






ORIGINAL RESEARCH

# Cardiac Dysfunction and Arrhythmias 3 Months After Hospitalization for COVID-19

Charlotte B. Ingul , MD, PhD; Jostein Grimsmo , MD, PhD; Albulena Mecinaj, MD; Divna Trebinjac , MD, PhD; Magnus Berger Nossen, MD; Simon Andrup, MD; Bjørnar Grenne, MD, PhD; Håvard Dalen, MD, PhD; Gunnar Einvik, MD, PhD; Knut Stavem , MD, MPH, PhD; Turid Follestad, PhD; Tony Josefsen, MD; Torbjørn Omland , MD, PhD, MPH; Torstein Jensen, MD, PhD

**BACKGROUND:** The extent of cardiac dysfunction post-COVID-19 varies, and there is a lack of data on arrhythmic burden.

**METHODS AND RESULTS:** This was a combined multicenter prospective cohort study and cross-sectional case-control study. Cardiac function assessed by echocardiography in patients with COVID-19 3 to 4 months after hospital discharge was compared with matched controls. The 24-hour ECGs were recorded in patients with COVID-19. A total of 204 patients with COVID-19 consented to participate (mean age, 58.5 years; 44% women), and 204 controls were included (mean age, 58.4 years; 44% women). Patients with COVID-19 had worse right ventricle free wall longitudinal strain (adjusted estimated mean difference, 1.5 percentage points; 95% CI,  $-2.6$  to  $-0.5$ ;  $P=0.005$ ) and lower tricuspid annular plane systolic excursion ( $-0.10$  cm; 95% CI,  $-0.14$  to  $-0.05$ ;  $P<0.001$ ) and cardiac index ( $-0.26$  L/min per  $m^2$ ; 95% CI,  $-0.40$  to  $-0.12$ ;  $P<0.001$ ), but slightly better left ventricle global strain ( $-0.8$  percentage points; 95% CI,  $0.2$ – $1.3$ ;  $P=0.008$ ) compared with controls. Reduced diastolic function was twice as common compared with controls (60 [30%] versus 29 [15%], respectively; odds ratio, 2.4;  $P=0.001$ ). Having dyspnea or fatigue were not associated with cardiac function. Right ventricle free wall longitudinal strain was worse after intensive care treatment. Arrhythmias were found in 27% of the patients, mainly premature ventricular contractions and nonsustained ventricular tachycardia (18% and 5%, respectively).

**CONCLUSIONS:** At 3 months after hospital discharge with COVID-19, right ventricular function was mildly impaired, and diastolic dysfunction was twice as common compared with controls. There was little evidence for an association between cardiac function and intensive care treatment, dyspnea, or fatigue. Ventricular arrhythmias were common, but the clinical importance is unknown.

**REGISTRATION:** URL: <http://clinicaltrials.gov>. Unique Identifier: NCT04535154.

**Key Words:** arrhythmias ■ cardiac function ■ COVID-19 ■ dyspnea ■ intensive care

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and primarily affects the lungs.<sup>1</sup> During the pandemic course, persistent organ dysfunction and symptoms, such as dyspnea and fatigue, during the convalescence have been emphasized.<sup>2,3</sup> Preexisting cardiovascular disease is common and associated with an increased risk of severe acute COVID-19.<sup>4</sup> Studies in hospitalized patients with COVID-19 have demonstrated impaired

right ventricular (RV) and left ventricular (LV) function.<sup>5,6</sup> These findings have been associated with an increased risk of COVID-19 mortality.<sup>5,6</sup> A prospective multicenter study of patients 2 to 3 months after COVID-19 infection found a high rate of diastolic dysfunction and signs of pulmonary hypertension, but few had LV dysfunction.<sup>7</sup> In contrast, an Italian single-center study compared survivors of COVID-19 with matched controls 41 days after hospital discharge and found no considerable

Correspondence to: Charlotte B. Ingul, MD, PhD, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Postboks 8905, 7491 Trondheim, Norway. E-mail: [charlotte.b.ingul@ntnu.no](mailto:charlotte.b.ingul@ntnu.no)

Supplemental Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023473>

For Sources of Funding and Disclosures, see page 9.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: [www.ahajournals.org/journal/jaha](http://www.ahajournals.org/journal/jaha)

## CLINICAL PERSPECTIVE

### What Is New?

- By comparing echocardiography of patients 3 months after hospitalization for COVID-19 with matched controls, we found mild right ventricular dysfunction and diastolic dysfunction in half of the patients with COVID-19.
- Cardiac arrhythmias of unknown clinical importance were common 3 months after COVID-19 hospitalization, with premature ventricular beats present in 20% and nonsustained ventricular tachycardia present in 5%.
- Half of the patients had persistent dyspnea, and nearly two-thirds had fatigue 3 months after hospitalization for COVID-19, but these symptoms were not associated with echocardiographic measures of cardiac function.

### What Are the Clinical Implications?

- Left ventricular dysfunction is not common after COVID-19 infection, and the mild right ventricular dysfunction was likely associated with pulmonary pathology.
- Patients with symptomatic palpitations 3 months after COVID-19 should be considered for at least 24-hour monitoring of heart rhythm.
- Persistent dyspnea and fatigue after COVID-19 are more likely caused by pulmonary pathology than cardiac dysfunction.

## Nonstandard Abbreviations and Acronyms

<b>EDV</b>	end-diastolic volume
<b>GLS</b>	global longitudinal strain
<b>HUNT4</b>	fourth wave of the Trøndelag Health Study
<b>NSVT</b>	nonsustained ventricular tachycardia
<b>RVLS</b>	right ventricle free wall longitudinal strain
<b>TAPSE</b>	tricuspid annular plane systolic excursion

structural or functional differences in cardiac function assessed by echocardiography.<sup>8</sup>

Direct cardiac involvement attributed to the virus has recently been shown in magnetic resonance imaging studies and from autopsies.<sup>9-11</sup> Conduction system damage and drug treatment could lead to arrhythmias.<sup>12</sup> In a multicenter study with non-intensive care unit (ICU) hospitalized patients with COVID-19, 28% developed supraventricular tachycardia, and serious arrhythmias were rare.<sup>13</sup> Whether dyspnea or fatigue after COVID-19 are related to cardiac function is not known.

There is limited information if hospitalized patients with COVID-19 will fully recover or have sustained impairment of the myocardium and the heart's electrical system. Therefore, we aimed to assess cardiac function and arrhythmias 3 to 4 months after hospitalization for COVID-19. We hypothesized that the patients had impaired cardiac function compared with controls and increased prevalence of arrhythmia. Furthermore, we hypothesized that the patients with the most severe disease, requiring ICU care, would have more pronounced cardiac dysfunction than patients with less severe disease not requiring ICU and that persistent dyspnea and fatigue would be associated with cardiac dysfunction.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Participant Population and Study Design

PROLUN (Patient-Related Outcomes and Lung Function After Hospitalization for COVID-19) is a multicenter prospective cohort study at 6 major hospitals in Norway, where patient-reported outcomes and lung function after hospital admission for COVID-19 were investigated.<sup>3</sup> Between February and June 2020, patients aged  $\geq 18$  years who had been admitted for  $>8$  hours with a discharge diagnosis of COVID-19 or viral pneumonia combined with a positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction test, were considered eligible. Exclusion criteria included living outside the hospitals' catchment areas, inability to provide informed consent, or participation in the World Health Organization Solidarity trial.

A total of 388 patients were eligible for PROLUN, and of these, 69 patients did not respond to the invitation, and 55 patients declined participation.

This substudy included patients from 5 hospitals because 1 hospital ( $n=28$ ) lacked the resources to perform echocardiography. In total, 236 consenting patients in PROLUN were invited to this substudy (Figure S1). Informed consent was obtained by returning a written signed consent form or through a secure digital consent form (Services for Sensitive Data, services for sensitive data [TSD], University of Oslo). The study was approved by the Regional Ethics Committee for South-Eastern Norway (no. 125384) and by data protection officers at each participating center and registered with the ClinicalTrials.gov database (NCT04535154).

### Clinical Data Collection

Baseline demographic characteristics (sex, age), comorbidities, and data from the COVID-19 hospital

admissions were obtained from the electronic patient records. World Health Organization Ordinal Scale for Clinical Improvement was used to score the severity of the COVID-19.<sup>14</sup> Height, weight, body mass index (BMI), current smoking status, and history of hypertension were collected by interview at follow-up after 3 months.

### Controls and Matching

The controls comprised participants from HUNT4 (the fourth wave of the Trøndelag Health Study; 2017–2019), a Norwegian population-based cohort. The HUNT4 echocardiography study collected data from a random sample and included 2448 participants.<sup>15</sup> A total of 204 patients with COVID-19 were matched with 204 controls from the HUNT4 echocardiography study on age, sex, BMI, systolic blood pressure, and comorbidity (previous myocardial infarction, congestive heart disease, chronic obstructive pulmonary disease, diabetes; Figure S1). A mixed model was used to match the controls with the patients with COVID-19. Sex and comorbidity were matched individually and age, BMI, and systolic blood pressure on a group level. From the total population of 2448 HUNT4 echocardiography study participants, the control population was matched according to mean (SD) for age, BMI, and systolic blood pressure.

### Echocardiography in Patients With COVID-19

A 2-dimensional transthoracic echocardiography of patients in the left lateral decubitus position was performed by 4 experienced operators according to standard methods<sup>16</sup> using commercially available ultrasound systems (Vivid E 95, GE Horten, Norway). Motion-mode was used in the apical 4-chamber view to measure tricuspid annular plane systolic excursion (TAPSE) and mitral annular plane systolic excursion. Pulsed tissue Doppler S', e', and A' velocities were obtained from the septal and lateral walls of the mitral annulus. Left atrial volume and end-diastolic volume (EDV) were measured in the apical 4-chamber and 2-chamber views and indexed to body surface area (EDV index). LV ejection fraction (EF) was calculated using Simpson's biplane method. Mitral valve E/A ratio, diastolic dysfunction, and E/e' were assessed according to the international recommendations from 2016<sup>17</sup> (Data S1). Systolic pulmonary artery pressure was calculated from the peak tricuspid regurgitant velocity and adding this to an estimate of right atrial pressure. LV global longitudinal strain (LV GLS) and RV free wall longitudinal strain (RVLS) were quantified by semiautomatic 2-dimensional speckle tracking software Automated functional imaging (AFI) based on the apical 4-chamber, 2-chamber, and long-axis views and the RV focus view.<sup>18</sup> Data were stored digitally for offline analysis (GE EchoPAC PC SWO versions 203 and 204). Analyses were performed blinded, and

only study-specific patient identifications were known. The LHL Hospital Gardermoen served as the echocardiography core laboratory.

### Echocardiography HUNT4 Reference Population

Echocardiographic recordings were performed according to standard operating procedures aligned with the current recommendations, which were the same used for the COVID-19 group.<sup>16</sup>

A total of 2 sonographers performed the echocardiography. Of these sonographers, 1 experienced in strain analyses performed offline analysis using the AFI package in EchoPAC SWO (203 version). The RV strain analyses were performed offline as for the patients using EchoPAC 204 version by a cardiologist experienced in strain analyses. The same ultrasound systems were used as for the patients with COVID-19.

### Ambulatory 24-Hour Electrocardiography Registration

A 24-hour ECG was obtained using Schiller Medilog FD12 Plus (Germany) and Philips DigiTrak XT (Germany) in the patients with COVID-19, but not in controls. Schiller Medilog Darwin 2 (Germany) and Philips Holter 2010 Plus (Germany) with Zymed Algorithm (Release 3.0.1.1, 2015) were used for the analysis. Clinically significant arrhythmias were defined as ventricular tachycardia (nonsustained or sustained), premature ventricular contractions (PVCs) >200/24 hours or coupled PVCs, atrial fibrillation/flutter, second-degree atrioventricular block type 2, complete atrioventricular block, sinoatrial block >3 seconds, premature atrioventricular nodal beats in bigeminy, supraventricular tachycardia >30 seconds, and extreme sinus bradycardia with <30 beats/min.

### Biochemistry

Nonfasting venous blood samples were collected during the hospital stay and at the 3-month follow-up to measure NT-proBNP (N-terminal pro-brain natriuretic peptide) and hs-cTnT (high-sensitive cardiac troponin T) (Roche Diagnostics, Rotkreuz, Switzerland).

### Assessment of Dyspnea

The modified Medical Research Council (dyspnea scale is a self-rating tool to measure the degree of disability that breathlessness poses on day-to-day activities on a scale from 0 (no dyspnea) to 4 (maximum dyspnea).<sup>19</sup>

### Assessment of Fatigue

Fatigue was assessed using the Chalder Fatigue Scale.<sup>20</sup> A bimodal scoring algorithm was used, where each item response was dichotomized 0 (0–1) or 1 (2–3)

and summed to a scale of 0 to 11. Conventionally, fatigue case status (fatigued versus nonfatigued) was defined using this scale with  $\geq 4$  denoted as fatigued.<sup>20,21</sup>

## Outcome Measures

The primary outcome measures were RVLS, LV GLS, and arrhythmias. The secondary outcome measures were RV dimension, TAPSE, systolic pulmonary artery pressure, pulmonary vein flow, mitral annular plane systolic excursion, S', EF, EDV index, cardiac index, mitral valve E/A ratio, e', E/e', and diastolic dysfunction.

## Data Storage

All collected data were stored in Services for Sensitive Data (TSD, University of Oslo, Norway), designed for storing and postprocessing sensitive data in compliance with the Norwegian Personal Data Act<sup>22</sup> and Health Research Act<sup>23</sup>.

## Statistical Analysis

Data are summarized as mean (SD), median (25th–75th percentiles), or number (percentage), as appropriate. Echocardiography variables were compared between the patients with COVID-19 and the controls using multiple regression analysis, adjusting for age, sex, BMI, resting systolic blood pressure, chronic obstructive pulmonary disease, diabetes, previous heart failure, and previous myocardial infarction. Because of the partly individual matching of controls, linear mixed models were first fitted to account for potential within-pair correlations. However, these correlations turned out to be very small, and thus ordinary regression models were used. The normal distribution for residuals from linear regression models was assessed by the Anderson-Darling test and visual inspection of normal QQ-plots. Generalized linear regression models using a gamma distribution with identity link were used when such models improved residual model fit compared with linear models. Logistic regression was used for dichotomized diastolic dysfunction. Similar models were used to compare the echocardiography variables between non-ICU and ICU patients with COVID-19, patients with or without dyspnea, and with or without fatigue, adjusting for age and sex. Correlations between variables were assessed using the Spearman correlation coefficient ( $\rho$ ).

Normal values from similar populations before the pandemic were used to compare the echocardiographic variables for the patients with COVID-19 and controls using z scores, that is, the z score indicates the difference from the mean of the age-specific and sex-specific strata of the reference population reported in number of SDs. Where possible, we used age-specific and sex-specific reference values from the Norwegian HUNT4 study, a large population-based cohort.<sup>24,25</sup>

Other large population-based cohorts were used in addition.<sup>16,26,27</sup>

The z scores for the patients with COVID-19 and the matched controls were calculated from normal values for means and SDs, specified by age group (<40, 40–60, >60 years) and sex. The z scores are summarized as medians with 2.5 and 97.5 percentiles.

All statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) or Stata version 16.1 (StataCorp., College Station, TX). To give some protection against false-positive results attributed to multiple testing, P values <0.01 were considered statistically significant.

## RESULTS

### Participant Characteristics

In total, 204 consented to participate in the substudy. The examinations were conducted a median of 102 days (range, 70–172 days) after discharge from the hospital. Of the patients, 3 did not undergo a 24-hour ECG and were excluded from this analysis. Baseline demographics and data from the hospital stay, laboratory measures, dyspnea rating, fatigue score, and World Health Organization ordinal scale are presented in Table 1.

There were 114 (56%) men. A total of 5 patients (3%) were current daily smokers, and 76 (41%) were former daily smokers. Table 2 summarizes the most important comorbidities.

Hypertension was found in 65 (32%) patients. The majority were White patients (82%), followed by Asian patients (8%) and African American patients (7%). Mean BMI was 28.3 (4.5) kg/m<sup>2</sup>, and obesity (BMI >30 kg/m<sup>2</sup>) was found in 70 patients (34%). In total, 32/236 (14%) of the patients invited from the main study did not participate in our substudy. The nonparticipants were older (61.3 years), and there were more men (73%) compared with the participants. There was no difference in comorbidity, World Health Organization severity scale, or dyspnea, but fewer nonparticipants had fatigue (41%).

### Cardiac Function and Morphology

Cardiac function and morphology are detailed in Table 3.

In a linear regression model adjusted for age, sex, BMI, blood pressure, and several comorbidities (Table 3), there was evidence of worse RVLS and slightly better LV GLS in the COVID-19 group versus controls. Cardiac index and EDV index were lower in the COVID-19 group than controls. Only weak or little evidence was found for a difference in EF or mitral annular plane systolic excursion between the COVID-19 group and controls. Patients with COVID-19 had lower e', and 30% had diastolic dysfunction compared with

**Table 1. Baseline Demographics, Data From Hospital, Risk Factors, and Comorbidity (n=204)**

	No. (%)	Mean (SD) (range)	Median (25th–75th percentiles)
Age at hospital discharge, y		58.5 (13.6) (30–83)	
Laboratory			
hs-cTn peak, hospitalization, ng L <sup>-1</sup>	169 (83)		10 (6–17)
hs-cTn at 3 mo, ng L <sup>-1</sup>	169 (83)		8 (5–11)
NT-proBNP peak, hospitalization, ng L <sup>-1</sup>	174 (85)		186 (70–526)
NT-proBNP at 3 mo, ng L <sup>-1</sup>	174 (85)		58 (41–120)
CRP peak, hospitalization, mg L <sup>-1</sup>	201 (99)		112 (39–190)
ICU stay			
Intubated and invasively ventilated	25 (12)		
No. of days in ICU	41	10.7 (2–22)	
No. of days on ventilator	24	11.9 (5–18)	
Length of stay in hospital, d	203	10.2 (1–55)	
mMRC dyspnea scale			
0	77 (47)		
1	50 (31)		
2	26 (16)		
3	8 (5)		
4	2 (1)		
mMRC 0 vs 1–4	86 (53)		
Chalder Fatigue Scale			
<4	62 (38)		
≥4	101 (62)		
WHO Ordinal Scale for Clinical Improvement			
3	71 (35)		
4	97 (48)		
5–7	35 (17)		

CRP indicates C-reactive protein; hs-cTn; high-sensitivity cardiac troponin; ICU, intensive care unit; mMRC, modified Medical Research Council; NT-proBNP, N-terminal pro–brain natriuretic peptide; and WHO, World Health Organization.

15% of the controls. There was evidence for reduced TAPSE, but no evidence for a difference in RV dimension or pulmonary vein flow compared with the controls. In the COVID-19 group, the median of the individual z scores was highest for RVLS, RDV, and LV GLS (Table 4). For the controls, LV GLS, RV dimension,

and Left atrial volume index had the highest median z scores (Table 4).

### Cardiac Function in Subgroups

When the COVID-19 group was differentiated into ICU stay or ward, the RVLS was slightly worse after ICU

**Table 2. Summary Statistics for the Additional Covariates in the Multiple Regression Models**

	Controls		COVID-19		P value*
	No.	Mean (SD) or n (%)	No.	Mean (SD) or n (%)	
Age, y	204	58.4 (13.4)	204	58.5 (13.6)	0.980
Male patients	204	114 (56%)	204	114 (56%)	1.000
Body mass index, kg/m <sup>2</sup>	204	28.1 (4.1)	202	28.2 (4.6)	0.796
Systolic blood pressure, mm Hg	204	135.8 (18.3)	199	135.8 (18.6)	0.976
Previous myocardial infarction	196	14 (7%)	203	14 (7%)	0.923
Congestive heart failure	192	7 (4%)	203	8 (4%)	0.878
COPD	196	7 (4%)	203	7 (3%)	0.947
Diabetes	201	18 (9%)	203	19 (9%)	0.888

COPD indicates chronic obstructive pulmonary disease.

\*Chi-square tests for dichotomous variables; t tests for continuous variables.

**Table 3. Summary Statistics and Estimated Mean Differences Between COVID-19 and Reference Population From Multiple Regression for the Echocardiographic Variables**

	Control		COVID-19		COVID-19 vs control		
	No.	Mean (SD) or n (%)	No.	Mean (SD) or n (%)	No.	Estimate* (95% CI)	P value
LV systolic function							
LV GLS, %	171	-17.8 (2.6)	187	-18.5 (2.8)	338	-0.8 (-1.3 to -0.2)	0.008
Ejection fraction, %	194	58.4 (7.2)	196	56.5 (6.7)	368	-1.7 (-3.1 to -0.3)	0.015
MAPSE, cm	202	1.5 (0.3)	201	1.4 (0.2)	382	-0.10 (-0.14 to -0.05)	<0.001
S', cm/s	199	8.3 (1.8)	183	8.0 (1.6)	361	-2.4 (-5.6 to 0.8)	0.135
Cardiac index, L/min per m <sup>2</sup>	196	2.9 (0.8)	193	2.6 (0.7)	369	-0.26 (-0.40 to -0.12)	<0.001
LV volumes							
EDV index, mL/m <sup>2</sup>	194	58.7 (15.9)	186	49.5 (13.8)	360	-8.8 (-11.4 to -6.1)	<0.001
LV diastolic function							
MV E/A ratio	191	1.1 (0.4)	200	1.1 (0.4)	371	0.01 (-0.06 to 0.07)	0.860
e', cm/s	198	9.1 (2.7)	193	8.4 (2.4)	370	-6.0 (-9.8 to -2.2)	0.002
E/e'	194	8.3 (2.3)	188	8.4 (3.1)	362	-0.03 (-0.46 to 0.40)	0.886
RV function and dimensions							
RV free wall strain, %	168	-26.2 (4.7)	165	-24.6 (5.0)	315	1.5 (0.5 to 2.6)	0.005
RVD, cm	136	3.8 (0.7)	196	3.9 (0.6)	314	0.11 (-0.03 to 0.25)	0.111
TAPSE, cm	187	2.5 (0.5)	199	2.4 (0.5)	366	-0.16 (-0.27 to -0.06)	0.002
SPAP, mm Hg	96	28 (6.8)	157	23.8 (8.7)	239	-3.9 (-6.1 to -1.8)	<0.001
Left atrial size and PV flow							
LA volume index, mL/m <sup>2</sup>	198	33.1 (14.3)	190	27.1 (8.3)	368	-5.0 (-7.0 to -3.1)	<0.001
PV systolic/diastolic ratio	170	1.3 (0.4)	174	1.4 (0.4)	326	0.09 (0.01 to 0.16)	0.023
Heart rate	200	68.2 (13.2)	201	66.9 (11.7)	379	-1.0 (-3.4 to 1.4)	0.409
Diastolic dysfunction*	200	29 (15%)	201	60 (30%)	380	2.4 (1.4 to 4.2)	0.001
DD with normal EF		11 (6%)		15 (8%)			
DD grade 1 with reduced EF		13 (6%)		38 (19%)			
DD grade 2 with reduced EF		3 (2%)		4 (2%)			
DD grade 3 with reduced EF		2 (1%)		3 (2%)			

DD indicates diastolic dysfunction; e', mean value of septal and lateral early diastolic pulsed tissue Doppler velocities; E/e', filling pressure; EDV, end-diastolic volume; EF, ejection fraction; GLS, global longitudinal strain; LA, left atrial; LV, left ventricular; MAPSE, mitral annular plane systolic excursion; MV E/A, mitral valve E wave velocity and A wave velocity ratio; PV, pulmonary vein; RV, right ventricular; RVD, right ventricular dimension; S', peak systolic tissue Doppler velocity; SPAP, systolic pulmonary artery pressure; and TAPSE, tricuspid annular plane systolic excursion.

\*Estimate is odds ratio from multiple logistic regression on dichotomized diastolic dysfunction, otherwise estimated mean difference. Estimates are adjusted for age, sex, body mass index, systolic blood pressure, previous myocardial infarction, heart failure, chronic obstructive pulmonary disease, and diabetes.

stay (23% [5.2%] versus 25.1% [4.8%]; adjusted mean difference, -2.2 percentage points; 95% CI, -3.9 to -0.4;  $P=0.016$ ), and there was no difference in LV GLS (-18.2% [3.8%] versus -18.6% [2.5%]; adjusted mean difference, 0.2 percentage points; 95% CI, -0.8 to -1.3;  $P=0.63$ ; Tables S1 and S2). There was little or no evidence of differences in other cardiac function variables. Moreover, there was little or no evidence of any differences in cardiac function if dyspnea or fatigue were present (Tables S2 through S4).

All patients with pulmonary hypertension ( $n=6$ ) had reduced RVLS, and half of the patients ( $n=3$ ) had both pulmonary hypertension and diastolic dysfunction.

In total, 60 of the patients with COVID-19 had diastolic dysfunction (Table 3). There was no difference in

age ( $P=0.22$ ), BMI ( $P=0.83$ ), comorbidities ( $P=0.07$ ), EF ( $P=0.21$ ), RVLS ( $P=0.02$ ), or cardiac index ( $P=0.26$ ) compared with those without diastolic dysfunction. Diastolic dysfunction was the same for patients treated at ICU compared with no ICU treatment (37% versus 29%;  $P=0.21$ ).

## Arrhythmias

Cardiac arrhythmias were detected in 27% of the patients with COVID-19 (Table 5). PVCs were the most frequent cardiac arrhythmia. More than 200 PVCs per day were observed in 37 patients (18%), with a mean of 1300 PVC/day, and in 35 (95%) of these patients, the PVCs were polymorphic (Table 5). Nonsustained

**Table 4. The Z Scores Derived From Normal Populations and Calculated for Controls and COVID-19**

	Control			COVID-19		
	Median	2.5 percentile	97.5 percentile	Median	2.5 percentile	97.5 percentile
LV systolic function						
LV GLS, %	1.67	-0.19	4.07	1.48	-0.37	3.79
Ejection fraction, %	-0.72	-5.11	1.38	-1.20	-4.20	1.40
MAPSE, cm	-0.13	-2.07	2.15	-0.56	-2.10	1.25
S', cm/s	0.13	-2.42	3.09	-0.17	-2.23	2.78
Cardiac index, L/min per m <sup>2</sup>	-0.20	-1.68	2.38	-0.50	-1.84	1.83
LV volumes						
EDV index, mL/m <sup>2</sup>	0.74	-1.52	4.04	-0.05	-2.66	2.81
LV diastolic function						
MV E/A ratio	-0.43	-1.53	1.41	-0.48	-1.67	1.51
e', cm/s	0.39	-1.43	2.08	0.52	-1.13	2.22
E/e'	0.46	-0.84	2.64	0.39	-1.67	3.37
RV function and dimensions						
RV free wall strain, %	1.04	-1.41	3.92	1.47	-1.08	4.15
RVD, cm	1.19	-2.37	5.56	1.50	-1.25	4.50
TAPSE, cm	0.11	-2.33	3.11	0.00	-2.57	2.86
SPAP, mm Hg	-0.22	-2.19	3.34	-1.08	-3.73	2.49
Left atrial size and PV flow						
LA volume index, mL/m <sup>2</sup>	1.47	-1.12	6.80	0.72	-1.32	3.88
PV systolic/diastolic ratio	-0.20	-2.29	2.08	-0.06	-1.30	2.63

DD indicates diastolic dysfunction; e' indicates mean value of septal and lateral early diastolic pulsed tissue Doppler velocities; E/e', filling pressure; EDV, end-diastolic volume; EF, ejection fraction; GLS, global longitudinal strain; LA, left atrial; LV, left ventricular; MAPSE, mitral annular plane systolic excursion; MV E/A, mitral valve E wave velocity and A wave velocity ratio; PV, pulmonary vein; RV, right ventricular; RVD, right ventricular dimension; S', peak systolic tissue Doppler velocity; SPAP, systolic pulmonary artery pressure; and TAPSE, tricuspid annular plane systolic excursion.

ventricular tachycardia (NSVT) was found in 10 (5%) of the patients with COVID-19. Of the patients with NSVT, 5 had previous cardiovascular diseases: coronary heart disease (n=1), atrial fibrillation (n=1), venous thromboembolism (n=2), and heart failure (n=4). The patients presenting with atrial fibrillation on 24-hour ECG all had atrial fibrillation before hospitalisation for COVID-19. Sinoatrial block >3 seconds was only observed in 1 patient.

### Cardiac Function, Arrhythmias, and Correlations With Biochemical Markers

PVCs showed a weak positive correlation with hs-cTn during hospitalization ( $\rho=0.30$ ; 95% CI, 0.15–0.43;  $P=0.0001$ ) and at 3 months ( $\rho=0.33$ ; 95% CI, 0.20–0.46;  $P<0.001$ ) and to peak NT-proBNP level during hospitalization ( $\rho=0.21$ ; 95% CI, 0.06–0.35;  $P=0.007$ ) and at 3 months ( $\rho=0.30$ ; 95% CI, 0.17–0.43;  $P<0.001$ ). There was a weak negative correlation between RVLS and NT-proBNP during hospitalization ( $\rho=-0.20$ ; 95% CI, -0.35 to -0.04;  $P=0.02$ ) but not at 3 months ( $\rho=-0.08$ ; 95% CI, -0.23 to 0.08;  $P=0.34$ ). There was no correlation between RVLS and hs-cTn during hospitalization or at 3 months.

## DISCUSSION

This combined cohort and cross-sectional case-control study reports the severity of cardiac dysfunction in patients with COVID-19 3 months after hospitalization compared with matched controls and describes the prevalence of cardiac arrhythmia. The main findings

**Table 5. Cardiac Arrhythmias (n=201)**

	No.	Percentage
Nonsustained ventricular tachycardia	10	5.0
Premature ventricular contractions >200/24 h	37	18
Atrial fibrillation/flutter*	7	4
Second degree or complete atrioventricular block	0	0
Extreme sinus bradycardia (<30 bpm)	0	0
Sinoatrial block >3 s	1	0
Premature atrioventricular-nodal beats in bigeminy	0	0
Supraventricular tachycardia >30 s	3	2

bpm indicates beats per minute.

\*Paroxysmal, persisting, or chronic.

were worse RV strain and TAPSE suggesting RV dysfunction and increased arrhythmic burden.

Recently, RV dilatation, reduced RV fractional area change, and TAPSE were demonstrated in hospitalized patients with COVID-19.<sup>28</sup> Another study showed that RVLS was reduced by 4.4 percentage points compared with controls in a hospitalized COVID-19 cohort.<sup>6</sup> We demonstrated slightly reduced RVLS compared with controls, with a value around the lower limits of normality.<sup>27</sup>

Patients with severe COVID-19 treated at an ICU exhibited a higher prevalence of pulmonary vascular defects, leading to pulmonary hypertension and subsequent RV dysfunction.<sup>5</sup> There was weak evidence in our study that patients with ICU treatment had worse RVLS than those without ICU treatment.

It is possible that decreased RV function may be attributed to abnormal pulmonary physiology from more severe COVID-related lung disease because there was no relationship between cardiac troponin and RV strain. In the acute and subacute settings, NT-proBNP production may be more responsive to increased RV stretch secondary to lung pathology than cardiac troponin release. This may partially explain the closer association observed between NT-proBNP and RVLS than between hs-cTn and RVLS. Elevated NT-proBNP can be seen in RV dysfunction related to pulmonary pathology.<sup>29</sup> Increased afterload and elevated pulmonary arterial pressure can affect the assessment of RV function. RV dysfunction in patients with COVID-19 could reflect impaired lung function and not myocardial function.

There was a tendency to a poorer LV cardiac function by EF and mitral annular plane systolic excursion among the patients with COVID-19. The difference in LV GLS was statistically significant, but hardly clinically different. The z scores for LV GLS indicated that LV GLS was worse than the normal values for patients with COVID-19 as well as controls. LV function by EF in patients with COVID-19 vary from relatively well preserved to a range of dysfunction between 11% and 20%.<sup>28,30</sup>

The cardiac index and EDV index were significantly lower in our patients compared with the controls. These findings may be attributed to inactivity over time.<sup>31</sup> We have recently shown in the same study population a reduction in peak oxygen uptake in every third patient with COVID-19 caused by deconditioning in the majority.<sup>32</sup>

A prospective multicenter study reported a high rate of diastolic dysfunction at 3 (55%) months after COVID-19.<sup>7</sup> We found that the odds ratio of diastolic dysfunction for patients with COVID-19 was 2.4 compared with the controls. The majority of the patients had mild diastolic dysfunction.

It was recently shown that hospitalized patients with COVID-19 had a higher likelihood of heart failure with preserved ejection fraction associated with structural and functional cardiac alterations and myocardial injury.<sup>33,34</sup> However, of 30% with diastolic dysfunction, only 25% of the patients with diastolic dysfunction had a normal ejection fraction.

Information concerning persisting cardiac arrhythmias has, to our knowledge, not been reported in previous studies of patients with COVID-19. In a worldwide survey of 4526 hospitalized patients with COVID-19, associated arrhythmias were common and found in 18%.<sup>35</sup> In a meta-analysis comprising 9 studies, cardiac arrhythmias during hospitalization with COVID-19 were found in 19% of patients,<sup>36</sup> slightly lower compared with our study. The clinical implications of persistent ventricular arrhythmia following COVID-19 are not clear, but ventricular ectopy has been linked to an increased risk of cardiac disease, including cardiomyopathy and sudden cardiac death.<sup>37</sup> Ventricular ectopy is usually a benign arrhythmia,<sup>38</sup> but may in some patients cause persisting palpitations, chest pain, and dizziness leading to reduced quality of life.<sup>39</sup> Potential serious ventricular arrhythmias such as NSVT were observed in 5%, which is twice as many compared with a Norwegian population-based study with 2.6% NSVT among 498 participants, and in total, 9% had complex ventricular ectopy (bigeminy, trigeminy, or NSVT).<sup>40</sup> Frequent PVCs (>5 per hour, 120 per 24 hours) were observed in 9% and were associated with significantly higher concentrations of NT-proBNP and high-sensitivity troponin I.<sup>40</sup> We found twice as many PVCs using a stricter definition (>200 PVCs per 24 hours). In healthy volunteers, >200 PVCs per 24 hours were observed in 3% and NSVT in 0.7%.<sup>41</sup> However, without a matched control group, it is difficult to conclude the relation to COVID-19. A modest correlation between PVCs and NT-proBNP and hs-cTn levels during hospitalization and at 3 months was found in our study. These arrhythmias may be more closely related to myocardial damage reflected in increased hs-cTn concentrations than RV function because there was no correlation between RVLS and hs-cTn. A recent retrospective cohort study, conducted by reviewing electronic medical records from a global federated health research network, showed that 718 365 patients with COVID-19 (6.5%) developed new-onset perimyocarditis.<sup>42</sup> The extent of micro scars is unknown in COVID-19, which could be triggers for arrhythmias.

Persistent dyspnea was common among our patients and were not associated with cardiac dysfunction. When performing cardiopulmonary exercise testing in the same study population, dyspneic participants were characterized by lower exercise capacity as a result of obesity and lower ventilatory efficiency.<sup>32</sup>



Earlier studies have demonstrated a lower cardiac index and in individuals with high fatigue than in individuals with moderate and low fatigue.<sup>43</sup> Fatigue was common among our patients but was not associated with cardiac dysfunction.

## Limitations

This study has some important limitations. RVLS and LV GLS could not be analyzed in 19% and 8% of the patients, respectively, similar to other studies.<sup>29,44</sup> The inconsistency in LV GLS with a 0.8 percentage point higher value (ie, better GLS) among patients with COVID-19 was not clinically significant and could be operator dependent.

Although there are limitations estimating tricuspid regurgitation jet velocity, it is included in the present guidelines for estimation of diastolic dysfunction, which we used.

Some variables, such as history of hypertension and cardiac disease, were self-reported and might not be precise, but this would be equal in the compared groups and should not cause differential misclassification. Dyspnea and fatigue represent subjective phenomena, which were based on self-reported questionnaires.

Being a multicenter study, the statistical analyses should ideally account for the possibility of center effects. However, the controls used in the primary analyses were population based, and 2 of the 5 centers had few patients.

The patients included in this study were reasonably representative of the patients hospitalized with COVID-19 in Norway, as it comprised about 25% of those discharged alive with COVID-19 in Norway as of June 1, 2020. The mean for age and BMI in our population was similar to those discharged in the whole country.

## CONCLUSIONS

At 3 months after COVID-19 hospitalization, patients had mildly impaired RV function, reduced diastolic function, and mainly preserved left ventricular function compared with matched controls. Premature ventricular contractions and nonsustained ventricular tachycardia were common, but the relation to COVID-19 is unknown. Patients treated in an ICU had similar cardiac function as those not admitted to an ICU. Persistent dyspnea or fatigue were not found to be associated with cardiac function.

## ARTICLE INFORMATION

Received August 1, 2021; accepted December 22, 2021.

### Affiliations

Department of Circulation and Medical Imaging (C.B.I., B.G., H.D.) and Department of Clinical and Molecular Medicine (T.F.), Norwegian University of

Science and Technology, Trondheim, Norway; The National Association for Heart, Lung diseases Hospital Gardermoen, Jessheim, Norway (C.B.I., J.G., D.T.); Department of Cardiology, Division of Medicine (A.M., T.O.), Pulmonary Department (G.E., K.S.) and Health Services Research Unit (K.S.), Akershus University Hospital, Lørenskog, Norway; Department of Cardiology, Østfold Hospital Trust Kalnes, Grålum, Norway (M.B.N., S.A., T. Josefsen.); Clinic of Cardiology, St. Olavs University Hospital, Trondheim, Norway (B.G., H.D.); Department of Medicine, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway (H.D.); Institute for Clinical Medicine, University of Oslo, Norway (G.E., K.S., T.O.); and Department of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway (T. Jensen.).

## Acknowledgments

Bioengineer Vilde Bertelsen has contributed greatly to the 24-hour ECGs and for help with organizing the study. Nurse Katrine Onshus Eriksen has contributed to the 24-hour ECGs. The HUNT (Trøndelag Health Study) is a collaboration between the HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. Drs Ingul, Stavem, and Follestad had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ingul, Jensen, Grimsmo, Einvik, and Stavem contributed to the study concept and design; Drs Ingul, Grimsmo, Jensen, Josefsen, Mecinaj, Berger Nossen, Andrup, Grenne, Dalen, and Trebinjac contributed to the acquisition, analysis, or interpretation of data; Drs Ingul, Jensen, Grimsmo, Einvik, Stavem, Dalen, Grenne, Omland, Follestad, Berger Nossen, Andrup, Grenne, Dalen, and Trebinjac contributed to manuscript drafting; Drs Ingul, Jensen, Grimsmo, Einvik, Stavem, Dalen, Grenne, Omland, and Follestad contributed to the critical revision of the manuscript for important intellectual content; Drs Follestad, Ingul, and Stavem contributed to the statistical analysis; Drs Ingul and Einvik obtained funding; Drs Stavem, Einvik, Ingul, and Omland contributed to the administrative, technical, or material support; and Drs Ingul, Jensen, Grimsmo, Josefsen, and Mecinaj provided study supervision.

## Sources of Funding

This work was supported by The National Association for Heart, Lung Diseases, the Norwegian Health Association, and Akershus University Hospital.

## Disclosures

Ingul and Grimsmo have received fees for lectures from Bayer AG. Omland has received consultancy and speaker honoraria from Abbott Diagnostics, Bayer, CardiNor, Roche Diagnostics, and Siemens and research support via Akershus University Hospital from Abbott Diagnostics, Novartis, SomaLogic, and Roche Diagnostics. Omland also has financial interests and serves as a fiduciary officer in Cardinor AS. Andrup has received fees for lectures from Bayer AG and Novartis. The remaining authors have no disclosures to report.

## Supplemental Material

Data S1  
Tables S1–S4  
Figure S1

## REFERENCES

- Geng YJ, Wei ZY, Qian HY, Huang J, Lodato R, Castriotta RJ. Pathophysiological characteristics and therapeutic approaches for pulmonary injury and cardiovascular complications of coronavirus disease 2019. *Cardiovasc Pathol*. 2020;47:107228. 10.1016/j.carpath.2020.107228
- Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Prevalence and determinants of fatigue after COVID-19 in non-hospitalized subjects: a population-based study. *Int J Environ Res Public Health*. 2021;18:2030. 10.3390/ijerph18042030
- Lerum TV, Aalokken TM, Bronstad E, Aarli B, Ikdahl E, Lund KMA, Durheim MT, Rodriguez JR, Meltzer C, Tonby K, et al. Dyspnoea, lung function and CT findings three months after hospital admission for COVID-19. *Eur Respir J*. 2020;57:2003448.
- Shi S, Qin MU, Shen BO, Cai Y, Liu T, Yang F, Gong W, Liu XU, Liang J, Zhao Q, et al. Association of cardiac injury with mortality in hospitalized

- patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* 2020;5:802–810. doi: 10.1001/jamacardio.2020.0950
5. Li Y, Li HE, Zhu S, Xie Y, Wang B, He L, Zhang D, Zhang Y, Yuan H, Wu C, et al. Prognostic value of right ventricular longitudinal strain in patients with COVID-19. *JACC Cardiovasc Imaging.* 2020;13:2287–2299. doi: 10.1016/j.jcmg.2020.04.014
  6. Lassen MCH, Skaarup KG, Lind JN, Alhakak AS, Sengeløv M, Nielsen AB, Espersen C, Ravnkilde K, Hauser R, Schöps LB, et al. Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study. *ESC Heart Fail.* 2020;22(7):4189–4197. doi: 10.1002/ehf2.13044
  7. Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, Kurz K, Koppelstätter S, Haschka D, Petzer V, et al. Cardiopulmonary recovery after COVID-19 - an observational prospective multi-center trial. *Eur Respir J.* 2021;57:2003481.
  8. Sechi LA, Colussi G, Bulfone L, Brosolo G, Da Porto A, Peghin M, Patruno V, Tascini C, Catena C. Short-term cardiac outcome in survivors of COVID-19: a systematic study after hospital discharge. *Clin Res Cardiol.* 2021;110:1063–1072. doi: 10.1007/s00392-020-01800-z
  9. Kotecha T, Knight DS, Razvi Y, Kumar K, Vimalesvaran K, Thornton G, Patel R, Chacko L, Brown JT, Coyle C, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J.* 2021;42(42):1866–1878. doi: 10.1093/eurheartj/ehab075
  10. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5:1265–1273. doi: 10.1001/jamacardio.2020.3557
  11. Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss H-P, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. *JAMA Cardiol.* 2020;5:1281–1285. doi: 10.1001/jamacardio.2020.3551
  12. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. *J Cardiovasc Electrophysiol.* 2020;31:1003–1008. doi: 10.1111/jce.14479
  13. Zareini B, Rajan D, El-Sheikh M, Jensen MH, Højbjerg Lassen MC, Skaarup K, Hansen ML, Biering-Sørensen T, Jabbari R, Kirk O, et al. Cardiac arrhythmias in patients hospitalized with COVID-19: the ACOVID study. *Heart Rhythm.* 2021;2(3):304–308. doi: 10.1016/j.hroo.2021.03.008
  14. World Health Organization. WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. 2020. [https://www.who.int/blueprint/priority-dis-eases/key-action/COVID-19\\_Treatment\\_Trial\\_Design\\_Master\\_Protocol\\_synop-sis\\_Final\\_18022020.pdf](https://www.who.int/blueprint/priority-dis-eases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synop-sis_Final_18022020.pdf)
  15. Letnes JM, Eriksen-Volnes T, Nes B, Wisloff U, Salvesen O, Dalen H. Variability of echocardiographic measures of left ventricular diastolic function. The HUNT study. *Echocardiography.* 2021;38:901–908. doi: 10.1111/echo.15073
  16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2015;16:233–270. doi: 10.1093/ehjci/jev014
  17. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2016;17:1321–1360. doi: 10.1093/ehjci/jev082
  18. Voigt J-U, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, Pedri S, Ito Y, Abe Y, Metz S, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *J Am Soc Echocardiogr.* 2015;28:183–193. doi: 10.1016/j.echo.2014.11.003
  19. Williams N. The MRC breathlessness scale. *Occup Med.* 2017;67:496–497. doi: 10.1093/occmed/kqx086
  20. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, Wallace EP. Development of a fatigue scale. *J Psychosom Res.* 1993;37:147–153. doi: 10.1016/0022-3999(93)90081-P
  21. Loge JH, Ekeberg O, Kaasa S. Fatigue in the general Norwegian population: normative data and associations. *J Psychosom Res.* 1998;45:53–65. doi: 10.1016/S0022-3999(97)00291-2
  22. Available at: <https://lovdata.no/dokument/NL/lov/2018-06-15-38>. Accessed January 7, 2022.
  23. Available at: <https://lovdata.no/dokument/NL/lov/2008-06-20-44>. Accessed January 7, 2022.
  24. Dalen H, Thorstensen A, Vatten LJ, Aase SA, Stoylen A. Reference values and distribution of conventional echocardiographic Doppler measures and longitudinal tissue Doppler velocities in a population free from cardiovascular disease. *Circ Cardiovasc Imaging.* 2010;3:614–622. doi: 10.1161/CIRCIMAGING.109.926022
  25. Stoylen A, Molmen HE, Dalen H. Relation between Mitral Annular Plane Systolic Excursion and Global longitudinal strain in normal subjects: the HUNT study. *Echocardiography.* 2018;35:603–610. doi: 10.1111/echo.13825
  26. Tsugu T, Postolache A, Dulgheru R, Sugimoto T, Tridetti J, Nguyen Trung M-L, Piette C, Moonen M, Manganaro R, Ilardi F, et al. Echocardiographic reference ranges for normal left ventricular layer-specific strain: results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging.* 2020;21:896–905. doi: 10.1093/ehjci/jeaa050
  27. Muraru D, Onciul S, Peluso D, Soriani N, Cucchini U, Aruta P, Romeo G, Cavalli G, Iliceto S, Badano LP. Sex- and method-specific reference values for right ventricular strain by 2-dimensional speckle-tracking echocardiography. *Circ Cardiovasc Imaging.* 2016;9:e003866. doi: 10.1161/CIRCIMAGING.115.003866
  28. Mahmoud-Elsayed HM, Moody WE, Bradlow WM, Khan-Kheil AM, Senior J, Hudsmith LE, Steeds RP. Echocardiographic findings in patients with COVID-19 pneumonia. *Can J Cardiol.* 2020;36:1203–1207. doi: 10.1016/j.cjca.2020.05.030
  29. Blyth KG, Groenning BA, Mark PB, Martin TN, Foster JE, Steedman T, Morton JJ, Dargie HJ, Peacock AJ. NT-proBNP can be used to detect right ventricular systolic dysfunction in pulmonary hypertension. *Eur Respir J.* 2007;29:737–744. doi: 10.1183/09031936.00095606
  30. Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, Gal Oz A, Rothschild E, Baruch G, Peri Y, et al. Spectrum of cardiac manifestations in COVID-19: a systematic echocardiographic study. *Circulation.* 2020;142:342–353. doi: 10.1161/CIRCULATIONAHA.120.047971
  31. Convertino VA. Cardiovascular consequences of bed rest: effect on maximal oxygen uptake. *Med Sci Sports Exerc.* 1997;29:191–196. doi: 10.1097/00005768-199702000-00005
  32. Skjorten I, Ankerstjerne OAW, Trebinjac D, Brønstad E, Rasch-Halvorsen Ø, Einvik G, Vigeland Lerum TV, Stavem K, Edvardsen A, Ingul CB. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. *Eur Respir J.* 2021;58:2100996.
  33. Freaney PM, Shah SJ, Khan SS. COVID-19 and heart failure with preserved ejection fraction. *JAMA.* 2020;324:1499–1500. doi: 10.1001/jama.2020.17445
  34. Caravita S, Baratto C, Di Marco F, Calabrese A, Balestrieri G, Russo F, Faini A, Soranna D, Perego GB, Badano LP, et al. Haemodynamic characteristics of COVID-19 patients with acute respiratory distress syndrome requiring mechanical ventilation. An invasive assessment using right heart catheterization. *Eur J Heart Fail.* 2020;22:2228–2237.
  35. Coromilas EJ, Kochav S, Goldenthal I, Biviano A, Garan H, Goldberg S, Kim JH, Yeo I, Tracy C, Ayanian S, et al. Worldwide survey of COVID-19-associated arrhythmias. *Circ Arrhythm Electrophysiol.* 2021;14:e009458.
  36. Pranata R, Huang I, Raharjo SB. Incidence and impact of cardiac arrhythmias in coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Indian Pacing Electrophysiol J.* 2020;20:193–198. doi: 10.1016/j.ipej.2020.08.001
  37. Abdalla IS, Prineas RJ, Neaton JD, Jacobs DR Jr, Crow RS. Relation between ventricular premature complexes and sudden cardiac death in apparently healthy men. *Am J Cardiol.* 1987;60:1036–1042. doi: 10.1016/0002-9149(87)90348-1
  38. Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA, Goldberg RJ. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. *N Engl J Med.* 1985;312:193–197. doi: 10.1056/NEJM198501243120401
  39. Sheldon SH, Gard JJ, Asirvatham SJ. Premature ventricular contractions and non-sustained ventricular tachycardia: association with sudden cardiac death, risk stratification, and management strategies. *Indian Pacing Electrophysiol J.* 2010;10:357–371.
  40. Skranes JB, Einvik G, Namtvedt SK, Randby A, Hrubos-Strøm H, Brynildsen J, Hagve TA, Somers VK, Rosjø H, Omland T.

- 
- Biomarkers of cardiovascular injury and stress are associated with increased frequency of ventricular ectopy: a population-based study. *BMC Cardiovasc Disord.* 2016;16:233. doi: 10.1186/s12872-016-0407-z
41. Hingorani P, Karnad DR, Rohekar P, Kerkar V, Lokhandwala YY, Kothari S. Arrhythmias seen in baseline 24-hour Holter ECG recordings in healthy normal volunteers during phase 1 clinical trials. *J Clin Pharmacol.* 2016;56:885–893. doi: 10.1002/jcph.679
  42. Buckley BJR, Harrison SL, Fazio-Eynullayeva E, Underhill P, Lane DA, Lip GYH. Prevalence and clinical outcomes of myocarditis and pericarditis in 718,365 COVID-19 patients. *Eur J Clin Invest.* 2021;51:e13679. doi: 10.1111/eci.13679
  43. Nelesen R, Dar Y, Thomas K, Dimsdale JE. The relationship between fatigue and cardiac functioning. *Arch Intern Med.* 2008;168:943–949. doi: 10.1001/archinte.168.9.943
  44. Karlsen S, Dahlslett T, Grenne B, Sjøli B, Smiseth O, Edvardsen T, Brunvand H. Global longitudinal strain is a more reproducible measure of left ventricular function than ejection fraction regardless of echocardiographic training. *Cardiovasc Ultrasound.* 2019;17:18. doi: 10.1186/s12947-019-0168-9

# **SUPPLEMENTAL MATERIAL**

## Data S1.

### Supplemental Methods

Measurement of diastolic dysfunction was based on the Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. The patients were separated into normal or depressed ejection fraction (left ventricle ejection fraction (EF) < 50%)<sup>18</sup>. An algorithm for diagnosis of LV diastolic dysfunction in subjects with normal LVEF was used (Figure 8 a in the Guidelines). Another algorithm was used in patients with depressed LVEFs (Figure 8 b in the Guidelines).

**Table S1. Summary statistics for cardiac variables for non-ICU and ICU patients.**

	Non-ICU		ICU		ICU vs. non-ICU		
	n	Mean (SD)	n	Mean (SD)	n	Estimate (95% CI)	P value
<i>LV systolic function</i>							
LV GLS, %	148	-18.6 (2.5)	39	-18.2 (3.8)	187	0.2 (-0.8 to 1.3)	.630
Ejection fraction, %	156	56.9 (6.4)	40	54.9 (7.7)	196	-1.9 (-4.2 to 0.5)	.119
MAPSE, cm	160	1.4 (0.2)	41	1.3 (0.2)	201	-0.07 (-0.14 to 0.01)	.068
LV S', cm/s	146	8.0 (1.6)	37	8.2(1.7)	183	0.1 (-0.4 to 0.7)	.692
Cardiac index, l/min/m <sup>2</sup>	154	2.6 (0.7)	39	2.7 (0.7)	193	0.14 (-0.09 to 0.39)	.252
<i>LV volumes</i>							
EDVi, mL/m <sup>2</sup>	146	48.8 (11.9)	40	51.8 (19.2)	186	2.3 (-2.3 to 7.4)	.341
<i>LV diastolic function</i>							
MV E/A Ratio	160	1.1 (0.4)	40	1.1 (0.3)	200	0.01 (-0.11 to 0.13)	.929
e', cm/s	154	8.6 (2.6)	39	8.0 (1.7)	193	-0.7 (-1.4 to 0.1)	.023
E/e'	150	8.3 (3.2)	38	8.9 (2.9)	188	0.88 (-0.04 to 1.89)	.076
<i>RV function and dimensions</i>							
RV Free wall strain, %	125	-25.1 (4.8)	40	-23.0 (5.2)	165	2.2 (0.4 to 3.9)	.016
RVD, cm	157	3.8 (0.6)	39	4.0 (0.5)	196	0.06 (-0.13 to 0.26)	.514
TAPSE, cm	158	2.4 (0.5)	41	2.3 (0.5)	199	-0.14 (-0.31 to 0.02)	.093
SPAP, mmHg	124	23.3 (8.5)	33	25.6 (9.3)	157	2.3 (-1.0 to 5.6)	.170
<i>Left atrial size and PV flow</i>							
LA volume index, mL/m <sup>2</sup>	151	26.5 (7.5)	39	29.3 (10.5)	190	2.7 (-0.1 to 5.8)	.073
PV S/D Ratio	137	1.4 (0.4)	37	1.4 (0.3)	174	-0.04 (-0.15 to 0.09)	.575
<i>Heart rate</i>	160	66.0 (11.7)	41	70.2 (11.2)	201	4.7 (0.7 to 8.7)	.021

Estimated mean differences between ICU and non-ICU patients, adjusted for age and sex by multiple regression. Estimate: Regression coefficient, ICU vs non-ICU; CI : confidence interval; LV, left ventricular; GLS, global longitudinal strain; MAPSE, mitral annular plane systolic excursion; S', peak systolic tissue Doppler velocity; EDVi, end-diastolic volume index; MV E/A, mitral valve E wave velocity and A wave velocity ratio; e', mean value of septal and lateral early diastolic pulsed tissue Doppler velocities; E/e'. filling pressure; RVD, right ventricular dimension; TAPSE, SPAP, systolic pulmonary artery pressure; PV, pulmonary vein; S/D, systolic/diastolic.

**Table S2. Summary of age and sex for COVID-19 patients by group.**

	Non-ICU (n=163)	ICU (n=41)	No dyspnea (n=77)	Dyspnea (n=86)	No fatigue (n=62)	Fatigue (n=101)
Age, mean (SD)	58.6 (14.4)	57.9 (10.0)	55.9 (14.5)	58.5 (12.9)	61.5 (14.0)	56.7 (13.3)
Males n (%)	86 (52.8)	28 (68.3)	51 (66.2)	42 (48.8)	35 (56.6)	53 (52.5)

ICU, intensive care unit

**Table S3. Summary statistics for cardiac variables for patients with and without dyspnea.**

	No dyspnea		Dyspnea grade 1-4		Dyspnea vs. no dyspnea		
	n	Mean (SD)	n	Mean (SD)	n	Estimate (95% CI)	P value
<i>LV systolic function</i>							
LV GLS, %	73	-18.5 (2.7)	75	-18.3 (3.2)	148	0.3 (-0.6 to 1.3)	.517
Ejection fraction, %	76	56.9 (5.3)	83	55.4 (7.7)	159	-1.7 (-3.8 to 0.4)	.121
MAPSE, cm	76	1.4 (0.2)	84	1.4 (0.2)	160	0 (-0.07 to 0.06)	.893
S', cm/s	71	8.2 (1.5)	74	7.9 (1.8)	145	-0.07 (-0.6 to 0.4)	.794
Cardiac index, l/min/m <sup>2</sup>	75	2.5 (0.6)	80	2.6 (0.7)	155	0.05 (-0.15 to 0.25)	.614
<i>LV volumes</i>							
EDVi, mL/m <sup>2</sup>	75	50.4 (12.4)	76	49.9 (15.5)	151	0.8 (-3.6 to 5.3)	.719
<i>LV diastolic function</i>							
MV E/A Ratio	75	1.1 (0.4)	85	1.1 (0.4)	160	-0.03 (-0.14 to 0.07)	.544
e', cm/s	74	8.9 (2.5)	80	8.3(2.3)	154	-0.4 (-1.0 to 0.2)	.214
E/e'	71	7.8 (3.1)	79	8.6 (3.2)	150	0.24 (-0.62 to 1.11)	.588
<i>RV function and dimensions</i>							
RV Free wall strain, %	66	-25.2 (3.7)	67	-23.6 (5.8)	133	1.5 (-0.3 to 3.2)	.094
RVD, cm	74	3.8 (0.5)	82	4.0 (0.6)	156	0.20 (0.02 to 0.38)	.029
TAPSE, cm	75	2.4 (0.5)	83	2.3 (0.5)	158	-0.09 (-0.25 to 0.07)	.250
SPAP, mmHg	60	24.1 (9.4)	70	22.9 (8.0)	130	-1.8 (-4.8 to 1.3)	.251
<i>Left atrial size and PV flow</i>							
LA volume index, mL/m <sup>2</sup>	76	26.0 (7.7)	82	27.9 (9.2)	158	1.1 (-1.5 to 3.8)	.393
PV S/D Ratio	63	1.3 (0.3)	73	1.4 (0.4)	136	0.05 (-0.06 to 0.15)	.374
<i>Heart rate</i>	76	64.8 (10.8)	85	69.4 (12.4)	161	4.2 (0.5 to 7.9)	.028

Estimated mean differences between patients with and without dyspnea, adjusted for age and sex by multiple regression.

Estimate: Regression coefficient, dyspnea vs non-dyspnea; CI : confidence interval ; LV, left ventricular; GLS, global longitudinal strain; MAPSE, mitral annular plane systolic excursion; S', peak systolic tissue Doppler velocity; EDVi, end-diastolic volume index; MV E/A, mitral valve E wave velocity and A wave velocity ratio; e', mean value of septal and lateral early diastolic pulsed tissue Doppler velocities; E/e'. filling pressure; RVD, right ventricular dimension; TAPSE, SPAP, systolic pulmonary artery pressure; PV, pulmonary vein; S/D, systolic/diastolic.

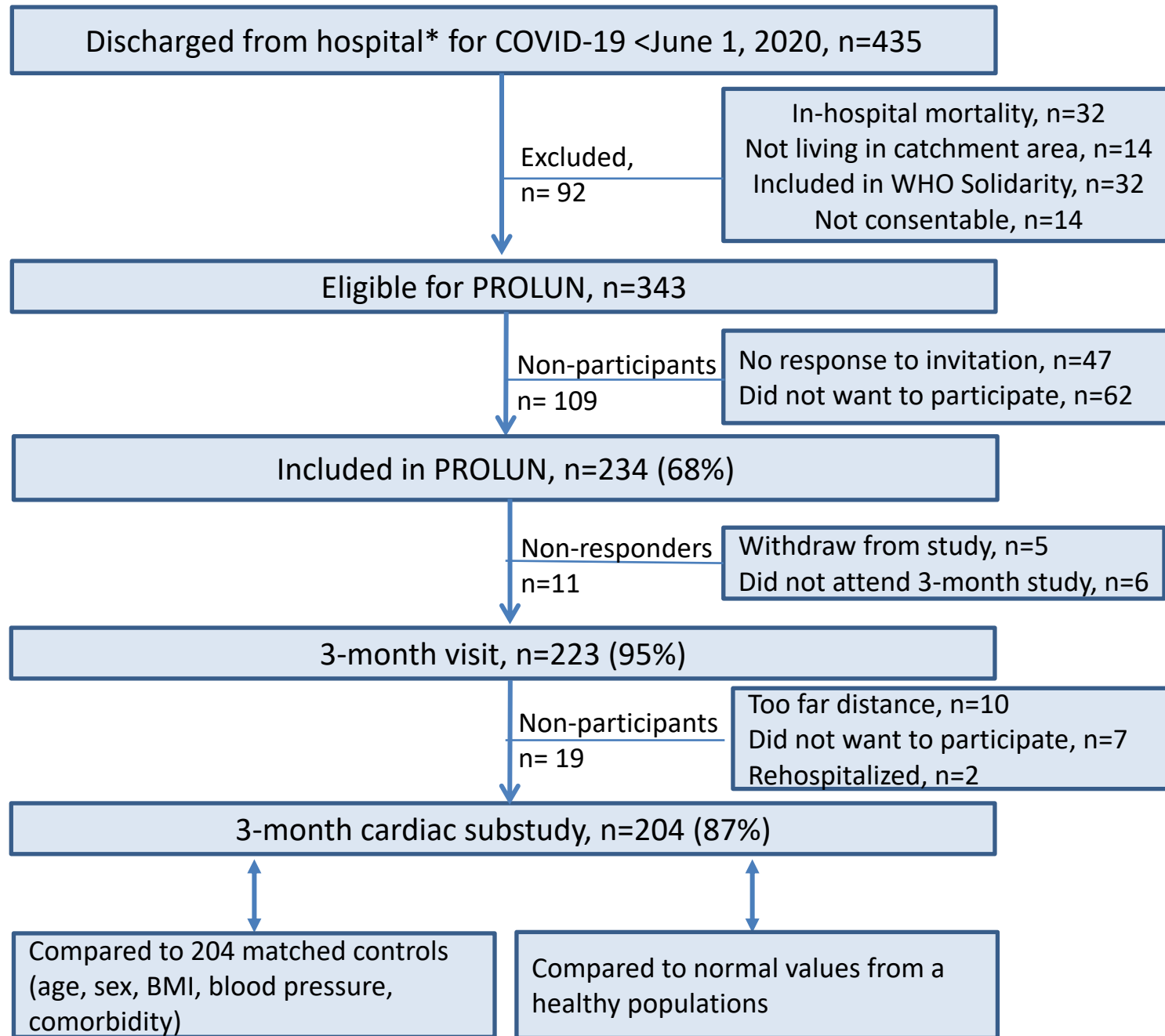
**Table S4. Summary statistics for cardiac variables for patients with or without fatigue.**

	No fatigue		Fatigue		Fatigue vs. no fatigue		
	n	Mean (SD)	n	Mean (SD)	n	Estimate (95% CI)	P value
<i>LV systolic function</i>							
LV GLS, %	57	-18.6 (3.5)	94	-18.2 (2.6)	151	0.5 (-0.5 to 1.5)	.303
Ejection fraction, %	60	56.5 (7.6)	97	56.6 (6.8)	157	-0.2 (-2.5 to 2.2)	.890
MAPSE, cm	61	1.3 (0.2)	101	1.4 (0.2)	162	0.02 (-0.06 to 0.09)	.676
S', cm/s	57	8.0 (1.5)	93	7.9 (1.6)	150	-0.3 (-0.7 to 0.2)	.263
Cardiac index, l/min/m <sup>2</sup>	60	2.6 (0.7)	95	2.6 (0.6)	155	0.07 (-0.14 to 0.28)	.505
<i>LV volumes</i>							
EDVi, mL/m <sup>2</sup>	59	49.7 (13.5)	92	50.4 (15.1)	151	0.8 (-3.8 to 5.3)	.725
<i>LV diastolic function</i>							
MV E/A Ratio	60	1 (0.3)	99	1.1 (0.4)	159	-0.01 (-0.13 to 0.11)	.859
e', cm/s	61	8.4 (2.5)	98	8.5 (2.3)	159	-0.5 (-1.1 to 0.06)	.078
E/e'	58	8.3 (3.3)	96	8.2 (2.6)	154	0.35 (-0.48 to 1.15)	.395
<i>RV function and dimensions</i>							
RV free wall strain, %	47	-25.2 (5.1)	83	-24.3 (5.2)	130	0.9 (-1.0 to 2.8)	.358
RVD, cm	61	3.8 (0.6)	96	3.9 (0.6)	157	0.06 (-0.13 to 0.24)	.537
TAPSE, cm	60	2.4 (0.5)	100	2.3 (0.5)	160	-0.01 (-0.17 to 0.16)	.945
SPAP, mmHg	51	25 (9.2)	76	22.9 (8.6)	127	-1.6 (-4.8 to 1.6)	.313
<i>Left atrial size and PV flow</i>							
LA volume index, mL/m <sup>2</sup>	59	28.9 (9.3)	98	26.1 (7.2)	157	-2.2 (-4.8 to 0.3)	.096
PV S/D Ratio	51	1.4 (0.5)	90	1.3 (0.3)	141	-0.02 (-0.14 to 0.10)	.773
<i>Heart rate</i>	62	65.6 (11.3)	99	68.2 (12.4)	161	2.6 (-1.2 to 6.5)	.183

Estimated mean differences between patients with and without fatigue, adjusted for age and sex by multiple regression.

Estimate: Regression coefficient, fatigue vs non-fatigue; CI, confidence interval ; LV, left ventricular; GLS, global longitudinal strain; MAPSE, mitral annular plane systolic excursion; S', peak systolic tissue Doppler velocity; EDVi, end-diastolic volume index; MV E/A, mitral valve E wave velocity and A wave velocity ratio; e', mean value of septal and lateral early diastolic pulsed tissue Doppler velocities; E/e'. filling pressure; RVD, right ventricular dimension; TAPSE, SPAP, systolic pulmonary artery pressure; PV, pulmonary vein; S/D, systolic/diastolic.

**Figure S1. Graph displaying the study flow with the total number of patients and dropouts.**



\*Haukeland hospital not included in this flowchart, as cardiac substudy was not performed there.