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Long Term Follow-Up of Unilateral Keratoconus Patients with Scheimpflug Camera

Tek Taraflı Keratokonusu Olan Hastaların Scheimpflug Kamera ile Uzun Dönem Takibi

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ABSTRACT Objective: The aim of the present study was to represent the long term follow-up of unilateral keratoconus (KC) patients with rotating Scheimpflug camera. **Material and Methods:** Medical records of 919 KC follow-up patients were reviewed. A total of 16 patients with at least 12 months of follow-up period were recruited. The KC positive eyes constituted the "KC group", normal fellow eyes constituted the "fellow eye group", and 24 eyes of 24 normal age-matched subjects "control group". All subjects underwent a complete ophthalmologic examination and were evaluated by rotating Scheimpflug imaging system. Also, 9 patients with at least 36 months of follow-up were evaluated separately. **Results:** The mean ages of KC and control groups were 30.38±9.34, 31.62±8.49, respectively (p= 0.664). The mean follow-up time in KC and control groups were 38.13±38.86 and 13.45±2.08, respectively. Demographic factors were similar between groups. At baseline examination, keratometry values , inferior superior difference at 4 mm (I-S), topometric indices and corneal thickness at apex and the thinnest point were significantly different between KC group and fellow eye group (p<0.05 for all comparisons). In the longer follow-up of 9 eyes in KC group for a mean of 59.67±26.68 months, KC progressed in 2 eyes, however the fellow eyes of these 9 remained stable. **Conclusion:** Although KC is known to be asymmetrical but bilateral, unilateral diseases might also be detected. Follow-up of unilateral KC patients is important to discrimiate asymmetrical keratoconus, which requires early progression analysis for crosslinking decision to protect better vision from really healthy fellow eyes that do not need intervention.

Keywords: Cornea; corneal topography; keratoconus

ÖZET Amaç: Bu çalışmanın amacı tek teraflı keratokonusu (KK) olan hastaların dönen Scheimpflug kamera ile elde edilen uzun dönem takip sonuçlarının sunulmasıdır. **Gereç ve Yöntemler:** KK tanılı 919 hastanın tıbbi verileri incelendi. En az 12 ay takibi olan 16 hasta çalışmaya alındı. KK olan hastalar "KK grubu", normal gözleri "diğer göz grubu" ve yaş ve cinsiyet uyumlu 24 normal olgunun 24 gözü "kontrol grubu" olarak kabul edildi. Tüm katılımcılara tam oftalmolojik muayene ile beraber Scheimpflug görüntüleme yapıldı. Ayrıca, en az 36 ay takibi olan 9 hasta ayrıca değerlendirildi. **Bulgular:** KK grubunda ve kontrol grubunda ortalama yaş sırasıyla 30,38±9,34, 31,62±8,49 (p=0,664) idi. Ortalama takip süresi KK ve kontrol gruplarında sırasıyla 38,13±38,86 ve 13,45±2,08 aydı. Demografik veriler iki grup arasında benzerdi. İlk muayenede keratometri değerleri, 4 mm de inferior superior farkı (I-S), topometric topometrik indeksler, apekste ve en ince noktadaki korneal kalınlık KK grubu ile diğer göz grubu arasında anlamlı derecede farklıydı (tüm karşılaştırmalarda p<0,05). KK grubunda daha uzun süre takip edilen 9 hastada ortalama 59,67±26,68 ay ortalama takip süresince 2 hastada KK ilerledi ancak tüm hastaların diğer gözleri stabil seyretti. **Sonuç:** KK iki taraflı ancak asimetrik olarak bilinmekle beraber tek taraflı görülebilir. Herhangi bir girişim gerektirmeyen tek taraflı KK hastalarını, iyi bir görme sağlamada çapraz bağlama tedavi kararı için erken progresyon analiz gerektiren asimetrik KK hastalarından ayırmak önemlidir.

Anahtar Kelimeler: Keratokonus; kornea; korneal topografi

Keratoconus (KC) is a non-inflammatory corneal disease characterized by corneal thinning, visual loss, severe myopic astigmatism and irregular astigmatism. In the diagnosis of KC although clinical examination gives essential clues, Placido disk-based corneal topography and rotating Scheimpflug imaging are needed to confirm diagnosis and for follow-up.[1,2] The disease is generally bilateral and might demonstrate asymmetric involvement. The fellow eye might show mildest form of the disease or may be totally normal.[3-5]

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With the development of highly sensitive diagnostic tools, unilateral KC ratio has changed significantly. Unilateral KC incidence was reported as 0.5% to 4.5%.[6-12] As KC is a multifactorial disease, genetic and enviromental factors cause progression, however the mechanism of the disease still remains unknown.[3,5,13,14]

Earlier, KC was diagnosed with clinical signs on slit-lamp examination and Placido disk-based corneal topography which examines only the anterior surface of the cornea. With the development of rotating Scheimpflug camera (Pentacam; Oculus Optikgerate GmbH, Wetzlar, Germany), which also examines the posterior surface of the cornea, KC has begun to be detected in earlier stages.[15,16]

The aim of this study was to evaluate the long term follow-up findings in keratometric, topometric and pachymetric parameters as measured with Pentacam in unilateral KC patients.

MATERIAL AND METHODS

This retrospective study was conducted at Department of Ophthalmology, Ege University School of Medicine and approved by local ethics committee of Ege University, İzmir (Number 18-9/21 and date 11.09.2018), also the study was conducted in accordance with the principles of Helsinki Declaration. The medical records of 919 patients with KC were revised. Although a total of 33 patients (3.59%) had unilateral KC at baseline examination, 16 of them were included in the study as they had a follow-up of at least one year. If the fellow eye had no clinical or topographical signs of KC the patient was diagnosed with unilateral KC. The control group was selected outpatient clinic among the patients with no refractive error who applied for a routine eye examination. All patients underwent a complete ophthalmic examination including the best corrected visual acuity (BCVA), anterior and posterior segment examination. Additionally, keratometric, topometric and pachymetric parameters obtained by Pentacam were evaluated. Pentacam measurements were performed in a dark room by an experienced researcher and only good-quality examinations were taken into consideration.

The patients were divided into 3 groups as KC eye of unilateral KC patients (KC group, 16 eyes), the normal fellow eyes of the patients with unilateral KC (fellow eye group, 16 eyes) and normal controls (control group, 24 eyes). Diagnosis and grading of KC were performed according to Amsler Krumeich classification system which is based on clinical signs (presence of corneal scarring, steepening of cornea, Fleischer ring or Vogt's stria), and keratometric, pachymetric and topometric parameters.[17] The patients with a previous eye surgery including cross-linking treatment, systemic and other ocular surface diseases such diabetes mellitus, dry eye syndrome were not included in the study. The keratometric parameters of the anterior surface [steep K (Ks), flat K (Kf), mean K (Km) and inferior-superior (I-S) difference at 4 mm], topometric indices (index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus-index (KI), center keratoconus-index (CKI), index of height asymmetry (IHA), index of height decentration (IHD), radii minimum (Rmin)), posterior elevation, corneal thickness at apex, the thinnest point and corneal volume (CV), minimum, maximum, average pachymetric progression indices were evaluated.

Statistical analyses were performed by using SPSS program v.20 (IBM corp. released 2011). The normality of all parameters were evaluated with Shapiro Wilk test. Comparisons between groups were determined by one way Anova test and Post hoc test was used for comparing two groups. Student t test and Friedman test were used to compare parameters which were obtained from the same patient at different times. A p value less than 0.05 was considered as statistically significant.

RESULTS

The mean ages of KC group and control group were 30.38±9.34 (range, 18-42), 31.62±8.49 (range, 20-45), respectively (p=0.664). Male to female ratio was 10/6 in KC group and 12/12 in the control group (p=0.372). The mean follow-up time in KC and the control groups were 38.13±38.86 (range, 12-120 months) and 13.45±2.08 (range, 11-18 months), respectively. The patients had no atopy history or rigid contact lens use at the first examination.

KC Group vs Fellow Eye Group: There was not a statistically significant difference between groups in terms of KI (p=0.124), IHD (p=0.333), PE (p=0.066)

and CV (p=0.604). However Ks, Kf, Km, I-S, ISV, IVA, CKI, IHA, Rmin, mean PE, minimum, maximum, average pachymetric progression indices, corneal thickness at apex and the thinnest point were significantly different (p<0.05 for all mentioned parameters) (Table 1). At the last visit, all parameters except CV were significantly different between KC and fellow eye groups (p<0.05) (Table 2).

TABLE 1: Baseline examination.

	KC Group	Fellow Eye Group	Control Group	KC vs Fellow Eye	KC vs Control	Fellow Eye vs Control
	Mean±SD (Min-Max)			p value		
Keratometry of anterior surface						
Ks	51.9±6.64 (43.1-67.1)	44.65±1.55 (41.3-46.6)	43.80±1.52 (41.5-46.3)	<0.001	<0.001	0.866
Kf	47.66±5.41 (40.2-61)	43.32±1.64 (40.4-45.8)	42.90±1.49 (40.0-45.3)	0.003	<0.001	0.947
Km	49.68±5.99 (42.2-64.1)	43.97±1.48 (41-46)	43.34±1.48 (41.1-45.7)	<0.001	<0.001	0.930
I-S	7.12±7.19 (-11.8-18.86)	1.36±1.21 (-1.33-2.73)	0.26±0.79 (-1.13-2.23)	<0.001	<0.001	0.671
Topometric index						
ISV	84.69±46.82 (23-175)	25.50±14.44 (15-76)	16.03±4.67 (9-36)	<0.001	<0.001	0.577
IVA	0.83±0.44 (0.11-1.76)	0.23±0.09 (0.09-0.51)	0.13±0.58 (0.04-0.33)	0.022	0.020	0.987
KI	1.22±0.19 (0.87-1.66)	1.05±0.26 (1-1.10)	1.02±0.20 (0.98-1.06)	0.124	0.096	0.996
CKI	1.06±0.57 (1-1.18)	1.00±0.02 (0.99-1.09)	0.99±0.006 (0.98-1.01)	<0.001	<0.001	0.107
IHA	35.49±35.19 (4.30-130.9)	8.66±5.38 (2.00-21.10)	3.20±3.35 (0.10-14.9)	<0.001	<0.001	0.666
IHD	0.09±0.76 (0.004-0.32)	0.02±0.008 (0.006-0.03)	0.007±0.005 (0.001-0.03)	0.333	0.550	0.897
Rmin	6.12±0.98 (4.56-7.52)	7.28±0.44 (5.94-7.90)	7.59±0.28 (7.16-8.09)	<0.001	<0.001	0.335
Posterior elevation						
Mean	6.01±0.38 (5.23-6.74)	6.33±0.22 (5.97-6.67)	6.44±0.26 (5.91-6.94)	0.066	<0.001	0.237
Corneal thickness						
Apex	492.85±34.86 (407-580)	529.19±19.84 (492-560)	558.24±29.71 (514-624)	0.003	<0.001	0.001
Thinnest	462.25±47.83 (356-523)	522±20.23 (490-557)	555.82±29.26 (510-619)	<0.001	<0.001	0.001
CV	59.16±2.93 (55.10-65.50)	60.41±2.82 (56-64.10)	61.41±4.04 (55.30-71.70)	0.604	0.003	0.044
Pachymetric progression index						
Maximum	3.26±1.87 (1.20-7.20)	1.58±0.33 (1.00-2.20)	1.20±0.19 (0.70-1.60)	<0.001	<0.001	0.440
Minimum	1.62±1.07 (0.70-4.20)	0.81±0.15 (0.50-1.10)	0.68±0.15 (0.40-1.00)	0.001	<0.001	0.463
Average	2.38±1.41 (0.90-5.40)	1.16±0.15 (0.80-1.40)	0.94±0.15 (0.50-1.20)	<0.001	<0.001	0.747

KC: Keratoconus, SD: Standard deviation, Ks: Steep K, Kf: Flat K, Km: Mean K, I-S: Inferior-superior, ISV: Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus-index, CKI: Center keratoconus-index, IHA: Index of height asymmetry, IHD: Index of height decentration, Rmin: Radii minimum, CV: Corneal volume.

TABLE 2: Last visit examination.

	KC Group	Fellow Eye Group	Control Group	KC vs Fellow Eye	KC vs Control	Fellow Eye vs Control
	Mean±SD (Min-Max)			P value		
Keratometry of anterior surface						
Ks	52.29±7.19 (44.10-68)	44.69±1.48 (41.9-47)	43.80±1.52 (41.50-46.30)	<0.001	<0.001	0.840
Kf	47.65±6.21 (39-61)	43.45±1.54 (40.30-45.8)	42.90±1.49 (40.4-45.3)	0.001	0.001	0.880
Km	49.81±6.62 (42-64)	44±1.40 (42-46.1)	43.33±1.48 (41.1-45.7)	<0.001	<0.001	0.886
I-S	7.31±8.93 (-18.47-19.30)	1.42±1.24 (-1.33-2.96)	0.26±0.79 (-1.13-2.23)	<0.001	<0.001	0.809
Topometric index						
ISV	92.25±51.13 (26-187)	26±14.85 (17-78)	16.03±4.67 (9-36)	<0.001	<0.001	0.606
IVA	0.91±0.55 (0.13-1.89)	0.23±0.09 (0.09-0.54)	0.13±0.05 (0.04-0.33)	<0.001	<0.001	0.619
CI	1.23±0.21 (0.83-1.65)	1.04±0.03 (0.98-1.11)	1.02±0.02 (0.98-1.06)	<0.001	<0.001	0.820
CKI	1.05±0.06 (0.94-1.17)	1.01±0.24 (0.98-1.09)	0.99±0.006 (0.98-1.01)	<0.001	<0.001	0.608
IHA	34.61±25.83 (0.4-92.8)	8.75±6.61 (1.50-19.9)	3.54±3.35 (0.10-14.9)	<0.001	<0.001	0.433
IHD	0.13±0.08 (0.006-0.33)	0.02±0.01 (0.007-0.04)	0.007±0.005 (0.001-0.03)	<0.001	<0.001	0.585
Rmin	6.08±0.99 (4.45-7.6)	7.26±0.50 (5.68-7.79)	7.59±0.28 (7.16-8.09)	<0.001	<0.001	0.263
Posterior elevation						
Mean	5.83±0.66 (4-6.7)	6.25±0.31 (5.88-7)	6.44±0.26 (5.91-6.94)	0.013	<0.001	0.463
Corneal thickness						
Apex	492.88±48.26 (398-575)	528.75±35.63 (480-619)	558.24±29.71 (514-624)	0.009	<0.001	0.018
Thinnest	466.94±66.02 (328-570)	519.50±37.66 (467-614)	555.82±29.26 (510-619)	0.002	<0.001	0.017
CV	60.59±6.85 (52-80)	60.53±3.67 (55-69)	61.41±4.03 (55.30-71.70)	0.994	0.284	0.330
Pachymetric progression index						
Maximum	3.61±2.39 (1.3-10)	1.81±0.56 (1-2.8)	1.25±0.19 (0.70-1.60)	<0.001	<0.001	0.307
Minimum	1.69±1.31 (0.00-5)	1.04±0.26 (0.8-2)	0.68±0.15 (0.40-1.00)	0.006	<0.001	0.416
Average	2.39±1.51 (1-7)	1.19±0.21 (1-1.7)	0.94±0.16 (0.50-1.2)	<0.001	<0.001	0.742

KC: Keratoconus, SD: Standard deviation, Ks: Steep K, Kf: Flat K, Km: Mean K, I-S: Inferior-superior, ISV: Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus-index, CKI: Center keratoconus-index, IHA: Index of height asymmetry, IHD: Index of height decentration, Rmin: Radii minimum, CV: Corneal volume.

KC Group vs Control Group: There was no statistically significant difference between KC group and control group in terms of KI (p=0.096) and IHD (p=0.550). The remaining parameters, Ks, Kf, Km, I-S, ISV, IVA, CKI, IHA, Rmin, mean PE, minimum, maximum, average pachymetric progression indexes, corneal thickness at apex and the thinnest point and CV were significantly different between groups

TABLE 3: Long term follow-up results of 9 patients.

	Km mean±SD (min-max)	I-S mean±SD (min-max)	ISV mean±SD (min-max)	IHA mean±SD (min-max)	IHD mean±SD (min-max)	Rmin mean±SD (min-max)	PE mean±SD (min-max)	CCTmin mean±SD (min-max)	PPI (mean±SD) (min-max)
KC	50.33±6.57 (43-64)	8.49±7.71 (2.2-25.2)	99.33±40.84 (40-154)	28.11±19.68 (6-65)	0.13±0.06 (0.04-0.22)	6±0.71 (5-7)	5.78±0.67 (5-7)	470.78±72.9 (336-570)	2.33±1.12 (1-5)
Fellow	44.11±1.76 (41-46)	3.03±5.08 (-0.60-16.10)	21.33±3.7 (17-26)	6.22±5.17 (2-18)	0.018±0.01 (0.006-0.04)	7.33±0.5 (7-8)	6.22±0.44 (6-7)	522.4±48.91 (467-614)	1.11±0.33 (1-2)
p value	0.04	0.015	<0.001	0.002	<0.001	0.001	0.19	0.11	0.003

KC: Keratoconus, SD: Standard deviation, Km: Mean K, I-S: Inferior-superior, ISV: Index of surface variance, IHA: Index of height asymmetry, IHD: Index of height decentration, Rmin: Radii minimum, PE: Posterior elevation, CCTmin: Central corneal thickness minimum, PPI: Pachymetry progression index.

($p<0.05$). In the follow-up examination, CV was similar between groups ($p=0.284$). Ks, Kf, Km, I-S, ISV, IVA, CKI, IHA, IHD, Rmin, mean PE, minimum, maximum, average pachymetric progression indices and corneal thickness at apex and the thinnest point were statistically different between groups ($p<0.05$).

Control Group vs Fellow Eye Group: No significant difference except corneal thickness parameters was detected between these two groups. Corneal thickness in apex, the thinnest point and CV were significantly higher in control group ($p<0.05$). However, in the last visit, CV was similar as the other parameters (Ks, Kf, Km, I-S, ISV, IVA, CKI, IHA, IHD, Rmin, mean PE, minimum, maximum, average pachymetric progression indices) ($p>0.05$). However the corneal thickness at the apex and the thinnest point pachymetry were higher in control group than the fellow eye group (p values 0.018 and 0.017, respectively).

Nine of the KC group patients had at least 36 months of follow-up and they were evaluated separately. Mean follow-up time was 59.67±26.68 (range 36-120) months and the mean age of the patients was 32.67±8.83 (range, 18-49) years at baseline examination. When Pentacam values of KC group were compared with the fellow eye group, anterior surface keratometry parameters, Ks, Kf, Km and I-S; topometric indices including ISV, IVA, IHA and Rmin; PI average were significantly different ($p<0.05$) (Table 3). One patient among these 9 long term follow-up patients progressed from stage 1 KC to stage 2, and another patient progressed from stage 2 KC to stage 3. The remaining 7 patients' KC stages did not change. None of the fellow eyes of these patients developed KC in the long term.

DISCUSSION

KC is a progressive disease characterized with corneal ectasia, protrusion, thinning and severe secondary myopic astigmatism. As the early KC mainly effects posterior cornea, it was hard to diagnose prior to development of Scheimpflug or slit-scan imaging - enabling posterior corneal surface analyse. Keratoconus incidence is approximately one per 2000 in general population and prevalance is 54.5 per 100.000.[3] KC is generally known as a bilateral disease. True unilateral KC is very rare. Imbornoni et al. reported 5 cases with advanced KC in one eye and normal fellow eyes.[18] They followed those patients for a mean of 59 months (range 39-86 months), and reported that none developed KC in their fellow eyes. Likewise, 9 of the 33 patients in the present study were followed up at for least 36 months (59.67±26.68; range 36-120 months), and no pathological finding supporting KC clinically or with Pentacam measurements was detected during this period.

Etiology of KC is multifactorial genetical association and some systemic disorders such as Down syndrome were reported to be responsible for disease emergence and progress.[3,13,19] Mechanical trauma (eye rubbing, contact lens use) and atopy are the other enviromental risk factors.[3,14] Although the KC is initially unilateral in 14% of the patients, only in a small portion of the patients (0.5-4%) the clinical course is unilateral.[7,8,11,19] Li et al. reported that nearly 50% of the patients with unilateral KC pro-

gressed to clinically significant KC in their precalled normal fellow eye in a mean follow-up period of 16.69 years.[18] In the present study, KC ratio was 3.59% at the initial examination and this ratio is lower when compared to previous studies. But differently, in this study none of the patients progressed to clinically significant KC in the follow-up. It may be due to the relatively shorter follow-up period or due to the absence of atopy and contact lens use. Holland et al. claimed that all unilateral KC patients might progress to bilateral KC with long enough follow-up time.[7] On the other hand, it may be possible to prevent or slow down the disease progression with the control of environmental factors such as mechanical trauma or atopy.[14,20] Gordon-Shaag et al. reported that asymmetric involvement of eyes in KC is related to habitually rubbing one eye more vigorously.[14] Additionally, Bawazeer et al. found an odds ratio of 3.98 between eye rubbing and KC.[20] As a limitation of the study, we take no account of eye rubbing for progression or as a prognostic factor.

In this era, KC diagnosis is based on clinical examination and mainly Scheimpflug imaging. Mihaltz et al. and Kamiya et al. suggested that mean keratometry, posterior and anterior elevation and pachymetric values can discriminate KC eyes from normal ones.[21,22] Muftuoglu et al. declared that to differentiate KC eyes from normal fellow eyes, all parameters had high sensitivity and specifity, but pachymetric parameters had the highest value.[23] Also, in comparison of the fellow eyes of KC patients with normal controls, they detected the highest sensitivity and specifity in topographic parameters and pachymetric progression index. In another study by de Sanctis et al. it was postulated that posterior corneal elevation discriminates KC from normal corneas, but in subclinical KC this effect is not so clear.[24] In the present study, most of the parameters in KC eyes were significantly different from the fellow eyes of the patients and normal controls which support the study by Sanctis et al. Although posterior elevation values at baseline examination were similar between KC and fellow eyes, in the follow-up they were significantly different.[24] Pachymetric progression indices of KC eyes were significantly different from fellow eyes and control eyes in both examinations as suggested by Muftuoglu et al.[23]

In a few reports, parameters evaluated with Pentacam were significantly different between KC and fellow normal eyes.[23] Also, a statistically significant difference between fellow eyes and normal controls were documented.[23,25] However, there are some studies reporting an opposite data. Bae et al. found a statistically significant difference between KC vs fellow eyes in most of the parameters, but in comparison of fellow eyes of KC patients with normal controls, no difference was found in all parameters except IVA, IHD, posterior and anterior elevation difference.[15] Kovacs et al. obtained similar results as well.[6] But, differently they reported limited number of parameters. In their study, in comparison of KC eyes with fellow normal eyes and normal controls showed a statistically significant difference at baseline and follow-up examinations in almost all parameters. Additionally, fellow eyes of KC patients were statistically similar to normal controls except corneal thickness at the apex and the thinnest point in both examinations. Orucoglu evaluated 22 patients diagnosed with unilateral KC and reported statistically similar results between fellow eyes of KC patients and normal controls.[26] The results of the present study, support the abovementioned studies. Safarzadeh et al. aimed to detect different stages of KC eyes with a new camera system.[27] In the light of the study, the determined corneal thickness and posterior elevation were found to be important parameters to diagnose different stages of KC. Corneal thickness at the apex and the thinnest point were significantly different between groups, but posterior elevation was different only between KC vs normal controls at baseline. However, at follow-up examination, PE was significantly different between KC vs fellow eye and KC vs normal controls.

CONCLUSION

KC is a progressive disease with the risk of visual loss. Although, the disease is known to be bilateral, unilateral diseases might also be detected. Follow-up of these unilateral KC patients is important to detect any early KC formation in the fellow eye. In the present study, none of the unilateral 16 KC patients (1.74%) developed KC in the fellow eye in a mini-

mum of 12 months. Moreover, 9 unilateral KC patients (0.97%) did not develop KC in the fellow eyes during a longer follow-up of minimum 36 months. Despite the small unilaterality percentage in keratoconus, reporting the presence of real unilaterality has an important moral support for young patients with this progressive disease. This might be related to even the course of the disease or to the taken precautions, such as preventing eye rubbing.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Melis Palamar;* ***Design:*** *Melis Palamar;* ***Control/Supervision:*** *Sait Eğrilmez, Ayşe Yağcı;* ***Data Collection and/or Processing:*** *Nergiz İsmayilova, Cumali Değirmenci;* ***Analysis and/or Interpretation:*** *Melis Palamar, Cumali Değirmenci;* ***Literature Review:*** *Nergiz İsmayilova, Cumali Değirmenci;* ***Writing the Article:*** *Melis Palamar, Cumali Değirmenci;* ***Critical Review:*** *Sait Eğrilmez, Ayşe Yağcı;* ***References and Fundings:*** *Cumali Değirmenci;* ***Materials:*** *Cumali Değirmenci.*

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