

# Two Dimensional Speckle Tracking Echocardiographic Evaluation of Left Ventricle in Post-COVID-19 Patients with or without Cardiac Symptoms: A Retrospective Clinical Study

## COVID-19 Enfeksiyonu Sonrasında Kardiyak Semptomu Olan ve Olmayan Hastalarda İki Boyutlu Speckle Tracking Ekokardiyografi ile Sol Ventrikül Fonksiyonlarının Değerlendirilmesi: Retrospektif Klinik Çalışma

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**ABSTRACT Objective:** In recent years, coronavirus disease-2019 (COVID-19) has been the primary health problem and because of the virus affinity to endothelial cells, it has become an important reason of vascular problems and cardiac injury. After mild COVID-19 infection, patients frequently attend cardiology clinics with cardiac symptoms and their primary cardiac tests are mostly normal. In this study we aimed to analyze if two-dimensional speckle tracking echocardiography shows any difference between symptomatic and asymptomatic post-COVID-19 patients when transthoracic echocardiography parameters are normal. **Material and Methods:** In this retrospective single center study, 2,741 transthoracic echocardiography records were assessed and 108 post-COVID-19 patients were detected and divided into symptomatic and asymptomatic patient groups and left ventricular global longitudinal strain (LV-GLS) values were compared. **Results:** The number of patients with normal LV-GLS values were equal in the groups and there were 4 patients whose values were borderline in the asymptomatic group, while there was none in the symptomatic group. The number of patients with impaired GLS values in the symptomatic group were higher than the asymptomatic group (15 vs 4 patients) and the difference was statistically different ( $p=0.008$ ). The average LV-GLS values were  $-18.88\pm 2.50$  in the asymptomatic group and  $-17.40\pm 3.68$  in symptomatic group but the difference was not statistically significant ( $p=0.098$ ). **Conclusion:** More symptomatic patients than the asymptomatic ones have impaired LV-GLS values according to the results of this study. Even if it is not statistically significant, the mean LV-GLS values are also reduced in symptomatic patients after mild COVID-19 infection.

**ÖZET Amaç:** Son yıllarda, koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] öncelikli bir sağlık sorunu olup, virüsün endotel hücrelerine olan afinitesi nedeniyle vasküler problemler ve kardiyak hasar açısından önemli bir sebep hâline gelmiştir. Hafif geçirilen COVID-19 enfeksiyonu sonrasında, hastalar kardiyoloji kliniklerine kardiyak şikâyetlerle başvurmakta ve primer kardiyak testleri çoğunlukla normal bulunmaktadır. Bu çalışmada, iki boyutlu speckle tracking ekokardiyografi kullanılarak, normal ekokardiyografik parametreleri olan semptomatik ve asemptomatik hastalar arasında fark olup olmadığının değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bu tek merkezli retrospektif çalışmada, 2.741 transtorasik ekokardiyografi kaydı incelenmiş olup, içlerinden 108 COVID-19 sonrası hasta seçilmiştir. Bu hastalar semptomatik ve asemptomatik olarak ikiye ayrılarak, sol ventrikül global longitudinal strain sonuçları [left ventricular global longitudinal strain values (LV-GLS)] kıyaslanmıştır. **Bulgular:** Her iki grupta normal LV-GLS olan hasta sayısı eşit olup, asemptomatik grupta 4 adet sınırda sonucu olan hasta izlenmekteydi. Semptomatik hasta grubunda GLS değeri bozulmuş olan hasta sayısı asemptomatik hasta grubundan anlamlı olarak fazla (15-4 hasta) bulundu ( $p=0,008$ ). Ortalama GLS değeri asemptomatik grupta  $-18,88\pm 2,50$  ve semptomatik grupta  $-17,40\pm 3,68$  olarak hesaplandı ancak aradaki fark istatistiksel olarak anlamlı bulunmadı ( $p=0,098$ ). **Sonuç:** Çalışmamızın sonucunda daha fazla semptomatik hastada bozulmuş GLS değerlerine ulaşılmıştır. İstatistiksel olarak anlamlı olmasa bile, ortalama LV-GLS değerleri de COVID-19 enfeksiyonu sonrasında semptomatik olan hastalarda azalmıştır.

**Keywords:** Echocardiography; speckle tracking echocardiography; global longitudinal strain; COVID-19; post-COVID-19

**Anahtar Kelimeler:** Ekokardiyografi; speckle tracking ekokardiyografi; global longitudinal strain; COVID-19; post-COVID-19

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In recent years, coronavirus disease-2019 (COVID-19) has been the primary health problem and because of the virus affinity to endothelial cells, it has become an important reason of vascular problems and cardiac injury. Acute pericarditis, acute myocarditis and myocardial infarction are the main clinical manifestations especially among patients treated in the intensive care unit.<sup>1-4</sup> Even though the potential pathogenesis of the cardiac injury is not clear, the direct effect to angiotensin converting enzyme 2 receptor and hyperimmune response during sitokin storm are highly suspected and up to 7% of the COVID-19-related deaths have been attributed to myocarditis.<sup>5-10</sup>

After mild COVID-19 infection, patients frequently attend cardiology clinics with cardiac symptoms like chest pain, shortness of breath, palpitations, and reduced exercise capacity and their primary cardiac tests are mostly normal. Because of the potential of possible myocardial injury of the disease, simply applicable advanced techniques like two-dimensional speckle tracking echocardiography (2D-STE) would be a better method than conventional transthoracic echocardiography (TTE) for evaluating regional and global myocardial deformation because it is independent of angle and can diagnose subclinical myocardial dysfunction earlier.<sup>11-14</sup>

The aim of the study is analyzing if the difference of cardiac deterioration could be shown with 2D-STE between symptomatic and asymptomatic post-COVID-19 patients when TTE parameters are normal.

## MATERIAL AND METHODS

In this retrospective single center study, a total of 2,741 TTE records in our hospital's echocardiography laboratory between January 2021-August 2021 were assessed. Post-COVID-19 patients (n=108) were detected. The echocardiograms were evaluated, and the images were recorded by 4 cardiologists experienced in echocardiography and speckle tracking echocardiographic measurements were studied by one of them who is blind to the patients' characteristics. The inclusion criteria of involvement to the study are having had COVID-19 diagnosis by polymerase chain reaction test positiveness in the last 6 months and to be older than 18 years old. Exclusion criteria were designated as; to be hospitalized because of moderate or severe COVID-19 infection, having passed more than 6 months after COVID-19 infection, severe valvular heart disease, segmental/global left ventricular systolic dysfunction, diastolic dysfunction more than Grade 2, known coronary artery disease, conduction disorder, rhythms other than normal sinus rhythm and not having enough imaging frames of echocardiography for calculating left ventricular global longitudinal strain (LV-GLS). After the exclusion criteria, 31 patients were detected for 'symptomatic group' throughout of total included 55 patients (Figure 1).

The study protocol was approved by the Koç University Ethics Committee (date: October 4, 2022, no: 2022.317.IRB1.126) as a retrospective single center study and was conducted according to the Declaration of Helsinki.

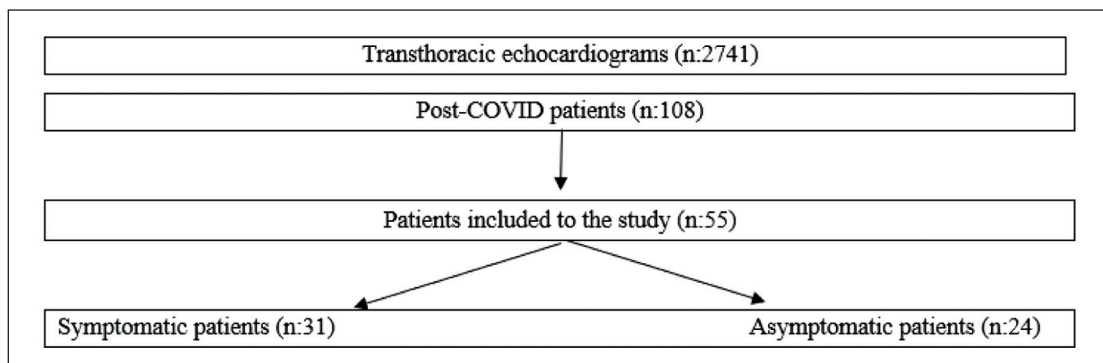


FIGURE 1: Study protocol.

## TTE

TTE was performed on the day the patient presented to the cardiology clinic with Phillips EPIC CVx, Phillips Healthcare, Inc., Andover, MA, USA X5-1 matrix transducer. Left ventricular end-diastolic and end-systolic diameters, left ventricular posterior wall thickness and interventricular septum thickness were measured from parasternal long axis view. Left atrium, right atrium (RA) and right ventricular end-diastolic basal diameters were measured from the apical four-chamber view. Left ventricular ejection fraction was calculated with modified Simpson's method from the apical four chamber view.<sup>15,16</sup> The systolic pulmonary artery pressure was calculated from the sum of tricuspid regurgitation peak velocity and estimated RA pressure.<sup>16</sup>

## STE

LV apical 4-chamber, 2-chamber, and 3-chamber views which were stored during TTE in a frame rate of 60 to 100 frames per second for images of 3 consecutive cardiac cycles were used for offline analysis.<sup>17</sup> Imaging analysis was performed on the Phillips EPIC CVx's QLAB software. The LV endocardial border of the end-systolic frame was automatically traced by the program and manually corrected if necessary. The software automatically created a region of interest including the entire transmural wall for all the patients and selected natural acoustic markers moving with the tissue. Automatic frame by-frame

tracking of these markers during the cardiac cycle [2-dimensional (2D) systolic time interval method] yielded a measure of strain, and strain rate at any point of the myocardium. LV-GLS were measured by averaging the values of all segments.

The standard normal LV-GLS limit was defined as  $>-18\%$ .<sup>18</sup> The impaired GLS level was accepted as  $<-16\%$ . The measurements between these levels were accepted as borderline ( $-18\%$ )-( $-16\%$ ).<sup>19</sup> Figure 2 and Figure 3 shows examples of normal and impaired GLS measurement images of study patients, respectively.

## STATISTICAL ANALYSIS

The statistical analysis was performed with SPSS version 26 (SPSS Inc, USA). Kolmogorov-Smirnov test was applied to show the normality of the distribution. Categorical variables were represented as percentages while the numerical variables were determined as arithmetic mean $\pm$ standard deviation. The student t-test was used for comparison of the averages of the data and chi-square test was used for the comparison of the percentages of the data between groups. The significance levels of 0.05 value were considered for the study and the p values are one-tailed.

Intra-observer variability analysis was assessed for 2D STE measurements from 10 randomly selected patients by the same echocardiographer in two different days by calculating intra-class correlation

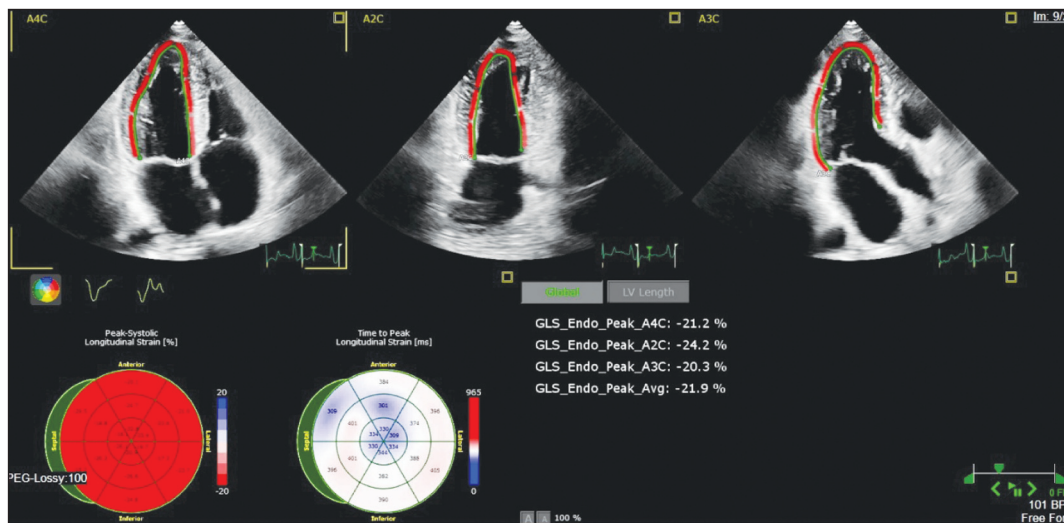


FIGURE 2: Image example of a normal global longitudinal strain measurement.

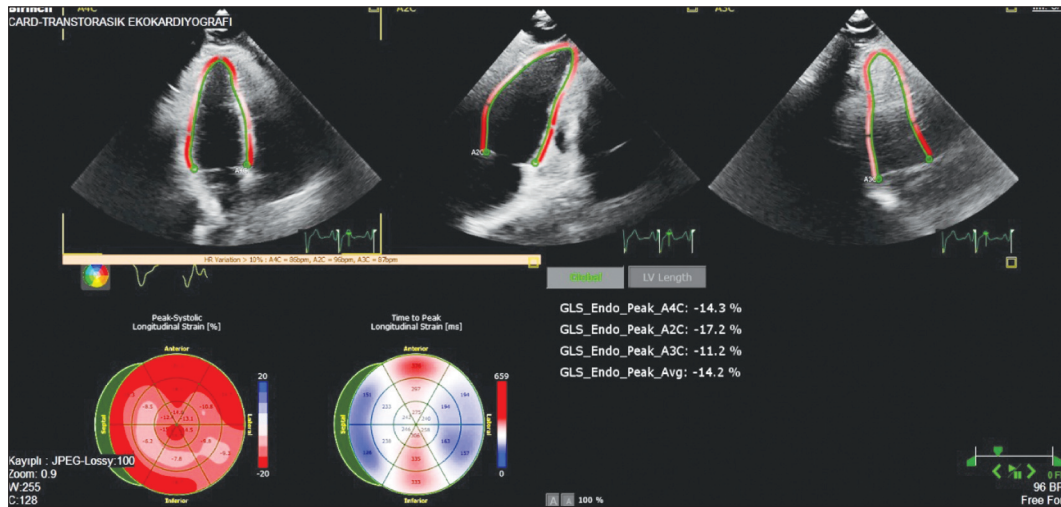


FIGURE 3: Image example of an impaired global longitudinal strain measurement.

coefficient (ICC). Values between 0.75-0.9 indicate good reliability and greater than 0.9 indicate excellent reliability. For intra-class correlation, a high degree of reliability was found for LV-GLS. The average ICC had a 95% confidence interval from 0.73-0.98.

## RESULTS

A total of 55 patients were in the study group and divided into symptomatic (n=31) and asymptomatic (n=24) groups. Only the average age of the patients between the groups was statistically different and there was not a statistically significant difference be-

tween the other demographic and clinic features of the groups. The number of female patients were 27 (49.09%) in the study group (Table 1).

The conventional echocardiographic parameters were similar and were not statistically different between the two groups (Table 2).

The number of patients with normal GLS values were equal in the groups and there were 4 patients whose GLS values were borderline in the asymptomatic group, while there was none in the symptomatic group. The number of patients with impaired GLS values in the symptomatic group were higher than the asymptomatic group (15 patients in the

TABLE 1: The demographic and clinical features of the study groups.

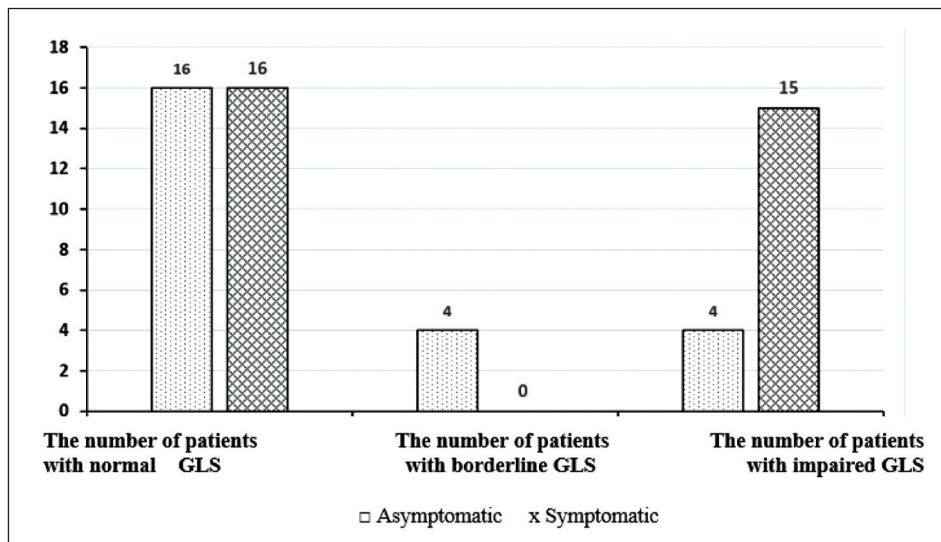
Parameter	Asymptomatic (n=24)	Symptomatic (n=31)	p value
Gender (female) (%)	13 (54.2%)	14 (45.2%)	0.508
Age (years)	52.25±14.98	44.38±11.98	0.036
BMI (kg/m <sup>2</sup> )	25.79±2.35	25.4±3.18	0.617
SBP (mmHg)	124.33±9.95	124.48±13.54	0.964
DBP (mmHg)	79.08±6.15	80.35±9.32	0.566
Heart rate (bpm)	70.3±11.15	74.8±11.8	0.063
Hypertension; n (%)	6 (25)	5 (16.7)	0.659
Diabetes mellitus; n (%)	4 (16.7)	1 (3.3)	0.227
Hyperlipidemia; n (%)	3 (12.5)	2 (6.7)	0.722
ACE-I n (%) ; n (%)	0 (0)	3 (10)	0.267
ARB n (%) ; n (%)	6 (25)	3 (10)	0.303
Beta blockers; n (%)	3 (12.5)	2 (6.7)	0.722
Statin; n (%)	2 (8.3)	2 (6.7)	0.935

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

**TABLE 2:** The echocardiographic measurements of the groups.

Parameter	Asymptomatic (n=24)	Symptomatic (n=31)	p value
LVEF (%)	60±3	60±2	0.494
PAPs (mmHg)	25.5 ± 3.9	24.9±5.4	0.297
IVS (cm)	0.95±0.13	0.94±0.14	0.601
PW (cm)	0.88±0.11	0.90±0.13	0.790
LVEDD (cm)	4.60±0.37	4.61±0.38	0.821
LVEDS (cm)	3.01±0.31	2.99±0.31	0.400
LA (cm)	3.41±0.26	3.42±0.34	0.120
RA (cm)	3.66±0.30	3.58±0.34	0.528
RV (cm)	3.31±0.39	3.31±0.38	0.678
E/A ratio	1.07±0.26	1.08±0.20	0.838

LVEF: Left ventricular ejection fraction; PAPs: Systolic pulmonary arterial pressure; IVS: Interventricular septal thickness; PW: Posterior wall thickness; LVEDD: Left ventricular end-diastolic diameter; LVEDS: Left ventricular end systolic diameter; LA: Left atrium; RA: Right atrium; RV: Right ventricle.



**FIGURE 4:** The GLS values in symptomatic and asymptomatic patients.  
GLS: Global longitudinal strain.

**TABLE 3:** The distribution of patients with impaired GLS values.

Parameter	Group	Asymptomatic	Symptomatic	p value
GLS	Impaired (number of patients)	4	15	0.008
	$\bar{X} \pm SD$ (%)	-18.88±2.50	-17.40±3.68	0.098

GLS: Global longitudinal strain; SD: Standard deviation.

symptomatic group and 4 patients in the asymptomatic group) and the difference was statistically different (p=0.008). The average GLS values were -18.88±2.50 in the asymptomatic group and -17.40±3.68 in symptomatic group but the difference

was not statistically significant (p=0.098). The distribution of the number of patients according to the GLS borders is shown in Figure 4 and the distribution of patients in the impaired GLS values and the average GLS values of the groups are shown in Table 3.

## DISCUSSION

TTE is the main imaging technique to investigate LV structure and functions, but conventional echocardiographic techniques may not be enough to show the pre-clinic mechanical deterioration. 2D-STE is a better method for evaluating regional and global myocardial deformation, can diagnose subclinical myocardial dysfunction earlier, and may detect patients who need further investigations, cardiac controls, and myocardial protection.<sup>11-14</sup>

In our study, we evaluated the difference of left ventricular myocardial functions with LV-GLS between asymptomatic and symptomatic patients who had mild COVID-19 infection. Uziębło-Życzkowska et al. also investigated mild COVID-19 infection's effects in heart functions including standard and advanced echocardiographic techniques but the result of the study did not show significant impairment in left ventricle functions.<sup>20</sup>

The real prevalence of the cardiac involvement in COVID-19 infection is not clear, and the study results are conflicting. It can be speculated that these results may be related to the study populations. In a study from a single tertiary center, Erdol et al. evaluated 100 consecutive COVID-19 proven patients after quarantine period with cardiac magnetic resonance (CMR) and cardiac involvement was detected in 49 patients in which 41 patients described cardiac symptoms that were not present before COVID-19 infection, and the results were statistically significant ( $p=0.001$ ). In 24 patients out of 51 who does not have cardiac involvement in CMR were asymptomatic and this result was statistically significant ( $p=0.001$ ).<sup>21</sup>

As it is known that the 2D-STE and CMR results are compatible with each other, 2D-STE for LV quantification has been validated against magnetic resonance imaging.<sup>22</sup> Puntmann et al. evaluated left ventricle with CMR after mild COVID-19 infection without known cardiac disease and showed more diffuse myocardial edema at follow-up in patients with ongoing symptoms as compared to the ones who have improved. They also investigated the LV-GLS values between the control and post-COVID-19 patients and even though the average values of LV-GLS were

in normal ranges in both groups, the difference was statistically different.<sup>23</sup> In our study, even the average LV-GLS value was lower in the symptomatic group; the difference was not statistically different.

In another hybrid study using both TTE, 2D-STE and CMR, Brito et al. evaluated young athletes who had mild to moderate degree COVID-19 infection. Even no athlete showed ongoing myocarditis imaging features, the result of this study shows that mild or asymptomatic COVID-19 is not a benign illness, as more than one-half of the younger individuals showed subclinical myocardial and pericardial disease.<sup>24</sup> The reduction of LV-GLS values seems to be obtained mostly in symptomatic patients or in patients who have an additional finding as pericardial involvement, and it is independent of the COVID-19 disease severity.

The limitations of our study are, it's a single center retrospective study and the GLS values of our study population are not known before the COVID-19 infection, and the number of the study population is low because we have stopped including patients after August 2021, the date that the m-RNA vaccines are applied to the general population in Türkiye to avoid the potential effects of m-RNA vaccine's myocardial damage and myocarditis side effect. In addition, the fact that our patient group was not compared with patients who had similar demographic characteristics and did not have COVID-19 can be considered among its limitations.

## CONCLUSION

Despite the small number of patients in the study group, the results of this study show that more symptomatic patients than the asymptomatic ones have impaired LV-GLS values. Even if it is not statistically significant, the mean LV-GLS values are also reduced in symptomatic patients after mild COVID-19 infection. It can be concluded that close follow-up of these patients in the future may be beneficial until randomized controlled studies with high numbers of patients are conducted.

### *Source of Finance*

*During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct con-*

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### Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

### Authorship Contributions

**Idea/Concept:** Hülya Gamze Çelik; **Design:** Hülya Gamze Çelik; **Control/Supervision:** Hülya Gamze Çelik, Vedat Aytekin, Saide Aytekin; **Data Collection and/or Processing:** Hülya Gamze Çelik, Betül Cengiz Elçioğlu, Şükrü Taylan Şahin, Saide Aytekin; **Analysis and/or Interpretation:** Hülya Gamze Çelik, Saide Aytekin; **Literature Review:** Hülya Gamze Çelik; **Writing the Article:** Hülya Gamze Çelik, Saide Aytekin; **Critical Review:** Hülya Gamze Çelik, Saide Aytekin; **References and Fundings:** Hülya Gamze Çelik, Saide Aytekin; **Materials:** Hülya Gamze Çelik.

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