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Evaluation of endothelial dysfunction with coronary flow reserve measurement in patients with fibromyalgia

Göksel Güz[1], Ekrem Bilal Karaayvaz[2], Baran Şimşek[3]

[1]Department of Cardiology, Medicana International Hospital, Istanbul, Türkiye
[2]Department of Cardiology, Istanbul University Faculty of Medicine, Istanbul, Türkiye
[3]Department of Cardiovascular Surgery, Medicana International Hospital, Istanbul, Türkiye

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ABSTRACT

Objectives: This study aims to investigate the role of increased inflammation and oxidative stress over endothelial functions with echocardiographic evaluation of coronary flow reserve in patients with fibromyalgia (FM).

Patients and methods: Between December 2021 and September 2022, a total of 38 female patients (mean age: 43.4±7.0 years; range, 34 to 51 years) with the diagnosis of FM and 35 healthy controls (15 males, 20 females; mean age: 41.1±6.3 years; range, 34 to 49 years) were included. The endothelial functions were evaluated by measuring coronary flow reserve. Coronary flow reserve of the left anterior descending coronary artery was measured from distal and middle portions with pulse wave Doppler at both baseline and hyperemic peak diastolic flow rate by transthoracic echocardiography.

Results: There were no significant differences in clinical, demographical and laboratory findings between the FM and control group, except for conventional C-reactive protein (CRP) levels. The mean hyperemic peak diastolic flow rate and coronary flow reserve values were significantly lower in FM patients ($p<0.001$).

Conclusion: Chronic stress and pain augment the sympathetic activity, resulting in endothelial dysfunction and increasing the cardiovascular risk. Endothelial dysfunction should be evaluated by measuring coronary flow reserve in FM patients.

Keywords: Coronary artery, endothelial dysfunction, fibromyalgia, two-dimensional Doppler echocardiography.

Fibromyalgia (FM) is defined as a chronic syndrome characterized with widespread musculoskeletal pain, fatigue, sleep disturbances, cognitive symptoms, anxiety, and depression.[1] Genetic, neurological, and immunological disorders are known to be the etiological causes of FM.[2] The prevalence of FM is reported to be 5.4% and increases with age, reaching a peak around the seventh decade of life and, at every age, it is more common in women than in men.[3] Risk factors include genetic disorders, female sex, and additional painful conditions. According to the 2010 American College of Rheumatology (ACR) criteria, FM has an approximately 2:1 female-to-male predominance and is reported to be 20 to 30% in patients with systemic lupus erythematosus and rheumatoid arthritis.[4] Symptoms and signs of FM are chronic (>3 months) widespread or multisite pain (≥6 of 9 body regions), fatigue, cognitive problems, sleep disturbances, other somatic symptoms (paresthesia, abdominal pain, headaches, dizziness) and significant soft tissue tenderness on physical examination. The differential diagnosis includes neurological, rheumatological, endocrine and infectious disorders.

Although the pathophysiology of FM has not yet been fully elucidated, endothelial dysfunction and inflammation have been suggested to occur in patients with FM.[5] There is a cerebral blood flow variability in FM patients with a positive correspondence between the emotional and cerebral functional variables which suggests a connection between both cerebral and vascular dysfunction.[6] The increase and overstimulation in sympathetic activity should

Corresponding author: Baran Şimşek, MD. Medicana International Hastanesi, Kalp ve Damar Cerrahisi Bölümü, 34520 Beylikdüzü, İstanbul, Türkiye.
E-mail: simsekbaran@yahoo.com

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be the main reason for the endothelial damage which can enhance the vascular response.[7] The enhanced vascular response may lead to endothelial dysfunction and damage which probably causes endothelium-mediated atherogenesis.[8] With regard to endothelial nitric oxide (NO) and/or endothelial-derived endothelin 1 (ET-1) releasing defects and decreases in serum NO and/or ET-1 levels, endothelium-related vasodilatation significantly reduces.[9] It has been reported that baroreflex sensitivity reduces in FM patients which accompanies the risk of endothelial dysfunction and enhanced arterial stiffness due to autonomic dysfunction.[10]

Endothelial dysfunction is one of the primary causes of atherosclerosis and, thus, inadequate vasodilatory response and endothelial dysfunction includes increased proinflammatory and prothrombotic states.[11] Endothelial functions can be evaluated with the coronary flow reserve (CFR), which is also known as myocardial flow reserve. It can be measured with both transthoracic and transesophageal echocardiography or invasively with a Doppler-tipped coronary guidewire to determine coronary velocity. A CFR value is defined as the ratio between the hyperemic peak diastolic flow rate (HPDFR) and baseline peak diastolic flow rate (BPDFR) assessed from middle or distal left anterior descending coronary artery (LAD). The normal value for CFR is 2 to 3, whereas ≤2.0 is considered abnormal.[12] Reduced CFR revealing coronary microcirculer dysfunction has been suggested to be the early sign of atherosclerosis.[12] Early stages of the atherosclerotic coronary artery disease is often associated with abnormal resistance of the coronary arteries before obvious stenosis.[13] Diffuse atherosclerotic disease of the epicardial coronary arteries frequently causes impaired CFR which may contribute to myocardial ischemia and perfusion deficiency.

PATIENTS AND METHODS

This single-center, prospective study was conducted at Medicana International Istanbul Hospital Department of Cardiology between December 2021 and September 2022. The study group included 38 female patients (mean age: 43.4±7.0 years; range, 34 to 51 years) who were admitted to either Physical Medicine and Rehabilitation or Rheumatology outpatient clinics of our hospital and diagnosed with FM according to the 2016 revised ACR criteria. The control group was consisted of 35 healthy, asymptomatic, and very low-risk individuals (15 males, 20 females; mean age: 41.1±6.3 years; range, 34 to 49 years) in terms of endothelial dysfunction who were admitted for a regular check-up with no cardiovascular or other systemic diseases. The control group was mainly consisted of those without hyperlipidemia, dyslipidemia and who did not smoke. Exclusion criteria included coronary artery disease, significant valvular heart disease, diabetes mellitus, hypertension, hyperlipidemia, dyslipidemia, psychiatric disease, and thyroid dysfunction. Demographic, clinical, and laboratory data of both groups were recorded.

Routine transthoracic echocardiographic evaluations were performed with VIVID 7 (General Electric, Horten, Norway) by using 3 MHz probe in the left lateral supine position. M-mode echocardiography and 2D measurements were performed according to the American Society of Echocardiography (ASE) guidelines.[14]

All CFR measurements were performed with apical two-chamber long-axis imaging of left ventricle. The middle and distal LAD flow was visualized by color Doppler with an optimal velocity of 12 to 15 cm/sec. Coronary flow of the middle or distal LAD was examined over the epicardial part of the anterior left ventricular wall by color Doppler flow mapping (Figure 1a). The BPDFR was measured initially. All patients had Doppler recordings with a dipyridamole infusion at a rate of 0.56 mg/kg over 4 min. Continuous heart rate and electrocardiographic monitoring was performed simultaneously, as well as blood pressure recordings at baseline, during dipyridamole infusion, and recovery. If the heart rate was increased less than 10% compared to baseline, additional 0.28 mg/kg of dipyridamole infusion over 2 min was administered intravenously. After recovery, the HPDFR was measured. The CFR was calculated by the ratio of the HPDFR-to-BPDFR. A CFR value between 2 and 3 considered normal, whereas <2 values were considered abnormal. The HPDFR measurements using M-mode echocardiography and two-dimensional (2D) Doppler echocardiography of a patient with FM and a healthy control are presented in Figure 1b, c.

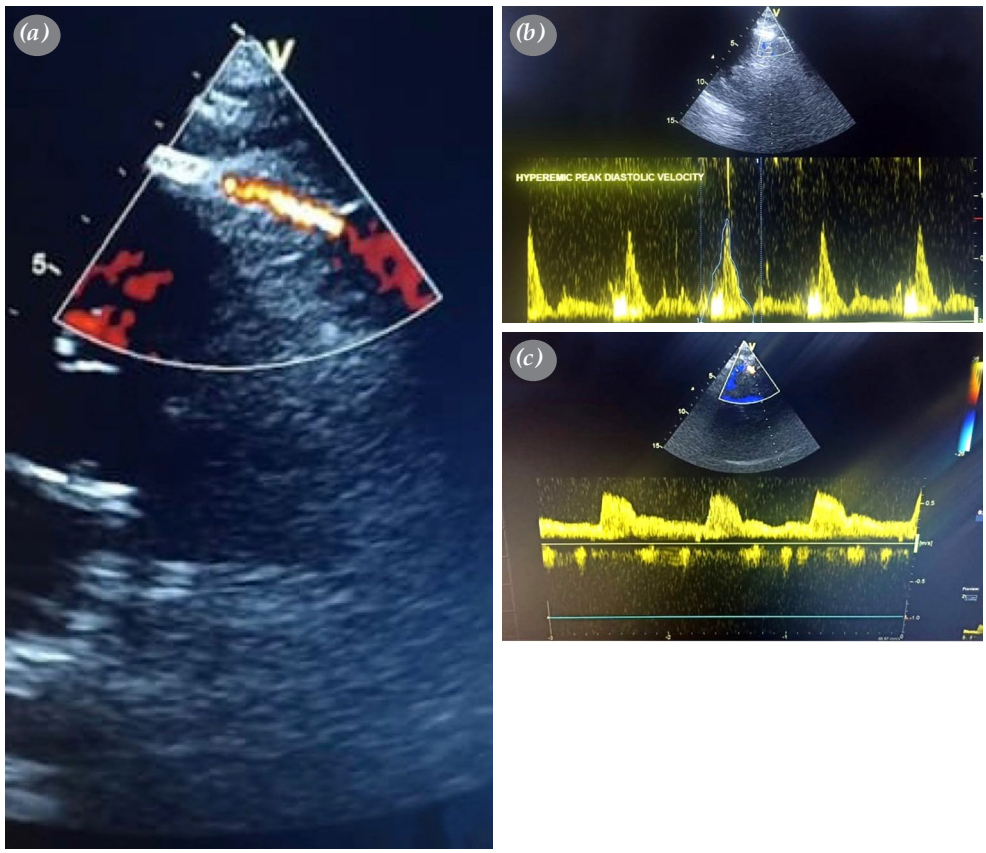

Figure 1. **(a)** Coronary flow reserve measurements were performed with apical two-chamber long-axis imaging of left ventricle. Middle and distal LAD flow was visualized by color Doppler with an optimal velocity of 12 to 15 cm/sec. Coronary flow of middle or distal LAD was examined over the epicardial part of the anterior left ventricular wall by color Doppler flow mapping. **(b)** Transthoracic echocardiographic images of a control group patient. Hyperemic diastolic flow was measured by pulsed-wave Doppler in distal LAD segment. **(c)** Transthoracic echocardiographic images of an FM patient. Hyperemic diastolic flow was measured by pulsed-wave Doppler in distal LAD segment.

LAD: Left anterior descending coronary artery; FM: Fibromyalgia.

Statistical analysis

Statistical analysis was performed using the SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Continuous data were presented in mean ± standard deviation (SD) or median (min-max), while categorical data were presented in number and frequency. The compatibility of quantitative data with a normal distribution was examined using the Shapiro-Wilk test. In terms of quantitative data, the Student t-test or Mann-Whitney U test was used for the comparisons of the groups. In terms of categorical data, the chi-square test was used to compare the groups. In order to predict the HPDFR, CFR and C-reactive protein (CRP) levels, area under curve (AUC), sensitivity and specificity values and 95% confidence intervals (CIs) under the receiver operating characteristics (ROC) curve were used and the diagnostic accuracy of significant variables in the univariate analysis was examined. The most optimal cut-off value was determined, as the value corresponding to the maximum Youden index (J=Sensitivity+Specificity-1). The HPDFR, CFR, and CRP levels were also determined in the univariate regression model with analysis of variance (ANOVA). The "pROC" library was used in the R program (by Xavier Robin, Switzerland) for ROC analysis. A p value of <0.05 was considered statistically significant.

Table 1
Demographic, clinical, and laboratory data of study participants

	FM patients (n=38)				Controls (n=35)				
	n	%	Mean±SD	IQR	n	%	Mean±SD	IQR	*p*
Age (year)			43.4±7.0	34-51			41.1±6.3	34-49	0.14‡
Sex									0.26*
Male					15	43			
Female	38	100			20	57			
BMI (kg/m²)			25.3±4.4	23.2-31.4			25.5±2.3	23.3-31.2	0.81‡
SBP (mmHg)			118.6±10.2	102-128			116.6±9.6	106-127	0.99‡
DBP (mmHg)			75.4±5.8	70-84			76.4±6.3	69-83	0.76‡
Heart rate (bpm)			73.7±3.5	66-82			73.4±10.6	61-85	0.85‡
FBS (mg/dL)			102.67±47.57	89-115			98.07±31.17	84-112	0.75‡
Total cholesterol (mg/dL)			183.5±28.8	152-198			181.6±31.1	140-186	0.74‡
HDL (mg/dL)			49.73±13.21	36-65			48.53±14.78	35-64	0.88‡
LDL (mg/dL)			115.67±26.16	100-130			107.76±20.80	92-125	0.45‡
Triglyceride (mg/dL)			130.4±27.26	104-198			147.2±33.49	98-182	0.33‡
Fibrinogen (mg/dL)			410.8±133.27	320-480			388.93±117.62	298-466	0.20‡
CRP (mg/mL)			2.29±1.39	0.6-3.8			1.49±1.04	0.5-2.9	**0.019**‡
HOMA-IR			2.45±1.93	1.8-2.9			2.42±1.21	1.7-2.6	0.72‡
Hemoglobin			12.5±1.3	10.6-13.0			13.3±0.90	10.8-13.2	0.12‡

FM: Fibromyalgia; SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein; HOMA-IR: Homeostasis model assessment-insulin resistance. P value extracted from † Student's t-test; ‡ Mann-Whitney U test (U); * Chi-square test.

RESULTS

Demographic, clinical, and laboratory data of the patients and healthy controls are summarized in Table 1. There were no significant differences in demographic, clinical, and laboratory findings between the FM and control group, except for the mean conventional CRP levels which were 2.29±1.39 (range, 0.6 to 3.8) mg/mL in the patient group and 1.49±1.04 (range, 0.5 to 2.9) mg/mL in the control group, respectively (p=0.019).

The mean global left ventricular ejection fraction (LVEF), end-diastolic (ED) septum and posterior

Table 2
Transthoracic echocardiographic parameters of the FM and control group patients

	FM patients (n=38)		Controls (n=35)		
	Mean±SD	IQR	Mean±SD	IQR	*p*
Septum-ED (cm)	0.94±0.13	1.1-0.7	0.94±0.14	1.1-0.8	0.74†
PW-ED (cm)	0.92±0.08	1.08-0.74	0.91±0.07	1.07-0.72	0.71†
LVEF (%)	66±4.59	58-67	65.5±2.57	59-69	0.67†
BPDFR (cm/sec)	31.6±8.3	25.6-39.1	33.45±7.37	27.8-41.6	0.912†
HPDFR (cm/sec)	64.8±9.12	53.5-72.9	78.15±14.32	66.7-91.3	<0.001†
CFR (cm/sec)	2.05±0.19	1.63-2.41	2.39±0.23	2.02-2.73	<0.001†

FM: Fibromyalgia; IQR: Interquartile range; ED: End-diastolic; PW: Posterior wall; LVEF: Left ventricular ejection fraction; BPDFR: Baseline peak diastolic flow rate; HPDFR: Hyperemic peak diastolic flow rate; CFR: Coronary flow reserve. P value extracted from † Mann-Whitney U test.

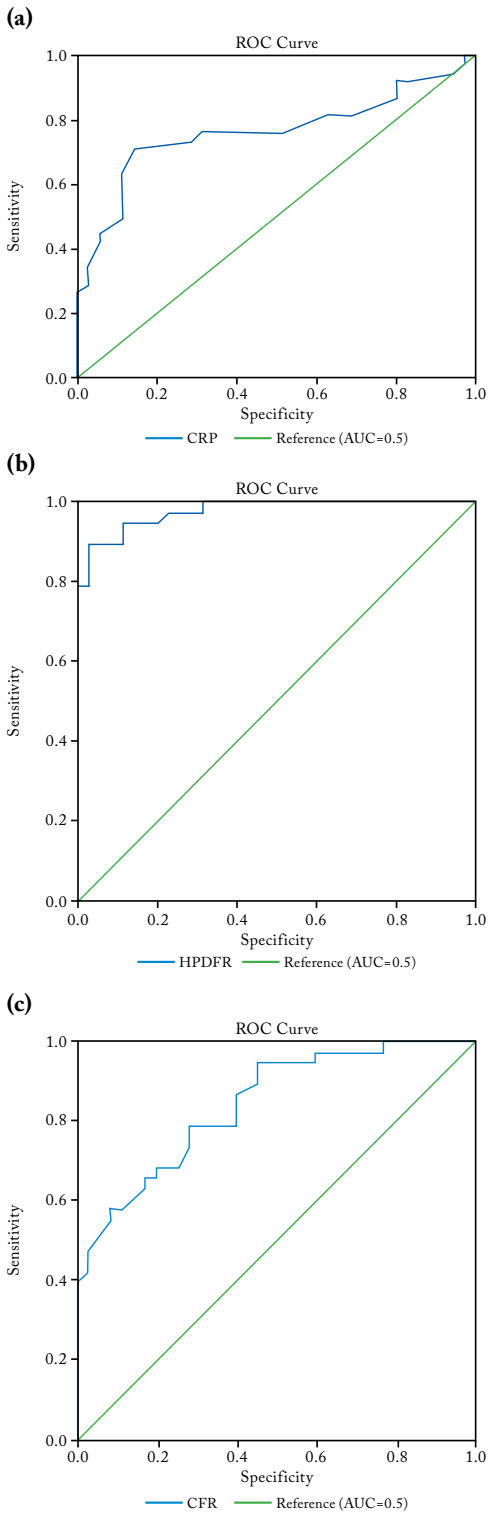

Figure 2. **(a)** Diagnostic accuracy of CRP values - ROC curve. **(b)** Diagnostic accuracy of HPDFR values - ROC curve. **(c)** Diagnostic accuracy of CFR values - ROC curve.

ROC: Receiver operating characteristics; HPDFR: Hyperemic peak diastolic flow rate; AUC: Area under curve; CRP: C-reactive protein; HPDFR: Hyperemic peak diastolic flow rate; CFR: Coronary flow reserve.

wall (PW) thicknesses, and BPDFR measurements were all within normal ranges for both the patient and control groups. However, the mean HPDFR and CFR values were significantly lower in FM patients ($p<0.001$). The transthoracic echocardiographic parameters of all participants are given in Table 2.

Diagnostic accuracy of CRP, HPDFR, and CFR values with the ROC diagrams and the ANOVA analysis are depicted in detail in Figure 2. Accordingly, conventional CRP levels, HPDFR and CFR values of the fibromyalgia patients were quantifying a diagnostic accuracy within the endothelial dysfunction.

DISCUSSION

The main objective of our study was to investigate the role of increased inflammation and oxidative stress over endothelial functions with transthoracic echocardiographic evaluation of the CFR and HPDFR in patients with FM. The primary endpoint of the study was to evaluate endothelial dysfunction which should be determined by CFR and HPDFR measurements to prove FM as a cardiovascular risk factor. The CFR is a combined measurement of the vasodilator capacity of coronary microcirculation, which is an independent predictor of long-term prognosis of atherosclerosis.[15] We evaluated endothelial dysfunction which was revealed by decreased levels of CFR and HPDFR in patients with FM. Our study results showed that HPDFR and CFR values were significantly reduced in FM patients. In addition, conventional CRP values were also higher in these patients. Similarly, Bote et al.[16] confirmed that FM patients had an inflammatory state accompanied by an altered stress response. This is mainly manifested by high circulating levels of interleukin (IL)-8 and CRP (in 100% of the FM group). There is also an increased release of inflammatory cytokines (IL-1β, tumor necrosis factor-alpha, IL-6, IL-10, IL-18 and monocyte chemoattractant protein-1) by monocytes, and enhanced activation of the functional capacity of neutrophils (chemotactic, phagocytic and fungicidal activities).[16] The etiopathogenesis of FM is multifactorial. Apart from neurohormonal and genetic factors, increased inflammatory activity and oxidative stress are known to play a role in the development of FM.[16,17] Thus, data on CRP are also controversial. A large-scale study showed a positive association between CRP and FM.[18] However, this association was attenuated after adding body mass index and

comorbidities in the model. The fact that these conditions, which are included in the pathophysiology of endothelial dysfunction and atherosclerosis, suggests that the endothelial functions of patients with FM may also be impaired and, thus, FM and endothelial dysfunction may accompany. Endothelial cells and endothelium-derived cytokines are other modulators of inflammation. A study by Mertoglu et al.[5] revealed that the level of endocan, a proteoglycan produced by endothelial cells, was significantly higher in patients with FM, compared to healthy controls. Increased levels of cytokines induced by inflammatory reaction and catecholamine-induced endothelial damage including microvascular spasm may be related with the pathophysiological mechanisms of decreased CFR in FM patients.[8] Vascular endothelial cells modulate the vascular tone either by secreting relaxing or constructing mediators. The ET1 is one of the potent vasoconstrictor peptides which is oversecreted by the endothelium and the vascular smooth cells as a result of inflammatory conditions. These levels increase in patients with FM.[8]

Coronary microvascular spasm plays a major role in affecting myocardial ischemia in patients without obstructive coronary artery disease and also associated with female predominance.[19] Similarly, Suwaidi et al.[20] reported that coronary endothelial dysfunction without obstructive coronary lesions was significantly associated with advanced cardiovascular disease. Likewise, endothelial and microvascular dysfunction, abnormal neurohormonal activity, and small vessel disorders may lead to coronary slow flow which ranges from 1 to 6% among patients with suspected coronary artery disease.[21] The coronary circulation may be sensitized to the circulating vasoconstrictor catecholamines by microvascular endothelial dysfunction in terms of inflammatory processes. Nevertheless, chronic pain may impair coronary circulation as a result of immoderate triggering of sympathetic nervous system (SNS) in FM patients.[22] Increased sympathetic activity can change cardiovascular responses and cause endothelial dysfunction. Nitric oxide, which is produced by catalyzing L-arginine, has a critical function in vasodilatation. Activated SNS decreases endothelial-derived vasodilatation caused by a loss of NO bioavailability in the vessel wall, although this process limits the relaxation ability of the artery and impairs the smooth cell functions.[23] The link between the immune and nervous systems is implicated in the pathophysiology of FM-related vascular disorders.

Flow-mediated vasodilation (FMD) test is the most accepted non-invasive test which reflects arterial endothelial-mediated vasomotor function.[24] Due to possible side effects of the administered drugs or invasive patterns of procedures to evaluate the endothelial functions, endothelial function measurement through FMD shows high accuracy.[25]

Cardiovascular diseases are considered major causes of morbidity and mortality.[26] Patients with FM can be also evaluated regarding the cardiovascular risk factors. Reducing the pain and diminishing the severity of disease can be crucial to prevent cardiovascular risk factors in patients with FM. Our findings suggest that CFR is a possible predictor of long-term prognosis of atherosclerosis in FM patients which would call attention to the long-term impacts of living with FM. Further studies are, therefore, required to confirm FM as a cardiovascular risk factor.

The fact that the entire population in the patient group was female is the main limitation to this study. During the study period, no male patients were admitted to either Physical Medicine and Rehabilitation or Rheumatology outpatient clinics of our center with the diagnosis of FM. Additionally, the menstrual cycle of the patients were not considered and different hormonal phases may have affected cardiovascular variables. Finally, the findings of our study are only preliminary data and further large-scale, prospective studies are needed for future considerations about coronary flow dynamics in FM patients.

In conclusion, chronic stress and pain augment the sympathetic activity, resulting in endothelial dysfunction and increasing the cardiovascular risk. Endothelial dysfunction should be evaluated by measuring coronary flow reserve in FM patients.

Ethics Committee Approval: This was a prospective and single-center study which was approved by the Medicana International Istanbul Hospital Ethics Committee (date: 03.11.2021, no: 022) and was conducted by the principles of the Helsinki Declaration. Ethical consent had also been obtained for intravenous drug administration during the CFR measurements.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, data collection and/or processing, design: G.G.; Design, analysis and/or interpretation: E.B.K.; Literature review, writing the article, critical review: B.Ş.

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