

# Relation of presence and severity of metabolic syndrome with left atrial mechanics in patients without overt diabetes: a deformation imaging study

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## ABSTRACT

**Objective:** We aimed to investigate left atrium (LA) function by speckle tracking echocardiography in patients with metabolic syndrome (MetSyn) and to show a possible relationship between the severity of MetSyn and LA function and to determine the predictors of low strain in MetSyn patients.

**Methods:** Our study design was observational and cross-sectional design consisted of 80 MetSyn patients without overt diabetes and 50 controls. The patients were classified into three groups based on the number of MetSyn criteria. The peak LA strain at the end of the ventricular systole (LAs-strain) as well as the LA strain with LA contraction (LAa-strain) was obtained. Correlation analysis performed to assess the association of LA strain parameters with the severity of MetSyn and logistic regression analysis performed to assess the relationship of low LA strain with MetSyn.

**Results:** Both LAs ( $37.5 \pm 8.7$  vs.  $26.0 \pm 10.2$ ,  $p < 0.001$ ) and LAa ( $19.9 \pm 6.3$  vs.  $13.0 \pm 6.4$ ,  $p < 0.001$ ) strain measurements were found to be significantly decreased in patients with MetSyn when compared to the control group. Moreover, both LAs and LAa were found to be significantly decreased with the increasing severity of the MetSyn. A multiple logistic regression analysis demonstrated that the presence of MetSyn [OR:0.26 (95% CI 0.06-0.89),  $p=0.032$ ] and left ventricular ejection fraction [OR:1.14 (95% CI 1.03-1.27),  $p=0.021$ ] were independent predictors of LAs strain.

**Conclusion:** MetSyn is associated with reduced LAs strain and LAa strain representing LA reservoir and pump function, respectively. Furthermore, LA mechanical function decreases even more with the increasing severity of the MetSyn.

(*Anadolu Kardiyol Derg 2014; 14: 128-33*)

**Key words:** metabolic syndrome, left atrial function, speckle tracking echocardiography, logistic regression analysis

## Introduction

The metabolic syndrome (MetSyn) is characterized by abdominal obesity, elevated triglycerides, low high-density lipoprotein cholesterol, elevated blood pressure, and impaired glucose tolerance (1). Recent studies have found that MetSyn is associated with a significant risk for new-onset atrial fibrillation (AF) (2). Additionally, it has been shown that this syndrome may lead to electrical and structural remodeling of the atria (3). However, the exact mechanisms relating the MetSyn to increased risk of developing AF are not fully understood. The development of new echocardiographic techniques, such as two-dimensional speckle tracking echocardiography (STE) has

enhanced the ability to evaluate left atrial (LA) function by using quantitative assessment of myocardial deformation. Studies have indicated that STE is a feasible and reproducible method in assessing LA function (4, 5). In some patient groups, as paroxysmal or permanent AF, LA strain measurements were found to be associated with episodes of paroxysmal AF and stroke risk in follow up (6, 7). This method may provide a more direct evaluation of LA myocardial contractility and passive deformation (5).

Therefore, in this particular study, we aimed to investigate LA function by STE in patients who have MetSyn without overt diabetes and to show a possible relationship between the severity of MetSyn and LA function and to determine the predictors of low strain in MetSyn patients.



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**Accepted Date:** 04.04.2013 **Available Online Date:** 14.01.2014

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DOI:10.5152/akd.2014.4686

## Methods

### Study design and protocol

Our study is designed as observational and cross-sectional. Included in the study were 65 patients who presented to the cardiology outpatient clinic from February 1, 2012 to March 15, 2012 and who had a diagnosis of MetSyn, and 65 age- and sex-matched healthy controls. Patients with a prior history of myocardial infarction, paroxysmal, persistent or permanent atrial fibrillation, left ventricular (LV) systolic dysfunction, left ventricular hypertrophy (septal wall thickness  $\geq 1.2$  cm for women;  $\geq 1.3$  for men) (8), moderate to severe valvular heart disease, chronic obstructive pulmonary disease, pre-excitation syndromes, atrioventricular conduction abnormalities, left bundle branch block, thyroid diseases or previously implanted cardiac pacemakers were excluded. Patients were also excluded if they had received any anti-diabetic medication or had a fasting blood glucose level  $\geq 7.0$  mmol/dL or random blood glucose level  $\geq 11.1$  mmol/L. The protocol was approved by the local ethical committee, and all enrolled subjects gave informed written consent.

### Definition of metabolic syndrome

MetSyn was diagnosed according to the International Diabetes Foundation (2005) criteria (9). These criteria require central obesity (defined as BMI  $>30$  kg/m<sup>2</sup> or waist circumference  $\geq 94$  cm in men and  $\geq 80$  cm in women) and the presence of at least two of the followings: (1) a high triglyceride (TG) level ( $\geq 1.7$  mmol/L) or specific treatment for this lipid abnormality; (2) a low high-density lipoprotein (HDL) cholesterol level ( $<1.0$  mmol/L for men and  $<1.3$  mmol/L for women) or specific treatment for this lipid abnormality; (3) a high blood pressure (BP) (systolic  $\geq 130$  mm Hg or diastolic  $\geq 85$  mm Hg, or use of an anti-hypertensive medication); (4) a high fasting plasma glucose (FBG) concentration ( $\geq 5.6$  mmol/L). Patients with MetSyn were classified into three groups based on the number of MetSyn criteria: Group 1 (patients with three MetSyn criteria), Group 2 (patients with four MetSyn criteria) and Group 3 (patients with five MetSyn criteria).

### Echocardiographic measurements

Echocardiography was performed using a GE Vivid 7 system (GE Vingmed Ultrasound AS, Norten, Norway) with a 2.5 MHz phased-array transducer. All measurements were made by two investigators blinded to the clinical data of the subjects. The left ventricular ejection fraction (EF) was calculated by the biplane Simpson's method. Interventricular septum, posterior wall thickness, left ventricular end-diastolic diameter, and left atrial volumes were also measured. Both LV mass and LA volume were indexed to body surface area. The mitral inflow velocity pattern was recorded from the apical four chamber view with the pulsed-wave Doppler sample volume positioned at the tips of mitral leaflets during diastole. Peak early diastolic velocity (E), peak late diastolic velocity (A), deceleration time and isovolumetric relaxation time were measured. The

early diastolic annular velocity (Em) was measured by means of tissue Doppler imaging at the septal and lateral border of the mitral annulus and averaged.

Two-dimensional echocardiography images for LA were obtained from the apical four-chamber view. All images were obtained during breath hold and stored in cine-loop format from three consecutive beats. The frame rate for images was between 50 and 90 frames/second. All data was transferred to a workstation for further offline analysis. After defining the endocardial border manually, tracing was developed by the software system automatically for each view. If the automatically obtained tracking segments were adequate for analysis, the software system was allowed to read the data, whereas analytically inadequate tracking segments were either corrected manually or excluded from the analysis. In STE analysis for LA, peak global LA strain during reservoir phase (LAs-Strain) and LA strain during LA contraction (LAa-Strain) were obtained (10).

### Statistical analyses

Continuous variables are expressed as mean $\pm$ SD. Categorical variables are expressed as percentages. Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. To compare parametric continuous variables, the Student's t test or analysis of variance was used; to compare nonparametric continuous variables, the Mann-Whitney U or Kruskal-Wallis tests was used. To compare categorical variables the chi-square test was used. Correlations between variables were tested by using the Pearson or Spearman correlation tests where appropriate. Two-tailed p values  $<0.05$  were considered to indicate statistical significance. LAs strain was categorized as normal and low according to the cut-off value of 32.2% (11). Multiple logistic regression analysis was applied to identify the independent predictors of the LAs strain. All variables showing significance values  $p<0.05$  on univariate analysis (presence of Metsyn, hypertension, LV mass index, LV ejection fraction, LA volume index, HDL-c, TG, fasting blood glucose levels and waist circumferences) were included in the model. Statistical analyses were performed using SPSS (SPSS inc, Chicago, Illinois), version 15.0 for Windows.

## Results

The study population was comprised of 80 MetSyn patients (51.3 $\pm$ 10.7, 37.5% male) and 50 controls (48.1 $\pm$ 12.9, 30% male). Baseline differences between the MetSyn group and the control group are shown in Tables 1. Both LAs (37.5 $\pm$ 8.7 vs. 26.0 $\pm$ 10.2,  $p<0.001$ ) and LAa (19.9 $\pm$ 6.3 vs. 13.0 $\pm$ 6.4,  $p<0.001$ ) strain measurements were found to be significantly decreased in patients with MetSyn when compared to the control group. Moreover, both LAs and LAa were found to be significantly decreased with the increasing severity of the MetSyn (Table 2), also LAs and LAa strain values in the patient group across the number of fulfilled criteria of MetSyn are shown in Figure 1 and 2. The correlation analyses for E/A, E/E', LA volume index, and LV mass-index with

LAs and LAa strain measurements within the overall population are shown in Table 3. The correlation analysis revealed that LAs and LAa strain measurements were found to be associated with LV-mass index, average E/Em and LA volume-index. LAs stain was categorized into two groups according to the cut-off value of 32.2% (normal or low LAs strain). All variables showing significance values  $p < 0.05$  on univariate analysis (Table 4) between low and normal LAs strain groups were included in the multiple logistic regression analysis. Accordingly, only the presence of MetSyn [OR: 0.26 (95% CI 0.06-0.89),  $p = 0.032$ ] and left ventricular ejection fraction [OR: 1.14 (95% CI 1.03-1.27),  $p = 0.021$ ] were found as an independent predictors of LAs strain (Table 5).

### Discussion

In this study, we investigated LA function by two-dimensional STE in MetSyn patients without overt diabetes. Our study results demonstrated that MetSyn patients without overt diabetes had significantly lower measurements of the peak LA strain (LAs) and LAa strain when compared with healthy control subjects. Furthermore, LA strain measurements decreased as the severity of MetSyn increased and the presence of MetSyn was an independent predictor of low LA strain. This study documents, for the first time in the literature, that LA function, assessed by two-dimensional strain imaging, was impaired in MetSyn patients, in parallel with the severity of the disease.

Recent studies have shown that MetSyn increases the risk of the development of AF (1). The mechanisms underlying the association between this syndrome and AF are uncertain. Obesity may increase atrial size and also be associated with left ventricular hypertrophy (12). Hypertension is associated with left ventricular hypertrophy, impaired ventricular filling and LA enlargement. The REGARDS study has shown that a MetSyn group with AF has increased blood pressure compared to healthy control subjects (13). Diabetes mellitus may cause metabolic stress on the atrium and could lead to myocardial ischemia, fibrosis (13, 14). Additionally, the MetSyn and its individual components may increase the risk of AF through the development of coronary artery disease or heart failure. Furthermore, Chang et al. (15) demonstrated that MetSyn is associated with larger LA size and an arrhythmogenic substrate and an increase in the risk of recurrence after the ablation of AF. These results may indicate electrical and structural remodeling of the atria in MetSyn. However, to our knowledge, there are no data evaluating the LA mechanics and intrinsic LA myocardial function in patients with MetSyn.

Atrial function plays an important role in providing optimum cardiac performance (16, 17). During LV systole and isovolumic relaxation, the LA serves as a reservoir, receiving blood from the pulmonary veins. This atrial function is modulated by LV contraction and LA relaxation/stiffness. During early LV diastole, the LA functions as a conduit. The conduit function is modulated by LV diastolic properties. During late LV diastole, the LA functions as a pump. The LA booster pump function is modulated by LV compli-

**Table 1. Baseline clinical and echocardiographic characteristics of control and metabolic syndrome groups**

	Control (n=50)	MetSyn (n=80)	P
Age, years	48.1±12.9	51.3±10.7	0.148
Sex, male %	30	37.5	0.384
Smoking, %	48	51.3	0.719
Systolic blood pressure, mm Hg	123±13	137±19	<0.001
Diastolic blood pressure, mm Hg	78±9.0	87±7.0	<0.001
Body mass index, kg/m <sup>2</sup>	23.3±2.5	29.9±4.9	<0.001
Waist circumference, cm	82.4±7.1	100.8±8.5	<0.001
HDL-C, mg/dL	44.1±10.6	38.8±9.3	0.002
LDL-C, mg/dL	100±27	112±31	0.031
TG, mg/dL	154±87	194±109	0.025
E/A ratio	1.36±0.66	1.29±0.70	0.613
Average E/Em ratio	10.6±3.9	12.4±6.4	0.046
Estimated PCWP, mm Hg	15.1±4.8	17.3±8.0	0.046
LV mass-index, gr/m <sup>2</sup>	111±25	122±24	0.011
LA volume-index, mL/m <sup>2</sup>	23±7.4	30±8.1	<0.001
LV-ejection fraction, %	63.6±4.7	61.7±5.2	0.051
LAs strain	37.5±8.7	26.0±10.2	<0.001
LAa strain	19.9±6.3	13.0±6.4	<0.001
<b>Medications, %</b>			
Aspirin	22	21	0.920
ACEI-ARB	16	32	0.038
Beta blocker	10	6	0.437
CCB	16	15	0.878
Statins	14	18	0.484
ACEI-ARB - angiotensin converting enzyme inhibitor - angiotensin receptor blocker; CCB - calcium channel blocker; HDL - high density lipoprotein; LA - left atrium; LAs strain - left atrial systolic strain; LA-a strain - left atrial strain; LDL - low density lipoprotein; LV - left ventricle; MetSyn - metabolic syndrome; PCWP - pulmonary capillary wedge pressure; TG - triglyceride Student-t, Mann-Whitney U and chi-square tests were used.			

ance, LV end-diastolic pressure, and LA intrinsic contractility (18). Although this phasic LA function has been mainly assessed using LA volumetric parameters, a new approach based on speckle tracking allows angle independent assessment for regional and global strain/strain rate from 2-D echocardiographic images (19). In the present study, we observed that global longitudinal LAs strain and LAa strain parameters are diminished in patients with MetSyn. While the early reservoir function depends on LA relaxation/stiffness, the late reservoir function depends on LV contraction through the descent of the base during systole. In our patient group, higher LA volume index, which reflects LV filling pressure and chronicity of the LV diastolic function, and higher LV mass index were observed. Camelli et al. (20) demonstrated that peak atrial longitudinal strain detected by STE representing atrial reservoir function was inversely correlated with LV filling pressure (PCWP) in patients with LV

**Table 2. Clinic and echocardiographic measurements according to metabolic syndrome subgroups**

Variables	Group 1 (n=21)	Group 2 (n=28)	Group 3 (n=31)	P value
Age, years	51±11	53±12	50±7.8	0.468
Sex, male %	47.6	42.9	25.8	0.098
E/A	1.51±0.77	1.10±0.59	1.31±0.71	0.123
Estimated PCWP, mm Hg	16.1±5.4	15.5±6.3	19.9±10.1	0.077
LV mass index	108±21	120±22	134±23	<0.05 <sup>*,**,&amp;</sup>
LA volume index	23.2±6.8	30.8±7.4	34.5±6.3	<0.05 <sup>*,**</sup>
LV-EF, %	62.7±4.8	62.9±5.1	60.1±5.4	0.081
LAs strain	33.3±9.6	29.1±9.6	18.3±4.8	<0.05 <sup>*,**,&amp;</sup>
LAA strain	18.1±6.6	14.6±5.2	8.1±3.4	<0.05 <sup>*,**,&amp;</sup>

LAs strain - left atrial systolic strain; LAA strain - left atrial strain  
Data presented as mean±SS and percentage  
\*Group1 vs. 2, \*\*Group 1 vs. 3, &Group 2 vs 3  
p value between group were obtained by ANOVA (LSD were choose as a posthoc test) or Kruskal-Wallis

**Table 3. Correlation analysis of LAs and LAA strain measurements with E/A, average E/Em, LA volume index and LV mass-index**

(r and p value)	LAs strain	LAA strain
E/A	0.09/0.298	0.109/0.216
Average E/Em	-0.307/<0.001	-0.254/0.003
LA volume index, mL/m <sup>2</sup>	-0.589/<0.001	-0.520/<0.001
LV mass index, gr/m <sup>2</sup>	-0.335/<0.001	-0.347/<0.001

LA - left atrium; LAs strain - left atrial systolic strain; LAA strain - left atrial strain; LV - left ventricle

systolic dysfunction. They speculated that elevated LV filling pressure might end with deterioration of LA reservoir function and LA remodeling by chronically exposing the LA under stress. Another study showed that the LAs strain rate was reduced in patients with hypertension who had significantly increased LV mass (21). LV hypertrophy and LA enlargement contribute to impaired reservoir function, resulting in reduced LAs strain rate. In our previous study, we found that LAs strain was more related with LV end-diastolic pressure and NT-pro-BNP level than LAA strain and suggested that LAs strain might be used clinically to predict increased LV end-diastolic pressure (22). Likewise, LV diastolic dysfunction, by impairing LA relaxation and increased LV mass, might also cause reduced LAs and LAA strain in our patients group.

**Study limitations**

This study had some limitations due to the small sample of patients with MetSyn. However, this cohort was exceptional in that none had additional valvular stenosis, insufficiency or any cardiac condition that affect LA function. In addition, we were not able to do any follow-up. As a result, we were not able to know whether reduced LAs strain and LAA strain predict AF episodes or heart failure in patients with MetSyn. One other limitation of the study is the lack of quantitative data about Hb A1c level.

**Table 4. Comparison of clinical and echocardiographic variables between low vs normal LAs strain**

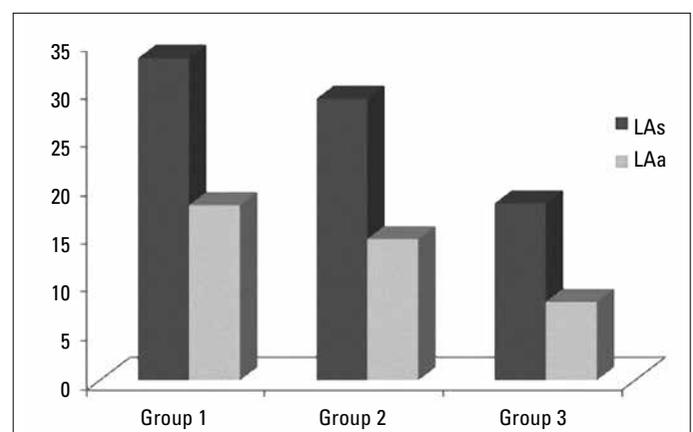
	LAs strain <32.2 (n=55)	LAs strain ≥32.2 (n=75)	P value
MetSyn, %	81	46	<0.001
Hypertension, %	90	72	0.001
LV mass index	124±25	108±23	<0.001
LV - ejection fraction	61±5	64±4	0.001
LA volume index	31±7	22±6	<0.001
Waist circumference	98±10	88±9	<0.001
Fasting blood glucose	112±28	96±17	<0.001

LA - left atrium; LV - left ventricle; MetSyn - metabolic syndrome; Student-t, Mann-Whitney U and chi-square tests were used.

**Table 5. Independent predictors of LAs strain in multiple logistic regression analysis**

Variables	Multiple OR, 95% CI	P
MetSyn, yes/no	0.26 (0.06-0.89)	0.032
Hypertension, yes/no	1.02 (0.37-3.07)	0.943
LV mass index	0.98 (0.96-1.01)	0.743
LV- Ejection fraction	1.14 (1.03-1.27)	0.021
LA volume index	0.91 (0.85-0.98)	0.093
HDL	1.00 (0.95-1.05)	0.997
TG	0.99 (0.98-1.00)	0.021
Waist circumference	0.97 (0.93-1.05)	0.467
Fasting blood glucose	0.99 (0.97-1.03)	0.578

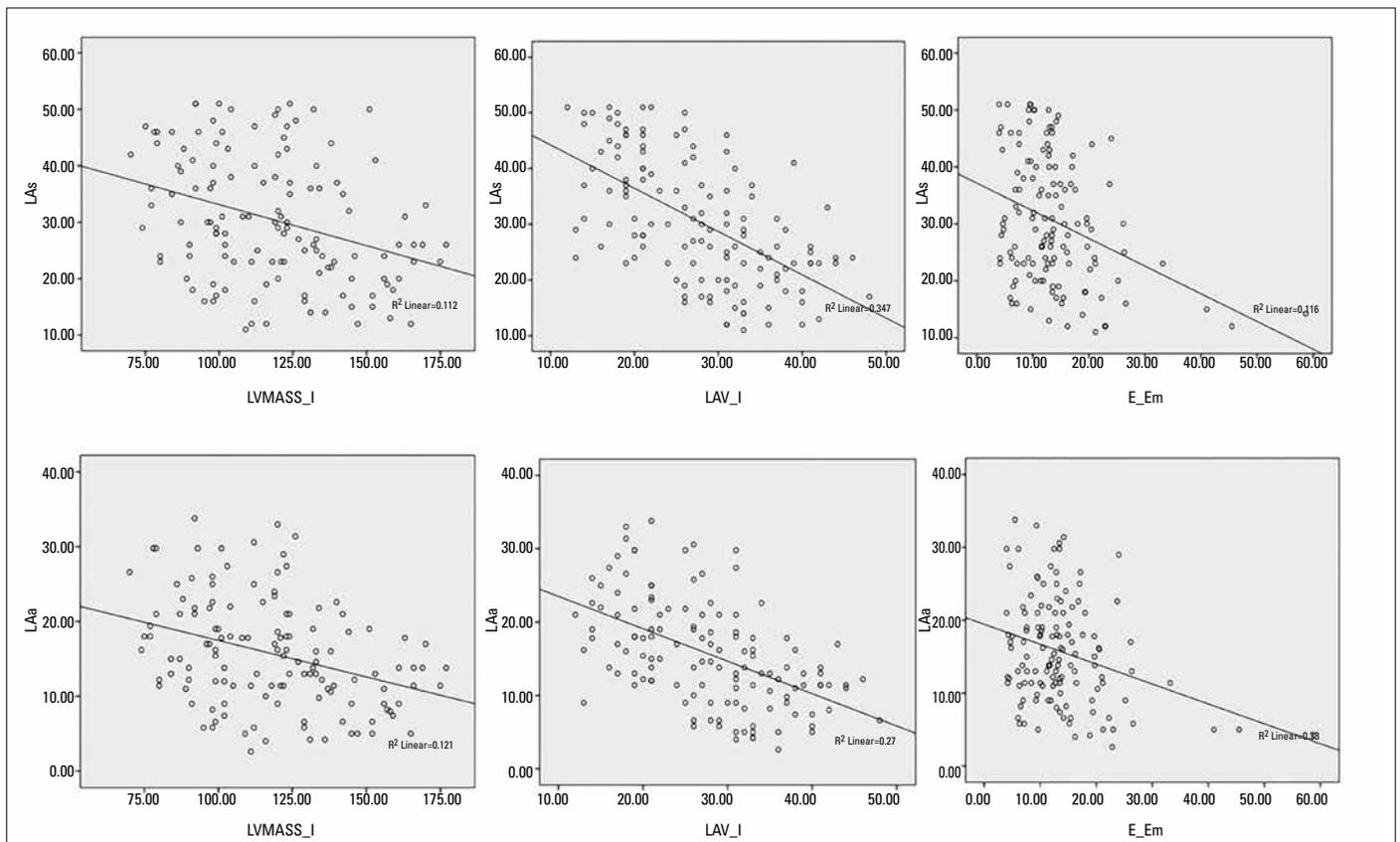
HDL - high density lipoprotein; LA - left atrium; LAs strain - left atrial systolic strain; LV - left ventricle; MetSyn - metabolic syndrome; TG - triglyceride



**Figure 1. Comparison of LAs strain measurements with the number of fulfilled criteria of MetSyn in overall population**

**Conclusion**

As a conclusion, the present study results revealed that MetSyn is associated with reduced LAs strain and LAA strain representing LA reservoir and pump function, respectively. The



**Figure 2. Correlation plots between LAs and LAa**  
Strain measurements and E\_Em, LA volume index (LAV\_I), LV Mass index (LVMASS\_I)

mechanisms may be due to left ventricular hypertrophy, impaired LV diastolic function, intrinsic LA myocardial dysfunction and LA remodeling. Therefore, diminished LA strain parameters might be an early manifestation of LA dysfunction in patients with MetSyn. Besides, reduced LA strain might be associated with increased risk of atrial fibrillation in patients with MetSyn.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - M.K., İ.H.T., E.B.; Design - M.K., İ.H.T., E.B.; Supervision - E.B., N.Ş., A.B.A.; Resource - M.K., İ.H.T., M.F.K.; Materials - M.K., İ.H.T., E.A.; Data collection &/ or processing - M.K., İ.H.T., E.B.; Analysis &/ or interpretation - M.K., İ.H.T., E.A.; Literature search - E.B., N.Ş., A.B.A.; Writing - M.K., İ.H.T., E.B.; Critical review - E.B., N.Ş., A.B.A.

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