



Recovery of a critically ill patient with COVID-19 myocarditis

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Abstract

Myocarditis is a concerning potential consequence of COVID-19 infection, attributed to ventricular dysfunction, cardiac fibrosis, ventricular arrhythmias, cardiogenic shock, and sudden cardiac death. Recently, the Israeli Health Ministry announced that a small number of cases of myocarditis may be linked to second dose of Pfizer's BioNTech-partnered COVID-19 vaccine. The long-term impact of COVID-19 myocarditis and coronary microthrombosis which has also been described and the best therapies for these complications remain unknown. Indeed, monomorphic ventricular tachycardia and regular ventricular arrhythmias have previously been found to be more common in those recovered from myocarditis than in acute myocarditis itself. Follow-up assessment of cardiac function has been suggested for this cohort to detect and possibly prevent further cardiac events in the rehabilitation phase. Functional capacity has been shown to be a better determinant of long-term morbidity than diagnostic testing alone, but integrated approach is likely the way forward in clinical follow-up. Assessment of residual complications in the post-COVID-19 recovery phase may identify the population burden of long-term cardiac disease as a direct consequence of COVID-19.

Keywords Cardiac function · Corticosteroids · COVID-19 myocarditis · Critical care · Outcomes · Troponin

Dear Editor,

Myocarditis is a concerning potential consequence of COVID-19 infection, attributed to ventricular dysfunction, cardiac fibrosis, ventricular arrhythmias, cardiogenic shock, and sudden cardiac death [1]. Recently, the Israeli Health Ministry announced that a small number of cases of myocarditis may be linked to second dose of Pfizer's BioNTech-partnered COVID-19 vaccine, with the majority discovered in men between 16 and 30 years. In their unpublished report, the Israeli Health Officials declared 27 cases of myocarditis were discovered following the first dose, out of a total of 5,401,150 vaccinated individuals. One hundred and twenty-one cases out of a total of 5,049,424 vaccinated individuals within 30 days of second dose were also revealed [2].

The long-term impact of COVID-19 myocarditis and coronary microthrombosis, which has also been described, and the best therapies for these complications remain unknown. Indeed, monomorphic ventricular tachycardia and regular ventricular arrhythmias have previously been found to be

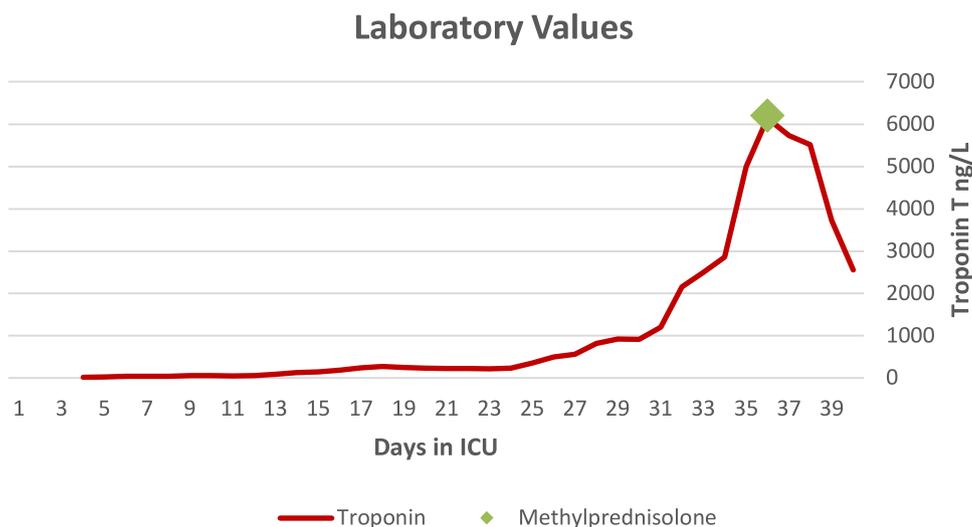
more common in those recovered from myocarditis than in acute myocarditis itself [3]. A follow-up assessment of cardiac function has been suggested for this cohort to detect and possibly prevent further cardiac events in the rehabilitation phase [4]. Functional capacity has been shown to be a better determinant of long-term morbidity than diagnostic testing alone, but integrated approach is likely the way forward in clinical follow-up [5]. Assessment of residual complications in the post-COVID-19 recovery phase may identify the population burden of long-term cardiac disease as a direct consequence of COVID-19. This case-based review describes a patient who required critical care treatment for COVID-19 pneumonitis and multi-organ failure. He was diagnosed with myocarditis during this critical period and is currently under surveillance in the COVID-19 ICU Survivorship Clinic. This letter should provide reassurance that this group may return towards their baseline in the medium term.

A 61-year-old gentleman was admitted to our intensive care unit (ICU) with coronavirus (COVID-19) pneumonitis during the first wave of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). His past medical history was significant for multiple cardiovascular risk factors such as hypertension, type 2 diabetes mellitus, and hyperlipidaemia; however, he had no history of previous myocardial

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Fig. 1 Laboratory values of troponin T (ng/L) graph illustrating daily rise in troponin T levels. Troponin level peaked at 6142 ng/L on day 35 in intensive care. Troponin T levels began to normalise following administration of methylprednisolone



infarction. Additional medical background included asthma, chronic obstructive pulmonary disease, hypothyroidism, and rectal cancer requiring anterior resection in 2017.

Following a trial of high flow oxygen via nasal cannulae, he was intubated and ventilated for refractory hypoxaemia using lung-protective ventilation and prone positioning. He developed multiorgan failure with hypotension requiring vasopressor support. He developed acute renal failure, which ultimately required renal replacement therapy. His renal function subsequently recovered prior to discharge from ICU. Routine monitoring detected an increase in troponin T (TnT) 3 weeks after admission to ICU, and 5 weeks after his diagnosis with SARS-Cov-2. TnT peaked at 6142 ng/L following increase over four sequential days, as shown in Fig. 1. Pro-BNP brain natriuretic peptide (BNP) serum level taken at that time was elevated at 2180 pg/ml. Differential diagnosis included acute coronary syndrome, sepsis-related cardiomyopathy, and stress-induced cardiomyopathy. There was no evidence of cardiac ischaemia or arrhythmia on electrocardiogram (ECG), and echocardiography depicted normal biventricular function with no regional wall motion abnormality, no significant valve abnormality, and no pericardial effusion. Cardiac angiography found no evidence of coronary artery disease.

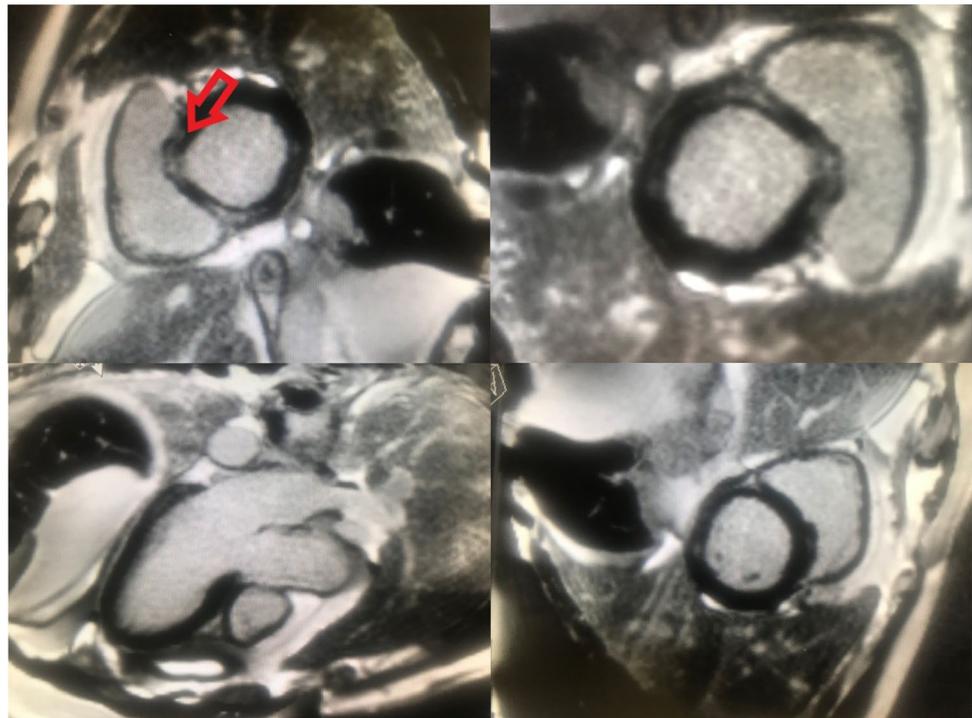
A definitive diagnosis of myocarditis could not be made without cardiac magnetic resonance (CMR) or endomyocardial biopsy, neither of which was appropriate for the patient at this time. A presumptive diagnosis of COVID-19 myocarditis was made in view of this day-on-day increase in cardiac enzymes, which was consistent with available literature, and pulsed methylprednisolone was commenced¹. Cardiac enzyme levels improved after

induction of steroids (Fig. 1); his ventilation was weaned, and he was discharged to the ward. A subsequent CMR performed at 3 months post-ICU discharge confirmed the diagnosis of myocarditis with fibrosis on the late gadolinium enhancement (LGE) sequences observed in mid-wall and subepicardial aspect of the basal segments of the septum, inferior septum, inferior and lateral walls. There was no evidence of myocardial oedema on the T2 STIR images and T2 maps. There was no evidence of subendocardial infarction on the late gadolinium enhancement sequence (Fig. 2).

He was discharged to the community and reviewed in the post-intensive care clinic at 6 months where he denied any cardiac symptoms relating to chest pain or dyspnoea. BNP was <50 pg/ml, and a repeat echocardiogram showed normal ventricular function with an ejection fraction of 55%. Pulmonary function tests showed a reduced FEV1/FVC at 68% and diffusion capacity of 55% predicted. There was evidence of resolution of COVID-19 pneumonitis on computed tomography (CT) thorax, although some peribronchovascular nodularity remained. He managed 380 m on 6-min walk test (6MWT) without desaturation, and 11 repetitions in the 30-s sit-to-stand test, demonstrating both good muscle strength and functional capacity. Grip strength was 27 kg on right, and 30 kg on left (right hand dominant). His self-assessed health status was in the second highest level of health, 'very good', which is higher than expected for his age and gender. Table 1 shows scores for the eight scales of SF36. On individual item questioning, he reported 'some' limitations in terms of strenuous activities, but 'no' limitations for moderate activities. He has not yet returned to work.

¹ This was prior to the publication of the recovery trial.

Fig. 2 Cardiac MRI — short-axis slices showing late gadolinium enhancement (LGE). Left ventricle is normal in size and volume with normal wall thickness and normal systolic function (LVEF 59%). There is no evidence of prior infarction on the LGE, but there are small foci of mild wall fibrosis in the basal segments of the septum, inferior septum, inferior and lateral walls and in the subepicardium of the basal antero-lateral and lateral walls. This is consistent with prior myocarditis. There is non-specific mid-wall fibrosis at the basal superior and basal mid inferior RV-LV insertion points. Findings are consistent with prior myocarditis with normal LVEF



Discussion

Myocarditis has been recognised as a cause of death in patients diagnosed with COVID-19 [6]. It is characterised by focal inflammation within the myocardium, with a subsequent risk of arrhythmias, fulminant heart failure, and cardiogenic shock [1, 7]. Putative pathophysiological mechanisms behind COVID-19 myocarditis include the cytokine storm induced by an imbalance between T helper-1 and T helper-2 cells with resulting cytokine-mediated cardiotoxicity, imbalance in the angiotensin converted enzyme (ACE)–angiotensin axis, direct viral myocardial and endocardial invasion-mediated via ACE tropism [8]. An additional mechanism of cardiac injury has been described by Pellegrini et al., from the Italian autopsy series. Cardiac myocyte necrosis from microthrombi was

different in composition from thrombi from catheter aspirates from patients with acute coronary syndrome [9].

Much has been learned regarding this novel viral myocarditis since January 2020, and while the European Society of Cardiology (ESC) and American Heart Association (AHA) recommend endomyocardial biopsy as the definitive method for diagnosis in myocarditis, there is a risk of false-negatives, as the disease can present in a focal manner [10, 11]. More recently, CMR has been suggested as an accurate diagnostic tool [12, 13]. Importantly, there are increasing reports of significant CMR changes in patients with COVID-19, despite clinically mild symptoms [14]. Based on these findings, it is now suggested that even patients with mild myocarditis should continue to be followed in the medium term, in particular in patients who had elevated cardiac enzymes and BNP [4]. Due to the novel nature of the disease, the literature is, of course, lacking in terms of medium-term and long-term outcomes of COVID-19 related myocarditis.

Prior literature from non-COVID-19 viral myocarditis suggests that the rate of sudden cardiac death or life-threatening ventricular arrhythmias may be as high as 6.6% [15]. While CMR with LGE, post-infection, could identify the at-risk group [3], functional capacity has been shown to be both independently and incrementally associated with prognosis in patients with cardiac disease and is a better predictor of outcome than diagnostic testing alone [16]. The late risk of arrhythmias in these patients is currently unknown and perhaps Holter or telemetry monitoring during rehab may be prudent.

Table 1 Eight domains of SF 36

	Scores (/100)
Physical functioning	95
Role limitation physical	100
Role limitation emotional	100
Energy	95
Emotional well-being	100
Social functioning	100
Pain	70
General health	95

Assessment of functional capacity is particularly important for patients who have required critical care for multi-organ failure either owing to, or concurrent with, their diagnosis of myocarditis. A relatively straightforward assessment of functional capacity can be performed in the outpatient clinic. While cardiopulmonary exercise testing remains the gold standard for prognostic stratification for long-term patients, the 6MWT can provide similar information [17]. The American Thoracic Society (ATS) has recommended 6MWT as a measure of functional status, and for prognostication in patients with respiratory disease and cardiac failure [18]. Maximal distance walked during the 6MWT is an indicator of submaximal exercise tolerance, and therefore similar to activity of daily living. A maximal distance of <300 m is predictive of morbidity in patients with mild-to-moderate heart failure [19].

Our patient managed 380 m, however, his functional limitations were also limited by his post-ICU status and diagnosis of ARDS. A recent systematic review of the 6MWT in ICU survivors found that the pooled mean distance was 360 m at 3 months post-ICU discharge, increasing to 395 m at 6 months [20]. A previous small prospective cohort study of 56 patients found that median 6MWT distance was 392 m [21]. Despite assumptions that ICU-related myopathy may be a driver of reduced distance, well-recognised risk factors such as severity of illness, use of steroids, and neuromuscular blockers have not been found to be associated with maximal distance achieved [20]. Therefore, the 6MWT is predominantly useful in assessing functional outcomes related to respiratory and cardiac disease in ICU patients.

The grip strength and sit-to-stand tests are a further reliable measure of functional capacity and muscle strength [22, 23]. Mean grip strength was shown to be 29.3 kg on the right and 27.3 kg on the left for cardiac patients already engaged in a rehab program [24]. Median grip strength in ICU survivors at 3 months was 20.4 kg [21]. Our patient's grip strength was above these scores.

While there are few papers examining the sit-to-stand test for ICU survivors, a quasi-example is the GymNAST study which found that recovery of speed to stand (as opposed to repetitions) returned at 2 months post-ICU discharge for those with ICU-acquired muscle weakness [25].

The majority of papers examining SF36 scores in the cardiac literature relate to congestive heart failure, post-myocardial infarction, and post-operative states, with no real evidence on quality of life scores for viral myocarditis. However, the health outcomes research literature does examine the eight domains of the SF36 for ICU patients. One particularly relevant paper found that SF36 scores were higher for Middle East Respiratory Syndrome (MERS) survivors than non-MERS ICU survivors [26].

Although there is an assumption that ICU survivors have poorer quality of life scores post-discharge than age and sex-matched population controls, a cross-sectional study from Sweden found that scores were relatively similar [27]. Those with worse outcomes than the population average were male, single, and on sick leave prior to ICU admission. Our patient had only one of these risk factors (although he has not yet returned to work post-discharge) and his scores are above expected values for all eight domains of the SF-36 survey.

While CMR is a useful tool to measure response to treatment in selected patients, there is no evidence on the optimal time to perform follow-up CMR [28] and there are no established myocarditis specific biomarkers that can predict outcome [29]. BNP has been shown to be associated with long-term outcomes for patients with cardiomyopathy [8] as well as medium- to long-term outcomes after ICU discharge [30]. Since BNP is recognised as an optimal means of guiding treatment in the ambulatory setting for patients with heart failure [31], it is reasonable to consider that this as an additional tool in the follow-up of ICU patients with myocarditis.

Conclusion

Viral myocarditis in patients can occur with SARS-CoV-2 infection, causing a fulminant cardiomyopathy. The diagnosis of COVID-19 associated myocarditis can be challenging, particularly in the critically ill population. This patient had no arrhythmogenic or anatomical insult. Currently, ESC guidelines do not recommend steroids in mild cases of COVID-19 myocarditis [32]. Aggressive treatment of isolated elevated troponin levels without cardiovascular compromise, in this case, may have prevented the development of chronic myocarditis and subsequent inflammatory cardiomyopathy. This incidental diagnosis highlights the importance of regular serum screening in all COVID-19 patients and the potential merits of early intervention.

As of June 2, 2021, the centre for disease control and prevention continues to advise COVID-19 vaccination for persons aged 12 years and older, taking into account the greater risk of COVID-19 illness possible severe complications.

Since even mild myocarditis is associated with long-term morbidity, it is important that this group of patients is followed in the recovery phase. Outpatient assessment of functional capacity can be used alongside diagnostic testing to detect the at-risk group. It is reassuring that good functional outcomes were observed in our patient who was affected by the double burden of myocarditis and COVID-19 pneumonitis, with associated multi-organ failure.

Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication Written consent was obtained from a patient.

Conflict of interest The authors declare no competing interests.

References

- Siripanthong B et al (2020) Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm* 17(9):1463–1471
- Carlson R (2021) Israel investigates heart issues related to Pfizer-BioNTech COVID-19 Vaccine
- Peretto G et al (2020) Ventricular arrhythmias in myocarditis: characterization and relationships with myocardial inflammation. *J Am Coll Cardiol* 75(9):1046–1057
- Mitrani RD, Dabas N, Goldberger JJ (2020) COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. *Heart Rhythm* 17(11):1984–1990
- Forman Daniel E et al (2017) Prioritizing functional capacity as a principal end point for therapies oriented to older adults with cardiovascular disease: a scientific statement for healthcare professionals from the American Heart Association. *Circulation* 135(16):e894–e918
- Ruan Q et al (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 846–848
- Esfandiari M, McManus BM (2008) Molecular biology and pathogenesis of viral myocarditis. *Annu Rev Pathol* 3:127–55
- Akita K, Tsurata H, Yuasa S et al (2018) Prognostic significance of repeated brain natriuretic peptide measurements after percutaneous transluminal septal myocardial ablation in patients with drug-refractory hypertrophic obstructive cardiomyopathy. *Open Heart* 5:e000786
- Pellegrini D et al (2021) Microthrombi as a major cause of cardiac injury in COVID-19. *Circulation* 143(10):1031–1042
- Kociol RD et al (2020) Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. *Circulation* 141(6):e69–e92
- Caforio AL et al (2013) Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 34(33):2636–48, 2648a–2648d
- Ferreira VM et al (2018) Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol* 72(24):3158–3176
- Grün S et al (2012) Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. *J Am Coll Cardiol* 59(18):1604–15
- McKinney J et al (2020) COVID-19-Myocarditis and return to play: reflections and recommendations from a Canadian Working Group. *Can J Cardiol*
- Marc-Alexander O et al (2018) Predictors of long-term outcome in patients with biopsy proven inflammatory cardiomyopathy. *J Geriatr Cardiol* 15(5):363–371
- Tang WH, Topol EJ, Fan Y et al (2014) Prognostic value of estimated functional capacity incremental to cardiac biomarkers in stable cardiac patients. *J Am Heart Assoc* 3(5):e000960
- Wegrzynowska-Teodorczyk K, Rudzinska E, Lazarczyk M et al (2013) Distance covered during a six-minute walk test predicts long-term cardiovascular mortality and hospitalisation rates in men with systolic heart failure: an observational study. *J Physiother* 59(3):177–187
- Society, A.T. (2002) ATS Statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 166:111–117
- Rostagno C, Olivo G, Comeglio M et al (2003) Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. *Eur J Heart Fail* 5(3):247–252
- Parry SM, Nalamalapu SR, Nunna K et al (2021) Six-minute walk distance after critical illness: a systematic review and meta-analysis. *J Intensive Care Med* 36(3):343–351
- Solverson KJ, Grant C, Doig CJ (2016) Assessment and predictors of physical functioning post-hospital discharge in survivors of critical illness. *Ann Intensive Care* 6(1):92
- Ozalevli S et al (2007) Comparison of the sit-to-stand Test with 6 min walk test in patients with chronic obstructive pulmonary disease. *Respir Med* 101(2):286–93
- Jones SE et al (2013) The five-repetition sit-to-stand test as a functional outcome measure in COPD. *Thorax* 68(11):1015–1020
- Puthoff ML, Saskowski D (2013) Reliability and responsiveness of gait speed, five times sit to stand, and hand grip strength for patients in cardiac rehabilitation. *Cardiopulm Phys Ther J* 24(1):31–37
- Thomas S et al (2016) Recovery of sit-to-stand function in patients with intensive-care-unit-acquired muscle weakness: results from the general weakness syndrome therapy cohort study. *J Rehabil Med* 48(9):793–798
- Batawi S et al (2019) Quality of life reported by survivors after hospitalization for Middle East respiratory syndrome (MERS). *Health Qual Life Outcomes* 17(1):101
- Orwelius L, Fredrikson M, Kristenson M et al (2013) Critical care (London, England), 17(5):R236, Health-related quality of life scores after intensive care are almost equal to those of the normal population: a multicenter observational study. *Crit Care* 17(5):R236. <https://doi.org/10.1186/cc13059>
- Bohnen S, Radunski UK, Lund GK et al (2017) Tissue characterization by T1 and T2 mapping cardiovascular magnetic resonance imaging to monitor myocardial inflammation in healing myocarditis. *Eur Heart J Cardiovasc Imaging* 18(7):744–751
- Tschope C, Ammirati E, Bozkurt B et al (2020) Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol*. <https://doi.org/10.1038/s41569020-00435-x>
- Gayat E, Cariou A, Deye N et al (2018) Determinants of long-term outcome in ICU survivors: results from the FROG-ICU study. *Crit Care* 22(8). <https://doi.org/10.1186/s13054-017-1922-8>
- Bhardwaj A, Rehman SU, Mohammed AA et al (2012) Quality of life and chronic heart failure therapy guided by natriuretic peptides: results from the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study. *Am Heart J* 164(5):793–799
- Ammirati E et al (2020) Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. *Circulation. Heart Fail* 13(11):e007405–e007405

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