

In patients with diabetic foot, improved left ventricular functions are detected by strain echocardiography after the diabetic foot treatment

A cross-sectional study

Derya Demirtas, MD^{a,*}, Mehmet Kucukosmanoglu, MD^b

Abstract

Diabetic foot is a macrovascular complication of diabetes mellitus (DM). In the literature, the relationship between diabetic foot and another macrovascular complication of DM is not clear. The aim of this study was to determine the current left ventricular (LV) systolic function in patients with diabetic foot and to investigate the effect of diabetic foot treatment on LV systolic functions.

In this study, 54 patients with diabetic foot and 22 patients without diabetic foot were included. Routine anamnesis, physical examination, echocardiography, and laboratory examinations were performed. In addition, LV global longitudinal strain (LV-GLS) was measured by strain echocardiography technique. LV ejection fraction (LV-EF) and LV-GLS measurements were repeated with echocardiography at the 3rd month of diabetic foot treatment.

The incidence of cardiovascular risk factors such as smoking, hypertension, and coronary artery disease was found to be higher in patients with diabetic foot. ($P < .05$ for each one). Similarly, in patients with diabetic foot, glucose, Hemoglobin A1c, neutrophil, sedimentation, urea, creatinine, potassium, uric acid, alanine aminotransferase, aspartate aminotransferase, C-reactive protein, and brain natriuretic protein were higher; high-density lipoprotein cholesterol level was found to be significantly lower. LV wall thicknesses and diameters were higher and LV-EF was lower in patients with diabetic foot ($P < .05$ each one). LV-GLS values were significantly lower in patients with diabetic foot ($P < .05$). Although no significant change was found in the LV-EF value at the 3rd-month follow-up echocardiography ($48.6\% \pm 7.0\%$ vs $48.5\% \pm 5.9\%$ and $P = .747$), it was detected that LV-GLS values (17.3 ± 2.1 vs 18.4 ± 2.3) were significantly increased ($P < .001$).

LV systolic function was significantly affected in patients with diabetic foot. This may be related to the increased frequency of cardiovascular risk factors in these patients. However, the significant improvement in LV-GLS values after the diabetic foot treatment showed that diabetic foot itself was an important cause of LV systolic dysfunction.

Abbreviations: A2B = apical 2-chamber, A4B = apical 4-chamber, DM = diabetes mellitus, HF = heart failure, LV = left ventricular, LV-EF = left ventricular ejection fraction, LV-GLS = left ventricular global longitudinal strain.

Keywords: diabetes mellitus, diabetic foot, strain echocardiography

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^a Department of Internal Medicine, University of Health Sciences, ^b Department of Cardiology, University of Health Sciences - Adana Health Practices and Research Center, Adana, Turkey.

* Correspondence: Derya Demirtas, Assistant Professor of Internal Medicine, University of Health Sciences - Adana Health Practices and Research Center, Dr. Mithat Özsan Bulvarı Kışla Mah. 4522 Sok. No: 1 Yüreğir, Adana, Turkey (e-mail: deryademirtas83@gmail.com)

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1. Introduction

Diabetes mellitus (DM) is a chronic, metabolic disease with hyperglycemia that occurs as a result of deficiency or resistance of insulin hormone secreted from the pancreas.^[1,2] In the context of neuropathy and ischemia associated with peripheral vascular disease, diabetic foot formed by the addition of infection may be in 15% of patients with DM. Diabetic foot is a serious complication of DM, which requires amputation in approximately 7% to 20% of patients.^[3] Peripheral artery disease is the most important factor in determining the outcome of the diabetic foot classified as neuropathic, ischemic and neuroischemic.^[4]

Dyslipidemia may also develop with a decrease in high-density lipoprotein cholesterol levels and increased triglyceride levels in patients with nonregulated blood glucose levels.^[5] Patients with DM may develop ischemia and subsequent heart failure (HF) due to increased atherosclerotic risk and decreased angiogenesis.^[5] Regardless of the etiology of HF, it is important to take protective measures before left ventricular (LV) systolic dysfunction becomes symptomatic.^[6,7] This is only possible with the early

diagnosis of HF. LV ejection fraction (LV-EF) obtained by echocardiography is the most commonly used method for the evaluation of LV functions.^[8] Although it is easy to applicable and prognostic, it has some limitations. The directly effect of image quality on the results, the preload and afterload dependence of the measurement and the limited information in early stages of heart disease has led to search new methods. However, there may be positive results with early diagnosis in heart diseases with limited structural changes and treatment strategies that may affect prognosis. Reduction in longitudinal functions occurs in early stages of myocardial diseases. LV-EF is maintained at normal limits with radial and circumferential compensation. Due to its ability to identify minimal changes in cardiac function and to enable early-stage diagnosis, strain measurement with echocardiography is used but not routinely nowadays.^[9] Strain monitoring shows improvement in subclinical dysfunctions after the treatment in hypertensive heart disease and obesity cases, especially in patients with DM.^[10]

There are not enough studies in the literature to predict the early stages of HF by conventional LV-EF and new examination strain measurements with echocardiography device in patients with diabetic foot. To the best of our knowledge, there is no study about the effect of diabetic foot on LV functions before the treatment and the effect of diabetic foot treatment on LV systolic function in patients with diabetic foot. We detected patient groups in the diabetic foot polyclinic during patient follow-up, in some cases with significant improvement in LV systolic function with diabetic foot treatment. However, because many patients have no symptoms, we have hypothesized that the LV global longitudinal strain (LV-GLS) value, which is a more sensitive and objective parameter, can be changed by diabetic foot treatment.

Therefore in this study, we aimed to determine whether there is a change in LV systolic function by performing traditional and strain echocardiography before and after the treatment in patients with diabetic foot.

2. Material and methods

2.1. Study population

For our study, the patients who were diagnosed as diabetic foot and hospitalized for diabetic foot treatment were screened in our outpatient clinic of Internal Medicine Department. We describe patients as diabetic; who have oral antidiabetic or insulin use history or at least the fasting blood glucose values were measured ≥ 126 mg/dL for 2 times. A total of 54 patients (16 females, 38 males and mean age 59.5 ± 9.8 years) were selected. All of patients were successfully treated with diabetic foot treatment and had good echocardiography image quality before the procedure. 22 control patients (14 females, 8 males and mean age 60.6 ± 8.2 years) who have DM and had no diabetic foot were enrolled in our study. Diagnosis of diabetic foot was defined according to 2018 Diabetic Foot Study Group guidelines. Acute or end-stage liver or kidney disease, acute coronary syndrome, end-stage chronic obstructive pulmonary disease, malignancy and/or active infection in the last 2 weeks, bleeding time disorder, prior hemorrhagic stroke history, severe aortic, and mitral valve disease, New York Heart Association III or patients with IV HF, LV systolic dysfunction (EF < 40), patients with a survival of less than 1 year, and patients who did not want to participate to study were excluded.

A detailed medical history was obtained from each patient and detailed physical examinations were performed. The pulse rate in normal sinus rhythm was recorded before the procedure. Concomitant cardiac and noncardiac systemic diseases and medications were recorded. Wagner–Megitt classification was used to classify the diabetic foot ulcers according to the depth of the ulcer and the width of the gangrene.^[11] Of the 54 patients with diabetic foot, 15 were Wagner 0, 18 were Wagner 1, 12 were Wagner 2, and 9 were Wagner 3. Blood samples were taken; biochemistry and hemogram of all patients were evaluated. Blood biochemistry was taken 12 hours after fasting and before the echocardiography procedure. Glucose, hemoglobin A1c (HbA1c), urea, creatinine, uric acid, sodium, potassium, triglyceride, low-density lipoprotein, high-density lipoprotein, alanine aminotransferase, aspartate aminotransferase, brain natriuretic protein, sedimentation, and C-reactive protein were studied. Neutrophil and white blood cell counts were obtained with complete blood count. Diagnosis of hyperlipidemia was defined as using these criteria, low-density lipoprotein cholesterol > 130 mg/dL or cholesterol-lowering drug usage history. Patients with low-density lipoprotein cholesterol levels greater than 130 mg/dL or a history of anti-hyperlipidemic drug use were identified as hyperlipidemia. Cigarette smoking has been defined by regular smoking in the last 12 months. For the definition of coronary artery disease, patients who were previously diagnosed with coronary artery disease by angiography or had myocardial infarction were accepted. Height, weight, and body mass index were calculated. The body surface area was also calculated with the Mosteller method $[(\text{length} \times \text{weight})/3600]^{1/2}$ formula. The patients' blood pressure values were measured using the appropriate cuff size from the right arm in the sitting position after resting for 10 minutes. The first Korotkoff sound was recorded as systolic blood pressure and the loss of Korotkoff sounds as diastolic blood pressure. Patients with systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and patients using anti-hypertensive drugs were considered hypertensive.

2.2. Ethics approval

All patients were informed about the study and approved consent forms were obtained. This study followed the recommendations of ethical principles published in The Declaration of Helsinki developed by World Medical Association and approved by local ethical committee (Cukurova University Medical Faculty Hospital Clinical Research Ethics Committee)

2.3. M-mode, Doppler, and 2D transthoracic echocardiography

All patients were taken to echocardiography laboratory for M-mode and 2-D transthoracic echocardiography measurements. Measurements were made by EPIQ 7C (Philips Healthcare 3000 Minuteman Road, Andover, MA). All measurements were performed in accordance with the European Society of Cardiovascular Imaging and the American Society of Echocardiography guidelines. LV diameters were evaluated in parasternal long-axis window. M-mode cursor positioned just above the mitral valve tips. LV was taken perpendicular to the long axis. LV-EF and volumes were calculated from apical 2-chamber (A2B) and apical 4-chamber (A4B) images by using the Simpson method. Aortic and left atrial diameter were evaluated from

parasternal long-axis images. Post-diastolic and end-systolic measurements were recorded. LV-E wave velocity, LVA wave velocity and mitral valve deceleration time were measured to correspond to the mitral valve end of the PW Doppler slider in A4B image. For the measurement of isovolumetric relaxation time, apical 5-chamber image was examined. PW Doppler slider was brought between aortic valve and mitral valve and measurement was achieved. For tissue Doppler measurements, the tissue Doppler slider was brought to the septal and lateral corner of the mitral valve annulus. Tissue Doppler images were taken by A4B image.

2.4. LV strain echocardiography

For the LV strain echocardiography, images were taken with the EPIQ 7C (Philips Healthcare 3000 Minuteman Road) echocardiography device. The frame rate of the device has been set 60 to 80 Hz; before images were taken. For LV strain analysis, A2B, A3B, and A4B chamber images were taken. Patients were brought to the left lateral decubitus position. Stable electrocardiographic record was obtained by holding the breath after expiration. Three consecutive pulses were recorded in each window. All patients were in normal sinus rhythm during the procedure. Recorded images analyzed with Philips QLAB (Version 10.5) software. While determining the LV endocardial border, 2 basal and 1 apical part of the LV were placed manually. The software automatically marked the remaining endocardial boundaries. The corresponding epicard limit was automatically drawn. After the analysis, the software divided LV into 7 separate segments for A2B, A3B, and A4B. LV A2B strain, LV A3B strain, LV A4B strain, and LV-GLS were calculated with the mean of these segmental values.

2.5. Diabetic foot diagnosis and treatment

Systematic screening examinations were performed for neuropathic and vascular involvement of the lower extremities of all diabetic patients who applied to the diabetes outpatient clinic due to standing infection. Wagner–Megitt classification revealed the depth and breadth of diabetic foot ulcers. Wound culture was taken from infected tissue and empirical antibiotic treatment was started. Direct radiographs were taken for the presence of osteomyelitis. Lower extremity arterial and venous Doppler ultrasonography was performed for accompanying peripheral arterial disease. Management of patients with diabetic foot was provided with appropriate medical treatment, surgical, or endovascular treatment with multidisciplinary approach including internal medicine specialist, endocrinologist, infectious diseases specialist, plastic surgery specialist, and orthopedist.

3. Results

Patients were divided into 2 groups with and without diabetic foot and all parameters were compared. Clinical, demographic, and laboratory data of patients with and without diabetic foot were compared. The incidence of hypertension, smoking, and coronary artery disease was found in patients with diabetic foot. Glucose, HbA1c, neutrophil, sedimentation, urea, creatinine, potassium, uric acid, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, and brain natriuretic protein were found to be significantly higher and high-density lipoprotein cholesterol level was significantly lower al diabetic

Table 1

Clinical, demographic, and laboratory data of patients with and without diabetic foot.

	Patients with diabetic foot n=54	Patients without diabetic foot n=22	P
Age, yr	59.5±9.8	60.6±8.2	.298
Gender (female/male)	16/38	14/8	.595
Pulse rate, beat/min	76.0±11.8	73.4±9.0	.856
Systolic BP, mm Hg	131.8±	132.3	.891
Diastolic BP, mm Hg	75.9±10.2	80.4±7.5	.065
BMI, kg/m ²	26.3±3.6	27.6±4.2	.193
BSA, m ²	1.90±0.4	2.05±0.7	.223
Cigarette, n (%)	40 (74)	9 (40.9)	.023
HT, n (%)	46 (85.2)	12 (55)	.045
CAD, n (%)	32 (59.3)	8 (36)	.022
Hyperlipidemia, n (%)	14 (25.9)	4 (18.2)	.563
Obesity, n (%)	11 (20.4)	9 (40.9)	.087
Chronic lung disease, n (%)	6 (11.1)	3 (13.6)	.713
Stroke, n (%)	4 (7.4)	3 (13.6)	.406
Glucose	221.4±115	201.4±101	.023
HbA1c	9.3±2.4	7.4±1.9	.012
White blood cell, 10 ³ /μL	9.5±3.4	7.6±2.5	.082
Neutrophil, 10 ³ /μL	6.5±2.9	4.6±1.7	.001
Sodium, mmol/L	136.6±5.6	138.4±3.7	.126
Potassium, mmol/L	4.7±0.4	4.4±0.6	.022
Urea, mg/dL	67.5±39.1	30.1±7.7	<.001
Creatinine, mg/dL	1.4±0.7	0.7±0.2	<.001
Uric acids, mg/dL	6.3±2.2	4.8±1	<.001
AST, U/L	26.5±12.1	17.0±9.1	.001
ALT, U/L	22.1±7.6	15.7±8.5	.001
LDL cholesterol, mg/dL	115.7±48.0	126.7±46.5	.381
HDL cholesterol, mg/dL	37.7±8.3	44.5±11.0	.005
Triglyceride, mg/dL	159.0±84.5	188±110.4	.248
CRP, mg/L	3.1±2.4	0.5±0.3	<.001
BNP, ng/L	5150.1±3549.3	105.2±95.6	<.001
Sedim, mm/h	32.7±11.8	13.8±11.5	.005

AF = atrial fibrillation, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BSA = body surface area, CAD = coronary artery disease, CRP = C reactive protein, HDL = high-density lipoprotein, HT = hypertension, LDL = low-density lipoprotein, BNP = brain natriuretic peptide.

foot patients. Other data were similar between the 2 groups (Table 1). Traditional echocardiography data of patients with and without diabetic foot were compared. LV wall thicknesses and diameters were higher and LV-EF was lower in patients with diabetic foot. The left atrium end systolic diameter was wider in patients with diabetic foot (Table 2). LV strain echocardiography data of patients with and without diabetic foot was compared. LV-GLS values were significantly lower in patients with diabetic foot (Table 3).

Three months after the treatment of diabetic foot, diabetic foot patients were evaluated again with LV systolic functions conventional and strain echocardiography. Although there was no significant change in LV-EF value (48.6% ± 7.0% vs 48.5% ± 5.9% and $P = .747$), LV-GLS values increased significantly (17.3 ± 2.1 vs 18.4 ± 2.3 and $P < .001$) (Table 3).

4. Discussion

One of the main findings of this study is that patients with diabetic foot have significantly decreased LV systolic functions compared to those without diabetic foot, both with traditional echocardiography and strain echocardiography. Another impor-

Table 2
Comparison of echocardiography findings of patients with and without diabetic foot.

	Patients with diabetic foot n=54	Patients without diabetic foot n=22	P
LVEF (%)	48.6±7.0	60.3±5.3	<.001
IVS diastolic thickness, mm	11.5±1.8	10.2±1.6	.004
IVS systolic thickness, mm	13.4±1.8	12.5±1.3	.019
LVPW diastolic thickness, mm	11.8±1.8	10.8±1.6	.037
LVPW systolic thickness, mm	13.6±1.9	13.1±1.3	.248
LV end diastolic diameter, mm	57.6±8.6	47.5±4.8	<.001
LV end-systolic diameter, mm	42.6±10.2	30.8±4.3	<.001
Aortic end diastolic diameter, mm	33.4±3.8	32.2±3.4	.062
LA end-systolic diameter, mm	39.7±3.9	37.0±3.8	.009
LA volume, mL	57.5±9.5	57.2±15.1	.936
EYK, mm	5.3±0.8	5.4±1.3	.725
Sol ventricles-E, cm/s	76.8±16.6	83.0±20.4	.168
Sol ventricles-A, cm/s	59.8±20.9	69.9±22.1	.068
Sol ventricles-E/A	1.3±0.5	1.2±0.3	.374
Deceleration time, ms	194.9±63.7	190.3±39.8	.753
Isovolumetric relaxation time, ms	96.1±18.9	97.1±31.4	.894
Septal S wave, cm/s	6.8±1.6	6.4±1.1	.359
Septal E' wave, cm/s	7.1±2.1	6.5±2.4	.304
Septal A' wave, cm/s	9.2±3.6	9.1±2.4	.661
Lateral S wave, cm/s	8.7±2.4	7.4±1.2	.005
Lateral E' wave, cm/s	9.9±3.0	7.8±2.3	.002
Lateral A' wave, cm/s	9.2±3.6	9.1±2.4	.908
Septal E/E' ratio	11.1±3.5	13.7±5.1	.028
Lateral E/E' ratio	8.5±3.7	11.7±5.1	.003
Septal E'/A' ratio	1.0±0.3	0.9±0.3	.096
Lateral E'/A' ratio	1.3±0.8	1.2±0.7	.792

AF=atrial fibrillation, EFT=epicardial fat thickness, IAS=interatrial septum, IVS=interventricular septum, LA=left atrium, LV=left ventricle, LVEF=left ventricular ejection fraction (Simpson), LVPW=left ventricle posterior wall.

tant finding is the significant increase in LV-GLS value determined by strain echocardiography in the early period by diabetic foot treatment.

Patients with diabetic foot have more cardiovascular mortality rates than diabetic patients without foot problems.^[12] The presence of metabolic syndrome characterized by insulin resistance, obesity, dyslipidemia, and hypertension in the majority of patients with diabetic foot is associated with increased risk of major cardiovascular events. Therefore, the presence of diabetic foot syndrome is now considered a tool for cardiovascular events and mortality.^[13,14] Baltzis et al reported that 26 patients with DM were followed up for 70 months and observed the emergence of cardiovascular events; reported a total of 39 events including 5 fatal myocardial ischemias and a fatal stroke. Other observed events; new-onset cardiac arrhythmias, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, carotid revascularization, nephropathy, peripheral arterial disease, and retinopathy. In these patients, the

Table 3
Comparison of LA strain echocardiography data of patients with and without diabetic foot.

	Patients with diabetic foot n=54	Patients without diabetic foot n=22	P
LV-GLS (%)	17.3±2.1	21.6±1.8	<.001

LV-GLS=left ventricle global longitudinal strain.

presence of any peripheral stenosis and the number of stenosis was correlated with cardiac events.^[15]

Cardiac problem is common in patients with chronic diabetic foot ulcers, even in the absence of known heart disease or hypertension. Therefore echocardiography is recommended as a screening procedure for the follow-up and treatment of diabetic patients with chronic foot ulcers.^[16] There are various echocardiography studies showing subclinical HF in patients with DM without known cardiovascular diseases.^[17] In a study conducted by Löndahl et al found that 62 out of 80 patients with chronic diabetic foot without a known history of cardiac disease had cardiac dysfunction in echocardiography.^[16] In our study, we found that the lower LV-EF and LV-GLS values of basal echocardiography in patients with diabetic foot might be associated with increased cardiovascular risk factor in these patients. These findings support the view that cardiac function should be evaluated routinely using echocardiography in all patients with chronic diabetic foot ulcers.

Chronic inflammation in patients with type 2 DM is a major cause of atherosclerosis and vascular complications. This is due to endothelial dysfunction mediated by the expression of vascular cell adhesion molecule 1 (intercellular adhesion molecule 1) in endothelial cells, leukocyte binding defects, changes in macrophages migration, proliferation of arterial smooth muscle cells, reduction of endothelium-induced nitric oxide production, elevated angiotensin-II secretion, plasminogen activator inhibitor-1, free fatty acids, and lipid oxidation.^[18,19] Increased inflammatory response in patients with diabetic foot causes insulin resistance and endothelial dysfunction, contributing to the development of cardiovascular complications.^[20] In the literature, it has been shown that in the presence of foot ulcers in diabetic patients, myocardial dysfunction, silent myocardial ischemia, and cardiac arrhythmias are observed due to increased circulating inflammatory cytokines, and in these patients, concomitant infection further decreases LV systolic functions in echocardiography and further decreases in LV-EF.^[21-23]

The prognosis of cardiovascular diseases is correlated with EF showing systolic functions. Strain echocardiography has been increasingly used in clinical trials, and some studies have shown that LV-GLS provides a better estimate of the diagnosis, survival, prognosis, and staging of cardiovascular diseases than EF measurement.^[24,25] Strain echocardiography has fast and accurate diagnostic advantages in the evaluation of LV functions. Recent studies have shown that there is a significant relationship between LV-GLS parameters and diagnosis, clinical progression, and side effect prediction in patients with coronary artery disease, HF and diabetes, patients receiving chemotherapy or cardiac transplantation.^[25-28] However, to the best of our knowledge, LV-GLS, which provides evaluation of LV functions, has never been used in patients with diabetic foot in the literature. Therefore, this study was the first to show the relationship between LV-GLS and cardiac function evaluation in the early period before and after treatment in patients with diabetic foot.

In our study, although LV-EF improvement was not observed with echocardiography at the early stages of diabetic foot treatment, significant improvement was observed in LV-GLS value. We believe that this result is due to the fact that LV-GLS is an indicator of early recovery in cardiac functions. Defining the early stage and using appropriate treatment strategies may slow, stop, or even reverse the progression of advanced grade HF. Therefore, LV-GLS measurement should be considered in patients with diabetic foot. In addition, if the treatment of

diabetic foot is received much earlier and more convenient, LV systolic function may be improved earlier.

This study has some important limitations. The number of patients is relatively small and it may be better to conduct a multicentric study involving more patients. The most important factor in the development of diabetic foot disease is peripheral atherosclerosis.^[3] We could not evaluate peripheral atherosclerosis due to lack of Doppler ultrasonography and angiography findings in patients with diabetic foot. Recently, cardiac functions are better analyzed by evaluation of fibrosis in magnetic resonance imaging.^[26] In our study, we could not evaluate the fibrosis. Chronic inflammation is a cardiovascular risk factor in patients with diabetic foot, and increased proinflammatory cytokines such as interleukin-1 and tumor necrosis factor are associated with poor prognosis. We could not evaluate these inflammatory markers in our study. If LV fibrosis and inflammatory cytokines were evaluated, the study could be more significant. LV-EF and LV-GLS measurements were performed at the 3rd-month follow-up of the patients, but LV-EF could also be altered if they were performed later.

5. Conclusion

In patients with diabetic foot, increased cardiovascular risk factors and increased inflammatory process cause a decrease in systolic function. LV-GLS value determined by strain echocardiography is an objective parameter that can be used to determine the change in LV systolic functions in the early period after diabetic foot treatment. However, the results of our study should be supported with larger and different patient groups because of the fact that this finding was shown for the first time.

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Author contributions

Conceptualization: Derya Demirtas.

Data curation: Derya Demirtas, Mehmet Kucukosmanoglu.

Formal analysis: Derya Demirtas, Mehmet Kucukosmanoglu.

Investigation: Derya Demirtas.

Methodology: Derya Demirtas, Mehmet Kucukosmanoglu.

Project administration: Derya Demirtas, Mehmet Kucukosmanoglu.

Resources: Derya Demirtas.

Software: Derya Demirtas.

Supervision: Derya Demirtas, Mehmet Kucukosmanoglu.

Validation: Derya Demirtas.

Visualization: Derya Demirtas.

Writing – original draft: Derya Demirtas, Mehmet Kucukosmanoglu.

Writing – review & editing: Derya Demirtas.

Derya Demirtas orcid: 0000-0001-9449-8759.

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