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Expression of miRNA-451 and miRNA-885 in Meningiomas

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Abstract. *Background/Aim: Meningiomas are one of the most common intracranial tumors, accounting for 30% of the tumors of the central nervous system. MicroRNAs (miRNAs) are noncoding RNAs containing approximately 18-22 nucleotides that regulate gene expression by interfering with transcription or inhibiting translation. Recent studies have reported that miRNAs could provide information about the molecular pathogenesis of several types of tumors. This study aimed to examine the expression levels of miRNA-885 and -451 and to determine their potential roles as biomarkers in meningioma. Materials and Methods: In total, 29 patients with meningioma (9 males and 20 females) were included in this study. The expression levels of miRNA were determined using real-time polymerase chain reaction. In addition, receiver operating characteristic curve analysis was used to analyze the predictive potential of miRNAs. Results: Our results indicated a significant increase in miRNA-451 expression levels (p=0.003); however, there was no significant change in miRNA-885 expression levels (p=0.139) in patients with meningioma compared with the control group. Moreover, miRNA-885 and miRNA-451 expression levels did not differ significantly based on the histopathological grade of meningioma. Conclusion: miRNA-451 may be a novel potential marker for the diagnosis and prognosis, and a target for meningioma treatment.*

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Meningiomas are a common group of intracranial tumors that originate from arachnoidal cap cells. They are classified into the following three types by the World Health Organization (WHO): benign, atypical, and anaplastic. Data from the United States between 2011 and 2015 indicated that meningioma is the most common central nervous system tumor, accounting for approximately 37.1% of all central nervous system tumors, with 80.6% meningiomas of grade I, 17.6% of grade II, and 1.7% of grade III (1, 2). The risk of recurrence of meningiomas based on their histopathological grade is 7%-25%, 29%-59%, and 60%-94% for grade I, grade II, and grade III tumors, respectively (3). Simpson degree of resection and histopathological grade are the two major factors related to the recurrence of meningioma (4). Although surgery is the first-line of treatment for meningiomas, radiation therapy is currently preferred as the primary treatment method for lesions located in specific areas, such as the cavernous sinus, where surgery can be difficult (5). However, adjuvant and systemic therapies should be used after surgery in patients with grade II and III meningiomas (6).

Although the mechanisms of meningioma formation remain incompletely understood, some factors are known to be involved in the pathogenesis of meningiomas, and these include radiation exposure, head trauma, genetic predisposition, and hormonal involvement (7). Some

specific genetic disorders, including those related to inactivation of tumor suppressor genes and overexpression of some oncogenes, have been implicated in the pathogenesis of meningioma (8, 9). In addition to the chromosome 22 deletion, 1p, 3p, 6q, 10q, and 14q deletions have been documented, particularly in patients with advanced meningiomas. Moreover, excessive secretion of growth factors is known to be involved in the pathogenesis of meningiomas (10). Various factors, including developments in molecular biology and genetics, the impossibility of complete resection of lesions in certain areas, the unpredictability and variability of the biological behavior of the tumor, and the risk of recurrence despite surgery and adjuvant therapies, have led to the search for new diagnostic, prognostic, and therapeutic procedures for meningiomas.

microRNAs (miRNAs) are members of noncoding 22-nucleotide RNAs. Some studies have reported that miRNAs are involved in neoplastic processes, such as metastasis, proliferation, apoptosis, tumorigenesis, and cell differentiation (11, 12). Moreover, numerous studies have investigated the role of various miRNAs in diseases, such as lung, colon, stomach, prostate, and breast cancers, as well as in tumors of different types, such as glial tumors and meningioma (9). The present study aimed to investigate the expression of miRNA-451 and -885 in the meningioma and control groups.

Materials and Methods

Study population and clinical procedures. The present study was conducted with the approval of the Ethics Committee of İstanbul Training and Research Hospital. The tumor tissue samples used in this study were collected from patients who underwent surgery at the İstanbul Training and Research Hospital, Neurosurgery Clinic between July 2019 and March 2021 and whose histopathological diagnoses confirmed meningioma. Informed consent was obtained from all the participants. The control group consisted of dura mater membranes from cadavers belonging to individuals who died because of extracranial causes and in whom no cerebral pathology was found at autopsy. Permission was obtained from the Forensic Medicine Institute to use these human materials, which were collected and used in accordance with the ethical principles. Informed consent was obtained from each patient before starting the study. In this study, sociodemographic characteristics and clinical findings of the participants were analyzed, and tumor staging was performed according to the WHO 2016 classification system.

miRNA isolation. Participants' tissue samples were stored at −80˚C before starting the miRNA experiments. The tissue samples were sliced into 0.06 g sections and weighed using a precision scale; subsequently, they were transferred to Eppendorf tubes with 0.06 g of zirconium beads (equal to the amount of tissue). After placing 200 μl of TRIzol on the tissue sample, the sample was crushed in the Bullet Blender Tissue Homogenizer machine (Next Advanced, Troy, NY, USA) and homogenized for 5 min. Overall, 500 μl of TRIzol was placed in the Eppendorf tubes and homogenized for 5 min using the Bullet Blender Tissue Homogenizer machine; thereafter, it was stored at room temperature for 5 min.

The miRCURY™ RNA Isolation Kit (Exiqon, Qiagen, Hilden, Germany) was used to isolate miRNA, according to the manufacturers' instructions. The technique of spin column chromatography, in which a proprietary resin is used as the separation matrix, is used in isolating miRNA. The serum samples were lysed using the given lysis solution, and the proteins were precipitated using the protein precipitation solution provided. Following the precipitation process, isopropanol was added to the collected supernatant, and the solution was then fed into the spin column. After that, the column was cleaned, and the microRNAs were extracted using water that did not contain RNase.

Measurement of miRNA purity. The purity of the isolated miRNA samples was measured using the NanoDrop 2000 (Thermo Scientific, Waltham, MA, USA) instrument based on the OD260/OD280 ratio. Tissue samples with optical density ratios of >2 were considered appropriate.

cDNA preparation. The isolated miRNAs were converted to cDNAs by reverse transcription using the miRCURY LNA RT Kit (Exiqon, Qiagen). The obtained samples were stored at −20˚C before the expression analysis.

Determination of miRNA levels. Accurate microRNA concentration levels were determined by fluorometric analysis using the Qubit 3.0 Fluorometer (Thermo Scientific).

miRNA expression analysis using real-time polymerase chain reaction (PCR). Expression levels of miRNA-451 and miRNA-885 were determined using an Applied Biosystems 7500 Fast Real-Time PCR instrument (Applied Biosystems, Foster City, CA, USA). Moreover, RNU6 (internal control) was used for the normalization of miRNA expression levels. Fold-change analysis results were estimated using the $2^{-\Delta\Delta CT}$ method from Ct values obtained through the PCR instrument.

Statistical analysis. Statistical analysis was performed using the Number Cruncher Statistical System 2007 (Kaysville, UT, USA) program. The study data were evaluated using descriptive statistical methods. The data are presented as mean, standard deviation, median, the first quartile, the third quartile, frequency, percentage, minimum, and maximum values. Quantitative data were tested for normality of distribution using the Shapiro-Wilk test and graphical examinations. The Mann-Whitney *U*-test was used for pairwise comparisons of non-normally distributed quantitative variables. In contrast, qualitative data were compared using the Fisher's exact test. The correlation among quantitative variables was evaluated using Spearman correlation analysis. A p-value of <0.05 was considered statistically significant.

The diagnostic value of miRNAs was determined based on receiver operating characteristic curve (13) analysis performed using the MedCalc software (Ostend, Belgium). Moreover, ROC curves were constructed based on sensitivity-specificity characteristics. Sensitivity values are presented on the vertical axis of the ROC curve and specificity values are presented on the horizontal axis. A confidence interval of 95% and a p-value <0.05 were considered statistically significant.

Table I. *Comparison of age and sex between groups.*

		Group		
		Tumor (n=29)	Control(n=6)	*p*-Value
Sex	Female	20 (69)	3 (50)	**0.391**[a]
	Male	9 (31)	3 (50)	
Age	Mean±SD	57.28±16.97	60.83±10.7	**0.511**[b]
	Median (Min-Max)	57 (19-92)	61 (47-74)	

[a]Fisher's Exact Test; [b]Mann-Whitney *U*-Test.

Results

The study included 35 patients [23 (65.7%) females, 12 (34.3%), males; mean age, 57.89±16 (range=19-92) years] from Istanbul Training and Research Hospital between July 2019 and March 2021. The Forensic Medicine Institute provided the control group. The age and sex of the patients did not differ significantly between the two groups ($p>0.05$) (Table I).

Participants presented with the following preoperative symptoms: 44.8% (n=13) with headache, 13.8% (n=4) with dizziness, 6.9% (n=2) with general medical conditions, 3.4% (n=1) with visual loss, 3.4% (n=1) with hydrocephalus, 10.3% (n=3) with speech disorders, and 10.3% (n=3) with weakness.

Neurological examination revealed that 65.5% (n=19) participants were normal, 10.3% (n=3) had an altered state of consciousness, 6.9% (n=2) had speech problems, 3.4% (n=1) had cranial nerve palsy, 10.3% (n=3) had weakness, and 3.4% (n=1) had cerebellar findings.

The lesion was located in the right hemisphere in 37.9% (n=11) of the participants, in the left hemisphere in 51.7% (n=15), and in the midline in 11.3% (n=3). Overall, 3.4% (n=1) of the lesions were falcine, 3.4% (n=1) were located in the foramen magnum, 3.4% (n=1) were intraventricular, 6.9% (n=2) were in the clivus, 24.1% (n=7) were in the convexity, 27.6% (n=8) were parasagittal, 13.8% (n=4) were in the cerebellopontine angle, 10.3% (n=3) were in the sphenoid canal, 3.4% (n=1) were tentorial, and 3.4% (n=1) were in the tuberculum sellae.

The mean number of surgeries performed in the participants was 1.24±0.51 (range=1-3).

In total, 62.1% (n=18) participants had pathological grade 1 meningioma and 37.9% (n=11) had pathological grade 2 meningioma. Moreover, 31% (n=9) of meningiomas were atypical, 3.4% (n=1) were clear-cell, 3.4% (n=1) were fibrous, 3.4% (n=1) were chordoid, 13.8% (n=4) were meningothelial, 10.3% (n=3) were psammomatous, 3.4% (n=1) were secretory, and 31% (n=9) were transitional.

Participants had a mean Ki-67 value of 6.10%±5.07% (range, 1%-20%). Overall, 24.1% (n=7) of participants had received radiotherapy and 6.9% (n=2) had received chemotherapy. Although 86.2% (n=25) of participants had no complications, 10.3% (n=3) had cerebrospinal fluid fistula and 3.4% (n=1) had

Table II. *Distribution of descriptive characteristics of the tumor group.*

Tumor group		n (%)
Preoperative complaint	Headache	13 (44.8)
	Dizziness	4 (13.8)
	General condition disorder	2 (6.9)
	Vision loss	1 (3.4)
	Hydrocephalus	1 (3.4)
	Speech disorder	3 (10.3)
	Motor weakness	3 (10.3)
	Seizure	2 (6.9)
Neurological examination	Normal	19 (65.5)
	Loss of consciousness	3 (10.3)
	Speech difficulty	2 (6.9)
	Cranial nerve disfunction	1 (3.4)
	Motor weakness	3 (10.3)
	Cerebellar disfunction	1 (3.4)
Side	Right	11 (37.9)
	Left	15 (51.7)
	Midline	3 (11.3)
Localization of the lesion	Falx	1 (3.4)
	Foramen magnum	1 (3.4)
	Intraventricular	1 (3.4)
	Clivus	2 (6.9)
	Convexity	7 (24.1)
	Parasagittal	8 (27.6)
	Cerebellopontine angel	4 (13.8)
	Sphenoid wing	3 (10.3)
	Tentorium	1 (3.4)
	Tuberculum sellae	1 (3.4)
Number of surgeries	Mean±SD	1.24±0.51
	Median (Min-Max)	1 (1-3)
Grade	Grade 1	18 (62.1)
	Grade 2	11 (37.9)
Pathology	Atypical	9 (31)
	Clear cell	1 (3.4)
	Fibrous	1 (3.4)
	Chordoid	1 (3.4)
	Meningothelial	4 (13.8)
	Psammomatous	3 (10.3)
	Secretory	1 (3.4)
	Transitional	9 (31)
Ki-67 (%)	Mean±SD	6.10±5.07
	Median (Min-Max)	5 (1-20)
Radiotherapy	Yes	7 (24.1)
	No	22 (75.9)
Chemotherapy	Yes	2 (6.9)
	No	27 (93.1)
Complication	No	25 (86.2)
	CSF fistula	3 (10.3)
	Hydrocephalus	1 (3.4)
Survival	Alive	25 (86.2)
	Exitus	4 (13.8)
Follow-up time (months)	Mean±SD	21.14±11.67
	Median (Min-Max)	22 (0.1-60)

Table III. *Comparison of miRNA measurements between groups.*

		Group		
		Tumor (n=29)	Control (n=6)	*p*-Value
miRNA-885-CT	Mean±SD	29.04±1.41	28.02±1.89	**0.220**[a]
	Median (Min-Max)	29.2 (26.3-31.5)	28.9 (24.3-29.2)	
miRNA-885-ΔCT	Mean±SD	5.65±1.47	4.23±1.94	**0.092**[a]
	Median (Min-Max)	5.4 (2-8.6)	4.5 (0.8-6.2)	
miRNA-451-CT	Mean±SD	24.26±4.32	19.95±1.11	**0.012**[a]*
	Median (Min-Max)	25.3 (14.4-30.6)	20.2 (17.8-21.1)	
miRNA-451-ΔCT	Mean±SD	0.85±3.52	-2.47±3.42	**0.044**[a]*
	Median (Min-Max)	1.6 (-8.5-5.8)	-2.9 (-5.7-4.1)	

[a]Mann-Whitney *U*-Test. *$p<0.05$.

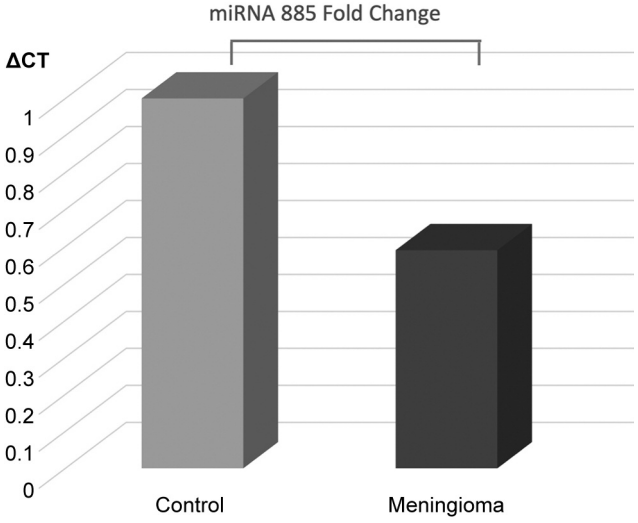

Figure 1. *Comparison of miRNA-885 expression levels between the meningioma and control groups. Differences between the two groups were analyzed using the Mann-Whitney U-test. *p-value <0.05.*

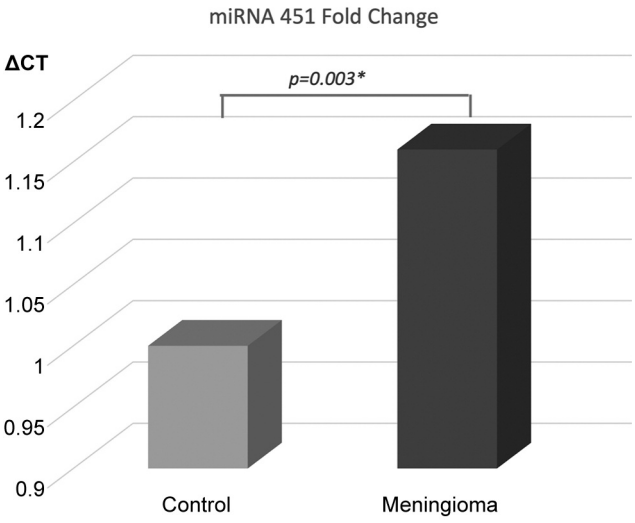

Figure 2. *Comparison of miRNA-451 expression levels between the meningioma and control groups based on fold change. Differences between the two groups were analyzed using the Mann-Whitney U-test. *p-value <0.05.*

hydrocephalus. In total, 86.2% (n=25) of participants survived and 13.8% (n=4) died. The mean duration of follow-up was 21.14±11.67 months (range=0.1-60 months). The characteristics of meningiomas are summarized in Table II.

Fold-change analysis of miRNA-885 and -451 expression is shown in Table III. There was no statistically significant difference between the two groups in terms of the miRNA-885 expression levels (p=0.139) (Figure 1), but the expression of miRNA-451 was found to be significantly increased in the meningioma group compared with the control group (p=0.003) (Figure 2). Furthermore, the diagnostic power of miRNA-451 was validated. ROC curve analysis was performed, and the area under the ROC curve was calculated to evaluate the diagnostic value. The results revealed that miRNA-451 expression levels could be used to determine the threshold values in the meningioma group (p=0.0002) (Figure 3).

There were no statistically significant differences in miRNA-885-CT, miRNA-885-ΔCT, miRNA-451-CT, and miRNA-451-ΔCT measurements in terms of the pathological grade (p>0.05) (Table IV). Moreover, no statistically significant correlation was found between the Ki-67 values and miRNA-885-CT, miRNA-885-ΔCT, miRNA-451-CT, and miRNA-451-ΔCT measurements (p>0.05) (Table V).

Discussion

This study provides valuable insights into the role of miRNA-885 and -451 in the development of meningiomas. The

Table IV. *Comparison of miRNA measurements between pathology stages.*

		Group		
		Grade 1 (n=18)	Grade 2 (n=11)	*p*-Value
miRNA-885-CT	Mean±Sd	29.39±1.5	28.47±1.1	**0.110**[a]
	Median (Min-Max)	29.6 (26.7-31.5)	28.8 (26.3-29.9)	
miRNA-885-ΔCT	Mean±Sd	5.92±1.21	5.21±1.8	**0.105**[a]
	Median (Min-Max)	5.7 (4-8.5)	4.9 (2-8.6)	
miRNA-451-CT	Mean±Sd	24.57±4.36	23.75±4.41	**0.458**[a]
	Median (Min-Max)	25.6 (14.4-30.6)	25.3 (15.9-29.3)	
miRNA-451-ΔCT	Mean±Sd	1.07±3.6	0.5±3.52	**0.621**[a]
	Median (Min-Max)	1.8 (-8.5-5.8)	1.5 (-5.8-4.8)	

[a]Mann-Whitney *U*-Test.

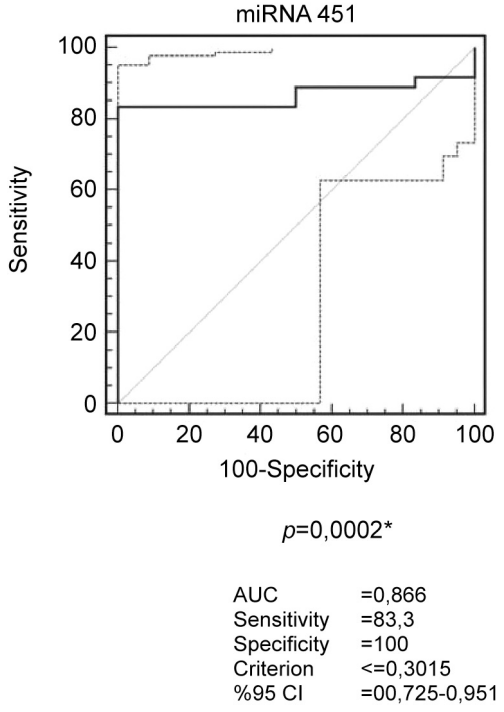

Figure 3. *ROC analysis graph of miRNA-451 expression levels in the control and meningioma groups. *p-value <0.05.*

Table V. *The relationship between miRNA measurements and Ki-67 values.*

		Ki-67 (%)
miRNA-885-CT	*r*‡	–0.162
	p	0.402
miRNA-885-ΔCT	*r*‡	–0.152
	p	0.431
miRNA-451-CT	*r*‡	–0.124
	p	0.522
miRNA-451-ΔCT	*r*‡	–0.042
	p	0.830

‡*r*: Spearman's correlation coefficient.

research on these miRNAs revealed intriguing results, which may help elucidate the complex process of meningioma tumorigenesis.

miRNAs, including miRNA-451 and miRNA-885, play crucial roles in regulating gene expression, cell proliferation, and apoptosis. Abnormal expression of miRNAs is often associated with various cancer types, including meningiomas (13, 14). Some miRNAs can promote tumor growth, while others inhibit it, suggesting that miRNAs have both oncogenic and tumor-suppressive properties (15-22).

Focusing on the specific miRNAs in question, research has indicated that miRNA-885 suppresses hepatocellular carcinoma metastases by inhibiting the Wnt/β-catenin signaling (23, 24). Other studies have suggested that high levels of miRNA-885 in cancer cells can regulate proliferation, colony formation, and invasion (24). These findings emphasize the therapeutic potential of miRNA-885 in cancer treatment, even though its role in meningiomas remains unclear (25-27).

Conversely, miRNA-451 is commonly known as a tumor suppressor in various types of cancer. The suppression of the BAP31 gene by miRNA-451 has been found to inhibit the proliferation of cancer cells and induce apoptosis (28). Furthermore, high plasma levels of miRNA-451 have been associated with recurrent lesions in non-small cell lung cancer (29). Moreover, in neuro-oncology, increased expression of miRNA-451 in glioma cell lines was found to inhibit cell proliferation and reduce invasion capacity, highlighting its potential suppressive role in gliomas (30-33).

Interestingly, in the present study, miRNA-451-CT and miRNA-451-ΔCT levels were significantly higher in the tumor group than in the control group. This contrasts with

other cancer studies, suggesting that miRNA-451 may have a different mechanism of action in meningiomas. No significant difference was found in the measurements of miRNA-885-CT and miRNA-885-ΔCT between tumor and control tissues, which aligns with many oncology studies. These findings open the door for further research to better understand the unique roles of these miRNAs in meningiomas.

Our control group consisted of samples from normal dura mater, with ethical committee approval. This choice was primarily due to the ethical and practical challenges of securing tissue samples from living individuals. In our study, cadaveric samples were utilized to ensure the minimal potential for damage to healthy tissue and to avoid the confounding influences of concurrent diseases or treatments. While this approach has its own challenges, including the potential for post-mortem changes to affect the samples, we concluded that it was the most feasible and ethically sound method available for obtaining control tissues. The ethical approval ensured that our research was conducted responsibly, respecting the dignity and rights of the individuals from whom samples were taken.

Overall, the emerging data from this study underscore the complexity of miRNA biology in meningiomas and suggest that the dysregulation of miRNAs, particularly miRNA-451 and miRNA-885, could be implicated in the pathogenesis of these tumors. Further studies are warranted to validate these findings and elucidate the exact molecular mechanisms underlying the role of these miRNAs in meningioma development and progression.

Our investigation has certain limitations. First, the sample size was relatively small, which may limit the generalizability of our results. Increasing the sample size would provide more robust and reliable findings. Second, our study was designed as a cross-sectional study. Longitudinal studies can provide more accurate information about the changes in the levels of miRNA-451 and miRNA-885 over time, especially during different stages of tumor progression and treatment. Last, while *in vitro* results may not accurately reflect the complex *in vivo* environment, we focused solely on the expression of these miRNAs in tissue samples and did not assess their potential functional role in cell lines or animal models. Further studies incorporating such investigations are needed to confirm and extend our findings.

Conclusion

miRNA-451 and miRNA-885 have been found altered in several cancer types, and based on their different expression levels, they could act as biomarkers, prognostic factors, and potential therapeutic targets. To the best of our knowledge, there is no study examining the expression of miRNA-451 and miRNA-885 in meningioma. Our study reports that miRNA-451 is expressed at significantly higher levels in tumor tissue than in normal meningeal tissue. Hence, miRNA-451 is a novel potential marker for diagnostic, prognostic, and therapeutic purposes in meningioma. We believe that this study will guide further studies on this topic.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding the publication of this article.

Authors' Contributions

Ozgur Baran: Conducted primary research, data collection, and manuscript writing. Adil Can Karaoglu: Assisted in research design and performed data analysis. Erdogan Kara, Orhan Budun: Provided samples for the experiments. Salim Katar, Seda Guleç Yilmaz, Fatma Tuba Akdeniz: Assisted in data collection and investigations. Mehmet Akif Ambarcioglu: Conducted literature review and provided critical feedback. Nail Demirel, Okan Turk, Nuriye Güzin Ozdemir: Participated in sample collection and patient interactions. Cumhur Kaan Yaltirik: Writing manuscript and editing. Turgay Isbir: Supervised the overall research and guided throughout.

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