ORIGINAL ARTICLE

DOI: 10.4274/nkmj.galenos.2023.20082
Nam Kem Med J 2023;11(4):328-333

Oxidized Low Density Lipoprotein Receptor 1 3'UTR 188C>T Gene Polymorphism in Patients with Coronary Artery Bypass Grafting

Koroner Arter Bypass Grefti Uygulanan Hastalarda Okside Düşük Yoğunluklu Lipoprotein Reseptör 1 3'UTR 188C>T Gen Polimorfizmi

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ABSTRACT

Aim: Coronary artery disease (CAD) is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries. Inflammation and high lipid levels play a role in pathological changes in atherosclerosis. Besides traditional risk factors, genetic factors such as single nucleotide polymorphism (SNPs) can be involved in disease process. In this study, we aimed to evaluate the effects of oxidized low density lipoprotein receptor 1 (OLR1) 3'UTR188C>T gene polymorphism, C-reactive protein (CRP), and lipid status in patients with coronary artery bypass grafting (CABG).

Materials and Methods: The study population consisted of 109 CAD patients who had undergone CABG, and 127 healthy controls. The OLR1 3'UTR188C>T polymorphism was genotyped using PCR-RFLP technique. Serum CRP, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) levels were measured with an automatic biochemistry analyzer.

Results: The distribution of the OLR1 3'UTR188C>T genotypes and alleles did not differ significantly between CAD patients with CABG and controls. Serum CRP levels were increased in patients compared to the control group ($p<0.001$), but HDL-C, and LDL-C levels were not different between two groups. Traditional risk factor such as cigarette smoking, alcohol use, family history, diabetes mellitus and hypertension were increased in patients compared to the control group ($p<0.001$, for each). The CRP levels were higher in patients with the TT, CT, and CC genotypes than in controls with the same genotypes ($p<0.001$, $p<0.01$, and $p<0.05$, respectively).

Conclusion: OLR1 3'UTR 188C>T polymorphism may not be involved in susceptibility to atherosclerosis. However, traditional risk factors in atherosclerosis such as smoking, alcohol consumption, family history, hypertension, diabetes mellitus, and circulating CRP levels were increased in our CABG population. The evaluation of OLR1 3'UTR188C>T and different OLR1 SNPs may be useful for their single and combined effects in atherosclerosis.

Keywords: Coronary artery bypass grafting, *OLR1* gene, 3'UTR188C>T polymorphism, CRP, lipid level

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Received: 25.07.2023 **Accepted**: 01.09.2023

ÖZ

Amaç: Koroner arter hastalığı (KAH), epikardiyal arterlerde aterosklerotik plak birikimi ile karakterize patolojik bir süreçtir. Enflamasyon ve yüksek lipid düzeyleri aterosklerozdaki patolojik değişikliklerde rol oynar. Geleneksel risk faktörlerinin yanı sıra, tek nükleotid polimorfizmi (SNP'ler) gibi genetik faktörler de hastalık sürecine dahil olabilir. Bu çalışmada koroner arter bypass greft (KABG) uygulanan hastalarda okside düşük yoğunluklu lipoprotein reseptörü 1 (OLR1) 3'UTR188C>T gen polimorfizmi, C-reaktif protein (CRP) ve lipid durumunun etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışma popülasyonunu KABG geçirmiş 109 KAH hastası ve 127 sağlıklı kontrol oluşturdu. OLR1 3'UTR188C>T polimorfizmi, PCR-RFLP tekniği kullanılarak genotiplendi. Otomatik biyokimya analizörü ile serum CRP, yüksek yoğunluklu lipoprotein-kolesterol (HDL-K) ve düşük yoğunluklu lipoprotein-kolesterol (LDL-K) seviyeleri ölçüldü.

Bulgular: OLR1 3'UTR188C>T genotiplerinin ve alellerinin dağılımı, KABG'li KAH hastaları ve kontroller arasında anlamlı farklılık göstermedi. Kontrol grubu ile karşılaştırıldığında hastalarda serum CRP seviyeleri yüksekti (p<0,001), ancak HDL-K ve LDL-K seviyeleri iki grup arasında farklı değildi. Sigara kullanımı, alkol kullanımı, aile öyküsü, diabetes mellitus ve hipertansiyon gibi geleneksel risk faktörleri hastalarda kontrol grubuyla karşılaştırıldığında yüksekti (her biri için p<0,001). CRP seviyeleri, TT, CT ve CC genotiplerine sahip hastalarda aynı genotiplere sahip kontrollere göre daha yüksekti (sırasıyla p<0,001, p<0,01 ve p<0,05).

Sonuç: OLR1 3'UTR 188C>T polimorfizmi, ateroskleroz duyarlılığında yer almayabilir. Ancak sigara, alkol tüketimi, aile öyküsü, hipertansiyon, diabetes mellitus ve dolaşımdaki CRP seviyeleri gibi aterosklerozdaki geleneksel risk faktörleri CABG popülasyonumuzda artmıştır. OLR1 3'UTR188C>T ve farklı OLR1 SNP'lerin değerlendirilmesi, aterosklerozdaki tek ve birleşik etkileri açısından yararlı olabilir.

Anahtar Kelimeler: Koroner arter bypass greftleme, *OLR1* geni, 3'UTR188C>T polimorfizmi, CRP, lipid düzeyi

INTRODUCTION

Coronary artery bypass grafting (CABG) is a surgical procedure in which vessels are used as grafts to bypass coronary arteries that are partially or completely occluded by atherosclerotic plaque[1]. Atherosclerosis is a disease characterized by the accumulation of lipids, fibrous elements, and calcification in the arteries. This process starts with the activation of the endothelium, and then a series of events that occur with the activation of the inflammatory response lead to vasoconstriction and atheroma plaque formation[2].

Many studies have tried to explain the biological and genetic basis of atherosclerosis[3-6]. Although experimental studies are helping to unravel the pathophysiology of atherosclerosis, clinical gaps remain[5]. Various methods used to study the genetic factors involved in chronic diseases such as atherosclerosis have focused on the genetic basis in the development of the disease. However, in most chronic diseases, multiple genes acting under the influence of several environmental factors have been used to determine the development of diseases such as atherosclerosis. The identification of these genes essentially followed a candidate gene approach. Based on the understanding of the pathogenesis of atherosclerosis genes involved in lipid mobilization, for example, the association with inflammation and endothelial function, the presence of atheroma or cardiovascular events has been studied[7]. It has been reported that genes associated with the coronary artery disease (CAD) process can be divided into three categories: disease-causing genes, susceptibility genes, and disease-associated genes[8,9].

The human gene encoding the oxidized low density lipoprotein receptor 1 (OLR1) maps to chromosome 12p13.1-p12.3 and consists of 6 exons interrupted by 5 introns. The *OLR1* gene is a good candidate gene for cardiovascular disease because of its location in a chromosomal region often associated with cardiovascular disorders and the biochemical role of its product in lipid metabolism pathways[10,11]. Six non-coding single-nucleotide polymorphisms (SNPs) in the 3'-terminal portion of OLR1 have been reported to be involved in alternative splicing of exon 5 and expression of the LOXIN transcript variant lacking exon 5 of OLR1. These 6 noncoding polymorphisms, including in 3'UTR (188C>T), intron 5 (IVS5-27G>T and IVS5-70A>G) and intron 4 (IVS4-14A>G, IVS4+27G>C, IVS4-73C>T), are located in a haplotype block region and affect the risk of developing CAD by changing LOXIN expression[12,13]. Studies have reported that OLR1 may play an important role in the pathophysiology of atherosclerosis and thrombosis[13,14]. 188C>T, a polymorphism in the 3'-UTR of the *OLR1* gene, has been found to be associated with CAD[13,15], but there are also studies reporting that this polymorphism is not altered in vascular diseases[16-18]. It has also been reported that C-reactive protein (CRP), which has proinflammatory effects, may play a role in the pathogenesis of CAD by showing proatherogenic and prothrombotic effects on vascular cells[19]. Considering this information, we aimed to investigate the OLR1 188C>T polymorphism and serum CRP and lipid levels in patients who underwent CABG in the Turkish population.

MATERIALS AND METHODS

Subjects

This prospective case-control study included 109 patients (30 women, and 79 men) who had undergone the CABG surgery and 127 healthy controls (47 women, and 80 men). The median age of patients and controls was 58 and 50 years, respectively. Healthy persons without any history of cardiovascular events and without any symptoms of CAD were selected for the control group. The exclusion criteria included cancer, autoimmune,

kidney, or hepatic disease. All study subjects were of Turkish origin and provided signed informed consent before the sample and data collection. This study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (no: 162, date: 20.05.2022). All procedures followed the ethical standards of the responsible committee on human experimentation (institutional and national) and/or the Helsinki Declaration of 1964 and later versions.

Blood Collection

Blood samples were collected in two tubes containing ethylenediaminetetraacetic acid (EDTA) after an overnight fast. One of the blood tubes containing EDTA was used for genotype analysis and stored as frozen at -80 °C until analysis. After centrifugation of the other tube at 400 x g for 10 minutes at 4 °C, plasma samples were separated into eppendorf tubes and frozen at -20°C until analysis.

Biochemical Measurements

The plasma concentrations of CRP were measured by nephelometric immunoassay using Dade Behring kits (BN II System Analyzer Dade Behring, Germany). In addition, plasma high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) levels were measured by automated colorimetric methods with commercially available kits (Cobas 8000, Roche Diagnostics GmbH, Mannheim, Germany).

DNA Isolation and Genotyping

Blood was drawn into EDTA-containing tubes for DNA isolation. The Roche DNA purification kit (Roche Diagnostics GmbH, Mannheim, Germany) was used to extract DNA from peripheral blood leukocytes in accordance with the manufacturer's instructions. Isolated DNA samples were kept frozen at -80 °C. The ORL1 188C>T polymorphism was genotyped using standard polymerase chain reaction (PCR) procedures and restriction enzyme digestion. There were two primer pairs used: F: 5'-TGTCAACATTTTTGATTCTAGCTA-3', and R: 5'-GTTCTCCATGTTCTGTCTTTCA-3'. The PCR mixture (20 µL total volume) consisted of 25 ng of gDNA, 10 pmol/µL of each primer, and 2 x PCR master mix solution (intron Biotechnology, Korea) which contents of 2.5 mM of each dNTPs, 2.5 U of i-Taq™ DNA polymerase, 1 x of PCR reaction buffer and 1 x of gel loading buffer. A Techne Thermal Cycler (Applied Biosystems Gene Amp PCR System 9700, Singapore) was used to perform the PCR. PCR conditions were as follows: initial denaturation at 94 °C for 2 min, followed by 40 cycles of denaturation at 94 °C for 20 sec, annealing at 51 °C for 10 sec, and elongation at 72 °C for 30 sec. The final amplicon extension was performed at 72 °C for 5 min. PCR amplicons were separated by electrophoresis in 2% agarose gel and visualized by ethidium bromide staining. The 188C>T PCR product was 207 bp. The amplified PCR products were directly digested by the KpnI (Invitrogen Life Tecnologies Corporation, Carlsbad, CA, USA) restriction enzyme (10 units/µL) at 37 °C for overnight. After KpnI restriction, two fragments were obtained: 184 and 23 bp for the C allele and a single fragment of 207 bp for the T allele. The digested DNAs were separated on 3% agarose gel in 1 x Tris borate EDTA buffer followed by staining with ethidium bromide solution. The 188C>T genotypes were detected using a Polaroid camera and viewed under ultraviolet light.

Statistical Analysis

The Statistical Package for the Social Sciences statistic 21.0 program was used for the analyses of the patients and control values. Hardy-Weinberg equilibrium was tested by chi-square analysis. Genotype and allele frequencies were compared between cases and controls by chi-square analysis. Odds ratio and respective 95% confidence intervals evaluated the effects of any difference between the allelic and genotype distributions. The unpaired Student's t-test (normally distributed variables) or Mann-Whitney U test (not normally distributed variables) were used for the comparison of other parameters. A value of $p<0.05$ was considered the minimum statistical significance.

RESULTS

The characteristics of patients undergoing CABG and the control groups were summarized in Table 1. There was no significant difference in terms of age, gender, body mass index (BMI), HDL-C, LDL-C, and systolic blood pressure between the patient and control groups ($p>0.05$). Cigarette smoking, alcohol use, family history, diabetes mellitus, CRP, hypertension, and diastolic blood pressure were increased in patients compared to the control group ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, and $p<0.05$, respectively).

We investigated the OLR1 3'-UTR 188C>T gene polymorphism, the frequencies of the genotypes in CABG patients and control groups were shown in Table 2. The distribution of TT, CT, and CC genotypes was 53.21%, 26.60%, and 20.18%, respectively, in the cases, and 46.45%, and 33.85%, and 19.69%, respectively, in the controls. No statistically significant difference was observed in the gene polymorphism between the two groups ($p>0.05$). Also, the distribution of T and C alleles was 66.51% and 33.48%, respectively, in the cases and 63.38 % and 36.61 %, respectively, in the controls ($p>0.05$) (Table 2).

To assess whether OLR1 3'-UTR 188C>T gene polymorphism had any effect on BMI, CRP, HDL-C, LDL-C, and blood pressure levels, we compared these parameters among the genotype groups in patients and controls (Table 3). The CRP levels were higher in patients with the TT, CT, and CC genotypes than in controls with the same genotypes ($p<0.001$, $p<0.01$ and $p<0.05$,

respectively). Also, the systolic blood pressure levels were higher in patients with the CC genotype than in controls with the same genotype (p<0.05). The diastolic blood pressure levels were higher in patients with the TT genotype than in controls with the same genotype (p<0.05). No significant difference was detected in the comparison of the same genotypes of other parameters between the patient and control groups.

Table 1. Clinical characteristics of patients undergoing coronary artery bypass grafting and healthy controls

Parameters	Patients (n=109)	Controls (n=127)	p
Age, median (min-max) (year)	58 (32-76)	50 (35-69)	NS
Gender (M/F)	79/30	80/47	NS
BMI (kg/m²)	27.66±5.15	27.01±4.05	NS
Cigarette smoking, n (%)	85 (77.98)	19 (14.96)	**0.001**
Alcohol use, n (%)	89 (81.65)	23 (18.11)	**0.001**
Family history, n (%)	75 (68.80)	59 (46.45)	**0.001**
Diabetes mellitus, n (%)	41 (37.61)	1 (0.79)	**0.001**
Hypertension, n (%)	68 (62.39)	1 (0.79)	**0.001**
LDL-C (mg/dL)	127.46±37.54	123.86±34.04	NS
HDL-C (mg/dL)	42.79±13.66	46.79±15.48	NS
CRP (mg/dL)	13.30±19.02	3.49±2.96	**0.001**
Systolic pressure (mmHg)	134.13±14.97	130.53±5.76	NS
Diastolic pressure (mmHg)	78.11±10.75	76.61±11.29	**0.030**

Data were presented as mean±SD, and n (%).

SD: Standard deviation, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, CRP: C-reactive protein, NS: Not significant, min-max: Minimum-maximum, BMI: Body mass index, M/F: Male/Female

Table 2. Distribution of genotypes and allele frequencies of OLR1 3'UTR188C/T polymorphism in patients undergoing coronary artery bypass grafting and control groups

Gene	Patients n (%)	Controls n (%)	p	OR (CI 95%)
LOX-1 3'UTR188C/T polymorphism	109	127		
Genotypes				
TT	58 (53.21)	59 (46.45)		1
CT	29 (26.60)	43 (33.85)	**0.276**	1.45 (0.74 -2.82)
CC	22 (20.18)	25 (19.69)	**0.156**	0.523 (0.21-21.28)
Alleles				
T	145 (66.51)	161 (63.38)		1
C	73 (33.48)	93 (36.61)	**0.357**	1.20 (0.82-1.75)

Genotypes and allele frequencies were shown as n (%).

OR: Odds ratio, CI: Confidence interval

DISCUSSION

It has been reported that the human gene encoding the lectin-like oxidized LDL receptor, also called OLR1, is a good candidate for cardiovascular disease and is located in a chromosomal region associated with cardiovascular disorders[10]. Also, SNPs in the *OLR1* gene have been reported to be associated with the risk of developing CAD[12]. OLR1 3' UTR 188C>T polymorphism can affect LOX-1 expression by altering its regulator binding site and thus modifying protein homeostasis[20]. Therefore, in our study, OLR1 3' UTR 188C>T polymorphism was investigated in patients who underwent CABG, and CRP, lipid, and blood pressure levels were evaluated in the same genotype distributions.

In the literature, studies investigating the OLR1 188C>T polymorphism in vascular diseases have reported conflicting findings[13,15,16,18,21]. Mango et al.[13] examined the 3' UTR 188C>T polymorphism in patients with acute myocardial infarction in the Italian population and they reported that there was a significant change between the patient and control groups, and T allele carriage increased the risk of cardiovascular events. Similarly, Guo et al.[21] observed that the frequency of the T allele in 188C>T polymorphism was significantly higher in patients with atherosclerotic cerebral infarction compared to healthy controls in the Chinese population. Novelli et al.[15] confirmed the association of the 3'UTR 188C>T SNP with myocardial infarction (p<0.003). Cheng et al.[22] studied a meta-analysis including 8 studies and reported that 3'UTR 188C>T increased CAD sensitivity. According to a meta-analysis study including findings of 11 researches suggested that variant genotype in the 188C>T polymorphism was associated with the increased risk of CAD[23].

However, there are also studies reporting any changes in OLR1 3'UTR 188C>T polymorphism in vascular diseases. Liu et al.[24] investigated the association between *LOX-1* gene polymorphism, 3'UTR 188C>T, and cerebral infarction in the northern Chinese Han population. However, they did not find an association between 3'UTR 188C>T and cerebral infarction risk. Sentinelli et al.[16] reported that there was no significant difference in the allele frequencies of the *OLR1* gene between CAD and controls in the Italian population, and that the 3' UTR 188C>T polymorphism was unlikely to play a role in the pathogenesis of CAD in the studied population. Similarly, Trabetti et al.[17] did not find a statistically significant difference in the allele or genotype distribution of 3'UTR SNPs in CAD in the Italian population when compared to subjects without CAD. Kurnaz et al.[18] reported that no correlation was observed between the 3'UTR 188C>T SNP and the presence of CAD in

Table 3. The levels of BMI, HDL-C, LDL-C, CRP, systolic blood pressure and diastolic blood pressure in patients undergoing coronary artery bypass grafting and controls according to OLR1 3'UTR188C/T polymorphism

Parameters	Patient group OLR1 3'UTR188C/T polymorphism			Control group OLR1 3'UTR188C/T polymorphism		
	TT	CT	CC	TT	CT	CC
BMI (kg/m^2)	27.93±4.64	27.21±3.02	27.58±7.99	27.23±4.27	29.09±3.69	26.89±3.93
HDL-C (mg/dL)	41.47±12.97	46.07±16.31	42.62±11.97	44.55±8.78	52.80±25.28	41.50±3.53
LDL-C (mg/dL)	123.71±39.31	126.30±36.34	145.69±32.17	122.87±27.53	127.10±49.74	119.00±16.67
CRP (mg/dL)	**12.55±15.82^{a***}**	**14.86±23.52^{b**}**	**13.01±20.16^{c*}**	3.52±2.39	3.44±3.83	3.57±2.32
Systolic blood pressure (mmHg)	134.68±14.86	133.00±17.07	**133.69±10.18^{c*}**	133.07±6.71	128.42±4.49	121.14±5.52
Diastolic blood pressure (mmHg)	**79.25±10.66^{a*}**	77.11±12.07	76.86±10.07	76.89±11.25	79.58±10.64	74.08±7.73

Data were presented as mean±SD. Bold values indicate statistical significance.

^{a}TT genotypes in patient group vs. TT genotypes in controls, ^{b}CT genotypes in patient group vs. CT genotypes in controls, ^{c}CC genotypes in patient group vs. CC genotypes in controls, *p<0.05, **p<0.01, and ***p<0.001, (Student's t-test or Mann-Whitney U test).

BMI: Body mass index, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, CRP: C-reactive protein

the Turkish population, and there was no difference in the comparison analysis between genotype groups and the mean values of cardiovascular risk factors. Tripathi et al.[25] reported that the 3'UTR 188C>T polymorphism in the North Indian population did not show a significant difference between CAD patients and healthy controls.

When the findings of our study were evaluated, it was observed that there was no significant change in the OLR1 3'UTR 188C>T genotype and allele distributions between CABG patients and healthy volunteers. The conflicting findings regarding the 3'UTR 188C>T polymorphism reported in the literature may be due to the limited size of the study populations, ethnic diversity of polymorphisms, and complex environmental factors.

In addition to genetic factors in the development of CAD, modifiable factors such as smoking, physical inactivity, overweight, uncontrolled stress, and unhealthy diet are also effective as well as non-modifiable factors such as advanced age, male gender, and race. Epidemiological studies report that risk factors such as high cholesterol level, hypertension, and diabetes mellitus also play a role in the development of atherosclerosis[26].

It is known that atherogenesis is promoted by high plasma and tissue levels of oxidized low-density lipoproteins (OxLDLs). Ox-LDLs increase the expression of proinflammatory genes, leading to monocyte recruitment to the vessel wall, and dysfunction of vascular endothelial cells. Ox-LDLs transform macrophages into foam cells that form atherosclerotic plaques[27].

Stancel et al.[19] suggested that CRP and LOX-1 constituted a cyclic mechanism with ox-LDL in atherogenesis. CRP is an acute phase protein primarily synthesized by hepatocytes. It has been reported that CRP may play a direct role in promoting the inflammatory component of atherosclerosis. In addition, an upregulation of CRP levels was detected in plaque tissues[2]. CRP is a ligand for OLR1, increases vascular permeability, impairs endothelium-dependent vasodilator function, and plays a role in monocyte-endothelial cell adhesion[19,27].

When the findings of our study were evaluated, it was noted that smoking, alcohol consumption, family history, hypertension, diabetes mellitus, and CRP levels increased in the CABG group compared to the control (Table 1). These data are compatible with the findings on risk factors affecting the development of atherogenesis. We also investigated the effect of the same genotype on BMI, HDL-C, LDL-C, CRP, systolic blood pressure, and diastolic blood pressure in the patient and control groups. CRP values were increased in all 3 genotypes compared to the control group, and the systolic blood pressure value in the CC genotype and the diastolic blood pressure value in the TT genotype were lower in the patient group compared to the control group (Table 3).

Unlike many other inflammatory mediators, CRP is not subject to diurnal fluctuation or biological variance. Therefore, CRP concentration seems to be proportional to the severity of the disease. However, the main limitation of CRP is its elevation in systemic inflammation, which may limit its use as a prognostic marker in postoperative patients[28]. It is thought that the increase in CRP values in our patient group may be related to the CABG operation.

Study Limitations

It should be noted that the limitations of our study are its small sample size and its being a single-center study, which may have influenced the statistical power of our analysis.

CONCLUSION

In conclusion, the results of the study indicate that, for our Turkish sample, OLR1 3'UTR 188C>T polymorphism may not be involved in susceptibility to atherosclerosis but traditional risk factors in atherosclerosis such as smoking, alcohol consumption,

family history, hypertension, diabetes mellitus, and circulating CRP levels were increased in our CABG population. The OLR1 3'UTR188C>T and different OLR1 SNPs may need to be evaluated with regard to their single and combined effects at risk of atherosclerosis.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (no: 162, date: 20.05.2022).

Informed Consent: All study subjects provided signed informed consent before the sample and data collection.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.H., Concept: O.B., C.A., Ç.T., R.H., B.Ar., G.K-S., Design: N.B., T.Ö., F.B.C., B.A., İ.O., G.K-S., Data Collection or Processing: N.B., O.B., Y.H., T.Ö., F.B.C., B.A., İ.O., C.A., Ç.T., R.H., B.Ar., A.R.K., Analysis or Interpretation: N.B., Y.H., T.Ö., F.B.C., A.R.K., İ.O., Literature Search: N.B., O.B., Y.H., T.Ö., F.B.C., B.A., İ.O., C.A., Ç.T., R.H., A.R.K., Writing: N.B., O.B., F.B.C., B.A., İ.O., C.A., Ç.T., R.H., A.R.K., G.K-S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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