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Research paper

Symptom Persistence Despite Improvement in Cardiopulmonary Health – Insights from longitudinal CMR, CPET and lung function testing post-COVID-19

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ABSTRACT

Background: The longitudinal trajectories of cardiopulmonary abnormalities and symptoms following infection with coronavirus disease (COVID-19) are unclear. We sought to describe their natural history in previously hospitalised patients, compare this with controls, and assess the relationship between symptoms and cardiopulmonary impairment at 6 months post-COVID-19.

Methods: Fifty-eight patients and thirty matched controls (single visit), recruited between 14th March - 25th May 2020, underwent symptom-questionnaires, cardiac and lung magnetic resonance imaging (CMR), cardiopulmonary exercise test (CPET), and spirometry at 3 months following COVID-19. Of them, forty-six patients returned for follow-up assessments at 6 months.

Findings: At 2-3 months, 83% of patients had at least one cardiopulmonary symptom versus 33% of controls. Patients and controls had comparable biventricular volumes and function. Native cardiac T_1 (marker of fibroinflammation) and late gadolinium enhancement (LGE, marker of focal fibrosis) were increased in patients at 2-3 months. Sixty percent of patients had lung parenchymal abnormalities on CMR and 55% had reduced peak oxygen consumption ($p\dot{V}O_2$) on CPET. By 6 months, 52% of patients remained symptomatic. On CMR, indexed right ventricular (RV) end-diastolic volume (-4·3 mls/m^2, P=0·005) decreased and RV ejection fraction (+3·2%, P=0·0003) increased. Native T_1 and LGE improved and was comparable to controls. Lung parenchymal abnormalities and peak $\dot{V}O_2$, although better, were abnormal in patients versus controls. 31% had reduced $p\dot{V}O_2$ secondary to symptomatic limitation and muscular impairment. Cardiopulmonary symptoms in patients did not associate with CMR, lung function, or CPET measures.

Interpretation: In patients, cardiopulmonary abnormalities improve over time, though some measures remain abnormal relative to controls. Persistent symptoms at 6 months post-COVID-19 did not associate with objective measures of cardiopulmonary health.

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Research in context

Evidence before this study

Several studies have shown that following hospitalisation with COVID-19, patients continue to experience a broad range of symptoms, together with evidence of cardiac and respiratory abnormalities accompanied by exercise limitations. However, research assessments have typically been undertaken at a single time point and do not reveal the natural history of cardiopulmonary pathology or how they relate with ongoing symptoms in patients.

Added value of this study

This study describes the longitudinal trajectories of cardiopulmonary symptoms and abnormalities in patients recovering from COVID-19. We demonstrate that among previously hospitalised patients both symptoms and early evidence of cardiopulmonary impairment improve over time from 3 to 6 months after the illness. However, some patients continue to have lung abnormalities and exercise limitation. Notably, more than half the patients continue to experience symptoms at 6 months and there was a dissociation between persistent symptoms and objective measures of cardiopulmonary health.

Implications of all the available evidence

Our findings suggest that contemporary tools that are used to assess cardiopulmonary health in the community remain poor at elucidating a cause for ongoing symptoms. Patients can have evidence of abnormalities on clinical tests and still be asymptomatic. The pathophysiological basis for cardiopulmonary symptoms is still unclear and alternative mechanisms for ongoing symptoms need to be explored.

1. Introduction

First described in December 2019 [1], severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a beta coronavirus, is responsible for coronavirus disease (COVID-19). Our understanding of how this virus came to invade human cell lines has rapidly evolved, as the role of angiotensin-converting enzyme-2 receptors (ACE2) in facilitating viral entry into cells was elucidated [2]. ACE2 receptors are not only present in type II pneumocytes but are ubiquitously expressed by the vascular cells and other visceral organs [3]. The effect of SARS-CoV-2 on the heart is of particular importance, as it can cause a range of abnormalities including myocardial dysfunction, inflammation, and ischaemic damage via direct (cytotoxic) and indirect (dysregulated immune response, thrombo-inflammation) mechanisms [4]. Myocardial injury is more common in moderate to severe infections and predictive of poor clinical outcomes among those admitted to hospital [5]. A number of recent studies have highlighted the role of cardiac magnetic resonance imaging (CMR) and cardiopulmonary exercise testing (CPET) in evaluating the mechanisms and functional consequences of cardiopulmonary injury in COVID-19 survivors [5-7]. Detailed assessments have typically been undertaken at a single time point within weeks to months after infection and do not reveal the natural history of cardiopulmonary pathology. A high burden of cardiopulmonary symptoms has also been reported and the role of contemporaneous investigations in elucidating the underlying cause for symptoms is unknown.

Previously, we undertook a holistic assessment of COVID-19 patients at 2-3 months following moderate to severe infection using symptom-based questionnaires, multiorgan magnetic resonance imaging (MRI), spirometry, and CPET [8]. We observed a high prevalence of tissue abnormalities involving the heart (26%) and lungs (60%) on MRI, together with reduced forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) and marked exercise intolerance on CPET in patients. Here, we sought to describe the time course evolution of cardiopulmonary symptoms, CMR, pulmonary function and CPET abnormalities in these patients from 2-3 months to 6 months and evaluate the relationship between symptoms and objective measures of cardiopulmonary health at 6 months.

2. Methods

2.1. Study population

Fifty-eight patients with moderate to severe laboratory-confirmed (SARS-CoV-2 polymerase chain reaction positive) COVID-19, admitted for inpatient treatment at the Oxford University Hospitals National Health Service Foundation Trust between 14th March - 25th May 2020, and 30 SARS-CoV-2 immunoglobulin negative controls, group-matched for age, sex, body mass index and risk factors (smoking, diabetes, and hypertension) from the community (recruited during the same period) were prospectively enrolled in this observational cohort study as previously described. A flow chart for recruitment is listed in the **Supplementary Material, p10**.

This study was registered at ClinicalTrials.gov (NCT04510025) and approved in the United Kingdom by the North West Preston Research Ethics Committee (reference 20/NW/0235).

2.2. Study procedures

Informed consent was obtained from all patients. Patient health questionnaires, cardiopulmonary magnetic resonance imaging (MRI), spirometry, CPET, electrocardiogram (ECG) and blood tests were undertaken in patients at 2-3 months and 6 months post-infection and at a single time point in controls. Gas transfer assessments were undertaken in patients at 6 months alone.

Disease severity was graded using the World Health Organisation ordinal scale for clinical improvement [9]. Patients with severe illness were defined as those having a score of $\geq$5 (high flow oxygen, non-invasive and invasive ventilation).

An electrocardiogram (ECG) was performed for every participant and interpreted according to the Minnesota Code of Electrocardiographic Findings [10].

Patient health questionnaire-15 (PHQ-15) [11] was completed using an electronic data capture platform (CASTOR EDC, https://www.castoredc.com). The Medical Research Council (MRC) dyspnoea

scale [12] and Fatigue Severity Scale (FSS) [13] were used to assess the prevalence and severity of breathlessness and fatigue, respectively (**Supplementary material, p3**).

CMR was carried out at 3 Tesla (Prisma, Siemens Healthineers, Erlangen, Germany) and included cine imaging to assess biventricular volumes, diastolic strain rate, T_1 and T_2 mapping to assess myocardial inflammation and oedema, and post-contrast T_1 mapping and late gadolinium enhancement (LGE) imaging to assess diffuse and focal/patchy fibrosis. Lung abnormalities were assessed using Half−Fourier−acquisition single−shot turbo spin−echo (HASTE) MRI before the administration of contrast (**Supplementary Material, p4**).

CMR studies were analysed using CVI42 5.11.4 (Circle Cardiovascular Imaging, Calgary, Canada). All cardiac images were anonymised and analysed by CMR experts (BR, MC) (**Supplementary Material, p4**). Lung images were qualitatively assessed for parenchymal involvement by an expert radiologist (CX), with the extent of lung parenchymal opacities scored as 0 (0%), 1 (1-25%), 2 (26-50%), 3 (51-75%), or 4 (76-100%) [14]. BR, MC and CX were blinded to the subject group allocation during analysis.

Spirometry, including FVC and FEV_1, was performed as per recommended guidance [15]. Diffusion capacity for carbon monoxide (DL_{CO}) and alveolar volume (Va) were measured using a ten-second single breath-hold technique with methane as the tracer gas, and adjusted for haemoglobin [16].

Symptom-limited incremental CPET was undertaken using a cycle ergometer as previously described. Following two minutes of unloaded cycling, the work rate was increased to 20W, followed by a 10W/min ramp (**Supplementary Material, p6**) [17].

Blood-based testing consisted of complete blood count, biochemical analysis, coagulation testing, liver and renal function assessment, markers of cardiac injury (troponin T and N-terminal pro-brain natriuretic peptide/NT-proBNP), and measures of electrolytes, C-reactive protein (CRP), and procalcitonin.

Details on clinical symptoms, signs, vitals, and laboratory findings during admission were extracted from electronic medical records.

2.3. Statistics

Continuous variables were described using mean and standard deviation for variables with parametric data across all groups. When non-parametric data was present in one or more groups, median and interquartile range (IQR) were used to facilitate comparison. Normality was assessed by the Shapiro-Wilk test. Group differences were evaluated using Student's t-tests, Mann-Whitney U-tests, paired Student's t-tests, and Wilcoxon Signed Ranks tests as appropriate. Categorical variables were reported as frequency and percentages, with group differences evaluated using the Chi-square test, Fisher's exact test, Fisher-Freeman-Halton exact test, Stuart-Maxwell test, or McNemar test as appropriate. Spearman's correlation coefficients were used to describe the relationship between two variables where relevant. Univariate and multivariate binary logistic regression were used to assess the association between cardiopulmonary symptoms (chest pain, palpitations, syncope, dyspnoea, or dizziness) and objective measures of cardiopulmonary health. To maintain the absence of collinearity, NT-proBNP ($<$125 ng/L or $\geq$125 ng/L), ECG (normal or abnormal), left ventricular ejection fraction, right ventricular ejection fraction, mid myocardial T_1, mid myocardial T_2, volume of late gadolinium enhancement, left ventricular diastolic strain rate, FEV_1, FVC, DL_{co}, peak oxygen consumption and $\dot{V}E/\dot{V}CO_2$ slope were included as independent variables in the multivariate analysis. The Box-Tidwell test was used to demonstrate maintenance of linearity in the logit.

In a separate analysis, determinants of breathlessness were also ascertained (**Supplementary Material, p11**). The conventional level of statistical significance of 5% was used. Statistical analyses were performed using SPSS Version 27.0 (IBM, Armonk, NY, USA).

3. Role of Funding

The sponsors played no role in the design of the study; collection, analysis and interpretation of data; in writing the manuscript, and in the decision to submit the paper for publication.

4. Results

Baseline characteristics of all patients and controls are listed in **Table 1**.

Of the 58 patients recruited, 46 (79%) returned for follow-up assessments. The mean age of patients was 55±13 years. Thirty-four (59%) were men (**Table 1**). Thirteen (22%) belonged to Black (7/13) and Asian (6/13) ethnic groups. Twenty (34%) patients required non-invasive ventilation or intubation, and 16 (28%) received steroids as part of their care (median duration 5 days, IQR 4-10 days). The median duration of hospitalization was 9 days (IQR 5-17). In all patients, readmission was due to increased breathlessness secondary to progression of COVID-19, within a week of the initial admission. The first assessment took place at a median interval of 2·3 months (IQR 2·1−2·5) from disease onset and second took place at 6·0 months (IQR 6·0 − 6·8).

On admission, all patients had a raised CRP ($>$10mg/L), 47% had lymphopenia, and 21% were anaemic. By 6 months, CRP was raised in 13%, compared to none in controls (P=0·076), lymphocyte count normalized, and the proportion of those with anaemia was comparable to controls (11% versus 13%, P=1·0) (**Table 2**).

As previously reported, troponin on admission (measured in 38 patients) was abnormal in three (5%) patients. By 2-3 and 6 months, all patients had troponin measured and none had elevated high-sensitivity troponin levels ($>$34ng/L).

Only four patients had NT-proBNP measured during admission. At 2-3 months, all patients had NT proBNP measured and NT proBNP was elevated in 11 (20%), reducing to eight (17%) patients at 6 months versus 11% in controls (P=0·52).

4.1. Electrocardiography

ECG analysis revealed atrial fibrillation in one patient at both assessments (2-3 months and 6 months), with all other study participants (both patients and controls) demonstrating sinus rhythm. The prevalence of bundle branch block, ST-segment elevation/depression and T wave inversion did not differ between patients (on both visits) and controls ($P>$0·05 for all variables).

4.2. Symptom burden

Symptom prevalence in patients and controls are listed in **Table 3**. As a whole, 98% had one or more symptoms (cardiopulmonary and non-cardiopulmonary) at 2-3 months from infection, reducing to 89% by 6 months. The prevalence of cardiopulmonary symptoms (chest pain, palpitations, syncope, dyspnoea or dizziness) in patients was 83% at 2-3 months and dropped to 52% at 6 months (P=0·0001). At 6 months, symptoms of breathlessness (MRC) and fatigue (FSS) were worse in patients than controls (MRC grade $\geq$2: 57% vs 10%, $P<$0·0001; Mean FSS $\geq$4: 44% vs 17%, P=0·023, **Table 3**); statistical significance was maintained after adjusting for a history of mild chronic lung disease.

4.3. Serial Cardiac Imaging

Left ventricular (LV) volumes, mass, and function (including diastolic strain rate) were not different between patients (at 2-3 months and 6 months) and controls (**Table 4**). At 6 months, two (4·5%) patients had an LV ejection fraction (LVEF) just below the cut-off of 50% (49·6 and 49·8%). Those with severe illness had lower LVEF at 6

Table 1
Demographics and baseline characteristics of COVID-19 patients who underwent single assessment, serial assessments (2-3 months & 6 months) and controls.

	COVID-19, 2-3m (N=58)	COVID-19, 6m (N=46)	Controls (N=30)	*P*-values		
				2-3m vs Controls	6m vs Controls	2-3m vs 6m
General demographics						
Age, years	55·4 (13·2)	55·2 (13·3)	53·9 (12·3)	0·62	0·67	0·96
Gender				1·00[a]	0·81[a]	0·69[a]
Female	24/58 (41·4%)	17/46 (37·0%)	12/30 (40·0%)			
Male	34/58 (58·6%)	29/46 (63·0%%)	18/30 (60·0%)			
BMI, kg/m^2	30·8 (26·2 - 36·4)	30·6 (26·6 - 35·6)	27·3 (23·1 - 35·1)	0·17[b]	0·19[b]	0·91[b]
Black/Asian and minority ethnic groups	13/58 (22·4%)	10/46 (21·7%)	1/30 (3·3 %)	0·03[c]	0·04[c]	1·00[a]
Current/Ex-smoker	20/58 (34·5%)	17/46 (37·0%)	7/30 (23·3%)	0·34[c]	0·31[c]	0·84[a]
Type 1 Diabetes	1/58 (1·7%)	1/46 (2·2%)	0/30 (0·0%)	1·00[c]	1·00[c]	1·00[c]
Type 2 Diabetes	8/58 (13·8%)	7/46 (15·2%)	3/30 (10·0%)	0·74[c]	0·73[c]	1·00[a]
Hypertension	22/58 (37·9%)	17/46 (37·0%)	9/30 (30·0%)	0·49[c]	0·62[c]	1·00[a]
Coronary artery disease	2/58 (3·4%)	1/46 (2·2%)	0/30 (0·0%)	0·55[c]	1·00[c]	1·00[c]
Cerebrovascular Disease	1/58 (1·7%)	0/46 (0·0%)	0/30 (0·0%)	1·00[c]	1·00[c]	1·00[c]
Asthma	20/58 (34·5%)	17/46 (37·0%)	6/30 (20·0%)	0·22[c]	0·13[c]	0·84[a]
COPD	3/58 (5·2%)	2/46 (4·3%)	0/30 (0·0%)	0·55[c]	0·51[c]	1·00[c]
Previous cancer	2/58 (3·4%)	2/46 (4·3%)	3/30 (10·0%)	0·33[c]	0·38[c]	1·00[c]
Depression	3/58 (5·2%)	3/46 (6·5%)	1/30 (3·3%)	1·00[c]	1·00[c]	1·00[c]
Admission details						
Median length of stay, days	8·5 (5·0 - 17·0)	9·0 (5·0 - 17·5)	..	..	..	0·85[b]
Readmitted	10/58 (17·2%)	9/46 (19·6%)	..	..	..	0·48[a]
Required ITU admission	21/58 (36·2%)	17/46 (37·0%)	..	..	..	0·55[a]
qSOFA						
0	17/58 (29·3%)	15/46 (32·6%)	..	..	..	0·94[d]
1	38/58 (65·5%)	29/46 (63·0%)	..	..	..	
2	3/58 (5·2%)	2/46 (4·3%)	..	..	..	
3	0/58 (0·0%)	0/46 (0·0%)	..	..	..	
Ordinal scale for clinical improvement (WHO)						
1	0/58 (0·0%)	0/46 (0.0%)	..	..	..	1·00[d]
2	4/58 (6·9%)	3/46 (6·5%)	..	..	..	
3	22/58 (37·9%)	16/46 (34·8%)	..	..	..	
4	5/58 (8·6%)	4/46 (8·7%)	..	..	..	
5	15/58 (25·9%)	12/46 (26·1%)	..	..	..	
6	7/58 (12·1%)	6/46 (13·0%)	..	..	..	
7	5/58 (8·6%)	5/46 (10·9%)	..	..	..	
Signs and symptoms on admission						
Fever	51/58 (87·9%)	40/46 (87·0%)	..	..	..	0·56[a]
Malaise	51/58 (87·9%)	41/46 (89·1%)	..	..	..	0·55[a]
Shortness of breath	51/58 (87·9%)	41/46 (89·1%)	..	..	..	0·55[a]
Cough	35/58 (60·3%)	26/46 (56·5%)	..	..	..	0·42[a]
Dysgeusia	29/58 (50·0%)	21/46 (45·7%)	..	..	..	0·70[a]
Anosmia	26/58 (44·8%)	20/46 (43·5%)	..	..	..	1·00[a]
Diarrhoea	17/58 (29·3%)	13/46 (28·3%)	..	..	..	1·00[a]
Chest pain	16/58 (27·6%)	13/46 (28·3%)	..	..	..	1·00[a]
Headache	13/58 (22·4%)	12/46 (26·1%)	..	..	..	0·82[a]
Vomiting	9/58 (15·5%)	6/46 (13·0%)	..	..	..	0·79[a]
Treatment						
Oxygen replacement	54/58 (93·1%)	43/46 (93·5%)	..	..	..	1·00[c]
Nasal cannula	14/58 (24·1%)	10/46 (21·7%)	..	..	..	1·00[d]
Simple face mask	7/58 (12·1%)	5/46 (10·9%)	..	..	..	
Venturi face mask	6/58 (10·3%)	5/46 (10·9%)	..	..	..	
High flow oxygen delivery	7/58 (12·1%)	5/46 (10·9%)	..	..	..	
CPAP	8/58 (13·8%)	7/46 (15·2%)	..	..	..	
Intubation	12/58 (20·7%)	11/46 (23·9%)	..	..	..	
ECMO	0/58 (0%)	0/46 (0.0%)	..	..	..	
Inotropic support	4/58 (6·9%)	4/46 (8·7%)	..	..	..	0·73[c]
Renal replacement therapy	2/58 (3·4%)	2/46 (4·3%)	..	..	..	1·00[c]
Antibiotics	57/58 (98·3%)	45/46 (97·8%)	..	..	..	1·00[c]
Antivirals	4/58 (6·9%)	2/46 (4·3%)	..	..	..	0·69[c]
Steroids	16/58 (27·6%)	14/46 (30·4%)	..	..	..	0·83[a]
Acute organ injury						
Acute liver injury[e]	18/58 (31·0%)	18/46 (39·1%)	..	..	..	0·41[a]
Acute kidney injury[f]	6/58 (10·3%)	6/46 (13·0%)	..	..	..	0·76[a]
Acute cardiac injury[g]	3/58 (5·2%)	0/46 (0.0%)	..	..	..	0·25[c]
Pulmonary embolism	7/58 (12·1%)	6/46 (13·0%)	..	..	..	1·00[a]
Central	1/58 (1·7%)	0/46 (0.0%	..	..	..	1·00[c]
Peripheral	6/58 (10·3%)	6/46 (13·0%)	..	..	..	0·76[a]

Data are mean (SD), median (IQR) and n/N (%), where N is the total number of participants with available data. P-values from independent Student's t-test, Chi-square ([a]), Mann-Whitney U test ([b]), Fisher's exact test ([c]), or Fisher-Freeman-Halton exact test ([d]), with bold values highlighting statistical significance. 2-3m = Two to three months. 6m = Six months. COPD = Chronic obstructive pulmonary disease. ITU = Intensive treatment unit. qSOFA = Quick sequential organ failure assessment. CPAP = Continuous positive airway pressure. ECMO = Extracorporeal membrane oxygenation. WHO = World health organization. e defined as blood levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 3x the upper reference limit (>135 IU/L or >126 IU/L, respectively), alkaline phosphatase or gamma-glutamyltransferase above 2x the upper reference limit (>260 IU/L or >80 IU/L, respectively). f defined as an increase in serum creatinine of at least 26 umol/L within 48 hours, or 1·5 to 2-fold increase from baseline. g defined as an acute rise in hypersensitive troponin I above the 99th percentile upper reference limit (>34 ng/L). Control subjects were matched for co-morbidities as closely as possible.

Table 2
Blood test results and symptom prevalence for patients with COVID-19 and controls.

	COVID-19 (admission) (N=58)	COVID-19, 2-3m (N=58)	COVID-19, 6m (N=46)	Controls (N=30)	*P*-values		
					2-3m vs Controls	6m vs Controls	2-3m vs 6m
Haematology and Coagulation							
White cell count, x10^9 / L	6·5 (5·0 - 8·1)	6·5 (1·8)	6·4 (2·1)	6·7 (1·6)	0·72	0·24[a]	0·072[b]
<4	6/58 (10·3%)	5/57 (8·8%)	5/46 (10·9%)	0/30 (0·0%)	0·16[c]	0·054[d]	0·73[e]
4-11	45/58 (77·6%)	52/57 (91·2%)	39/46 (84·8%)	30/30 (100%)			
>11	7/58 (12·1%)	0/57 (0·0%)	2/46 (4·3%)	0/30 (0·0%)			
Neutrophil count, x10^9 / L	5·2 (3·5 - 6·6)	3·6 (2·9 - 4·6)	3·4 (2·8 - 4·5)	3·9 (2·8 - 4·3)	0·65[a]	0·50[a]	0·70[b]
Lymphocyte count, x10^9 / L	0·9 (0·7 - 1·3)	1·8 (1·6 - 2·3)	1·7 (1·4 - 2)	1·9 (1·6 - 2·5)	0·91[a]	**0·016**	**0·002[b]**
<1·0	27/58 (46·6%)	0/57 (0·0%)	0/46 (0·0%)	0/30 (0·0%)			
Haemoglobin, g/L	141·0 (125·5 - 150·5)	135·4 (13·2)	140·2 (14·7)	139·0 (14·4)	0·25	0·65	**0·008[f]**
<120 (females)/<130 (males)	12/58 (20·6%)	8/57 (14·0%)	5/46 (10·9%)	4/30 (13·3%)	1·00[c]	0·73[c]	1·00[g]
Platelet count, x10^9 / L	207·5 (168·8 - 259·5)	261·0 (213·5 - 285·5)	243·5 (213·0 - 267·3)	269·0 (220·0 - 292·0)	0·63[a]	0·24	**0·0002[b]**
<100	1/58 (1·7%)	0/57 (0·0%)	0/46 (0·0%)	0/30 (0·0%)			
D-dimer, μg/L	780·0 (636·0 - 1490·0)	418·0 (253·8 - 829·3)	390·0 (255·0 - 625·0)	337·0 (227·0 - 498·75)	0·054[a]	0·23[a]	**0·003[b]**
Hepatic panel							
Total bilirubin, mmol/L	10·0 (7·0 - 13·8)	10·0 (6·8 - 14·0)	10·5 (7·0 - 14·3)	8·0 (7·0 - 11·5)	0·51[a]	0·17[a]	0·17[b]
ALT, IU/L	34·0 (22·3 - 62·8)	23·5 (18·8 - 39·0)	24·0 (18·8 - 37·0)	23·5 (16·0 - 28·0)	0·19[a]	0·20[a]	0·63[b]
>135 IU/L (>3xULN)	4/56 (7·1%)	1/58 (1·7%)	0/46 (0·0%)	0/30 (0·0%)			
Alk Phos, IU/L	..	72·0 (60·0 - 85·5)	69·0 (54·8 - 83·0)	65·5 (55·8 - 80·3)	0·21[a]	0·46[a]	0·20[b]
>260 IU/L (>2xULN)	..	0/58 (0·0%)	0/46 (0·0%)	0/30 (0·0%)			
AST, IU/L	..	23·0 (18·0 - 28·0)	21·0 (18·0 - 26·0)	21·0 (18·0 - 27·0)	0·36[a]	0·87[a]	0·07[b]
>126 IU/L (>3xULN)	..	0/55 (0·0%)	0/46 (0·0%)	0/25 (0·0%)			
GGT, IU/L	..	33·0 (21·8 - 52·3)	30·5 (22·0 - 42·3)	29·0 (18·5 - 47·5)	0·25[a]	0·74[a]	**0·002[b]**
>80 IU/L (>2xULN)	..	6/54 (11·1%)	1/46 (2·2%)	1/25 (4·0%)	0·42[c]		
Renal function and electrolytes							
Potassium, mmol/L	3·8 (3·7 - 4·1)	3·9 (0·3)	3·9 (0·3)	3·9 (0·3)	0·92	0·23	0·55[f]
Sodium, mmol/L	136·0 (2·9)	141·0 (139·0 - 141·3)	141·0 (139·0 - 142·0)	140·0 (139·0 - 141·0)	0·12[a]	0·050[a]	0·11[b]
Creatinine, umol/L	75·5 (69·0 - 91·0)	69·5 (60·0 - 79·3)	74·5 (64·8 - 86·0)	79·0 (63·0 - 89·0)	0·16[a]	0·64[a]	**0·012[b]**
≤133	55/58 (94·8%)	57/58 (98·3%)	44/46 (95·7%)	30/30 (100%)			
>133	3/58 (5·2%)	1/58 (1·7%)	2/46 (4·3%)	0/30 (0%)			
eGFR, ml/min/1·73m^2							
≥90	31/58 (53·4%)	38/58 (65·5%)	26/46 (56·5%)	17/30 (56·7%)	0·53[d]	0·74[d]	0·22[e]
60-89	21/58 (36·2%)	17/58 (29·3%)	18/46 (39·1%)	13/30 (43·3%)			
45-59	3/58 (5·2%)	1/58 (1·7%)	0/46 (0·0%)	0/30 (0·0%)			
30-44	2/58 (3·4%)	2/58 (3·4%)	2/46 (4·3%)	0/30 (0·0%)			
15-29	1/58 (1·7%)	0/58 (0·0%)	0/46 (0·0%)	0/30 (0·0%)			
<15	0/58 (0·0%)	0/58 (0·0%)	0/46 (0·0%)	0/30 (0·0%)			
Inflammatory markers							
C-reactive protein, mg/L	119·1 (75·9 - 185·5)	2·0 (0·9 - 5·0)	1·7 (0·9 - 5·6)	1·2 (0·7 - 2·6)	0·058[a]	0·23[a]	0·98[b]
>10	58/58 (100%)	4/58 (6·9%)	6/46 (13·0%)	0/30 (0·0%)	0·29[c]	0·076[c]	0·45[g]
Procalcitonin, ug/L	..	0·020 (0·020 - 0·040)	0·020 (0·010 - 0·030)	0·02 (0·020 - 0·030)	0·80[a]	0·22[a]	0·083[b]
Heart failure, cardiac injury							
NT-proBNP, ng/L	..	56·8 (32·3 - 113·6)	56·3 (31·2 - 98·3)	48·1 (23·0 - 88·4)	0·22[a]	0·50[a]	0·20[b]
≥125		11/56 (19·6%)	8/46 (17·4%)	3/28 (10·7%)	0·37[c]	0·52[c]	0·75[g]
Troponin I, ng/L	..	2·0 (2·0 - 3·0)	2·0 (2·0 - 4·0)	2·0 (2·0 - 3·0)	0·49[a]	0·27[a]	0·14[b]
>34		0/58 (0·0%)	0/46 (0·0%)	0/27 (0·0%)			

Data are median (IQR) for non-parametric data and mean (SD) for parametric data, and n/N (%), where N is the total number of participants with available data. *P*-values comparing COVID-19 groups (post-discharge) and control group are from independent t-test, Mann-Whitney U test ([a]), Wilcoxon Signed Ranks test ([b]), Fisher's exact test ([c]), Fisher-Freeman-Halton exact test ([d]), Stuart Maxwell test ([e]), paired t-test ([f]) or McNemar ([**]) test, with bold values highlighting statistical significance. 2-3m = Two to three months. 6m = Six months. ALT = Alanine aminotransferase. Alk Phos = Alkaline phosphatase. AST = Aspartate aminotransferase. GGT = Gamma-glutamyl transferase. eGFR = Estimated Glomerular Filtration Rate. CRP = C-reactive protein. NT-proBNP = N-terminal pro-brain natriuretic peptide.

months than other patients (60·8±6·6% vs 64·8±6·5%, *P*=0·049). None of the patients had a history of pre-existing cardiac failure.

Right ventricular (RV) volumes, mass and function did not differ between patients (at 2-3 months and 6 months) and controls (**Table 4**). In patients, indexed RV end-diastolic volume decreased (mean difference -4·3 mls/m^2, *P*=0·005) and function (RVEF) increased (mean difference +3·2%, *P*=0·0003) from 2-3 months to 6 months (**Figure 1**). At 6 months, RVEF tended to be lower in patients with severe illness (58·5±5·1% vs 62·1±6·9%, *P*=0·055).

Basal and mid-ventricular native T_1 (a biomarker sensitive to inflammation) values were higher in patients than controls (**Table 4**). By 6 months, myocardial native T_1 decreased and was no longer statistically different from control T_1 (**Table 4**; **Figure 1**). Native T_2 (a biomarker sensitive to oedema) was not significantly different between patients and controls at both time points.

Extracellular volume fraction (ECV, a biomarker sensitive to diffuse fibrosis) did not differ between patients and controls. In patients, slice-averaged ECV decreased (mean difference -1·13%, *P*=0·005) from 2-3 months to 6 months post-infection.

LGE (measured as % of myocardial volume, a biomarker of focal fibrosis) was slightly higher in patients than controls at 2-3 months (*P*=0·023). By 6 months, this did not differ from controls (*P*=0·62). There were six patients with LGE in a myocarditis pattern and one with evidence of a subendocardial infarction (elevated troponin during admission). None of the patients satisfied the updated Lake Louise criteria [18] for active myocarditis (increased native T_1/LGE and increased native T_2) at 6 months.

4.4. Lung imaging and functional assessment

At 2-3 months, 60% of patients had lung parenchymal abnormalities, becoming less extensive (**Table 4**) with time, but were still more common compared to controls at 6 months (*P*<0·0001). Forty percent

Table 3
Symptom prevalence, Fatigue Severity Score and MRC dyspnoea scale in patients at follow-up and controls.

	COVID-19, 2-3m	COVID-19, 6m	Controls	*P*-values		
				2-3m vs Controls	6m vs Controls	2-3m vs 6m
Symptoms at follow-up						
Stomach Pain	12/57 (21·1%)	12/46 (26·1%)	5/30 (16·7%)	0·78[a]	0·41[a]	1·00[b]
Back Pain	38/57 (66·7%)	24/46 (52·2%)	11/30 (36·7%)	**0·012[a]**	0·24[a]	0·33[b]
Pain in the arms, legs or joints	45/57 (78·9%)	27/46 (58·7%)	17/30 (56·7%)	**0·045[a]**	1·00[a]	0·077[b]
Feeling tired or too little energy	49/57 (86·0%)	28/46 (60·9%)	16/30 (53·3%)	**0·002[a]**	0·64[a]	**0·004[b]**
Trouble falling asleep or sleeping too much	42/57 (73·7%)	29/46 (63·0%)	16/30 (53·3%)	0·093[a]	0·48[a]	0·29[b]
Headaches	24/57 (42·1%)	16/46 (34·8%)	13/30 (43·3%)	1·00[a]	0·48[a]	0·63[b]
Constipation or diarrhoea	17/57 (29·8%)	12/46 (26·1%)	6/30 (20·0%)	0·44a	0·59a	1·00b
Chest pain	18/57 (31·6%)	8/46 (17·4%)	1/30 (3·3%)	**0·002[c]**	0·079[c]	0·11[b]
Dizziness	19/57 (33·3%)	13/46 (28·3%)	5/30 (16·7%)	0·13[a]	0·283[a]	1·00[b]
Syncope	5/57 (8·8%)	1/46 (2·2%)	1/30 (3·3%)	0·66[c]	1·00[c]	0·13[b]
Palpitations	23/57 (40·4%)	13/46 (28·3%)	6/30 (20·0%)	0·093[a]	0·59[a]	0·092[b]
Shortness of breath	45/57 (78·9%)	20/46 (43·5%)	3/30 (10·0%)	**<0·0001[c]**	**0·002[c]**	**<0·0001[b]**
Any of the above	56/57 (98·2%)	41/46 (89·1%)	26/30 (86·7%)	**0·031[c]**	0·73[c]	0·063[b]
Presence of cardiopulmonary symptoms	47/57 (82·5%)	24/46(52·2%)	10/30 (33·3%)	**<0·0001[c]**	0·16[c]	**0·0001[b]**
Fatigue Severity Scale[12]						
Median (IQR)	34·0 (18·0-49·0)	29·0 (14·0- 44·5)	17·0 (11·0-24·0)	**0·001[d]**	**0·035[d]**	**0·001[e]**
Mean FSS ≥4	30/55 (54·5%)	20/45 (44·4%)	5/29 (17·2%)	**0·001[c]**	**0·023[c]**	0·34[b]
Medical Research Council Dyspnoea Scale[11]						
MRC grade 2 - 5	36/56 (64·3%)	26/46 (56·5%)	3/29 (10·3%)	**<0·0001[c]**	**<0·0001[c]**	0·42[b]

Data are n/N (%), where N is the total number of participants with available data. *P*-values are from Chi-square ([a]), McNemar ([b]) test, Fisher's exact test ([c]), Mann-Whitney U test ([d]) or Wilcoxon Signed Ranks test ([e]), with bold values highlighting statistical significance. Cardiopulmonary symptoms defined as any of chest pain, dizziness, syncope, palpitations or shortness of breath. 2-3m = Two to three months. 6m = Six months. MRC = Medical research council. FSS = Fatigue severity scale.

of patients had lung parenchymal abnormalities involving more than half the lungs at 2-3 months. This reduced to 9% by 6 months.

At 2-3 months, patients had lower FEV_1 and FVC compared to controls but most values remained within the normal range (**Table 5**). At 6 months, FEV_1 was no longer different from controls (*P*=0·10), whereas FVC remained slightly lower (*P*=0·024). Reduced gas transfer (DL_{CO} <80% predicted) and reduced accessible lung volume (V_A) were seen in 24 patients (52%). Reduced transfer coefficient for carbon monoxide (K_{co}) was present in six patients (13%). Patients with parenchymal abnormalities had lower DLco compared to those without (77% vs 91%, *P*=0·009). DLco was not significantly different in patients with severe illness at admission versus non-severe patients (77·4% vs 84·5%, *P*=0·15).

4.5. Serial Cardiopulmonary Exercise Testing

As previously reported, patients had reduced peak oxygen consumption ($\dot{V}O_2$) at 2-3 months. By 6 months, this improved but was still reduced relative to controls (**Table 6**, **Figure 2**).

Maximal test criteria consisted of a respiratory exchange ratio ≥ 1·1 and plateau in oxygen uptake [19]. At 2-3 months, 49% of patients had submaximal tests (versus 15% of controls, *P*=0·003). By 6 months, this prevalence reduced to 26% (*P*=0·37 for comparison with controls).

In those with a maximal test, maximal $\dot{V}O_2$ was lower in patients at 2-3 months but was no longer so by 6 months (*P*=0·12 for comparison with controls).

The ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) slope, a marker of ventilatory efficiency, was abnormal in patients at 2-3 months and improved by 6 months (*P*=0·033). In spite of this, the $\dot{V}E/\dot{V}CO_2$ slope remained borderline abnormal (median 31·3 (IQR 28·6-34·5)) versus controls (median 28·2 (IQR 26·7-30·0, *P*=0·002)). Reduced ventilatory efficiency had little effect on exercise capacity, with respiratory limitation (defined as a breathing reserve of less than 20% at peak exertion) only occurring in 6% and 5% of patients at 2-3 and 6 months, respectively. This did not differ from controls (4%, *P*=1·0).

At 2-3 months, oxygen (O_2) pulse in maximal tests (a surrogate marker of exercise stroke volume, oxygen delivery and tissue oxygen extraction) was lower in patients versus controls and was accompanied by earlier attainment of the anaerobic threshold (AT). By 6 months, O_2 pulse improved and became comparable to controls (95% of predicted vs 103% of predicted, *P*=0·13). Despite improvement in the AT, occurring later during exercise, it remained different from controls (42% of predicted $\dot{V}O_2$max vs 47% of predicted $\dot{V}O_2$max, *P*=0·041, **Table 6**).

The 13 patients with reduced $\dot{V}O_2$peak, 6 months post-infection, had lower serum creatine kinase levels (75 IU/L [47·5 – 133] vs 133 IU/L [70-210], *P*=0·039) and a shallower $\dot{V}O_2$/Work rate (WR) relationship (10·8 mls/min/watt [9·9 - 11·6] vs 11·6 mls/min/watt [11·0 – 12·4], *P*=0·035) compared to patients with normal oxygen consumption. Seven terminated exercise in the absence of any cardiorespiratory limitation (submaximal tests) due to fatigue, breathlessness and lower back/lower limb pain. Of the six patients with impaired exercise tolerance and a maximal test, despite reduced oxygen pulse seen in five patients and four having an early AT, none had significant anaemia, cardiac impairment on MRI, elevated NT-proBNP or reduced breathing reserve at peak exercise.

Heart rate recovery (HRR) in the first minute following exercise cessation was slower in patients compared to controls (16·6 vs 21·9 beats, *P*=0·018). By 6 months, HRR improved significantly (22·2 beats, *P*=0·001), and became comparable to controls (*P*=0·67). The severity of illness during admission was not associated with a reduction in peak or maximal oxygen consumption at 2-3 months and 6 months (*P*>0·20 for all comparisons).

4.6. Relationship between symptoms and cardiopulmonary health

At 6 months from infection, bivariate analysis and multivariate modelling showed that neither CMR (including diastolic strain rate) nor pulmonary function parameters, NT-proBNP, ECG abnormalities or CPET measures associated with cardiopulmonary symptoms (**Figure 3**) or breathlessness (**Supplementary Material, p11**). Longitudinal improvement in CMR and CPET parameters did not associate with improvement in cardiopulmonary symptoms from 2-3 months to 6 months (*P*>0·05). There was no correlation between the extent of lung abnormalities on MRI, lung function parameters (FEV_1, FVC, FEV_1/FVC, DLco) and breathlessness scores (**Supplementary Material, p8**). The dissociation between physiological measurements and symptoms were further highlighted by the fact that of the twenty

Table 4
Cardiopulmonary MRI parameters in patients and controls.

	COVID-19, 2-3m	COVID-19, 6m	Controls	*P*-values		
				2-3m vs Controls	6m vs Controls	2-3m vs 6m
Lung MRI						
Lung parenchymal abnormalities, %	32/53 (60·4%)	30/44 (68·2%)	3/28 (10·7%)	**<0·0001**[a]	**<0·0001**[a]	0·344[b]
0%	21/53 (39·6%)	14/44 (31·8%)	25/28 (89·3%)	**0·0003**[c]	**<0·0001**[c]	0·005[d]
1-25%	3/53 (5·7%)	21/44 (47·7%)	0/28 (0·0%)			
26 - 50%	8/53 (15·1%)	5/44 (11·4%)	2/28(7·1%)			
51 - 75%	9/53 (17·0%)	4/44 (9·1%)	0/28 (0·0%)			
>75%	12/53 (22·6%)	0/44 (0·0%)	1/28 (3·6%)			
Cardiac MRI						
Left ventricular cine analysis						
End-diastolic volume, mls	143·8 (127·3 - 165·9)	151·1 (125·0 - 183·4)	153·3 (124·5 - 178·5)	0·59[e]	0·78	0·21[f]
End-diastolic volume (indexed), mls/m^2	73·3 (64·5 - 83·5)	76·7 (66·4 - 86·6)	75·6 (63·4 - 87·5)	0·51[e]	0·90	0·59[f]
End-systolic volume, mls	53·1 (41·5 - 71·7)	54·6 (44·3 - 71·0)	53·1 (47·7 - 70·3)	0·81[e]	0·90[e]	0·31[f]
Mass (diastole), g	116·1 (100·1 - 135·1)	119·5 (98·8 - 134·0)	107·3 (84·3 - 138·3)	0·39[e]	0·25	0·25[f]
Mass (indexed), g/m^2	58·9 (49·8 - 66·2)	57·0 (50·2 - 65·2)	53·8 (48·6 - 63·6)	0·21[e]	0·37[e]	0·15[f]
Stroke volume, mls	89·6 (79·5 - 104·7)	94·2 (80·5 - 109·1)	95·0 (78·4 - 116·5)	0·59[e]	1·00	0·058[g]
Ejection fraction, %	63·0 (7·7)	62·7 (6·8)	63·6 (6·32)	0·70	0·58	0·27[g]
Left Ventricular Diastolic Strain Analysis						
Global Longitudinal Strain Rate	0·83 (0·21)	0·81 (0·16)	0·78 (0·15)	0·30	0·53	0·24[aa]
Right ventricular cine analysis						
End-diastolic volume, mls	164·4 (36·6)	160·1 (40·4)	169·3 (46·5)	0·61	0·38	**0·023**[g]
End-diastolic volume (indexed), mls/m^2	81·8 (14·0)	78·8 (15·8)	84·3 (18·5)	0·51	0·18	**0·005**[g]
End-systolic volume, mls	70·4 (23·6)	65·1 (23·0)	72·7 (24·2)	0·69	0·19	**0·0001**[g]
Mass, g	28·8 (25·8 - 35·5)	32·6 (28·8 - 39·8)	33·2 (23·7 - 41·8)	0·26[e]	0·88[e]	0·13[f]
Mass (indexed), g/m^2	14·4 (12·6 - 17·2)	16·4 (14·4 - 19·1)	16·7 (13·9 - 19·3)	0·19[e]	0·90[e]	0·31[f]
Stroke volume, mls	94·0 (19·3)	95·1 (20·9)	96·6 (25·6)	0·61	0·78	0·68[g]
Ejection fraction, %	57·9 (7·8)	60·2 (6·2)	57·6 (6·0)	0·85	0·085	**0·0003**
T_1 and T_2 map analysis						
Native T_1 (basal myocardium), ms	1179·7 (34·4)	1152·6 (37·3)	1149·3 (24)	**0·0001**	0·65	**<0·0001**[g]
>1197 ms (>2SD from control mean)	13/50 (26·0%)	4/44 (9·1%)	1/28 (3·6%)	**0·015**[a]	0·64[a]	0·065[b]
Native T_1 (mid myocardium), ms	1173·1 (33·6)	1145·6 (41·2)	1150·2 (32·4)	**0·004**	0·62	**<0·0001**[g]
>1215 ms (>2SD from control mean)	4/51 (7·8%)	1/43 (2·3%)	0/28 (0%)	0·29[a]	1·00[a]	0·38[b]
Native T_1 (apical myocardium), ms	1177·4 (44·7)	1153·8 (45·5)	1168·3 (53·2)	0·42	0·22	**0·001**[g]
>1275 ms (>2SD from control mean)	1/50 (2·0%)	1/43 (2·3%)	1/28 (3·6%)	1·00[a]	1·00[a]	1·00[b]
ECV (basal myocardium), %	30·4 (28·3 - 31·3)	27·4 (25·9 - 30·0)	28·3 (26·8 - 31·5)	0·12	0·19[e]	**0·001**[f]
>34.52% (>2SD from control mean)	1/35 (2·9%)	2/36 (5·6%)	0/21 (0·0%)	1·00[a]	0·53[a]	1·00[b]
ECV (mid myocardium), %	30·1 (27·2 - 31·4)	27·8 (26·1 - 30·8)	29·4 (27·1 - 30·7)	0·41[e]	0·35	**0·030**[f]
>35.87% (>2SD from control mean)	0/37 (0·0%)	0/42 (0·0%)	1/23 (4·3%)	0·38[a]	0·35[a]	
ECV (apical myocardium), %	28·7 (27·0 - 31·6)	28·8 (27·0 - 30·5)	29·7 (27·2 - 31·5)	0·51[e]	0·24[e]	0·32[g]
>37.87% (>2SD from control mean)	1/40 (2·5%)	0/36 (0·0%)	1/23 (4·3%)	1·00[a]	0·39[a]	1·00[b]
T_2 (basal myocardium), ms	41·7 (2·2)	41·4 (2·1)	41·6 (2·2)	0·80	0·80	0·71[g]
>46 ms (>2SD from control mean)	3/50 (6·0%)	1/43 (2·3%)	1/28 (3·6%)	1·00[a]	1·00[a]	1·00[b]
T_2 (mid myocardium), ms	41·8 (2·2)	41·4 (1·8)	41·1 (2·3)	0·21	0·53	0·50[g]
>46 ms (>2SD from control mean)	1/50 (2·0%)	1/42 (2·4%)	1/28 (3·6%)	1·00[a]	1·00[a]	1·00[b]
T_2 (apical myocardium), ms	43·5 (3·0)	42·9 (2·4)	43·7 (3·5)	0·81[e]	0·33	0·51[f]
>51ms (>2SD from control mean)	1/50 (2·0%)	0/43 (0·0%)	1/28 (3·6%)	1·00[a]	0·39[a]	1·00[b]
Late gadolinium enhancement analysis						
% LGE volume enhancement	0·8 (0·5 - 1·9)	0·7 (0·1 - 2·2)	0·6 (0·3 - 1)	**0·023**[e]	0·62[e]	0·91[f]
Myocarditis pattern	6/52 (11·5%)	5/43 (11·6%)	2/28 (7·1%)			
Myocardial infarction	1/52 (1·9%)	0/43 (0·0%)	0/28 (0·0%)			
LV/RV insertion point	7/52 (13·5%)	5/43 (11·6%)	1/28 (3·6%)			
Mixed	0/52 (0·0%)	0/43 (0·0%)	0/28 (0·0%)			
Other	0/52 (0·0%)	0/43 (0·0%)	0/28 (0·0%)			
Pericardial effusion >10mm	1/52 (1·9%)	0/43 (0·0%)	0/52 (0·0%)			

Data are median (IQR) for non-parametric data and mean (SD) for parametric data, and n/N (%), where N is the total number of participants with available data. *P*-values are from independent t-test, Fisher's exact test ([a]), McNemar ([b]) test, Fisher-Freeman-Halton exact test ([c]), Stuart-Maxwell test ([d]), Mann-Whitney U test ([e]), Wilcoxon Signed Ranks test ([f]), or paired t-test ([aa]), with bold values highlighting statistical significance. 2-3m = Two to three months. 6m = Six months. MRI = Magnetic resonance imaging. ECV = Extracellular volume. LGE = Late gadolinium enhancement.

patients who did not report significant breathlessness (MRC grade <2) at 6 months, 55% had abnormal gas transfer (DLco <80% predicted).

5. Discussion

The main findings from our study are as follows: First, serial measures of cardiopulmonary health on CMR in moderate to severe COVID-19 improve over time. Second, exercise tolerance in patients improves at 6 months post-infection but remains abnormal in some when compared to controls, potentially due to symptomatic limitation and muscular fatigue. Third, by 6 months, more than half the patients remain symptomatic, and neither CMR nor pulmonary function or CPET measures associate with persistent symptom burden.

Since the start of the pandemic, several studies have harnessed the power of CMR to better understand the mechanisms underlying myocardial injury associated with COVID-19 [6,20]. Prevalence estimates of injury have varied due to differences in cohort characteristics and methodologies used. In the largest CMR follow-up study of patients with elevated troponin, Kotecha and colleagues observed that up to 49% of patients have evidence of either myocarditis or myocardial ischemia/infarction [20]. In contrast, similar-sized studies of younger athletes [21] and older individuals [6] with milder infections (predominantly non-hospitalised) have reported variable

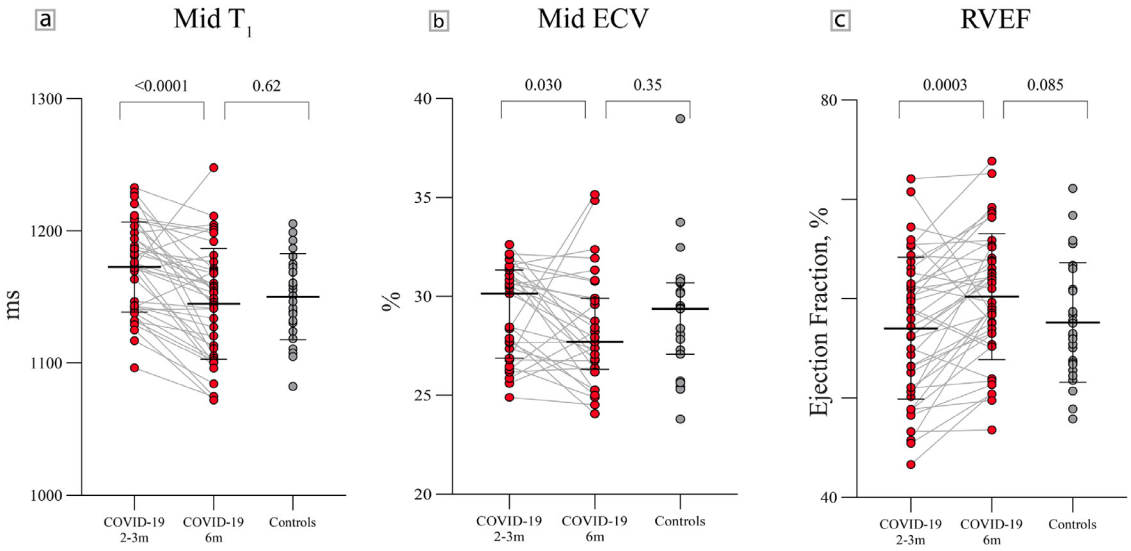

Figure 1. Serial CMR findings in previously hospitalised COVID-19 patients and controls. A: Mid ventricular native T_1 (mean + SD) in patients at 2-3 months was higher than controls, and normalized by 6 months. B: Mid ventricular extracellular volume fraction (ECV, median + IQR) in patients at 2-3 months was comparable to controls, but decreased in patients by 6 months. C: Right ventricular ejection fraction (mean + SD) in patients at 2-3 months was comparable to controls, and increased by 6 months. *P*-values are for group differences (COVID-19 2-3 months vs COVID-19 6 months and COVID-19 6 months vs controls).

estimates of myocardial injury (ranging from 1·5% to 70%). The present study is unique to others in the literature, as we prospectively recruited hospitalised COVID-19 patients and risk factor matched controls (who served as our reference) and longitudinally evaluated changes in CMR myocardial tissue characteristics in patients. Here, we show that whilst there were some patients with abnormal myocardial native T_1 (a marker of oedema and inflammation) at 2-3 months, native T_1 normalized in the majority by 6 months and was accompanied by a decrease in extracellular volume. These findings highlight two important points. The first is that early tissue abnormalities on CMR are likely due to dynamic alterations in the extracellular environment (hyperaemia [22] or changes in extracellular proteins/matrix) influenced by circulating cytokines and importantly, not explained by comorbidities alone. This is in line with recent studies that have also demonstrated temporal improvement in inflammatory cytokines (IL-1, IL-2, IL-6, IL-18, TNF, IFNL1) in COVID-19 patients on serial assessments [23,24]. The second is that cardiac health is restored in the majority of patients by 6 months. Only two patients had borderline low LV function, RV parameters were normal, and there were no cases of active myocarditis (as per

Table 5
Spirometry and gas transfer testing results in patients at follow-up and controls.

	COVID-19, 2-3m	COVID-19, 6m	Controls	*P*-values		
				2-3m vs Controls	6m vs Controls	2-3m vs 6m
Spirometry						
FVC, % predicted	108·3 (22·8)	119·2 (22·0)	131·4 (21·8)	**<0·0001**	**0·024**	**<0·0001**[a]
<80%	7/56 (12·5%)	0/46 (0·0%)	0/28 (0·0%)	0·090[b]	..	**0·016**[c]
FEV_1, % predicted	101·4 (19·7)	110·7 (18·6)	118·7 (22·1)	**0·0004**	0·10	**<0·0001**[a]
<80%	6/56 (10·7%)	1/46 (2·2%)	1/28 (3·6%)	0·42[b]	1·00[b]	0·063[c]
FEV_1/FVC	0·77 (0·73 - 0·80)	0·76 (0·73 - 0·80)	0·75 (0·70 - 0·78)	**0·027**[d]	0·24	0·051[a]
Peak expiratory flow, % predicted	105·7 (27·7)	108·8 (21·7)	114·5 (24·7)	0·16	0·31	0·74[a]
Gas Transfer						
DL_{CO}, % of predicted	..	80·9 (16·9)	..	..	..	..
<80%	..	24/46 (52·2%)	..	..	..	..
K_{CO}, % of predicted	..	101·8 (18·2)	..	..	..	..
<80%	..	6/46 (13·0%)	..	..	..	..
V_a, % of predicted	..	79·9 (14·7)	..	..	..	..
<80%	..	24/46 (52·2%)	..	..	..	..

Data are median (IQR) for non-parametric data, mean (SD) for parametric data, and n/N (%), where N is the total number of participants with available data. *P*-values from independent t-test, paired t-test ([a]), Fisher's exact test ([b]), McNemar test ([c]) or Mann-Whitney U test ([d]), with bold values highlighting statistical significance. 2-3m = Two to three months. 6m = Six months. FVC = Forced vital capacity. FEV_1 = Forced expiratory volume in 1 second. DL_{CO} = Diffusion capacity for carbon monoxide. K_{CO} = Transfer coefficient for carbon monoxide. Va = Alveolar volume.

Table 6
CPET parameters in patients at follow-up and controls.

	COVID-19, 2-3m	COVID-19, 6m	Controls	*P*-values		
				2-3m vs Controls	6m vs Controls	2-3m vs 6m
Cardiopulmonary exercise testing						
Maximal tests performed	26/51 (51·0%)	31/42 (73·8%)	23/27 (85·2%)	**0·003**[a]	0·37[a]	0·057[b]
SpO_2 at peak exercise, %	95·0 (93·8 - 97·0)	96·0 (95·0 - 97·0)	96·0 (95·0 - 98·0)	**0·003**[c]	0·10[c]	**0·002**[d]
<94%	12/51 (23·5%)	3/41 (7·3%)	1/27 (3·7%)	**0·028**[a]	1·00[a]	**0·016**[b]
$\dot{V}O_2$peak (all tests), mls/kg/min	18·0 (14·4 – 21·9)	20·5 (17·5 - 26·1)	28·1 (22·1 – 34·0)	**<0·001**[c]	**0·001**	**0·001**[d]
$\dot{V}O_2$max (maximal tests), mls/kg/min	21·1 (16·1 – 27·9)	22·7 (19·4 - 27·1)	28·1 (22·1 – 34·5)	**0·012**[c]	**0·044**[c]	**0·006**[d]
Anaerobic threshold, mls/kg/min	9·7 (8·3 - 10·7)	10·4 (9·0 - 12·2)	11·9 (9·3 - 13·9)	**0·001**[c]	**0·023**[c]	**0·018**[d]
$\dot{V}O_2$peak (all tests), % of predicted $\dot{V}O_2$max	80·5 (23·1)	93·3 (29·3)	112·7 (27·0)	**<0·0001**	**0·007**	**0·0001**[e]
< 80%	28/51 (54·9%)	13/42 (31·0%)	2/27(7·4%)	**<0·0001**[a]	**0·034**[a]	**0·012**[b]
$\dot{V}O_2$max (maximal tests), % of predicted	95·5 (19·9)	100·7 (27·1)	112·3 (27·0)	**0·016**	0·12	**0·003**[e]
<80%	5/26 (19·2%)	6/31 (19·4%)	1/23 (4·3%)	0·13[a]	0·22[a]	0·63[b]
Anaerobic threshold (% of predicted $\dot{V}O_2$max)	40·7 (36·2 - 47·5)	42·0 (39·0 - 51·6)	46·8 (43·3 - 51·3)	**0·0005**[c]	**0·041**[c]	**0·030**[d]
<40% of predicted $\dot{V}O_2$max	20/48 (41·7%)	14/40 (35·0%)	0/27 (0·0%)	**<0·0001**[a]	**0·0004**[a]	0·55
O_2pulse, % of predicted max	81·8 (18·2)	90·2 (28·3)	102·8 (20·8)	**<0·0001**	**0·020**[c]	**0·003**[d]
O_2pulse (maximal tests), % of predicted max	91·4 (18·3)	95·2 (2 6·5)	103·3 (20·9)	**0·039**	0·13[c]	**0·011**[e]
Breathing reserve, % of predicted $\dot{V}E$max	44·8 (15·3)	42·4 (15·5)	40·7 (11·0)	0·22	0·62	0·71[e]
<20%	3/51 (5·9%)	2/42 (4·8%)	1/27 (3·7%)	1·00[a]	1·00[a]	1·00[b]
Breathing reserve (maximal tests), % of predicted $\dot{V}E$max	34·9 (12·1)	38·1 (12·6)	38·9 (9·9)	0·21	0·80	0·79[e]
HR recovery slope (maximal tests), bpm	16·6 (7·1)	22·2 (11·1)	21·9 (7·5)	**0·018**	0·67[c]	**0·001**[d]
$\dot{V}E/\dot{V}CO_2$ Slope	33·4 (29·2 - 40·3)	31·3 (28·6 - 34·5)	28·2 (26·7 - 30·0)	**<0·0001**[c]	**0·002**[c]	**0·033**[d]
Oxygen Uptake Efficiency Slope	1·9 (1·6 - 2·4)	2·1 (1·7 - 2·8)	2·7 (2·0 - 3·2)	**0·001**[c]	0·065[c]	0·11[d]

Data are median (IQR) for non-parametric data, mean (SD) for parametric data, and n/N (%), where N is the total number of participants with available data. *P*-values are from independent t-test, Fisher's exact test ([a]), McNemar ([b]) test, Mann-Whitney U test ([c]), Wilcoxon Signed Ranks test ([d]) or paired t-test ([e]), with bold values highlighting statistical significance. 2-3m = Two to three months. 6m = Six months. $\dot{V}O_2$ = oxygen consumption. $\dot{V}E/\dot{V}CO_2$ = Ventilatory equivalent for carbon dioxide.

the updated Lake Louise criteria [18]). These findings are in keeping with the low prevalence (7%) of cardiac dysfunction (defined by levels of NT-proBNP) reported by a large UK-wide prospective follow-up study of post-hospitalised COVID-19 patients by Evans and colleagues [25].

A number of studies have also described diastolic dysfunction following COVID-19, both during admission and at follow-up [26-28]. However, patients with pre-existing cardiac conditions were included in these studies which makes it difficult to ascertain if diastolic dysfunction was specific to COVID-19 or an indicator of co-

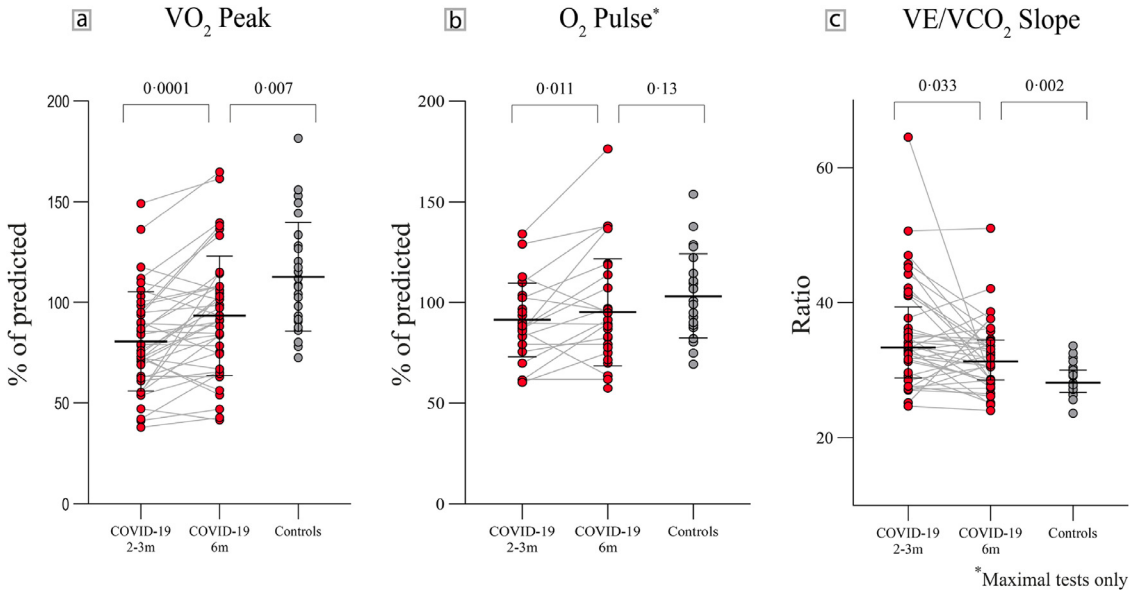

Figure 2. Serial CPET assessments in previously hospitalised COVID-19 patients and controls. A: Peak oxygen consumption ($\dot{V}O_2$ peak, mean + SD) in patients improved from 2-3 months to 6 months, but remained lower than controls. B: Peak oxygen pulse (O_2 pulse, mean + SD) in patients with maximal tests at 2-3 months was lower compared to controls. By 6 months, this improved and became comparable to controls. C: The ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$, median + IQR) slope in patients improved from 2-3 months to 6 months, but remained high versus controls. *P*-values are for group differences (COVID-19 2-3 months vs COVID-19 6 months and COVID-19 6 months vs controls).

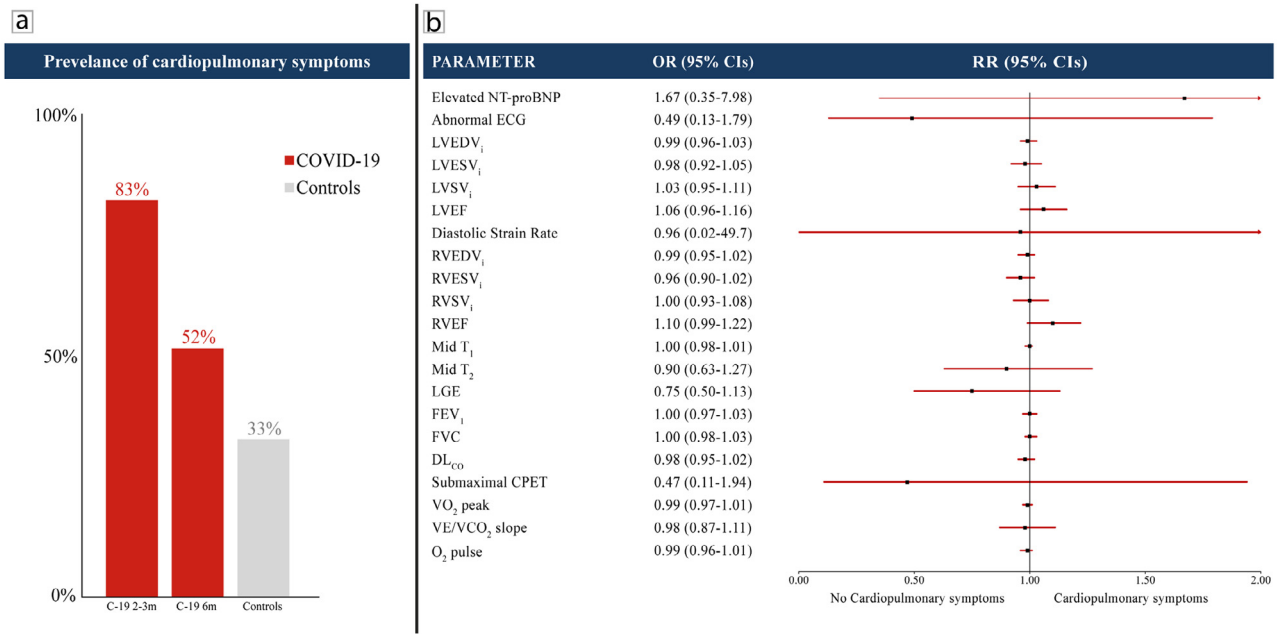

Figure 3. Prevalence and determinants of cardiopulmonary symptoms (chest pain, palpitations, syncope, dyspnoea, or dizziness) among previously hospitalised COVID-19 patients. A: At 2-3 months, 83% of patients experienced at least one cardiopulmonary symptom. By 6 months, this improved to 52% and was comparable to controls. B: Forest plot depicts the odds ratio and 95% confidence intervals of having any cardiopulmonary symptom at 6 months given the changes on ECG, CMR, PFT, and CPET measures. An abnormal ECG was defined as rhythm abnormalities and/or the presence of bundle branch block, ST-segment elevation/depression or T wave inversion. Elevated NT-proBNP was defined as ≥125 ng/L. (OR - Odds ratio. CI - Confidence interval. ECG – Electrocardiogram. NT-proBNP - N-terminal pro b-type natriuretic peptide. LVEDVi - Left ventricular end-diastolic volume (indexed), mls/m^2. LVESVi - Left ventricular end-systolic volume (indexed). LVSVi - Left ventricular stroke volume (indexed), mls/m^2. RVEDVi - Right ventricular end-diastolic volume (indexed), mls/m^2. RVESVi - Right ventricular end-systolic volume (indexed), mls/m^2. RVSVi - Right ventricular stroke volume (indexed), mls/m^2. LGE - Late gadolinium enhancement, %. FEV$_1$ – Forced expiratory volume in 1 second, % of predicted. FVC – Forced vital capacity, % of predicted. DL$_{co}$ - Diffusing capacity for carbon monoxide, % of predicted. pVO$_2$ - Peak oxygen consumption, % of predicted. VE/VCO$_2$ - Ventilatory equivalent for carbon dioxide. O$_2$ pulse - Oxygen pulse, % of predicted.)

morbid status. In our study, only patients with mild co-morbidities were included and compared to an age, sex and risk-factor matched control group, and we did not see a significant difference in diastolic strain rate.

Six months following symptom onset, impaired gas transfer (as measured by DL$_{CO}$) was the predominant abnormality seen on lung function testing. A high burden of gas transfer impairment accompanied by improvements on spirometry have been documented by others [5,29] and may be potentially secondary to abnormalities in pulmonary vascular homeostasis (dysfunctional pulmonary vasoconstriction [30] or thrombosis [31]) and persistent injury to the alveolar-capillary barrier [32]. Further studies are required to investigate whether such abnormalities will persist, together with their long-term impact on symptom burden in patients.

Exercise intolerance is common among patients recovering from coronavirus infections (SARS, MERS, and COVID-19) [7,8,33,34]. We had previously shown that at 2-3 months [8], CPET revealed a number of abnormalities in patients. By 6 months, many of these parameters improved, though a proportion of patients (31%) still had a reduction in peak oxygen consumption. Of importance, the majority of these patients with limited exercise tolerance on CPET terminated exercise due to fatigue, breathlessness and musculoskeletal symptoms in the absence of physiological limitation. Of the six patients in our study with impaired exercise capacity despite maximal effort, no limitations in cardiorespiratory function or oxygen-carrying capacity were seen. These findings, together with the lower levels of serum creatine kinase and stunted $\dot{V}O_2$-WR relationship observed in patients with impaired exercise capacity, suggest that reduced muscle mass and alterations in skeletal muscle metabolism are likely contributors to exercise limitation [35,36]. This is in line with other studies that have attributed exercise limitation to muscular deconditioning [7,37,38]. Early AT and reduced oxygen pulse despite the absence of cardiorespiratory abnormalities were commonly reported in these studies in support of this hypothesis. Taken together, these findings highlight the role of dedicated rehabilitation in augmenting recovery.

Postural orthostatic tachycardia and other manifestations of dysautonomia have frequently been described among patients post-COVID-19 [39,40]. Here, we showed that at 2-3 months, heart rate recovery on CPET, an indirect measure of autonomic health, was impaired in patients compared to controls [41]. By six months, heart rate recovery improved, implying that dysautonomia may be transient and does spontaneously recover in some patients.

As the COVID-19 pandemic has progressed, our understanding of the long-term effects of SARS-CoV-2 infection has evolved [42-44]. Multiple studies [5,25] have demonstrated that some patients recovering from COVID-19 experience a diverse range of persistent symptoms months beyond infection, commonly referred to as “long haul COVID” or “post-COVID-19 syndrome” [44,45]. In the present study, 1 in 2 patients reported persistent cardiopulmonary symptoms (chest pain, palpitations, syncope, dyspnoea, or dizziness) at 6 months, despite an improvement in symptoms from 3 months. Neither CMR nor CPET or pulmonary function measures were associated with enduring symptoms. These findings highlight the reduced yield of standard clinical investigations in elucidating a cause for persistent symptoms and the need to explore other mechanisms (sarcopenia, muscle weakness, neurohormonal factors, autoantibodies, nociceptive alterations, mast cell activation syndrome) that may be relevant [46-50]. Another important finding from this study is that more than half the patients who were asymptomatic had impaired DLco at 6 months, implying that physiological recovery may not be reliably captured by subjective measures of cardiopulmonary health (e.g. symptom questionnaires). Further efforts are needed to better understand the determinants of impaired DLco and persistent parenchymal abnormalities associated with COVID-19, as we seek to develop effective treatments that could potentially reverse the long-term sequelae of COVID-19.

The small sample size, lack of generalizability and the potential for residual confounders are some limitations of this study. However, to our knowledge, this is the first study to comprehensively (cardiopulmonary imaging, static physiology, whole-body exercise testing, patient health questionnaires) evaluate the longitudinal trajectory of cardiopulmonary abnormalities on CMR and CPET in patients at 3 and 6 months post-infection. From a diagnostic perspective, our study provides important insights into the lack of association between symptoms and results from standard clinical investigations. The longitudinal design and incorporation of a risk-factor matched control group clarified the relevance of some early abnormalities.

Patients were enrolled from the first wave only, at a time where the evidence in support of steroid use was limited. While this could, in theory, affect prevalence estimates of symptoms, a recent large follow-up study of hospitalised patients did not see an association between steroid use and ongoing symptom burden [25]. Ethno-racial differences between enrolled controls and patients were also present. However, even after relevant adjustments (**Supplementary Material, p8**), previously observed associations and differences in multiple parameters remained. Another important limitation was the lack of arterial blood gas sampling or echocardiography during CPET, which did not permit assessment of tissue oxygen extraction, cardiac output during exercise and pulmonary dead space. The use of patient health questionnaires may have introduced self-reporting bias. Finally, not all the patients came back for follow-up assessments (due to work commitments or having moved abroad; see supplement for details). While this could have inflated prevalence estimates of symptom burden in this study, it would not be expected to affect the relationship between symptoms and objective measures of cardiopulmonary health.

Our study provides novel insights into the trajectory of cardiopulmonary symptoms and abnormalities on serial CMR, spirometry and CPET in patients. At 6 months, cardiac abnormalities on CMR improved in the majority of patients and were not different to matched controls. Parenchymal abnormalities, lung function impairment and CPET improved but were still abnormal relative to controls. Nearly half the patients continue to experience symptoms at 6 months. There was a surprising dissociation between persistent cardiopulmonary symptoms and CMR/CPET parameters, underscoring the need to examine alternative mechanisms for symptom persistence in patients.

Author Contributions

SN and BR contributed to the conception of this study. MC, EMT, AJL, MM, NPT, DH, SN and BR contributed to its design. MC, MM, AHAS and BR contributed to data acquisition. MC, EMT, CX and BR contributed to the analysis of data. MC, EMT, NP, AJL, RAE, CEB, LH, SKP, NPT, DH, VMF, SN and BR contributed to interpretation of data. All authors contributed to drafting the article, and had full access to all the data in the study and accept responsibility to submit for publication.

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The views expressed are those of the authors and not necessarily those of the National Health Service, NIHR, or the United Kingdom Department of Health.

Declaration of Competing Interest

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Data sharing statement

The data underlying this article will be shared on reasonable request to the corresponding author, subject to institutional and ethical committee approvals.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101159.

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