Evaluation of Post-COVID-19 Chest Pain and Dyspnea in Outpatients Using Speckle Tracking Echocardiography

Timor Omar (✉ tbigmurad@gmail.com)

Kars Harakani State Hospital: Kars Harakani Devlet Hastanesi <https://orcid.org/0000-0002-2481-0505>

Doğan İliş

Kars Harakani State Hospital: Kars Harakani Devlet Hastanesi

Yusuf Oflu

Kars Harakani State Hospital: Kars Harakani Devlet Hastanesi

Muammer Karakayalı

Kars Harakani State Hospital: Kars Harakani Devlet Hastanesi

Halil Murat Bucak

Kars Harakani State Hospital: Kars Harakani Devlet Hastanesi

İnanç Artaç

Kafkas University Faculty of Medicine: Kafkas Üniversitesi Tıp Fakültesi

Research Article

Keywords: COVID-19, Left ventricular global longitudinal strain, post COVID-19 syndrome, Transthoracic echocardiography, chest pain

Posted Date: November 2nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1032704/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Clinicians are frequently facing patients complaining of post-COVID-19 chest pain and dyspnea. However, it remains to be seen if these symptoms indicate pathology of the cardiovascular system. We aimed to evaluate heart functions in outpatients with post-COVID-19 chest pain and dyspnea, using 2D-speckle tracking echocardiography (2D-STE). This cross-sectional study recruited consecutive patients who presented to cardiology outpatient clinics between June 15 and July 15, 2021. Subjects had recovered from COVID-19 1-2 months prior to admission. ECG, echocardiography including 2D-STE images, were obtained for all patients. Findings were compared with sex and an age-matched control group consisting of 67 healthy adults. A total of 78 patients were included. The median age was 38 (IQR, 34-45) years, and 64.1% were female. There were no significant differences between the patients and control group regarding laboratory, ECG, and echocardiography findings. Moreover, left ventricle global longitudinal strain (LVGLS) measurements in both patient and control groups were within the normal ranges and did not show a significant difference [-20.5 (-21.8- -17.9) vs. -19.8 (-21.4- -18.9), $p=0.894$]. Post-COVID-19 chest pain and dyspnea are unlikely signs of cardiovascular involvement in outpatient young adults who had not been hospitalized with COVID-19.

Introduction

Post-Acute COVID19 Syndrome (PACS) is defined as persistent symptoms 3-4 weeks longer than the initial onset of COVID-19 symptoms [1, 2]. Two of the most common symptoms, suggestive of cardiovascular involvement, present in PACS are chest pain and dyspnea, affecting ~20% of patients recovering from COVID-19 [2]. However, whether these symptoms are a component of the non-specific PACS milieu or indicate pathology in the cardiovascular system has remained elusive. This uncertainty adds to patients', as well as clinicians' concerns: clinicians, particularly family physicians, are increasingly confronting a significant number of patients with post-COVID-19 chest pain and dyspnea [3].

2D speckle-tracking echocardiography (2D-STE) is a valuable technique for evaluating myocardial function in many conditions, including subclinical myocardial dysfunction in post-COVID-19 patients [4, 5].

The literature lacks detailed data investigating post-COVID-19 chest pain and dyspnea in outpatients from a cardiological perspective exclusively. To better understand this issue from a cardiological view of point, we aimed to evaluate heart functions using electrocardiogram (ECG) and echocardiography, including 2D-STE, in outpatients presenting with chest pain and dyspnea and in those recovered from COVID-19. Thereby, we could provide informative data to clinicians who are increasingly facing many so cases.

Materials And Methods

Consecutive patients who presented to the cardiology outpatient clinic with persistent chest pain and dyspnea were included in this cross-sectional study. The subjects had recovered from COVID-19 1-2 months before admission. Emergency conditions, and comorbidities that may cause deterioration in LVGLS analysis, were determined as exclusion criteria. Acute coronary syndrome, heart failure (left ventricle ejection fraction <50%), atrial fibrillation, severe cardiac valve disorders, renal failure (eGFR<30ml/min/1.73m²), severe chronic obstructive pulmonary disease, anemia (hemoglobin level under 11.9 for females and 13.6 for males) and being under 18 years old were the exclusion criteria.

Demographics and laboratory results on admission were recorded. Findings were compared with sex and an age-matched healthy control group consisting of 67 adults.

ECG analysis was performed by a blinded cardiologist (M.K), using a standardized comprehensive ECG reading protocol [6]. It included intervals, rate, QRS morphology, premature atrial and ventricular contract, and T-wave abnormalities. Corrected QT interval (QTc) was calculated using the Fridericia formula [7].

Echocardiographic images were obtained using Philips Epiq7 (Philips Healthcare, Inc., Andover, MA, USA) and recorded by standard techniques. According to the American Echocardiography Association guidelines [8], left ventricular end-systole and end-diastolic diameters, left atrium diameter, interventricular septum thickness, left ventricular posterior wall thickness, right atrium and ventricle diameters were measured. Measurements of mitral inflow included the peak early (E-wave) and late (A-wave) diastolic filling velocities and calculation of E/A ratio. Early diastolic mitral, septal and lateral annular velocities (e') were measured in the apical four-chamber view [9]. Left ventricular ejection fraction (LVEF) was measured using the modified Simpson's rule [10].

Left ventricular global longitudinal strain (LVGLS) was analyzed by another cardiologist (D.İ), blinded to study data, using the Qlab13 (Philips Healthcare, Andover, Massachusetts) program (Fig. 1). While the end-diastole is regarded as the peak R wave of the electrocardiogram, end-systole was estimated aortic valve closure. Mean global longitudinal strain (GLS) was calculated by averaging the peak GLS values of apical two-chamber, apical three-chamber, and apical four-chamber images. Automatic endocardial margins were perceived at the end-systole. Manual corrections were made to secure accurate tracking where required and to include left ventricle (LV) wall thickness. Speckle-tracking analysis was performed per the Consensus Document of the EACVI/ASE/Industry Task Force to Standardize right ventricle (RV) and LV myocardial Deformation Imaging [11, 12].

The country's ministry of health and ... Ethics Committee approved the study protocol (Date: 26 May, 2021; Number 80576354-050-99/180)

Statistical analysis

SPSS software (Version 20.0, SPSS, Inc., Chicago, IL, institutionally registered software) was used for statistical analyses. The Kolmogorov- Smirnov test was used for normality test. Continuous variables were represented as mean±standard deviation for normally distributed and median (IQR) for not normally

distributed variables. Categorical variables were defined as a percentage. While an independent T-test was used to analyze continuous data showing normal distribution, Mann-Whitney U-test was used to analyze variables not showing normal distribution. A p-value of less than 0.05 was considered statistically significant.

Results

Demographic, medical, and echocardiographic data of 95 consecutive patients presenting to cardiology outpatient clinics from 06.15.2021 to 07.15.2021 were recorded. 17 cases (2 heart failure, one hypertrophic cardiomyopathy, two anemia, one renal failure, two chronic obstructive pulmonary disease, nine because of inadequate echocardiographic for STE analysis) were excluded due to exclusion criteria. After that, the final study group included 78 patients [median age 38 (IQR, 34-45) years, 64.1% female]. Demographic, clinical and laboratory characteristics are summarized in Table 1. Of 78 patients, only three had been hospitalized for COVID-19, and the high sensitive troponin T (hs-TnT) level of two patients had been elevated (33 pg/ml and 42 pg/ml, respectively, reference limit < 14 pg/ml) during hospitalization.

Table 1
Demographic, clinical and laboratory characteristics

	Overall (n=145)	Patient (n=78)	Control (n=67)	<i>P</i> - value
Female, n(%)	93 [64.1]	54 [69.2]	39 (58.2]	0.168
Age (years), median [IQR]	38 [34-45]	38.5 [34-46)	37 [34-44.5]	0.426
BMI (kg/m2) median [IQR]	26 [24-28.4]	25.19 [23-28.3]	26.26 [24.4-28.7]	0.062
Laboratory findings at admission				
Hgb (g/dL), mean±SD	14.43±1.58	14.24±1.53	14.65±1.63	0.123
WBC (× 103/μL), median [IQR]	7.1 [6.1-8.2]	7 [6-8.2]	7.2 [6.4-8.1]	0.527
PLT (× 103/μL), median [IQR]	270 [247-303]	281 [258-325]	265 [244-288]	0.004
Glucose mg/dL median [IQR]	91 [86-98]	92 [87-102]	90 [85-96]	0.192
Hs-TnT(ng/L), median [IQR]	6.42 [5.20-7.97]	6.55 [5.5-8]	6.2 [5-7.75]	0.495
ProBNP (pg/mL), median [IQR]	21 [12-50]	22 [15-44]	20 [10-53]	0.556
CRP (mg/L), median [IQR]	2.78 [1–4]	3 [1.57-4.12]	2.2 [0.76-3.89]	0.003
Creatinine (mg/dL), mean±SD	0.71±0.15	0.70±0.15	0.73±0.15	0.215
D-Dimer (μg/mL), median [IQR]	204 [155-307]	205 [165-305]	201 [150-307]	0.405
Lymphocyte (× 103/μL), median [IQR]	2.2 [1.8-2.69]	2.1 [1.7-2.5]	2.27 [3.4-4.96]	0.071
Neutrophil (× 103/μL), median [IQR]	4.2 [3.4-4.96]	4.34 [3.35-4.9]	4.18 [3.47-4.96]	0.774
Comorbidities				
Hypertension, n (%)	16 (11)	10 (12.8)	6 (9)	0.459
Diabetes, n (%)	13 (9)	7 (9)	6 (9)	0.997
Cigarette smoking, n (%)	27 (18.6)	13 (16.7)	14 (20.9)	0.514
Hyperlipidemia, n (%)	8 (5.5)	5 (6.4)	3 (4.5)	0.611
Asthma, n(%)	7 (4.8)	5 (6.4)	2 (3)	0.337
BMI, body mass index; Hgb, hemoglobin; WBC, white blood count; PLT, platelet; hs-TnT, high-sensitivity troponin T; BNP, B type natriuretic peptide; CRP, C-reactive protein				

Table 2
Electrocardiographic and echocardiographic characteristics

	Overall (n=145)	Patient (n=78)	Control (n=67)	<i>P</i> value
Electrocardiogram features				
Heart rate (b.p.m), median [IQR]	75 [70-88]	80 [74-90]	75[67-80]	0.004
PR interval (msec) median [IQR]	144 [132-159]	144 [130-160]	144 [132-155]	0.855
QRS interval (msec) median [IQR]	94 [88-100]	91 [88-98]	94 [88-100]	0.147
QTc (msec), median [IQR]	424 [412-440]	426 [415-446]	424 [412-434]	0.181
T-wave change, n(%)	11 (7.6)	6 (7.7)	5 (7.5)	0.958
fragmented QRS, n(%)	12 (8.3)	6 (7.7)	6 (9)	0.783
Bundle branch block, n (%)	7 (4.8)	6 (7.7)	1 (1.5)	0.082
Premature atrial/ventricular contraction, n(%)	5 (3.4)	2 (2.6)	3 (4.5)	0.529
Echocardiography features.				
LVDD (mm), median [IQR]	46 [42-48]	46 [44-48]	44 [41-48]	0.075
LVSD (mm), median [IQR]	30 [28-34]	30 [28-33]	30 [28-34]	0.839
IVS (mm), median [IQR]	8.5 [8–9]	8.25 [8–9]	8.5 [8–9]	0.872
PW (mm), median [IQR]	7 [7–8]	7 [7–8]	7 [7–8]	0.135
LA (mm), median [IQR]	32 [30-34]	32 [30-34]	32 [30-34]	0.656
RV (mm), median [IQR]	32 [30-34]	32 [30-34]	32 [29-34]	0.544
RA (mm), median [IQR]	32 [31-35]	32 [31-35]	33 [31-36]	0.239
Ejection Fraction (%), median [IQR]	65 [61-67]	65 [60-66]	65 [61-67]	0.211
E/A, median [IQR]	1.2 [1.03-1.5]	1.16 [0.9-1.51]	1.3 [1.1-1.47]	0.123
E/E', median [IQR]	6.4 [5.3-7.67]	6.35 [5.4-7.08]	6.4 [5.55-8]	0.474
TAPSE, median [IQR]	21 [20-23]	21 [20-23]	21 [20-22]	0.527
R', median [IQR]	12 [12.8-13.8]	12.8 [12.2-13.5]	13 [12-14.45]	0.304
PASB, median [IQR]	9 [8–12]	9 [8–12]	8 [8–12]	0.286
LVGLS, median [IQR]	-20 [-21.7-18.15]	-20.5 [-21.8-17.9]	-19.8 [-21.4-18.9]	0.894

	Overall (n=145)	Patient (n=78)	Control (n=67)	P value
QTc, Corrected QT; LVDD, left ventricle end-diastolic diameter; LVSD left ventricle end-systolic diameter; IVS, interventricular septum thickness; PW, left ventricular posterior wall thickness; LA, left atrium diameter; RV, right ventricle diameter; RA, right atrium diameter; TAPSE, tricuspid annular plane systolic excursion; PASP, pulmonary arterial systolic pressure; LVGLS, left ventricle global longitudinal strain				

The distribution of the symptoms on examination was as follows; atypical chest pain in 59, atypical chest pain and dyspnea in 5, typical chest pain in 3, typical chest pain and dyspnea in 4, and dyspnea in 7 patients. Treadmill exercise test of those with typical chest pain was negative. Besides, no pathological finding was found on the chest x-ray of patients with dyspnea.

There were no significant differences between the patients and control group regarding demographic characteristics and comorbidities, including hypertension (HT), diabetes (DM), smoking, hyperlipidemia (HPL9, and asthma. Laboratory findings were within the normal range and were similar between the groups, except for platelet and C-reactive protein (CRP) levels, which were within normal ranges also (Table 1).

Considering electrocardiogram, all features showed similarity between patient and control groups except for heart rate, which was clinically within normal ranges though [80 (74-90) vs 75 (67-8), $p=0.004$]. Frequencies of T-wave change, fQRS, bundle branch block and premature contraction were similar between patient and control groups (7.7% vs 7.5%, $p=0.958$, 7.7% vs 9%, $p=0.783$, 7.7% vs 1.5%, $p=0.082$ and 2.6% vs 4.5%, $p=0.529$, respectively (Table 2).

Regarding echocardiographic characteristics, all parameters, including left and right side functions, were found within normal ranges in both groups and did not show a significant difference (table). Moreover, LVGLS measurements in both patient and control groups were within the normal ranges and did not show a significant difference [-20.5 (-21.8- -17.9) vs. -19.8 (-21.4- -18.9), $p=0.894$] (Table 2).

Discussion

Our study provides data that laboratory and cardiological features, including LVGLS of young adults suffering from post-COVID-19 chest pain and dyspnea, were ordinary and similar to healthy populations'. Of note, our study comprised only outpatient subjects and young adults beyond crucial cardiovascular risk factors and comorbidities. Moreover, only three had been hospitalized with COVID-19, and only two had been suggestive of cardiac involvement (elevated hs-TnT level) during hospitalization.

To our knowledge, the literature lacks data investigating post-COVID-19 chest pain and dyspnea from a cardiological perspective; in this context, our study is preliminary. On the other hand, many papers are available investigating post-COVID-19 cardiac involvement irrespective of symptoms and reporting discordant results. According to a study [5], in 80 COVID-19 survivors, most heart functions, which had been impaired during hospitalization, improved three months after discharge. However, a quarter of

patients still had abnormal LVGLS compared with the initial analysis. Similarly, Özer et al. [13] demonstrated impaired LVGLS values in over half of those who had a myocardial injury during hospitalization and in one-third of all at 1-month follow-up. Dissimilarly to our study, both studies involved an older population (57.7 and 59.9 years, respectively). Besides, they included hospitalized patients, indicating more severe COVID-19 infection, and those with more frequent cardiac risk factors and comorbidities. Another point worth mentioning is that the follow-up analysis was performed irrespective of the presence of symptoms.

On the contrary, there are also studies showing the opposite. A study demonstrated no proof of persistent cardiac dysfunction on echocardiography performed 40 days after hospital discharge following recovery from COVID-19 [14]. Of note, this study did not involve an STE study to identify more subtle myocardial changes. Another research, which is very similar to ours regarding population demographics, is a prospective study of 149 healthcare workers. There were no differences in cardiac magnetic resonance (CMR) characteristics, including cardiac functions, hs-TnT level, and N-terminal pro-BNP at six months post-infection versus age, sex, and ethnicity matched seronegative controls [15]. Similar to our study, the population had relatively fewer comorbidities, and only one patient had severe COVID-19. This report did not include ECG and LVGLS analysis, however.

One of the primary aims of this study was to raise awareness amongst primary care professionals, who are increasingly confronting with many patients with post-COVID-19 chest pain and dyspnea. In reference to the current study, post-COVID19 chest pain and dyspnea in young adults who have not required hospitalization and those without comorbidity and laboratory abnormalities are unlikely due to cardiovascular pathology. Nevertheless, it should be kept in mind that PACS may have significant cardiovascular manifestations, particularly in patients who have been hospitalized with COVID-19, the elderly, and those with significant cardiovascular risk factors and comorbidities. Further studies compromising elderly and heterogeneous populations with cardiovascular risk factors and comorbidities are needed in this field.

Limitations

The study was a single-center, and the number of patients included in the study was relatively small. The study population lacked an older population; thus, it was without significant cardiovascular risk factors and comorbidities. In addition, only three patients had been hospitalized because of COVID-19, and only two had been suggestive of cardiac involvement (elevated hs-TnT level) during hospitalization. In this regard, the study population did not include patients who had suffered from severe COVID-19 infection.

Conclusion

This study could give helpful insights into the currently mostly enigmatic issue, that post-COVID-19 chest pain and dyspnea are unlikely signs of cardiovascular involvement in outpatient young adults who had not been hospitalized with COVID-19.

Declarations

Conflict of interest:

All authors declare that they have no conflict of interest.

Funding:

The authors received no financial support for the research, authorship, and/or publication of this article.

Acknowledgements:

None

References

1. Baig, A.M., *Chronic COVID syndrome: Need for an appropriate medical terminology for long-COVID and COVID long-haulers*. J Med Virol, 2021. **93**(5): p. 2555-2556.
2. Dixit, N.M., et al., *Post-Acute COVID-19 Syndrome and the cardiovascular system: What is known?* Am Heart J Plus, 2021. **5**: p. 100025.
3. Pavli, A., M. Theodoridou, and H.C. Maltezou, *Post-COVID Syndrome: Incidence, Clinical Spectrum, and Challenges for Primary Healthcare Professionals*. Arch Med Res, 2021. **52**(6): p. 575-581.
4. Marques-Alves, P., et al., *Two-dimensional speckle-tracking global longitudinal strain in high-sensitivity troponin-negative low-risk patients with unstable angina: a "resting ischemia test"?* Int J Cardiovasc Imaging, 2018. **34**(4): p. 561-568.
5. Baruch, G., et al., *Evolution of right and left ventricle routine and speckle-tracking echocardiography in patients recovering from coronavirus disease 2019: a longitudinal study*. Eur Heart J Cardiovasc Imaging, 2021.
6. Borys Surawicz, T.K.K., *Chou's Electrocardiography in Clinical Practice*. 6 ed. 2008: Saunders.
7. FRIDERICIA, L.S., *Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken*. 1920. **53**(1): p. 469-486.
8. Lang, R.M., et al., *Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging*. J Am Soc Echocardiogr, 2015. **28**(1): p. 1-39 e14.
9. Nagueh, S.F., et al., *Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging*. J Am Soc Echocardiogr, 2016. **29**(4): p. 277-314.

10. Schiller, N.B., et al., *Left ventricular volume from paired biplane two-dimensional echocardiography*. Circulation, 1979. **60**(3): p. 547-55.
11. Voigt, J.U., et al., *Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging*. Eur Heart J Cardiovasc Imaging, 2015. **16**(1): p. 1-11.
12. Badano, L.P., et al., *Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging*. Eur Heart J Cardiovasc Imaging, 2018. **19**(6): p. 591-600.
13. Ozer, S., et al., *Evaluation of left ventricular global functions with speckle tracking echocardiography in patients recovered from COVID-19*. Int J Cardiovasc Imaging, 2021. **37**(7): p. 2227-2233.
14. Catena, C., et al., *Echocardiographic Comparison of COVID-19 Patients with or without Prior Biochemical Evidence of Cardiac Injury after Recovery*. J Am Soc Echocardiogr, 2021. **34**(2): p. 193-195.
15. Joy, G., et al., *Prospective Case-Control Study of Cardiovascular Abnormalities 6 Months Following Mild COVID-19 in Healthcare Workers*. JACC Cardiovasc Imaging, 2021.

Figures

Fig.1 An example of left ventricle global longitudinal strain speckle tracking of a patient from apical four chamber view.

Figure 1

An example of left ventricle global longitudinal strain speckle tracking of a patient from apical four-chamber view.