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Erratum

In this article titled "The Relationship Between AKR1B1 rs759853 (C-106T) Polymorphism and the Diabetic Retinopathy Severity in Turkish Type 2 Diabetes Mellitus Patients" published in Medical Records Journal 2023;5(1):146-52,
-The institution of the third author, Murat Atabey Ozer is written incompletely. Corrected Murat Atabey Ozer iss institution information "Giresun University Faculty of Medicine, Department of Ophthalmology, Giresun, Türkiye
-Result sentence corrected.

Research Article

The Relationship Between AKR1B1 rs759853 (C-106T) Polymorphism and the Diabetic Retinopathy Severity in Turkish Type 2 Diabetes Mellitus Patients

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Abstract

Aim: Diabetes mellitus (DM) is an important health problem with an increasing incidence worldwide and causes many complications. Diabetic retinopathy (DR) is one of the most serious complications of DM. Polymorphisms of the AKR1B1 gene, which encodes an aldose reductase enzyme, have been associated with development of DM and DR in some studies. The current study aims to investigate the relationship of AKR1B1 rs759853 polymorphism with type 2 DM (T2DM), DR and DR severity in the Turkish population.
Materials and Methods: A total of 437 individuals, including 141 T2DM patients without DR, 125 T2DM patients with DR, and 171 healthy controls, were included in the study. Genotyping was performed using PCR-RFLP method.
Results: An association between T allele / TT genotype and increased risk of proliferative diabetic retinopathy (PDR) was detected. In the logistic regression analysis in which other risk factors were included, rs759853 polymorphism and diabetes duration were found to be associated with the PDR development. There was no significant relationship between the AKR1B1 rs759853 variation and the development of T2DM and DR.
Conclusion: Obtained data showed that AKR1B1 rs759853 polymorphism is not associated with the development of T2DM and DR in the Turkish patients, but TT genotype and diabetes duration are independent risk factors for the development of PDR.

Keywords: Type 2 diabetes mellitus, diabetic retinopathy, AKR1B1, aldose reductase, rs759853, polymorphism

INTRODUCTION

The prevalence of Diabetes mellitus (DM) is rising worldwide. Turkey has the highest DM prevalence with a rate of 11.1% among European countries according to the International Diabetes Federation 2019 data (1). Diabetic retinopathy (DR), an important microvascular complication of both type 2 DM (T2DM) and type 1 DM (T1DM), is a neurovascular disease characterized by progressive structural and functional disorders in the retina. It causes health problems such as vision loss and blindness in approximately 75% of patients who have had diabetes for at least 15 years (2,3). The early phase of DR is called nonproliferative DR (NPDR) when the late phase is called proliferative DR (PDR). While progressive microvascular changes are observed in the retina in NPDR, these changes are also observed outside the retina in PDR. PDR is also characterized by the growth of newly formed

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vessels in the retina and optic disc. Diabetic maculopathy (DMP), which can be seen in both NPDR and PDR causes decreased vision in patients with DM. Diabetic macular edema (DME), the most common form of DMP, is a thickening of the posterior pole of the retina (4). Diabetes duration, uncontrolled glucose level of blood and high blood pressure have influence on the development and progression of DR. Other risk factors include dyslipidemia, smoking and high body mass index (BMI). However, there are fundamental differences between individuals in terms of DR risk and disease severity, and these differences cannot be explained only by the risk factors listed above (5). Studies have shown that variations in many different genes are among the reasons for this difference between individuals. Vascular endothelial growth factor-A (VEGF-A), erythropoietin (EPO), protein kinase C-β (PKC-β), methylenetetrahydrofolatereductase (MTHFR), angiotensin-converting enzyme 1 (ACE-1), intercellular adhesion molecule 1 (ICAM-1) and aldo-keto reductase family 1, member B1 (AKR1B1) are counted among the genes associated with susceptibility to DR development (2,6).

AKR1B1, a NADPH-dependent aldo-keto reductase, is expressed in many tissues, such as retinal capillary pericytes (6). It is one of the best known enzymes of the polyol pathway and catalyzes the reduction of glucose to sorbitol using NADPH as a cofactor (7). Under normal glycemic conditions, AKR1B1 has low affinity for glucose and less than 3% of glucose is converted to sorbitol by AKR1B1. In the case of chronic hyperglycemia, glucose affinity of AKR1B1 increases (about 30% of glucose is converted to sorbitol) and this results with sorbitol accumulation as well as increased NADPH use. Sorbitol accumulation leads changes in cell membrane osmotic pressure, diffusion of water into the cell, electrolyte imbalance, and ultimately cell damage and oxidative stress. On the other hand, the increased use of NADPH by AKR1B1 causes a decrease in the amount of NADPH to be used for other metabolic processes such as nitric oxide synthesis. Decreased nitric oxide synthesis leads to vasoconstriction, ischemia, and slowing of nerve conduction. NADPH also acts as a cofactor of antioxidant enzymes such as glutathione reductase, and a decrease in its amount again causes increased oxidative stress. Oxidative stress is one of the main causes of DM and DM complications such as DR (7,8).

The AKR1B1 gene is on the 7q35 locus and contains 10 exons. The rs759853 (C-106T) polymorphism is in the AKR1B1 promoter region (6,7). In the literature, various polymorphisms of AKR1B1, including rs759853, have been associated with micro and macro complications of diabetes, such as DR, diabetic neuropathy, diabetic nephropathy, and stroke in some populations (6,7,9–12). To the best of our knowledge, the association between AKR1B1 polymorphisms and susceptibility to T2DM and DR has not been explored in the Turkish population. The present study aims to explore the relationship between the AKR1B1 rs759853 polymorphism and the susceptibility to T2DM and DR and the clinical features of the disease.

MATERIAL AND METHOD

Patients

The approval of the current study was provided by Giresun University's Faculty of Medicine Clinical Trials Ethics Committee (Approval No:23.12.2021-08). All participants gave their signed informed consent before recruitment. Power analysis revealed that a total of 421 patients should be included in the study for an analysis with an effect size of 0.3 (medium) and a power of 90%. A total of 437 individuals (141 T2DM cases without DR, 125 T2DM cases with DR, and 171 healthy subjects) were included in the current study. The patient group was between the ages of 44-84, and the control group was between the ages of 38-84. American Diabetes Association (ADA) criteria were used for the diagnosis of T2DM. All patients underwent a comprehensive eye examination with evaluation of visual acuity, fundoscopic examination, and fundus photography for the diagnosis of DR. Afterwards, staging was performed. Patients with one of the signs of hard exude, cotton wool spot, hemorrhage and intraretinal microvascular anomalies or venous segmentation in addition to microaneurysms but without PDR findings were staged as NPDR. Cases with at least one of the signs of neovascularization, preretinal hemorrhage, vitreous hemorrhage, or fibrovascular proliferation in the disc or elsewhere were staged as PDR. Individuals with other types of diabetes, malignant or inflammatory diseases did not include the study. Healthy individuals without diabetes and any eye disease were selected for the control group. Fasting venous blood samples were taken from all participants for genomic DNA extraction and biochemical analysis. In addition to the age, gender, height, weight and hypertension status of all participants, the duration of diabetes, insulin use, DME and DMP presence in the patient group were recorded. Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) were measured using blood samples. BMI was calculated as weight/height2 (kg/m2).

DNA extraction and genotyping

DNA isolation was carried out by the High pure PCR template preparation kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's protocol. Polymerase Chain Reaction - Restriction Fragment Length Polymorphism (PCR-RFLP) method was used for genotyping. PCR reaction was conducted using following primers; F 5' TTCGCTTTCCCACCAGATAC 3'; R 5' CGC CGT TGT TGA GCA GGA GAC 3'. PCR protocol was 95°C for 5 min, followed by 30 cycles of 95°C for 1 min, 65°C for 1 min, 72°C for 1 min, and a final extension at 72°C for 5 min. The size of the PCR amplification product was 326 bp and all PCR amplicons are run on a 2% agarose gel. The BfaI enzyme was used to digest the PCR amplicons and the resulted amplicons were run on 3% agarose gel electrophoresis. Two bands of 234bp and 92bp for the CC

genotype, 4 bands of 234bp, 175bp, 92bp and 59bp for the CT genotype, 3 bands of 175bp, 92bp and 59bp for the TT genotype were observed.

Statistical analysis

A statistical software package (SPSS, Windows version release 15.0; SPSS Inc.; Chicago, IL, USA) was used to perform statistical analyses. Shapiro-Wilk Normality test was used to evaluate whether the data were normally distributed. Continuous variables were expressed as mean ± SD. Categorical data were presented as numbers and percentages. The genotype distribution of rs759853 among groups was tested for the Hardy–Weinberg equilibrium (HWE) using the $\chi 2$ test. Genotypes and allele frequencies among the groups were compared using $\chi 2$ tests. Mann–Whitney U and Kruskal Wallis tests were used to determine difference between the groups in terms of continuous variables. Binary logistic regression analysis was used to test the factors affecting the development of PDR. P values below 0.05 were considered as statistically significant.

RESULTS

Demographic and clinical characteristics of the patient and control groups are summarized in Table 1. As expected, BMI (p=0.046), presence of hypertension (p<0.001), lipid profiles (p<0.001 for total cholesterol and LDL, p=0.002 for HDL and triglyceride), HbA1c (p<0.001) and fasting blood glucose (p<0.001) were significantly different between DM (with and without DR) and control groups (Table 1). In addition, a difference was observed in terms of gender distribution (p=0.046). The frequency of male gender was found to be lower in the T2DM group compared to control group (Table 1). There was a significant difference between the patients with and without DR in case of BMI (p=0.013), duration of diabetes (p<0.001), total cholesterol (p=0.001), LDL (p=0.022), HbA1c (p<0.001), fasting blood glucose (p=0.027), presence of DME (p<0.001) and DMP (p<0.001) (Table 1). Genotype frequency of AKR1B1 rs759853 polymorphism was found to be compatible with HWE in all three groups (Tables 2 and 3). Genotype and allele frequencies did not differ between the T2DM group and the control group (table 2), and between T2DM patients with and without DR (table 3). As shown in Table 4, the total T2DM group and the T2DM group with DR were divided into groups according to rs759853 genotypes and it was evaluated whether there was a difference in terms of clinical parameters. Accordingly, no significant difference was found between individuals with different genotypes in case of BMI, duration of diabetes, presence of hypertension, total cholesterol, fasting blood sugar, LDL, triglyceride, HDL, DME and DMP presence in both the total T2DM group and the T2DM group with DR (Table 4). On the other hand, a significant relationship was found between the presence of PDR and genotype (p=0.017) and allele frequencies (p=0.003) in the T2DM group with DR (Table 5). According to logistic regression analysis including AKR1B1 rs759853 polymorphism, BMI, duration of diabetes, presence of hypertension, total cholesterol, LDL, HDL, triglyceride, HbA1c, and fasting blood glucose, TT genotype (p=0.019, OR=5.204, 95% CI=1.307- 20.718) and duration of diabetes (p=0.038, OR=1.108, 95% CI=1.006-1.222) were associated with the development of PDR (Table 6).

Table 1. Demographic and clinical characteristics of study groups

Variables	T2DM (without DR)[a] N=141	T2DM (with DR)[b] N=125	Controls [c] N=171	P [a+b/ c] value	P [a / b] value
Sex (% male)	41.8	44	52.6	0.046	0.723
Age at study (years)	62.9 ± 8.4	62.7 ± 7.5	62.4 ± 11.8	0.783	0.980
BMI (kg/m^2)	29.8 ± 3.6	31.3 ± 4.8	29.5 ± 4.5	0.045	0.013
Diabetes duration (years)	8.4 ± 3.7	15.6 ± 5.1	-		<0.001
Presence of hypertension (%)	37.6	47.2	11.7	<0.001	0.113
Total cholesterol (mg/dl)	192.9 ± 34.5	213.7 ± 56.5	154 ± 30.5	<0.001	0.001
LDL (mg/dL)	109.2 ± 29.4	119 ± 36.2	102.9 ± 25.4	<0.001	0.022
HDL (mg/dL)	50.3 ± 12.4	47.1 ± 10.6	50.6 ± 8	0.002	0.070
Triglyceride (mg/dL)	181.2 ± 132.9	171.4 ± 131.3	131.3 ± 18.6	0.002	0.656
HbA1c (%)	7.3 ± 1.2	8.1 ± 1.5	4.7 ± 0.6	<0.001	<0.001
Fasting glucose level (mg/dL)	163 ± 51	187.3 ± 87.8	85.6 ± 9.9	<0.001	0.027
DME (%)	3.5	72.8	-		<0.001
DMP (%)	2.1	88	-		<0.001
PDR (%)	-	32	-		

T2DM: Type II Diabetes Mellitus, DR: Diabetic retinopathy, BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, DME: Diabetic macular edema, DMP: Diabetic maculopathy, PDR: Proliferative diabetic retinopathy

Table 2. Comparison of AKR1B1 genotype and allele frequencies between total T2DM patients and controls

AKR1B1 rs759853 Genotypes and alleles		Control N (%)	T2DM patients N (%)	OR (95% CI)	p value
Multiplicaptive	CC	84 (49.1)	127 (47.7)	Ref	-
	CT	69 (40.4)	109 (41)	1.045 (0.694-1.572)	0.833
	TT	18 (10.5)	30 (11.3)	1.102 (0.578-2.103)	0.767
Dominant	CC	84 (49.1)	127 (47.7)	Ref	0.778
	CT+TT	87 (50.9)	139 (52.3)	1.057 (0.719-1.552)	
Resesive	CT+CC	153 (89.5)	236 (88.7)	Ref	0.806
	TT	18 (10.5)	30 (11.3)	1.081 (0.582-2.006)	
Over dominant	TT+CC	102 (59.6)	157 (59)	Ref	0.896
	CT	69 (40.4)	109 (41)	1.026 (0.694-1.518)	
Alleles	C	237 (69.3)	363 (68.2)	Ref	0.740
	T	105 (30.7)	169 (31.8)	1.051 (0.784-1.409)	
		HWE: 0.489	HWE: 0.372		

T2DM: Type II Diabetes Mellitus, OR: Odds ratio, CI: Confidence interval, HWE: Hardy-Weinberg equilibrium

Table 3. Comparison of AKR1B1 genotype and allele frequencies between T2DM patients with and without DR

AKR1B1 rs759853 Genotypes and alleles		Control N (%)	T2DM patients N (%)	OR (95% CI)	p value
Multiplicaptive	CC	66 (46.8)	61 (48.8)	Ref	-
	CT	59 (41.8)	50 (40)	0.917 (0.549-1.531)	0.740
	TT	16 (11.3)	14 (11.2)	0.947 (0.427-2.101)	0.893
Dominant	CC	66 (46.8)	61 (48.8)	Ref	0.746
	CT+TT	75 (53.2)	64 (51.2)	0.923 (0.570-1.495)	
Resesive	CT+CC	125 (88.7)	111 (88.8)	Ref	0.970
	TT	16 (11.3)	14 (11.2)	0.985 (0.460-2.110)	
Over dominant	TT+CC	82 (58.2)	75 (60)	Ref	0.760
	CT	59 (41.8)	50 (40)	0.927 (0.568-1.512)	
Alleles	C	191 (67.7)	172 (68.8)	Ref	0.791
	T	91 (32.3)	78 (31.2)	0.952 (0.660-1.372)	
		HWE:0.612	HWE:0.445		

T2DM: Type II Diabetes Mellitus, DR: Diabetic retinopathy, OR: Odds ratio, CI: Confidence interval, HWE: Hardy-Weinberg equilibrium

Table 4. Comparison of clinical characteristics stratified by genotypes of AKR1B1 rs759853 polymorphism among total T2DM patients and T2DM patients with DR

Parameters	Total T2DM patients				T2DM patients (with DR)			
	CC	CT	TT	p	CC	CT	TT	*P* value
BMI (kg/m²)	30.3±4.3	30.4±4.2	31.6±4.2	0.117	31.8±4.9	31.8±4.9	32.2±4.8	0.262
Diabetes duration (years)	11.4±5.3	12±5.7	12.9±7	0.638	16.2±5	16.2±5	16.8±5.8	0.502
Hypertension N(%)								
No	68 (44.2)	66 (42.9)	20 (13)	0.325	29 (43.9)	29 (43.9)	7 (10.6)	0.635
Yes	59 (52.7)	43 (38.4)	10 (8.9)		21 (35.6)	21 (35.6)	7 (11.9)	
Total cholesterol (mg/dl)	200.2±46.2	204.6±47.7	206.4±51	0.652	216.6±54.8	216.6±54.8	221.1±63.3	0.276
LDL (mg/dL)	115±36.1	111.9±28.7	115.8±35.2	0.844	117.1±28.4	117.1±28.4	122.4±37	0.899
HDL (mg/dL)	48.5 ± 11.2	48.9 ± 12.8	49.8 ± 9.4	0.532	47.4±12.7	47.4±12.7	47.4±9.3	0.800
Triglyceride (mg/dL)	176.7 ±136.4	170.7 ±103.2	193.2±195.7	0.990	156.8±65	156.8±65	244.8±275.3	0.691
HbA1c (%)	7.7±1.4	7.7±1.5	7.7±1.1	0.625	8±1.7	8±1.7	8.2±1.2	0.358
Fasting blood glucose level (mg/dL)	172.6±83.1	175.3±59.4	178.8±61.1	0.149	179.9±66	179.9±66	195.9±60.9	0.308
DME N (%)								
No	83 (48.8)	69 (40.6)	18 (10.6)	0.847	13 (38.2)	13 (38.2)	3 (8.8)	0.804
Yes	44 (45.8)	40 (41.7)	12 (12.5)		37 (40.7)	37 (40.7)	11 (12.1)	
DMP N (%)								
No	74 (48.4)	62 (40.5)	17 (11.1)	0.972	5 (33.3)	5 (33.3)	1 (6.7)	0.625
Yes	53 (46.9)	47 (41.6)	13 (11.5)		45 (40.9)	45 (40.9)	13 (11.8)	

T2DM: Type II Diabetes Mellitus, DR: Diabetic retinopathy, BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, DME: Diabetic macular edema, DMP: Diabetic maculopathy

Table 5. Comparison of AKR1B1 genotype and allele frequencies between PDR and NPDR subgroups

Groups	Genotypes			*p* value	Alleles		*p* value
	CC	CT	TT		C	T	
NPDR N(%)	48 (56.5)	31 (36.5)	6 (7.1)	**0.017**	127 (73.8)	45 (26.2)	**0.003**
PDR N(%)	13 (32.5)	19 (47.5)	8 (20)		43 (55.1)	35 (44.9)	

PDR: Proliferative diabetic retinopathy, NPDR: Nonproliferative diabetic retinopathy

Table 6. Risk factors for PDR using logistic regression analysis

Variables	Odds ratio	95% CI	P value
BMI	1.063	0.969 - 1.167	0.194
Diabetes duration	1.108	1.006 - 1.222	**0.038**
Presence of hypertension	1.429	0.590 - 3.465	0.429
Total cholesterol	1.001	0.987 - 1.015	0.933
LDL	1.004	0.983 - 1.025	0.734
HDL	0.993	0.951 - 1.037	0.756
Triglyceride	0.999	0.995 - 1.003	0.628
HbA1c	0.788	0.535 - 1.161	0.228
Fasting glucose level	1.006	0.999 - 1.012	0.075
AKR1B1 CT genotype	2.281	0.900 - 5.780	0.082
AKR1B1 TT genotype	5.204	1.307 - 20.718	**0.019**

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

DISCUSSION

Even if the blood glucose level is effectively controlled, some DM patients develop DR, while others do not. The data obtained from the studies showed that in addition to other risk factors such as long-term exposure to hyperglycemia and the presence of hypertension, genetic factors also involved in the development of DR (6,13). In the past, the relationship of AKR1B1 polymorphisms with the development and severity of DR in DM patients has been investigated, in various populations (12–17). To the best of our knowledge, present study is the first study exploring the association between AKR1B1 variations and the development of T2DM and DR in the Turkish population. In our study, there were three groups: T2DM patients with and without DR, and the control group. A relationship was detected between the AKR1B1 rs759853 variation and the severity of DR. When DR patients were divided into two groups as NPDR and PDR, it was observed that frequencies of TT genotype and T allele was statistically significantly higher in the PDR group. As a result of the logistic regression analysis, which included other risk factors, it was determined that diabetes duration and rs759853 TT genotype were risk factors for PDR. Our findings seem to be compatible with the data of a study conducted in Han Chinese patients (18) that reports patients with CT+TT genotype to have an increased risk for PDR. On the other hand, in a study performed in Brazilian patients, contrary to our study, it was reported that CC carriers had an increased risk of PDR development (19). Another study showed that, there was no relationship between DR severity and AKR1B1 rs759853 variation in Jordanian population (20).

In our study, no significant association was found between AKR1B1 rs759853 polymorphism and T2DM and DR susceptibility. There was also no relationship between rs759853 polymorphism and other clinical features except the presence of PDR. Similar to our study, no relationship was found between rs759853 polymorphism and T2DM susceptibility in studies performed by Abu Hassan et al. and Watari et al. in Jordanian and Japanese populations (10,20). On the other hand, Shawki et al. (21) found TT genotype to be associated with increased T2DM risk in the Egyptians. Opposite of this study, Sivenius et al. reported a relationship between C allele and T2DM susceptibility in the Finnish population (22).

In the literature, studies investigating the rs759853 polymorphism and DR susceptibility have also reported different results in different populations. For example, in 3 different studies conducted in Chinese and Brazilian populations, it was revealed that there is no significant relationship between rs759853 polymorphism and DR susceptibility, similar to our results (19,23,24). In addition, two different meta-analyses reported no association between rs759853 polymorphism and DR susceptibility (6,25). However, Cao et al. performed a subgroup analysis depending on the type of diabetes and they found that this polymorphism has a protective effect on the development of DR in T1DM patients (6,25). In another meta-analysis conducted in recent years, including 4313 DR and 5218 diabetes patients from 23 different studies, the T allele and CT+TT genotype were associated with a lower risk of DR (26). Conversely, studies performed in Jordanian, Chinese and Indian populations showed that TT+CT genotypes or T allele were associated with increased DR risk (12,18,20).

In one of the studies evaluating the effects of the rs759853 polymorphism on AKR1B1 expression, it was reported that the AKR1B1 protein content in erythrocytes was higher in TT and CT carriers compared to the CC carriers (10). High expression of AKR1B1 causes an increase in conversion from glucose to sorbitol and sorbitol accumulation. It is known that the sorbitol accumulation in the retina can cause osmotic stress and ultimately retinopathy (18). Moreover, it has been reported that inhibition of AKR1B1 suppresses the expression of genes involved in angiogenesis and reduces neovascularization, which is one of the characteristic features of PDR (27). The higher frequency of TT genotype and T allele in patients with PDR compared to NPDR patients in our study may partially result in high AKR1B1 expression and higher sorbitol accumulation in these individuals. However, in our study, similar to many studies in the literature, no relationship was found between AKR1B1 genotype and allele frequency and the development of DR. Therefore, we think that the effect of AKR1B1 rs759853 in Turkish T2DM patients may not be very important at the onset of DR but may be effective in the increase of retinal vessel anomalies and the development of PDR once the disease has started. In another study on the effect of rs759853 on AKR1B1, it was claimed that the C allele showed higher transcriptional activity (28). Such a scenario suggests that different mechanisms may be dominant in the regulation of glucose conversion and sorbitol accumulation in Turkish patients.

Different results in various populations regarding the relationship between the AKR1B1 rs759853 variation and the development of T2DM, DR and PDR may be due to different ethnicity, the number of individuals included in the study, differences in environmental factors, and differences or errors associated with the statistical methods used.

CONCLUSION

To conclude, in this study, we revealed that there is no relationship between the AKR1B1 rs759853 variation and the development of T2DM and DR in Turkish individuals, but that the rs759853 variation and diabetes duration are independent risk factors for the PDR development. The relatively small number of patients and the inability to study other polymorphisms of AKR1B1 can be counted among the limitations of the current study. Therefore, future studies with more patients in the Turkish population are important to support our data.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *The approval of the current study was provided by Giresun University's Faculty of Medicine Clinical Trials Ethics Committee (Approval No:23.12.2021-08).*

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