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Repolarization Parameters in Patients with Premature Coronary Artery Disease

Prematür Koroner Arter Hastalığında Repolarizasyon Parametreleri

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Abstract

Objectives: Coronary artery disease (CAD) in young adults is relatively rare. Few data on CAD in young adults are available in the literature. In the current study, repolarization parameters were evaluated in patients with newly diagnosed premature CAD.

Materials and Methods: A total of 200 patients [128 male, 38.0 (29.3-42.0) years] were included and 100 cases with newly diagnosed premature coronary heart disease (aged ≤ 45 years) formed the study group. Remaining 100 cases were well-matched controls. Repolarization parameters including QTc interval, Tp-e interval and Tp-e/QTc in leads DII, V2 and V6 were compared between the two groups.

Results: The median QTc interval (430.3 ms vs 405.3 ms, $p < 0.001$) in lead D2, (433.8 ms vs 404.7 ms, $p < 0.001$) in lead V2 and (430.2 ms vs 401.7 ms, $p < 0.001$) in lead V6; the median Tp-e interval (80 ms vs 64 ms, $p < 0.001$) in lead D2, (82 ms vs 74 ms, $p < 0.001$) in lead V2 and (88 ms vs 72 ms, $p < 0.001$) in lead V6; and the median Tp-e/QTc (0.188 vs 0.158, $p < 0.001$) in lead D2, (0.190 vs 0.181, $p = 0.022$) in lead V2 and (0.196 vs 0.183, $p < 0.001$) in lead V6 were significantly higher in patients with premature CAD compared controls, respectively.

Conclusion: In conclusion, premature coronary heart disease may be related to abnormal dispersion of repolarization and subsequent arrhythmic risk.

Key Words: Coronary, Dispersion, Premature, Repolarization

Öz

Amaç: Genç bireylerde koroner arter hastalığı nispeten nadir görülür. Literatürde genç yaşta koroner arter hastalığı ile ilgili sınırlı veri mevcuttur. Bu çalışmada yeni tanı almış prematür koroner arter hastalığı olanlarda repolarizasyon parametreleri değerlendirildi.

Gereç ve Yöntem: Çalışmaya toplam 200 hasta [128 erkek, 38,0 (29,3-42,0) yaş] dahil edildi ve bunlardan 100'ü yeni tanı prematür koroner arter hastalığı (yaş ≤ 45) olan çalışma grubunu oluşturdu. Kalan 100 hasta iyi eşleştirilmiş kontrol grubunu oluşturdu. İki grup arasında DII, V2 ve V6 derivasyonlarında ölçülen, QTc intervali, Tp-e intervali ve Tp-e/QTc den oluşan repolarizasyon parametreleri karşılaştırıldı.

Bulgular: Median QTc intervali D2 derivasyonunda (430,3 ms ve 405,3 ms, $p < 0,001$), V2 derivasyonunda (433,8 ms ve 404,7 ms, $p < 0,001$) V6 derivasyonunda (430,2 ms ve 401,7 ms, $p < 0,001$); median Tp-e intervali D2 derivasyonunda (80 ms ve 64 ms, $p < 0,001$), V2 derivasyonunda (82 ms ve 74 ms, $p < 0,001$), V6 derivasyonunda (88 ms ve 72 ms, $p < 0,001$); ve median Tp-e/QTc oranı; D2 derivasyonunda (0,188 ve 0,158, $p < 0,001$), V2 derivasyonunda (0,190 ve 0,181, $p = 0,022$) ve V6 derivasyonunda (0,196 ve 0,183, $p < 0,001$) olmak üzere sırasıyla prematür koroner arter hastalığı olanlarda kontrol grubuna göre anlamlı olarak daha yüksek saptandı.

Sonuç: Sonuç olarak, prematür koroner arter hastalığı anormal repolarizasyon dispersiyonu ve dolayısıyla aritmik risk ile ilişkili olabilir.

Anahtar Kelimeler: Dispersiyon, Koroner, Prematür, Repolarizasyon

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Introduction

Coronary artery disease (CAD) is relatively rare in subjects below 45 years of age. Nevertheless, it has been reported in younger age groups more frequently in recent years (1-3). Onset of CAD before 45 years of age is considered as premature CAD (4). However, various studies have considered the age limit differing from 35 years to 55 years in the spectrum of premature CAD (5-8). The prevalence of coronary atherosclerosis in young adults is difficult to establish and likely underestimated because asymptomatic young patients generally do not undergo diagnostic studies. Several studies have reported the incidence of the disease between 4% and 10% (9-12). Most coronary events in young subjects are related to atherosclerosis and at least one conventional cardiovascular risk factor is typically present as in older adults. Sudden cardiac death, which is the most severe complication of CAD, is the most common cause of sudden death also in adults under 45 years (13,14). However, the problem of CAD in young adults has not been characterized as in older individuals, because CAD in this young population is less common.

Heterogeneity of ventricular repolarization is associated with malignant ventricular arrhythmias (15). Ventricular repolarization abnormalities can be reflected by spatial dispersion (QT) QT interval on surface electrocardiogram (ECG). Although QT interval and its correction (QTc) have been satisfactorily used to predict cardiac arrhythmias, another marker Tp-e interval, the interval between the peak and the end of the T-wave, has been created and implemented in clinical practice. Commonly, it is considered a reflection of the transmural cardiac repolarization. Prolonged Tp-e interval can predict ventricular arrhythmias and mortality (16,17). Recently Tp-e/QT ratio has been proposed to be a better marker of ventricular repolarization (18,19). It incorporates the value of transmural dispersion (Tp-e) and QT of ventricular repolarization avoiding possible confounding effect of heart rate.

To the best of our knowledge, no trial has evaluated the QTc interval, Tp-e interval and Tp-e/QTc ratio as markers of ventricular arrhythmogenesis in patients with premature CAD. Therefore, in this study we aimed to investigate the relationship between repolarization parameters and premature CAD.

Materials and Methods

Study Population

We have retrospectively analyzed consecutive coronary angiography results of patients aged <45 years who were evaluated for stable angina in our institution from June 2016 to June 2017 in this cross-sectional study. Onset of CAD before 45 years of age was considered as premature CAD. The study

population consisted of 100 consecutive patients [66 male; median age, 37.0 (31.0-42.0) years] with newly diagnosed premature CAD (study group) and 100 well-matched subjects [62 male; median age, 38.0 (30.3-41.0) years] who proved to have normal coronary arteries (control group). All study participants had standard resting 12-lead surface electrocardiography (ECG) before the intervention. Each patient underwent a careful investigation of cardiovascular risk factors. Conventional CAD risk factors, such as cigarette smoking, diabetes mellitus, hypertension, dyslipidemia, obesity, and family history of CAD were recorded for all study participants.

Patients with unstable ischemic conditions (unstable angina pectoris and myocardial infarction), known previous myocardial infarction, known CAD, LV dysfunction [left ventricular ejection fraction (LVEF) <50%] and hypertrophy, valvular heart disease, atrial fibrillation, renal or hepatic dysfunction, systemic diseases, detection of coronary slow flow after selective coronary artery angiography, bundle branch blocks, ventricular preexcitation and any other intraventricular conduction abnormalities were excluded from the study. Also, patients on any antiarrhythmic drug that may influence ECG parameters were excluded. The study was approved by the local ethics committee (approval number: E7415).

Coronary Angiography

Selective coronary angiography was performed by the Judkins technique. All angiograms were analyzed by two experienced observers blinded to the study. Angiograms without stenotic lesions and atherosclerotic plaques in any major epicardial coronary arteries and their branches were considered normal angiograms. Presence of CAD was defined as $\geq 50\%$ luminal diameter stenosis in at least 1 major coronary artery and its branches on coronary angiography. The patients were grouped into single-vessel disease, two-vessel disease, and three-vessel disease according to the number of major epicardial coronary arteries involved.

Electrocardiography

The resting 12-lead surface ECG was recorded at a paper speed of 25 mm/s and 10 mm/mV amplitude in the supine position in all study subjects. All ECGs were scanned and transferred to a personal computer and then magnified by 400% to avoid error in measurements. Two independent electrophysiologists blinded to clinical details measured the QT and Tp-e intervals. Three consecutive beats in selected leads were measured manually and a mean value of three readings was calculated. The QT interval was measured from the beginning of the QRS complex to the end of the T-wave where the T-wave returns the isoelectric line when available. In unavailable cases, the end of the T-wave was determined as the intercept between the isoelectric line and the tangential line drawn through the maximum slope of the T-wave. QTc was calculated from the QT, which is corrected for

heart rate using the Bazett's formula: $QTc=QT\sqrt{(R-R \text{ interval})}$. The Tp-e interval was defined as the interval from the peak of T-wave to the end of the T-wave where the T-wave returns the isoelectric line when available. In unavailable cases, previously described method was used. Measurements of the QTc and Tp-e intervals were performed in leads D2, V2 and V6. The Tp-e/QTc ratio was calculated from these measurements. Inter-observer and intra-observer variability were found to be less than 5%.

Statistical Analysis

Statistical analysis was performed using the SPSS 15.0 Statistical Package Program for Windows (SPSS, Inc., IL, USA). Continuous variables were presented as mean \pm SD and median with interquartile ranges as appropriate and categorical variables as frequency and percentage. To test normality of distribution, Shapiro-Wilk test was used. Differences between groups were evaluated by using Student's t-test for normally distributed variables and Mann-Whitney U test for variables without normal distribution. The chi-square or Fisher's Exact test was used to compare categorical variables as appropriate. Spearman's correlation analysis was performed to examine the relationship between repolarization parameters and the number of the diseased vessel. Multivariate logistic regression analysis was used to evaluate the independent effects of the investigated variables on the risk of premature CAD. The odds ratios and 95% confidence intervals were calculated. A p value <0.05 (using a two-sided test) was considered significant.

Results

Patient Characteristics

Clinical and demographic characteristics of the premature CAD and control groups were presented in Table 1. Both groups were similar in terms of age, gender, left ventricular ejection fraction, body mass index, and cardiovascular risk factors including hypertension, smoking, diabetes, dyslipidemia, and family history of CAD (all $p>0.05$). The mean heart rate for the premature CAD group and the control group were 76.0 (70.0-83.8) bpm and 76.0 (72.0-85.0) bpm, respectively. Patients were divided into three groups according to the number of the diseased vessel. Among 100 cases with premature CAD, single-vessel disease was the most prevalent (58 patients, 58.0%), followed by two-vessel disease (29 patients, 29.0%) and three-vessel disease (13 patients, 13.0%).

ECG Comparison Between Premature Cad and Control Groups

All predefined repolarization parameters were presented in table 2. The results are as follows;

QTc Interval

The median QTc interval (430.3 ms vs 405.3 ms, $p<0.001$) in lead D2, (433.8 ms vs 404.7 ms, $p<0.001$) in lead V2 and (430.2 ms vs 401.7 ms, $p<0.001$) in lead V6 were significantly higher in the study group compared to the control group, respectively.

Tp-e Interval

The median Tp-e interval (80 ms vs 64 ms, $p<0.001$) in lead D2, (82 ms vs 74 ms, $p<0.001$) in lead V2 and (88 ms vs 72 ms, $p<0.001$) in lead V6 were significantly higher in the premature CAD group compared to the control group, respectively.

Tp-e/QTc Ratio

The median Tp-e/QTc (0.188 vs 0.158, $p<0.001$) in lead

Table 1: Baseline characteristics

Characteristic	Study group (n=100)	Control group (n=100)	p value
Age (years)	37.0 (31.0-42.0)	38.0 (30.3-41.0)	0.738
Male, n (%)	66 (66.0)	62 (62.0)	0.556
Hypertension, n (%)	32 (32.0)	31 (31.0)	0.879
Smoking, n (%)	38 (38.0)	39 (39.0)	0.884
Diabetes, n (%)	17 (17.0)	18 (18.0)	0.852
Dyslipidemia, n (%)	26 (26.0)	28 (28.0)	0.750
Family history of CAD, n (%)	34 (34.0)	35 (35.0)	0.882
BMI (kg/m ²)	27.5 (24.0-30.5)	27.4 (24.7-30.6)	0.649
LVEF (%)	65.0 (62.0-68.0)	65.0 (60.0-67.8)	0.758
Heart rate (bpm)	76.0 (70.0-83.8)	76.0 (72.0-85.0)	0.425
CAD severity, n (%)			
1- Vessel	58 (58.0)	-	-
2- Vessel	29 (29.0)	-	-
3- Vessel	13 (13.0)	-	-

BMI: Body mass index, CAD: Coronary artery disease, LVEF: Left ventricular ejection fraction. Values are presented as median and interquartile ranges (25th and 75th)

Table 2: Repolarization parameters

Parameter	Study group (n=100)	Control group (n=100)	p value
QTc in lead DII (ms)	430.3 (400.2-461.6)	405.3 (388.0-420.7)	<0.001
QTc in lead V2 (ms)	433.8 (406.0-465.6)	404.7 (379.0-415.4)	<0.001
QTc in lead V6 (ms)	430.2 (409.4-473.2)	401.7 (387.2-423.3)	<0.001
Tp-e in lead DII (ms)	80 (70-90)	64 (58-71)	<0.001
Tp-e in lead V2 (ms)	82 (72-94)	74 (66-76)	<0.001
Tp-e in lead V6 (ms)	88 (78-96)	72 (67-76)	<0.001
Tp-e/QTc in lead DII	0.188 (0.164-0.221)	0.158 (0.144-0.179)	<0.001
Tp-e/QTc in lead V2	0.190 (0.159-0.226)	0.181 (0.166-0.193)	0.022
Tp-e/QTc in lead V6	0.196 (0.173-0.235)	0.183 (0.163-0.193)	<0.001

Values are presented as median and interquartile ranges (25th and 75th)

D2, (0.190 vs 0.181, $p=0.022$) in lead V2 and (0.196 vs 0.183, $p<0.001$) in lead V6 were significantly higher in the study group compared to the control group, respectively.

Table 3 shows the results of the univariate analyses performed to identify the factors associated with premature CAD. In

Table 3: Univariate analysis

Variable	OR	95% CI	p value
Age	1.008	0.966-1.052	0.711
Male	1.190	0.667-2.121	0.556
Hypertension	1.047	0.577-1.902	0.879
Smoking	0.959	0.542-1.695	0.884
Diabetes	0.933	0.450-1.936	0.852
Dyslipidemia	0.903	0.484-1.687	0.750
Family history of CAD	0.957	0.534-1.714	0.882
BMI	0.978	0.911-1.051	0.548
LVEF	1.015	0.945-1.090	0.688
Heart rate	0.988	0.960-1.018	0.442
QTc in lead DII	1.020	1.011-1.029	<0.001
QTc in lead V2	1.025	1.015-1.035	<0.001
QTc in lead V6	1.027	1.017-1.037	<0.001
Tp-e in lead DII	1.164	1.116-1.215	<0.001
Tp-e in lead V2	1.133	1.089-1.178	<0.001
Tp-e in lead V6	1.232	1.161-1.308	<0.001
Tp-e/QTc in lead DII	1.029	1.019-1.040	<0.001
Tp-e/QTc in lead V2	1.016	1.006-1.025	0.001
Tp-e/QTc in lead V6	1.026	1.015-1.036	<0.001

Abbreviations as per table 1

CAD: Coronary artery disease, BMI: Body mass index, LVEF: Left ventricular ejection fraction

univariate analyses, significant associations were observed with all predefined intervals with premature CAD. No association was observed with other variables including hypertension, smoking, diabetes, dyslipidemia, family history of CAD, and LVEF. After adjustment for major cardiac risk factors, multivariate analyses showed that repolarization parameters were not significant independent predictors of premature CAD. Mean repolarization parameters were compared in 3 groups according to the number of the diseased vessel to clarify the relationship between CAD severity and repolarization parameters (Figure 1). There was no significant trend through the number of diseased vessel regarding repolarization parameters in selected ECG leads.

Discussions

In this study, we demonstrated that QTc interval, Tp-e interval and Tp-e/QTc ratio, as indices of ventricular arrhythmogenesis, were significantly higher in patients with newly diagnosed premature CAD compared with healthy controls. This is the first study to demonstrate the relationship between repolarization parameters and premature CAD.

Cardiovascular diseases continue to be the leading cause of morbidity and mortality worldwide and they are related to atherosclerosis and its complications (20). CAD occurring in less than 45 years of age is defined as premature or young CAD (4). The profile of risk factors important for the etiology of CAD in young patients is similar to that seen in middle-aged and elderly patients. However, the severity of specific risk factors and their individual contribution to the progression of CAD is different (21). These differences in etiologies and risk profiles of younger and older CAD patients culminate in differences

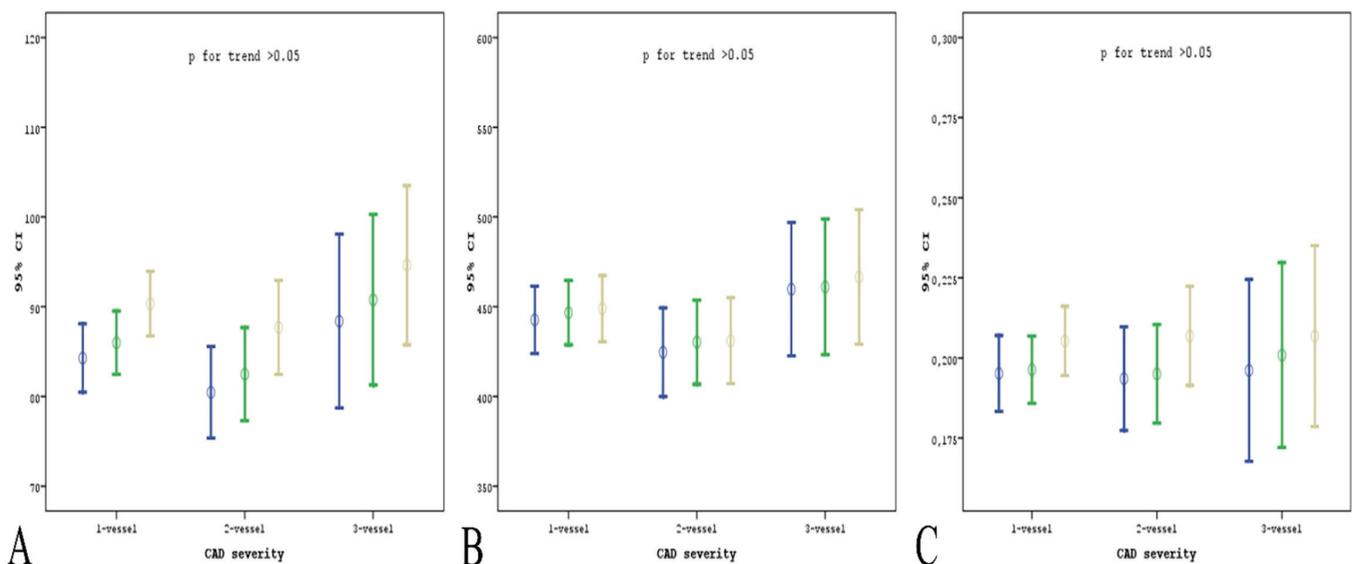


Figure 1: Distribution of repolarization parameters according to CAD severity. A) No significance was observed for Tp-e interval, B) QTc interval and C) Tp-e/QTc ratio. Blue, green and yellow bars represent lead DII, V2 and V6, respectively.

CAD: Coronary artery disease

in disease progression and prognosis. Unfortunately, few data are available in the literature on the course of CAD, its risk factors, and outcomes in this population. Earlier studies have suggested that outcomes are more favorable in premature CAD patients than any group of older patients especially in terms of in-hospital and short-term mortality (12,22,23). However, long-term mortality studies have suggested otherwise. Cole et al. have described an alarming longer-term mortality rate in 843 young CAD patients: 15-years overall mortality rate was 30%, and it was 45% in young patients with prior myocardial infarction (24). Additional studies have also indicated that sudden death may be higher in the younger population (25,26). Increased prevalence in cardiovascular risk factors and subsequently CAD in the young population could lead to a rise in sudden cardiac death from atherosclerotic origin in young individuals, but few data in this respect are available at present.

Currently, there is a growing evidence to support the use of electrocardiographic repolarization markers to evaluate the risk of ventricular arrhythmias. A prolonged QT interval has been shown to be closely associated with increased sudden cardiac death risk in multiple medical conditions (16,17). Recently, the Tp-e interval and Tp-e/QT ratio have emerged as novel electrocardiographic markers of increased dispersion of ventricular repolarization (18,27). As already reported by Gupta et al. Tp-e/QT seems to represent a more precise measure of arrhythmogenesis (18). Nowadays, the predictive capacities of these markers have demonstrated to be useful in a lot of clinical situations in the spectrum of CAD. The QTc interval, Tp-e interval and Tp-e/QTc ratio have been found to be useful to predict ventricular arrhythmias in patients after myocardial infarction (28-31). Recently, Wang et al. have demonstrated that repolarization markers were significantly increased in vasospastic angina patients with malignant arrhythmic events than those without (32). Also, Sucu et al. have reported that coronary slow flow was associated with prolonged duration of repolarization parameters and possible association with ventricular arrhythmias (33). In various patient populations such as patients with coronary artery ectasia (34,35), stable CAD with coronary collateral circulation (36), patients treated with reperfusion methods (19,37), these electrocardiographic repolarization markers have been found to be more prolonged than control patients. The underlying mechanism may be ischemia or microvascular dysfunction observed in this group of patients. As far as we know, there is no study available in the literature regarding the relation between premature CAD and above-mentioned repolarization parameters. Most sudden deaths from arrhythmia are thought to be ischemic in origin though rarely related to acute coronary thrombosis (38). Therefore, we speculated that patients with newly diagnosed premature CAD could be prone to development of ventricular repolarization abnormalities as a consequence of ischemia and/or microvascular dysfunction.

A recently published manuscript focused on the relationship between inflammation and repolarization parameters. Acar et al. have found that electrocardiographic indices of ventricular repolarization are correlated with systemic inflammation (39). Therefore, inflammation may be one of the reasons behind the increased values for repolarization indices and an explanation of heterogeneity of ventricular repolarization in premature CAD patients. Because, pro/anti-inflammatory cytokines play a clear role in the pathogenesis of premature CAD and correlate well with the severity of premature CAD.

Mozos have demonstrated that prolonged QTc and Tp-e could be markers of endothelial dysfunction, arterial stiffness, impaired coronary perfusion, and accelerated arterial aging (40). In our study, a significant association was observed between repolarization indices and the risk of premature CAD in univariate analysis. Therefore, we thought that the prolongation of these repolarization markers may signify either ventricular repolarization abnormality with an arrhythmogenic tendency or the presence of premature CAD. We tested for interactions between these parameters and premature CAD. In multivariate analysis, repolarization markers were not independent risk factors for the presence of premature CAD. However, the cross-sectional design does not demonstrate cause-effect relations. Further studies are needed to demonstrate that link.

In this study, most cases with CAD had single-vessel disease, followed by two-vessel disease and three-vessel disease. These results were in accordance with earlier studies. Also, we found that there was no significant association between repolarization parameters and the severity of CAD, which was graded based on the number of significantly diseased vessel. This could be due to the small sample size and the presence of premature CAD cases with mostly single-vessel disease.

Study Limitations

There are some limitations of this study. First, our study has relatively small sample size. Second, the study is a single-center study. One of the major limitations of our study is its cross-sectional design and lack of follow-up of the study patients. We did not evaluate the association between ventricular arrhythmias with repolarization indexes. Also, the study population could not be followed-up prospectively for mortality or ventricular arrhythmic episodes with holter monitoring or event recorder. Therefore, we could not assess the potential prognostic role of the electrocardiographic ventricular repolarization parameters with respect to future adverse events. Therefore, long-term follow-up and large-scale prospective studies are needed to investigate the predictive value of the Tp-e interval and Tp-e/QTc ratio in patients with premature CAD. Also, we did not routinely use the intravascular ultrasound. Since we had no data on Syntax or Gensini scores, we were unable to evaluate

the association between ECG findings and these scores. Finally, non-atherosclerotic coronary disease was not directly evaluated and there was no attempt to detect the presence of coronary vasospasm by provocation tests in patients with normal coronary arteries.

Conclusion

We have shown for the first time that patients with premature CAD had higher QTc interval, Tp-e interval and Tp-e/QTc ratio compared to controls. Our data suggests that the increasing values for repolarization parameters might contribute to higher incidence of sudden cardiac death in these young subjects, which needs to be studied further.

Ethics

Ethics Committee Approval: This study was submitted to and approved by the Ethics Commission of Türkiye Yüksek İhtisas Training and Research Hospital (Reference number: E.7415).

Informed Consent: This is a retrospective study, so the consent to participate is not applicable.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.A.E, S.Ç., B.T.T., Design: F.A.E, S.Ç., H.K., Ö.Ö., F.Ö., S.T., B.T.T., D.A., Data Collection or Processing: A.E., S.Ç., Analysis or Interpretation: A.E., S.Ç., Literature Search: A.E., S.Ç., B.T.T., H.K., Writing: A.E., S.Ç.

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