Ventricular Changes in Patients with Acute COVID-19 Infection: Follow-Up of The World Alliance Societies of Echocardiography (WASE-COVID) Study

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Abbreviations:
2CH – 2-chamber
4CH – 4-chamber
AI – artificial intelligence
ASE – American Society of Echocardiography
BNP – brain natriuretic peptide
COVID-19 – Coronavirus disease 2019
CRP – C-reactive protein
EACVI – European Association of Cardiovascular Imaging
ICU – intensive care unit
LDH – lactic dehydrogenase
LV – left ventricular
LVEDV – left ventricular end-diastolic volume
LVEF – left ventricular ejection fraction
LVESV – left ventricular end-systolic volume
LVLS – left ventricular longitudinal strain
MICE – Multiple Imputations by Chained Equations
PCR – polymerase chain reaction
RV – right ventricular
RVBD – right ventricle basal diameter
RVFWS – right ventricular free-wall strain
RVGLS – right ventricular global longitudinal strain
SARS-CoV-2 – severe acute respiratory syndrome coronavirus-2
TTE – transthoracic echocardiogram
WASE – World Alliance Societies of Echocardiography
Abstract

Background- COVID-19 infection is known to cause a wide array of clinical chronic sequelae but little is known regarding the long-term cardiac complications. We aim to report echocardiographic follow-up findings and describe the changes in left and right ventricular function that occur following acute infection.

Methods- Patients enrolled in the WASE-COVID study with acute COVID-19 infection were asked to return for a follow-up transthoracic echocardiogram (TTE). Overall, 198 returned at a mean of 129 days of follow-up, of which 153 had paired baseline and follow-up images that were analyzable, including left ventricular (LV) volumes, ejection fraction (EF), and longitudinal strain (LVLS). Right-sided echocardiographic parameters included right ventricular (RV) global longitudinal strain (RVGLS), RV free wall strain (RVFWS), and RV basal diameter (RVBD). Paired echocardiographic parameters at baseline and follow-up were compared for the entire cohort and for subgroups based on the baseline LV and RV function.

Results- For the entire cohort, echocardiographic markers of LV and RV function at follow-up were not significantly different from baseline (all p>0.05). Patients with hyperdynamic LVEF at baseline (>70%), had a significant reduction of LVEF at follow-up (74.3±3.1% vs. 64.4±8.1 %, p<0.001), while patients with reduced LVEF at baseline (<50%) had a significant increase (42.5±5.9% vs 49.3±13.4% , p=0.02), and those with normal LVEF had no change. Patients with normal LVLS (<-18%) at baseline, had a significant reduction of LVLS at follow-up (-21.6±2.6 % vs. -20.3±4.0% , p=0.006), while patients with impaired LVLS at baseline, had a significant improvement at follow-up (-14.5±2.9 % vs. -16.7±5.2%, p<0.001). Patients with abnormal RVGLS (>20%) at baseline, had significant improvement at follow-up (-15.2±3.4 % vs. -
17.4±4.9 %, p=0.004). Patients with abnormal RVBD (>4.5 cm) at baseline, had significant improvement at follow-up (4.9±0.7 cm vs 4.6±0.6 cm, p=0.019).

**Conclusions**- Overall, there were no significant changes overtime in LV and RV function of patients recovering from COVID-19 infection. However, differences were observed according to baseline LV and RV function, which may reflect recovery from the acute myocardial injury occurring in the acutely ill. LV and RV function tends to improve in those with impaired baseline function, while it tends to decrease in those with hyperdynamic LV or normal RV.

**Keywords:**

Echocardiography; WASE; COVID-19; Left Ventricular Function; Right Ventricular Function; Strain
**Introduction**

The International World Alliance Societies of Echocardiography (WASE) COVID-19 Study identified echocardiographic parameters associated with in-hospital mortality in patients with acute COVID-19 infection and highlighted the differences in acute cardiac manifestations in various geographic regions around the world.  

COVID-19 infection is known to cause a wide array of clinical chronic sequelae such as fatigue and muscle weakness, sleep difficulties, sinus tachycardia, anxiety, depression, or abnormal pulmonary function tests, a phenomenon referred to as “long COVID syndrome”. However, little is known regarding the long-term cardiac complications of this disease, with a paucity of data regarding longitudinal echocardiographic findings.

In this follow-up sub-study of the WASE COVID-19 patient cohort, we report echocardiographic follow-up findings up to nine month after the original infection and describe the changes in cardiac structure and function that occurs following acute SARS CoV-2 infection.
Methods

Data Collection

Adult patients (≥18 years old) admitted with SARS-CoV-2 infection (confirmed by positive antigen or PCR test) during the first wave of the pandemic (January-September 2020) were considered for the study if a transthoracic echocardiogram (TTE) was performed during the initial COVID-19-related hospitalization. Patients were consented for any prospective encounter or image acquisition and the study was approved by the local ethics or IRB committees. Patients were enrolled retrospectively, and follow-up was conducted prospectively. The follow-up echocardiograms were ordered and acquired based on local clinical practices at a minimum of 3 months after the initial hospitalization. Acceptable TTEs included both comprehensive and limited studies, as long as at least the apical 4-chamber view was acquired. Patients were enrolled at 13 medical centers in four world regions (Asia, Europe, United States, and Latin America), 12 of which participated in this follow-up sub-study.

All clinical information and DICOM cardiac ultrasound images were collected from the medical records, PACS systems and echo machines, deidentified, and transferred via a web-based system (Ultromics, Oxford, United Kingdom; Castor EDC, United Kingdom) to the Core Laboratories at MedStar Health (Washington, DC) and University of Chicago (Chicago, Illinois).

Image Analysis

Image transfer was facilitated by a 2-step anonymization process to a cloud-based image analysis software. Image analysis of baseline and follow-up echocardiograms was conducted following the methodology previously reported in the WASE COVID initial report.1 Left ventricular (LV) analyses were performed through commercially available artificial intelligence (AI) algorithms...
created by machine learning (EchoGo, Ultromics, United Kingdom), which automatically traced the endocardium and, using the Simpson’s method of disks, calculated the LV ejection fraction (LVEF), end systolic and end diastolic volumes (LVESV, LVEDV), and longitudinal strain (LVLS); additional details on this software have been described in our original publication and are presented in Supplemental Material S1. All LV measurements were repeated twice manually by board-certified echocardiographers (human reads 1 and 2) blinded to other reads and to clinical information. These echocardiographers were randomly selected from a pool of 7 independent operators. For both methods (AI and human analysis), only cases with acceptable quality LV views (as determined by the expert echocardiographers) were included, which was defined as lack of apical foreshortening with adequate visualization of all segments in the apical 4-chamber (4CH) view. LVLS was calculated as the average of all available segments from the 4CH and 2CH views. The mean of the three LV reads (automated AI, human reads 1 and 2) was taken as the final value. Cut-offs for mildly, moderately, and severely reduced LVEF as well as normal and abnormal LVLS were determined by the 2015 ASE/EACVI Guidelines for Cardiac Chamber Quantification.

Right ventricular (RV) analysis was performed using a semi-automated RV-specific package (TOMTEC Image Arena, Build No. 494368, Unterschleissheim, Germany) and included RV global longitudinal strain (RVGLS), RV free wall strain (RVFWS), and RV basal diameter (RVBD). Only cases with acceptable quality RV views were included (among those patients with paired LV data), which was defined as presence of an RV-focused view with adequate visualization of the RV free wall. Abnormal RVFWS was defined as >-20%. Inter-and intra-observer reproducibility of the methodology used in this study for LV and RV analysis was very good to excellent and has been previously reported in detail.
Statistical Analysis

Continuous variables were expressed as mean (±SD) or median (interquartile range (IQR)) according to data distribution. Markers of LV (LVEF, LVLS) and RV (RVGLS, RVFWS, RVBD) function were compared between baseline and follow-up echos using paired t-tests and mean of differences (Δ) was calculated.

To determine accurate values and to build a homogeneous database, missing data for calculation of biplane LVEF and LVLS were determined using a multiple imputation model, following guidelines from the European Medicines Agency on confirmatory clinical trials. Specifically, a Multiple Imputation by Chained Equations (MICE) method was used to derive the 2CH values for cases with a 4CH value but missing 2CH (n=19 of the follow-up echos), in order to calculate biplane measures.
Results

Original Cohort Follow-Up

Over a nine-month period (January to September 2020), 870 patients were enrolled at 13 centers in nine countries. The baseline clinical and echocardiographic characteristics of our original cohort of 870 patients have been previously reported. ¹

Follow-Up Cohort

In-hospital mortality was 21.6% (188 patients) and increased to 27.4% (238 patients) through a follow-up of 230 +/- 115 days. Of the original 870 patients, 198 survivors had a follow-up echocardiogram (129 +/- 60 days following the initial admission), of which 184 had a successful bi-plane or 4Ch endocardial tracing. Of the 184 with analyzable follow-up studies, 153 had paired baseline echocardiograms (Figure 1), including 80 with paired RV analysis. Baseline characteristics of all enrolled patients as well as those with paired follow-up echocardiograms are listed in Table 1.

Echocardiographic Findings

Echocardiographic findings for the patients with paired follow-up examinations are detailed in Table 2. Using a pairwise analysis to compare baseline and follow-up echocardiograms, there were no significant differences in LV and RV function between baseline and follow-up: LVEF Δ = -0.26 %, p = 0.77 (t = -0.290, df = 151); LVLS Δ = -0.1 %, p = 0.85 (t = -0.19, df = 152); RV GLS Δ = -0.6 %, p = 0.21 (t = -1.28, df = 66); RVFWS Δ = -0.8 %, p = 0.18 (t = -1.353, df = 66); and RVBD Δ = -0.1 cm, p = 0.14 (t = -1.5, df = 79) (Figure 2). Similar findings were seen when including only patients that were in the intensive care unit (ICU) or on mechanical ventilation at the time of the initial echocardiogram (Table 2), and when considering those with longer and shorter follow-up (above and below the median -143 days-, Supplemental Figure S1).
Echocardiographic findings in baseline and follow-up echos, grouped by their baseline LV and RV function categories are detailed in Table 3. In patients with hyperdynamic LVEF at baseline (>70%), there was a significant reduction of LVEF at time of follow-up \([\Delta = -8.8 \%, p < 0.001 \text{ (t = -6.13, df = 32)}]\) due to an increase in LVESV with no significant change in LVEDV; while in patients with normal LVEF (50-70%) at baseline, there was no significant change in LVEF \([\Delta = 1.3 \%, p = 0.15 \text{ (t = -1.44, df = 131)}]\) or LV volumes. In patients with abnormal LVEF at baseline (<50%), there was a significant increase of LVEF \([\Delta = 6.7\%, p = 0.02 \text{ (t = 2.60, df = 19, Figure 3)}]\) with a non-significant decrease in LVESV and LVEDV (comparatively larger decrease in LVEDV).

Similarly, in patients with normal LVLS (<-18%) at baseline, there was a significant decrease of LVLS at time of follow-up: \(\Delta = 1.2\%, p = 0.006 \text{ (t = 2.79, df = 94)}\); while in patients with impaired LVLS at baseline, there was a significant increase: \(\Delta = -2.2 \%, p < 0.001 \text{ (t = -3.67, df = 57, Figure 4)}\). Overall, 25 of the 95 patients with normal LVLS at baseline became abnormal at follow-up, while 15 of the 58 that were initially abnormal became normal at follow-up.

As for the evaluation of the RV, in patients with normal RVFWS at baseline (<-20%), there was no significant change in RVFWS: \(\Delta = -0.2 \%, p = 0.82 \text{ (t = -0.23, df = 47)}\). In patients with abnormal RVFWS (>20%) at baseline, there was a borderline but non-significant improvement at the time of follow-up: \(\Delta = 2.3 \%, p = 0.055 \text{ (t = 2.07, df = 16)}\). In patients with normal RVGLS at baseline (<-20%), there was no significant change in RVGLS: \(\Delta = 0.7 \%, p = 0.24 \text{ (t = 1.19, df = 36)}\); while in patients with abnormal RVGLS at baseline, there was significant improvement in RVGLS: \(\Delta = -2.3 \%, p = 0.004 \text{ (t = -3.11, df = 29, Figure 5)}\). In patients with normal RVBD (<4.5 cm) at baseline, there was no significant change at time of follow-up: \(\Delta = <\)
- 0.1 cm, p = 0.55 (t = 0.61, df = 63); while in patients with abnormal RVBD (>4.5 cm) at baseline, there was significant improvement: Δ = -0.4 cm, p = 0.019 (t = -2.66, df = 14) (Figure 6).

The total number of patients in each clinical category at baseline and time of follow-up is described in Table 4.
Discussion

In this follow-up report of surviving patients from the WASE COVID-19 study, we have shown that while LV and RV function did not change significantly over time in our entire cohort, different patterns of change were observed according to baseline function. In patients with baseline hyperdynamic LVEF and normal LVLS, there was significant reduction at time of follow-up. Conversely, in patients with baseline impaired LVEF, LVLS, RVGLS, and RVBD, there was significant improvement at the time of follow-up.

These findings above can be explained by differences in cardiac structural and functional changes in different sub-groups of patients with acute COVID-19 infection. In our cohort, 14% of patients demonstrated hyperdynamic LV function at baseline, likely an adaptive physiologic response to COVID-19 infection or acute stress response from critical illness or sepsis. In this subset of patients, follow-up echos showed a significant decrease in LVEF towards normalization, which can likely be explained by resolution of the acute infection and inflammation. This was in contrast to patients with normal EF, in whom no significant differences were seen, and those with reduced baseline LVEF, in whom LVEF improved at follow-up. This pattern of “regression to the mean” is probably the result of resolution of the acute physiology of the acutely ill patient.

Interestingly, in patients with normal LVLS at baseline, a similar pattern was observed to that of patients with hyperdynamic LVEF, with significant reduction noted at time of follow-up echo, perhaps due to resolution of the hyperdynamic component of the acute systemic inflammatory response. Conversely, in patients with impaired LVLS at baseline, presumably due to myocardial dysfunction, follow-up echos showed significant improvement in LVLS, possibly indicative of
recovery from acute SARS-CoV-2 infection. Multiple previous studies have shown that LV longitudinal strain is more sensitive at detecting subtle changes in LV function compared to LVEF. This may be the case in our patient cohort, with LVLS but not LVEF showing significant reduction over time in patients with normal LV function at baseline. Related to patients with sepsis in particular, it has been postulated that LVEF could be affected by the presence of myocardial dysfunction but also to be load-dependent (hypovolemia, decreased preload, etc), while longitudinal strain should reflect mostly myocardial dysfunction, therefore reflecting different aspects of the pathophysiology of sepsis-induced cardiac response.

In terms of right-sided function, in patients with impaired RVGLS at baseline, there was significant improvement noted at time of follow-up echo. Because the lungs are the main target organ of SARS-CoV-2 and given the large prevalence of acute respiratory distress syndrome (ARDS) in critically ill patients with COVID-19 infection, the RV is thought to be particularly susceptible to dysfunction following COVID-19 infection. Previous studies have demonstrated RV failure as a sequelae of acute lung injury and acute respiratory distress syndrome, as the RV is easily affected by changes in pulmonary vascular resistance. Thus, the improvement seen in RVGLS in patients with impaired RV function in our study may be indicative of improvement in lung function from the time of baseline echo to the time of the follow-up study. This was also reflected by significant improvement in RVBD in patients with increased RVBD at baseline, suggestive of RV reverse remodeling during the follow-up period possibly associated with recovery in lung function or to interim changes in the need for lung-supportive strategies (mechanical or non-invasive ventilation, etc).
Few studies have reported results of follow-up echocardiograms in patients with COVID-19. In most other studies, the follow-up echocardiograms were performed during the initial hospital admission, probably in response to clinical improvement or even clinical deterioration. In a report of 79 patients with follow-up echocardiogram after 3 months, it was found that the proportion of cases with RV abnormalities decreased from 51% during the acute illness to 19%, and that the proportion with LV systolic dysfunction decreased from 13% to 9%. A recent study on patients recovered from COVID-19 infection using cardiac magnetic resonance reported high prevalence of myocardial inflammation, even in patients that were not hospitalized for their initial COVID-19 infection. Our findings in a larger, international cohort of surviving patients, with a longer follow-up, utilizing sensitive echocardiographic techniques (longitudinal RV and LV strain) and centralized readings, advance the knowledge in cardiovascular recovery from COVID-19 infection, a field that is still in need of further exploration.

Limitations

The limitations of our study include a relatively small number of patients with paired follow-up echos (n = 153) as well as a relatively short length of follow-up (mean 129 days). However, given the overall short time course of the global COVID-19 pandemic, our study is one of the first to report on cardiac structural and functional changes in patients with acute COVID-19 infection. We also recognize that our patient cohort is limited to those with clinical indications for serial echocardiographic follow-up, and that these patients are more likely to have cardiac involvement and to be in the more severe spectrum of disease compared to the general population of patients with COVID-19 infection. On the other hand, this analysis does not include patients that died, which probably would have had the most severe abnormalities in cardiac structure and function. Nevertheless, this study provides valuable insights into
longitudinal echocardiographic trends in patients with acute SARS-CoV-2 infection, and
demonstrates differences depending on baseline LV and RV function.

Conclusions

Overall, there were no significant changes in LV and RV function over time in patients
recovering from COVID-19 infection. However, differences in changes of cardiac function were
observed according to baseline LV and RV function. LV and RV function tends to improve in
those with impaired baseline function, while it tends to decrease in those with hyperdynamic LV
or normal RV.

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References


Figure Legends.

**Figure 1 - Study flow chart.** After excluding patients without analyzable echoes at either baseline or follow-up (dashed lines and boxes), 153 patients with paired echocardiograms were included in the current sub-study. These were all surviving patients that returned for follow-up, which occurred 129 +/- 60 days after the initial admission for acute COVID-19 infection. FU= follow up.

**Figure 2 – Overall trends in LV and RV function from baseline to follow-up.** Using a pairwise analysis to compare baseline and follow-up echos, there were no significant differences between baseline and follow up in LV and RV function. The width of each “violin” reflects the number of cases for each echo variable in the vertical axis, a compact display of a continuous distribution of each data population. The central values displayed on these plots are the mean and SD values. LV= left ventricular; EF=ejection fraction; LS=longitudinal strain; RV=right ventricular; GLS= global longitudinal strain; FWS=free wall strain.

**Figure 3 - Changes in LVEF grouped by baseline LV function.** In patients with hyperdynamic EF (>70%) at baseline, there was a significant decrease in LVEF at time of follow-up. In patients with normal but not hyperdynamic LVEF (50-70%), there was no significant change. In patients with abnormal LVEF at baseline (<50%), there was significant improvement in LVEF at the time of follow-up. The width of each “violin” reflects the number of cases for each echo variable in the vertical axis, a compact display of a continuous distribution of each data population. The central values displayed on these plots are the mean and SD values. LVEF= left ventricular ejection fraction.
Figure 4 - Changes in LVLS grouped by baseline function. In patients with normal LVLS (<-18%) at baseline, there was a significant worsening of LVLS at time of follow-up, while in patients with reduced LVLS at baseline, there was a significant improvement. The width of each “violin” reflects the number of cases for each echo variable in the vertical axis, a compact display of a continuous distribution of each data population. The central values displayed on these plots are the mean and SD values. LVLS= left ventricular longitudinal strain.

Figure 5 - Changes in RVGLS and RVFWS grouped by baseline RV function. Patients with reduced RV function (GLS or FWS) improved at time of follow-up (significant only for RVGLS), and there was no change in those with normal baseline RV function. The width of each “violin” reflects the number of cases for each echo variable in the vertical axis, a compact display of a continuous distribution of each data population. The central values displayed on these plots are the mean and SD values. RVGLS= right ventricular global longitudinal strain; RVFWS= right ventricular free wall strain.

Figure 6 - Changes in RV basal diameter grouped by baseline RV size. In patients with abnormal RV basal diameter (>4.5 cm) at baseline, there was significant improvement at time of follow-up, while in patients with normal RV basal diameter (<4.5 cm) at baseline, there was no significant change. The width of each “violin” reflects the number of cases for each echo variable in the vertical axis, a compact display of a continuous distribution of each data population. The central values displayed on these plots are the mean and SD values. RV= right ventricular.
### Tables.

**Table 1. Baseline Characteristics of All Enrolled Patients and Patients with Paired Follow-Up Echos**

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=870)</th>
<th>Paired echos (n=153)</th>
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<tbody>
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<td><strong>Age, years (median, Q1-Q3)</strong></td>
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<td>57 (49-66)</td>
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<tr>
<td><strong>Gender (n, %)</strong></td>
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<tr>
<td>Female</td>
<td>381 (43.8%)</td>
<td>73 (48.0%)</td>
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<tr>
<td>Male</td>
<td>488 (56.1%)</td>
<td>79 (52.0%)</td>
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<tr>
<td><strong>Race (n, %)</strong></td>
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<tr>
<td>White non-Hispanic</td>
<td>197 (22.6%)</td>
<td>49 (32.0%)</td>
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<tr>
<td>White Hispanic</td>
<td>152 (17.5%)</td>
<td>31 (20.3%)</td>
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<td>Black</td>
<td>136 (15.6%)</td>
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<td>Asian</td>
<td>271 (31.1%)</td>
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<td>Mixed</td>
<td>72 (8.3%)</td>
<td>7 (4.6%)</td>
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<tr>
<td>Other</td>
<td>34 (3.9%)</td>
<td>7 (4.6%)</td>
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<tr>
<td><strong>Geographic Region (n, %)</strong></td>
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<td>USA</td>
<td>125 (14.4%)</td>
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<td>Europe</td>
<td>160 (18.4%)</td>
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<td>83.29±14.8</td>
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<td><strong>Previous Medical Conditions (n, %)</strong></td>
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<tr>
<td>Cardiac (all)</td>
<td>513 (58.9%)</td>
<td>79 (51.6%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>64 (7.3%)</td>
<td>9 (5.9%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>120 (13.8%)</td>
<td>15 (9.8%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>32 (3.6%)</td>
<td>6 (3.9%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>175 (20.1%)</td>
<td>30 (19.6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>374 (42%)</td>
<td>56 (36.6%)</td>
</tr>
<tr>
<td>Lung</td>
<td>126 (14.5%)</td>
<td>18 (11.8%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>75 (8.6%)</td>
<td>17 (11.1%)</td>
</tr>
<tr>
<td><strong>Serum Biomarkers (n, %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-Reactive Protein (CRP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>106 (12.2%)</td>
<td>20 (13.1%)</td>
</tr>
<tr>
<td>Borderline</td>
<td>51 (5.9%)</td>
<td>7 (4.6%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>635 (73.0%)</td>
<td>111 (72.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>78 (9.0%)</td>
<td>15 (9.8%)</td>
</tr>
<tr>
<td>Test</td>
<td>Normal</td>
<td>Borderline</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td>Brain Natriuretic Peptide (BNP)</td>
<td>153 (17.6%)</td>
<td>7 (4.6%)</td>
</tr>
<tr>
<td>Troponin</td>
<td>18 (2.1%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Lactate Dehydrogenase (LDH)</td>
<td>117 (13.4%)</td>
<td>50 (32.7%)</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>85 (9.8%)</td>
<td>12 (7.8%)</td>
</tr>
<tr>
<td>Baseline Hospital Status (n, %)</td>
<td>402 (46.2%)</td>
<td>49 (32.0%)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Baseline</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Left Ventricle</strong></td>
<td>(n = 153)</td>
<td>(n = 153)</td>
</tr>
<tr>
<td>LVEDV, ml *</td>
<td>106.0 +/- 43.9</td>
<td>105.7 +/- 42.4</td>
</tr>
<tr>
<td>LVESV, ml *</td>
<td>44.1 +/- 28.4</td>
<td>44.8 +/- 32.6</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>61.6 +/- 10.1</td>
<td>61.3 +/- 10.6</td>
</tr>
<tr>
<td>ICU</td>
<td>60.8 +/- 11.0</td>
<td>60.1 +/- 10.3</td>
</tr>
<tr>
<td>Ventilation</td>
<td>61.0 +/- 9.2</td>
<td>61.4 +/- 8.3</td>
</tr>
<tr>
<td>LVLS, %</td>
<td>-18.8 +/- 4.4</td>
<td>-18.9 +/- 4.8</td>
</tr>
<tr>
<td>ICU</td>
<td>-18.0 +/- 5.0</td>
<td>-18.8 +/- 4.4</td>
</tr>
<tr>
<td>Ventilation</td>
<td>-18.4 +/- 5.1</td>
<td>-18.3 +/- 4.19</td>
</tr>
<tr>
<td><strong>Right Ventricle</strong></td>
<td>(n=80)</td>
<td>(n=80)</td>
</tr>
<tr>
<td>RVBD, cm</td>
<td>3.9 +/- 0.8</td>
<td>3.8 +/- 0.7</td>
</tr>
<tr>
<td>RVFWS, %</td>
<td>-23.8 +/- 5.8</td>
<td>-24.7 +/- 5.7</td>
</tr>
<tr>
<td>ICU</td>
<td>-21.5 +/- 5.7</td>
<td>-24.1 +/- 4.7</td>
</tr>
<tr>
<td>Ventilation</td>
<td>-22.8 +/- 4.7</td>
<td>-24.8 +/- 4.9</td>
</tr>
<tr>
<td>RVGLS, %</td>
<td>-19.8 +/- 5.1</td>
<td>-20.4 +/- 4.8</td>
</tr>
<tr>
<td>ICU</td>
<td>-17.5 +/- 4.9</td>
<td>-20.4 +/- 5.2</td>
</tr>
<tr>
<td>Ventilation</td>
<td>-18.4 +/- 4.1</td>
<td>-21.5 +/- 6.2</td>
</tr>
</tbody>
</table>

Data presented includes the entire cohort and those who were in the ICU and on mechanical ventilation at time of the initial echocardiogram. LV= left ventricular; LVEDV= LV end diastolic volume; LVESV= LV end systolic volume; LV EF= LV ejection fraction; LVLS= LV longitudinal strain; ICU= intensive care unit; RV= right ventricular; RVBD= RV basal diameter; RVFWS= RV free wall strain; RVGLS= RV global longitudinal strain.
Table 3. Echocardiographic Characteristics of paired Baseline and Follow-up Echos, grouped by Baseline LV and RV Function

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline level</th>
<th>N</th>
<th>Baseline values</th>
<th>FU values</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVESV, mL</td>
<td>Hyperdynamic (EF &gt;70)</td>
<td>33</td>
<td>24.6 +/- 9.1</td>
<td>32.5 +/- 9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Normal (EF 50-70)</td>
<td>99</td>
<td>39.0 +/- 15.9</td>
<td>38.0 +/- 19.8</td>
<td>0.826</td>
</tr>
<tr>
<td></td>
<td>Reduced (EF &lt; 50)</td>
<td>20</td>
<td>92.8 +/- 36.0</td>
<td>81.8 +/- 56.2</td>
<td>0.529</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>Hyperdynamic (EF &gt;70)</td>
<td>33</td>
<td>90.2 +/- 29.4</td>
<td>91.8 +/- 20.8</td>
<td>0.818</td>
</tr>
<tr>
<td></td>
<td>Normal (EF 50-70)</td>
<td>99</td>
<td>98.9 +/- 34.5</td>
<td>98.9 +/- 32.1</td>
<td>0.606</td>
</tr>
<tr>
<td></td>
<td>Reduced (EF &lt; 50)</td>
<td>20</td>
<td>160.6 +/- 57.5</td>
<td>140.9 +/- 68.2</td>
<td>0.279</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>Hyperdynamic (EF &gt;70)</td>
<td>33</td>
<td>73.3 +/- 3.1</td>
<td>64.4 +/- 8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Normal (EF 50-70)</td>
<td>99</td>
<td>61.5 +/- 5.3</td>
<td>62.7 +/- 9.1</td>
<td>0.228</td>
</tr>
<tr>
<td></td>
<td>Reduced (EF &lt; 50)</td>
<td>20</td>
<td>42.5 +/- 5.9</td>
<td>49.3 +/- 13.4</td>
<td>0.017</td>
</tr>
<tr>
<td>LVLS, %</td>
<td>Normal (&lt; -18)</td>
<td>95</td>
<td>-21.5 +/- 2.6</td>
<td>-20.3 +/- 4.0</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Reduced (&gt; -18)</td>
<td>58</td>
<td>-14.5 +/- 2.9</td>
<td>-16.7 +/- 5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVFWS, %</td>
<td>Normal (&lt; -20)</td>
<td>48</td>
<td>-26.7 +/- 3.5</td>
<td>-26.8 +/- 4.0</td>
<td>0.821</td>
</tr>
<tr>
<td></td>
<td>Reduced (&gt; -20)</td>
<td>17</td>
<td>-16.3 +/- 3.9</td>
<td>-18.7 +/- 5.5</td>
<td>0.055</td>
</tr>
<tr>
<td>RVGLS, %</td>
<td>Normal (&gt; -20)</td>
<td>37</td>
<td>-23.5 +/- 2.3</td>
<td>-22.8 +/- 3.1</td>
<td>0.243</td>
</tr>
<tr>
<td></td>
<td>Reduced (&lt; -20)</td>
<td>30</td>
<td>-15.2 +/- 3.4</td>
<td>-17.4 +/- 4.9</td>
<td>0.004</td>
</tr>
<tr>
<td>RVBD, cm</td>
<td>Normal (&lt; 4.5)</td>
<td>64</td>
<td>3.6 +/- 0.6</td>
<td>3.6 +/- 0.5</td>
<td>0.545</td>
</tr>
<tr>
<td></td>
<td>Increased (&gt; 4.5)</td>
<td>15</td>
<td>4.9 +/- 0.7</td>
<td>4.6 +/- 0.6</td>
<td>0.019</td>
</tr>
</tbody>
</table>

FU= follow-up; LV= left ventricular; ESV= end systolic volume; EDV= end diastolic volume; EF= ejection fraction; LS= longitudinal strain; RV= right ventricular; RVFWS= RV free wall strain; RVGLS= RV global longitudinal strain; RVBD= RV basal diameter.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clinical Category</th>
<th>N at Baseline</th>
<th>N at Follow-up</th>
<th>N changed groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td>Hyperdynamic (EF &gt;70)</td>
<td>33</td>
<td>29</td>
<td>23 became normal; 2 became reduced</td>
</tr>
<tr>
<td></td>
<td>Normal (EF 50-70)</td>
<td>99</td>
<td>104</td>
<td>20 became hyperdynamic; 6 became reduced</td>
</tr>
<tr>
<td></td>
<td>Reduced (EF &lt; 50)</td>
<td>20</td>
<td>19</td>
<td>1 became hyperdynamic; 8 became normal</td>
</tr>
<tr>
<td>LVLS, %</td>
<td>Normal (&lt; -18)</td>
<td>95</td>
<td>85</td>
<td>25 became abnormal</td>
</tr>
<tr>
<td></td>
<td>Reduced (&gt; -18)</td>
<td>58</td>
<td>68</td>
<td>15 became normal</td>
</tr>
<tr>
<td>RVFWS, %</td>
<td>Normal (&lt; -20)</td>
<td>48</td>
<td>42</td>
<td>7 became abnormal</td>
</tr>
<tr>
<td></td>
<td>Reduced (&gt; -20)</td>
<td>17</td>
<td>23</td>
<td>1 became normal</td>
</tr>
<tr>
<td>RVGLS, %</td>
<td>Normal (&gt; -20)</td>
<td>37</td>
<td>45</td>
<td>5 became abnormal</td>
</tr>
<tr>
<td></td>
<td>Reduced (&lt; -20)</td>
<td>30</td>
<td>22</td>
<td>13 became normal</td>
</tr>
<tr>
<td>RVBD, cm</td>
<td>Normal (&lt; 4.5)</td>
<td>64</td>
<td>64</td>
<td>5 became increased</td>
</tr>
<tr>
<td></td>
<td>Increased (&gt; 4.5)</td>
<td>15</td>
<td>15</td>
<td>5 became normal</td>
</tr>
</tbody>
</table>

*number of patients that moved into a different clinical category at time of follow-up

Figures (see Figure Legends above)
Figure 1

870 enrolled → 198 FU echos → 14 non-analyzable FU echos

148 non-analyzable baseline echos → 722 analyzable baseline echos → 184 analyzable FU echos

238 died during follow-up → 153 paired baseline/FU

31 unpaired FU echos

Figure 2

Figure 3
Figure 4

Figure 5
Figure 6
Figures (see Figure Legends above)

Figure 1

![Diagram showing data flow and analysis process]

Figure 2

![Graphs showing changes in LV, RV parameters over time]

Legend:
- LVEF: Left Ventricular Ejection Fraction
- LVLS: Left Ventricular Longitudinal Strain
- RVGLS: Right Ventricular Global Longitudinal Strain
- RVFWS: Right Ventricular Free Wall Strain
- RV Basal Diameter

Statistical Significance:
- P = 0.773
- P = 0.852
- P = 0.181
- P = 0.207
- P = 0.343
Figure 3

[Graph showing LVEF (%) for Hyperdynamic baseline, Normal baseline, and Reduced baseline at baseline and follow-up with statistical significance indicated by P values: P < 0.001, P = 0.228, P = 0.017.]

Figure 4

[Graph showing LVLS (%) for Normal baseline and Reduced baseline at baseline and follow-up with statistical significance indicated by P values: P = 0.006, P < 0.001.]
Figure 5

Figure 6
Highlights

- Little is known about long-term cardiac complications of COVID-19 infection.
- We compare echo findings during hospitalization and follow-up in the WASE-COVID study.
- No changes in population mean values for LV and RV parameters after COVID-19.
- LV and RV function improve in patients with impaired baseline function.
- LV and RV function decrease in patients with hyperdynamic LV or normal RV.
Ventricular Changes in Patients with Acute COVID-19 Infection: Follow-Up of The World Alliance Societies of Echocardiography (WASE-COVID) Study

Supplemental Material

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14Northwestern University, Chicago IL
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16MedStar Health Research Institute, Washington DC
17Full List of additional WASE-COVID investigators is provided after Conclusions, in page 15.
Supplemental Material – Description of EchoGo Methods

Development of View classification

Model development and validation was based on a dataset of clinical information and images extracted from several multicenter studies. Images had been acquired from hospitals with a range of sizes, type of operators and ultrasound vendor equipment representative of “real world” echocardiography. Data was accessed with participants informed consent and ethical approval for the study was obtained from Health Research Authority NRES Committee South Central – Berkshire (IRAS reference: 14/SC/1437). For model training, a set of images were identified that: included apical-4-chamber (A4C) and apical-2-chamber (A2C) views; had endocardial visualization in at least 14 of 16 segments in available images (based on consensus review by three 3 BSE accredited cardiac physiologists); had end-diastolic (ED) and end-systolic (ES) frames with a minimum of 4 frames between ED and ES. The echocardiograms were used to develop a series of sequential image processing algorithms. All studies consisted of a set of Digital Imaging and Communications in Medicine (DICOM) format 2D videos. Convolutional Neural Network (CNN) frameworks were developed using Python 3.5 with Keras 2.2.4 and TensorFlow 1.13. For the view classification model, a bespoke CNN was built using 10 convolutional layers which identifies A2C, A4C, SAX and apical-3-chamber (A3C) views acquired with and without contrast, respectively. Training data comprised of 1250 2D echocardiograms from 1014 subjects.

Development of View classification

Prior to view classification model training, images were processed using standard techniques to ensure homogenous and normalized image inputs to the training pipeline. Before processing, the data was split into 90% for model training (211,958 image frames), and 10% used as a testing dataset (23,946 frames). Image frames from different subjects were separated out entirely amongst the training and testing datasets. Furthermore, a separate validation dataset of 240 studies was acquired from the US testing data and used as an independent test dataset (39,401 frames).

Development of LV Segmentation

Following view classification, a U-net based CNN segmentation frameworks was developed to contour the LV endocardium in A2C and A4C views. End-diastolic (ED) and end-systolic (ES) image labels were used to train the CNNs images initially contoured manually by three British Society of Echocardiography (BSE) accredited echocardiographers. The model was trained from
data comprised of 5,692 frames. The datasets were split into 80% training and 20% testing datasets for training the CNNs. Raw images were processed and fed into the modified U-net CNN framework. The CNNs produced contours that were able to track the endocardial walls smoothly through time. The efficacy of the network’s segmentation performance was assessed using the Sørensen-Dice Coefficient (DC). An algorithm was established from the image clips and LV contours to identify the cardiac cycle and end-diastole and end-systole frames, comprising assessment of contour areas and R-wave triggers. Where the R-wave trigger was not available, the heart rate was inferred from the image LV segmentation. The HR extraction required the reduction of image dimensionality, followed by signal period extraction, using dimensionality reduction methodologies.

**Performance of Auto-View Classification**

Using an unseen dataset of 240 studies (23,946 frames), an overall accuracy of 95% was achieved for the CNN view classifier used to identify and label 8 echocardiographic views. Classification accuracy of non-contrast views (A2C, A3C, A4C and SAX) exceeded 97% while the accuracy of contrast A3C, A4C and SAX view classification was >93% and contrast A2C views was 85%. The differentiation between contrast from non-contrast views was 100%.

**Performance of LV contouring and segmentation**

For the auto-contouring model, a testing dataset of 436 image frames were contoured by the model, which demonstrated high concordance with manual contours from three BSE accredited echocardiographers, as measured by the Sørensen-Dice Coefficient (DC). The model achieved a mean contrast A2C and A4C DC of 93.25%, exceeding that seen in other works. The auto-contouring model performed consistently well on data captured using multiple ultrasound vendors and models and did not exhibit significant declines in DC scores across the range of image quality considered clinically acceptable for stress echocardiography.
Supplemental Figure S1. Changes in LV and RV according to time of follow-up. Patients were divided in 2 groups according to the time to follow-up echocardiograms (above and below the median -143 days-)