

Long Term Effects of Mild Severity COVID-19 on Left Ventricular Functions

Hafif Şiddette COVID-19'un Sol Ventrikül Fonksiyonları Üzerindeki Uzun Dönem Etkileri

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Abstract

Objective	We aimed to evaluate the long-term effects of COVID-19 disease on left ventricular function using speckle tracking echocardiography.
Materials and Methods	In our study, 96 non-hospitalized patients diagnosed with COVID-19 disease in our center between August 15, 2020, and September 1, 2020, and 96 age and gender-matched control subjects were included.
Results	The mean follow-up duration was 137 ± 7 days. White blood cells, neutrophils, and lymphocytes were significantly lower, and C-reactive protein (CRP) and neutrophil to lymphocyte ratio (NLR) were significantly higher in the COVID-19 group. (6.6 ± 2.8 vs. 24.4 ± 21.8, p < 0.001 and 4.1 ± 2.5 vs. 7.1 ± 4, p < 0.001, respectively). Global longitudinal strain (LV-GLS) and global circumferential strain (LV-GCS) were significantly lower in the COVID-19 group. (-20.1 ± 3.1 vs -15.9 ± 2, p < 0.001 and -29.3 ± 2.1 vs -26.3 ± 2.1, p < 0.001, respectively). LV-GLS and LV-GCS were found to be negatively correlated with CRP (rs = -0.515, p < 0.001 and rs = -0.466, p < 0.001, respectively) and NLR (rs = -0.494, p < 0.001 and rs = -0.434, p < 0.001, respectively).
Conclusion	Deteriorating effects of COVID-19 disease on both LV-GCS and LV-GLS can be seen even in the long term. These detrimental effects seem to be associated with CRP levels and NLR measured during active infection.
Keywords	Covid-19, left ventricular dysfunction, echocardiography

Öz

Amaç	COVID-19 hastalığının, sol ventrikül fonksiyonu üzerindeki uzun dönem etkilerini speckle tracking ekokardiyografi kullanarak, değerlendirmeyi amaçladık.
Gereç ve Yöntem	Çalışmamıza 15 Ağustos 2020 - 01 Eylül 2020 tarihleri arasında merkezimizde COVID-19 hastalığı tanımlanan ve hastaneye yatmayan 96 hasta ile yaş ve cinsiyet olarak uyumlu, 96 kontrol olgusu dahil edildi.
Bulgular	Ortalama takip süresi 137 ± 7 gündü. Beyaz kan hücreleri, nötrofil ve lenfosit, COVID-19 grubunda önemli ölçüde daha düşüktü ve C-reaktif protein (CRP) ve nötrofil lenfosit oranı (NLR) önemli ölçüde daha yüksekti. (sırasıyla 6,6 ± 2,8 - 24,4 ± 21,8, p < 0,001 ve 4,1 ± 2,5 - 7,1 ± 4, p < 0,001). Global longitudinal strain (LV-GLS) ve global circumferential strain (LV-GCS), COVID-19 grubunda önemli ölçüde daha düşüktü. (-20,1 ± 3,1 vs -15,9 ± 2, p < 0,001 ve -29,3 ± 2,1 vs -26,3 ± 2,1, p < 0,001). LV-GLS ve LV-GCS'nin CRP (sırasıyla rs = -0,515, p < 0,001 ve rs = -0,466, p < 0,001) ve NLR (rs = -0,494, p < 0,001 ve rs = -0,434, p < 0,001, sırasıyla).
Sonuç	COVID-19 hastalığının hem LV-GCS hem de LV-GLS üzerindeki olumsuz etkileri uzun süre devam etmektedir. Bu olumsuz etkiler, aktif enfeksiyon sırasında ölçülen CRP seviyeleri ve NLR ile ilişkili görünmektedir.
Anahtar Kelimeler	Covid-19, Sol ventrikül disfonksiyonu, Ekokardiyografi

INTRODUCTION

COVID-19 disease, which was firstly identified in Wuhan, China, in December 2019, is an infectious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ The world is still under the influence of the disease, which later became a pandemic.²

In addition to lung involvement in interstitial pneumonia, multiorgan failure can develop in more severe cases. Along with respiratory system involvement, it has been found that cardiovascular and mental disorders are also seen during COVID-19 infection.³ Previous reports have revealed myocardial damage in 20-40% of COVID-19 cases hospitalized due to cardiac chest pain, fulminant heart failure, cardiac arrhythmias, and cardiac arrest.³

Conventional echocardiographic assessment may sometimes be insufficient to evaluate global ventricular systolic function. Studies showed that left ventricular systolic function, which appears to be normal with traditional echocardiographic methods, can be found to have deteriorated in speckle tracking echocardiographic (STE) imaging.⁴ Echocardiographic imaging techniques enable a more quantitative evaluation of complex ventricular movements.⁵ Among these imaging techniques, speckle tracking is an operator and angle-independent method for evaluating regional and global wall movements and is more sensitive in detecting subclinical right and left ventricular dysfunction.⁶ In a recent study, the left ventricular global longitudinal strain (LV-GLS) was affected by COVID-19 infection. Furthermore, it was found to be an independent predictor of mortality in COVID-19 patients.⁷

In this study, we aimed to investigate possible subtle changes in left ventricular systolic function in patients with COVID 19 disease using STE and determine whether the improvement in clinical and laboratory findings is accompanied by cardiac improvement in the long term.

MATERIAL and METHODS

This cross-sectional, single-center study was performed at the University of Ordu Training and Research Hospital, which was determined to treat COVID-19 patients by the Turkish Republic Ministry of Health between November 15 August 2020, and September 1, 2020. The mild severity COVID-19 patients; were defined as patients who were followed outpatient, non-hospitalized, and who had constitutional symptoms including fever, muscle and/or joint pain, cough, sore throat, without respiratory distress (respiratory rate <24/minutes, peripheral capillary oxygen saturation (SpO₂) > 93% at the room) according to the World Health Organization and the Republic of Turkey Ministry of Health COVID-19 Treatment Guidelines. 120 patients with mild severity COVID-19 disease who were older than 18 and treated with only hydroxychloroquine and/or favipiravir were enrolled in the study. Patients with systolic heart failure (LVEF ≤ 50%), coronary artery disease, chronic inflammatory disease, hypertension, severe chronic renal and liver failure, right or left ventricular failure, atrial fibrillation, complete or incomplete branch block, moderate-severe valve pathology, pacemaker, anemia, chronic renal failure, thyroid dysfunction, pulmonary embolism, cancer, chronic lung disease, body mass index (BMI) > 30 kg/m² were excluded. In addition, patients who were given steroids and/or heparin treatments along with hydroxychloroquine and/or favipiravir due to COVID-19 and those who had any other active infection disease and used antibiotics and poor echocardiographic images were excluded. After the exclusion criteria were applied, the study continued with 96 mild severity COVID-19 patients. Age and sex-matched 96 healthy individuals forming the control group were selected consecutively from the outpatient clinic. Demographic data, baseline characteristics, medical history, drugs and medications used for COVID-19, smoking habits, and laboratory values were obtained using the hospital's medical database. Laboratory parameters, including; complete blood count (CBC), C - reactive protein (CRP), D-dimer, ferritin, cardiac troponin I (cTnI), and other biochemical parameters, were measured at the first

admission to the hospital before COVID-19 treatment started. The entire study population was evaluated via two-dimensional echocardiography and speckle tracking echocardiographic imaging. On average, the COVID-19 patients' echocardiographic examinations were performed 4.⁵ (3-6 months) months after the COVID-19 diagnosis. The research procedures were revised and approved by the Ordu University (by decision number 251 on 10.12.2020.) ethics committee and the Ministry of Health Scientific Research Platform (No: 2020-11-07T18_44_00) according to the ethical considerations stipulated in the Helsinki Declaration.

Diagnosis of COVID-19

According to the World Health Organization and the Republic of Turkey Ministry of Health according to the COVID-19 Treatment Guidelines, patients who matched the definition of probable SARS-CoV-2 infection case underwent testing with molecular methods to scan for viruses. Throat and nasopharynx swab samples were collected from all patients in our study to extract SARS-CoV-2 RNA. The real-time reverse transcription polymerase chain reaction assay (RT-PCR) molecular method was applied for RNA analysis of the SARS-CoV-2 virus. Cases with SARS-CoV-2 RNA in the RT-PCR method were accepted as COVID-19.

Two-dimensional echocardiography (2DE)

Conventional 2D echocardiographic examination was performed using a commercially available echocardiography device (EPIQ 7C; Philips Medical Systems, Andover, Massachusetts) in line with the recommendations of the American Echocardiography Association.⁸ All these echocardiographic examinations were performed by two experienced operators. Echocardiographic analyses were performed in the left lateral decubitus position after resting for at least 15 min. Blood pressures of the study population were measured before the echocardiographic examination; the right arm's average systolic blood pressure was measured at 118.5 mmHg / diastolic blood pressure was measured

at 78.5 mmHg, left arm's average systolic blood pressure was measured 120.5 mmHg / diastolic blood pressure was measured 80.5 mmHg. All measurements were taken in three consecutive cycles, and average values were calculated. Patients with optimal views of the left ventricular for STE analysis were included in the study. 12 patients were excluded due to poor echocardiographic images. The patients were monitored by electrocardiogram throughout the procedure. M-mode echocardiography measured left ventricle (LV) and left atrium (LA) diameters and LV wall thicknesses from parasternal long axis views. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method using the apical 4-chamber and 2-chamber images.⁹ Pulsed wave Doppler velocity recordings were obtained in apical four-chamber images via placing the sample volume at the tips of the mitral valve.

E/A ratio was calculated following the assessment of mitral early peak velocity (E) and mitral late peak velocity (A). Stroke volume (EDV—ESV, ml) and cardiac output (stroke volume x heart rate, l/m) were driven after the calculation of LV end-diastolic volume (LV EDV, ml) and end-systolic volume (LV ESV, ml). Tricuspid regurgitation peak velocity was used to measure systolic pulmonary artery pressure (sPAP). Devereux formula was used to calculate the LV mass.¹⁰ Finally, all measurements were re-analyzed considering the body mass index (BMI).

Speckle Tracking Echocardiography

The myocardial deformation quantitative analysis function of 2D-STE was used to evaluate myocardial function. The end of systole was defined as the time the aortic valve is closed, and the end of diastole was defined as the peak R wave in the electrocardiogram. Endocardial borders were monitored within the frame of 2D images at the end of the systole. A wide myocardial width was adjusted to determine the epicardial border. An automatic function determined the midpoints between the endocardial and epicardial borders and the middle myocardial border. A manual adjustment was performed to ensure accurate tracking and

involve all LV wall thickness for 2D speckle viewing width. Apical four-, three-, and two-chamber views were used to evaluate LV-GLS.

All images used for speckle-tracking echocardiographic analysis were obtained using the QLAB-CMQ software program Philips Epiq 7C at a frame rate of 50 to 70 fps. Peak systolic strain measurements of each segment were automatically taken by a software (analysis) program. Following the assessment of longitudinal strain values of 18 segments, the mean value was determined as the global strain.¹¹ The circumferential strain used to evaluate myocardial shortening/ lengthening along the LV curvature was measured from the LV mid-ventricular short-axis view. The global circumferential strain was calculated from the average peak systolic strain value of 16 segments. Negative values were used to determine global longitudinal and circumferential strains, and less negative values indicated lower strains.

Statistical analyses

SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used in all statistical analyses. To test the normality of distribution, Kolmogorov-Smirnov test was used. Quantitative variables were specified as the mean \pm standard deviation. Categorical variables were shown as numbers and percentage values. Differences between groups were evaluated using Student's t-test and the Mann-Whitney U test. Categorical variables were compared with the Chi-square test. Spearman correlation analysis was performed to examine the relationship between LV GCS, LV GLS, and NLR, CRP. A p-value of <0.05 was accepted as statistically significant.

RESULTS

A total of 96 patients who had recovered from COVID-19 disease and 96 healthy controls were included in the study. The mean follow-up duration in the patient group was 137 ± 7 days. The mean age was similar in the COVID-19 and control groups. (43.4 ± 12.8 vs. 44.3 ± 13.1 , $p = 0.590$, res-

pectively). There was no statistically significant difference between the groups regarding gender, BMI, heart rate, diabetes, hypertension, and smoking status. White blood cells, neutrophils, and lymphocytes were significantly lower in the COVID-19 group. On the other hand, C-reactive protein levels and NLR were significantly higher in the COVID-19 group. (2.6 ± 1.8 vs. 24.4 ± 20.1 , $p < 0.001$ and 4.1 ± 2.5 vs. 7.1 ± 4 , $p < 0.001$, respectively). Average levels of C-reactive protein (CRP), ferritin, and D-dimer were higher than normal values in only patients with COVID-19. cTnI level was higher than normal values in only three patients with COVID-19. The baseline characteristics and laboratory findings of the study population are summarized in Table 1.

Parameters	Control (n=96)	COVID-19 (n=96)	P value
Age, years	43.4 \pm 12.8	44.3 \pm 13.1	0.590
Gender, male, n (%)	45 (46.8)	43 (44.7)	0.772
Body mass index, kg/m ²	24.8 \pm 2.1	24.2 \pm 2.5	0.145
Hypertension, n (%)	21 (21.6)	18 (18.7)	0.590
Diabetes mellitus, n (%)	14 (14.5)	12 (12.1)	0.673
Hyperlipidemia, n (%)	9 (9.3)	10 (10.4)	0.549
Smoking, n (%)	47 (48.9)	42 (43)	0.469
White blood cell, 10 ³ uL	6.4 \pm 1.6	7.8 \pm 3.2	0.004
Neutrophil, 10 ³ uL	4.2 \pm 2.2	5.5 \pm 2.3	<0.001
Lymphocyte, 10 ³ uL	1.1 \pm 0.4	0.8 \pm 0.3	<0.001
Monocyte, 10 ³ uL	0.59 \pm 0.3	0.61 \pm 0.3	0.634
Platelet, 10 ³ uL	233 \pm 77	244 \pm 81	0.289
Hemoglobin, g/dl	13.1 \pm 1.6	12.7 \pm 1.7	0.113
Glucose, mg/dl	97.0 \pm 8.5	95.5 \pm 9.2	0.516
Aspartate aminotransferase, IU/l	29.9 \pm 7.6	27.9 \pm 9.7	0.348
Alanine aminotransferase, IU/l	29.5 \pm 9.4	28.2 \pm 15.5	0.485
Creatinin mg/dl	0.87 \pm 0.22	0.86 \pm 0.23	0.469
Sodium, mEq/L	137 \pm 3	137.1 \pm 3.1	0.611
Calcium, mg/dl	9.40 \pm 0.55	9.45 \pm 0.57	0.619
Potassium, mmol/L	4.2 \pm 0.3	4.1 \pm 0.3	0.203
cTnI, ng/mL	N.A.	0.534	N.A.

Hydroxychloroquine, n (%)	N.A	19 (19.7)	N.A.
Favipiravir, n (%)	N.A	77 (80.3)	N.A.
Hydroxychloroquine and Favipiravir, n (%)	N.A.	19 (19.7)	N.A.
C - reactive protein, mg/L	2.6 (0-3)	24.4 (46 - 3)	<0.001
Neutrophil to lymphocyte ratio	4.1 ± 2.5	7.1 ± 4	<0.001
D-dimer, ng/mL	N.A.	340 ± 190	N.A.
Ferritin, ng/mL	N.A.	208 ± 98	N.A.

Data are given as mean ±SD, (%), maximum and minimum. cTnI: Cardiac troponin I; N.A.: Not applicable

When conventional 2D echocardiographic findings were compared, LVEF, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular septal wall thickness (LVSWT), posterior wall thickness (PWT), left ventricular mass index (LVMI) and left atrium diameter was similar between two groups (Table 2).

Parameters	Control (n=96)	COVID-19 (n=96)	P value
Heart rate, bpm	78.7 ± 8	77.2 ± 6	0.301
LVEF, %	62.5 ± 1.4	62.7 ± 1.2	0.216
LVESD, mm	36.1 ± 1.9	35.5 ± 2.3	0.125
LVEDD, mm	45.2 ± 16.3	45.1 ± 2.3	0.783
LVSWT, mm	10.2 ± 0.7	10 ± 0.6	0.264
PWT, mm	9.2 ± 0.5	9 ± 0.6	0.207
LVMI, g/m2	73.4 ± .4	74.2 ± 3.7	0.484
LAD, mm	35.8 ± 2.2	36.2 ± 2.6	0.339
Average E/e' ratio	10.7 ± 1.1	10.1 ± 1.1	0.770
sPAP, mmHg	23.4 ± 2.4	24.1 ± 2.5	0.520
LV GLS, %	-20.1 ± 3.1	-15.9 ± 2	<0.001
LV GCS, %	-29.3 ± 2.1	-26.3 ± 2.1	<0.001

Data are given as mean ±SD or (%), Bpm: beats per minute; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter LVSWT: Left ventricular septal wall thickness, PWT: Posterior wall thickness, LVMI: Left ventricular mass index LAD: Left atrium diameter, sPAB: Systolic pulmonary arterial pressure, LV: Left ventricular, GLS: Global longitudinal strain, GCS: Global circumferential strain,

LV-GLS and LV-GCS values were significantly lower in the COVID-19 group compared to controls. (-20.1 ± 3.1 vs. -15.9 ± 2, p <0.001 and -29.3 ± 2.1 vs. -26.3 ± 2.1, p <0.001, respectively). (Table 2). Spearman correlation analysis showed that there was a statistically significant negative correlation between LV-GLS and LV-GCS values and CRP levels (rs = -0.515, p <0.001 and rs = 0.466, p <0.001, respectively) (Figure 1A, 1B) as well as NLR (rs = -0.494, p <0.001 and rs = -0.438, p <0.001, respectively). (Figure 2A, 2B) .Left ventricular systolic function was similarly affected in both men and women. LV GLS -15.7 ± 2.1 vs.-15.9 ± 2, p=0.498, LV GCS -26.1 ± 2.1 vs -26.2 ± 2.0 p=0.646

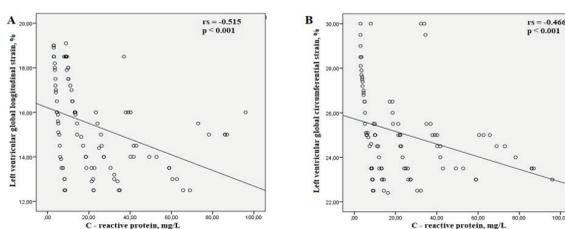


Figure 1. (A) Correlation between LV GLS and CRP. (B) Correlation between LV GCS and CRP

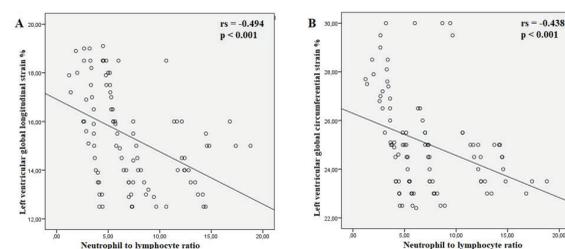


Figure 2. (A) Correlation between LV GLS and NLR. (B) Correlation between LV GCS and NLR.

DISCUSSION

Our study results revealed that LV-GLS and LV-CLS values decreased in patients who had recovered from COVID-19 disease compared to controls. Moreover, these decreased values had a significant negative correlation with C-reactive protein (CRP) levels and neutrophil-lymphocyte ratio (NLR), which are inflammatory markers showing the severity of the disease during the active infection. The long-term subclinical deterioration in left ventricular systolic function indicates that even recovered COVID-19 infection may have prolonged cardiac effects.

The novel coronavirus COVID-19 outbreak, first reported on December 8, 2019, in the Hubei province of China, was recognized as a pandemic by the World Health Organization (WHO) on March 11, 2020. Now available data in public databases signifies that the infection and mortality risk increases in men and elderly individuals.³ However, in our study, left ventricular systolic function was similarly affected in both men and women.

Systemic inflammation, pro-inflammatory cytokine storm, and sepsis resulting in multiorgan failure and death can be seen in severe COVID-19 disease.¹² Cardiac arrhythmia is also an expected finding in COVID-19 disease, and the possible pathophysiologic mechanisms are metabolic dysfunction, myocardial inflammation, and activation of the sympathetic nervous system.¹³ Following Acute Respiratory Distress Syndrome (ARDS), arrhythmia is the second most common clinical finding in severe COVID-19 and was detected in 16.7 % of the patients. The frequency of arrhythmia was 7% in patients who did not require ICU treatment and 44% in those admitted to the ICU.¹⁴ The most common arrhythmia types were atrial fibrillation, conduction block, ventricular tachycardia, and ventricular fibrillation.

Fulminant myocarditis is one of the catastrophic cardiac complications of COVID-19 disease. A recent report in China reported heart failure in 23% of COVID-19 pa-

tients. Heart failure was evident in 12% of the survivors and in approximately 52% of those who lost their lives.¹⁵ In another study, LV-GLS was found to be impaired even in patients who did not have severe COVID-19 disease and had relatively low troponin levels.⁷ Subtle myocardial deterioration was defined as a predictor of death in COVID-19 disease. Therefore, LV longitudinal strain was adopted to be a precise prediction tool for COVID-19 disease considering its early and more robust detection capacity compared to conventional Echocardiography.⁷

The Neutrophile-Lymphocyte ratio (NLR) can be calculated simply by dividing the absolute neutrophil count by the lymphocyte count. The increase in NLR is valuable in reflecting the patient's general inflammatory status.¹⁶ It has been reported that neutrophils are the first inflammatory cells to migrate to the ischemic myocardial tissue. They inflict damage via proteolytic enzymes, reactive oxygen radicals, and stimulating secretion of the other neutrophils.¹⁷ Inflammation is known to be the starting point for all cardiovascular disorders. In many epidemiological studies, NLR has been reported to have a strong relationship with cardiovascular diseases.¹⁸ The main reason is that NLR consists of two separate inflammation markers. It is well known that especially severe cases of COVID 19 have a higher rate of NLR.¹⁹ In a study including 245 hospitalized patients, NLR was identified as an independent predictor of in-hospital mortality for COVID-19 disease.²⁰ In our study, the relationship between LV-GLS and LV-GCS values and CRP levels and NLR supports the hypothesis that active inflammation indicates long-term cardiac outcomes. Based on these findings, it can also be speculated that Evaluation of NLR during the active course of the disease may help in identifying individuals with high cardiac risk. High lactate dehydrogenase (LDH) levels, serum creatine kinase (CK), and CRP were detected in patients with COVID-19.²¹ Moreover, elevated CRP level was positively correlated with lung lesions in the early stage and reflected the severity of COVID-19 disease.²² Another study revealed that CRP levels increase significantly and predi-

ct severe COVID-19 disease before findings are detected in computerized lung tomography (CT) imaging.²³ These studies emphasize the prognostic value of CRP levels in COVID-19 disease.

We speculate that the reasons for the subclinical deterioration in LV systolic function even after an average of 4.5 months following active disease may be the delay in healing of COVID-19 myocarditis and/or the damage caused by the inflammation itself in the acute period. The negative correlation between increasing CRP levels and NLR levels and decreasing LV-GLS and LV-CS values seems to support this hypothesis. However, longer-term follow-up is needed to monitor how long the cardiac effect will continue or whether it will be permanent.

Limitations

Single center design, small sample size, and short follow-up can be considered our study's limitations. Other inflammatory markers such as interleukin-6 and erythrocyte sedimentation rate could also be evaluated. Lack of data about myocardial function before COVID-19 disease can hinder the interpretation of our outcomes. Comorbidities and medications used are possible confounders for strain measurements. Finally, adding a confirmation method for the Evaluation of myocardial impairment, such as magnetic resonance imaging, would strengthen the scientific power of our study.

Consequently, both LV-GCS and LV-GLS were decreased in patients with COVID-19 disease in the long term. This decrease is associated with an increase in CRP levels and NLR. Since subclinical LV systolic dysfunction can not be detected by conventional echocardiographic assessment, we believe in the necessity of STE to evaluate left ventricular systolic function in COVID-19 patients in the long term. Close follow-up of the patients with subclinical LV systolic dysfunction may be reasonable in preventing more severe cardiac complications.

Declarations

Conflict of interest; The authors declare that they have no conflict of interest.

Declaration of Contribution

OB: Data processing, Literature review, Writing
AK: Conception, Design, Supervision, Materials,
SD: Data collection, Writing, Critical review
FNTY: Data interpretation,
CK: Analysis,
YK: Supervision, Critical review

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