Alternation in follow-up echocardiographic indices in patients with COVID-19: a prospective cohort study

Yeganeh Pasebani[1], Zohre Kahe[1], Ali Rafati[1], Nastaran Salimi[2], Yousef Rezaei[1], Zahra Rahnamoun[1], Nasrin Mousavi[1], Arezoo Vadadi Haghighattalab[1], and Niloufar Samiei[1]

[1]Rajaie Cardiovascular Medical and Research Center
[2]Iran University of Medical Sciences

October 3, 2022

Abstract

Background Cardiovascular complications are frequently reported among patients with pulmonary coronavirus disease 2019 (COVID-19) infection. Echocardiography has been immensely implemented for diagnosing cardiovascular involvements. We aimed to evaluate the changes in echocardiographic parameters in health care workers infected with COVID-19 during follow-up. **Methods** This prospective study was conducted during Iran's third COVID-19 wave in November 2020 among health care workers who were infected with COVID-19 but otherwise healthy. A total of 100 patients underwent echocardiographic examination six to eight weeks following recovery, an early follow-up. Six months after the COVID-19 diagnosis, as the late follow-up, 63 subjects underwent echocardiographic evaluations. Moreover, based on clinical and radiological evidence, individuals were categorized into two groups of non-severe and severe COVID-19. **Results** The participants' mean age was 40.4±8.1 years. In the non-severe COVID-19 group, Right Ventricle Free-Wall Global Longitudinal Strain (RVFWGLS) significantly decreased in the follow-up echocardiogram (-32.3±4.6% vs. -28.8±5.8%, p-value=0.002). RV Fraction Area Change (RV-FAC) (46.6% [43.6-53] vs. 39.7% [25-43] , p-value <0.001) and, Tricuspid Annular Plane Systolic Excursion (TAPSE) (21 mm [19-24] vs. 23 mm [20-25], p-value=0.09) did not show a significant change. In the severe COVID-19 group in late echocardiogram, RVFWGLS showed no statistically significant change (-28.3%±3.5 vs. -28.6%±5.1, p-value=0.79). The RV-FAC (47.2% [42.3-52.2] vs. 36.4% [31.1-45], p-value=0.002) showed a significant decrease, and TAPSE (22.5 mm [19.1-24.2] vs. 23 mm [21-25], p-value= 0.55) was comparable. **Conclusion** Although LV and RV functions did not vary significantly over time in our entire cohort, different patterns of changes were discovered according to baseline function.

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Running title: Late echocardiogram and COVID-19

Zohre Kahe[1+], MD; Yeganeh Pasebani[1,2*, +], MD; Ali Rafati[1,2], MD, MPH; Nastaran Salimi[3], MD; Yousef Rezaei[2], MD; Zahra Rahnamun[1], MD; Nasrin Mousavi[1]; Arezoo Vadadi Haghighattalab[1]; Niloufar Samiei[2], MD.

1. Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
2. Heart Valve Disease Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran,
3. School of Medicine, Iran University of Medical Sciences Tehran Iran

+ These two authors contributed equally.

*Correspondence: Yeganeh Pasebani, MD

Rajaie Cardiovascular Medical and Research Center, Vali-e-Asr Avenue, Tehran, Iran. 1995614331. Tel: +989193364629

Email: yeganehpasebani@gmail.com

ORCID:

Yeganeh Pasebani: 0000-0001-5136-6860

Ali Rafati: 0000-0001-5578-9668

Nastaran Salimi: 0000-0002-3653-4798

Yousef Rezaei: 0000-0002-6804-4232

Niloufar Samiei: 0000-0003-2762-9872

Ethics

The institutional review board of RCMRC in Tehran, Iran, has evaluated and approved the study's protocol and goals. All patients provided written informed consent and consented to use their data for clinical research. In all stages of the study, we strictly behaved in line with the declaration of Helsinki.

Sources of Funding

None.

Conflict of interests:

The authors declare no conflict of interest.

Data availability:

Data are available upon reasonable request.

Background

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Methods

This prospective study was conducted during Iran's third COVID-19 wave in November 2020 among health care workers who were infected with COVID-19 but otherwise healthy. A total of 100 patients underwent echocardiographic examination six to eight weeks following recovery, an early follow-up. Six months after the COVID-19 diagnosis, as the late follow-up, 63 subjects underwent echocardiographic evaluations. Moreover, based on clinical and radiological evidence, individuals were categorized into two groups of non-severe and severe COVID-19.

Results

The participants' mean age was 40.4±8.1 years. In the non-severe COVID-19 group, Right Ventricle Free-Wall Global Longitudinal Strain (RVFWGLS) significantly decreased in the follow-up echocardiogram (-32.3±4.6% vs. -28.8±5.8%, p-value=0.002). RV Fraction Area Change (RV-FAC) (46.6% [43.6-53] vs. 39.7% [25-43] , p-value <0.001) and, Tricuspid Annular Plane Systolic Excursion (TAPSE) (21 mm [19-24] vs. 23 mm [20-25], p-value=0.09) did not show a significant change. In the severe COVID-19 group in late echocardiogram, RVFWGLS showed no statistically significant change (-28.3%±3.5 vs. -28.6%±5.1, p-value=0.79). The RV-FAC (47.2% [42.3-52.2] vs. 36.4% [31.1-45], p-value=0.002) showed a significant decrease, and TAPSE (22.5 mm [19.1-24.2] vs. 23 mm [21-25], p-value= 0.55) was comparable.

Conclusion

Although LV and RV functions did not vary significantly over time in our entire cohort, different patterns of changes were discovered according to baseline function.

Keywords

COVID-19; Echocardiography; Ventricular Function, Left; Ventricular Function, Right

Introduction

Pulmonary coronavirus disease 2019 (COVID-19) has been a multifaceted viral infection with subsequent immunologic complications not only engaging the respiratory system but also with more studies emerging, more details are being discovered about the potential maladies inflicts upon many organs and systems of the body (1). The spectrum of COVID-19 infection spans from mild, self-limiting respiratory tract sickness to fatal progressive pneumonia and multiorgan failure (2, 3).

A variety of cardiac complications, comprising of stress-induced myocarditis, acute myocardial infarction, acute failure of right and left ventricles with subsequent elevations in right ventricular afterload as a result of pulmonary embolism or pneumonia, tamponade, and cardiomyopathy, have been reported in hospitalized COVID-19 patients in the acute phase of the disease (4, 5). It has been suggested that cardiac problems are frequent (20 to 25%) with COVID-19 infection and are associated with in-hospital mortality. In those reports, cardiac problems were determined only based on clinical and laboratory data (e.g., troponin levels) and without systematic cardiac imaging (6).

Transthoracic echocardiography (TTE) is the principal imaging modality for the evaluation of the heart, which is a widely accessible and inexpensive tool. Echocardiography has been remarkably useful in assessing the aforementioned complications throughout the era of COVID-19 (7). However, studies concerning the long-term cardiac effects of this infection in non-hospitalized patients have remained scarce (5).

In this study, we aimed to evaluate the long-term alterations of echocardiographic findings in health care workers of a tertiary center who are young, productive, and without prior cardiac complications based on their clinical COVID-19 severity six months after being diagnosed with COVID-19 infection.

Methods and materials

Study setting and protocols

This prospective cohort study was performed during Iran's third COVID-19 wave in November 2020 in Rajaie Cardiovascular Medical and Research Center's (RCMRC) employees who had been previously infected with COVID-19. A total of 63 Individuals with an earlier positive reverse transcriptase-polymerase chain reaction test (RT-PCR) were planned to undergo echocardiography at two different time points. The early echocardiography was performed 6 to 8 weeks after COVID-19 recovery, and the late follow-up echocardiography was done six months after the COVID-19 onset. Participants who had undergone both early and late echocardiographic examinations were enrolled in this study. Written informed consent was obtained before each subject's study participation. The manuscript is written and formulated in accordance with the STROBE checklist (8).

Eligibility

We conducted the study during Iran's third COVID-19 wave in November 2020. The study population included RCMRC's health care workers infected with COVID-19. An overall 319 employees in this period were advised to be quarantined due to suspicious symptoms by infectious disease specialists. We enrolled 137 individuals with a definite COVID-19 infection confirmed by a positive RT-PCR test. Of these, 33 patients refused to undergo echocardiography, and four were excluded from the study due to preexisting cardiovascular disease (3 had a history of cardiac surgery, and 1 had moderate valvular aortic stenosis). Therefore, in the early echocardiography, 100 patients underwent comprehensive echocardiographic examination 6 to 8 weeks after recovery and returning to work. Of those who were performed early echocardiography, 63 patients

agreed to undergo the late echocardiography six months after the COVID-19 diagnosis. They were otherwise healthy with no underlying disease (e.g., structural heart disease, chronic obstructive pulmonary disease, and chronic kidney disease).

Variables

Our outcomes of interest were alteration in echocardiographic indices of all four cardiac chambers, including the Left Ventricular (LV), comprised of evaluating the 3D volumes, Ejection Fraction (EF), Stroke Volume Index (SVI), Global Longitudinal Strain (GLS), Global Circumferential Strain (GCS), Global Radial Strain (GRS), twist and torsion, and The diastolic indexes, Right Ventricular (RV) anatomical evaluation, including RV volumes, EF, and Fractional Area Change (FAC), Peak basal systolic RV tissue velocity, RV function parameters (RVsm), RV Free-Wall Global Longitudinal Strains (RVFWGLS) and Peak Strain Rate (Peak SR), Tricuspid Annular Plane Systolic Excursion (TAPSE), Left and Right Atrial evaluation (LA and RA) for atrial peak strain rate and systolic Pulmonary Arterial Pressure (sPAP) during the follow-up period. Normal ranges for echocardiographic indices were all defined based on the 2015 ESC Echocardiographic Cardiac Chamber Quantification guideline (7).

Patient's demographic data consists of age, Cardiovascular risk factors, Body Surface Area (BSA), and laboratory findings at the time of infection, including White Blood Cell (WBC) count, lymphocyte count, and presence of anemia; defined as hemoglobin (Hb) level<12 gr/dl in women and Hb level <13 gr/dl in men, and highly sensitive CRP (hsCRP) level were also recorded.

COVID-19 severity assessment

Judged by clinical and radiological findings, patients were assigned into two groups of non-severe, and severe COVID-19 infection:

Non-severe infection was defined as mild symptoms (e.g., cough, fever, and change in smell/taste) without dyspnea.

Severe infection was defined as clinical or radiographic evidence of lower respiratory tract disease; respiratory rate [?] 30 breaths/min or lung infiltrates on chest computed tomography scan (CT-scan); oxygen saturation might be lower than 94%.

Chest CT-scan scoring

These patients had previously undergone chest CT-scan in the acute phase of the infection. A "Lung Total Severity Score" (LTSS) done by a radiologist at that time designated the severity of lung infiltration. This scoring which was based on the method introduced by Kunwei Li et al. (9), was calculated by assessing each of the lung lobes and assigning a score to them (from 0 to 4) based upon the percentage of ground-glass opacity or consolidation as follows: 0 (0%), 1 (1-25%), 2 (26-50%), 3 (51-75%), or 4 (76-100%). Then, the sum of all the lobes' scores gave out the TLSS, which was expected to be a number ranging from 0-20. According to this scoring, we divided the patients into two categories. LTSS=0 delineated no lung involvement, and LTSS[?] 1 was considered to have some extent of lung involvement.

Echocardiographic examination

Two- and three-dimensional (2D and 3D) TTE was performed on each participant using Philips Epic 7C system (Philips Medical Systems, Andover, MA, USA) and Philips X5-1 matrix Probe. One echocardiographer performed the 2D and 3D TTE and further measurements and analysis using post-processing software (TomTec version 4.6).

The 3D LV evaluated the 3D volumes, EF, SVI, GLS, GCS, GRS, twist, and torsion values using Tomtec dedicated application for 3D LV analysis. The diastolic indexes were determined using tissue Doppler imaging. An RV anatomical evaluation, including 3D RV volumes, EF, and FAC, was performed using a 3D RV analysis method (TomTec V 4.6). TAPSE by M-Mode and Peak basal systolic RV tissue velocity by

tissue Doppler imaging served as RVsm. RVFWGLS strain and Peak SR were determined using the RV-focus view of the 2D Tomtec strain software.

Left and right atrial (LA and RA) evaluation performed via speckle tracking technique and TomTec V 4.6 dedicated application for atrial strain, utilizing standard four-chamber views, and in accordance with the expert consensus recommendations for standardization of LA and RA strain published in the European Journal of echocardiography (10). The calculation of sPAP was based on tricuspid regurgitation gradient plus RA pressure (defined by inferior vena cava size and collapsibility).

Valvular regurgitation and severity were examined, and patients with moderate or severe regurgitation or stenosis were eliminated from the research.

Ethics

The institutional review board of RCMRC in Tehran, Iran, has evaluated and approved the study's protocol and goals. All patients provided written informed consent and consented to use their data for clinical research. In all stages of the study, we strictly behaved in line with the declaration of Helsinki.

Statistical analysis

Continuous variables which followed a normal distribution pattern were presented as mean +- SD, and non-normal variables were reported as median (interquartile range (IQR)). Categorical variables were reported as numbers and percentages. To compare the categorical variables, Chi-squared test or Fisher's exact test was performed. For normally and non-normally distributed data, paired T-test and Wilcoxon signed-rank test were performed, respectively. A two-sided p-value$<$0.05 was considered statistically significant. The statistical analysis was conducted using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

Results

Original and Follow-Up Cohorts

This cohort consisted of 100 patients from health care workers of RCMRC. Overall, 63 participants consented to undergo the late follow-up echocardiography. The baseline characteristics of the enrolled patients are presented in Table 1.

Of the participants, 66.7% were women, and the mean age was 40.48+-8.1 years. The late session was at six months passed the onset of COVID-19 infection.

Echocardiographic Findings

Comparing the pairwise echocardiographic findings of patients based on the clinical severity and the extent of COVID-19 pneumonia was conducted. Echocardiographic findings in early and late echocardiograms, grouped by their clinical severity category, are detailed in Tables 2 and 3.

Clinically non-severe COVID-19

In the non-severe intensity COVID-19 group, within which 41 patients were followed up, 4DLVEDVI significantly increased over time (39.9+-8.7 cc/m^2 vs. 44.6+-1 cc/m^2, p-value=0.02). In addition, 4DLVSVI (24.7+-4.1 cc/m^2 vs. 29.7+-7.0 cc/m^2, p-value$<$0.001) and LVEF (61.9% [59.8-64.5] vs. 63.8% [58.2-68.9], p-value=0.029) increased significantly. All the diastolic indices, including E and A wave velocity and lateral and septal E' velocity, were in the normal range in both follow-up sessions. However, there was a significant change in lateral E wave velocity (14.7 m/s [12.7-16.7] vs. 13.2 m/s [12-16], p-value=0.006). The RV function indices were all in the normal range in both early and late echocardiograms. RVFWGLS significantly decreased in the late echocardiogram (-32.3+-4.6% vs. -28.8+-5.8%, p-value=0.002). RV-FAC (46.6% [43.6-53] vs. 39.7% [25-43], p-value$<$0.001) and TAPSE (21 mm [19-24] vs. 23 mm [20-25] , p-value=0.093) did not show a significant change. LA peak SR significantly decreased in the late follow-up (1.4% +-0.3 vs.

1.3% +-0.3, p-value<0.015). There was no significant difference in systolic PAP between the early and late echocardiograms. Other variables are described in detail in Table 2.

Clinically severe COVID-19

When 22 patients in the severe intensity COVID-19 group were observed in late echocardiography, 4DLVEDVI increased significantly (39.2+-5.7 cc/m^2 vs. 44.7+-7.6 cc/m^2, p-value=0.003), as did 4DLVSVI (22.6+-5.7 cc/m^2 vs. 29.4+-5.4 cc/m^2, p-value<0.001) and LVEF (61.5% [55-65] vs. 64.45% [59-69], p-value=0.009), respectively. The LVGLS was increased significantly over the follow-up period (-20% [-21.4--19] vs. -23.9% [-25.3–21.9], p-value=0.004). At both follow-up appointments, all diastolic indices, including E and A wave velocity, and lateral and septal E' velocity, were within normal range and not significantly changed. RVFWGLS showed no statistically significant change during the study period (-28.3% +-3.5 vs. -28.6% +-5.1, p-value=0.79). The RVESVI decreased significantly in the late echocardiogram (14.5%+-3.9 vs. 12.1%+-3.5, p-value=0.01). The RV-FAC (47.2% [42.3-52.2] vs. 36.4% [31.1-45], p-value=0.002) showed a significant decrease and TAPSE (22.5 mm [19.1-24.2] vs. 23 mm [21-25], p-value= 0.55), was not significantly different but both altered within the normal range. None of the LA indices, including LAESV and LA peak SR, changed significantly. RA peak strain rate significantly decreased (1.8% [1.3-1.9] vs. 1.3% [1.2-1.5], p-value=0.007). (Table 3)

Patients without COVID-19 pneumonia

Amongst 25 patients who had undergone spiral chest CT scan, 12 patients showed no signs of COVID-19 pneumonia on their spiral chest CT scan. These 12 patients demonstrated no significant changes in none of the LV systolic or diastolic indices. Also, any other RV, LA, and RA parameters did not show a statistically significant change during the follow-up period. All variables are described in detail in Supplementary Table S1.

Patients with COVID-19 pneumonia

From a total of 25 patients who were prescribed to perform spiral chest CT-scan, 13 showed non-severe and severe COVID-19 pneumonia. On the late echocardiogram, LVSVI and LVEF showed significant rise (21.3+-4.1 vs. 29.1+-5.5, p-value=0.03 and 57.5 [53.3-64.4] vs. 64 [59.5-66.1], p-value=0.01, respectively) in comparison with the baseline echocardiogram. There was an increase, though not statistically significant, in LVGLS (-20.3% [-22.1- -18.8] vs. -23.2% [-24.3- -20.6], p-value=0.08) and LVGCS (-27.9% +-3.6 vs. -30.2% +-4.3, p-value=0.34) over the study time frame. Amongst RV echocardiographic indices, RVFAC and TAPSE showed a decrease which was not statistically significant (48.7 % [42.7-52] vs. 36.55 % [30.7-49.5], p-value=0.059 and 23 mm [21.5-25] vs. 22 mm [21-25], p-value=0.96, respectively). Also, none of the other indices changed significantly, including RVEDVI, RVESVI, RVEF, RVFAC, RVsm, and RV strain rate. Of LA parameters consisting of LA peak SR and LAESV, none showed a statistically significant change on the late echocardiogram. RA parameters, including systolic PAP and peak SR, did not demonstrate any significant change over the follow-up time. (Supplementary Table S2)

Discussion

There are growing links between COVID-19 and cardiovascular morbidity (6). Although cardiac biomarkers such as high-sensitivity troponin appear as good predictors of prognosis in COVID-19 patients, data on echocardiographic abnormalities in these individuals are scarce (10). To the best of our knowledge, this is the first prospective health care workers cohort with a long-term follow-up about the impact of COVID-19 and its severity on echocardiographic indices. In this cohort follow-up report, we demonstrated that although LV and RV function did not change substantially over time in our cohort, various patterns of change were seen based on the early echocardiogram.

In both severe and non-severe COVID-19 severity groups, among systolic indices, 4DLVEDVI increased significantly, and in turn, 4DLVSVI and LVEF increased significantly in the follow-up echocardiogram which may indicate that in the early-time echocardiogram, patients had a higher pulse rate in order to improve oxygenation in response to diseased lung and after the lung recovery phase the heart rate slowed down and

the stroke volume increased naturally in response. An echocardiographic study by Szekely et al. proved that patients with more COVID-19 clinical severity had significantly higher heart rates, and the stroke volume was reported non-significantly lower in the group with more severe COVID-19(6).

In the severe COVID-19 group, 4DLVGLS increased significantly, presenting that LV function is improved during the time, and the fall in the 4DLVGLS in the early echocardiogram might have been a consequence of the compensatory tachycardia mentioned above. It was expressed previously in the ECHOVID study that LVGLS was lower in patients hospitalized for COVID-19 compared to the healthy population (11). Moreover, it was shown in Croft et al. study that the LVGLS in hospitalized COVID-19 patients were lower than the assumed lower limit of the normal range. They hypothesized that the decrease in LVGLS associated with COVID-19 infection might be attributable to a combination of causes. Direct and indirect processes may cause myocardial damage. Viral invasion of the myocardium directly results in cardiomyocyte death and inflammation. Indirect mechanisms include cardiac stress caused by insults such as respiratory failure and hypoxemia, as well as cardiac inflammation in the presence of substantial systemic hyper inflammation (12-14).

In the non-severe COVID-19 group, of the diastolic indices, lateral E' decreased significantly in the normal range, indicating the hyperactivity of LV in the early phase and relaxation of LV far after COVID-19 relief.

Global RV function indicators demonstrate hyperactivity of RV during the early COVID-19 recovery phase, as the 4DRVFAC in both non-severe and severe COVID-19 groups decreased significantly in the follow-up echocardiogram in comparison with the early echocardiogram while it still lies within normal range. Furthermore, RVFWGLS decreased significantly in the non-severe COVID-19 group. Among COVID-19 patients, a cytokine storm is prevalent. Cardiac myofibroblasts and cardiomyocytes are the major generators of various proinflammatory cytokines (15). As a result of systemic inflammation in COVID-19, the afterload increases (16); thus, the rise in RVFWGLS in early echocardiogram among the non-severe COVID-19 group demonstrates hyperactivity of the RV in order to overcome the risen afterload.

A study of the right ventricle in COVID-19 proved that Interleukin 6 (IL-6) serum levels are associated with respiratory dysfunction, ARDS, and poor clinical outcomes. The proinflammatory cytokine cascade may lead to RV dysfunction through adverse inotropic effects on the myocardium. Taken together, reduced RV contractility and abruptly high pulmonary vascular resistance due to ARDS and pulmonary embolism in COVID-19 may be fatal (15). The present study's findings showed no RV failure amongst patients as it was the study of non-critically ill patients. It seems that in non-severe cases of COVID-19, in the absence of a cytokine storm healthy heart will increase its contractility during the acute phase. Although the higher afterload is previously suggested to fail RV, in this circumstance was not to an extent capable of failing the RV.

In a study of the prognostic value of RV strain, Li et al. stated that non-survivors had RV enlargement and dysfunction. The SARS-CoV-2 infection has been shown to generate both pulmonary and systemic inflammation, which may lead to RV failure via RV overload and direct cardiomyocyte injury. This research reveals that RVLS is an independent predictor of clinical outcomes in COVID-19 patients. Significantly, this index may have more predictive value than other echocardiographic markers. Therefore, individuals with COVID-19 should undergo an examination of RV function by investigating RVLS for risk stratification (17). In agreement with our findings, the WASE-COVID study, which provided participants with a follow-up echocardiogram, revealed an improvement in RVGLS in patients with impaired RV function, which may be solid evidence of advancement in lung function between the time of the baseline echocardiogram and the time of the follow-up study (18).

Although TAPSE altered non-significantly in none of the COVID-19 severity groups, 4DRVFAC decreased significantly on the follow-up echocardiogram in both severe and non-severe COVID-19 groups, suggesting the RV hyperactivity to improve oxygenation against the COVID-19 affected lung in the early phase recovery period. Paternoster et al., in a systematic review and meta-analysis, defined the RV dysfunction in COVID-19 patients based on the recommended cut-offs of echocardiographic guidelines that the cut-offs for RV

failure determinants also assessed in this study were FAC <35%, TAPSE < 17 mm and, (PAP) > 25 mmHg. Thereafter, in line with the present study, none of the mentioned indices in either severe or non-severe groups had a significant alternation toward RV failure (7, 19, 20).

Limitations and strengths

There were limitations and strengths in this study's design and running, as follows. The most accurate way to evaluate chambers' volumes and strains is cardiac magnetic resonance imaging (CMR) (21). Although it was better to evaluate the heart condition with CMR, echocardiography is still the most accessible and inexpensive way to carry out the global cardiac status (7). So, in case of having access and enough budgets to perform CMR for research purposes, it would be more reliable to perform this study with CMR, which would probably lead to higher inter-and intra- observer reproducibility. Another noteworthy limitation is the limited sample size. It was a single-center cohort of health care workers, and the COVID-19 pandemic, by its nature of being highly contagious, made it difficult to provide a sample of patients with proper size in different clinical COVID-19 severity groups that may have affected the present results.

Moreover, as the participants were all health care workers and thus aware of alarm signs and symptoms ending to severe COVID-19, they received proper care right away. Consequently, there were fewer patients with cytokine storm and severe COVID-19 pneumonia to measure the impact on the cardiopulmonary system. The bright point of the current study is considering patients without cardiac indication for echocardiography which provides evidence for silent long-term effects of COVID-19 on the cardiovascular system. On the other hand, having a population bare of known cardiac problems excludes the impact of the baseline cardiac complications on the outcomes of the patients. Another novelty of the current study is the duration of the follow-up period (6 months), which is not practiced in any other similar study. It is of note that the participants of this cohort were all young, otherwise healthy, without any history of cardiac disease, and still productive people working as healthcare staff. Hence, the considered response to COVID-19 systemic implications was assessed to be the response of a healthy heart to sepsis. Thus, it can practically be generalizable to the non-complicated heart response to the COVID-19 crisis. The current results may not present the outcomes of aged or, to any extent, previously damaged hearts against the multi-system-involving COVID-19 infection.

Conclusion

Overall, this research revealed that while LV and RV functions did not change considerably over time in our complete cohort, varied patterns of change were found dependent on baseline function. It implies that in healthy and young individuals, COVID-19 may potentially damage the cardiac system but will go back to its baseline status eventually.

Acknowledgments

We hereby thank all the patients whose data are used in this study.

Sources of Funding

None.

Conflict of interests

The authors declare no conflict of interest.

Data availability

Data are available upon reasonable request.

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Table 1- Baseline demographic and laboratory characteristics in groups of COVID-19 severity defined by clinical features

	Non-severe COVID-19 (n = 42)	Severe COVID-19 (n = 14)	P value
Baseline characteristics	**Baseline characteristics**	**Baseline characteristics**	**Baseline characteristics**
Age, year	40±8.3	41.3±7.6	0.38
BSA, m^2	1.7±0.1	1.8±0.2	0.06
Male%	31 %	40.9 %	0.58
Homestay duration, day	15 (14-17)	18.5 (15-23.7)	0.002*
HTN %	9.5%	4.5%	0.65
DM%	0 %	4.5%	0.34
smoker%	2.4%	0.0%	1.0
Laboratory data	**Laboratory data**	**Laboratory data**	**Laboratory data**
Anemia	5.6%	6.7%	1.0
WBC, 10^9 mm^3	6.36±1.61	6.4±2.3	0.19
Lymphocyte count, 10^9 mm^3	1.78±7.13	1.67±7.91	0.53
CRP, mg/dL	2 (0.77-4.22)	8.5 (2.00-26.75)	0.04*

All values are represented as number (%), mean ± SD, and median (IQR)

BSA, Body Surface Area; HTN, Hypertension; DM, Diabetes Mellitus; WBC, White Blood Cell; CRP, C-Reactive Protein.

Table 2- Comparison of the echocardiographic findings of early and late phases in the non-severe COVID-19 group defined by clinical features

	Early phase (n =41)	Late phase (n =41)	P-value
Echocardiographic findings	**Echocardiographic findings**	**Echocardiographic findings**	**Echocardiographic findings**
LV	**LV**	**LV**	**LV**
4D-LV end-diastolic volume index, cc/m^2	39.9±8.7	44.6±10	0.02*
4D-LV end-systolic volume index, cc/m^2	14.9 (13-17.5)	15.3 (12.5-19.8)	0.29

	Early phase (n =41)	Late phase (n =41)	P-value
4D-Stroke volume index, cc/m^2	24.7±4.1	29.7±7.05	<0.001*
4D LV Ejection fraction, %	61.9 (59.8-64.5)	63.8(58.2-68.9)	0.02*
4D LV Global Longitudinal Strain, %	-22.3(-23.5- -21.3)	-21.2 (-24.3- -19.6)	0.51
4D LV Global Circumferential Strain, %	-28.7±3.8	-30.4±5.1	0.18
4D LV Global Radial Strain, %	41.4 (37.6-43.9)	41.5 (39.6-46.1)	0.41
Twist, degree	13.5±9.7	12.5±9.1	0.66
Torsion, degree/cm	1.6 (0.9-2.3)	1.4 (0.8-2.2)	0.61
Diastolic parameters	**Diastolic parameters**	**Diastolic parameters**	**Diastolic parameters**
E wave velocity, m/s	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.68
A wave velocity, m/s	0.5 (0.5-0.6)	0.6 (0.5-0.7)	0.44
Septal E' velocity, cm/s	10.7 (8-12)	10 (9-12)	0.26
Lateral E' velocity, cm/s	14.7 (12.7-16.7)	13.2 (12-16)	0.006*
RV	**RV**	**RV**	**RV**
4D-RV end diastolic volume index, cc/m^2	33.6±8.8	29.3±28.3	0.06
4D-RV end-systolic volume index, cc/m^2	13.6±4.5	12.5±3.4	0.21
4D-RV Ejection fraction, %	58.1 (53.5-62.5)	57.9 (54.5-62.7)	0.455
4D-RV FAC, %	46.6 (43.6-53)	39.7 (25-43)	<0.001*
4D-RV free wall Global Longitudinal Strain, %	-32.3±4.6	-28.8±5.8	0.002*
TAPSE, mm	21 (19-24)	23(20-25)	0.09
RVsm, cm/sec	13 (12-14)	12 (11-13)	0.12
RV Strain rate, s^{-1}	-1.19±0.44	-1.31±0.29	0.14
LA	**LA**	**LA**	**LA**
LA end-systolic volume, cc	35 (27.7-44.3)	37.8 (31.8-44.5)	0.19
LA peak Strain rate, s^{-1}	1.4±0.3	1.31±0.32	0.01*
RA	**RA**	**RA**	**RA**
RA peak Strain rate, s^{-1}	1.50 (1.20-1.92)	1.30 (1.07-1.50)	0.09
Systolic PAP, mm Hg	25.00 (22-29.00)	25.00 (21.75-27.50)	0.80

All values are represented as number (%), mean ± SD, and median (IQR)

FAC, Fractional Area Change; LA, left atrium; LV, Left Ventricle; PAP, pulmonary artery pressure; RV, Right Ventricle; RA, right atrium; RVSm, Reduced Vertical Separation minimum; TAPSE, tricuspid annular plane systolic excursion

Table 3- Comparison of the echocardiographic findings of early and late phases in the mode-

rate/severe COVID-19 group defined by clinical features

	Early phase (n =22)	Late phase (n =22)	P-value
Echocardiographic findings	**Echocardiographic findings**	**Echocardiographic findings**	**Echocardiographic findings**
LV	**LV**	**LV**	**LV**
4D-LV end-diastolic volume index, cc/m^2	39.2±5.7	44.7±7.6	0.003*
4D-LV end-systolic volume index, cc/m^2	14.5 (13.5-17.1)	16.4 (13.5-18.6)	0.27
4D-Stroke volume index, cc/m^2	22.6±5.7	29.4±5.4	<0.001*
4D LV Ejection fraction, %	61.5 (55-65)	64.4 (59-69)	0.009*
4D LV Global Longitudinal Strain, %	-20 (-21.4- -19)	-23.9 (-25.3- -21.9)	0.004*
4D LV Global Circumferential Strain, %	-28.7±4.31	-29.1±5.2	0.81
4D LV Global Radial Strain, %	39.6 (36.3-43.6)	43.3 (39.9-46.9)	0.13
Twist, degree	11.2±8.6	8.8±7.3	0.38
Torsion, degree/cm	1.3 (0.7-2.3)	1.2 (0.2-2.3)	0.61
Diastolic parameters	**Diastolic parameters**	**Diastolic parameters**	**Diastolic parameters**
E wave velocity, m/s	0.8 (0.6-0.9)	0.7 (0.6-0.8)	0.25
A wave velocity, m/s	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.27
Septal E' velocity, cm/s	10.5 (8-12.1)	8 (10-11.5)	0.34
Lateral E' velocity, cm/s	13.5 (11.52-16)	13 (11.5-15)	0.46
RV	**RV**	**RV**	**RV**
4D-RV end diastolic volume index, cc/m^2	34.6±7.4	30.6±9	0.14
4D-RV end-systolic volume index, cc/m^2	14.5±3.9	12.1±3.5	0.01*
4D-RV Ejection fraction, %	59.4 (54.9-60.8)	57 (54.7-61.8)	0.88
4D-RV FAC, %	47.2 (42.3-52.2)	36.4 (31.1-45)	0.002*
4D-RV free wall Global Longitudinal Strain, %	-28.3±3.5	-28.6±5.1	0.79
TAPSE, mm	22.5 (19.1-24.2)	23 (21-25)	0.55
RVsm, cm/sec	12.8 (12-14.1)	12.1 (12-13.2)	0.65
RV Strain rate, s^{-1}	-1.31±0.29	-1.30±0.22	0.91
LA	**LA**	**LA**	**LA**
LA end-systolic volume, cc	29.8 (21.4-42.8)	33 (27.7-41.5)	0.11
LA peak Strain rate, s^{-1}	1.7±0.3	1.5±0.5	0.17
RA	**RA**	**RA**	**RA**
RA peak Strain rate, s^{-1}	1.8 (1.3-1.9)	1.3 (1.2-1.5)	0.007

	Early phase (n =22)	Late phase (n =22)	P-value
Systolic PAP, mm Hg	25 (21.5-28.5)	25 (25-30)	0.06

All values are represented as number (%), mean ± SD, and median (IQR)

FAC, Fractional Area Change; LA, left atrium; LV, Left Ventricle; PAP, pulmonary artery pressure; RV, Right Ventricle; RA, right atrium; RVSm, Reduced Vertical Separation minimum; TAPSE, tricuspid annular plane systolic excursion