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Myocardial fibrosis occurs in non-hospitalised patients with chronic symptoms after COVID-19

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1. Introduction

Persistent symptoms have been observed in patients recovering from SARS-CoV-2 infection [1–3], post-acute sequelae of COVID-19 (PASC) [2]. Acute COVID-19 infection is associated with multi-organ sequalae, including pulmonary and cardiac, at short to medium term follow-up especially in those with severe illness [4–6]. We conducted an observational study to evaluate the prevalence and extent of residual myocardial injury in a group of patients recovering from mild COVID-19, managed in the community, with persistent symptoms post infection, to help determine if PASC may relate to cardiac and pulmonary fibrosis in mild disease.

Twenty patients with positive real time polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), who were treated in the community for initial infection, with persistent symptoms at >4 months after COVID-19 infection were evaluated with comprehensive cardiac and pulmonary investigations. Informed consent was obtained for all participants and the study conducted in accordance with the Declaration of Helsinki.

CMR imaging was performed on a 3.0-Tesla scanner (Achieva, Philips Medical Systems, Best, the Netherlands) using institutional standardised imaging protocols. Myocardial T1 and T2 mapping were acquired over a single midventricular short-axis slice using a validated variant of a modified Look-Locker imaging sequence. T2-maps were acquired with a respiratory-navigated black-blood, turbo-spin-echo sequence on a midventricular short-axis slice, sampled at different echo-times to reconstruct a T2-map. Late gadolinium enhancement (LGE) images were acquired with administration of 0.1 mmol/kg of body weight of gadobutrol (Gadovist; Bayer) using a phase-sensitive inversion recovery sequence (PSIR).

CMR images were evaluated using cvi42, v5.2 (Circle Cardiovascular Imaging, Calgary, Canada). The presence or absence of LGE was determined visually and quantified as proportion of total myocardium, with an LGE region being captured if SI > 2 SD's above the mean SI of the remote reference myocardium.

Complete lung function testing and arterial blood gas analysis was performed at 12–16 weeks' follow-up. All participants were evaluated with non-contrast computed tomography (CT) of the chest and pathology for high-sensitivity troponin-I (hsTrI), C-reactive protein (CRP) and inflammatory cytokines at 8 months after COVID-19 infection.

In our cohort of recovering patients, managed in the community for initial COVID-19 infection and complaining of persistent symptoms, there is a larger than expected burden of myocardial injury demonstrated by presence of scar on LGE imaging by 12 months.

The median (IQR) duration between positive RT-PCR for SARS-CoV-2 and CMR examination was 328 (288–348) days. On CMR, the major findings were an absence of abnormal native T1 or T2 relative to sequence and institution specific cut-offs and presence of LGE in six

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Table 1
Patient characteristics, pathology, cardiac MRI and lung function test findings.

	Group (n = 20)	LGE present (n = 6)	LGE absent (n = 14)	*P* value
Patient Characteristics				
Age, y	55 (40–61)	61 (49–72)	50 (40–59)	0.30
Male	8 (40)	3 (50)	5 (36)	0.64
BMI, kg/m^2	26 (24–28)	27 (26–30)	26 (24–27)	0.27
Hypertension	3 (15)	3 (50)	0 (0)	**0.01**
Diabetes	4 (20)	2 (33)	2 (10)	0.20
Dyslipidemia	8 (40)	4 (66)	4 (29)	0.16
Smoking	6 (30)	3 (50)	3 (21)	0.30
COPD/Asthma	2 (10)	1 (17)	1 (7)	0.13
Pathology				
hsTrI, ng/mL	3 (2–4)	4.5 (2.5–6.5)	2.5 (2–4)	0.14
CRP, mg/mL	1 (0.5–2)	1.8 (1.2–2)	0.8 (0.5–2.3)	0.32
Cardiac MRI Findings				
Days post infection	328 (252–348)	308 (252–332)	329 (305–357)	0.27
LVEF, %	64 (61–68)	63 (58–64)	63 (61–68)	0.45
LVEDV, mL/m^2	133 (117–168)	155 (136–169)	131 (116–168)	0.33
RVEF, %	58 (56–69)	56 (51–61)	56 (53–58)	0.90
Native T1, ms	1192 (1168–1204)	1203 (1191–1240)	1175 (1155–1200)	0.06
Abnormal native T1	1 (5)	1 (17)	0 (0)	0.30
Native T2, ms	39 (37–41)	40 (38–43)	38 (37–39)	0.36
Abnormal native T2	1 (5)	1 (17)	0 (0)	0.30
LGE				
No. %	6 (30)			
Mass (g)	6.0 (5.2–14.3)			
LGE: normal myocardium, %	17 (12–25)			
Lung Function Results				
DLCO, % predicted	86 (80–95)	77 (75–85)	89 (83–99)	0.04
Abnormal	1 (5)	1 (17)	0 (0)	0.3
TLC, % predicted	97 (92–103)	90 (87–97)	99 (95–106)	0.9
Abnormal	1 (5)	1 (17)	0 (0)	0.3
Capillary PO_2, mmHg	81 (75–92)	81 (72–83)	81 (75–93)	0.82
Pulmonary Fibrosis on CT, %	2 (10)	2 (33)	0 (0)	0.18

BMI – body mass index, *CAD* – Coronary artery disease, *COPD* – Chronic obstructive pulmonary disease, *CRP* – C-reactive protein, *CT* – Computed tomography, hsTrI – high sensitivity troponin-I, *LGE* – Late gadolinium enhancement, *LVEDV* – left ventricular end diastolic volume, *LVEF* – left ventricular ejection fraction, PO_2 – partial pressure of oxygen, *RVEF* – right ventricular ejection fraction.
Continuous data expressed as median (IQR), categorical data expressed as No. (%)
P-value using Mann-Whitney *U* test for continuous variables and Fisher exact test for categorical variables.
$P < 0.05$ considered statistically significant.

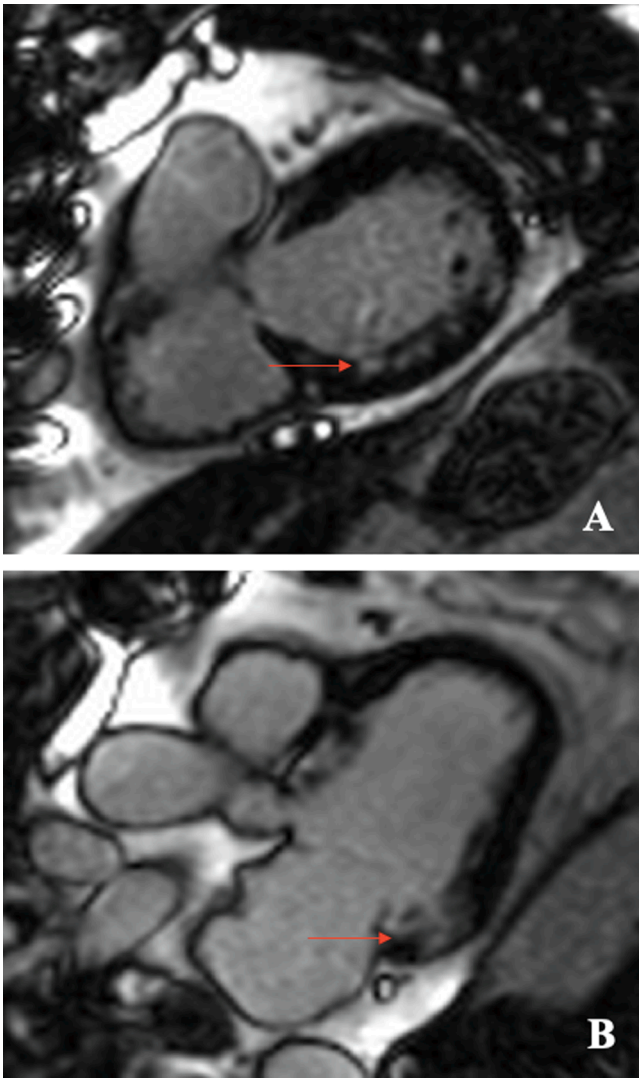

Fig. 1. (A) Representative short-axis CMR image showing mid-wall inferolateral late gadolinium enhancement (arrow). (B) Representative long-axis CMR image showing mid-wall basal septal and lateral wall late gadolinium enhancement (arrow).

patients (30%), suggesting an absence of myocardial oedema and presence of myocardial scar respectively. Descriptive CMR results are summarised in Table 1 and example CMR images are shown in Fig. 1. A typical mid-wall pattern of LGE involving the basolateral and inferolateral segments was found in five patients, with one patient displaying scattered hazy LGE.

The incidence of myocardial fibrosis in our series of patients is comparable to studies by Huang et al. (2020) (31% of patients), and Puntmann et al. (2020) (32% of patients) with a similar distribution of injury [4,5]. All patients in the study by Huang et al. (2020) reported cardiac symptoms at follow-up and all had been hospitalised with COVID-19 infection. In the study by Puntmann et al (2020), one third of patients required hospitalisation, and 19% required ventilatory support.

Of interest, only one patient had evidence of ongoing myocardial oedema on T2 weighted imaging in these studies at median 328 days follow-up, compared to up to 60% of patients in previous studies [4,5], suggesting myocardial oedema resolves in most patients, perhaps with a downregulation of a pro-inflammatory milieu, upregulation of pro-fibrotic cytokines and promotion of myocardial fibrosis. Tumour necrosis factor-α (TNF-α; $r = 0.78$, $p < 0.001$) and transforming growth factor-β (TGF-β; $r = 0.61$, $p = 0.03$) levels at 8 months post infection had positive correlation with LGE burden, but interleukin-1β (IL-1β; $r = 0.35$, $p = 0.20$) and interferon-γ (IFN-γ; $r = 0.447$, $p = 0.10$) did not.

A greater proportion of patients with LGE had a history of hypertension (3/6) compared to those without (0/14; $p = 0.01$). There was no greater proportion of pre-existing lung disease ($p = 0.13$), obesity ($p = 0.27$) or diabetes ($p = 0.20$) in those with LGE. Differences between clinical characteristics in those with and without LGE on CMR are summarised in Table 1. There was no difference between those with or without LGE in terms of the presence of chest pain ($p = 0.20$) or dyspnoea ($p = 0.13$) at follow-up. Overall, those with LGE on CMR had a greater proportion of cardiac risk factors that may have contributed to observed abnormalities. This may represent pre-existing subclinical cardiac disease or may represent a risk factor profile that predisposes to myocardial injury secondary to COVID-19 infection. Further studies with longitudinal data and a control group are required to elucidate.

The median (IQR) duration between positive RT-PCR for SARS-Cov-2 and lung function tests was 111 (90–115) days**.** There was no significant difference between the median (IQR) total lung capacity in patients with LGE on CMR (90%-pred; 87–97), compared to those without (99% pred; 95–106; $p = 0.09$). Of note, the median (IQR) DLCO was significantly lower in those with CMR LGE (77%-pred; 75–85) compared to those without (89%-pred; 83–99; $p = 0.04$). In the absence of reduction to lung volumes, this could suggest pulmonary vascular disease. Lung function data is also summarised in Table 1.

The prevalence of cardiac fibrosis in patients recovering from mild COVID-19 infection cannot be derived from this study alone, given its small sample size, absence of longitudinal imaging data or control group. Overall, these results suggest that patients with mild initial infection should not be excluded from studies evaluating PASC, as there may be a burden of myocardial injury that warrants further evaluation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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