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DIAGNOSTIC COMPARABILITY OF RATIO OF TISSUE DIELECTRIC CONSTANT (TDC) BETWEEN PATIENTS WITH LIPEDEMA AND THOSE WITH LOWER LIMB LYMPHEDEMA (LLL): A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Lipedema is usually thought of as a disease of women. Potentially diagnostic comparative data is needed between patients with lipedema and those with lower limb lymphedema (LLL). Since there is no gold standard to diagnose lipedema, some promising modalities such as Tissue Dielectric Constant (TDC) need to be investigated among patients with lipedema and lymphedema. This study was completed with a total of 26 patients (14 lipedema, 12 LLL). Local tissue water was assessed with Moisture MeterD compact (DelfinTech, Kuopio, Finland) according to the TDC method at 300 MHz within a 2.5 mm tissue penetration depth via the following reference points: Thigh, calf (20 cm upper and lower point of knee level, respectively), and malleoli (5 cm upper point of medial malleolus). Patients with LLL showed significantly higher TDC values and interlimb TDC ratios in all affected points and unaffected malleolus points compared to patients with lipedema. No significant difference was achieved between genders with LLL in all reference points. The area under the curve (AUC) for thigh, calf, and malleolus reference points were found as 0.851 (95%CI .678-1.00), 0.801 (95% CI 0.612-0.989) and 0.786 (95%CI 0.596-0.976), respectively. Patients with LLL showed significantly higher TDC values compared to patients with lipedema, these differences should be carefully interpreted in patients with bilateral LLL and those with lipo-lymphedema.

Keywords: Lipedema, lymphedema, lower limb lymphedema, tissue dielectric constant

Lipedema or "painful fat syndrome" can be described as the deposition and accumulation of fat tissue predominantly localized in both lower extremities symmetrically (1). Although it was reported that there are five subtypes of lipedema exist (2), the vast majority of patients suffer from type III lipedema, which is characterized by symmetrical enlargement of both lower extremities from buttocks through ankles and sparing of the feet. The incidence of lipedema was reported as 11% (3); however, information about the correct rate is still lacking. Lipedema nearly exclusively affects women, and patients with lipedema suffer from a wide range of symptoms. Yet, the exact pathophysiology of lipedema has not been elucidated except for some mechanisms such as familial history, genetic predisposition, and hormonal mechanisms (4). On the other hand, lymphedema is a chronic accumulation of protein-rich fluid in interstitial spaces due to the disrupted lymphatic transport caused by embryonic malformation(s) of lymphatic vascularity (primary

lymphedema) or excision/external trauma of lymphatic structure(s) (secondary lymphedema). The incidence of cancer-related secondary LLL was reported with an overall incidence of 28.8% (5). Other researchers also reported that the incidence of LLL can reach up to 33% and 45%, respectively (6).

Differential diagnosis of both diseases is mainly based on physical examination. Since there are no gold standard criteria for diagnosing lipedema as well as lymphedema, some controversial biased results might occur. Bertsch et al (7) reported that edema is not a discriminative sign for lipedema, thereby the authors eliminated the term "lipo-lymphedema". However, Herbst et al (8) reported contrasting evidence of the edema mechanism in lipedema. For instance, nearly 20% of patients with lipedema were reported to be referred to as lymphedema (9). Although lymphoscintigraphy is known as the gold standard for diagnosing lymphedema (10), it brings additional need for trained personnel and can be costly (11). Indocyanine green lymphography (ICG) has been also reported as a promising option to diagnose LLL due to the ability of real-time imaging of lymphatic vessels (12). Although there are strict differences between both diseases, misdiagnosing might cause loss of time, disappointment, increased healthcare costs, and diminished management efficacy. Due to the great majority of patients with lipedema having a body mass index (BMI) that is nearly or above the threshold of being overweight or obese, misdiagnosing lipedema as obesity is common in clinical practice (13-15). Therefore, patients with lipedema are usually frustrated for being stigmatized as obese, and this can cause deteriorated physical and emotional function as well as remarkably decreased quality of life (16).

There are some promising modalities to perform a differential diagnosis between patients with lipedema and lower limb lymphedema (LLL). High-resolution ultrasonography (17), near-infrared fluorescent lymphography (18), Tissue dielectric constant (TDC) (14), and Dual-energy X-ray absorptiometry (19,20) are reported to be reliable and might be able to differentiate both diseases. However, some of them not only need special equipment and training but also are time-consuming and expensive. Yet, there is an emerging need for easily repeatable, feasible, clinically objective, and reliable modalities that can empower the physical examination of both diseases and may aid in clinical decision-making among clinicians. In this regard, the TDC method, which can be used non-invasively and locally, may help to differentiate both diseases (14,21). Since the differentiation of both diseases can be controversial, especially in some cases, even among experienced specialized clinicians, the TDC method can be a feasible and valuable option to manage not only in clinical decision-making but also to track interventions (21,22).

Since LLL can affect both females and males compared to lipedema, which nearly affects only women (13), there is a lack of comparative information about how males with LLL, irrespective of having primary or secondary LLL, show differences in terms of the TDC values of their extremities compared to patients with lipedema. Therefore, this study aimed to compare the TDC values and ratios between patients with lipedema and those with LLL to gain a value that can be used to differentiate lipedema and LLL from each other.

METHODS

Study Design

This study was designed as a prospective observational study. Non-probability sampling method was used. This study was conducted between January 2018 and April 2018 in an outpatient lymphedema clinic. All procedures and measurements were performed according to the 1964 Helsinki Declaration, and ethical board approval was granted from the Bolu Abant Izzet Baysal University Ethical Board of Clinical Research Studies (protocol number 2018/72-173). All participants were informed before the enrolment of this study, and written informed consent was obtained from all.

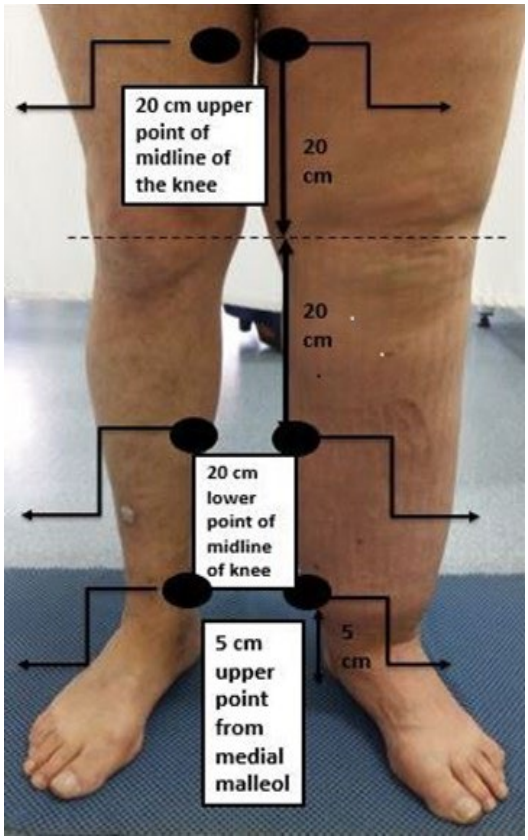

Fig. 1. *Location of points utilized for tissue dielectric constant measurements.*

Patients

Patients diagnosed with LLL, or lipedema were referred to the outpatient lymphedema clinic. Inclusion criteria included consent to participate, having communication skills in the Turkish language, and being over eighteen years old. Exclusion criteria included active metastasis for patients with secondary LLL, having systemic and/or erysipelas infection, being under active systemic treatment for cancer, having mental or cognitive disabilities, or other comorbidities which may hinder to participation process were set as exclusion criteria. Most of both patient groups had suffered from lipedema or LLL for five years or more. Neither patients with lipedema nor patients with LLL had conservative treatment before.

Assessment

Demographic data form

A simple data form was used to gather patients' demographic and clinical information such as age, BMI, lipedema, or LLL (type of LLL, grade, bilateral/unilateral affection, etc.).

Tissue Dielectric Constant (TDC) measurement

Tissue Dielectric Constanta (TDC) was assessed with MoistureMeterD™ compact (Delfin Technologies, Kuopio, Finland) which has a 2.5 mm unique effective measurement depth in predefined reference points as shown in *Fig. 1*. Briefly, a 300 MHz electromagnetic wave which is produced in the control unit is absorbed by the tissues where the probe of the device contacted. Some portions of the wave are absorbed while others are reflected in the control unit. The reflected portion is assumed to be reflected from the fluids of tissue which are attributed to the Tissue dielectric constant, and it is processed in the control unit of the device. Dielectric values of pure water and air are accepted as 78 and 1 at room temperature, respectively. The operational procedure of the measurement was extensively reported previously (23,24).

Patients' reference points were cleaned with a wet wipe prior to marking them with a soft pen. It was noted that there was no cream or lotion on the measurement sites. The patients were requested to rest supine at least for 5 minutes before the measurement. Triplicate measurements were performed in each reference point and the mean was calculated as tissue dielectric constant (TDC). The TDC ratio was calculated for each reference point by dividing the TDC value of the most affected limb by the opposite limb for patients with LLL. Since patients with lipedema show symmetrical involvement of both lower extremities, the ratio was calculated by dividing the TDC value of the dominant site by the other. All measurements were performed a 25 C° room temperature.

TABLE 1
Clinical and Sociodemographic Characteristics of Patients

	LLL n=12	Lipedema n=14
n=26	**Mean (SD)**	**Mean (SD)**
Age (years)	50.58±16.39	52.86±11.37
BMI (kg/m^2)	30.94±8.74	36.45±5.60
Duration	**n (%)**	**n (%)**
0-1 year	1 (8.3%)	1 (7.1%)
1-3 years	1 (8.3%)	1 (7.1%)
3-5 years	2 (16.7%)	2 (14.3%)
5 years or more	8 (66.7%)	10 (71.4%)
Gender	**n (%)**	**n (%)**
Male	5 (41.7%)	-
Female	7 (58.3%)	14 (100%)
Type of LLL	**n (%)**	**n (%)**
Primary	7 (58.3%)	-
Secondary	5 (41.7%)	-

LLL: Lower limb lymphedema, **BMI:** Body mass index, **SD:** Standard deviation

Statistical Analysis

The data was shown as means and standard deviation for continuous variables or number and percent for categorical variables. The normality was assessed with KS-SW tests as well as skewness and kurtosis. Independent t-tests or Mann-Whitney U tests were used whether the data were distributed normally or not between groups. According to the post hoc power analysis, it was seen that we achieved over 90% power via having a larger (>.80) effect size for t-tests within 95% CI with a total of 26 patients (25). The significance level of alpha was accepted as 0.05. Statistical analyses were performed via IBM SPSS 20 (IBM Corp.).

RESULTS

A total of 26 patients (14 lipedema, 12 LLL) participated in this study. Half of the patients with LLL had primary LLL (3 males, 3 females). 5 out of 12 patients with LLL were male while all patients with lipedema were female. All patients with LLL had grade III unilateral LLL according to the ISL (26) grading. All patients with lipedema had type III lipedema (buttocks through ankles) according to the Wold (2) criteria. There was no significant difference in age between patients with lipedema and with LLL (t (24) =0.416, p=0.681) however, patients with lipedema showed significantly higher BMI compared to patients with LLL (z=-3.088, p=0.002). The clinical and sociodemographic characteristics of patients are shown in *Table 1*.

Patients with LLL showed a significantly higher TDC in all affected reference points as well as unaffected malleolus reference points compared to patients with lipedema. The details of TDC values are shown in *Table 2*. The variation of TDC values may vary in a wide range, therefore using the TDC ratio by

TABLE 2
Mean TDC Values Between Patients with Lipedema and Those with LLL

n=26	Lipedema n= (14)	LLL n= (12)	t	p
Affected side				
Thigh	28.03±3.49	39.32±9.61	-3.860	0.002
Calf	30.16±5.74	41.71±10.59	-3.526	0.002
Malleolus	28.98±5.10	45.40±8.05	-6.092	<0.001
Unaffected side				
Thigh	26.38±3.55	28.41±7.18	-0.931	0.361
Calf	27.21±4.19	31.25±7.48	-1.734	0.096
Malleolus	26.49±4.44	33.74±4.49	-4.129	<0.001

LLL: Lower limb lymphedema, **t**: independent t-test, **p**<0.05

TABLE 3
Mean TDC Ratios Between Patients with Lipedema and Those with LLL

n=26	Lipedema n= (14)	LLL n= (12)	t	p
Thigh	1.06±0.05	1.43±0.39	-3.119	0.009
Calf	1.11±0.11	1.35±0.27	-2.906	0.011
Malleolus	1.09±0.06	1.37±0.31	-2.975	0.012

LLL: Lower limb lymphedema, t: independent t-test, p<0.05
Ratios were calculated by dividing the affected side's TDC value by the unaffected side's TDC value for each reference point.

dividing the value of the affected point by the unaffected point, might provide a more comprehensible and conservative interpretation in terms of its diagnostic feature. There were significantly higher TDC ratios in patients with LLL than in those with lipedema (*Table 3*).

Although males with LLL showed higher TDC values and interlimb TDC ratios in thigh and calf reference points compared to women with LLL, no significant difference was achieved between genders in all reference points (p>0.05). Yet, males and females with LLL showed significantly higher TDC values and interlimb TDC ratios compared to women with lipedema in all reference points (p<0.05) (*Table 4*).

The ability of the TDC method to discriminate lipedema from lymphedema was assessed with ROC curve analysis in each reference point separately. The area under the curve (AUC) for thigh, calf, and malleolus reference points were found as 0.851 (95%CI .678-1.00), 0.801 (95% CI 0.612-0.989) and 0.786 (95%CI 0.596-0.976), respectively. The details of the ROC curve analysis as well as

TABLE 4
Comparison of TDC Values and Interlimb TDC Ratios Between Genders in LLL and Lipedema

	Mean (SD)			
LLL	**Males (n=5)**	**Females (n=7)**	**z**	**p**
Thigh	40.96±10.10	38.15±9.86	-.813	.416
Calf	45.76±15.21	38.81±5.28	-1.705	.088
Malleolus	45.54±8.55	45.30±8.38	-.244	.808
Ratio Thigh	1.56±0.55	1.33±0.25	.-568	.570
Ratio Calf	1.38±0.29	1.33±0.28	.-406	.685
Ratio Malleolus	1.28±0.26	1.43±0.35	-1.056	.291
LLL vs Lipedema	**Males (n=5)**	**Females (n=14)**	**z**	**p**
Thigh	40.96±10.10	28.02±3.49	-2.129	.033
Calf	45.76±15.21	30.16±5.74	-1.991	.046
Malleolus	45.54±8.55	28.98±5.10	-3.057	.002
Ratio Thigh	1.56±0.55	1.06±0.05	-2.963	.003
Ratio Calf	1.38±0.29	1.11±0.11	-2.037	.042
Ratio Malleolus	1.28±0.26	1.09±0.06	-1.574	.116
LLL vs Lipedema (Women)	**LLL(n=7)**	**Lipedema (n=14)**	**z**	**p**
Thigh	38.15±9.86	28.02±3.49	-2.835	.005
Calf	38.81±5.28	30.16±5.74	-2.724	.006
Malleolus	45.30±8.38	28.98±5.10	-3.433	.001
Ratio Thigh	1.33±0.25	1.06±0.05	-2.014	.044
Ratio Calf	1.33±0.28	1.11±0.11	-2.127	.033
Ratio Malleolus	1.43±0.35	1.09±0.06	-2.313	.021

LLL: Lower limb lymphedema, **SD:** Standard deviation, **z:** Mann Whitney u test, p< 0.05.
Thigh, calf, and malleolus values refer to the affected side and dominant side for patients with LLL and those with lipedema, respectively. Ratios were calculated as dividing the affected side's TDC value to the unaffected side's TDC value.

TABLE 5
AUC, Sensitivity, and Specificity Values of Patients According to the ROC Curve

n=26	AUC	95% CI	p	TDC ratio (SD)	Mean+(2SD) TDC ratio	Sensitivity	Specificity
Thigh	0.851	0.678-1.00	0.002	1.10 (0.32)	1.74	0.83	0.78
Calf	0.801	0.612-0.989	0.009	1.10 (0.23)	1.56	0.83	0.64
Malleolus	0.786	0.596-0.976	0.014	1.09 (0.25)	1.59	0.83	0.57

***AUC**: Area under the curve, 95% **CI**: 95% confidence interval, **TDC**: Tissue dielectric constant, p<0.05*

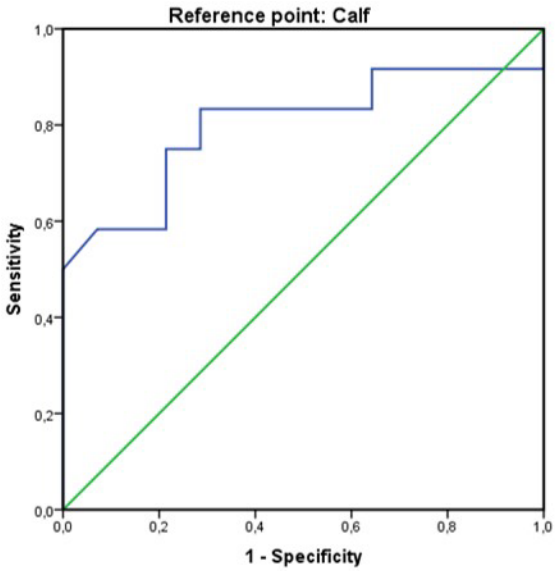

***Fig. 2.** Graphical representations of ROC curve analysis for reference points of patients for the Thigh (A), Calf (B), and Malleolus (C).*

sensitivity and specificity values are shown in *Table 5* and *Fig. 2*, respectively.

DISCUSSION

This study showed that TDC measurement showed a relatively good discriminatory feature in an acceptable to excellent range in different reference points between patients with lipedema and those with LLL. Since patients with LLL showed significantly higher TDC values in their affected extremities compared to patients with lipedema, these differences should be carefully interpreted especially in patients with bilateral LLL and those with lipo-lymphedema. Nevertheless, the TDC method might be a useful option to discriminate between LLL and lipedema in cases with a complex clinical presentation by providing features such as easy repeatability, cheapness, and the opportunity to measure locally.

Diagnosing lipedema is mainly based on physical examination criteria released in the ’50s by Wold et al (2). Since patients with lipedema suffer from difficulty being diagnosed as lipedema except for those who are stigmatized as obese, correct discrimination of lip-

edema is of utmost importance (1,4,13). Patients with lipedema usually experience decreased quality of life, and increased aesthetic problems along with clinical signs such as heaviness, easy bruising, and sensitivity to pressure due to increased fragility of the fat tissue (16). To achieve the best clinical outcomes, focused discrimination of both diseases each other acts as a milestone. Nevertheless, this might be difficult, especially in some complex cases (17). Birkballe et al (14) used TDC and assessed its discriminatory efficacy between patients with lipedema and those with LLL along with healthy controls, and they reported that patients with LLL had significantly higher TDC values in all reference points compared to the others. Similarly, we also have found significantly higher TDC values in LLL than in patients with lipedema. On a physiological basis, this finding was an expected result since fat, which is the primary problem in lipedema, and subcutis are known as having lower TDC values (27). They also reported above 90% sensitivity and specificity according to the cut-off value of TDC as 40. In our study, we analyzed sensitivity and specificity, which were found relatively lower compared to theirs, according to the ROC curve analysis as well as considering inter-limb TDC ratio instead of pure TDC value contrary to their study. Though it was also reported that the use of interlimb TDC ratios reflects better results due to the relatively wide range of TDC values, this finding was reported in healthy subjects in which having a ratio above 1.2 is indicative of lower limb edema (28). Yet, we think using an interlimb ratio might be more advantageous since discrimination of both diseases may be cumbersome especially if both lower extremities are affected in patients with primary lymphedema.

Although a detailed medical history might be adequate to discriminate both diseases, failing to discriminate both diseases in some complex cases can cause increased health costs and morbidity as well as frustration among patients (1,29,30). Thus, there is a growing need for tools that can be used to reach the correct diagnosis to improve clinical outcomes in patients with lipedema and lymphedema. Naouri et al (17) reported no significant difference in dermal thickness between patients with lipedema and healthy controls in reference measurement points while patients with LLL showed significantly higher dermal thickness compared to other groups in all reference points. In the same study, high cutaneous ultrasound examination was reported to be advantageous in terms of its features as well as its ability to discriminate both diseases. Nonetheless, this finding can be disputable especially for patients with preclinic or mild LLL since dermo-epidermal changes might not be manifested in earlier phases of the disease. In addition, the frequency of ultrasound is important to differentiate both diseases since those with low frequency were reported to be unable to discriminate between LLL and lipedema (15,29). Amato et al (15) reported significantly higher dermal thickness in patients with lipedema compared to healthy controls. They have also stated that using 11.7 mm thickness in the pretibial region as a threshold provides nearly 80% sensitivity and over 90% specificity in lipedema diagnosis. Recently, Mackie et al (18) reported that ICG lymphography is a valuable tool to discriminate patients with lipedema from LLL by underpinning the normal lymphatic morphology in patients with lipedema. Buso et al (20) used DEXA by calculating the fat mass (FM) and they reported that the leg-to-total FM ratio can be used to discriminate whether patients with lipedema or LLL. They also reported nearly 0.90 AUC value along with over 90% over sensitivity and 70% specificity by setting the threshold 0.38 (leg/total FM) for diagnosing lipedema from healthy controls. Yet their study did not include any patients with LLL, therefore comparing those values to ours might not be explanative. Dietzel et al (19) used another method which is characterized by the ratio of leg FM to BMI to discriminate lipedema from healthy subjects by using DEXA. They reported the ratio of 0.46 (leg FM/BMI) provides 0.87 sensitivity and 0.68 specificity. On the other hand, Crescenzi et al (31) reported a decreased impedance value in patients with severe lipedema which can be interpreted as an increased accumulation of

fluid in the chronic form of lipedema also known as lipo- lymphedema (32). Yet, we think the regional measurement of FM to diagnose lipedema might be elusive since many patients with lipedema show themselves with different rates of truncal obesity.

In our study, we used interlimb TDC ratios as diagnostic criteria in patients with lipedema and LLL. Since there can be variation in TDC values, it was recommended to use interlimb TDC ratios by calculating the mean +2SD (28). According to this calculation, having a 1.74 or above interlimb TDC ratio in the thigh region provided a good AUC as well as nearly 80% sensitivity and specificity in our study. Yet, diagnostic specificity was found insufficient in calf and malleoli regions in our study. These results might be attributable to the symptom duration of both diseases since Buso et al (33) reported that lymphatic functioning was significantly correlated with symptom duration in patients with lipedema. Since it is well known that prolonged periods of lipedema cause accumulation of lymph and named lipo-lymphedema after that (34), a relatively great variation among interlimb TDC ratios might have occurred. Nevertheless, there were no cases of lipo-lymphedema according to the physical examination in our patients. On the other hand, Mayrovitz et al (22) also stated that it might be useful to use interlimb ratios (calf/forearm or foot/forearm) by considering 1.35 or above to indicate LLL. Yet, these findings were gathered in healthy subjects, and this ratio should be tested further in chronic conditions such as lipedema and LLL.

This study showed a relatively good discriminatory ability of TDC measurement as parallel with the literature findings (14,21). Since the TDC method does not contain any ionizing radiation as well as its easily repeatable, reliable cheap, and non-invasive features, it can be assumed that this method can be more advantageous compared to others. Nonetheless, standardizing measurement procedures as well as reference points might provide a solid basis for more objective interpretations and comparisons.

This study has some strengths and limitations. Since enrolment was performed only in the single outpatient clinic and nearly all our patients were White Caucasian, the generalizability of our findings can be arguable. In addition, there has been limited research as well as researchers using TDC, and thus comparability of the findings can sometimes be restricted. Yet, including male patients with primary LLL might be considered a strength of this study. Yet, further multicenter studies are needed to confirm those diagnostic criteria.

CONCLUSION

Since correct diagnosis in a timely manner can act as a first step to reaching the best clinical outcomes, there is an emerging need for time-efficient and objective approaches regarding the discrimination of patients with lipedema from those with LLL. Not only to improve clinical outcomes but also to use sources and time effectively, easily interpretable and objective, time-efficient and cost-effective solutions are needed. Due to no reporting of superiority in diagnostic tools to one another regarding LLL and lipedema, choosing the optimal and objective approach in addition to the physical examination might augment reaching the correct diagnosis. In this regard, the TDC method might provide valuable insight into clinical practice. We suggest that using the interlimb TDC ratio of patients with lipedema and those with LLL might provide a more focused intuition.

AUTHOR CONTRIBUTIONS

Alper Tuğral, Yeşim Bakar: Conceptualization, Methodology, Software. Alper Tuğral, Yeşim Bakar: Data curation, Writing- Original draft preparation. Alper Tuğral, Yeşim Bakar: Visualization, Investigation. Alper Tuğral, Yeşim Bakar: Supervision. Alper Tuğral: Software, Validation, Statistical analyzing. Alper Tuğral, Yeşim Bakar: Writing- Reviewing and Editing.

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CONFLICT OF INTEREST

All authors declare no competing financial interests.

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