TURKISH JOURNAL OF UROLOGY Turk J Urol 2019; 45(Supp. 1): S84-S91 • DOI: 10.5152/tud.2018.25295

GENERAL UROLOGY

Original Article

Do AB0 blood groups affect lower urinary tract symptoms?

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Cite this article as: Benli E, Çırakoğlu A, Öğreden E, Kaya Y, Ayyıldız A, Yüce A. Do AB0 blood groups affect lower urinary tract symptoms? Turk J Urol 2019; 45(Supp. 1): S84-S91.

ABSTRACT

Objective: The aim of this study is to investigate whether there is a correlation between AB0 blood group antigens and Rhesus factor and lower urinary tract symptoms (LUTS).

Material and methods: A total of 556 male patients applying to our clinic with LUTS complaints from April 2012-2015 and complying with the study criteria were included in the study. The patients were divided into two groups as those with (Group 1; n=283) and without LUTS (Group 2; n=273) complaints. The effect of blood groups on LUTS complaints was compared using univariate logistic regression analyzes.

Results: According to AB0 blood groups, blood groups A (56.7%) and AB (56.9%) were most common in the LUTS group. But 0 blood group (44.1%) was the least common. According to rhesus factor, the incidence of LUTS in Rh (+), and Rh (-) groups were 48.9%, and 66.7%, respectively. Compared to 0 blood group, the LUTS incidence was 1.65, and 1.66 times higher for individuals with blood groups A, and AB, respectively. The same risk increased 2.09 times for individuals with Rhesus factor negative.

Conclusion: This study identified a correlation between AB0 blood group and Rhesus factor and LUTS. The risk of LUTS risk increased in individuals with blood group A Rh (). Additionally there was a clear risk increase observed for AB blood group, though this did not reach statistical significance.

Keywords: AB0 blood group; LUTS; rhesus factor; vascular disease.

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Submitted:
21.05.2018

Accepted:
03.07.2018

Available Online Date:
19.11.2018

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Available online at
www.turkishjournalofurology.com

Introduction

With advancing age, benign prostatic hyperplasia (BPH) and related lower urinary tract symptoms (LUTS/BPH) occur with increasing frequency. About 90% of males from 50-80 years of age are estimated to be affected by these complaints.[1] LUTS comprises storage and urinary symptoms and affects quality of life of patients, especially sleep cycle, daily performance and sexual activity.[2] Another problem frequently encountered in this age group, and with close relationship to urinary complaints, is erectile dysfunction (ED) which is thought to be a vascular disorder.[3] The simultaneous onset of both diseases and their frequent coexistence brings to mind the presence of a common pathology. Increasing amount of evidence indicates that this pathology may have a vascular source.[4,5]

Studies in recent times have reported a correlation between AB0 blood group antigens and rhesus factor (Rh) and many diseases. Among these diseases, the most interesting are vascular diseases like coronary artery disease, myocardial infarctus and thromboembolism. Additionally a close relationship has been demonstrated with some cancers like pancreas, bladder and renal cancers.[6,7]

Blood group antigens, genetically transmitted and known from birth, may be an appropriate biomarker for early diagnosis of some

Table 1. Distribution of the examined variables among patients with different blood groups

	Blood group					
	0 group	A group	B group	AB group	Total	p values for $\chi 2$
Hypertension, n (%)	58 (32.6)	76 (33.3)	32 (38.1)	20 (40.0)	186	0.668
Heart diseases, n (%)	25 (14.0)	49 (21.7)	21 (25.0)	12 (24.0)	107	0.102
Diabetes mellitus, n (%)	35 (19.4)	53 (23.2)	13 (15.5)	4 (8.0)	105	0.067
Alcohol consumption, n (%)	22 (12.2)	19 (8.5)	14 (16.9)	3 (6.0)	58	0.110
Smoking, n (%)	81 (45.0)	103 (45.0)	36 (43.4)	26 (52.0)	246	0.792

diseases, so necessary precautions may be taken beforehand. According to our hypothesis, with correlation to vascular events, blood markers may also have a correlation with LUTS. The evidence showing urinary symptoms are affected by vascular disorders is increasing in the literature. To the best of our knowledge the correlation between blood groups and LUTS has not been investigated in the literature.

As a result, this study was designed to investigate whether there was a correlation between AB0 blood group antigens and Rh and LUTS.

Material and methods

The files of 1121 male patients applying to our clinic from April 2012 to 2015 LUTS linked to BPH and without overactive bladder (OAB) findings were retrospectively reviewed. Atotal of 556 patients abiding by the study criteria were included in the study. The patients were classified as patients with (Group 1, n=283) and without (Group 2, n=273) LUTS complaints Ordu University Local Ethics Committee granted permission for the study (Decision date 05.02.2016 no. 2016/2) and written informed consent was obtained from patients who participated in this study.

The ages, AB0 blood groups/Rh, international prostatic symptom scores (IPSS), quality of life scores (Q-Life), prostate volume (PV), post-voiding residual urine amount (PVR), uroflowmetry (Qmax and Qave) values and additional diseases of the patients were recorded. Male patients above the age of 40 years, with at least 6 months of continuing LUTS complaints, were included in the study. Prostate volume ≥25 mL, IPSS total score ≥8 and maximum flow rate (Q max) of 4=15 mL/s on uroflowmetry urinary tests were accepted as BPH secondary LUTS.[8]

The exclusion criteria for this study included presence of prostate and bladder cancer, inability of patient or relative to complete the IPSS forms, urethral stenosis, neurogenic bladder, interstitial cystitis, pelvic surgery, prostatitis history, PSA >4 ng/mL, urinary system infection, psychiatric treatment, hematuria with unknown cause, liver and renal failure. Additionally patients with uncontrolled hypertension, diabetes and heart disease, or who took their medication irregularly were excluded from the study.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences 17.0 for Windows software (SPSS Inc.; Chicago, IL, USA). Data were presented as the number (%) of cases for categorical variables (blood group, smoking, alcohol consumption, heart, HT, diabetes mellitus, LUTS). Data were also presented as the number of cases, mean, median, IQR, minimum and maximum values for the parametres (ages, Q-Life, IPSS, PV, PVR) according to the blood groups. Chi-square analysis was applied to investigate whether HT, heart, diabetes mellitus, alcohol consumption and smoking of patients statistically correlated with their blood groups. One way ANOVA was used to evaluate the ages according to blood groups. Also, Kruskal Wallis H test was used to evaluate the Qlife, IPSS, prostate volume, and PVR values according to the blood groups. Univariate logistic regression analysis was performed to assess the main factors associated with LUTS. Variables in univariate analysis associated with diagnosis of disease ($p<0.20$ in the likelihood ratio test [–2LL]) were selected for multivariate logistic regression analyses. All identified individual variables were analyzed with a manual forward elimination procedure starting with a full multivariable logistic regression model. Variables were kept in the model if the –2LL ratio test of the model with and without the variable was significant ($p<0.05$). Odds ratios (ORs) were presented with 95% confidence intervals (95% CI). The individual model was tested with the Hosmer-Lemeshow for goodness-of-fit test.

Results

There was no statistically significant difference between male patients with and without LUTS complaints in terms of age and additional diseases ($p>0.05$). The distribution of participants according to blood groups was 132 with A blood group (46.5%), 40 with B blood group (14.1%), 29 with AB blood group (10.2%)

Turk J Urol 2019; 45(Supp. 1): S84-S91
DOI:110.5152/tud.2018.25295

Table 2. Descriptive statistics of the examined variables in terms of blood groups

Variables	n	Mean	SD	Median	IQR	Minimum	Maximum	p
Ages								
0 group	185	62.79	9.69	-	-	38.00	92.00	0.514
A group	234	62.63	9.07	-	-	40.00	86.00	
B group	87	62.51	8.68	-	-	43.00	83.00	
AB group	51	64.69	8.71	-	-	36.00	82.00	
IPSS score								
0 group	133	12.35	7.60	12.0	10.0	1.00	33.00	0.520
A group	169	11.48	7.42	11.0	11.0	0.00	31.00	
B group	63	11.02	7.83	9.0	11.0	1.00	38.00	
AB group	37	12.08	7.05	14.0	10.5	0.00	28.00	
Qlife								
0 group	132	2.97	1.25	3.0	2.0	0.00	5.00	0.148
A group	168	2.85	1.32	3.0	2.0	0.00	5.00	
B group	63	2.56	1.22	3.0	1.5	0.00	5.00	
AB group	37	3.08	1.21	3.0	1.0	0.00	5.00	
Prostate volume (mL)								
0 group	122	50.04	37.42	37.0	23.5	13.00	335.00	0.439
A group	149	46.30	29.09	41.0	24.0	8.00	177.00	
B group	52	38.98	18.17	40.0	27.5	0.00	83.00	
AB group	34	46.68	28.10	34.0	38.5	14.00	131.00	
Post Voiding Residue (mL)								
0 group	123	29.18	54.37	0.0	40.0	0.00	360.00	0.426
A group	160	27.74	52.91	9.0	33.0	0.00	441.00	
B group	56	24.20	45.23	0.0	41.5	0.00	235.00	
AB group	33	32.61	46.92	15.0	52.5	0.00	187.00	
Q ave (mL/sec)								
0 group	113	7.22	3.55	6.9	5.7	0.90	19.00	0.681
A group	137	6.71	3.21	6.2	5.0	1.30	20.00	
B group	54	7.03	3.69	6.4	4.2	1.10	22.10	
AB group	30	6.91	2.80	6.1	4.6	1.40	13.60	
Qmax (mL/sec)								
0 group	115	16.00	7.38	15.2	9.9	2.90	43.20	0.907
A group	139	15.53	6.91	14.6	9.9	2.40	49.90	
B group	54	16.14	7.41	15.8	7.4	2.10	40.20	
AB group	32	16.00	6.48	15.8	8.3	2.70	36.80	

SD: standard deviation; IQR: interquartile range; IPSS: International prostatic symptom scores; Qlife: quality of life scores; Qave: average flow rate; Qmax: maximum flow rate

and 83 (29.2%) with 0 blood group in Group 1. Group 2 contained 101 cases with A blood group (36.7%), 47 with B blood group (17.1%), 22 with AB blood group (8%) and 105 patients with 0 blood group (38.2%).

Among individuals in the study hypertension was most common with AB blood group, and least common with 0 blood group, though there was no difference identified in the incidence of hypertension between blood groups (p=0.668). Heart disease

Table 3. Potential risk factors associated with LUTS in the univariate logistic regression equation

Variable	No	Total	No Prevalence (%)	B	S.E.	Wald	Sig.	Exp(B)	95% C.I. for Exp(B) Lower	Upper
Constant				0.032	0.085	0.145	0.703	1.033		
Ages				0.043	0.010	19.352	<0.001	1.044	1.024	1.064
Blood Group										
0	83	188	44.1			8.039	0.045			
A	132	233	56.7	0.503	0.198	6.474	0.011	1.653	1.122	2.435
B	40	87	46.0	0.074	0.260	0.080	0.777	1.077	0.646	1.794
AB	29	51	56.9	0.511	0.319	2.576	0.108	1.668	0.893	3.114
RH										
Positive	244	499	48.9							
Negative	40	60	66.7	0.737	0.288	6.547	0.011	2.090	1.188	3.677
Diabetes mellitus										
No	224	437	51.3							
Yes	56	104	53.8	0.104	0.219	0.225	0.635	1.109	0.723	1.703
Smoking										
Yes	122	245	49.8							
No	158	296	53.4	0.144	0.173	0.689	0.407	1.154	0.822	1.620
Alcohol consumption										
Yes	23	58	39.7							
No	253	479	52.8	0.533	0.284	3.528	0.060	1.704	0.977	2.970
HT										
No	181	353	51.3							
Yes	98	186	52.7	0.057	0.181	0.097	0.755	1.058	0.742	1.510
Heart diseases										
No	215	430	50.0							
Yes	64	107	59.8	0.398	0.220	3.282	0.070	1.488	0.968	2.289

LUTS: lower urinary tract symptoms; RH: rhesus factor; HT: hypertension

was least frequent in 0 blood group compared to A, B and AB blood groups; however there was no difference observed between the groups as for heart disease (p=0.102). Diabetes mellitus was most common with A blood group, though there was no difference observed in the distribution between blood groups (p=0.067). According to blood group there was no difference in terms of smoking and alcohol consumption of individuals included in the study (p>0.05) (Table 1).

There was no differences observed in variations between measured parameters of IPSS total score, Q-Life, prostate volume (PV), and post-voiding residue (PVR) in terms of blood groups (p>0.05). Additionally there was no statistical difference identified for uroflowmetry parameters like Qmax and Qave in terms of blood groups (p>0.05) (Table 2).

According to AB0 blood group, LUTS were most common in the A (56.7%) and AB (56.9%) blood groups, and least common in 0 blood group (44.1%). According to rhesus factor 48.9% of Rh (+), and 66.7% of Rh (-) individuals had symptoms of LUTS. According to the results of univariate logistic regression analysis, the incidence of risk of LUTS complaints increased with age. LUTS incidence increased 1.65, and 1.66 times in individuals with A or AB blood groups compared to 0 blood group. For rhesus factor negative individuals the risk of LUTS increased 2.09 times. There was no effect of diabetes mellitus, hypertension and heart disease on LUTS complaints. Additionally there was no correlation between smoking and alcohol consumption and LUTS (Table 3).

Five variables were included in the initial multivariate logistic regression model (three variables excluded according to p>0.20

Turk J Urol 2019; 45(Supp. 1): S84-S91
DOI:110.5152/tud.2018.25295

Table 4. Potential risk factors associated with LUTS in the multivariate logistic regression equation

						95% C.I. for Exp(B)	
Variables	**B**	**S.E.**	**Wald**	**Sig.**	**Exp(B)**	**Lower**	**Upper**
STEP 1[a] (Initial model)							
Age (years)	0.048	0.010	22.390	<0.001	1.050	1.029	1.071
Constant	-2.961	0.647	20.955	<0.001	0.0528		
STEP 3[b] (Final model)							
Blood Groups							
O			7.490	0.058			
A	0.526	0.204	6.660	0.010	1.692	1.135	2.522
B	0.099	0.268	0.138	0.710	1.104	0.654	1.866
AB	0.389	0.327	1.417	0.234	1.475	0.778	2.798
Rh(-)	0.724	0.295	6.010	0.014	2.062	1.156	3.678
Age (years)	0.043	0.010	19.240	0.000	1.044	1.024	1.064
Constant	-3.019	0.640	22.238	0.000	0.049		

[a]Variable(s) entered in step 1: Age. [b]Variable(s) entered in step 3: Rh (-) and Blood groups.

LUTS: lower urinary tract symptoms; RH: rhesus factor; HT: hypertension

in the likelihood ratio test: diabetes mellitus, smoking and HT). The model fit was tested using the Hosmer-Lemeshow test. The H-L statistic had a significance of 0.191 which meant that the final model demonstrated a nonsignificant result, indicating that the model was a good fit. In the final model the following parametres were associated with LUTS: age (OR: 1.044), blood group (OR for A group: 1.692; OR for AB group: 1.475) and Rh (-) (OR: 2.062) (Table 4).

Discussion

The results of our study found a correlation between A Rh (-) blood group and LUTS. The risk of LUTS complaints among AB0 blood groups was highest for blood group A, and for Rh (-) people. Additionally a clear increase in risk which did not reach statistical significance was observed in AB blood group. The increase in incidence of LUTS complaints identified in the study was not due to factors such as diabetes mellitus, heart disease and hypertension (Table 1).

Lower urinary tract symptoms are thought to be due to obstruction caused by growing prostate tissue around the bladder neck and urethra.[9] As a result, for the treatment of LUTS, α1-blockers and 5α-reductase inhibitors, which are frequently used for prostate growth are employed. However a some patients do not fully respond to these treatments for prostate growth.[2,10] Current treatment guidelines recommend focusing on patient complaints more than prostate size.[11] Thus when urinary tract symptoms occur, understandably other factors independent of prostate size may be important. The occurrence of ED, known as a vascular/endothelial disorder, related to LUTS in the same age group may indicate a common pathological process. Studies have mostly focused on causes such as atherosclerotic/endothelial disorder causing vascular hemostasis disorder, aging, increased endothelin and rhokinase activity, and reduction in nitric oxide synthesis/NO levels in the pelvic region.[12-14] It is understood that the underlying cause of LUTS is related to a vascular/endothelial disorder.

AB0 blood group antigens comprise complex carbohydrate molecules and Rh factor consists of carbohydrate fragments found on the extracellular surfaces of red blood cells.[15] Blood group antigens are reported to be found in many tissues and cells such as epithelium, sensory neurons, thrombocytes and vascular endothelium, in addition to erythrocytes.[16] A and B alleles carried genetically on 9q34 cause transformation of precursor H antigens coding glycosyl transferase enzyme into A and B surface antigens. As this enzyme is not found or dysfunctional in the 0 blood group, this transformation of precursor H antigen does not occur and it remains as it is.[17]

Studies have proposed increasing evidence supporting effects of AB0 blood group in the development of cardiovascular diseases, infections and neoplastic diseases.[18,19] However, it is not fully known how and why blood groups affect these diseases. It has been proposed that there may be changes in genes at the AB0 locus or disruption of enzymatic activity of the AB0 glycosyl transferase enzyme. The intercellular adhesion process of this enzyme is known to play a role in cell membrane signaling and immune response.[20] Studies have shown that polymorphism

at the AB0 gene locus is related to plasma levels of soluble intercellular adhesion molecule (ICAM)-1, e-selectin, p-selectin and tumor necrosis factor-alpha (TNF-α).[16,21,22] These materials have been shown to be effective mediators of the atherosclerosis, inflammation and immune system stimulation processes.[23]

The atherosclerotic process beginning as a result of abnormal glycosylation occurring in vascular endothelial cells may correlate between blood groups and LUTS identified in our study. Previous research has reported a correlation between blood groups and vascular diseases which supports our results. However, the cause of the correlation is not fully known. The close proximity of ABCA2 gene, with close correlation to cholesterol balance, to the AB0 blood group genes on the 9th chromosome may affect this correlation. Additionally plasma levels of molecules like von Willebrand factor (vWF), factor 8, sP-selectin, sICAM and e-selectin, affected by blood group, may be responsible for this correlation.[24,25]

Studies related to blood groups have proposed that A and B antigens, especially, play a role in the development of vascular diseases. Incidence and severity of coronary atherosclerotic disease (CAD) has increased in individuals with non-0 blood groups compared to 0 blood group.[26] A study by Carpeggiani et al.[27] reported increased family history of coronary artery disease and hypercholesterolemia in individuals with non-0 blood group. Other studies reported increased incidence of vascular diseases like myocardial infarction, peripheral vein disease and thromboembolism in individuals with non-0 blood group compared to those with 0 blood group.[26,27]

In our study, in the patient group with LUTS complaints, the risk of coronary heart disease was identified to be 1.48 times higher for non-0 blood groups compared to 0 blood group. Though this increase was not statistically significant, it was very close to significant values (p=0.07).

The cause of the correlation between blood groups and LUTS identified in this study may be due to the correlation between blood groups and vascular diseases. A study on this topic reported that blood groups induce development of atherosclerosis affecting pelvic blood flow, which may cause the development of LUTS. Reduced blood flow occurring in the lower urinary tract has been shown to cause a reduction in NO synthesis playing an important role in venous tonus.[28] Studies on this topic have reported that erectile dysfunction and variations in NO levels may be the first signs of systemic atherosclerotic diseases.[29] In conclusion, variations occurring in venous tonus and associated blood flow affect perfusion of tissues and are known to induce many vascular diseases like ED and coronary artery disease.[30] Under ischemic conditions, reduction in the relaxation response to nerve stimulation in rabbit prostates has been reported to be possibly related to reductions in NO levels.[31] Occurrence of urinary complaints is another proof indicating that vascular pathologies which are very sensitive in terms of development of atherosclerotic lesions in the abdominal aorta and iliac aorta bifurcation, are important for perfusion of the pelvic region. Thus obstructive vein disease involving this region may cause reduced perfusion of the bladder, prostate and erectile tissue found in the pelvic region.[32] A study using Doppler ultrasound showed that a reduction in lower urinary tract perfusion caused LUTS complaints.[4] The same study reported that the severity of urinary complaints was related to the reduction in perfusion. The sensitivity of prostate tissue to hypoxia was supported by another study using human prostate tissue cultures.[32]

In the light of this knowledge reduction occurring in NO levels or perfusion as a result of an atherosclerotic vascular pathology affected by blood group is clearly seen to contribute to the development of LUTS complaints. This opinion supports the recent entry of phosphodiesterase 5 (PDE5) enzyme inhibitors, marketed for ED treatment basically, into the treatment guidelines for LUTS. PDE5 enzymes have been shown to be present in prostate, bladder smooth muscle, neuron and venous tissue apart from cavernous tissue. Studies have shown that PDE5 enzyme inhibitors reduce the increase in LUTS complaints occurring due to lower urinary tract perfusion.[33,34] A study by Brock et al.[35] reported that PDE5 inhibitors improved LUTS complaints (independent of the presence of ED). Later placebo-controlled studies proved the efficacy of PDE5 inhibitors.[10,36]

The Rh factor gene is carried on the short arm of the 1st chromosome and apart from erythrocytes, it is found in many epithelial cells.[37] These proteins are thought to be effective in oxygenation of tissues and in removing factors damaging DNA.[38] Thus in Rh (-) individuals the development of a variety of cancers such as skin, esophagus and breast cancer may be eased.[39] In our study Rh (-) individuals had a 2-fold increase in LUTS incidence compared to Rh (+) individuals.

Blood groups have been shown to be correlated with other diseases, predominantly cancer. A study by Pelzer et al.[7] reported a correlation between AB0 blood group and pancreas cancer. The results of the study identified an increased pancreatic cancer risk especially for A blood group ($p<0.001$). Engel et al.[6] identified a close relationship between bladder tumor load and AB0 blood group in a study. Some studies have reported that AB0 blood group affects survivals from some cancers. A study reported that AB0 blood groups are independent risk factors for general survival of patients with renal cancer.[40]

The results of our study showed a significant correlation between AB0 blood groups and Rh (-) factor and LUTS. Individuals

Turk J Urol 2019; 45(Supp. 1): S84–S91
DOI:110.5152/tud.2018.25295

with A and AB blood groups had a 1.6 times increased LUTS risk compared to individuals with 0 blood group. According to Rhesus factor LUTS complaints significantly, and nearly 2-fold increased in Rh (-) individuals. We believe the correlation between LUTS and blood group is affected by a vascular/endothelial disorder occurring in the pelvic region and resulting in reduced NO/cGMP.

Previous studies have reported a correlation between LUTS and diabetes mellitus, hypertension and heart disease.[41] In our study this correlation was not shown. The reason for this may be that we excluded patients with uncontrolled diabetes mellitus, hypertension and heart disease and patients who did not regularly use their drug treatments. Additionally there was no correlation identified between AB0 blood groups and Rh factor with these diseases.

The retrospective, single-center design of the study, and the lack of lipid panel and laboratory values related to vascular pathologies like NO, vWF and F8 of patients comprise the limitations of the study. Another deficiency of the study is the lack of data related to the vascular system of patients. In spite of the limitations of the study, we believe that this study is very important in that it firstly demonstrated the presence of a correlation between AB0 blood group and LUTS. To confirm the results of this study randomized, controlled studies investigating laboratory results are required.

In conclusion, this study identified a close correlation between A blood group and Rh (-) blood groups with LUTS. This correlation is similar to the previously reported relationship between blood groups and atherosclerotic events; however we believe that a very complicated process resulting in endothelial dysfunction is involved. These results lead to the consideration that a vascular pathology affected by blood group affects lower urinary tract perfusion causing LUTS complaints. As a result AB0 blood group and Rh factor appear to be simple, easy and accessible markers that may be used for early identification of LUTS.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ordu University School of Medicine (Decision date 05.02.2016 no. 2016/2).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.B., A.Ç.; Design – E.B., A.A.; Supervision – E.B., A.A.; Resources – A.Ç., A.Y.; Materials – E.B.; Data Collection and/or Processing – E.B., A.Ç.; Analysis and/or Interpretation – E.B., A.Y., A.Ç.; Literature Search – E.B.; Writing Manuscript – E.B., A.Y.; Critical Review – E.B., E.Ö., Y.K., A.A.; Other – E.B., A.A., Y.K., E.Ö.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that they haven't received any financial support for this study.

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