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RESEARCH ARTICLE

Recovery of cardiac function following COVID-19 – ECHOVID-19: a prospective longitudinal cohort study

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Aims The degree of cardiovascular sequelae following COVID-19 remains unknown. The aim of this study was to investigate whether cardiac function recovers following COVID-19.

Methods and results A consecutive sample of patients hospitalized with COVID-19 was prospectively included in this longitudinal study. All patients underwent an echocardiographic examination during hospitalization and 2 months later. All participants were successfully matched 1:1 with COVID-19-free controls by age and sex. A total of 91 patients were included (mean age 63 ± 12 years, 59% male). A median of 77 days (interquartile range: 72–92) passed between the two examinations. Right ventricular (RV) function improved following resolution of COVID-19: tricuspid annular plane systolic excursion (TAPSE) (2.28 ± 0.40 cm vs. 2.11 ± 0.38 cm, $P < 0.001$) and RV longitudinal strain (RVLS) (25.3 ± 5.5% vs. 19.9 ± 5.8%, $P < 0.001$). In contrast, left ventricular (LV) systolic function assessed by global longitudinal strain (GLS) did not significantly improve (17.4 ± 2.9% vs. 17.6 ± 3.3%, $P = 0.6$). N-terminal pro-B-type natriuretic peptide decreased between the two examinations [177.6 (80.3–408.0) ng/L vs. 11.7 (5.7–24.0) ng/L, $P < 0.001$]. None of the participants had elevated troponins at follow-up compared to 18 (27.7%) during hospitalization. Recovered COVID-19 patients had significantly lower GLS (17.4 ± 2.9% vs. 18.8 ± 2.9%, $P < 0.001$ and adjusted $P = 0.004$), TAPSE (2.28 ± 0.40 cm vs. 2.67 ± 0.44 cm, $P < 0.001$ and adjusted $P < 0.001$), and RVLS (25.3 ± 5.5% vs. 26.6 ± 5.8%, $P = 0.50$ and adjusted $P < 0.001$) compared to matched controls.

Conclusion Acute COVID-19 affected negatively RV function and cardiac biomarkers but recovered following resolution of COVID-19. In contrast, the observed reduced LV function during acute COVID-19 did not improve post-COVID-19. Compared to the matched controls, both LV and RV function remained impaired.

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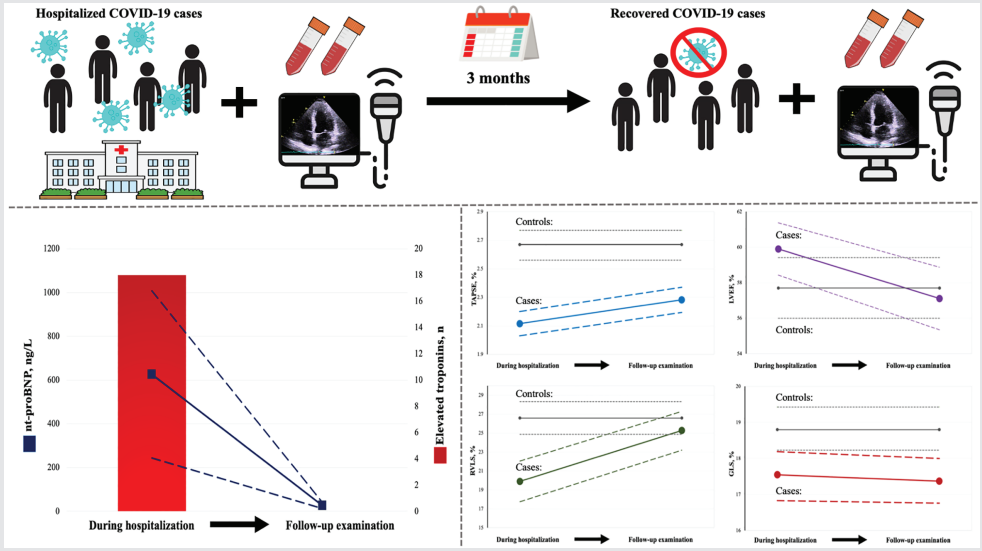
Graphical Abstract



Recovered COVID-19 cases who participated in both rounds of the study. (*Left*) Diagram displaying mean N-terminal pro-B-type natriuretic peptide (NT-proBNP) and prevalence of elevated troponins during hospitalization and 2–3 months after. (*Right*) Diagram displaying mean values of tricuspid annular plane systolic excursion (TAPSE), right ventricular longitudinal strain (RVLS), global longitudinal strain (GLS), and left ventricular ejection fraction (LVEF) assessed during hospitalization and median 77 days (interquartile range: 72–92) after. Additionally, reference values based on matched controls are illustrated as well. Dotted lines indicate 95% confidence intervals.

Keywords COVID-19 • Recovery following COVID-19 • Follow-up • Strain echocardiography

Introduction

The global coronavirus disease 2019 (COVID-19) pandemic continues to spread worldwide causing significant morbidity and mortality. In a number of case series, COVID-19 has been found to directly affect the cardiovascular system by causing acute myocardial injury[1] and myocarditis.[2–4] Additionally, larger studies have found that COVID-19 can exacerbate heart failure in patients with prevalent cardiac disease.[5–7] We have previously reported from our prospective multicentre study, the ECHOVID-19 study, that cardiac biomarkers were elevated and echocardiographic parameters of left (LV) and right ventricular (RV) function were affected compared to controls free from COVID-19.[8,9] A range of pathophysiological mechanisms have been proposed including cardiac stress due to a demand for increased cardiac output, plaque rupture, and systemic endotheliosis, which may lead to compromised local myocardial blood flow and cause ischaemia-related cardiovascular complications.[10,11]

The presence of acute myocardial injury during the acute phase of COVID-19 naturally raises the question of potential long-term cardiac implications. Recently, two echocardiographic studies investigated the presence of persisting cardiac dysfunction following COVID-19 resolution.[12,13] They had contradicting results, as one found evidence of persisting adverse remodelling of the heart[12] and the other did not.[13] However, one study lacked an echocardiography during the acute infection,[13] and the other study's baseline echocardiography was retrospectively obtained.[12] The ECHOVID-19 study is so far the only study to have prospectively included patients with COVID-19 in an unselected manner and let them all undergo an echocardiographic examination according to a pre-determined research protocol. In the present study, we sought to investigate how echocardiographic parameters and cardiac biomarkers developed in patients hospitalized with COVID-19 from the time of acute infection to 2–3 months following discharge from the hospital. Our overall aim was, therefore, to investigate cardiac recovery following COVID-19 (*Graphical Abstract*).

Methods

Population

The ECHOVID-19 study is a prospective longitudinal study of consecutive hospitalized adults with COVID-19.[8,9] The study was designed to investigate cardiac involvement in COVID-19 and potential long-term cardiac sequelae following resolution of acute infection. A single team of investigators visited one to two of the eight inclusion sites (covering almost haft of the Danish population) each day to enrol patients

in the period 30 March to 3 June 2020 and none of the patients were mechanically ventilated at the time of inclusion. All adult patients from the COVID-19 wards (not intensive care units) were invited to participate if able to sign a written informed consent. Patients willing to participate underwent an echocardiographic examination immediately after recruitment. Thus, no participants died in the time from inclusion to the primary echocardiographic examination. The method of inclusion has previously been described in detail.[9] Surviving participants were invited for a follow-up examination 2–3 months following hospital discharge. Participants were invited by telephone and excluded after three failed attempts of contact on three separate days. All participants answered a questionnaire (only at inclusion), underwent echocardiography, and had blood samples and an electrocardiogram taken during hospitalization and at follow-up. All participants had their electronic health records reviewed for retrieval of clinical data and baseline information following inclusion into the study.

Inclusion criteria were (i) hospitalized for laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, (ii) age ≥18 years, (iii) provided written informed consent, and (iv) willingness to participate in a follow-up examination. Exclusion criteria were (i) death prior to follow-up examination, and (ii) non-responsiveness to follow-up invitation. All included participants gave written informed consent. The study was performed in accordance with the second Declaration of Helsinki and approved by the regional ethics board. The ECHOVID-19 study is registered at ClinicalTrials.gov (NCT04377035).

Controls and matching

All follow-up participants were matched 1:1 by age (5-year age intervals) and sex with participants of the 5th Copenhagen City Heart Study. The Copenhagen City Heart Study is a prospective cohort study investigating cardiovascular disease and risk factors in the general population. The study sample consisted of 4466 randomly invited members of the general population. The 5th Copenhagen City Heart Study has been described in detail elsewhere.[14]

Echocardiography

Baseline echocardiography were performed bedside with portable Vivid IQ Ultrasound Systems (GE Healthcare, Horten, Norway). Follow-up echocardiography were performed with Vivid 9 Ultrasound System (GE Healthcare, Horten Norway). Both examinations were performed according to a pre-determined comprehensive echo-protocol by trained sonographers. All images were analysed with EchoPAC version 203 (GE, Vingmed Ultrasound AS) offline by a single experienced investigator blinded to all clinical information to avoid inter-observer variability. All echocardiographic measurements were performed according to existing guidelines.[15,16] LV ejection fraction (LVEF) was measured using the Simpson's biplane method, and the tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode in the apical 4-chamber projection. A detailed description of the conventional echocardiography analysis methods in the ECHOVID-19 study has been published previously.[9]

Two-dimensional speckle tracking

Images within optimal frame rate intervals were used for two-dimensional speckle tracking analysis. Median frame rate was 64 (60–66) frames/s. RV longitudinal strain (RVLS) was defined as the mean peak longitudinal strain of the three segments of the RV lateral wall measured in the apical 4-chamber view optimized for RV visualization. Global longitudinal strain (GLS) was calculated as the mean peak systolic strain values of the 16 segments of (15, 20–22) the left ventricle obtained from the apical 4-, 2- and 3-chamber views. We have previously reported the intra- and inter-observer variability for TAPSE, RVLS, and GLS in the ECHOVID-19 cohort.[9] Abnormal LVEF (<52% for males and <54% for females), GLS (<16%), TAPSE (<17 mm), and RVLS (<20%) were defined according to current guidelines.[15]

Statistics

A *P*-value of <0.05 was defined as statistical significance and STATA statistics/data analysis, SE 15.1 (StataCorp, College Station, TX, USA) was used for all data analysis. Q–Q plots were used to test for Gaussian distribution. Gaussian distributed continuous variables are presented as mean ± standard deviation, while non-Gaussian distributed continuous variables are presented as median with interquartile range (IQR). Categorical values are presented as frequencies with percentages. Paired *t*-test was used to compared continuous variables measured at baseline and at follow-up. A sensitivity analysis was carried out in which a univariable and a multivariable fixed effects linear regression model for repeated measures adjusted for the difference in haemodynamic changes between the two timepoints (heart rate, systolic and diastolic blood pressure) were used to compare the echocardiographic parameters at baseline and at follow-up. Both unadjusted and adjusted *P*-values are reported.

As N-terminal pro-B-type natriuretic peptide (NT-proBNP) did not follow a Gaussian distribution, it was log-transformed when used in paired *t*-test. Prevalence of elevated troponins at baseline and follow-up were compared with chi-squared test. This was done because only one type of troponin was measured at each recruitment site and only troponin I was assessed at follow-up. Two-sampled *t*-test was used to compare follow-up participants with non-participants and cases with matched controls. Cases and controls were matched by age and sex to ensure complete matching of all cases and then multivariable linear regression analysis was used to adjust for significant differences between cases and controls (smoking status, hypertension, diabetes mellitus, and hypercholesterolaemia) when comparing echocardiographic findings. Diagrams and box plots were utilized to illustrate TAPSE, RVLS, LVEF, and GLS at hospitalization, at follow-up, and in matched controls.

Results

Initially, 215 patients were included in the ECHOVID-19 study and had a protocolized echocardiogram and cardiac biomarkers measured during their initial hospitalization for COVID-19. Of these, 43 did not survive to the time of their follow-up examinations. Of the remaining 171 participants, 11 did not respond to the invitation, while 70 declined to participate in the follow-up examination. Hence, a total of 91 patients were included in this longitudinal assessment of the effect of COVID-19 on the heart. *Figure 1* illustrates the inclusion process. Baseline characteristics of patients who participated in follow-up and all patients who did not participate in the follow-up examination (including those that did not survive until follow-up) are depicted in online supplementary *Table S1*. The time from hospital admission to the first examination was median 3 days (IQR: 2–8), while median 77 days (IQR: 72–92) passed between the first and second examination. Mean age of

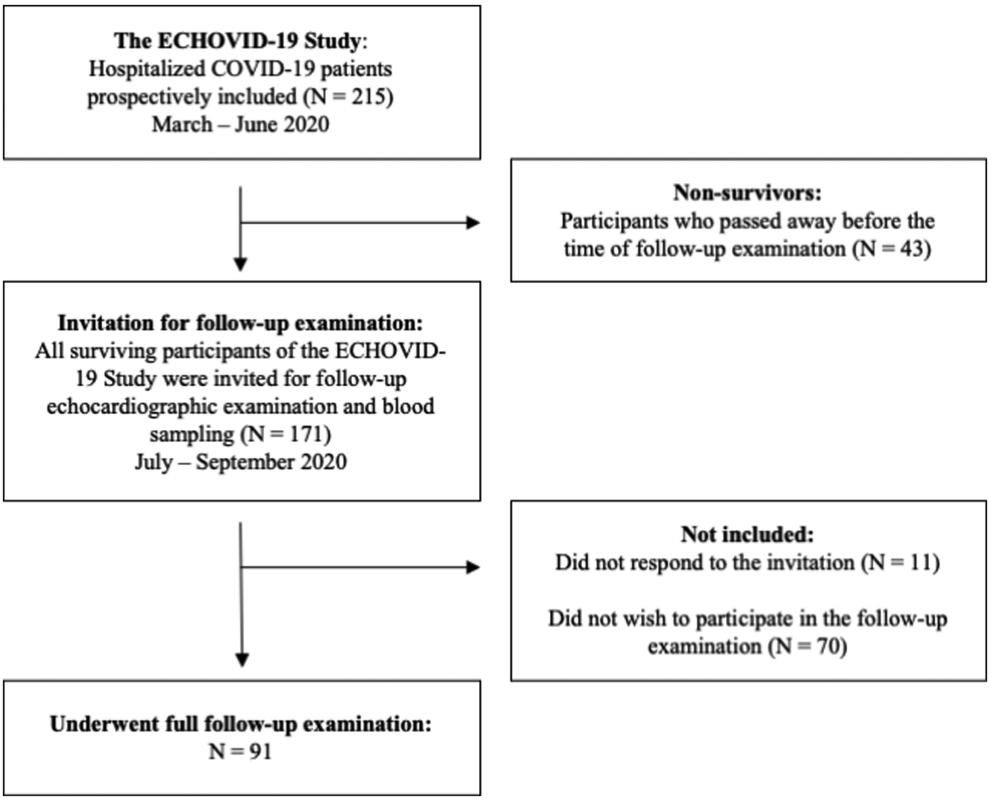


Figure 1 Flow diagram of the exclusion process for the ECHOVID-19 study ending with the included participants in the follow-up part of the study.

the study sample was 63 ± 12 years and 59% were male. *Table 1* lists baseline characteristics, comorbidities and complications during hospitalization in addition to biochemistry at baseline and at follow-up. Participants of the follow-up examination were significantly younger and suffered less frequently from heart failure and hyperlipidaemia than those participants who were alive at follow-up but chose not to partake in the follow-up examination (online supplementary *Table S2*).

Comparison of cardiac parameters at baseline and follow-up

Table 1 lists the frequency of abnormal echocardiographic findings during hospitalization and at follow-up. In total, 39 (46.4%) participants suffered from subclinical myocardial injury during hospitalization for COVID-19 (defined as abnormal TAPSE, RVLS, LVEF, or GLS), when excluding the seven participants with prevalent heart failure or ischaemic heart disease. Of these 39 participants, 18 (46.2%) continued to display LV systolic dysfunction (abnormal LVEF or GLS) at follow-up. Continuous measures of echocardiographic-assessed cardiac function are reported in *Table 2*. Measures of RV function such as TAPSE (2.28 ± 0.40 cm vs. 2.11 ± 0.38 cm, $P < 0.001$) and RVLS (25.3 ± 5.5% vs. 19.9 ± 5.8%, $P < 0.001$) both significantly improved following the resolution of COVID-19. Measure of RV area size and tricuspid regurgitation (TR) maximum gradient were not significantly different between visits. In contrast, LVEF significantly decreased between the two echocardiographic examinations (57.1 ± 7.4% vs. 59.9 ± 6.2%, $P = 0.003$). Meanwhile, GLS (17.4 ± 2.9% vs. 17.6 ± 3.3%, $P = 0.64$) did not improve after recovery from COVID-19. LV structural measurements [LV end-systolic volume (44 ± 15 mL vs. 40 ± 16 mL, $P < 0.001$] were larger at follow-up. These findings remained unchanged besides LV end-systolic volume (unadjusted $P = 0.001$, adjusted $P = 0.18$) in the sensitivity analysis (TAPSE: unadjusted: $P < 0.001$, adjusted: $P = 0.02$; RVLS: unadjusted: $P < 0.001$, adjusted: $P = 0.008$; RV end-diastolic area: unadjusted $P = 0.90$, adjusted $P = 0.82$; RV end-systolic area: unadjusted $P = 1.0$, adjusted $P = 0.82$; TR maximum gradient: unadjusted $P = 0.57$, adjusted $P = 0.78$; LV internal diameter: unadjusted $P = 0.42$, adjusted $P = 0.49$; LV end-diastolic volume: unadjusted $P = 0.74$, adjusted $P = 0.50$; LVEF: unadjusted $P = 0.003$, adjusted $P = 0.005$; GLS: unadjusted $P = 0.64$, adjusted $P = 0.33$). Of the measured cardiac biomarkers, NT-proBNP was observed to decrease significantly between the two visits [177.6 ng/L (IQR: 80.3–408.0) vs. 11.7 ng/L (IQR: 5.7–24.0), $P < 0.001$]. None of the participants had elevated troponins at follow-up, whereas 18 (27.7%) had elevated troponins during hospitalization [median troponin I at follow-up: 4 ng/L (IQR: 3–7]. *Figure 2* illustrates NT-proBNP during hospitalization and at follow-up.

Table 1 Baseline characteristics of cases and controls

	Cases		Controls
Number	91		91
Male sex, *n* (%)	54 (59)		54 (59)
Age, years	62.5 ± 12.1		62.1 ± 12.2
BMI, kg/m^2	27.5 ± 5.8		27.1 ± 5.2
Pack-years if smoking history, median (IQR)	17.5 (6.5–25.0)		20.0 (7.8–35.5)
Smoking status, *n* (%)			
Current	3 (4)		21 (24)*
Former	43 (51)		40 (47)
Never	39 (46)		25 (29)
Hypertension, *n* (%)	44 (48)		27 (30)*
Diabetes, *n* (%)	18 (20)		7 (8)*
Hyperlipidaemia, *n* (%)	33 (36)		17 (19)*
Prevalent heart failure, *n* (%)	3 (3)		2 (2)
Previous ischaemic heart disease, *n* (%)	7 (8)		7 (8)
Clinical parameters at inclusion, mean ± SD			
Respiratory rate, breaths/min	20 ± 5		–
Oxygen saturation, %	95 ± 2		–
Early warning score, *n* (%)			
0	16 (18)		–
1	20 (22)		–
2	23 (25)		–
3	8 (9)		–
4	14 (15)		–
5	9 (10)		–
6	1 (1)		–
COVID-19 complications			
Length of hospitalization, days, median (IQR)	7.0 (4.0–20.0)		–
Acute respiratory distress syndrome, *n* (%)	26 (29)		–
Venous thromboembolic event, *n* (%)	8 (9)		–
Admission to intensive care unit, *n* (%)	17 (19)		–
Biochemistry and haemodynamics	**During hospitalization**	**At follow-up**	
D-dimer, mg/L, median (IQR)	1.2 (0.7–2.1)	–	
Creatinine, µmol/L,median (IQR)	72.0 (57.0–89.0)	65.0 (58.0–79.0)	
Leucocytes, ×10^9/L, median (IQR)	6.1 (5.0–9.1)	6.3 (5.3–7.3)	–
Neutrophils, ×10^9/L, median (IQR)	4.2 (3.2–6.4)	3.7 (3.0–4.1)	–
Lymphocytes, ×10^9/L, median (IQR)	1.3 (0.8–1.6)	1.8 (1.3–2.2)	–
CRP, mg/L, median (IQR)	54 (17–93)	0.0 (0.0–0.0)	–
Systolic blood pressure, mmHg, mean ± SD	124 ± 17	126 ± 16	
Diastolic blood pressure, mmHg, mean ± SD	72 ± 11	78 ± 7	
Heart rate, bpm, mean ± SD	78 ± 16	73 ± 11	
Abnormal echocardiographic findings, *n* (%)			
Abnormal LVEF	6 (8)	19 (27)	11 (16)
Abnormal GLS	29 (34)	27 (30)	11 (13)
Abnormal TAPSE	9 (11)	6 (7)	1 (1)
Abnormal RVLS	24 (62)	9 (13)	8 (12)

BMI, body mass index; CRP, C-reactive protein; GLS, global longitudinal strain; IQR, interquartile range; LVEF, left ventricular ejection fraction; RVLS, right ventricular longitudinal strain; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.
*Statistically significant.

Comparison of follow-up measurement with matched controls

All 91 follow-up patients were matched 1:1 by sex and age with participants of the 5th Copenhagen City Heart Study. Baseline characteristics of the control sample are displayed in *Table 1*. Some difference remained between the two samples. Cases suffered more frequently from hypertension, diabetes, hyperlipidaemia, and were less likely to be current smokers. Recovered COVID-19

Table 2 Differences in echocardiographic parameters and cardiac biomarkers between cases at hospitalization and at follow-up and controls

	Cases during hospitalization	Cases at follow-up	*P*-value	Controls	*P*-value	Adjusted *P*-value
Number	91	91		91		
LV parameters						
LVEF, %	59.9 ± 6.2	57.1 ± 7.4	0.003	57.7 ± 7.1	0.55	0.55
GLS, %	17.6 ± 3.3	17.4 ± 2.9	0.64	18.8 ± 2.9	<0.001	0.004
LV end-diastolic volume, mL	98 ± 32	99 ± 30	0.74	110 ± 27	0.03	0.020
LV end-systolic volume, mL	40 ± 16	44 ± 15	<0.001	49 ± 16	0.11	0.15
LV internal diameter, cm	4.5 ± 0.6	4.6 ± 0.6	0.42	4.7 ± 0.5	0.063	0.23
RV parameters						
TAPSE, cm	2.11 ± 0.38	2.28 ± 0.40	<0.001	2.67 ± 0.44	<0.001	<0.001
RVLS, %	19.9 ± 5.8	25.3 ± 5.5	<0.001	26.6 ± 5.8	0.50	<0.001
TR max gradient, mmHg	19.7 ± 8.6	18.9 ± 8.9	0.56	22.2 ± 5.8	0.13	0.13
RV diastolic area, cm^2	16.9 ± 3.6	16.7 ± 4.3	0.89	18.9 ± 4.9	0.10	0.53
RV systolic area, cm^2	10.6 ± 2.7	10.6 ± 2.9	0.99	12.1 ± 3.2	0.07	0.53
Cardiac biomarkers						
Elevated troponins, *n* (%)	18 (27.7)	0 (0)	–			
NT-proBNP, ng/L, median (IQR)	177.6 (80.3–408.0)	11.7 (5.7–24.0)	<0.001			

Values are given as mean ± standard deviation, unless otherwise stated.
GLS, global longitudinal strain; IQR, interquartile range; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular; RVLS, right ventricular longitudinal strain; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

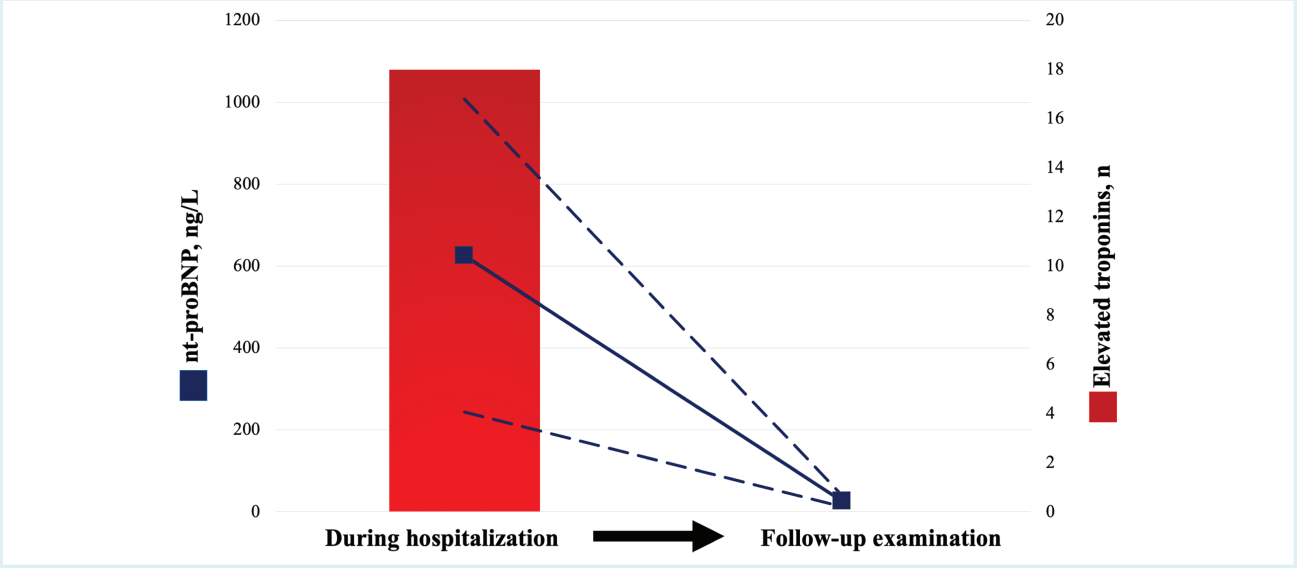


Figure 2 Cardiac biomarkers during hospitalization and after recovery from COVID-19. Diagram displaying mean N-terminal pro-B-type natriuretic peptide (NT-proBNP) and prevalence of elevated troponins during hospitalization and 2–3 months after. Dotted lines indicate 95% confidence intervals.

patients had significantly lower GLS (17.4 ± 2.9% vs. 18.8 ± 2.9%, $P < 0.001$ and adjusted $P = 0.004$), TAPSE (2.28 ± 0.40 cm vs. 2.67 ± 0.44 cm, $P < 0.001$ and adjusted $P < 0.001$), and RVLS (25.3 ± 5.5% vs. 26.6 ± 5.8%, $P = 0.50$ and adjusted $P < 0.001$) compared to controls. *Figures 3* and *4* illustrate the changes in echocardiographic parameters and the reference values observed in the control group.

Discussion

The present study is the first prospective longitudinal study investigating cardiac recovery following COVID-19 with full echocardiographic examinations along with cardiac biomarker sampling performed both during the acute course of the infection and again in the convalescent phase. In this prospective

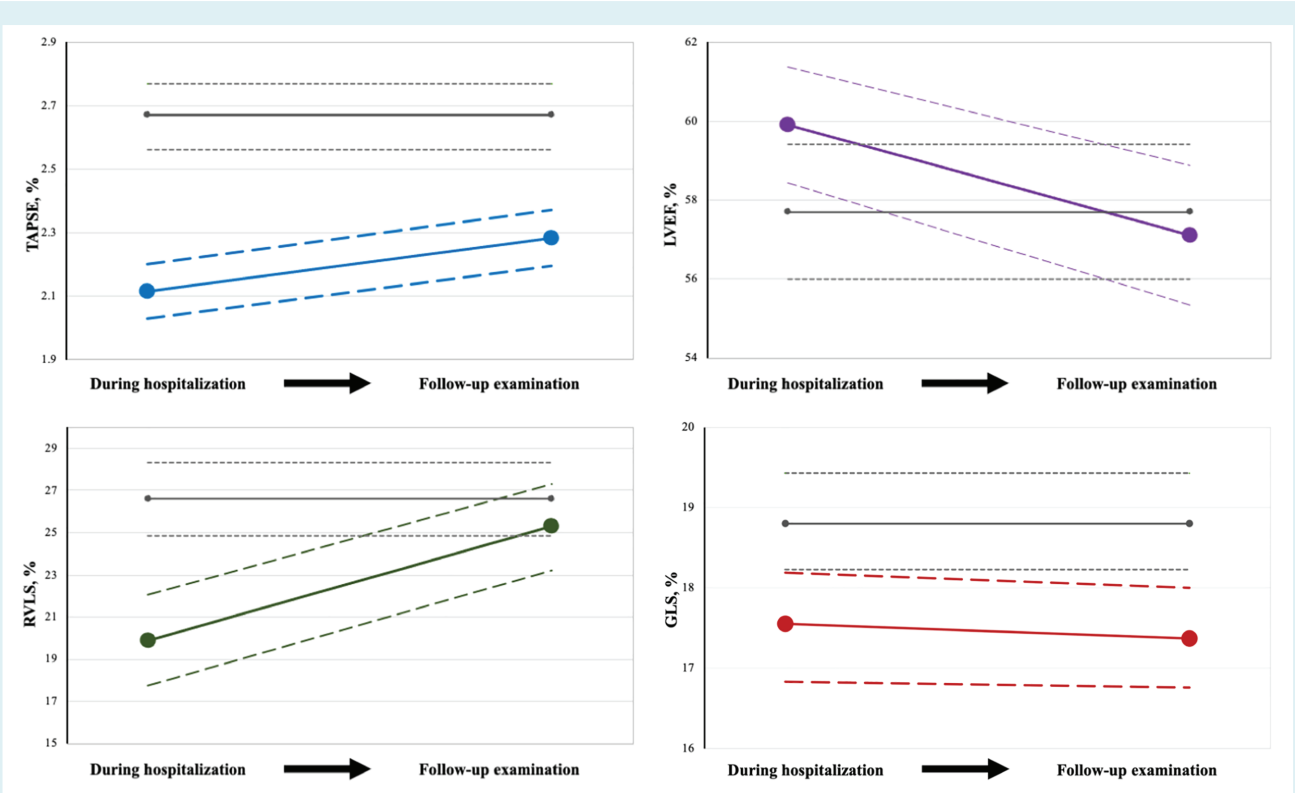


Figure 3 Echocardiographic parameters during hospitalization and after recovery from COVID-19. Diagram displaying mean values of tricuspid annular plane systolic excursion (TAPSE), right ventricular longitudinal strain (RVLS), global longitudinal strain (GLS), and left ventricular ejection fraction (LVEF) assessed during hospitalization and 2–3 months after. Additionally, reference values based on matched controls are illustrated as well. Dotted lines indicate 95% confidence intervals.

multicentre study, we found that (i) echocardiographic measures of RV function and cardiac biomarker levels improved following resolution of COVID-19 infection, (ii) LVEF decreased following recovery of the disease but was not significantly different from LVEF in COVID-19-free matched controls, while GLS remained unchanged following recovery, and (iii) recovered COVID-19 patients had lower GLS, TAPSE and RVLS compared to matched controls while still being within the normal range of clinically acceptable values.

The ECHOVID-19 study was initiated with the aim of investigating how COVID-19 impacts the heart, both during acute COVID-19 and following resolution. We have previously demonstrated that myocardial function, as assessed by echocardiography, was reduced in patients hospitalized with acute COVID-19 compared to matched controls.[9] Additionally, we also found that COVID-19 patients with impaired LV and RV function as assessed by echocardiography and cardiac biomarkers were on a more adverse disease trajectory than patients without elevated levels of troponins and NT-proBNP and normal LV and RV function.[8]

The frequency of myocardial injury,[1,17] vascular dysfunction[18] and elevated risk of thromboembolic events,[19] even in patients without severe course of infection, raises important concerns about long-term cardiac sequelae.[20] The present longitudinal cohort study is the first fully prospective study to investigate the presence of persistent cardiac sequelae assessed by changes in echocardiographic parameters between time of hospitalization and following resolution of COVID-19 infection in COVID-19 survivors. A recent study by Moody *et al.*[12] investigated the presence of adverse ventricular remodelling in 79 COVID-19 survivors. They found that COVID-19 survivors had persisting adverse remodelling in 29% of their population. However, their population was highly selected as they only included patients who had an echocardiography performed due to a clinical complication during their hospitalization for COVID-19. The baseline echocardiography used in their study was therefore retrospective and not necessarily performed using the same protocol and by the same personnel. Furthermore, 95% of their population had their baseline echocardiography performed while on mechanical ventilation support. These factors may explain why they observed a much higher degree of cardiac sequelae in their patient population. Our study is the only echocardiographic study with baseline examinations performed according to a pre-determined research protocol on a sample of consecutive unselected patients and the follow-up examinations performed according to the same protocol. Therefore, we believe our reported results paint a truer picture of the level of cardiac sequalae in survivors of COVID-19.

Other imaging techniques have been used to investigate long-term cardiac sequelae. Puntmann *et al.*[21] conducted a study

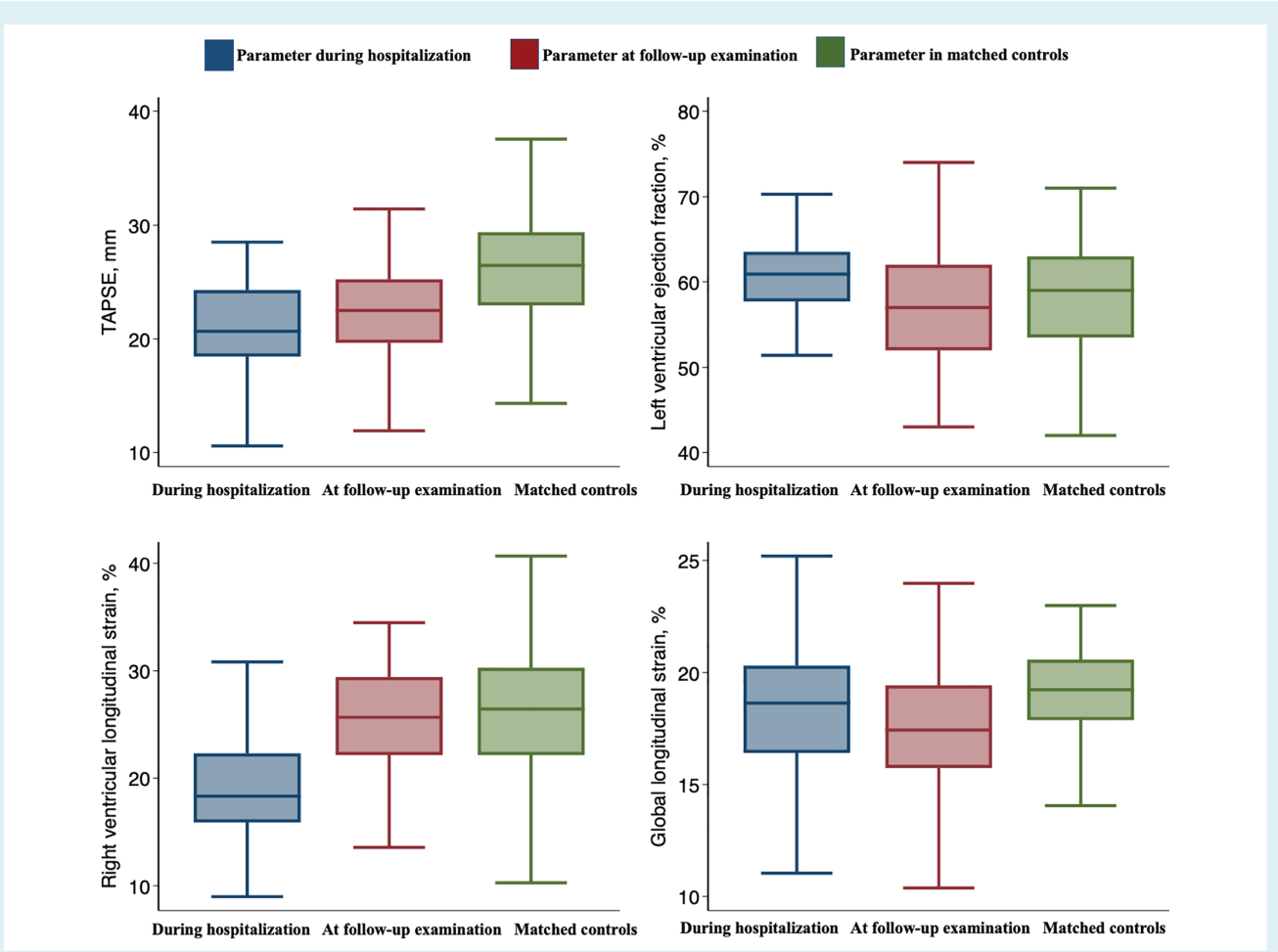


Figure 4 Echocardiographic parameters during hospitalization and after recovery from COVID-19 presented in box plots. Box plots displaying median values of tricuspid annular plane systolic excursion (TAPSE), right ventricular longitudinal strain, global longitudinal strain, and left ventricular ejection fraction with interquartile range along with upper and lower adjacent values during hospitalization, at follow-up, and in matched controls.

evaluating the presence of myocardial injury with cardiac magnetic resonance imaging (cMRI) and inflammation in a cohort of 100 unselected patients recently recovered from COVID-19. They found that 78% had cardiac involvement and 60% had ongoing myocardial inflammation.[21] However, cMRI was only performed following resolution of the infection and therefore lacked information on cardiac involvement at the time of acute infection and they did not use a control population free from COVID-19 for comparison. Some discrepancy in the level of cardiac sequelae following COVID-19 exist, as Catena *et al.*[13] performed an echocardiographic examination on 64 patients previously hospitalized for COVID-19 at a median of 41 days following hospital discharge in which they concluded that there was no evidence of persistent cardiac dysfunction on echocardiography. Unfortunately, Catena *et al.* were also missing both an examination performed during the acute infection to compare their follow-up data with COVID-19-free control group. Also, they did not perform any two-dimensional speckle tracking analysis to detect more subtle myocardial changes.[22]

The results of the present study provide essential knowledge on the prevalence of cardiovascular sequelae following SARS-CoV-2 infection in patients with COVID-19 that required hospitalization and were alive after 3 months following discharge. Our findings demonstrate that cardiac function is affected in patients hospitalized with acute COVID-19, it persists despite resolution of the disease, and it is worse than in matched controls. Although we observed a significant decrease in LV function following resolution of COVID-19 and that all measures of both LV and RV function remain reduced compared to matched controls free of COVID-19, we wish to stress that LVEF, TAPSE, RVLS and GLS were all within the normal range of clinically acceptable values[15] and the clinically meaningful decrease in cardiac function observed is thus quite small in terms of need for clinical intervention. However, sub-clinical changes in myocardial function have been associated with a worse prognosis in several long-term studies.[22,23] However, it must be mentioned that evidence of the value of interventions based on sub-clinical myocardial changes is still lacking.

Our results are in line with evidence found by smaller studies using cMRI to evaluate diffuse inflammatory involvement of the heart in COVID-19[24,25] and with what Puntmann *et al.*[21] found. Unlike these previous studies, we were able to show the changes in cardiac function both during the acute infection and following resolution. Although we observed a relatively large degree of cardiac involvement at the time of acute infection with COVID-19,[9] with the present study we can show that RV function improves significantly following convalescence whereas LV function remains largely unchanged or even slightly decreases. This was the case even when adjusting for differences in haemodynamic parameters between baseline and follow-up in the sensitivity analysis. This may indicate that once the pneumonic state caused by SARS-CoV-2 resolves, acute RV impairment due to pulmonary pathology-induced elevation in RV afterload due to elevated pulmonary vascular resistance disappears, and RV function thereafter improves. However, the diffuse inflammation that may cause decreased LV function could still remain in the early convalescent phase. Of course, what remains unknown is what exactly causes the reduced LV myocardial function. It may happen as a result of SARS-CoV-2 attacking the heart directly with lasting effects, as a secondary consequence of the systemic inflammation, or both. Also, we cannot rule out that there may be a higher prevalence of undetected sub-clinical heart disease in COVID-19 patients requiring hospitalization compared to patients with COVID-19 who did not require hospitalization. However, at the time of the follow-up visit, C-reactive protein had dropped to zero in almost all participants of the study, which makes the presence of systemic inflammation unlikely to be the sole explanation for the slightly decreased LV function. The discussed mechanisms are speculative as there remains a lack of definitive evidence in this area.

The present study provides important new mechanistic knowledge to the cardiac pathology of a disease that continues to spread across the globe. Our findings indicate that the right ventricle recovers its function following resolution of the disease, whereas LV function is largely unchanged. These temporal relationships have not been reported before, and we believe they will aid in the understanding of the potential cardiac involvement in COVID-19.

Strengths and limitations

The sample size of this study is relatively small, and not all participants wished to partake in the follow-up examination or did not survive until this timepoint. Nevertheless, the usage of repeated measures in the same individuals improves the power of the study and should limit the effect of selection bias. In this study, we could not investigate differentiated long-term cardiac involvement as analyses of interaction and stratification according to e.g. gender or age groups or to specific adverse events during hospitalization such as myocardial infarction or myocarditis would require a larger sample size. Important strengths of this prospectively planned and conducted study are that we performed repeated echocardiographic measurements both during acute infection and following resolution. Thus, patients were not selected to undergo an echocardiography due to a perceived increased risk or clinical worsening, which is a great limitation to many of the previously published retrospective cardiac imaging data often resulting in a biased overestimation the true prevalence of impaired cardiac function. Lastly, it is important to stress that our results are representative only of patients that were hospitalized for COVID-19, that survived until 3 months following discharge and is probably limited by a degree of healthy volunteer effect.

Conclusion

In this cohort of 91 COVID-19 survivors, the right ventricle was affected during acute COVID-19, but its function improved after resolution of the infection. However, the reduced LV function during acute COVID-19 did not improve at follow-up. Furthermore, LV and RV function remained impaired as compared to matched controls. Finally, NT-proBNP, troponin levels and markers of inflammation were normalized at follow-up. These findings are based on a limited sample of COVID-19 survivors and should be considered hypothesis-generating.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: T.B.S. reports receiving research grants from Sanofi Pasteur, and GE Healthcare, is a Steering Committee member of the Amgen financed GALACTIC-HF trial, on advisory boards for Sanofi Pasteur and Amgen, and speaker honorariums from Novartis and Sanofi Pasteur. All other authors have nothing to disclose.

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