the control group than in the AAA group, similar to other studies.

Inflammatory cells increase infiltration in the aortic wall and the cytokines secreted by these cells trigger the development of AAA[21,22]. NLR is increased based on increased neutrophil counts due to acute inflammation. In our study, we found the NLR value to be significantly higher in the AAA group than in the control group. Similar to our study, in a study by Güngör et al.[9], NLR value was found to be significantly higher in the AAA group. In another study, it was stated that NLR could be an important indicator of rupture in symptomatic AAA[23]. In a study by Cem et al.[22], NLR level was stated as an independent and strong predictor of AAA in newly diagnosed hypertensive patients. We believe that the effect of high NLR on the development of AAA is due to increased inflammation-related wall degeneration and thinning of the aortic wall. SII value is a combination of NLR and PLR values and is a new marker of inflammation and the immune system. In our study, the SII value was found to be higher in the AAA group than in the control group. Su et al.[6] stated that SII can be used in risk stratification to determine long-term

outcomes after hospitalization and discharge in patients with Type B aortic dissection treated with endovascular methods.

Despite an increasing number of studies, it is still controversial whether elevated serum uric acid levels are an independent risk factor for cardiovascular diseases[24,25].

Study Limitations

There were some limitations to our study. A prominent limitation was that it was a single-center and a retrospective study with a low number of patients. Another limitation may be counted as making the diagnosis of AAA only by echocardiography. The use of advanced imaging techniques, such as CTA and magnetic resonance, could provide a more detailed evaluation of the aneurysm. Extensive prospective studies are needed to reveal the pathophysiology of AAA more clearly.

Conclusion

As a result, in our study, we found that inflammatory parameters such as NLR and SII, and serum uric acid level were increased in patients with AAA compared with the control group. We also found that uric acid is an independent predictor of AAA development. Considering that serum uric acid levels and inflammatory parameters are increased in patients with AAA, we think that controlling these parameters in these patient groups may be effective in controlling the disease.

Ethics

Ethics Committee Approval: This study was received for the study from the Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (protocol number: 2021/331).

Informed Consent: Patient data were retrospectively collected.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Atay M, Çalışkan S, Concept: Atay M, Çalışkan S, Güngören F, Design: Atay M, Çalışkan S, Güngören F, Data Collection and/or processing: Atay M, Çalışkan S, Analysis and/or Interpretation: Atay M, Çalışkan S, Güngören F, Literature Search: Atay M, Çalışkan S, Güngören F, Writing: Atay M, Çalışkan S, Güngören F.

Conflict of Interest: The authors report no financial relationships or conflicts of interest regarding the content here.

Financial Disclosure: This research received no specific grant from any funding agency.

References

1. Günay Ş, Güllülü NS. Approach to aortic aneurysms in the elderly. Turk Kardiyol Dern Ars 2017;45:93-5.
2. Esen AM, Akcakoyun M, Esen O, et al. Uric acid as a marker of oxidative stress in dilatation of the ascending aorta. Am J Hypertens 2011;24:149-54.
3. Herron GS, Unemori E, Wong M, Rapp JH, Hibbs MH, Stoney RJ. Connective tissue proteinases and inhibitors in abdominal aortic aneurysms. Involvement of the vasa vasorum in the pathogenesis of aortic aneurysms. Arterioscler Thromb 1991;11:1667-77.
4. Güngören F, Beşli F. Evaluation of the Relationship Between Uric Acid Levels and Etiology in Patients With Heart Failure. Journal of Harran University Medical Faculty 2019;16:478-83.
5. Chen JH, Zhai ET, Yuan YJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World J Gastroenterol 2017;23:6261.
6. Su S, Liu J, Chen L, et al. Systemic immune-inflammation index predicted the clinical outcome in patients with type-B aortic dissection undergoing thoracic endovascular repair. Eur J Clin Invest 2021;52:e13692.
7. Lang RM, Bierig M, Devereux RB, et al. Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standarts Committee and the Chamber Quantification Writing Group, Developed in Conjuction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
8. Patel HJ, Deeb GM. Ascending and arch aorta: pathology, natural history, and treatment. Circulation 2008;118:188-95.
9. Güngör B, Özcan KS, Karadeniz FÖ, et al. Red cell distribution width is increased in patients with ascending aortic dilatation. Turk Kardiyol Dern Ars 2014;42:227-35.
10. Uluganyan M. Identification of the thoracic aortic aneurysm and related conditions in echocardiography laboratory. Med Res Rep 2018;1:28-30.
11. McCormick ML, Gavrila D, Weintraub NL. Role of oxidative stress in the pathogenesis of abdominal aortic aneurysms. Arterioscler Thromb Vasc Biol 2007;27:461-9.

12. Glantzounis G, Tsimoyiannis E, Kappas A, Galaris DA. Uric acid and oxidative stress. Curr Pharm Des 2005;11:4145-51.

13. Desai RJ, Franklin JM, Spoendlin-Allen J, Solomon DH, Danaei G, Kim SC. An evaluation of longitudinal changes in serum uric acid levels and associated risk of cardio-metabolic events and renal function decline in gout. PLoS One 2018;13:e0193622.

14. Cai J, Zhang Y, Zou J, et al. Serum uric acid could be served as an independent marker for increased risk and severity of ascending aortic dilatation in Behçet's disease patients. J Clin Lab Anal 2019;33:e22637.

15. Acar B, Yayla C, Gul M, et al. Monocyte-to-HDL-cholesterol ratio is associated with Ascending Aorta Dilatation in Patients with Bicuspid Aortic Valve. Afr Health Sci 2021;21:96-104.

16. Zharikov S, Krotova K, Hu H, et al. Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. Am J Physiol Cell Physiol 2008;295:C1183-C90.

17. Kanellis J, Watanabe S, Li JH, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension 2003;41:1287-93.

18. Şerefli D, Saydam O, Kıvanç Metin S. Relationship of homocysteine level with abdominal aortic aneurysm and coronary artery disease. Turk J Vasc Surg 2019;28:91-4.

19. Halazun KJ, Bofkin KA, Asthana S, Evans C, Henderson M, Spark JI. Hyperhomocysteinaemia is associated with the rate of abdominal aortic aneurysm expansion. Eur J Vasc Endovasc Surg 2007;33:391-4.

20. Endo M, Nabuchi A, Okuyama H, et al. Differing relationship between hypercholesterolemia and a bicuspid aortic valve according to the presence of aortic valve stenosis or aortic valve regurgitation. Gen Thorac Cardiovasc Surg 2015;63:502-6.

21. Li W-F, Huang Y-Q, Feng Y-Q. Serum uric acid concentration is associated with ascending aortic dilatation in newly diagnosed nondiabetic hypertensive patients. Clin Exp Hypertens 2020;42:75-80.

22. Cem Ö, Yilmaz S, Korkmaz A, Fahrettin T, Sahin I, Demir V. Evaluation of the neutrophil–lymphocyte ratio in newly diagnosed nondiabetic hypertensive patients with ascending aortic dilatation. Blood Press Monit 2016;21:238-43.

23. Lareyre F, Raffort J, Le D, et al. High Neutrophil to Lymphocyte Ratio Is Associated With Symptomatic and Ruptured Thoracic Aortic Aneurysm. Angiology 2018;69:686-91.

24. Bickel C, Rupprecht HJ, Blankenberg S, et al. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. Am J Cardiol 2002;89:12-7.

25. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. JAMA 2000;283:2404-10.