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Flow diverter stent treatment for unruptured supraclinoid segment internal carotid artery aneurysms: a Turkish multicenter study

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OBJECTIVE Despite the relatively high success of surgical clipping of supraclinoid segment aneurysms of the internal carotid artery (ICA), flow diverter (FD) stent therapy is becoming increasingly used for these aneurysms. This study aims to evaluate the characteristics of FD placement for unruptured ICA supraclinoid segment aneurysms at 6 different centers with different experience levels in Türkiye.

METHODS In this retrospective, multicenter study, the authors reviewed the demographic information, aneurysm shape/dimensions (neck, aspect ratio, dome/neck ratio, and maximum diameter), preoperative antiplatelet regimen, FD stent brand, perioperative complications, intervention time, clinical (modified Rankin Scale) and radiological (O'Kelly-Marotta [OKM] grading scale) outcomes, and follow-up time of 54 patients.

RESULTS A total of 55 interventions for 61 aneurysms (58 supraclinoid ICA aneurysms) were performed in the 54 patients included in the study. The female/male ratio in this population was 44/10, and the mean age was 53.5 ± 13.6 (range 21–82) years. The most common form and location of the aneurysms were saccular 91.4% (53/58) and ophthalmic segment 69% (40/58), respectively. The preferred antiplatelet regimen was acetylsalicylic acid plus ticagrelor 50% (27/54). The overall complication rate was 25.5% (14/55), and the mean follow-up time was 25.76 ± 17.88 months. The successful radiological outcome (OKM grade C or D) rate at the 6-month follow-up was 92.6%. No perioperative complications led to any permanent or transient neurological deficit.

CONCLUSIONS The results of this first multicenter study evaluating FD stent use for unruptured ICA supraclinoid segment aneurysms showed that FD stent treatment is a feasible method for replacing clipping and coil embolization with manageable complications and a high success rate.

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KEYWORDS aneurysm; supraclinoid segment; flow diverter stent; unruptured; endovascular

Open microsurgical clipping has long been accepted as the primary surgical treatment for internal carotid artery (ICA) aneurysms.[1] However, at the outset of the endovascular era, the ISUIA (International Study of Unruptured Intracranial Aneurysms) trial[2] and the California Unruptured Aneurysm Database[3] reported lower risks of morbidity and mortality with the endovascular treatment (EVT) of ICA aneurysms. In the early stages of EVT, the aneurysm fundus was filled with liquid or metallic coils, or the parent artery was sacrificed.[4] In contrast, flow diversion therapy aims at progressive aneurysm thrombosis and parent artery reconstruction with neointi-

ABBREVIATIONS DSA = digital subtraction angiography; EVT = endovascular treatment; FD = flow diverter; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale; OKM = O'Kelly-Marotta; PTIA = partially thrombosed intracranial aneurysm; P2Y12 = P2Y12 reaction units.

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mal proliferation rather than direct aneurysm embolization.[5]

Flow diverter (FD) treatment, a new approach to aneurysm treatment introduced in the early 2000s,[6] is currently used worldwide. FD stents were initially designed and licensed for large, intracranial, and unruptured ICA aneurysms.[5] To this end, FDs have also been combined with coiling for ruptured or unruptured aneurysms[7–9] and blister-like/dissecting aneurysms.[10] Although van Rooij et al.[11] considered EVT dangerous and not yet an alternative for unruptured ICA aneurysms in 2013, EVT is now preferred as first-line treatment in many centers.[7] In addition to technological developments, the increasing clinical experience in EVT has made this an option for aneurysm treatment. This study aimed to evaluate the use of FD application for unruptured ICA supraclinoid segment aneurysms at 6 different centers with different experience levels in Türkiye.

Methods

Study Design

The supraclinoid segment of the ICA was defined as the part extending from the point where the artery enters the subarachnoid space to the bifurcation of the ICA and is divided into three segments: ophthalmic, communicating, and choroidal.[12]

This retrospective study included patients who underwent flow diversion as the initial treatment for ICA supraclinoid segment aneurysms between 2015 and 2022 at 6 centers in Türkiye. The 54 consecutive patients had 61 aneurysms: 58 supraclinoid segment aneurysms, 2 cavernous segment aneurysms, and 1 middle cerebral artery (MCA) bifurcation aneurysm. All aneurysms were treated with FD stents in 55 interventions. Indications for FD placement were defined as follows: dome size > 10 mm, neck > 4 mm or dome/neck ratio < 2, and aneurysm location in the ICA supraclinoid segment. In case of a tandem aneurysm, the chosen stent length had to cover ≥ 2 aneurysm necks. Adjunctive coil embolization was not performed in any patient. In cases in which stagnation could not be achieved with a single FD (e.g., when the stent fell into the aneurysm or could not adequately close the neck), a second stent was deployed. All procedures were performed in a single session. Retrospectively collected data included patient demographics (sex, age, symptoms, comorbidities, and preoperative antiplatelet usage), aneurysm characteristics (blister-like, fusiform, or saccular shape; neck size; aspect ratio [height/neck]; dome/neck ratio; and maximum diameter), antiplatelet regimen, periprocedural details (intervention time), FD stent brand, perioperative complications, clinical and radiological outcomes, and follow-up time. Written informed consent was obtained from either patients or their relatives, which implies that their medical records and images can be used for research in the future. The study was approved by the local institutional ethics committee.

Endovascular Procedure

During the preprocedural period, cranial CT, contrast-enhanced MRI, and diagnostic 6-vessel digital subtraction angiography (DSA) were performed in all patients. All interventions were performed with the patient under general anesthesia via the femoral approach using flat-detector monoplane angiography units. First-generation cephalosporin was administered 1 hour before surgery and for the next 3 days. In addition, trimethoprim-sulfamethoxazole was administered to patients with a penicillin allergy.

After the femoral puncture, a bolus of 4000–5000 IU of unfractionated heparin was injected intravenously. During the procedure, the target activated clotting time was > 250 seconds, and an additional 1000 IU of heparin was administered each hour. Moreover, 6-Fr guide catheters were positioned into the targeted cervical ICA segment. The FD was deployed through a triple coaxial system with a 6-Fr guide catheter (Heety, Zhejiang Barty Medical Technology), various sizes of distal access catheters, and microcatheters. The FD was fully deployed across the aneurysm neck. The Surpass Evolve (Stryker Neurovascular), FRED (MicroVention), Derivo (Acandis), and Pipeline Flex (Medtronic) were used in the procedures. DynaCT was used to check whether the stent covered the aneurysm neck. If vasospasm occurred during catheterization, nimodipine (Nimotop, Bayer) was injected through the catheter. Hemostasis was maintained at the access site with a 7-Fr, 11-cm sheath. Patients recovered in the intensive care unit and were tested for the appearance of new neurological deficits.

Antiplatelet Regimen

Premedication consisted of dual antiplatelet therapy with aspirin (100–300 mg) (Coraspin, Bayer Turk) and 75 mg clopidogrel (Plavix, Sanofi S.A.) or 90 mg ticagrelor (Brilinta, AstraZeneca AB) or 10 mg prasugrel (Effient, Daiichi Sankyo Europe GmbH) for ≥ 5 days before surgery. On the day of the intervention, platelet function was monitored with aspirin and the P2Y12 response assay (VerifyNow, Accumetrics). The periprocedural target aspirin reaction units and P2Y12 reaction units (PRU) were < 500 and 60–220, respectively. Therefore, for patients with aspirin reaction units > 550, the daily aspirin dose increased to 200 mg. In patients hyporesponsive to clopidogrel, it was discontinued and a loading dose of 20 mg of prasugrel was administered continued by 3.75 mg after the intervention. In contrast, the clopidogrel dose was reduced in patients with PRU < 60 (hyperresponders). In centers in which PRU could not be evaluated, prasugrel or ticagrelor was administered instead of clopidogrel. Clopidogrel or ticagrelor/prasugrel was discontinued 6 months after the procedure; however, the use of aspirin was continued throughout the patients' lifetime.

Follow-Up Assessment

Cranial CT and diffusion MRI were performed within 24 hours after interventions for hemorrhagic and ischemic complications. All patients underwent MR angiography 3 months postoperatively and DSA at 6 months. The radiological outcome was evaluated according to the O'Kelly-Marotta (OKM) grading scale[13] on DSA. The grades of occlusion were as follows: A, total filling (> 95%); B, subtotal filling (5%–95%); C, entry remnant (< 5%); and D, no filling (0%). An OKM grade of C or D was defined as ad-

equate aneurysm occlusion. Patients with adequate occlusion were followed up by annual MR angiography. Clinical outcomes were evaluated using the modified Rankin Scale (mRS). Major procedural complications were those resulting in death or morbidity with an mRS score > 2. Conversely, good clinical outcome was defined as an mRS score of 0 or 1.

Statistical Analysis

SPSS (version 11.5, SPSS Inc.) was used for data analysis. Mean ± standard deviation and median (minimum–maximum) were used as descriptors for quantitative variables, and the number of patients, aneurysms, or interventions (percentage) was used for qualitative variables. Fisher's exact test was used to examine the relationship between two qualitative variables with normal distribution, and the Wilcoxon signed-rank test was used when the assumption of normal distribution was not met. The statistical significance level was $p < 0.05$.

Results

Baseline Population and Aneurysm Features

Forty-four (81.5%) of the 54 patients included in the study were women. The mean age was 53.52 ± 13.63 years. The most common complaints at presentation to the clinics were headache (61.1%, 33/54), dizziness (18.5%, 10/54), diplopia (5.6%, 3/54), and tinnitus (3.7%, 2/54). Aneurysms were incidentally detected in 6 (11.1%) patients. The most common comorbidity was hypertension (46.3%, 25/54). Other frequent comorbidities were coronary artery disease (24.1%, 13/54), diabetes mellitus (18.5%, 10/54), thyroid dysfunction (9.3%, 5/54), asthma (7.4%, 4/54), polycystic kidney disease (1.9%, 1/54), and the presence of a solitary congenital kidney (1.9%, 1/54). Four (7.4%) patients had used single or dual antiplatelet therapy preoperatively for different comorbidities.

The most common aneurysm shapes were saccular (91.4%, 53), fusiform (5.2%, 3), and blister-like (3.4%, 2). Sixty-one aneurysms were present in the 54 patients. There were 58 aneurysms in the supraclinoid segment: 40 (69%) in the ophthalmic segment, 15 (25.9%) in the communicating segment, and 3 (5.2%) in the choroidal segment. Two of the aneurysms in the communicating segment were partially thrombosed intracranial aneurysms (PTIAs). In addition, 4 patients had 2 ipsilateral aneurysms, 1 had 3 ipsilateral aneurysms, and 1 had bilateral aneurysms. The mean aneurysm neck size, aspect ratio, and dome/neck ratio were 4.44 ± 2.3 mm, 1.46 ± 0.67, and 1.39 ± 0.66, respectively. The mean maximum aneurysm diameter was 7.18 ± 6.18 mm.

Regarding dual antiplatelet therapy, acetylsalicylic acid and ticagrelor (50%, 27/54) were preferred, followed by clopidogrel (35.2%, 19/54) and prasugrel (14.8%, 8/54). Four patients who were hyporesponsive to clopidogrel received prasugrel as well. All patient and aneurysm characteristics are shown in Table 1.

TABLE 1. Demographic data of patients and radiological features of aneurysms

	Value
Sex	
Female	44 (81.5)
Male	10 (18.5)
Age, yrs	
Mean ± SD	53.52 ± 13.63
Median (range)	52.00 (21.00–82.00)
Aneurysm shape	
Saccular	53 (91.4)
Fusiform	3 (5.2)
Blister-like	2 (3.4)
Aneurysm location	
Ophthalmic	40 (69.0)
Communicating	15 (25.9)
Choroidal	3 (5.2)
Aneurysm neck size, mm	
Mean ± SD	4.44 ± 2.30
Median (range)	4.00 (1.20–12.00)
Aneurysm aspect ratio (height/neck)	
Mean ± SD	1.46 ± 0.67
Median (range)	1.37 (0.55–3.55)
Aneurysm dome/neck ratio	
Mean ± SD	1.39 ± 0.66
Median (range)	1.35 (0.46–3.88)
Aneurysm max diameter, mm	
Mean ± SD	7.18 ± 6.18
Median (range)	5.15 (2.20–35.00)
Dual-antiplatelet therapy	
ASA + ticagrelor	27 (50.0)
ASA + clopidogrel	19 (35.2)
ASA + prasugrel	8 (14.8)

ASA = acetylsalicylic acid.
Values represent the number of patients (%) unless stated otherwise.

Technical Details of the Procedure

The most preferred FD stent brand was Derivo (38.7%, 24), followed by FRED (33.9%, 21), Surpass Evolve (25.8%, 16), and Pipeline Flex (1.6%, 1). Multilayer stents (two stents) were used in 8 patients; the neck of the aneurysm could not be closed entirely with the first stent in 5 patients, the first stent prolapsed into the aneurysm in 2 patients, and a concomitant aneurysm in a different segment was found in 1 patient. The mean intervention time was 113.78 ± 28.60 minutes.

Periprocedural Complications

Fourteen (25.5%) complications occurred in 55 interventions. Intraoperative vasospasm was observed in 6 patients, which resolved in all patients after a Nimotop injection. A perioperative hemorrhagic/ischemic complication was detected in 4 patients, for which a conservative approach was applied. In 1 patient, impending flow was observed in the anterior cerebral artery during the procedure, but retrograde flow was observed in the opposite

TABLE 2. Perioperative findings and data at follow-up

	Value
FD brand	
Derivo	24 (38.7)
FRED	21 (33.9)
Surpass Evolve	16 (25.8)
Pipeline	1 (16)
Intervention time, mins	
Mean ± SD	113.78 ± 28.60
Median (range)	109.50 (65.00–180.00)
Complication*	
No	41 (74.5)
Yes	14 (25.5)
Preop mRS score	
Mean ± SD	0.76 ± 0.87
Median (range)	1.00 (0.00–3.00)
30-day mRS score	
Mean ± SD	0.72 ± 0.86
Median (range)	1.00 (0.00–3.00)
6-mo OKM grade	
Grade A–B	4 (7.4)
Grade C–D	50 (92.6)
Follow-up time, mos	
Mean ± SD	25.76 ± 17.88
Median (range)	20.00 (3.00–64.00)

Values represent the number of patients or interventions (%) unless stated otherwise.
* Values represent the number of interventions (%).

ICA. In-stent thrombosis developed in 1 patient, but no additional intervention was planned since the opposite ICA provided the flow. The MCA flow pattern was impaired in 1 patient at the 6-month follow-up DSA, but because the patient was asymptomatic, the condition was treated conventionally. In 1 patient, extravasation from the femoral artery was detected because of hypotension and tachycardia during the early postoperative period. The patient was treated with a covered stent application following a blood transfusion. No death or permanent/transient neurological deficit was detected among the recorded complications (Table 2).

Clinical and Radiological Follow-Up Outcomes

Good clinical outcome (mRS score of 0 or 1) was achieved in 41 patients (76%). The mean mRS score in the preoperative period was 0.76 ± 0.87. Changes in mRS scores were observed in 6 patients; half improved and the other half worsened. The mean mRS score was 0.72 ± 0.86 on the 30th postoperative day. The successful aneurysm occlusion rate (OKM grade C or D) was 92.6% (50/54) on 6-month DSA. For 3 saccular and 1 fusiform aneurysms, successful occlusion could not be achieved (OKM grade A or B). In the saccular aneurysms, DynaCT showed that the aneurysm neck was covered but occlusion could not be achieved. In the fusiform aneurysm, there was still blood flow to the aneurysm from the distal end of the stent at the ICA bifurcation. Multilayer FD stent treatment was recommended for all 4 patients, but they refused the treatment (Table 2). No significant difference in mRS scores between the preoperative period and 30 days postoperatively was observed in patients with complications ($p > 0.99$; Table 3), and there was no difference according to the OKM grade or FD stent brands ($p = 0.178$; Table 4).

TABLE 3. Change in mRS score in patients with complications

	Mean ± SD	Median (range)	p Value
Preop mRS score	0.69 ± 1.03	0.00 (0.00–3.00)	>0.99*
30-day score	0.69 ± 1.10	0.00 (0.00–3.00)	

* Wilcoxon signed-rank test.

Discussion

FD stents can be placed in unruptured aneurysms in the supraclinoid segment of the ICA because of the difficulty of surgical access or the wide neck/irregular shape of the aneurysms. This study achieved a success rate of 92.6% when treating 58 supraclinoid ICA aneurysms in 54 patients, producing no permanent or transient neurological deficits. This first multicenter study applying FD stents specifically for unruptured ICA supraclinoid segment aneurysms showed that FD stents result in manageable complications and are an effective treatment method with low morbidity and mortality for this type of aneurysm.

Several clinical trials of the Pipeline,[14,15] FRED,[16] Surpass,[17] and Derivo[18] devices have evaluated the efficacy of FD stents in anterior and posterior circulation aneurysms. These stents, designed initially for complex aneurysms (giant, fusiform, and blister-like) in clinical use, over time have been applied to aneurysms suitable for surgical clipping or coiling.[4] During coiling or clipping, the main goal is to exclude the aneurysm fundus from the circulation to preserve other arteries branching from the parent artery. These branches may be occluded by FD stents causing neointimal proliferation. However, even with multilayer FD stenting, occlusion has been shown to be very rare in the ophthalmic artery, superior hypophyseal artery, posterior communicating artery, or anterior choroidal artery.[14,19–21] In contrast, occlusion can be observed

TABLE 4. Relationship between FD brand and OKM grade

FD Brand	OKM Grade		p Value
	A–B	C–D	
Derivo	2 (10.0)	18 (90.0)	0.178*
FRED	0 (0.0)	21 (100.0)	
Pipeline	0 (0.0)	1 (100.0)	
Surpass Evolve	2 (16.7)	10 (83.3)	

Values represent the number of patients (%) unless stated otherwise.
* Fisher's exact test.

in perforating arteries.[22] Although impending flow can be observed in the ophthalmic artery with a Pipeline embolization device, it does not cause clinical sequelae.[20,23] In our series, no permanent or temporary occlusion was observed in any branches in the supraclinoid segment. Therefore, the surgeon's choice was the main factor in choosing the FD brand in our series. Despite the limited number of cases in our study, no significant difference was found between stent brands in complete occlusion rates, functional outcome, and complications, which is similar to previous reports.[24]

There is no clear consensus for the treatment of blister-like aneurysms. These aneurysms originate from nonbranching points of the supraclinoid ICA probably by dissection, as fragile and false walls without a well-defined neck are characteristic features of blister-like aneurysms.[25] Regardless of the treatment option, their treatment has high complication and rebleeding rates.[26] In general, multilayer[26] or covered[27] stents are recommended for ruptured blister aneurysms. We could not find any publications in the literature review for unruptured blister-like aneurysms. In our series, a single FD stent was used in two unruptured aneurysms achieving total occlusion (OKM grade D).

We detected three challenges when placing FD stents in the patients in this study. First, in giant aneurysms, there may be prolapse of the stent into the aneurysm during FD deployment. In this case, limited methods can be recommended for rescue: filling the aneurysm fundus by supporting the stent with coil embolization, applying a telescopic stent, or parent artery occlusion.[28] Prolapse of the stent occurred in two giant aneurysms in our series, which was managed by telescopic stent application. No complications were observed in either patient. Second, we encountered 2 PTIAs. These aneurysms are usually large or giant and may present with subarachnoid hemorrhage, but findings due to mass effects are more common.[29] While mortality rates with surgical clipping have been reported to be 6%,[30] growth and recanalization after endovascular coil embolization rates can reach 78%.[31] Foreman et al.[32] treated 51 PTIAs with flow diversion with a successful occlusion rate of 77.1%. The rate of complete aneurysm occlusion was lower in patients with an aneurysm thrombosis rate > 50% before treatment. The rate of symptomatic ischemic complications was 7.8%, and mortality was observed in 2 (4.2%) patients in their study. In our series, complete occlusion was achieved in the 2 PTIAs and no thromboembolic complications were observed in the perioperative period. Third, we encountered tandem ICA aneurysms. A complete occlusion rate of 85% was reported in a series of 47 aneurysms that underwent flow diversion for tandem ICA aneurysms;[33] thus, flow diversion was evaluated as feasible, safe, and effective. In our series, two patients had cavernous segment aneurysms as ICA tandem aneurysms. In addition, another patient had an MCA bifurcation aneurysm accompanying supraclinoid segment aneurysms. Complete occlusion was achieved in all three aneurysms.

Previously, a 90.8%–95% aneurysm occlusion rate was reported at the 12-month follow-up after FD placement;[34] accordingly, our occlusion rate (92.6%) is consistent with the literature. Three of the aneurysms for which complete occlusion could not be achieved were saccular and one was fusiform. Daou et al.[35] reported a 16.4% treatment failure rate with FD stents because of age > 65 years, prior stent placement across the target aneurysm, aneurysm location in the distal anterior circulation, and longer follow-up duration. The fusiform aneurysm in our series was in the distal anterior circulation and in a patient > 65 years. However, the other 3 patients did not have any of the risk factors reported by Daou et al.[35] In addition, recanalization can occur. The reported recanalization rates with balloon-assisted and stent-assisted coil embolization are 10% and 12%, respectively.[36] In the flow diversion series, this rate was 0%–3.4%.[37,38] The overall complication rate and perioperative fatality of FD stent placement have been reported as 17% and 2.8%–4%, respectively.[39,40] In our series, the overall complication rate was 25.5% and no patient died.

The main shortcoming of FD therapy is that aneurysm occlusion is not immediate and the risk of rupture continues until complete occlusion.[41] The rate of postoperative early subarachnoid hemorrhage has been reported as 2%.[2] The underlying mechanism for aneurysm ruptures after FD stent treatment is still unclear.[42] Kulcsár et al.[43] proposed four mechanisms for delayed rupture: large and giant aneurysms, symptomatic aneurysms, saccular aneurysms with an aspect ratio > 1.6, and inertia-driven inflow. Death due to hemorrhages associated with the use of FD stents alone in giant aneurysms has been previously reported[42] and could be explained by the permanent blood entry within the aneurysm as a result of stent deformation to cross the aneurysm neck and the direct stress of blood flow on the aneurysm wall caused by the residual blood flow in the entrance area close to the neck during thrombosis.[42] It has also been hypothesized that stenosis developing in the parent artery after FD stent placement may lead to rupture by hyperfusion.[44] A recent study reported that the velocity of blood flow entering the aneurysm did not effectively decrease after FD stent placement and that high wall shear stress could lead to a delayed aneurysm rupture.[41] Increasing the metal density at the proximal end of FD stents could solve this problem. Rerupture has been reported in giant aneurysms, even with the combination of FD stents and coil embolization.[45] These patients were managed with ICA obliteration and flow alteration (extracranial-intracranial bypass).[45] No early or delayed rupture was detected in our series.

Limitations

The main limitation of the study is its retrospective nature, which may cause selection bias. Other limitations are that the data for the analysis arises from centers with different levels of experience in the use of FD stents and using different stent brands. The case numbers provided by 6 different centers participating in the study ranged from 4 to 28. Because of this irregularity in the distribution of case numbers, it was not statistically possible to compare complication rates with angiography units or surgical teams. Moreover, the sample size was small, but this was to be expected, as we only included aneurysms located in a specific segment. In the future, extensive prospective studies evaluating long-term follow-up in terms of com-

plications and recanalization, as well as heterogeneity in outcomes, are warranted.

Conclusions

This study, the first multicenter study to investigate exclusive FD stent use for unruptured ICA supraclinoid segment aneurysms, showed an increasing use of this treatment method in this segment because of its high rate of aneurysm occlusion with manageable complications and low morbidity/mortality. FD stents, which emerged as an option in treating complex aneurysms in the endovascular era, can now be recommended as the first-line treatment for unruptured aneurysms that would have been treated with surgical clipping or coil-based endovascular methods. More extensive prospective studies evaluating long-term follow-up in terms of complication and recanalization, as well as heterogeneity in outcomes, are indicated.

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Disclosures

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Conception and design: Yakar, Keskin, Gel, Aydın, Kiraz, Çiltemek, Acar, Coşkun, Türkoğlu. Acquisition of data: Yakar, Elbir, Civlan, Ülkü, Keskin, Gel, Fesli, Bakirarar, Aydın, Kiraz, Çiltemek, Arıcı, Acar, Coşkun, Türkoğlu. Analysis and interpretation of data: Gel, Daltaban, Aydın, Kiraz, Çiltemek, Acar, Coşkun, Türkoğlu. Drafting the article: Yakar, Civlan, Ülkü, Gel, Daltaban, Kiraz, Çiltemek, Arıcı, Türkoğlu. Critically revising the article: Yakar, Coşkun. Reviewed submitted version of manuscript: Yakar, Civlan, Ülkü, Keskin, Aydın, Arıcı, Acar. Approved the final version of the manuscript on behalf of all authors: Yakar. Statistical analysis: Daltaban, Bakirarar. Administrative/technical/material support: Civlan, Keskin, Fesli.

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