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Investigating dizziness symptom in adult cases with Crimean-Congo hemorrhagic fever using various scales

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Abstract

Background: This study was to investigate the frequency of self-reported dizziness symptom in cases with Crimean-Congo hemorrhagic fever (CCHF) and the severity of dizziness, if any, by using various scales. The frequency and severity of the self-reported dizziness symptom of CCHF patients, level of disability caused by dizziness, and to what extent vestibular symptoms affected activities of daily living were assessed by various scales. The frequency and severity of the self-reported dizziness symptom of CCHF patients, level of disability caused by dizziness, and to what extent vestibular symptoms affected activities of daily living were assessed by various scales.

Results: The frequency of dizziness in CCHF cases included in the study was 11.11% and all the cases were involved in the mild category in terms of disease severity. When the results of the scales applied to all of the cases were evaluated in general, it was seen that there was no vertigo or dizziness.

Conclusion: According to the results of the present study, we consider that multicenter studies with large series investigating pathophysiological mechanisms underlying these clinical symptoms are needed in order to evaluate dizziness symptom and to make definitive interpretations in CCHF disease.

Keywords: Crimean-Congo hemorrhagic fever, Vestibular symptoms, VSS-short form, VADL, VAS, DHI

Background

Crimean–Congo hemorrhagic fever virus (CCHFV) is a single-stranded RNA virus belonging to the genus *Orthonairovirus* of the family *Nairoviridae*. The overall CCHFV acute infections prevalence was 22.5% (95% CI = 15.7–30.1) in humans [1]. Crimean-Congo hemorrhagic fever (CCHF) is an acute viral hemorrhagic disease with a fatality rate of 3–30% [2].

The pathogenesis of CCHF is not exactly known. Besides, Endothelin-1 (ET-1), angiopoietin-2 (Ang-2), and endothelial cell-specific receptor tyrosine kinase (Tie-2) are believed to have an important role among the factors having a role in the pathogenesis of the disease [3]. The

pathogenesis of CCHF is likely derived from a complex interaction between the virus and host cells [4, 5].

The virus is transmitted to human beings through tick bites or by direct contact with infected animal blood. After a tick bite, the incubation period is usually between 1 and 3 days (maximum 12 days) and following contact with blood and body fluids it is usually between 5 and 6 days (maximum 13 days) [6, 7].

Patients may apply with complaints such as sudden rising fever, shivering, headache, dizziness, gastrointestinal system complaints (diarrhea, vomiting, etc.), muscle pain, and internal or external bleeding [8]. Laboratory findings such as leukopenia, thrombocytopenia, and high liver enzyme arise with the progression of the disease [9]. Starting with epistaxis, CCHFV is known to cause various symptoms in terms of Ear Nose Throat (ENT) such as dizziness, hear loss, and nasal congestion. In the

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literature, we can reach concerning these symptoms; all symptoms except for the dizziness complaint in particular were seen to be evaluated with various previous studies [10–12].

Balance disorders presenting with symptoms of dizziness and vertigo are due to various diseases. Vertigo is a multisensory symptom that otolaryngologists are confronted with every day. Approximately, 50% of dizzy patients have general medical conditions (e.g., gastrointestinal bleeding, new antihypertensive medications, orthostatic hypotension) [13]. Beside the frequent classical syndromes for which vertigo is the leading symptom (e.g., positional vertigo, vestibular neuritis, Meniere's disease), vertigo may occur as main or accompanying symptom of a multitude of ENT-related diseases involving the inner ear. It also concerns for example acute and chronic viral or bacterial infections of the ear with serous or bacterial labyrinthitis and also disorders due to injury (e.g., barotrauma, fracture of the oto-base, contusion of the labyrinth), chronic-inflammatory bone processes, and inner ear affections in the perioperative course [14].

In the light of this information, it is thought that dizziness symptom can be frequently encountered in CCHF cases depending on general medical conditions and viral infections. We could not find a publication in the databases we could reach when we search if there is a study investigating the vestibular symptoms in CCHF cases in the literature by using keywords such as "Crimean-congo hemorrhagic fever and vertigo," "crimean-congo haemorrhagic fever and vestibular neuritis." However, we reached two publications in Pubmed database we made using the keywords "dizziness and Crimean-Congo Hemorrhagic Fever" [15, 16]. In both studies, it was mentioned that dizziness was involved among the symptoms followed after incubation period of CCHF cases. When we use the same keywords in databases other than Pubmed, we saw that there are different studies mentioning that dizziness symptom was seen in this patient group [17–19]. When we specified our search criteria and narrowed them as "bunyaviridae and vertigo," we found the study of Ahlm et al. [20] who pointed out that Puumala virus belonging to the Hantavirus family in the Bunyaviridae family and causing epidemic nephropathy can cause symptoms leading us to think central nervous system involvement such as blurred vision, headache, dizziness, and vomiting. Starting from this point, when we conducted a database search again by changing our keywords as "orthonairovirus and vertigo," "orthonairovirus and labyrinthitis," and "orthonairovirus and Vestibular Neuritis," we could not reach any study.

As a result, the aim of this prospective study was to determine the frequency and severity of the self-reported dizziness symptom in CCHF cases and its severity if any

via Visual Analog Scale (VAS); the imbalance, somatic symptoms, autonomic symptoms, and anxiety levels with Vertigo Symptom Scale Short Form (VSS-Short Form); to evaluate its effects on activities of daily living with various scales such as Vestibular Disorders Activities of Daily Living Scale (VADL) and Dizziness Handicap Inventory (DHI) and to identify if or not there is any correlation between this symptom and CCHF severity.

Methods

Study design

The study was conducted at the Departments of Otorhinolaryngology and Infectious Diseases and Clinical Microbiology at **Sivas Cumhuriyet** University, Turkey, between April 2018 and October 2019. Those, who were hospitalized during period of the present study, met the inclusion criteria, and agreed to participate in the study, were included in the study. The study was conducted in patients hospitalized at the Department of Infectious Diseases and Clinical Microbiology.

The Human Ethics Committee of **Sivas Cumhuriyet** University approved this study in accordance with declaration of Helsinki (Decision no: 2018-10/11; Date: October 10, 2018). After written consents of the patients were obtained, they were included in the study.

Patients

The diagnosis of CCHF infection was based on typical clinical and epidemiological findings and serological tests with enzyme-linked immunosorbent assay (ELISA) and/or reverse transcriptase-polymerase chain reaction (RT-PCR).

At the beginning, 71 patients hospitalized with CCHF pre-diagnosis [30 females (42.3%) and 41 males (57.7%)] were included in the study but 17 patients were excluded from the study since CCHF diagnosis of 54 patients was confirmed by National Reference Center. The mean age of CCHF patients ($n = 54$) was 46.50 ± 17.75 (min-max, 17-86) years. In this study, 59.3% ($n = 32$) of CCHF PCR (+) patients were male, whereas 40.7% ($n = 22$) of CCHF PCR (+) patients were female.

The patients with CCHF were divided into mild, intermediate, and severe patient groups based on severity grading scores (SGS) established by Bakir et al. [21]. However, in the evaluation of the results of the study, the cases were divided into two groups as mild and moderate-severe since there was statistically insufficient number of cases in moderate and severe groups. When the patients in CCHF were classified based on the severity of their diseases, 81.48% ($n = 44$) fell into mild category and 18.51% ($n = 10$) fell into moderate-severe category [21].

Principally, a detailed medical history was obtained from the volunteers, who underwent a detailed

otorhinolaryngological examination. The otorhinolaryngological examination was performed by the same physician (AB) at baseline.

Since we did not find a study evaluating specifically vertigo and/or dizziness symptoms in CCHF cases, symptom evaluation was made in all patients without applying any specific exclusion criteria for any patient. But, patients with previous history of hearing loss, vertigo, migraine, peripheral vestibular disorders (such as benign paroxysmal position vertigo, Meniere's disease, vestibular neuronitis), central vestibular disorders (such as posterior circulation infraction, tumors, vestibular migraine whiplash injury), or other neurologic diseases were excluded from the study. Therefore, the exclusion criterion was simply the patient's reluctance to participate in the study or decline to answer the survey questions.

Assessments

Before filling out the questionnaires, a standard "Preliminary Interview Form" to specify demographic characteristics and information about the background and complaints of the cases included in the study was filled out by conducting face-to-face interview with the patients at the service where they were hospitalized. Then, after considering the patient's complaints within the last week, if any, severity of dizziness by using Visual Analog Scale (VAS), frequency and duration of imbalance and anxiety by using Vertigo Symptom Scale Short Form (VSS-Short Form), how much vestibular symptoms affect activities of daily living by using Vestibular Disorders Activities of Daily Living Scale (VADL), and disability level caused by dizziness by using Dizziness Handicap Inventory (DHI) were evaluated.

Visual analog scale for evaluation of severity of dizziness

In order to evaluate the presence of dizziness symptom which is one of the clinical symptoms of CCHF cases and its severity in patients suffering from this symptom, VAS developed by Cohen et al. [22] was used. VAS is the mostly used scale for subjective evaluation of vertigo, severity of dizziness and its frequency in patients. VAS is numbered between 1 and 10, and dizziness severity is categorized according to numbers. Accordingly, it was categorized as "1=None," "2-3=Very Mild," "4-5=Mild," "6-7=Moderate 8-9=Severe," "10=Very severe." The patients are asked to think about the situation in their condition over a certain period of time such as the last 2 days, 7 days, or 1 month while marking the scale. In this study, the patients were asked to mark by thinking their last 7-day period [23, 24].

Vertigo symptom scale-short form (VSS-short form)

VSS is a scale that has both long and short forms and is used to evaluate the frequency of symptoms such as anxiety and panic, autonomic symptoms, somatic symptoms, imbalance that are frequently seen in patients having vertigo-dizziness [25]. Turkish validity reliability of VSS-Short Form was conducted by Yanık et al. [26] in 2008.

The scale consists of two sub-sections: Vertigo Symptom Scale—Vertigo Part (VSS-V) related to vertigo and balance disorders [8 questions (0-32 points)] and Vertigo Symptom Scale—Anxiety Part (VSS-A) related to autonomic disorders and anxiety symptoms [7 questions (0-28 points)].

The patients were asked to answer these questions about their dizziness, considering their last week. High scores (maximum 60) indicate that the patients have an increased frequency of feeling symptoms about vertigo [26–28]. The points of ≥ 12 are described as severe dizziness.

Vestibular disorders activities of daily living scale (VADL)

VADL is a scale developed to determine the independence levels of patients especially with vestibular disorders while doing their daily activities due to vestibular complaints and the deficiencies perceived about themselves [29]. Turkish validity and reliability of VADL, which was developed by Cohen et al. [30] and whose validity studies were conducted by them were conducted by Çınar et al. [31] in 2017. VADL consists of three subscales and a total of 28 questions. The subscales were named as Functional-F (12 activities of daily living), Ambulation -A (9 activities of daily living), and Instrumental-I (7 activities of daily living) [29, 30].

Dizziness handicap inventory (DHI)

This scale is a scale that consists of three sub-groups and evaluates handicap caused by dizziness and is used commonly to evaluate the specific handicap effects of vestibular system diseases, determine the patient's insufficiency of the patient's dizziness in daily life, and evaluate the perception of the patient about his/her disease [32]. Turkish validity and reliability of DHI were conducted by Canbal et al. [33] in 2016.

Statistical methods

The Statistical Package for Social Science (SPSS) 22.0 software (SPSS Inc., Chicago, IL, and USA) was used for statistical analysis. In data assessment, Kolmogorov-Smirnov was used when the parametric test assumptions were not met. On the other hand, Mann-Whitney *U* test and chi-square test were used in independent groups. Significance level was taken as 0.05.

Results

The mean age of CCHF mild category and moderate-severe category patients was 47.77 ± 16.72 (min-max, 22-86) and 40.90 ± 21.80 (min-max, 17-72) years, respectively. In this study, 59.1% ($n = 26$) of CCHF mild category patients and 60.0% ($n = 6$) of CCHF moderate-severe category patients were male, whereas 40.9% ($n = 18$) of CCHF mild category patients and 40.1% ($n = 4$) of CCHF moderate-severe category patients were female.

When the cases included in the study were grouped according to the disease severity, their data about smoking, alcohol, tea and coffee habits, education levels, their histories of dizziness, and systemic diseases are given in Table 1.

When all cases included in the study were examined in terms of dizziness symptom, 11.11% ($n = 6$) of them had dizziness symptom and all of these cases were involved in mild category according to disease severity. A total of 79.2% ($n = 38$) of 48 cases with CCHF who did not experience dizziness were involved in mild category and 20.8% ($n = 10$) were involved in moderate-severe category. When these results were evaluated, there was no statistically significant difference between the

dizziness complaint and disease severity of CCHF cases ($p > 0.05$; $p = 0.215$).

All of the cases were questioned for symptoms such as hearing impairment, tinnitus, pressure in the ear, fullness, discharge, nausea and vomiting, diplopia, dysarthria, dysphagia, dysphonia, pain in the head and neck, initially sensation of space, difficulty in getting up and down, and tendency to fall. When CCHF cases were grouped as mild and moderate-severe category in terms of the severity of the disease, it was seen that pressure feeling in the ear and fullness symptoms were present in a case in the moderate-severe category and this difference was statistically significant ($p < 0.034$). However, we think that this difference caused by a single case should be ignored (Table 2).

Although the patient had no dizziness complaint in symptom questioning, a complete physical examination was conducted to all cases (Ear Nose Throat, neurotological examination; for example, Romberg test, cranial nerve, and cerebellar functions; bedside tests; for example, head shaking and head thrust). In nystagmus evaluation, only one CCHF patient from the mild category in terms of disease severity had nystagmus. The

Table 1 Data of CCHF cases on their smoking, alcohol, tea and coffee habits, education levels, and family histories about systemic diseases and dizziness

Evaluated parameter		Mild category	Moderate-severe category	p value
		% (n)	% (n)	
Cigarette	Smoking	75.0 (6)	25.0 (2)	0.566
	Not smoking	81.0 (34)	19.0 (8)	
	Quitted	100.0 (4)	0.0 (0)	
Alcohol	Drinking	100.0 (2)	0.0 (0)	0.087
	Not drinking	82.4 (42)	17.6 (9)	
	Quitted	0.0 (0)	100.0 (1)	
Tea	Drinking	81.1 (43)	18.9 (10)	0.630
	Not drinking	100.0 (1)	0.0 (0)	
Coffee	Drinking	83.7 (41)	16.3 (8)	0.194
	Not drinking	60.0 (3)	40.0 (2)	
Education status	No	90.0 (9)	10.0 (1)	0.206
	Primary	86.7 (26)	13.3 (4)	
	Secondary	55.6 (5)	44.4 (4)	
	High school	66.7 (2)	33.3 (1)	
	University	100.0 (2)	0.0 (0)	
	Master	0.0 (0)	0.0 (0)	
History of systemic disease	Yes	82.4 (14)	17.6 (3)	0.911
	No	81.1 (30)	18.9 (7)	
	Family history	100.0 (1)	0.0 (0)	
No	81.1 (43)	18.9 (10)		

Table 2 Symptoms accompanying dizziness in CCHF patients

Symptom	Severity grading scores		p value
	Mild category % (n)	Moderate-severe category % (n)	
Hearing loss	80.0% (4)	20.0% (1)	0.929
Tinnitus	75.0% (3)	25.0% (1)	0.729
Pressure feeling in the ear	0.0% (0)	100.0% (1)	0.034
Fullness	0.0% (0)	100.0% (1)	0.034

nystagmus detected in this patient was horizontal-rotatory nystagmus and was detected by bedside evaluation.

When CCHF cases were examined in terms of hearing loss, one case from moderate-severe category (20.0%) and 4 cases (80.0%) from the mild category had hearing loss complaint and otoscopic examination of 5 cases was normal. In addition, when pure-tone audiological evaluation was performed in all cases having hearing loss complaint, their hearing thresholds were found to be normal.

Since the frequency of self-reported dizziness symptom of 54 CCHF cases included in the study was low, the results obtained when the responses given by all cases to the scales were assessed below:

When the vertigo and dizziness severity of all cases were examined with VAS, the mean was seen to be 0.31 ± 1.19 (min-max, 0-8). When the cases were evaluated as mild and moderate-severe category in terms of disease severity, VAS scores were 0.39 ± 1.32 (min-max, 0-8) and 0.0 ± 0.0 (min-max, 0-0), respectively ($p > 0.05$; $p = 0.221$). These results showed that the patients generally did not have vertigo and dizziness complaints.

According to VSS-Short Form (0-60), it was seen that the mean score of all 54 cases included in the study was 1.83 ± 6.56 (min-max, 0-40) and the cut-off score of the scale was below 12. When two sub-sections of the scale were evaluated separately in terms of the mean scores of the cases, it was observed that VSS-V (0-32 points) was 1.17 ± 3.93 (min-max, 0-20) and VSS-A (0-28 points) was 0.67 ± 2.91 (min-max, 0-20). When the cases were grouped in terms of the disease severity and compared in terms of the mean values obtained from VSS-Short Form and its subscales, it was found that there was no statistically significant difference ($p > 0.05$). These results also suggested that the cases had no vertigo or dizziness complaint in general.

According to VADL used to evaluate the independence levels in activities of daily living, the total mean score of all 54 cases included in the study was 31.26 ± 14.30 (min-max, 28-121); the mean values for functional, ambulation, and instrumental subscales were 13.35 ± 5.62 (min-max, 12-48), 10.06 ± 5.31 (min-max, 9-45),

and 7.85 ± 3.62 (min-max, 7-28), respectively. When the cases are grouped based on severity of the disease and compared in terms of the mean values obtained from VADL and its subscales, it was determined that there was no statistically significant difference ($p > 0.05$). According to these obtained values, it was considered that no dizziness symptom that may cause restriction generally in activities of daily living in cases was observed.

According to DHI (0-100) applied to determine the patient's insufficiency in dizziness in daily life and to evaluate the patient's own perception, the total mean score of all 54 cases included in the study was 3.30 ± 14.79 (min-max, 0-96); the mean values for functional, physical, and emotional subscales were 1.22 ± 5.64 (min-max, 0-36), 1.00 ± 5.06 (min-max, 0-36) and 1.07 ± 4.51 (min-max, 0-24), respectively. When the cases were grouped in terms of the disease severity and compared in terms of the mean values obtained from DHI and its subscales, no statistically significant difference was found ($p > 0.05$). According to these values, it is shown that there was no inadequacy perception in patients about dizziness in daily life (Table 3).

Discussion

In Turkey, CCHF is seen as an endemic especially in Central Anatolia region since 2002 [34]. CCHF disease clinically presents in four stages: incubation, pre-hemorrhagic, hemorrhagic, and convalescence stage. The clinical presentation of CCHF can range from self-limiting flu-like to life-threatening symptoms [34]. The most frequent clinical symptoms of the disease in human beings include sudden onset of high fever (89.4%), fatigue (92.3%), myalgia (69.7%), headache (68.1%), nausea (64.7%), dizziness, diarrhea, and internal or external bleeding (23%) [8, 34–36]. Dizziness symptom is mostly observed in hemorrhagic period [15, 16, 37]. However, we could not find any publication that mentioned about the pathophysiological mechanism underlying the symptoms or its incidence. We aimed firstly to evaluate the frequency of self-reported dizziness and vertigo symptoms in CCHF patients. According to our results, the frequency of dizziness symptom in our series of 54 CCHF cases was 11.11%. However, in Turkey, CCHF is reported from almost all regions with varying frequency and we believed that it is not appropriate to make a

Table 3 VAS, VSS-Short Form, VADL, and DHI mean scores of the cases

	CCHF patients (n = 54) (mean ± SD (min-max))	Severity grading scores		p value
		Mild category (n = 44) (mean ± SD (min-max))	Moderate-severe category (n = 10) (mean ± SD (min-max))	
VAS	0.31 ± 1.19 (0-8)	0.39 ± 1.32 (0-8)	0.0 ± 0.0 (0-0)	0.221
VSS-Short Form	1.83 ± 6.56 (0-40)	2.25 ± 7.21 (0-40)	0.0 ± 0.0 (0-0)	0.182
VADL	31.26 ± 14.30 (28-121)	32.0 ± 15.78 (28-121)	28.0 ± 0.00 (28-28)	0.268
DHI	3.30 ± 14.79 (0-96)	4.05 ± 16.33 (0-96)	0.0 ± 0.0 (0-0)	0.327

VAS Visual Analog Scale, VSS-Short Form Vertigo Symptom Scale Short Form, VADL Vestibular Disorders Activities of Daily Living Scale, DHI Dizziness Handicap Inventory

definitive judgment such as “dizziness and dizziness complaint is not a frequently seen symptom in CCHF cases” or “its incidence rate is 11.11%” by considering these results we obtained from only our case series. We also thought that it would be an appropriate approach to reach such a judgment or outcome only by conducting a multi-centered study covering large series and cases from all cities where the disease is seen as endemic in Turkey.

Endothelial dysfunction is the most important step in the pathogenesis of CCHF. Examination of autopsy materials from patients with CCHF showed the presence of viral antigens and RNA in endothelial cells. Endothelial dysfunction is a broad term expressing impairment of nitric oxide (NO) production and/or imbalance in endothelium-derived relaxing and contracting factors such as endothelin-1 (ET-1), angiotensin, and oxidants [38]. In conclusion, inflammation caused by CCHFV increases the oxidative stress and release of proinflammatory proteins and may lead to damage in the vascular endothelium. If this situation leads to vestibular neuritis by affecting vestibular nerve, it may cause dizziness in patients. However, it is not clear whether the dizziness observed in CCHF cases is secondary to vestibular neuritis or seen metabolic and hematological changes. We believe that the mechanisms underlying this clinical symptom said to be seen commonly in these cases should be revealed with new studies to be conducted in the future.

Our second purpose in this study was to evaluate the severity of the symptom in cases having dizziness, its effects on activities of daily living, and the levels of clinical findings that may accompany dizziness (imbalance, somatic signs, autonomic symptoms, and anxiety) with various scales and find out if there is a correlation between CCHF severity and this symptom. However, this assessment could not be made since the number of cases having dizziness was small to make a statistically reliable assessment. Besides, in accordance with the results we obtained in the evaluation made by using these scales in all of the cases, low VAS and VSS-Short Form scores of

CCHF cases showed that there was no vertigo and dizziness complaints in general, VADL and DHI scores showed that dizziness did not cause any limitation in activities of daily living of the cases. Undoubtedly, the evaluation should be made by considering the scores of cases who specifically had dizziness symptom to make more accurate and precise interpretations about the results of the applied scales. This is the most important limitation of the present study.

Conclusion

According to the results of the present study, the frequency of dizziness symptom in our series of 54 CCHF cases was 11.11%. When the scores obtained from the applied scales were considered, it was observed that there was generally no vertigo and dizziness complaint in our patient group.

As a conclusion, we believe that multi-centered studies covering large series in which possible pathophysiological mechanisms underlying in these clinical symptoms are needed in order to evaluate vertigo and dizziness symptoms in CCHF disease and to make definitive interpretations.

Abbreviations

CCHF: Crimean-Congo hemorrhagic fever; CCHFV: Crimean-Congo hemorrhagic fever virus; ET-1: Endothelin-1; Ang-2: Angiopoietin-2; Tie-2: Endothelial cell-specific receptor tyrosine kinase; ENT: Ear Nose Throat; VAS: Visual Analog Scale; VSS-Short Form: Vertigo Symptom Scale Short Form; VADL: Vestibular Disorders Activities of Daily Living Scale; DHI: Dizziness Handicap Inventory; ELISA: Enzyme-linked immunosorbent assay; RT-PCR: Reverse transcriptase-polymerase chain reaction; VSS-V: Vertigo Symptom Scale—Vertigo Part; VSS-A: Vertigo Symptom Scale—Anxiety Part

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Authors' contributions

Concept—E.E.A., A.B., S.A.B., K.D.; design—E.E.A., K.D., A.B., S.A.B.; supervision—E.E.A., A.B., S.A.B.; resource—E.E.A.; materials—A.B., S.A.B., B.B.D., C.O., Y.S.; data collection and/or processing—A.B., K.D., S.A.B., B.B.D., Y.S., C.O.; analysis and/or interpretation—E.E.A., S.A.B., A.B.; literature search—K.D., A.B., S.A.B., B.B.D., C.O., Y.S.; writing—E.E.A., S.A.B., A.B.; critical reviews—E.E.A., K.D., S.A.B., A.B. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations**Ethics approval and consent to participate**

The Human Ethics Committee of Sivas Cumhuriyet University approved this study in accordance with declaration of Helsinki (Decision no: 2018-10/11; Date: October 10, 2018). After written consents of the patients were obtained, they were included in the study.

Consent for publication

Written and verbal consent forms were obtained from the subjects included in the study.

Competing interests

The authors declare that they have no competing interests.

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