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Evaluation of novel ventricular repolarization parameters in patients with acromegaly

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ABSTRACT

Objectives: T wave's peak and end interval (Tp-e), Tp-e/QT ratio and Tp-e/QTc ratio are novel markers of ventricular repolarization and are associated with ventricular arrhythmias. Increased ventricular arrhythmia incidence is reported in patients with acromegaly. The purpose of this study is to evaluate ventricular repolarization using the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with acromegaly.

Methods: Thirty-five patients with acromegaly were included in the study. The control group was consisted of forty-one subjects without acromegaly that having similar age, sex ratio and comorbidities. The Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio, and other ventricular repolarization parameters of all patients were evaluated using electrocardiography.

Results: Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio were significantly prolonged in patients with acromegaly compared to the control group. Furthermore, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio showed a significant correlation with plasma GH levels and LVMI values.

Conclusions: Our study revealed that Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio are prolonged in patients with acromegaly. We believe that the Tp-e interval, Tp-e/QT ratio, and Tpe/QTc ratio can be used in the evaluation of increased cardiovascular risk in patients with acromegaly.

Keywords: Acromegaly, ventricular repolarization, novel electrocardiographic parameters

Acromegaly is a rare disease and the total prevalence ranges between 2.8 and 13.7 cases per 100,000 people and the annual incidence rates range between 0.2 and 1.1 cases/100,000 people [1, 2]. Acromegaly is a disorder that associated with increased cardiovascular morbidity and mortality, and around 60% of these patients die due to several cardiovascular complications, including cardiac arrhythmia [1, 2]. Especially, malign ventricular arrhythmias are the primary cause of sudden cardiac deaths [3, 4]. Increasing growth hormone (GH) and insulin-like growth factor 1 (IGF-1) in patients with acromegaly may cause the development of acromegalic cardiomyopathy (CMP) which in turn results in the development of myocardial hypertrophy and interstitial fibrosis [2, 5, 6]. The presence of acromegalic CMP becomes a source for the development of various arrhythmias and therefore, cardiac rhythm disorders occur more frequently and more severely in patients with acromegaly compared to the overall population

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[1, 7]. Therefore, knowing the predictors of arrhythmic events are crucial in the follow-ups of these patients [1, 6].

Traditionally, QT, dQT, QTc, dQTc QT, and transmural dispersion of repolarization are simple, non-invasive arrhythmogenic markers that are utilized to evaluate the homogeneity of cardiac repolarization. Recently, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio have been used widely to evaluate the transmural dispersion of repolarization (TDR) [8-10]. Also, studies have shown that, in ECG, the Tp-e interval can be used as an index for total dispersion of repolarization, and furthermore, increased Tp-e interval can be a useful index to predict tachyarrhythmias and cardiovascular mortality [9-12]. In addition, the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio are able to measure ventricular dispersion of repolarization better compared to QT and QTc, in that these methods are not affected by heart rate unlike QT and QTc [13-15]. As a result, membrane protein alterations and anatomical deterioration of cardiomyocytes the occur in patients with acromegaly can explain the impaired transmural dispersion of repolarization and prolonged ventricular repolarization [1, 2].

The purpose of this study is to evaluate the ventricular polarization using Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with acromegaly.

METHODS

Study Population

A total of 35 patients with acromegaly were included in the study. Afterward, 41 subjects with similar risk profiles were designated as the control group after they were evened out in terms of age and gender. 28 acromegaly patients had a previous transsphenoidal surgery history and 2 acromegaly patients had a previous transcranial surgery history. Furthermore, 5 acromegaly patients have radiotherapy or radiosurgery in their patient histories.

Acromegaly diagnoses have been made in line with the current guidelines [16]. The designated criteria for the diagnosis were the presence of clinical findings, high serum GH and IGF-1 confirmed with laboratory tests, serum GH value above 1 µg/L after 75 g oral glucose loading, and the presence of pituitary gland adenoma that is shown radiologically [16]. All patients are evaluated in terms of concomitant diabetes mellitus (DM), hypertension (HT), panhypopituitarism, thyroid dysfunction, and all other systemic disorders, and the diagnosis of these diseases are determined in line with the current guidelines. All medicines used by patients were determined.

In our study, the follow-up period of acromegaly patients after the diagnosis were 96 (41-125) months (between minimum 12 months and maximum 296 months). In the evaluation after the follow-up, 23 patients were in remission, while 12 patients were on the active course of the disorder. Active disorder and remission conditions were defined in line with the latest acromegaly guidelines of the Endocrine Society [16].

Patients with coronary artery disease, moderate to severe valvular heart disease, chronic pulmonary disease, obstructive sleep apnea, chronic renal or hepatic impairment, thyroid disfunction, persistent or uncontrolled HT, heart failure (Left ventricule ejection fraction of < 50%), hematologic disorders, electrolyte imbalance were not included in the study. Furthermore, all of the patients were within the sinus rhythm and patients with QT segments that cannot be analyzed in QT, any conduction problem, ST-T anomalies, pacemaker rhythm, atrial fibrillation, or arrhythmia or those who take any medicine that can affect Tp-e distance or QT interval (such as antiarrhythmics, tricyclic antidepressants, antihistamines, and antipsychotics) were not included in the study. The study protocol was approved by the local ethics committee in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent.

Hormonal and Biochemical Evaluation

Serum GH and IGF-I levels of all patients were measured at the time of diagnosis and in follow-ups using chemiluminescence enzyme immunoassay commercial kits (IGF; Immulite 2000, Siemens healthcare, Diagnostic Products Ltd., Glyn Rhonwy, Llanberis, Gwynedd LL55 4EL United Kingdom and GH; Cobas e601, Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Manheim, Germany). Furthermore, intra- and inter-test variation coefficients for IGF-1 were found to be 3.5% and 6.1% respectively, while intra- and inter-test variation coefficients for GH were 6.7% and 9.2% respectively. The reference interval for GH was 0.126-9.88 ng/mL. While IGF-I values are

given, these values were expressed as a percentage of the upper limit of the age-adjusted normal values and the age-specific reference intervals for IGF-1 were evaluated as recommended in the guidelines. The references were set as 80-330 ng/mL for patients aged 19 to 29, as 60-240 ng/mL for patients aged 30-39, as 50-220 ng/mL patients aged 40 to 49, as 40-210 ng/mL for patients aged 50 to 59, as 30-220 ng/mL for patients aged 60 to 130. Routine biochemical serum glucose, creatine, sodium, potassium, calcium, phosphorus, and magnesium levels of each patient were measured and all other hypophyseal hormones were routinely measured as well. All of these parameters were also measured for each person in the control group at least once. All other parameters were determined using routine methods. All serum samples were taken from the cubital venous vessel area in the early hours of the morning after 8 hours of fasting. None of the patients had pituitary insufficiencies or additional hormone secretion apart from GH and IGF-1.

Electrocardiography (ECG)

ECG with 12 leads was recorded in the supine position at 50 mm/s paper rate. To reduce erroneous measurements, all ECGs were scanned and transferred to a PC, zoomed in by × 400% using Adobe Photoshop and the measurements were conducted using suitable programs. In ECG, the results with U waves were excluded. For each value, the mean of three different derivations was calculated. QT interval was determined as the distance between the start of the QRS complex to the end of the T wave, and the QTc value was calculated according to heart rate using the Bazett formula (QTc = QT/RR1/2). The difference between the measured QT max and QT min was defined as QT dispersion. dQTc dispersion was defined as the difference between QTc max and QTc min. The interval between the peak point of the T wave to the end of the T wave was defined as the Tp-e interval. Tp-e was performed via precordial leads, as recommended [14]. From these measurements, the Tp-e/QT ratio and Tp-e/QTc ratio were calculated. The inter-observer variation coefficient was determined as 2.8%.

Echocardiography

All patients underwent transthoracic echocardiography (TTE) with a Phillips Affiniti 50C system (Philips Medical Systems, Netherlands). The examinations were performed with the patient in the left decubitus position. Throughout the evaluation, patients were monitored using standard techniques. Echocardiographic evaluations included M-mode, two dimensional, and Doppler evaluation performed according to current guidelines [17]. Left atrial diameter (LAD) was measured using a parasternal long-axis view. Inter-ventricular septal (IVS) and posterior wall (PW) thicknesses and left ventricule end-diastolic (LVEDD) and end-systolic diameters (LVESD) were measured in parasternal long-axis view with M-mode. The left ventricular ejection fraction (LVEF) was calculated using Biplane Simpson's method [18]. The mean of three measurements was taken for all parameters. Left ventricle mass (LVM) was calculated using the equation previously recommended by Devereux et. al. [17]. Afterward, LVM was proportioned to the body surface area and left ventricle mass index (LVMI) was calculated [17].

Statistical Analysis

For all statistical analyses, SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used. Kolmogorov-Smirnov test was used to determine the normality of the dispersion. While the numerical data with normal dispersion is given as mean ± standard deviation, numerical variables with non-normal dispersion were given as medians (interval between quarters). Categorical variables were presented as numbers and percentage values. The chi-square test was used when comparing categorical variables between the groups. Student t-test or Mann- Whitney U test was used to compare continuous variables between the groups. Pearson correlation analysis was performed to analyze the relation between repolarization parameters, and GH levels and LVMI. $P < 0.05$ value was considered to be statistically significant.

RESULTS

There was no significant difference between the acromegaly patients and the control group in terms of age, sex, body mass index (BMI), DM and HT frequencies, systolic and diastolic blood pressures, and smoking (Table 1). The basal, demographic, and laboratory parametres of both groups were given in Table

1. While the basal GH and IGF-1 levels of acromegaly patients were significantly higher compared to the control group, no other difference was detected in other blood parameters (Table 1).

Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio values of the acromegaly patients were significantly longer compared to the control group (Table 2). Also QT, QTc, dQT, dQTc, values of the acromegaly patients were significantly longer compared to the control group (Table 2). While there was no

Table 1. The baseline characteristics and laboratory findings of study patients

	Control group (n = 41)	Acromegaly patients (n = 35)	*p* value
Demographic parameters			
Age, (years)	50.7 ± 9.8	51.5 ± 10.2	0.351
Female, n (%)	25 (60.9)	22 (62.8)	0.218
HT, n (%)	9 (21.9)	8 (22.8)	0.257
Smoking, n (%)	8 (19.5)	7 (20.0)	0.217
DM, n (%)	11 (26.8)	10 (28.5)	0.174
Body mass index (kg/m^2)	26.4 ± 4.5	26.8 ± 4.7	0.475
Family history of CAD, n (%)	6 (14.6)	5 (14.2)	0.237
Heart rate, (beat/minute)	78.4 (13.6)	80.5 (21.9)	0.817
Systolic blood pressure, (mm Hg)	127.8 (12.8)	129.3 (14.5)	0.345
Diastolic blood pressure, (mm Hg)	82.8 (7.9)	83.3 (9.2)	0.156
Follow-up duration, (months)	-	96 (41-125)	-
Laboratory parameters			
GH	0.6 ± 0.2	17.2 ± 10.2	**< 0.001**
IGF-1	123.2 ± 39.5	582.8 ± 125.1	**< 0.001**
Glucose (mg/dL)	120 ± 25	121 ± 31	0.325
HbA1c (%)	5.7 ± 1.3	5.7 ± 1.5	0.347
Hg (mg/dL)	13.5 ± 2.2	13.9 ± 2.4	0.152
Creatinine (mg/dL)	0.89 ± 0.16	0.91 ± 0.18	0.234
Total cholesterol (mg/dL)	159 ± 26	162 ± 31	0.123
Triglyceride (mg/dL)	149 ± 44	155 ± 53	0.239
Low-density lipoprotein (mg/dL)	129 ± 19	131 ± 21	0.329
High-density lipoprotein (mg/dL)	41 ± 10	39 ± 9	0.516
WBC Count, (×10^3/µL)	7.4 ± 2.9	7.3 ± 3.1	0.476
PLT Count, (×10^3/µL)	318 ± 42	321 ± 46	0.149
C-Reactive protein, (mg/dL)	0.65 ± 0.27	0.68 ± 0.29	0.521
Na (mmol/L)	141 ± 9	142 ± 7	0.236
K (mmol/L)	4.15 ± 0.23	4.12 ± 0.35	0.274
Ca (mg/dL)	8.9 ± 1.2	9.1 ± 1.4	0.574
TSH (µIU/mL)	2.35 ± 0.08	2.31 ± 0.09	0.138

Ca = calcium, CAD = coronary artery disease, DM = diabetes mellitus, GH = growth hormone, Hg = hemoglobin, HT = hypertension, IGF-1 = Insulin-like growth factor 1, K = potassium, Na = *Sodium,* PLT = Platelet count, TSH = thyroid-stimulating hormone, WBC = White blood cell

Table 2. The Electrocardiographic and echocardiographic findings of study patients

	Control group (n = 41)	Acromegaly patients (baseline) (n = 35)	*p* value
Electrocardiographic measurement (at baseline)			
Tp-e interval	67.6 ± 8.3	85.3 ± 12.7	**< 0.001**
Tp-e/QT ratio	0.192 ± 0.021	0.234 ± 0.030	**< 0.001**
Tp-e/QTc ratio	0.184 ± 0.023	0.223 ± 0.032	**< 0.001**
QT interval	361.6 ± 24.2	382.9 ± 35.4	**< 0.001**
cQT interval	382.3 ± 20.1	415.4 ± 41.6	**< 0.001**
QTd interval	62.5 ± 11.6	71.1 ± 10.4	**< 0.001**
cQTd interval	69.2 ± 14.1	78.1 ± 13.2	**0.002**
Echocardiographic parameters			
LV ejection fraction (%)	61.9 ± 4.8	63.5 ± 5.2	0.375
LV end-diastolic diameter (cm)	4.81 ± 0.83	4.92 ± 0.91	0.198
LV end-systolic diameter (cm)	2.81 ± 0.8	2.75 ± 0.7	0.321
Interventricular septal thickness (cm)	0.92 ± 0.10	1.19 ± 0.21	**< 0.001**
Posterior wall thickness (cm)	0.91 ± 0.09	1.17 ± 0.21	**< 0.001**
Left atrial diameter (cm)	36.9 ± 2.1	37.1 ± 2.3	0.102
LVMI	82.4 ± 21.7	117.3 ± 35.1	**< 0.001**
E/e’	6.37 ± 1.7	8.25 ± 3.1	**< 0.001**

LV = left ventricular, LVMI = left ventricular mass index

echocardiographic difference between the groups in terms of EF, LVEDD, LVEED, and LA diameter, the values for IVS, PW, LWMI, and E/e’ were significantly higher in the acromegaly patients (Table 2). The basal electrocardiographic and echocardiographic findings of the acromegaly patients and the control group are summarized in Table 2.

In addition, no significant difference was observed between the patients in remission (n = 23) and the patients in active phase (n = 12) in terms of QT interval, cQT interval, QTd interval, cQTd interval (for all parameters, $p > 0.05$). However Tp-e interval, Tp-e/QT

Table 3. Electrocardiographic findings after follow-up according to the active or remission status of the study patients

Variables	Acromegaly patients on remission (n = 23)	Acromegaly patients on active disease (n = 12)	*p* value
Tp-e interval	81.8 ± 11.5	91.4 ± 14.3	**0.003**
Tp-e/QT ratio	0.229 ± 0.021	0.242 ± 0.027	**0.002**
Tp-e/cQT ratio	0.219 ± 0.029	0.229 ± 0.033	**0.007**
QT interval	381.7 ± 31.2	383.9 ± 32.4	0.102
cQT interval	412.4 ± 36.6	415.9 ± 37.4	0.763
QTd interval	70.5 ± 6.2	72.8 ± 5.7	0.325
cQTd interval	79.2 ± 8.1	81.4 ± 7.7	0.271

Tablo 4. Correlation analysis showing the between new ventricular depolarizations parameters and GH levels, IGF-1 levels, LMVI and disease duration time

	Tp-e Interval		Tp-e/QT Ratio		Tp-e/QTc Ratio	
	r	*p value*	*r*	*p*	*r*	*p value*
GH	0.612	**< 0.001**	0.523	**< 0.001**	0.549	**< 0.001**
IGF-1	0.456	**< 0.001**	0.478	**< 0.001**	0.449	**< 0.001**
LVMI	0.502	**< 0.001**	0.487	**< 0.001**	0.479	**< 0.001**
Disease duration	0.506	**0.002**	0.496	**0.002**	0.530	**< 0.001**

GH = growth hormone, IGF-1 = Insulin-like growth factor 1, LVMI = left ventricular mass index

ratio and Tp-e/QTc ratio were significant higher in patients with active disease (Table 3).

A significant positive correlation was observed between Tp-e, Tp-e/QT, Tp-e/QTc values and GH level, IGF-1 level and LVMI values (Table 3). Also a significant positive correlation was observed between Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio values and disease duration (Table 4).

DISCUSSION

In this study, we focused on determining the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with acromegaly. We found out that the Tp-e, Tp-e/QT, Tp-e/QTc, QT, QTc, dQT, and dQTc values were measured for the acromegaly patients were significantly longer compared to the control group. In addition, while there was no difference between the QT, QTc, dQT and dQTc values in patients with the active phase and remission, we found that the Tp-e interval, Tp-e/QT, Tp-e/QTc ratio to be significantly higher in patients with the active phase. Therefore, we demonstrated that new generation parameters are superior to traditional methods in evaluating ventricular repolarization, especially in patients with acromegaly in the active phase. Furthermore, we have seen a significant correlation between Tp-e interval, Tp-e/QT ratio, Tp-e/QTc ratio, and disease duration. This study is the first study that evaluates Tp-e, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with acromegaly.

In this study, we have found out that QT, QTc, dQT, and dQTc values of the acromegaly patients are significantly longer compared to the control group. QT, QTc, dQT, and dQTc are reported to be associated with sudden cardiac death and the development of ventricular arrhythmia in different clinical circumstances [8, 19]. QT, QTc, dQT, and dQTc are the traditionally well-known markers of ventricular repolarization [8, 19]. Similarly, it has been shown that QT, QTc, dQT, and dQTc values are prolonged in patients with acromegaly [15, 20, 21]. That the changes occurring in the ventricle after acromegalic CMP causes prolongation in ventricular repolarization and ventricular dishomogeneization can explain the increased QT, QTc, dQT, and dQTc intervals [21, 22]. Recently, the use of Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio as the new markers of ventricular repolarization dispersion are becoming more and more common [14, 23]. In our study, we have found that Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios were significantly higher in patients with acromegaly than control subjects. According to the results of our study, we have revealed that acromegaly disorder causes impaired repolarization anomalies. Furthermore, prolonged Tp-e interval and increased Tp-e/QT ratio and Tp-e/QTc ratio have been shown to be associated with increased mortality in various diseases such as, firstly, Brugada syndrome, long QT syndrome, hypertrophic cardiomyopathy syndrome, and acute ST-segment elevation myocardial infarction, and the ventricular repolarization anomalies [9, 10, 14, 24, 25]. It is well known that pathologic left ventricular hypertrophy is a risk factor for the development of ventricular arrhythmia and sudden cardiac death [22, 26]. Pathological hypertrophy developing in patients with acromegaly makes the ventricle more susceptible to malign tachycardias by causing electrical instability in

cardiomyocytes [4-6]. Furthermore, it has been shown that the presence of LVH increases ventricular repolarization time [24, 25].

In our study, we have found the left ventricular wall thickness, as well as LVMI values in patients with acromegaly significantly higher compared to the control group. Furthermore, in our study, the finding of a significant correlation between Tp-e interval, Tp-e/QT, Tpe/QTc values, and LVMI is supported by the mechanisms above. Zhao *et al*. demonstrated that LVH was closely related to increased QT interval, Tp-e interval, and Tp-e/QT ratio [25]. Similarly, in a previous study, a correlation was found between cardiac arrhythmia frequency and echocardiographic LVM in patients with acromegaly [1]. In the same study, it was also shown that the severity of ventricular arrhythmias increases with the increase in left ventricular mass [1]. Our results support that the increased LVMI is closely associated with prolonged Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio values that signify ventricular repolarization anomalies. The receptors of GH and IGF-1 hormones are present in cardiomyocytes as well, and these hormones form the basis of cardiovascular complications by affecting the myocardial structure and function via endocrine, autocrine, paracrine systems [6, 27]. As a result of these impacts, a complication like myocarditis occurs with the development of increased myocardial collagen tissue, impairment of myocyte necrosis areas, lymphonuclear myocarditis, and as a consequence, a gradual impairment occurs in the structure of the heart [28].

Another important finding of our study is that we found a significant relationship between disease duration and Tpe, Tpe/QT and Tpe/QTc values at follow-up. This shows that the longer the disease duration, the more risky the patients are in terms of developing arrhythmia. It was shown that ventricular arrhythmia occurs more frequently and in a more complex manner in patients with acromegaly [1, 5, 6]. It was also shown that ventricular arrhythmias among in patients with acromegaly affect life quality and even are the most significant cause of death [1, 3, 4]. Therefore, early detection of the parameters that may be related to the development of arrhythmia is crucial for acromegaly patients.

In addition, while there was no difference between the QT, QTc, dQT and dQTc values in patients with the active phase and remission, we found that the Tp-e interval, Tp-e/QT, Tp-e/QTc ratio to be significantly higher in patients with the active phase. In other words, we determined that the risk of arrhythmia is still high in patients with active disease and traditional repolarization parameters are insufficient in this case. Therefore, we demonstrated that new generation parameters are superior to traditional methods in evaluating ventricular repolarization, especially in patients with acromegaly in the active phase.

When we consider the effects of GH and IGF-1 hormones on cardiomyocytes, our results are not surprising and according to our study, closer follow-up may be required for the development of arrhythmia. When we evaluate all our findings, we recommend measuring the next generation ventricular repolarization parameters to determine the risk of cardiac arrhythmia in all patients with acromegaly.

Limitations

The main limitations of our study are that it is a retrospective study. Another limitation is that we have not evaluated the relation between ventricular arrhythmia and Tp-e interval, Tp-e/QT, and Tp-e/cQT ratio, as the patients were not followed up for a long time. Furthermore, the study population was not monitored for ventricular arrhythmic episodes or mortality prospectively. Large-scale prospective studies are needed to determine the predicted value of prolonged Tp-e interval and increased Tp-e/QT, and Tp-e/cQT.

CONCLUSION

For the first time, we have shown that Tp-e interval, Tp-e/QT, and Tp-e/cQT ratios are longer in patients with acromegaly. Our results show the increased ventricular repolarization heterogeneity in these patients and may contribute to understanding the pathophysiologic mechanisms of ventricular arrhythmia prevalence and cardiovascular mortality risk. Increased ventricular arrhythmia and sudden cardiac death frequency can be explained by transmural dispersion. Improvement in new ventricular repolarization parameters in patients with remission phase suggests

that mortality can be reduced with treatment in patients with acromegaly.

Ethical Approval

İnönü University Scientific Research and Publication Ethics Committee, Health Sciences Non-Invasive Clinical Research Ethics Committee. Date : 22-12-2020, Decision no.: 2020/1406

Authors' Contribution

Study Conception: HE, SG, BE, İŞ; Study Design: HE, SG, BE, İŞ; Supervision: HE, SG, BE, İŞ; Funding: HE, SG, BE, İŞ; Materials: HE, SG, BE, İŞ; Data Collection and/or Processing: HE, SG, BE, İŞ; Statistical Analysis and/or Data Interpretation: HE, SG, BE, İŞ; Literature Review: HE, SG, BE, İŞ; Manuscript Preparation: HE, SG, BE, İŞ and Critical Review: HE, SG, BE, İŞ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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