The Relationship Between Sarcopenia Detected In Newly Diagnosed Colorectal Cancer Patients And FGF21, Irisin And CRP Levels.

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Research Article

Keywords: Sarcopenia, irisin, FGF21, colorectal cancer. bio-electric impedance analysis

Posted Date: September 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-577872/v1

Version of Record: A version of this preprint was published at European Geriatric Medicine on March 11th, 2022. See the published version at https://doi.org/10.1007/s41999-022-00635-3.

Abstract

Aim: Sarcopenia is a progressive and generalized syndrome that can be linked to many causes such as cancers, and is caused by a quantitative and qualitative disorder (loss of muscle strength and / or physical performance) of skeletal muscle mass. Although sarcopenia has some hypothetical explanation in clinical practice, the mechanisms underlying this condition have not been clearly differentiated in patients with cancer. We aimed to investigate the relationship between irisin and FGF21 in detecting sarcopenia in colorectal cancer patients.

Material and Method: Current prospectively study included non-metastatic newly diagnosed colorectal cancer patients. Patients were divided into two groups of 25 people, those with and without sarcopenia. Body composition measurements by examined by BIA. To measure the level of iris and FGF21 from patients, blood samples were taken into the biochemistry tube and their levels were measured.

Results: The median age of the patients included in the study was 60 years (range: 21-81), 68 % were men. It was found that there was a significant relationship between sarcopenia and gender and BMI measurement. When Spearman correlation analysis was performed between skeletal muscle mass index and FGF21, irisin and CRP, there was a positive correlation between skeletal muscle mass index and irisin and FGF21, while there was a negative correlation between skeletal muscle mass index and CRP. [respectively: (r: 0.282, p: 0.048), (r: 0.564, p: <0.001) and (r: -0.360, p: 0.010). Similar results were found between hand grip strength and FGF21, irisin and CRP. [respectively: (r: 0.342, p: 0.015), (r: 0.290, p: 0.041) and (r: -0.476, p <0.001)]. When sarcopenia was treated as the dependent variable in the logistic regression analysis, and FGF21, irisin, CRP, gender and BMI were treated as the independent variables, irisin and CRP levels were determined as independent predictors.

Conclusion: This study was revealed that there is a negative relationship between sarcopenia and irisin and FGF-21 in operated non-metastatic colorectal cancer patients and there may be a relationship between sarcopenia and inflammation. It suggest that these biomarkers may play a role in the pathophysiology of sarcopenia. However, our results need to be validated in different types of cancer and with more patients.

Introduction

As defined by the European Society of Parenteral and Enteral Nutrition (ESPEN) and the European Working Group on Sarcopenia in Older People (EWGOSP), sarcopenia is a syndrome characterized by progressive and generalized muscle loss, which can be associated with a wide range of causes and may lead to falls, physical injuries, treatment complications, as well as negative impacts on survival, and accompanied by quantitative and qualitative deterioration of the skeletal muscle mass (loss of muscle and/or physical performance) [1, 2].

Many functional tools are recommended by international workgroups to identify the quantitative muscle mass [1–3]. These include bio-electric impedance analysis (BIA), computed tomography (CT), dual x-ray

absorptiometry (DXA) and magnetic resonance imaging (MRI). Among these tools, BIA is an alternative that can be easily applied, cheaper, repeatable, portable, and which do not generate radiation exposure for the patient (in comparison to DXA and CT) [4, 5].

Adipose tissue and muscle synthesize and release molecules that play a role in the control of systemic inflammatory response and metabolism. Pro-inflammatory adipokines, released from white adipose tissues, promote insulin resistance and atherosclerotic changes in obese individuals [6]. Conversely, it is believed that myokines released from the skeletal muscle improve glucose and lipid metabolism and reduce the risk of chronic metabolic disease [7]. Recently, irisin has been identified as a new myokine that accelerates the beige adipocytes' turning into brown [8] as well as glucose intake and fatty acid oxidation process [9]. Irisin is a peptide that consists of 112-amino acid that is proteolytically digested by fibronectin type III and largely expressed in the skeletal muscle [10]. In particular, irisin levels are correlated positively with muscle mass and muscle strength [11]. The accumulated evidence has shown that the levels of irisin in circulation are increased by exercise in humans and animals, which indicates that irisin production depends on the muscular state [12]. However, many studies have concluded that irisin levels in circulation are not only related to fat-free mass but also to muscle strength and function [11, 12]. All these findings suggest a positive connection between irisin and muscle physiology and metabolism, and that irisin has a potential regulatory role [11, 13] (15,25). However, the relation between irisin levels and sarcopenia developed by cancer patients has not been explicated.

Fibroblast growth factors are found as signaling proteins in many tissues and participate in growth and metabolism [14]. FGF21 in skeletal muscle has been demonstrated to play a role in glucose intake to myocytes [15]. FGF21 has a role in controlling lipid homeostasis and glucose in other organs such as skeletal muscle and liver [16, 17]. Although it is shown to play a role in energy metabolism, FGF21 is a myokine that is very poorly addressed in cachexia and sarcopenia studies.

Some studies have demonstrated that patients with advanced cancer develop sarcopenia associated with disease progression or chemotherapy [18–21]. While many factors have been suggested as the cause of this phenomenon in advanced cancer patients, most of the reasons suggested in operated tumor-free patients are hypothetical and remain controversial. No previous study has examined the relationship between sarcopenia detected in newly diagnosed cancer patients and the level of FGF21 and irisin. Therefore, in this study, we planned to investigate the location of inflammation and its relationship with FGF21 and irisin levels to better understand the physiopathology of sarcopenia in newly diagnosed and non-metastatic colorectal cancer patients operated for primary tumors.

Material And Method

Patient selection and inclusion criteria:

This study included newly diagnosed and non-metastatic colorectal cancer patients who underwent curative surgery for the primary tumor in Izmir Katip Çelebi University Atatürk Research and Training

Hospital Medical Oncology Clinic between May 2019 and May 2020. These patients' pre-treatment baseline body composition measurements (using by BIA), muscle strength (using by a hand-grip dynamometer), as well as baseline anthropometric measurements (height, weight, body mass index, etc.), demographic data and CRP, FGF21 and irisin were checked. After these measurements, a biochemical analysis was performed on single blood samples taken from the patients using a 3-cc biochemistry tube. In total, 50 patients were planned to be included in the study: patients were divided into two groups as sarcopenic (n: 25) and non-sarcopenic (n: 25).

The study included operated and non-metastatic patients who were diagnosed with colorectal cancer, above 18 years of age, and who did not receive chemotherapy or radiotherapy before diagnosis, with sufficient liver and kidney functioning, non-diabetes mellitus, receiving no anti-inflammatory treatment, no oral enteral nutrition support, presenting no serious comorbidity, and who agreed to participate in the study. Patients with physical deformations and impossible to test for muscle strength have been disabled. All patients provided written informed consent to participate in the study. The study was approved by the Institutional Ethics Review Board of Izmir Katip Celebi University. (IKCU-2019/98)

Body composition measurement assessment:

Body composition was assessed using BIA (TANITA SC 330). Bioelectric resistance was also measured using a BIA with an operating frequency of 50 kHz at 800 mA.

BIA is an analytical method based on a fat-free tissue mass and the difference in electrical conductivity of fat. The electrical and biological parameters measured by the BIA vary from person to person. At the same time, the hand-grip dynamometer and muscle functions will be evaluated. The hand-grip dynamometer is an instrument used to measure muscle strength with 2 hand-held apparatus. It is a measurement instrument based on squeezing the hand-held apparatus, which is totally harmless for the patient.

The impedance will be measured with the BIA. The Skeletal Muscle Mass was calculated by the formula previously reported in available studies in the literature [22–26].

This formula is as follows: Skeletal Muscle Mass (kg) = [0.401 x (Height^2/resistance) + (3.825 x gender) – (0.071 x age) + 5.102]; height: cm, resistance: ohms, gender: 1 for men, 0 for women. In order to convert the skeletal muscle mass into the skeletal muscle mass index, the height must be divided by its square in meters. The cutoff points set by EGSWOP are defined as reduced skeletal muscle mass if less than 10.76 for men and 6.76 for women [1].

Assessment of muscle strength:

The hand-grip dynamometer test (TAKEI 5401 Hand-Grip Dynamometer, 100 kg) was used to assess patient muscle strength. To obtain the optimal test result, patients were asked to grip the device and squeeze it three times as good as possible with min. two-minute breaks between the attempts. With this

test, the peak of patients (the highest value obtained) and the highest one of the three repeated measurements were determined in kilograms. Patients were asked to use their dominant hand.

Sarcopenia definition and thresholds:

The sarcopenia diagnosis was established based on the EWSGOP consensus [1], both describe sarcopenia as reduced skeletal muscle mass plus low muscle strength and/or low physical performance. The cutoff values were determined based on the values recommended by the European Working Group on Sarcopenia in Older People (EWSGOP) for skeletal muscle mass index (SMI) and hand grip strength [1].

Thresholds for gender-specific SMI were for men: low SMI < 10.76 kg/m2, for women: low SMI < 6.76 kg/m2 and low hand grip strength for men: <27 kg, and < 16 kg for women. Both low skeletal muscle mass and low muscle strength were identified as sarcopenia [27].

Body mass index:

A regular standardized gauge was used to measure weight and height. During measurements, patients wore light clothes without shoes. The body weight and height were measured up to the nearest 0.1 kg and the nearest 0.1 cm. The body mass index (BMI) was calculated by dividing the patient's weight by the square (kg/m2) of their height. BMI categories: < 20.0 kg/m^2, weak; 20.0 to 24.9 kg/m^2, normal weight; 25.0 to 29.9 kg/m^2, overweight; and > 30 kg/m^2, obese.

Biochemical analysis:

Blood samples were taken from patients upon their inclusion in the study, and then serum samples were separated after centrifuging at 3000 rpm. They were stored in clean and dry Eppendorf tubes at -20 C^0 until being studied. After pipetting serum samples into the wells covered with antibodies, they were incubated for 2 hours at 37 C^0. A biotin-marked antibody was added to each well and after incubating for 1 hour at 37 C^0, the wells were washed 3 times using 200 microliters of washing solution. The streptavidin-marked HRP enzyme was added, and after incubating at 37 C^0 for an hour, they were washed 5 times using 200 microliters of washing solution. After adding a substrate for the HRP enzyme, the reaction was terminated using H2SO4 after incubation in the dark at 37 C^0. The absorbance rates at 450 nm were read on the Elisa plate reader, and the concentration was calculated according to the standard absorbance curve. For ELISA method, FGF21 on Biotek (ELx800, USA) semi-automatic ELISA device and Irisin ELISA kit (Catalog no.: CSB-E16844h, Lot no: P12221948, Catalog No.: CSB-EQ027943HU, Lot no.: p16221949, CUSABIO, Wuhan, China) were used.

Statistical analysis:

The data were expressed as mean and standard deviation for continuous variables, and in number and percentage for categorical variables. Numerical variables were evaluated to show whether they showed skewed or normal distribution using Kolmogorov-Smirnov testing and histograms. Normally distributed continuous data and independent samples were compared using the t-test. Continuous data with non-

normal distribution were compared using the Mann-Whitney U-test. The categorical data were compared using the Fischer-Exact test or the Chi-square test. A single variable analysis was used to identify potential risk factors for sarcopenia. Variables with $P < 0.05$ were included in the multi-variable advanced logistic regression analysis.

The correlations were analyzed by Spearman's correlation method. Linear regression and logistic regression equations were also used for analysis. Logistic regression analysis was performed to estimate probability rates (PR) and 95% confidence intervals (CI) for sarcopenia.

Since there was no previous study conducted in this context on newly diagnosed colorectal cancer patients, we calculated the number of sarcopenic patients that we expected to detect within 1 year (the period in which we planned to finish the study) based on the prevalence of sarcopenia in newly diagnosed cancer patients that had been published by Oflazoglu et al. In that study, Oflazoglu et al. reported the prevalence of sarcopenia in newly diagnosed patients with non-metastatic colorectal cancer as 19%. Again, as part of that study, in total, 21 of 111 patients were found sarcopenic in the last 1 year [28]. Since the present study will also be a pilot study and represents the first research conducted in Turkish society, the number of prospective sarcopenic patients is 21. In total, the study included 50 non-metastatic colorectal cancer patients (25 sarcopenic and 25 non-sarcopenic). $P < 0.05$ was considered to indicate statistical significance. The SPSS was used to perform statistical analysis (version 20.0, SPSS Inc., Chicago, IL, 2018).

Results

In the present study, 220 patients with colorectal cancer were scanned until a total of 50 subjects (25 sarcopenic and 25 non-sarcopenic) were included. The median age of patients was 60 years (range: 21–81). 16 patients (32 %) were women, and 34 (68%) were men. The number of patients with any chronic disease was 27 (54%). 36 (72 %) patients' ECOG performance score was 0. All the subjects were non-metastatic patients. 66 % of patients (n: 33) were under 65 years of age, while 34 % (n: 17) were over 65 years of age. The number of patients with albumin levels below < 3 was 6 (12 %), while the number of patients with albumin level > 3 was 44 (88%). When we grouped patients by Body Mass Index (BMI), 26 % (n: 13) were obese, 42 % (n: 21) were overweight, 30 % (n: 15) were normal weight, and 2% (n: 1) were low weight. Table 1 summarizes the demographic characteristics of patients based on the overall and sarcopenic condition.

Table 1. Associations of participant and disease characteristics by sarcopenic status.

Variables	*No Sarcopenia (n, %)*	*Sarcopenia (n, %)*	*P value*
All patients	25 (100%)	25 (100%)	
Age(mean/SD)	58.8 (10.4)	57.5 (14.1)	0.961
Gender			**0.015**
Men	13 (48%)	21 (84%)	
Women	12 (52%)	4 (16%)	
BMI status			0.069
BMI < 25	5 (20%)	11 (44%)	
BMI ≥ 25	20 (80%)	14 (56%)	
ECOG status			1.0
0	18 (72%)	18 (72%)	
1 and 2	7 (28%)	7 (28%)	
Age			
< 65 years	17 (68%)	16 (64%)	0.765
≥ 65 years	8 (32%)	9 (36%)	
Any chronic disease			0.500
Yes	14 (56%)	13 (52%)	
No	11 (44%)	12 (48%)	
Albumine levels			0.384
< 3 *≥ 3*	2 (8%) 23 (92%)	4 (%16) 21 (%84)	
BMI (mean/SD)	28.8 (5.4)	25.2 (4.1)	**0.019**
SMI (mean/SD)	13.1 (1.7)	8.9 (1.1)	**<0.001**
HGS (mean/SD)	34.4 (6.5)	23.1 (3.9)	**<0.001**

ECOG: Eastern Cooperative Oncology Group , BMI: Body mass index, SD: Standart error,

SMI: Skeletal muscle mass index, HGS: Hand-grip strength,

Given the factors that may be associated with sarcopenia (age, gender, BMI, ECOG performance score, chronic disease, albumin level) only gender and BMI level were found to be associated with it (p: 0.015 and p: 0.019, respectively).

Respectively, FGF21, irisin and CRP mean levels were 175.3 (SD: 382.9), 256.3 (SD: 198.2) and 1.6 (SD: 2.4) in the non-sarcopenic patient group, which were found as 55.8 (SD: 22.4), 76.1 (SD: 50.1) and 4.6 (SD: 4.4) in the sarcopenic group (p: 0.007, < 0.001 and < 0.001, respectively) (Table 2).

Table 2
Associations of FGF21, Irisin and CRP results by sarcopenic status.

Variables (mean,SD)	Non-Sarcopenic(n:25)	Sarcopenic(n:25)	p value*
FGF21(pg/mL)	*175.3 (SD:382.9)*	*55.8 (SD:22.4)*	*0.007*
Irisin(pg/mL)	*256.3 (SD:198.2)*	*76.1 (SD:50.1)*	*< 0.001*
CRP(mg/dL)	*1.6 (SD:2.4)*	*4.9 (SD:4.4)*	*< 0.001*
* The comparison of sarcopenic patients and non-sarcopenic patients in terms of inflammatory markers was performed using Mann-Whitney-U test.			
SD: Standart deviation			

A Spearman's correlation analysis between skeletal muscle mass index (SMI) and FGF21, irisin and CRP showed a positive correlation in terms of FGF21 and irisin, while CRP was negatively correlated [respectively: (r: 0.282, p: 0.048), (r: 0.564, p: <0.001) and (r: -0.360, p: 0.010)]. When Spearman's correlation analysis was performed between the hand-grip strength and these markers, FGF21 presented a positive correlation in terms of irisin, while there was a negative correlation in terms of CRP [respectively: (r: 0.342, p: 0.015), (r: 0.290, p: 0.041) and (r: -0.476, p < 0.001)]. They were shown in Table 3.

Table 3. Spearman's correlation analysis with skeletal muscle mass index (SMI), hand-grip strength (HGS) and inflammatory factors.

	FGF21 level		*Irisin level*		*CRP level*	
	r	*p value*	*r*	*p value*	*r*	*p value*
- ***SMI***	0.282	0.048	0.564	<0.001	-0.360	0.010
- ***HGS***	0.342	0.015	0.290	0.041	-0.476	<0.001

SMI: Skeletal muscle mass index, HGS: Hand-grip strength,

*: Spearman's correlation analysis was used to test the parameters, p<0.05 statistically significant.

As part of the logistic regression analysis, when we treated sarcopenia as a dependent variable and FGF21, irisin, CRP, gender and BMI as independent variables, the irisin and CRP levels proved to be an independent predictors. (respectively, for irisin, OR: 0.974, CI: (0.952–0.996), p: 0.022; for CRP, OR:1,883, CI: (1.092–3.547), p:0.048). (Table 4)

Table 4
Logistic-regression analysis with inflammatory markers and sarcopenia

Variables	*β*	*SE*	Confidence interval	Odds ratio	p value
-Constant	9.211	5.072		10004.6	0.069
-FGF21	-0.030	0.016	0.940–1.001	0.970	0.058
-Irisin	-0.027	0.012	0.952–0.996	0.974	0.022*
-CRP	0.633	0.323	1.092–3.547	1.883	0.048*
-Gender	0.156	1.213	0.108–12.603	1.169	0.898
-BMI	-0.188	0.180	0.583–1.179	0.829	0.297
N:50, R^2:0.789 (Nagelkerke), Model: $\chi 2$ (2):44.762, $p < 0.05$					
*: $p < 0.05$, SE: standard error, BMI: Body mass index					

Discussion

In this prospective observational study, FGF-21 and Irisin levels were found to decrease in the sarcopenic patient group compared to non-sarcopenic patients, while CRP was found to increase in comparison with non-sarcopenic patients. In this context, this study is the first one for new patients diagnosed with operated colorectal cancer, which has shown that FGF-21 and irisin can be associated with sarcopenia and inflammation, and inflammation may also play a role.

Previously, there were discussions about the relationship between levels of irisin in circulation and aerobic capacity [29, 30]. Some previous studies have demonstrated that circulating irisin levels are not associated with fat-free mass [31] but also ALM (appendicular fat-free mass) and HGS (muscle strength) [32, 33]. Building on them in the present study, we have shown reduced irisin levels in sarcopenic patients with cancer, despite other studies conducted on certain non-cancer patients that reported no association with sarcopenia. In a study conducted in healthy women, the levels of irisin circulating were shown to be in a positive relationship with the biceps muscle circumference (used as a backup marker for muscle mass) [34]. Stengel et al. reported that concentrations of irisin in circulation showed a positive correlation with fat-free mass using a bioelectric impedance analyzer [35]. In a study conducted by Chang et al. in 715 Korean individuals without cancer, the average levels of irisin in the sarcopenic group were lower than the non-sarcopenic group. The same study determined that in logistic regression models, the relationship between serum irisin concentration and event sarcopenia continued even after being

adjusted to potential contradictions such as gender, age and fat indices [36]. In another study of non-cancer patients, the levels of irisin in circulation in sarcopenic patients were determined to be no different than those of control subjects, and skeletal muscle mass index was reported to indicate no correlation with such levels [37]. Although there are contradicting studies in the literature, these studied differed in terms of design and sarcopenia definitions as well as the methods they used to identify sarcopenia, which may account for inconsistent results. In our study, we determined sarcopenia by measuring it based on the current definition and recommended test method recommended by the EGSWOP. Moreover, unlike other studies, we conducted it in cancer patients. All these findings suggest a positive relationship between irisin and muscle physiology and metabolism, and that irisin also has a potential regulatory role.

Although FGF21 is shown to play a role in energy metabolism [15–17], it is a myokine that has been treated very poorly in the studies of cachexia and sarcopenia, and the available data are limited. Some studies have found a positive correlation between serum FGF21 levels and aging-sarcopenia [38, 39]. A study conducted by Hojman et al. reported a negative relationship between the FGF-21 level and the fat-free mass [40]. The degeneration of various body tissues and changes in metabolic activity, considered as part of the aging process, may affect the synthesis and release of FGF21. Adipocytes have been shown to be an important source of FGF21 production, whereas the liver was previously considered to be the main source of FGF21 in circulation [41]. More recently, the skeletal muscle expression and the release of FGF21 have been shown to cause a five-fold increase in the concentration of FGF21 in circulation [42]. This suggests that there may be a relationship between the quantity of muscle tissue and the level of FGF-21. Although our understanding of the systemic effects of muscular FGF21 has increased, FGF21's direct contribution to muscle function has not yet been investigated. With this study, we have shown that there may be a relationship between sarcopenia and FGF-21.

Our study detected a positive relationship between sarcopenia and CRP. Moreover, this relationship was maintained in the logistical regression analysis as well. In a study evaluating 100 patients with advanced lung cancer, 69% and 47% of patients presented cachexia and sarcopenia, respectively. That study found no significant difference in terms of CRP, IL-6 and albumin concentrations when compared with non-cachectic patients ($p = 0.020$, $p = 0.040$, $p = 0.003$); however, the relationship between inflammatory markers and sarcopenia was not investigated [43]. Although some studies detected a relationship between inflammation and sarcopenia [44–46], there are others that reported no relation [47]. A meta-analysis that did not include cancer patients showed no difference between basal sarcopenia and inflammatory markers (IL-6, TNF-a), but a positive relationship with CRP was reported [47]. Another study was reported to have a positive relationship between sarcopenia and highly-sensitive CRP (HsCRP), which continued in logistic regression [48].

In the present study, when assessing factors that may be associated with sarcopenia (age, gender, BMI, ECOG performance score, chronic disease, albumin level) there was an association only with male gender and BMI < 25. (p values, respectively: 0.015 and 0.019). The results of the present study were confirmed in a study conducted by Oflazoglu et al. in cancer patients [49]. Also, a meta-analysis published by Pamoukdjian on sarcopenia in patients with cancer reported that sarcopenia was more frequent in men

[50]. In addition, we found that the incidence of sarcopenia was lower in obese and overweight patients (BMI > 25) than those with normal and low weight (BMI < 25). Supporting the findings of the present study, a study conducted by Brougmann et al. in 87 patients over the age of 70 with early-stage colorectal cancer reported that sarcopenia was associated with low BMI (p = 0.03) [51].

The present study was designed as a prospective observational study, but there were certain limitations. The first is that it was conducted with a limited number of patients. On the other hand, the recommended gold standard method for detecting sarcopenia is computed tomography. However, we used the bioelectric impedance device, which is a non-invasive method. Although the bioelectric impedance analyzer is a fast, non-invasive method for measuring body composition, its reliability can vary with an individual's hydration level, ethnicity, physical suitability, even if optimal conditions are provided.

In conclusion, the present study has shown that sarcopenia, irisin and FGF-21 have a negative relationship in operated non-metastatic colorectal cancer patients and pointed to a potential relationship between sarcopenia and inflammation. This suggests that these biomarkers could play a role in the physiopathology of sarcopenia. It further suggests that there may be a positive relationship between sarcopenia and inflammation. However, our results should be validated with different types of cancer and more patients.

Declarations

Acknowledgments: The authors gratefully acknowledge the support from friend Songul Uluc Ozaltaş.

Authors' contributions: Study concept: A. Alacacioglu, U. Oflazoglu. Study design: U. Oflazoglu, A. Alacacioglu. Data acquisition: S. Caglar, T. Salman, S. Unal, Z.G. Guc, Y Yildiz. Quality control of data: U. Oflazoglu, A. Alacacioglu, Y Kucukzeybek. Data analysis and interpretation: U. Oflazoglu, A. Alacacioglu, Y. Kucukzeybek. Biochemical analysis of blood: H.T. Onal, H.E. Yilmaz. Statistical analysis: U.Oflazoglu, A. Alacacioglu, Y. Kucukzeybek. Preparation: U. Oflazoglu, U. Varol. Manuscript editing: U. Varol, A. Alacacioglu. Manuscript review: U. Varol, A. Alacacioglu, Y. Kucukzeybek, M. O. Tarhan.

Funding: The authors did not receive support from any organization for the submitted work.

Conflicts of interest: The authors declare that they have no conflict of interest.

Availability of data and material: All core data are available upon request

Code availability: Not applicable.

Ethics approval: The study was approved by the Institutional Ethics Review Board of Izmir Katip Celebi University. (IKCU-2019/98)

Consent to participate: Informed consent was obtained from all participants.

Consent for publication: Informed consent for publication was obtained from all participants.

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