



# Effect of Waist Circumference on Mortality and Morbidity in Patients with Acute Coronary Syndrome with St-Segment Elevation

## St-Segment Yüksekliği Olan Akut Koroner Sendromlu Hastalarda Bel Çevresinin Mortalite ve Morbidite Üzerine Etkisi

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### Abstract

**Aim:** Obesity is a known risk factor for cardiovascular diseases. However, there are also studies showing that increased body mass index is unexpectedly protective in myocardial infarction. More studies are needed to elucidate this situation, known as the obesity paradox. This study was conducted to investigate the relationship between waist circumference and mortality and morbidity in acute ST elevated myocardial infarct (STEMI).

**Material and Method:** This is a prospective and observational study. Patients diagnosed with STEMI on electrocardiography (ECG) were included in the study. Immediately after the exhalation, waist circumference (WC) was measured on a horizontal plane at a point equidistant from the lowest floating rib and the upper border of the iliac crest. The role of waist circumference in the development of mortality and major cardiac events within 1 month was evaluated.

**Results:** A total of 106 patients admitted to the emergency department with STEMI were included in the study. While increased waist circumference was associated with mortality, it was insignificant in terms of major adverse cardiovascular event (MACE) development. Low BMI is significant in terms of decreased mortality and MACE.

**Conclusions:** The use of WC as an indicator of body fat ratio rather than weight in STEMI may be more valuable in the evaluation of mortality and MACE.

**Keywords:** Waist circumference, mortality, acute coronary syndrome, obesity

### Öz

**Amaç:** Obezite kardiyovasküler hastalıklar için bilinen bir risk faktörüdür. Ancak artan vücut kitle indeksinin miyokard enfarktüsünde beklenmedik şekilde koruyucu olduğunu gösteren çalışmalar da mevcuttur. Obezite paradoksu olarak bilinen bu durumu aydınlatmak için daha fazla çalışmaya ihtiyaç vardır. Bu çalışma, akut ST yükselmeli miyokard enfarktüsünde (STEMI) bel çevresi ile mortalite ve morbidite arasındaki ilişkiyi araştırmak amacıyla yapılmıştır.

**Gereç ve Yöntem:** Bu prospektif ve gözlemsel bir çalışmadır. Elektrokardiyografide STEMI tanısı alan hastalar çalışmaya dahil edildi. Ekshalasyondan hemen sonra, bel çevresi yatay bir düzlemde, en alttaki yüzen kaburgadan ve iliak krestin üst sınırından eşit uzaklıkta bir noktada ölçüldü. Bel çevresinin 1 ay içinde mortalite ve majör kardiyak olayların gelişimindeki rolü değerlendirildi.

**Bulgular:** Acil servise STEMI ile başvuran toplam 106 hasta çalışmaya dahil edildi. Artan bel çevresi mortalite ile ilişkili iken majör anormal kardiyak olay (MAKO) gelişimi açısından önemsizdi. Düşük vücut kitle indeksi, azalmış mortalite ve MAKO açısından önemlidir.

**Sonuç:** STEMI'de vücut ağırlığından ziyade vücut yağ oranının bir göstergesi olan bel çevresinin kullanılması mortalite ve majör kardiyak olayların değerlendirilmesinde daha değerli olabilir.

**Anahtar Kelimeler:** Bel çevresi, mortalite, akut koroner sendrom, obezite



## INTRODUCTION

Obesity is a progressively growing health problem that is threatening the entire world. Among 75% of adults are considered overweight and 41% obese in the United States.<sup>[1]</sup> Obesity has been found to be associated with the early development of cardiovascular (CV) events, and to contribute to the elevation of morbidity and mortality rates worldwide related to such events. Increased body mass index (BMI) is known to be an independent risk factor for myocardial infarct.<sup>[2,3]</sup> Obesity is encountered together with an unexpected "preventive effect" in patients presenting with acute myocardial infarct that is referred to as the obesity paradox, and although the association between obesity and CV disease has been determined the etiology of this paradoxical association remains unexplained.<sup>[4-6]</sup> Recently, anthropometric measurements, which are considered to be predictors of body fat distribution and visceral fat, have gained popularity since little is known about the development of this paradoxical association.

In particular, waist circumference and waist/hip ratio measurements have started to guide physicians on issues of body adiposity. A comparison of waist circumference, with BMI may increase the accuracy of risk estimation in the presence of CV disease.<sup>[7-9]</sup>

In the present study we evaluate the effect of waist circumference on the development of major cardiac events (MACE) in patients diagnosed with myocardial infarct with ST elevation (STEMI).

## MATERIALS AND METHOD

This prospective and observational study was launched after approval was carried out with the permission of İzmir Katip Çelebi University Ethics Committee (Decision No: GOKAEK-99). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was conducted between June and October 2019 in the emergency department of the hospital, which deals with approximately 350,000 emergency clinic presentations every year.

Patients diagnosed with STEMI on electrocardiography (ECG) were included in the study. A diagnosis of STEMI was made in cases presenting to the emergency clinic with chest pain or an equivalent symptom, and with >0.1 mV ST elevation in two consecutive derivations, except V2 and V3 derivations on ECG; >0.2 mV ST elevation in males over 40 years of age, >0.25 mV ST elevation in males aged <40 years, >0.15 mV ST elevation in females <40 years of age in V2 and V3 derivations; or signs of cardiac necrosis such as elevated troponin I and CKMB accompanied by left branch block on ECG.<sup>[10]</sup>

## Study Inclusion Criteria

Patients aged 18 years or above.

Patients matching the criteria of STEMI on the obtained ECG.

## Exclusion Criteria

Pregnant women

Patients in whom measurement procedures would lead to a delay in percutaneous coronary intervention,

Presence of any deformity in the region determined for waist circumference measurement (including operation scars),

Patients who refused to participate in the study

## Anthropometric Measures

The measurements were performed while the patient was on the patient stretcher. WC was measured on a horizontal plane at a point equidistant from the lowest floating rib and the upper border of the iliac crest. In all cases, the measurement was taken after exhalation. Increased risk was considered to be present when the waist circumference was greater than 94 cm in males and 80 cm in females, and high risk was considered to be present when greater than 102 cm in males and 88 cm in females.<sup>[11,12]</sup> BMI was calculated as weight (kg)/height squared (m<sup>2</sup>). BMI <18.5 was accepted as slim, 18.5–24.9 as normal, 25.0–29.9 as overweight and BMI >30 as obese.<sup>[13]</sup>

The age, gender, vital signs (pulse, arterial blood pressure, blood glucose), comorbid diseases, ECG findings, vascular occlusions detected from angiography, blood test results and duration of hospitalization of the patients were recorded. Mortality at 1 month and the state of development of MACE parameters (reinfarction, coronary artery restenosis and/or new stenosis, cardiac and non-cardiac rehospitalization, cerebrovascular insult, urgent CABG, mortality) were evaluated.

## Statistics

Data obtained in the study were analyzed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Categorical variables were expressed as numbers and percentages, while numerical variables were expressed as mean and standard deviation when presenting the descriptive statistics. Histogram curves, kurtosis-skewness values and a Shapiro-Wilks test were used to test the normal distribution of the data. Mean and standard deviation values were presented since the data were distributed normally. A Student's t-test was used for the comparison of two independent groups. A Chi-square test and Fisher's exact test were used for the comparison of two categorical variables. The results were expressed at a 95% confidence interval. A p value less than 0.05 was considered statistically significant.

## RESULTS

The study included 106 patients who met the study inclusion criteria, of which 78.3% (n=83) were male. The demographic data of the patients are presented in **Tables 1 and 2**.

**Table 1. Distribution of the demographic data of the patients**

Parameter	Sub Parameter	n (%)
Gender	Female	23 (21.7)
	Male	83 (78.3)
History of HT	None	57 (53.8)
	Yes	49 (46.2)
History of DM	None	76 (71.7)
	Yes	30 (28.3)
History of DL	None	90 (84.9)
	Yes	16 (15.1)
Cigarette Smoking	None	53 (50.0)
	Yes	53 (50.0)
History of CAD	None	67 (63.2)
	Yes	39 (36.8)
History of MI	None	68 (64.2)
	Yes	38 (35.8)
BMI	Underweight (<18.5)	1 (0.9)
	Normal (18.5-25.0)	40 (37.7)
	Overweight (>25-30)	43 (40.6)
	Obese (>30)	22 (20.8)
Waist Circumference	Normal	18 (17.0)
	Increased Risk	33 (31.1)
Type of ST Segment Elevation	High risk <45	55 (51.9)
	Anterior STEMI	33 (31.1)
	Inferior STEMI	51 (48.1)
	Lateral STEMI	2 (1.9)
	Posterior STEMI	6 (5.7)
	Anterolateral STEMI	6 (5.7)
	Inferolateral STEMI	4 (3.8)
Vascular Occlusion	Inferoposterior STEMI	4 (3.8)
	LAD	21 (19.8)
	RCA	26 (24.5)
	Cx	9 (8.5)
Status of Referral from Emergency Service	Multiple Vessel	50 (47.2)
	Yes	16 (15.1)
Outcome	None	90 (84.9)
	Discharge	93 (86.8)
Status of Cardiogenic Shock	Exitus	14 (13.2)
	Yes	12 (11.3)
Arrest at Emergency Clinic	None	94 (88.7)
	Yes	7 (6.6)
Status of MACE	Positive	20 (18.9)
	Negative	86 (81.1)
Total		106 (100.0)

HT: Hypertension, DM: Diabetes Mellitus, DL: Dislipidemia, CAD: Coronary artery disease, MI: Myocard infarctus, MACE: Major cardiac event, LAD: left anterior descending, RCA: right coronary artery, Cx: Circumflex

**Table 2. Evaluation of numerical data of the cases**

Parameter	Mean $\pm$ SD	Minimum	Maximum
Age (years)	60.89 $\pm$ 11.70	36	91
Height (cm)	170.32 $\pm$ 9.03	130	187
Weight (kg)	79.78 $\pm$ 13.07	58	120
BMI (kg/m <sup>2</sup> )	27.61 $\pm$ 4.99	20.07	48.24
Waist Circumference (cm)	102.88 $\pm$ 12.88	83.0	145.0
Arm Circumference (cm)	29.59 $\pm$ 3.61	23.0	44.0
Pulse (beats/min)	77.98 $\pm$ 18.63	38	122
Systolic Blood Pressure (mmHg)	134.54 $\pm$ 34.63	54	243
Diastolic Blood Pressure (mmHg)	76.13 $\pm$ 18.98	40	141
Blood Glucose (mg/dl)	175.49 $\pm$ 79.36	94	400
HDL (mg/dL)	36.95 $\pm$ 10.02	20	64
LDL (mg/dl)	116.19 $\pm$ 41.46	38	350
Triglyceride (mg/dl)	169.10 $\pm$ 115.47	52	887
Length of Hospital Stay (days)	5.41 $\pm$ 5.14	1	41

HDL: High density lipoprotein, LDL: Low density lipoprotein

### Primary Outcome

When the numerical data of the cases were compared for mortality, cases with mortality were found to be more advanced in age, to be thinner and to have a lower BMI, but with a greater waist circumference and a longer duration of hospital stay (p=0.012, p=0.045, p=0.034, p=0.018 and p=0.002 respectively). Cases with MACE were found to be more advanced in age, to be thinner and to have a lower BMI, but with a greater waist circumference and a longer duration of hospital stay (p=0.032, p=0.025, p=0.028, p=0.033, p=0.008 respectively). Evaluation of vital findings and laboratory findings in terms of mortality and MACE were presented in **Table 3**.

Cases were evaluated according to the status of development of MACE and the outcome of BMI binary categorical parameters. The rates of both mortality and MACE development were significantly higher in patients with an underweight-normal BMI (pOutcome=0.001 and pMACE<0.001). When the waist circumference of the cases was evaluated categorically, mortality was found to be statistically significantly higher in cases with increased waist circumference (p=0.039), while no statistically significant association was found between waist circumference and development of MACE (p=0.185) (**Table 4**).

When the waist circumference was evaluated categorically together with BMI, the rate of development of MACE was found to be significantly elevated with increases in waist circumference in cases with both a high and normal BMI (p<0.001). Furthermore, mortality was found to be significantly increased with increases in waist circumference (p<0.05) (**Table 5**).

**Table 3. Primary Outcome (Comparison of mortality and MACE rates of cases by numerical data)**

Parameter	Status of Outcome			Status of MACE		
	Positive Mean±SD	Negative Mean±SD	p*	Survivor Mean±SD	Died (n) Mean±SD	p*
Age (years)	60.12±11.57	69.15±14.04	0.012	66.63±14.49	60.05±11.40	0.032
Height (cm)	171.17±9.35	172.38±7.15	0.655	171.84±6.14	171.21±9.64	0.784
Weight (kg)	80.22±12.86	72.77±8.05	0.045	73.47±6.45	80.58±13.24	0.025
BMI (kg/m <sup>2</sup> )	27.52±4.76	24.60±2.98	0.034	25.03±2.76	27.63±4.88	0.028
Waist Circumference (cm)	102.43±11.98	108.07±10.16	0.018	102.36±9.68	107.39±12.19	0.033
Pulse (beats/min)	80.09±19.65	72.54±26.10	0.217	73.68±34.82	80.36±15.94	0.201
Systolic Blood Pressure (mmHg)	133.70±31.53	120.23±35.66	0.159	112.74±36.12	136.26±29.86	0.003
Diastolic Blood Pressure (mmHg)	75.76±17.93	65.85±16.87	0.063	63.79±16.20	76.90±17.62	0.004
Blood Glucose (mg/dl)	175.11±75.99	213.62±101.53	0.104	207.53±102.01	173.78±73.68	0.096
HDL (mg/dL)	37.44±10.12	32.80±6.61	0.318	33.20±11.09	37.78±9.67	0.181
LDL (mg/dl)	116.71±41.45	109.00±16.00	0.682	115.70±29.50	116.22±41.88	0.97
Triglyceride (mg/dl)	172.43±113.87	125.60±64.04	0.369	140.10±51.01	173.97±118.27	0.378
Duration of Hospitalization (days)	4.31±2.12	9.10±11.93	0.002	7.56±9.54	4.25±2.14	0,008

Based on an Independent T Test. BMI: Body mass index, HDL: High density lipoprotein, LDL: Low density lipoprotein,

**Table 4. Evaluation of cases according to BMI binary categorical parameters and outcome**

	BMI Categorical Parameters		p	Waist Circumference Categorical Parameters		p
	Underweight-Normal n (%)	Overweight-Obese n (%)		Normal n (%)	Increased n (%)	
<b>Status of Mortality</b>						
Survivor	30 (73.2)	62 (95.4)	0.001	Survivor	18 (100.0)	74 (84.1)
Exitus	11 (26.8)	3 (4.6)		Exitus	0 (0)	14 (15.9)
<b>Development of MACE</b>						
Positive	26 (63.4)	60 (92.3)	<0.001	Positive	17 (94.4)	69 (78.4)
Negative	15 (36.6)	5 (7.7)		Negative	1 (5.6)	19 (21,6)

Based on a Pearson Chi Square Test. BMI: Body mass index, MACE: Major cardiac event

**Table 5. Evaluation of cases in terms of development of MACE and mortality based on a categorical classification of the cases according to waist circumference and BMI.**

Parameter	Status of MACE		p	Status of Outcome		p
	Positive n (%)	Negative n (%)		Survivor n (%)	Died n (%)	
BMI Normal Waist Circumference Normal	16 (94.1)	1 (5.9)	<0.001	17 (100.0)	0 (0.0)	
BMI Normal Waist Circumference Increased	11 (64.7)	6 (35.3)		13 (76.5)	4 (23.5)	
BMI Normal Waist Circumference Very High	2 (20.0)	8 (80.0)		3 (30.0)	7 (70.0)	
BMI High Waist Circumference Normal	2 (100.0)	0 (0.0)		2 (100.0)	0 (0.0)	
BMI High Waist Circumference Increased	15 (100.0)	0 (0.0)		15 (100.0)	0 (0.0)	
BMI High Waist Circumference Very High	40 (88.9)	5 (11.1)		42 (93,3)	3 (6.7)	

Based on a Fisher's Exact Test. BMI: Body mass index, MACE: Major cardiac event

## DISCUSSION

The prevalence of obesity is increasing worldwide. Diseases such as coronary artery disease (CAD), stroke, heart failure, hypertension and diabetes have been shown to be associated with obesity.<sup>[5,14]</sup> BMI has been used in the evaluation of obesity,<sup>[14]</sup> although studies have determined that BMI fails to take into account cardiometabolic risk, and that visceral adiposity is associated with abdominal adiposity.<sup>[8]</sup> Central obesity is related to excess visceral fat. Visceral adiposity is associated directly with insulin resistance, which leads to smooth muscle cell proliferation in vessels, and such compensating inflammatory conditions as hyperinsulinemia and dyslipidemia. Calcium and cholesterol ester accumulate in the arteries, and atherosclerotic vascular disease emerges eventually.<sup>[7]</sup> For this reason, waist circumference has started to be assessed alongside BMI in evaluation of cardiovascular

disease (CVD) risk, and has been found to be more valuable as a risk indicator in patients with MI than BMI.<sup>[8,15]</sup>

In Lubree et al.'s study following-up 150 diabetic male patients aged 30–50 years compared WC and BMI among the different social classes in India, and found BMI (24.3 kg/m<sup>2</sup>) and WC (90.4 cm) to be higher in the urbanite group than in the other two groups (peasants and immigrants).<sup>[16]</sup> Adegbiya et al. carried out body measurements and monitored the CVD status of volunteers for 20 years in their study, and analyzed the predictive value of WHR (waist to hip ratio), WC and BMI in CVD risk, reporting that an increase of one unit in these values led to increased CVD risk. Increased risk was determined for both genders when other risk factors for cardiovascular disease (age, smoking, selenium deficiency, and alcohol) were also considered in the evaluation, in addition to WC, BMI and WHR. The authors reported that the initial WC measurement



predicted CVD risk, and that an increase in WC over time led to increased CVD risk. The authors concluded that the increase of WC with age also increased CVD risk.[17,18] Olson et al. studied patients aged 45–76 years with type 2 DM and BMI $\geq$ 25 kg/m<sup>2</sup>, analyzing CVD risk following the application of a lifestyle change and behavioral weight loss program. The risk of cardiovascular events was found to be increased in individuals with an increased WC (independent of the weight changes), while no difference was found in the risk faced by patients in whom WC decreased in spite of weight gain, and that of those who lost weight and decreased their WC.[19] Zeller et al., in their study of 2,229 patients with acute MI, concluded that neither BMI nor WC could independently predict mortality after acute MI. The authors found that patients with a higher WC but with a normal BMI had a worse prognosis.[15] The findings of the present study concur with those of the above studies. We also found in the present study that BMI and WC were effective in the development of mortality and MACE. Compatible with the obesity paradox, we found that the rate of mortality and development of MACE were low in patients with a high BMI. However, when BMI was considered together with WC, the rates of both mortality and MACE were high in patients with a high or normal BMI, but a high WC. WC, as a predictor of visceral adiposity and the primary factor affecting mortality and MACE, would appear to be responsible for both mortality and morbidity, independent of the weight of the individual.

Jelavicet al. evaluated 250 patients with STEMI, new-onset LBBB and NSTEMI, among whom WHR and waist to height ratio (WHtR) measurements were found to better predict clinical severity (major proximal/middle coronary segment stenosis, heart failure and dyspnea against total in-hospital complications) than BMI.[7] Concurring with the results of the present study, the authors reported that BMI was required for a diagnosis of obesity, but provided no information on body adiposity, nor was it a risk predictor of acute coronary syndrome. Ratios such as WHR and WHtR have been reported to be more successful in predicting mortality and morbidity, since body fat accumulates primarily in the abdomen and these ratios represent visceral adiposity. Jelavicet also suggested a positive association between abdominal obesity and decreasing BMI, and high mortality in individuals with an acute myocardial infarct.[7] This state, referred to as the obesity paradox above, has been attributed to the understanding that BMI does not differentiate between body fat (especially abdominal) and lean muscle mass.[5,6] A higher BMI was reported to be associated with a better short term outcome after PCI in a study supporting the obesity paradox by Grm et al.[20] Similarly, Gruberg et al. found that underweight and normal weight patients with a BMI of <25 kg/m<sup>2</sup> had a worse outcome in the short and long term when compared with overweight and obese patients following percutaneous coronary interventions (PCI).[21] Lancifield et al. classified patients with a high BMI as class I obese (BMI 30.1 to 35 kg/m<sup>2</sup>, n=1,021), and class II–III obese (BMI 35 kg/m<sup>2</sup>, n=405), and reported that class II–III obese patients experience a

substantially lower rate of in-hospital cardiac complications, including periprocedural MI, arrhythmia, CCF and MACE, and a low rate of in hospital death than normal weight patients. A statistically significant linear decrease was found in 12-month MACE (21.4% and 11.9%, p 0.008) and mortality (7.6% and 2.0%, p 0.001) when BMI was increased from 20 to 35 kg/m<sup>2</sup>. That said, the underweight and normal weight patients included in the study were considerably older, and the possibility of renal failure and peripheral vascular disease in the group higher. Furthermore, the number of patients with chronic lung disease, present congestive heart failure, previous MI and previous PCI was higher among the underweight patients.[5] Similarly, obese and overweight patients were demonstrated to have a better short- and long-term prognosis than underweight patients in a study by Kang et al. evaluating the risk factors for mortality in AMI.[6] Similar to the study by Lancifield et al., this study also included younger patients in the overweight and obese group, and these patients were found to have worse baseline properties, including hypertension, diabetes, cigarette smoking and hyperlipidemia. Underweight patients, on the other hand, had poor profiles associated with instability such as advanced age, low blood pressure, a higher Killip class and a lower left ventricle ejection fraction.[6] An interesting point in both of these studies reporting the preventive role of high BMI was that the underweight patients were more advanced in age and had comorbidities.[5,6] YuKang et al. attributed this to the fact that these patients were more frequently prescribed B blockers, angiotensin converting enzyme inhibitors and statins, since obesity is a known risk factor. Additionally, the younger age of these patients was influential in the initiation of a more aggressive treatment. Generally, age was found to be an independent risk factor for mortality in the analyses, meaning that overweight and obese patients were generally accepted to be in the low risk group for mortality in terms of age, since they were in the young age group.[6] Underweight and normal weight patients were found to have a higher rate of mortality and MACE also in the present study. Cases with mortality and MACE were found to be of a more advanced age with lower weight and lower BMI, but a higher waist circumference. The increased WC in normal or increased BMI patients led also to an increase in the development of MACE.

In a different study, Martinet al. evaluated patients with STEMI, non ST segment elevation myocardial infarction (NSTEMI) and unstable angina using a model in which WC was added to the Grace-RS score. It was reported that WC evaluation failed to improve the predictive accuracy of GRACE RS, and the authors stated also that WC was not an independent risk factor. WC was suggested not to be a prognostic factor for the prediction of 6-month mortality or myocardial infarct in patients with acute MI. Contrary to the present study, patients with NSTEMI and unstable angina were included in the above study, and the rate of obese patients were found to be higher (70%, compared to 61%).[22] This difference may originate from the inclusion of different patient groups in the study.

Iakobishvili et al. classified patients with STEMI in their study according to their BMI's, and evaluated the association between BMI and 30-day survival. Patients with a BMI of >30 were more dyslipidemic and hypertensive, and were less frequently fitted with stents. No other major differences were noted in demographic or clinical properties in these patients other than a higher systolic blood pressure at admission. No association was found between a higher BMI and better survival and MACE.<sup>[23]</sup> Abdominal obesity is associated with insulin resistance, hypertriglyceridemia, diabetes and hypertension.<sup>[24]</sup> The obesity paradox that has been proposed for acute coronary syndrome may have many origins. The primary cause may be the fact that the muscle-fat ratio is not included in the calculation of BMI, and visceral adiposity is overlooked. Other potential causes may be that obesity was a known risk factor in this group, meaning that hospital admissions could be high due to this or other comorbidities.

The main limitation of the study could be the low number of patients. Furthermore, regional nutritional changes and other regional factors may affect the results of the study, and so multicenter studies involving larger patient groups are required. Other than STEMI, studies may be carried out on patients with NSTEMI and angina pectoris.

## CONCLUSION

Muscle weight should be evaluated during anthropometric measurements for the prediction of cardiac risk secondary to obesity. The use of WC, as an indicator of body fat ratio rather than weight, may be more valuable in the evaluation of outcomes and risk analyses. The studies performed to date suggest that measurements reflecting the visceral fat ratio will replace general measurements such as BMI in the coming years..

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of İzmir Katip Çelebi University Ethics Committee (Decision No: GOKAEK-99).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

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

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