Cardiovascular Magnetic Resonance for Patients with Coronavirus Disease 2019 (COVID-19)

Brief title: Cardiovascular Magnetic Resonance for Patients with COVID-19

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Unstructured abstract
Coronavirus disease 2019 (COVID-19) is associated with myocardial injury due to ischemia, inflammation, or myocarditis. Cardiovascular magnetic resonance (CMR) is the noninvasive reference standard for cardiac function, structure, and tissue composition. CMR is a potentially valuable diagnostic tool in COVID-19 patients presenting with myocardial injury and evidence of cardiac dysfunction. Although COVID-19-related myocarditis is likely infrequent, COVID-19 related cardiovascular histopathology findings have been reported in up to 48% of patients raising the concern for long-term myocardial injury. Studies to date report CMR abnormalities in 26-60% of hospitalized patients recovered from COVID-19, including functional impairment, myocardial tissue abnormalities, late gadolinium enhancement, or pericardial abnormalities. In the athlete post COVID-19, CMR has detected myocarditis-like abnormalities. In children, multi-system inflammatory syndrome may occur 2-6 weeks after infection; associated myocarditis and coronary artery aneurysms are evaluable by CMR. At this time, our understanding of COVID-19-related cardiovascular involvement is incomplete, and multiple studies are planned to evaluate patients with COVID-19 using CMR. In this review, we summarize existing studies of CMR for COVID-19 patients and present ongoing research. We also provide recommendations for clinical use of CMR for patients with acute symptoms or who are recovering from COVID-19.

Condensed abstract
Coronavirus disease 2019 (COVID-19) is associated with myocardial injury due to ischemia, inflammation, or myocarditis. In the convalescent patient, reports of cardiovascular magnetic resonance (CMR) detected abnormalities include functional abnormalities, myocardial edema, late gadolinium enhancement, and pericardial abnormalities. In the athlete post COVID-19, CMR has detected myocarditis-like abnormalities. In children, multi-system inflammatory syndrome associated myocarditis and coronary artery aneurysms are evaluable by CMR. In this review, we summarize existing studies of CMR for COVID-19 patients and present ongoing research. We also provide recommendations for clinical use of CMR for patients with acute symptoms or who are recovering from COVID-19.

Key words: cardiovascular magnetic resonance; coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); myocarditis; ischemia; myocardial injury; multi-system inflammatory syndrome

Highlights:

- Given the high rate of acute cardiovascular abnormalities in COVID-19 reported in clinical and pathologic series, concern exists for long-term myocardial injury in the convalescent patient.
- We review existing studies of CMR in COVID-19 and discuss the use of CMR for the acute and convalescent patient, including athletes.
- Existing evidence is limited by small cohort sizes, absence of longitudinal follow up, and, in some cases, lack of appropriate controls.
- Evaluation of emerging evidence from ongoing and planned international studies will be essential for more robust evidence-based clinical decision making.

Abbreviations

CMR: cardiovascular magnetic resonance

COVID-19: coronavirus disease 2019

cTn: cardiac troponin

ECG: electrocardiogram

ECV: extracellular volume

NT-proBNP: N-terminal pro–brain natriuretic peptide

LGE: late gadolinium enhancement

LV: left ventricle

MI: myocardial infarction

MIS-C: multisystem inflammatory syndrome in children

RV: right ventricle

SARS-CoV2: severe acute respiratory syndrome coronavirus 2

Introduction

As of July 2021, the worldwide number of confirmed coronavirus disease 2019 (COVID-19) cases has reached more than 180 million with almost 4 million related deaths (1). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 preferentially infects epithelial cells of the respiratory tract via the angiotensin-converting enzyme 2 (ACE2) receptor (2). However, both the heart and myocardial vessels are also potential targets of SARS- CoV2 via the angiotensin-converting enzyme 2 receptor. Myocardial injury in association with COVID-19 has been linked to greater risk of in-hospital mortality (3).

Cardiovascular magnetic resonance (CMR) is the reference standard for evaluation of myocardial structure and function. In addition, CMR is unique in its capability to probe myocardial tissue composition. The American College of Cardiology, the European Society of Cardiology and the Society for Cardiovascular Magnetic Resonance concur that CMR is a potentially valuable diagnostic tool in COVID-19 patients presenting with myocardial injury and evidence of cardiac dysfunction (4–7).

The purpose of this report is to review the use of CMR to evaluate cardiac disease in association with COVID-19.* We assess clinical evidence for myocardial injury and pathologic findings of COVID-19 relevant to diagnostic use of CMR for patients. Next, we summarize reports to date that have used CMR for patients and athletes recovering from COVID-19. Expert opinion is presented regarding appropriate use of CMR in the setting of COVID-19.

*The Society of Cardiovascular Magnetic Resonance has endorsed the contents of this report.

Background: myocardial injury in COVID-19

Manifestations of myocardial injury

Reports of myocardial injury in association with COVID-19 have included acute ischemic injury (type 1 myocardial infarction [MI] (8)) as well as non-ischemic injury (i.e., myocarditis) (9–11), stress cardiomyopathy (12), acute heart failure (13), and secondary cardiac injury due to sepsis and critical illness (14). Mechanisms of myocardial may be direct (viral infection, thought to be less common) or indirect via systemic inflammatory response. Activation of a proinflammatory response secondary to an immune response to SARS-CoV-2 results in cytokine release and prothrombotic state (15,16). Giustino et al. reported 305 patients hospitalized with COVID-19 from 7 hospitals in Milan and New York. Myocardial injury (defined as cardiac troponin [cTn] elevation above the 99th percentile upper reference limit (17)) at any time during admission was common – present in 62% of patients (18). Elevated cTn was associated with older age, pre-existing cardiovascular disease, COVID-19 severity, and clinical deterioration (15,19). In other studies, patients with elevated cTn were at higher risk for adverse events during hospitalization including a higher death rate, acute respiratory distress syndrome, and malignant arrhythmias (19–21).

Myocardial injury in patients with COVID-19 can be detected by cardiac imaging. Giustino et al. indicated that nearly two-thirds of patients with myocardial injury by cTn had major echocardiographic abnormalities (18). Abnormalities included LV wall motion abnormalities (24%), right ventricular dysfunction (26%), global LV dysfunction (18%), diastolic dysfunction grades II or III (13%) and pericardial effusion (7%). In-hospital mortality was 5.2% without cardiac involvement but rose to 32% in those with myocardial injury and echocardiographic abnormalities (18). These findings were supported by Rath et al. who showed a significantly higher mortality in patients with impaired LV ejection fraction, impaired right ventricular (RV) function, and tricuspid regurgitation. (22) In 100 consecutive

individuals hospitalized with COVID-19, Szekely et al. reported RV dilatation and dysfunction in 39% patients (23). Dweck et al.(24) performed a prospective multicenter survey of 1,216 hospitalized acute COVID-19 patients with clinical indications for echocardiography. They reported abnormal echocardiograms in 55% of patients. In most cases, the underlying cause of LV abnormalities was not identified. Thus, although echocardiography is a first line imaging tool, its ability to discern specific diagnoses is suboptimal.

Given the high rate of acute COVID-19 associated cardiac abnormalities, concern exists for long-term myocardial injury in the convalescent patient. In a report of 1,733 previously hospitalized patients evaluated 6 months after symptom onset, 11% of patients reported palpitations and 5% reported on-going chest pain, raising the question of long-term cardiac injury (25). In a multi-center study, cardiopulmonary damage in 109 hospitalized patients and 37 outpatients recovering from COVID-19 was assessed (26). At follow-up, echocardiography revealed a high rate of diastolic dysfunction (55%) but only 2.8% had reduced LV ejection fraction; N-terminal pro–brain natriuretic peptide (NT-proBNP) was elevated in 23% of the COVID-19 patients (26).

Histopathology evidence for myocardial injury in COVID-19

The histopathologic basis of myocardial injury due to COVID-19 has been studied. In the heart, the angiotensin-converting enzyme 2 receptor is more highly expressed in pericytes that line the vasculature compared to than myocytes (27). Basso et al. (28) reported myocarditis (defined as lymphocytic infiltration plus myocyte necrosis) in 3/21 (14%) selected autopsy cases of COVID-19. Halushka and Vander Heide reviewed 22 publications describing autopsy results in 277 patients who died of COVID-19 (29). These authors suggested myocarditis was infrequent (1.4%). However, at least one acute, potentially COVID-19-

related cardiovascular histopathology finding (e.g., micro- or macrovascular thrombi, interstitial inflammation, and/or intraluminal megakaryocytes) was common (48% of cases) (29). Lindner et al. demonstrated the presence of SARS-CoV-2 viral particles in the heart in 24/39 (59%) consecutive autopsies (30). Of note, viral particles were not present in myocytes, but rather within the interstitial space. In addition to the aforementioned inflammatory processes, Bois et al. reported microthrombi in association with COVID-19 (31). In another series of 40 hearts from patients who died from COVID-19, myocardial necrosis (primarily of the LV) was present in 14 (35%); the majority of these had small (11/14) or large (2/14) vessel thrombosis (32).

In summary, myocardial injury in the hospitalized COVID-19 patient is frequent and portends a worse prognosis. Based on limited autopsy information, the pathogenesis of SARS-CoV-2 infection was infrequently lymphocytic myocarditis; instead, macrophage infiltration, inflammation and microthrombi were more common at autopsy. Early evidence indicates that myocardial abnormalities are present in only a proportion of convalescent patients and current data is limited. In the following section, we review information to date showing the use of CMR as a highly sensitive method to detect myocardial abnormalities in association with COVID-19.

CMR of acute and convalescent COVID-19 patients

Assessment of myocardial injury using CMR

CMR identifies myocardial injury associated with both nonischemic and ischemic disease. CMR assesses both myocardial function and tissue characterization, including myocardial edema that is present in inflammatory disease. For acute myocarditis-like presentations, CMR may support or exclude active myocardial inflammation by use of the so-called Lake Louise criteria (33). The Lake Louise criteria comprise at least one T2-based criterion with at least

one T1-based criterion (see Table 1 for definitions of CMR terminology). Supportive criteria include pericardial effusion and systolic LV dysfunction.

The Lake Louise criteria have been validated in the context of clinically suspected acute myocarditis. The Lake Louise have not been validated in patients recovering from acute COVID-19 or presenting with prolonged symptoms. Nevertheless, CMR allows assessment of a wide range of functional and tissue characterization parameters (Table 1). Especially in patients with chronic inflammatory conditions, T2-mapping (reflecting myocardial edema) is reported to inform the CMR diagnosis (34). However, the optimal combination of CMR criteria to characterize myocardial disease in patients recovering from COVID-19 remains to be determined. Suggested Society for Cardiovascular Magnetic Resonance imaging protocols for patients with active or convalescent phase COVID-19 infection have been reviewed by Kelle et al. (35)

CMR for patients with acute COVID-19

The use of CMR in the acute setting has been infrequently reported, in part due to concerns of infection control in the hospital environment. Case reports have shown abnormal myocardial T2 and native T1 times, pericardial abnormalities (myopericarditis) and non-ischemic pattern of late gadolinium enhancement (LGE) (9,36). In patients with high pre-test probability for acute myocardial injury and myocarditis-like injury, CMR may improve diagnostic specificity, guide management decisions and affect prognosis (33). CMR can provide a noninvasive, biopsy-like method to identify imaging features of myocardial inflammation.

CMR for the convalescent COVID-19 patient

Several early reports raised concern for myocardial injury in association with COVID-19. In an early study, Ng et al. (37) reported results from 16 patients who had been hospitalized with

COVID-19 and who had elevated cTn or abnormal ECG during the acute illness (**Table 2**). At 2 months after the initial COVID-19 diagnosis, CMR was abnormal in 9/16 (56%) patients. Three patients (19%) had CMR criteria for myocarditis-like injury. That study was buttressed by a report from Germany: Puntmann et al. (38) performed a prospective study of 100 recovered patients, the majority (49%) of whom had mild-moderate COVID-19 and 2/3rds of whom were *not* hospitalized. At 2 to 3 months after a positive test result, 78/100 patients with prior COVID-19 had an abnormal CMR. Mean LV and RV ejection fraction were lower, and median native T1 and T2 were higher (indicative of edema and/ or collagen deposition) than controls. Pericardial enhancement was frequent (22%). There were greater proportions of patients with ischemic (32% vs 17%) *and* non-ischemic (20% vs 7%) LGE patterns than the risk factor-matched control group. The prevalence of CMR abnormalities was more frequent than identified by cardiac blood biomarkers (38). However, individuals not hospitalized for COVID-19 had fewer CMR abnormalities compared to the hospitalized patients. This result was confirmed by Joy et al, who evaluated 74 healthcare workers with mild or asymptomatic COVID-19 (39); CMR abnormalities at 6 months post SARS-CoV-2 infection was similar to control subjects.

CMR of patients hospitalized for COVID-19. Rates of CMR-identified abnormalities in patients hospitalized due to COVID-19 have shown wide variation. Li et al. (40) used CMR to evaluate 40 patients who had been hospitalized with moderate-severe COVID-19. The authors excluded patients with known cardiovascular disease or diabetes. At approximately 5 months after hospital discharge, 24/40 (60%) patients had elevated extracellular volume (ECV) compared to controls and 28/40 had subclinical LV dysfunction (by global longitudinal strain). However, only 1/40 patients had LGE. In 44 hospitalized COVID-19 patients free from pre-existing baseline cardiovascular disease, Wang et al.(41) found non-

ischemic LGE in 13/44 (30%) patients after 3 months. Patients with LGE had worse LV and RV function by strain analysis compared to controls.

Knight et al. (42) described CMR findings in 29 patients who had been hospitalized with COVID-19 and who had unexplained cTn elevation during the acute illness. At a mean of about 1 month after hospital admission, 32% of patients had occult ischemic heart disease (by LGE or stress perfusion) and 45% had a "myocarditis-like" pattern of LGE. In an expanded report from the same group, Kotecha et al. (43) reported convalescent CMR findings from 148 patients hospitalized with severe COVID-19. At 2 months after hospital discharge, the authors reported a myocarditis-like pattern of LGE in 26% (39/148) and myocardial infarction or inducible ischemia in 22% (32/148).

Huang et al. (44) published a retrospective study of 26 patients hospitalized with moderate-severe COVID-19, who underwent CMR post-recovery (at approximately 1.5 months) for investigation of cardiac symptoms (chest pain 12%, palpitation 88%, chest distress 23%). Fifteen patients (58%) had abnormal CMR (defined as increased myocardial T2 time and/or the presence of LGE); these patients had lower RV function than controls (e.g., lower ejection fraction and stroke volume). Their results suggested a link between LV myocardial inflammation and lower RV function, a proxy indicator of COVID-19 severity. Knight et al.(42) also noted a link between sustained pulmonary and cardiac involvement, with high rates of persistent lung parenchymal changes (69%) and pleural effusion (14%) on post-recovery CMR. These observations give rise to the concept that cardiac involvement associated with COVID-19 may not be a specific effect on the heart, but rather a consequence of pulmonary and systemic inflammatory processes. The concept of a systemic inflammatory activity in multiple organs (rather than cardiac specific injury) is also supported by findings of Raman et al, indicating multi-organ involvement after recovery (45).

In summary, reports of CMR-identified abnormalities in patients hospitalized due to COVID- range from 26-60% of individuals at 1-5 months after hospital discharge. Reassuringly, patients with mild COVID-19 and asymptomatic individuals are reported to have low rates of CMR abnormalities (39,46). Comparison of early CMR studies is hampered by variable time of patient follow-up, associated-comorbidities, prevalence of cardiovascular risk factors and potentially in-hospital treatment. CMR methods have also varied between published reports. Future studies with standardized CMR protocols are needed to evaluate the longer term (1 year or more) effect of COVID-19 disease on the heart. Due to the high sensitivity of CMR for myocardial scar (particularly in patients with cardiovascular risk factors and pre-existing cardiovascular disease), these longer term follow-up studies should include carefully matched risk factor control groups (47).

Evaluation of the athlete after COVID-19

As a result of close congregation and contact of players during practice and competition, there is an increased risk of COVID-19 infections among athletes. Exercise initiated too early after viral infection or in occult myocarditis may have serious consequences (48,49). Indeed, non-COVID-19 myocarditis accounts for 4-8% of sudden cardiac deaths in athletes (50,51) or may lead to long term complications such as myocardial scarring, arrhythmias and myocardial dysfunction. The ORCCA registry of 19,378 collegiate athletes indicated a prevalence of cardiac involvement of 0.5-3% in individuals undergoing return-to-play cardiac evaluation following SARS-CoV-2 (n=3,018) infection (52).

CMR of the athlete recovered from COVID-19

Table 3 summarizes publications to date that have used CMR to evaluate athletes recovering from COVID-19. In the first publication on CMR in athletes, Rajpal et al.(53) studied 26

college athletes who underwent CMR 11-53 days after having tested positive for COVID-19 (Table 3). 46% had mild to moderate symptoms of COVID-19 infection and 54% were asymptomatic. Twelve athletes (46%) had myocardial LGE, with 4 (15%) having myocarditis-like findings on CMR.(54)

Subsequent publications have reported lower rates of CMR abnormalities (Table 3). Brito et al. (55) described CMR findings in 48 college athletes at median of 27 (range 22-33) days after positive COVID-19 test. None had CMR defined myocarditis although approximately 1 in 3 athletes had pericardial abnormalities. Similarly Małek et al (56), and Vago et al. (57) reported on 26 and 12 athletes, respectively; none had CMR defined myocarditis. Clark et al. described 59 college athletes recovered from COVID-19 (58) with CMR a median of 22 days (range 10-162) following diagnosis. Two athletes (3%) had myocarditis-like findings on CMR.

Starekova et al. (59) studied a consecutive cohort of college athletes (n=145), who underwent standardized screening including CMR. Two patients (1.4%) had myocarditis-like CMR findings. Finally, Martinez et al. (60) reported the evaluation of 789 professional US athletes after COVID-19 recovery. Twenty-seven patients underwent CMR and 3 (11%) of these had myocarditis-like findings. However only a small fraction of the professional athletes underwent CMR. Hendrickson et al. evaluated 137 collegiate athletes, with 5 patients referred for CMR due to abnormal testing results (e.g., elevated cTn, coronary artery ectasia (61). No abnormal findings were detected by CMR. No athlete has an abnormal ECG.

In the ORCCA prospective registry, collegiate athletes with at least one positive component of a triad of initial testing (ECG, cTn or transthoracic echocardiography) were more than 4 times more likely to have a positive CMR compared to primary screening CMR (15/119

[12.6%] versus 6/198 [3%], respectively) (62)Another large multicenter study conducted by Daniels et al. (54) included 13 universities and 2461 athletes, of whom 1597 had CMR. In 37/1597 (2.3%) athletes, myocarditis was diagnosed clinically. Of these 37 athletes, 31 had CMR findings meeting the Lake Louise criteria for myocarditis. The prevalence of abnormal CMR findings varied from 0% to 7.6% among the included institutions (54)

In summary, the prevalence of myocarditis-like findings on CMR for athletes after COVID-19 appears to be highly variable across the studies (range: 0% to 15%, Table 3). Larger multicenter studies have tended towards lower prevalence rates. Approximately 50% of athletes who had myocarditis-like findings on CMR in single centre studies were asymptomatic, and all but two had normal troponin and ECG. A potential false-positive CMR finding was LGE at the RV insertion point (0-26% prevalence) that has been previously reported in association with athletic activity (63) and unlikely to be related to COVID-19. An important limitation of these reports is either lack or insufficient matching of a control group (e.g., by age, gender, type of sport - endurance or strength, see supplemental Table 1).

Multisystem inflammatory syndrome in children (MIS-C)

Multisystem inflammatory syndrome in children (MIS-C), also called pediatric inflammatory multisystem syndrome, is characterized by a severe inflammatory response after SARS-CoV2 infection. Multiple definitions of the syndrome have been published (64–66). The United States Centers for Disease Control and Prevention defines MIS-C as individuals younger than 21 years old who have a fever for at least 24 hours, laboratory evidence of inflammation, multisystem involvement, severe illness requiring hospitalization, no alternative plausible diagnosis, and recent or current SARS-CoV-2 infection or exposure (65). MIS-C is felt to be a delayed immune response occurring after SARS-CoV-2 infection, typically occurring 2-6

weeks after infection (67–69). The immunologic profile for acute COVID-19 appears to be distinct from MIS-C (70).

Patients presenting with MIS-C are frequently otherwise healthy and may present with symptoms similar to Kawasaki disease (e.g. rash, conjunctival injection) or myocarditis, sometimes in shock, in addition to frequent gastrointestinal symptoms (67). Older pediatric patients (13-20 years old) more often present with myocarditis-like symptoms (73%) as opposed to younger patients (0-5 years old, 39%), but younger patients more often present with symptoms similar to Kawasaki disease (48% vs. 11%) (71). Patients have markedly abnormal laboratory testing, including elevated inflammatory markers, thrombocytopenia, elevated BNT and/or cTn, and abnormal coagulation markers (68). Potential mechanisms contributing to the pathophysiology of MIS-C include a hyperactive post-viral immunological response to COVID-19 leading to systemic inflammation. However this is the subject of ongoing investigation (72).

Cardiac involvement in children with MIS-C is common, including most frequently diminished LV systolic function, in addition to arrhythmias, pericardial effusion and coronary artery dilation and/or aneurysms (67). In a case series of 570 children, the median length of stay was 6 days with 64% requiring intensive care, and while most children ultimately recover, the mortality rate was reported as 1-2% (67). Feldstein et al. described reduced LV ejection fraction in 172/503 (34%) of patients with MIS-C; all but 1 patient recovered function at 90 days (73). In the same study, coronary artery aneurysms were present in 57/424 (13%) of patients with normalization in all evaluated patients at 90 days.

There have been several small studies to date evaluating CMR findings in patients with MIS-C, encompassing over 130 patients. CMRs that were performed during the initial

hospitalization or soon after discharge frequently identified myocardial edema on T2 weighted images, hyperemia and capillary leak (using T1 weighted images prior to and immediately after gadolinium administration), and LGE(74–79). However, in a few studies evaluating CMRs closer to 2-3 months after discharge, there were frequently no abnormalities (80,81).

CMR for patients with COVID-19: Planned and ongoing studies

The use of CMR in the context of COVID-19 is driven by the accuracy and reproducibility of the method as well as its unique role in myocardial tissue characterization. Supplemental Table 2 is a list of planned and ongoing studies using CMR to investigate the cardiovascular manifestations of COVID-19, identified primarily from clinical trial registration sites (e.g., clinialtrials.gov). Overall, almost 10,000 participants will be included across all studies, which are planned in a range of settings and in diverse patient populations. Global sharing of CMR databases may further augment the power of these proposed investigations. Indeed, recent national and international initiatives have been established to create research databases of CMR studies of COVID-19 patients (82,83).

Recommendations for use of CMR in patients with COVID-19

The appropriate use of CMR and its role in the management of patients with COVID-19 must be considered within the multifactorial context of disease severity, availability of CMR versus other cardiovascular imaging resources, and pretest probability. Evidence-based knowledge regarding appropriate use of CMR for patients with COVID-19 is expected to evolve over several years as the long-term complications of the disease are currently under intense study (supplemental Table 2). To address the current gap in knowledge, a diverse group of authors from 9 countries (principally cardiologists and radiologists with extensive experience in CMR

were assembled to offer expert opinion regarding appropriate CMR use. The opinions that follow have been informed by each author's experience with COVID-19 patients and after extensive literature review and group discussion. Definitions of COVID-19 severity were based on established disease classifications relevant to each practitioner (84,85). 80% or higher agreement on the direction of recommendation was considered concurrence. In all discussions, the expert panel recommended consideration of CMR testing only when the test would likely impact on clinical decision making, such as altering therapeutic decisions. The consensus recommendations regarding four distinct patient scenarios are detailed below and summarized in Table 4:

1. CMR for patients with acute COVID-19

CMR should be considered for COVID-19 patients with high pre-test probability for acute myocardial injury due to inflammation *and* when CMR findings are likely to have an impact on clinical decision-making. In suspected acute myocardial injury, acute coronary syndrome (e.g. myocardial infarction types 1 and 2 (17)) should be excluded prior to CMR to avoid diagnostic delay and treatment.

2. CMR for convalescent patients after recovery from COVID-19

CMR should be considered for COVID-19 patients after recovery from COVID-19 in the following circumstances and when CMR findings are likely to have an impact on clinical decision making:

1. Patients with otherwise unexplained, persisting, or recurring cardiovascular symptoms (e.g., exertional dyspnea, palpitations, chest pain, fatigue or other symptoms of myocardial injury or heart failure) as a part of a systemic inflammatory post-COVID syndrome more than 4 weeks after COVID-19 recovery.

2. Patients who had CMR in the acute setting that showed clinically significant acute myocardial injury. The convalescent CMR should be performed 4 weeks or more after the baseline (acute) CMR.

3. CMR for the recovering high-performance athlete: return to play (see also (86) for more detail)

1. CMR should be considered for high-performance athletes after COVID-19 recovery and prior to returning to training in the following settings:
    a. History of moderate COVID-19 and high-pretest probability of myocardial injury by diagnostic testing or clinical suspicion.
    b. History of severe COVID-19.

2. CMR should be considered for high-performance athletes who have returned to play with new onset cardiovascular symptoms with suspicion of myocardial injury.

4. CMR for patients with suspected MIS-C (Multisystem Inflammatory Syndrome in Children)

CMR should be considered for patients with MIS-C in the following settings:

1. Clinical suspicion of myocardial injury or with significantly diminished ventricular function during inpatient hospitalization for acute illness, particularly if not clinically improving.

2. Approximately 1-6 months after the acute MIS-C presentation in patients with prior moderately or severely diminished left ventricular systolic function or baseline abnormal CMR.

3. Concern for coronary artery aneurysm.

Due to evolving clinical information, these recommendations may be revised as additional information becomes available. CMR recommendations also need to be modified based on a patient's individual cardiovascular risk factors, change in clinical status or unexplained symptoms. CMR practitioners should be aware of magnetic resonance imaging parameters

(supplemental Table 3), special considerations and clinical guidelines for certain patient populations such as high-performance athletes (e.g., (86), supplemental Table 1) and pediatric patients including MIS-C (87).

Conclusion

Public health guidelines and vaccine development are expected to result in fewer incident cases of COVID-19. Yet, the clinical spectrum of recovery after acute COVID-19 with regards to cardiovascular disease is unresolved. Reports to date have raised the potential of sustained cardiac injury in patients recovered from COVID-19. CMR is a key, noninvasive clinical and research tool due to its comprehensive evaluation of myocardial function, structure and tissue composition. Given the high sensitivity of CMR, important caveats to application of CMR include a) detection of subclinical cardiac disease that may have occurred prior to SARS-CoV-2 infection and b) detection of CMR abnormalities that may not functionally impact quality of life nor increase the risk of future cardiovascular events. Longer term studies are necessary to determine the clinical importance of CMR metrics and their association with incident health outcomes. Comparison to control groups (matched for cardiovascular risk factors, and severity-matched non-COVID-illness when feasible) will ultimately help determine the relationship of CMR findings to long-term patient outcomes.

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Table 1. Cardiovascular Magnetic Resonance (CMR) Terminology and Methods for Tissue Characterization

CMR Method or Terminology	Definition	CMR application	Interpretation in COVID-19 patients
T1 relaxation parameters*			
T1weighted images	Images dominated by T1 relaxation magnetic relaxation. Signal intensity is relative (not quantitative)	Typically used for depiction of myocardial anatomy. Post gadolinium administration images depict the distribution of the intravenous contrast agent	Acute: evidence for myocardial injury Chronic: evidence for myocardial fibrosis/ scar
Native T1 mapping	Pixel by pixel presentation of T1 values (in msec) of the myocardium *without* gadolinium-based contrast agent	Increased T1 times indicate increased interstitial space (e.g., collagen or amyloid deposits) or increased (intracellular or extracellular) tissue water (i.e., myocardial edema) Decreased T1 times indicate intracellular lipid or iron deposition	
Late gadolinium enhancement (LGE)	T1-weighted images acquired 10 to 15 minutes after intravenous administration of a gadolinium-based contrast agent	Infarction/scar: typically subendocardial involvement in a coronary artery distribution. Nonischemic necrosis/scar: typically mid or epicardial myocardial involvement, not in a coronary artery distribution	
Extracellular volume fraction (ECV)	Proportion of the extracellular volume in the myocardium compared to total myocardial volume. Estimated using native T1 and post gadolinium T1 mapping methods	Increased ECV is present in diffuse myocardial fibrosis as well as myocardial inflammation. ECV may also be elevated in infiltrative disease such as amyloidosis	
T2 relaxation parameters*			
T2 weighted images	Images dominated by effects of T2 magnetic relaxation. Signal intensity is relative (not quantitative)	Signal intensity is markedly increased in areas of tissue edema.	Evidence for myocardial edema, may be associated with inflammation
T2 mapping	Pixel by pixel presentation of T2 values (in msec) of the myocardium	Increased T2 time indicates myocardial edema	

*T1 relaxation, or longitudinal magnetic relaxation time, in msec. After a radiofrequency pulse, T1 is the time constant for regrowth of (1 − 1/e) or about 63% of its initial maximum magnetic strength.
**T2 relaxation, or, transverse magnetic relaxation time, in msec. After a radiofrequency pulse, T2 is the time constant for transverse magnetization to fall to approximately 37% (1/e) of its initial value.

Table 2. Summary of studies of CMR in patients after recovery from COVID-19

Authors and study design	*n* (cases)	Men (%)	Age (years)†	Timing of CMR	Patient characteristics during acute COVID-19	Patient characteristics during the post-acute stage	Comparator(s)	LGE	Myocardial parametric mapping	LV/RV structure and function, pericardial disease
Ng et al. (37) Retrospective observational study	16	56	68 [53-69]	56 days (median) after recovery.	All hospitalized, 94% (n=15) had mild-moderate symptoms. On admission, 7 (44%) patients had troponin elevation (n=7, 44%) and 88% (n=14) had ECG abnormalities.	At ≥2 weeks' post-discharge, 11 (69%) patients were asymptomatic; 5 (31%) had symptoms such as cough, shortness of breath, and mild chest pain.	None	Three (19%) had non-ischemic LGE and elevated T2 (57 to 62ms. One patient (6%), had ischemic LGE corresponding to previous known MI.	In 6 patients (all without LGE), 4 had elevated T1 only, 1 had elevated T2 only, and 1 had both elevated T1 and T2.	Not reported
Puntmann et al.(38) Prospective observational cohort study	100	53	49 (±14)	71 (64-92) days from positive test.	67% recovered at home. 18% asymptomatic, 49% mild-moderate symptoms, 33% severe disease. 15% had significant TnT elevation.	On day of CMR, 17 patients reported atypical chest pain and 20 reported palpitations. Compared with pre–COVID-19 status, 36 patients (36%) reported ongoing shortness of breath and exhaustion. 5% had significant TnT elevation at time of CMR.	1. Healthy controls (n=50): age- and sex-matched normotensive adults, normal cardiac volumes and function *2*. Risk factor matched controls (n=57)	There was greater proportion of cases with LGE in (ischemic 32% vs 17%) and non-ischemic (20% vs 7%) patterns compared to matched controls.	Cases had significantly higher native T1 (1125ms vs 1111ms), and higher T2 (38.2ms vs 35.4ms) than matched controls. Greater proportion of cases with abnormal native T1 (73% vs 58%) and abnormal T2 (60% vs 26%) than matched controls.	Cases had significantly lower LVEF (57% vs 62%), lower RVEF (54% vs 59%), and larger LVEDVi (86ml/m^2 vs 76ml/m^2) than controls Pericardial effusion (20% vs 7%) was observed more frequently in cases than controls.
Huang et al.(44) Retrospective observational study	26	38	38 [32-45]	47 (36-58) days from onset of cardiac symptoms.	All hospitalized. 85% (n=22) with moderate and 15% (n=4) severe symptoms. 81% (n=21) required supplemental oxygen, of these 3 (12%) required NIV or high flow oxygen.	All had ≥1 cardiac symptoms (chest pain 12%, palpitation 88%, chest distress 23%) after discharge. Patients with history of CAD or myocarditis were excluded. None had elevated HsTnT at time of CMR.	Healthy controls (n=20): age- and sex-matched controls.	15 (58%) had "positive" CMR (elevated T2 and/or LGE). 27% (n=7) had both elevated T2 and positive LGE, 27% (n=7) had elevated T2 alone, and one patient had positive LGE alone.	Compared to healthy controls, "CMR positives" had significantly higher native T1 (1271ms vs 1224ms), higher T2 (42.7ms vs 39.1ms), and higher ECV (28.2% vs 23.7%).	"CMR positives" had significantly lower RVEF (36.5% vs 46.1%), lower RVSVi (15.9ml/m^2 vs 21.3ml/m^2), and lower RVCI (1.2l/min/m^2 vs 1.5l/min/m^2)
Raman et al.(45) Prospective observational cohort study	58	59	55.4 (±13.2)	2.3 (2.1-2.5) months after COVID-19 onset.	All hospitalized with moderate or severe COVID-19. 36% (n=21) required critical care, 21% were	Individuals with pre-existing severe/end-stage multi-system comorbidities were excluded.	Risk factor matched controls (n=30): matched on age, sex, BMI, smoking, hypertension,	The proportion of cases with LGE was not statistically different to controls in myocardial (11.5% vs 7.4%) or	Basal and mid myocardial T1 were elevated in 13 (22%) and 4 (7%) patients respectively.	Not reported

					intubated, 3% had dialysis, and 7% required inotropic support. 5% (n=3) had significantly elevated hsTnI*.		diabetes, CAD, and stroke.	ischemic (1.9% vs 0%) patterns.	Cases had higher native T1 in the basal (1179ms vs 1149ms) and mid-level (1173ms vs 1150ms) sax slices than controls.	
Li et al.(40) Prospective observational cohort study	40	60	54 (±12)	158 ±18 days after admission and 124 ±17 days after discharge.	Hospitalized with moderate (60%) or severe (40%) COVID-19/	Discharged for ≥90 days. Individuals with pre-existing CAD, myocarditis, abnormal ECG, abnormal blood cardiac biomarkers, or cardiac symptoms were excluded.	Healthy controls (n=25): age- and sex- matched controls without history of cardiovascular disease, with normal ECG, echo, and CMR.	One patient (3%) had LGE located at the middle inferior wall.	Global ECV was significantly higher in cases compared to controls (30% vs 25%). -Global native T1 was not significantly different between cases and controls (1137ms vs 1138ms).	2D global longitudinal strain was significantly poorer in cases - compared to controls (-12.5% vs -15.4%). - There were no differences in LV or RV size or function between cases and healthy controls.
Wang et al. (41) Prospective observational cohort study	44	43.2	47.6 (±13.3)	102.5 ± 20.6 days from discharge	Hospitalized with moderate (n=32, 73%), severe (n=11, 25%), or critically ill (n=1, 2%) symptoms. One patient had abnormal ECG at admission. 9.1% (n=4) and 43.2% (n=19) had renal and liver injury respectively.	Recovered and discharged for 12 weeks. Individuals with the following pre-existing uncontrolled hypertension, CAD, valvular disease, atrial fibrillation, heart failure, myocarditis, cardiomyopathy, pacemaker placement were excluded.	Healthy controls (n=31): Age and sex matched; known to have normal ECG, echo, and CMR.	LGE was identified in 13 (30%) of patients, compared to none of the controls. All LGE lesions were in the mid myocardium and/or sub-epicardium with a scattered distribution.	Native T1 not significantly different in LGE positive vs negative cases (1286ms vs 1253ms). Not available in controls for comparison.	LGE-positive patients had significantly decreased LV and RV peak global circumferential strain (GCS), and poorer RV peak global longitudinal strain as compared to non-LGE patients ($p < 0.05$), while no difference was found between the non-LGE patients and healthy controls.
Knight et al.(42) Prospective observational study	29	83	64 (±9)	37±10 days after diagnosis.	Hospitalized with COVID-19 and unexplained elevated hsTnT* during admission. 10 patients (34%) required critical care ventilatory support.	Recovered and discharged from hospital. Individuals with ACS, PE, known cardiac pathology likely to cause scar, and those aged ≥80 years were excluded.	None	45% (n=13) had "myocarditis-like" LGE, 7% (n=2) had mid-wall LGE only. 7% (n=2) patients had ischemic LGE. For 31%(n=9) elevated hsTnT was attributed to an ischemic cause. Of these, 7 had inducible ischemia, 1 had prior myocardial	In patients with "myocarditis-like LGE", there was no significant difference in peak myocardial T2 compared to the rest of the cohort.	Mean biventricular systolic function for the overall cohort was normal (LVEF: 67.7%, RVEF: 63.7%). One (3%) patient had mild LV dysfunction, and one (3%) had severe biventricular dysfunction. 7% (n=2) had pericardial effusions.

								infarction and 1 had both inducible ischemia and a prior infarction by CMR.		
Kotecha et al. (43) Prospective observational study NB. This study includes the 29 patients in study by Knight et al. (45)	148	56	64±12	68 days after diagnosis.	Hospitalized with moderate-severe COVID-19 and hsTnT* during admission. 32% (n=48) required critical care or ventilatory support.	Recovered and discharged from hospital. Patients with medical unsuitability for CMR assessed by the referring clinician (e.g., severe comorbidities, frailty), or ACS as the primary reason for hospitalization were excluded.	1. Risk factor matched controls (n=40): matched for age, sex, diabetes, and hypertension. 2. Healthy volunteers (n=40): with no cardiac symptoms, history of cardiovascular disease or hypertension.	No differences in the proportion of cases/controls with any LGE (49% vs 45%), subendocardial/transmural LGE (16% vs 15%), or mid-myocardial LGE (11% vs 15%). % of patients with subepicardial LGE was greater than controls (22% vs 5%).	There was no significant difference in proportion of patients with abnormal septal T1 (13% vs 13%), remote native T1 (1033ms vs 1028ms), abnormal septal T2 (3% vs 3%), or remote T2 (46ms vs 47ms) compared to matched controls.	Cases had significantly larger RVEDVi ($70ml/m^2$ vs $65ml/m^2$), larger RVESVi ($28ml/m^2$ vs $23ml/m^2$), and lower RVEF (61% vs 64%). There was no statistical difference in LV volume and function metrics.
Joy et al. (39) Prospective observational study	74	42	37 (31-48)	6 months post infection.	Seropositive healthcare workers. 11 (15%) were asymptomatic, the remainder had mild symptoms. One patient was admitted to hospital.	At the time of CMR, 16 (11%) reported symptoms: 5 (3%) sore throat; 4 (3%) fatigue; 4 (3%) rhinorrhea; 3 (2%) shortness of breath; with no difference between seropositive and seronegative subjects (8% vs 13%).	Matched controls (n=75): seronegative healthcare workers matched on age, sex, and ethnicity.	No difference in LGE% between cases and controls (0.27% vs 0.32%). No between cases and controls in the proportion of individuals with RV insertion point LGE (11% vs 8%) or non-RV insertion point LGE (8% vs 9%).	Amongst cases and controls, there was no difference in septal T1 (1020ms vs 1016ms), global T1 (1010ms vs 1007ms), septal T2 (48.8ms vs 48.6ms), global T2 (48.7ms vs 48.4ms), septal ECV (22.3% vs 22.1%), or global ECV (21.6% vs 21.5%).	There were no significant differences in LV structure or function metrics between cases and controls.

Table footnotes: ACS: acute coronary syndrome; CAD: coronary artery disease; CMR: cardiovascular magnetic resonance; COVID-19: coronavirus disease 2019; ECG: electrocardiogram; Echo: echocardiogram; ECV: extracellular volume; IHD: ischemic heart disease; LGE: late gadolinium enhancement; LV: left ventricle; LVEF: left ventricular ejection fraction; LVEDVi: left ventricular end-diastolic volume index; NIV: non-invasive ventilation; RV: right ventricle; RVCI: right ventricular cardiac index; RVEF: right ventricular ejection fraction; RVSVi: right ventricular stroke volume index; sax: short axis. †Age is reported as mean (±standard deviation) or median [interquartile range]; *Elevated HsTnT indicates, level > 99th percentile URL; high-sensitivity troponin T (hsTnT), N-terminal pro–b-type natriuretic peptide. §discharging criteria: normal temperature lasting >3 days, resolved respiratory symptoms, substantially improved exudative lesions on chest computed tomography, and 2 consecutive negative RT-PCR results ≥ 24 hours apart.

Table 3. CMR of athletes recovered from COVID-19 (all retrospective studies except prospective for (53) and (57))

Authors	Patient cohort (cases)			LGE positive	Abnormal T1+T2, myocarditis-like findings on CMR[§]	LGE pattern/location in patients with myocarditis[§§]	Troponin in patients with myocarditis[§]	ECG, TTE in patients with myocarditis[§]	Pericardium pathology
Rajpal et al. (53)	*n*	Men (%)	Age (years)[†]	12/26 (46%)	4/26 (15%) 2 asymptomatic 2 symptomatic	Epicardial, segment 3,9 Patchy, segment 3,9 Patchy, segment 2,3,8,9 Linear, segment 8,9	No	No	Effusion: 2/26 (8%) in athletes with myocarditis[§]
	26	58	19±1.5						
	54% asymptomatic, 46% mild-moderate symptoms. CMR 11-53 days after positive test.								
Brito et al. (55)	*n*	Men (%)	Age (years)	1/48 (2%)	0%	N/A	N/A	N/A	Pericardial LGE: 19/48 (40%) Effusion: 28/48 (58%)
	54 (48*)	85	19 (19, 21)						
	30% asymptomatic, 66% mild symptoms, 4% moderate symptoms. CMR 27 (range 22-33) days after positive test.								
Małek et al. (56)	*n*	Men (%)	Age (years)	1/24 (4%)	0%	N/A	N/A	N/A	Effusion: 2/26 (8%)
	26	19	24 [21-27]						
	23% asymptomatic, 54% mild, 19% moderate symptoms. CMR 32 [22-62] days after positive test.								
Vago et al. (57)	*n*	Men (%)	Age (years)	0/12 (0%)	0%	N/A	N/A	N/A	No
	12	17	23 [20-23]						
	17% asymptomatic, 83% mild-moderate symptoms. CMR 17 [17-19] days after positive test in women; 67 days and 90 days in men								
Clark et al. (58)	*n*	Men (%)	Age (years)	16/59 (27%)	2/59 (3%) 1 asymptomatic 1 symptomatic	Segment 3 Segment 3,11	No	1 of 2 patients developed LV dysfunction (LVEF 45%) on a follow-up TTE	Pericardial LGE: 1/59 (2%)
	59	37	20 [19, 21]						
	22% asymptomatic, 78% mild-moderate symptoms. CMR 22 [13-37] days after positive test.								
Starekova et al. (59)	*n*	Men (%)	Age (years)	42/145 (29%)	2 (1.4%) 1 asymptomatic 1 symptomatic	Segment 11,12,13,15,16 Segment 4, 10	1 of 2	1 of 2 patients new nonspecific ST-T-wave ECG abnormalities and mild reduction in GLS in TTE	Pericardial LGE: 1 (in patient with myopericarditis)
	145	75%	19.6±1.3						
	12% asymptomatic, 49% mild symptoms, 28% moderate symptoms. CMR median of 15 (range: 11-194) days after positive test.								
Martinez et al. (60)	*n*	Men (%)	Age (years)	2/27 (7%)	3/27 (11%)[§§] 0.4% of the total cohort; 3 symptomatic	N/A	1 of 3	1 of 3 patients ECG abnormalities 1 of 3 patients regional wall motion; mildly reduced LVEF	Pericardial LGE: 2/27 (7.4%)
	789 (27*)	99	25±3						
	42% asymptomatic or minimally symptomatic, 58% moderate to severe symptoms. CMR mean of 19±17 (range: 3-156) days after positive test.								

								(50%); dilated RV by TTE	
Hendrickson et al. (61)	*n*	Men (%)	Age (years)	0/5 (0%)	0%	N/A	N/A	N/A	Small effusion in TTE: 4/137 (2.9%)
	137 (5*)	68%	20 (18-27)						
	67% mild symptoms, 33% moderate symptoms. CMR range: 15-44 days								
Moulson et al. (62)	*n*	Men (%)	Multicenter (n=42) study			Definite, probable or possible cardiac involvement overall *n* = 21/3018 (0.7%) - 15/2820 (0.5%) who underwent clinically indicated CMR (*n*=119) - 6/198 (3%) who underwent primary screening CMR			
	3018 (198**)	68%							
Daniels et al. (54)	*n*	Men (%)	Multicenter (n=13) study			Myocarditis *n* = 37/1597, range 0-7% (overall 2.3%, [95% CI, 1.6%-3.2%]) - 31/37 myocarditis-like findings on CMR§			
	2461 (1597*)	67%							

Table 3 footnote. †age given as mean ± standard deviation, (range), or median [interquartile range]; *number who underwent CMR; **number who underwent primary screening CMR; § myocarditis diagnosis based on CMR findings as per updated Lake Louise criteria (59); §§ CMR criteria for myocarditis not specified; $ segment location given according to 17-segment American Heart Association model of the left ventricle. CMR, cardiac magnetic resonance imaging, ECG, electrocardiogram; GLS, global longitudinal strain; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; N/A, not applicable or not given; RV, right ventricle; TTE, transthoracic echocardiography

Table 4: CMR for patients with COVID-19: CMR should be considered only when results are likely to have an impact on clinical decision-making.	
Clinical scenario	**Consider CMR for the following patients:**
1. Patients with acute COVID-19	High pre-test probability for acute myocardial injury due to inflammation
2. Convalescent patients after recovery from COVID-19	1. Unexplained, persisting, or recurring cardiovascular symptoms as a part of a systemic inflammatory post-COVID syndrome (4 weeks after recovery) 2. For follow-up, when CMR in the acute setting that showed clinically significant acute myocardial injury (4 weeks after baseline/acute CMR)
3. Recovering high-performance athlete: return to play	1. Prior to returning to training for patients with: a. History of moderate COVID-19 and high-pretest probability of myocardial injury b. History of severe COVID-19 2. Return to play with new onset cardiovascular symptoms and suspicion of myocardial injury
4. Patients with suspected MIS-C (Multisystem Inflammatory Syndrome in Children)	1. Clinical suspicion of myocardial injury during hospitalization for acute illness. 2. At approximately 1-6 months after the acute MIS-C presentation in patients with prior moderately or severely diminished left ventricular systolic function or baseline abnormal CMR. 3. Concern for coronary artery aneurysm in setting of Kawasaki disease-like presentation

Central illustration

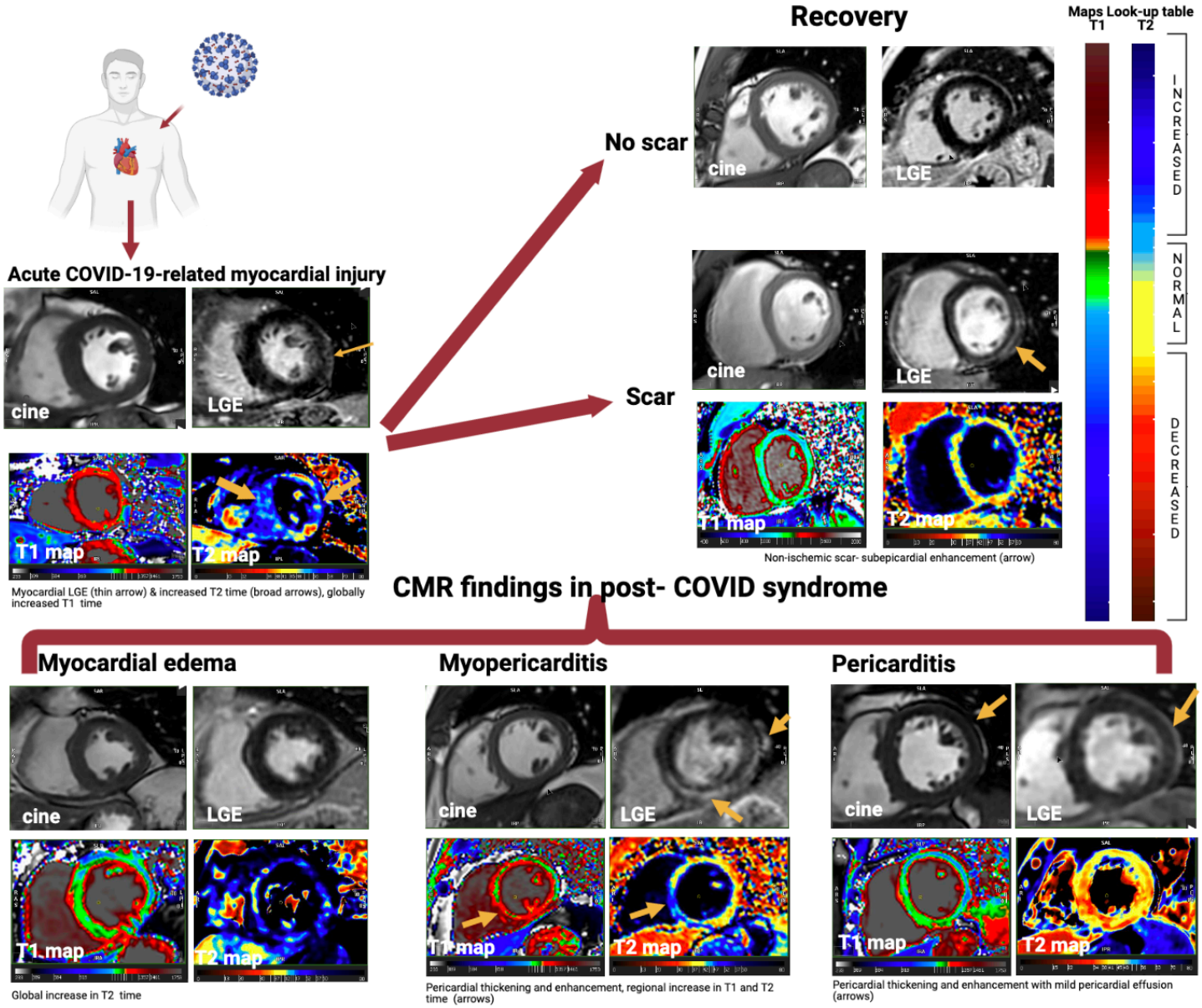

Figure: The role of cardiac magnetic resonance (CMR) in characterization of COVID-19 disease.

Supplemental Material

Supplemental Table 1. Cardiac evaluation/ Pitfalls in athletes recovered from COVID-19.

Test	Possible pitfalls	Comments
Troponin	• Increase in values may be exercise-induced (1,2)	• If isolated abnormal finding, consider repeated testing after at least 24-48h exercise pause (2) • In case of persistence, but absence of specific symptoms and pathology on imaging, other systemic causes should be considered (3)
ECG	• Physiological vs. pathologic LV wall thickening (4) • Electrical remodeling in female/male athletes (5) • Ascending concave ST segments in the lateral and inferior leads and tall T wave seen in athletes may mimic myopericarditis (6)	• Findings that may indicate viral-induced myocardial injury: pathological Q waves, ST segment depression, (new) diffuse ST segment elevation and T-wave inversion (7) • Findings indicating pathologic LV hypertrophy: pathologic Q waves, abnormal ST segments, T-wave changes beyond the anterior precordial leads, and left bundle block (4) • Findings seen in healthy athletes: isolated axis shifts and atrial abnormalities (4) sinus bradycardia, unspecific intraventricular conduction delay
CMR (Volumetry, Mapping, Strain)	• Structural changes are influenced by sporting activity, sex (5,8,9) • Normal values for tissue relaxation times may differ from non-athletes and according to sex (9), and MRI systems (10,11) • Strain values for athletes are not widely established; may differ from non-athletes and between sporting types (12–14) and according to sex, age, loading conditions (15) as well as evaluation software (15,16)	• Consider performing when indicated (in high pretest probability, clinical symptoms suggestive of myocarditis with isolated or combined objective pathologic criteria) • Consider normative athletic control group matched to age, BMI, gender, sporting activity • For quantitative parameters, consider normative values for specific athlete cohort in the literature • T1 mapping, consider ECV (parameter independent of field strengths, vendors, and acquisition techniques) (17) • There are limited data reported on the utility of strain in the athletes for detection of myocarditis in COVID-19
CMR (Edema, LGE)	• Myocardial edema may be present after endurance activity (18) • Epi- and pericardial fat can mimic epicardial enhancement using inversion recovery techniques (19) • Partial volume effects, ghosting artifacts • Perforator branches may mimic linear enhancement (19)	• Consider exercise pause of at least 48h before CMR • Consider performing when indicated (in high pretest probability based on clinical syndrome suggestive of myocarditis with isolated or combined objective pathologic criteria) • Consider quality check • Consider pathological, if late gadolinium enhancement presents in at least two consecutive slices (19) and/or imaging planes; Isolated LGE at the RV insertion point has been previously reported in association with athletic activity and is unlikely to be related to COVID-19

Notes.– BMI, body mass index; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; ECV, extracellular volume; LGE, late gadolinium enhancement; LV, left ventricle; MRI, magnetic resonance imaging; TI, inversion time

Supplemental Table 2. Summary of selected planned and ongoing studies including cardiac MRI in the context of coronavirus disease 2019.

Study name (country)	Study design	n*	Study population	Control group	Selected relevant investigations proposed	Stage	Estimated completion
C-MORE (UK)(20)	Prospective observational cohort study	616	Adults (>18 years) with PCR confirmed SARS-CoV-2 infection and moderate to severe COVID-19 (≥2 days in hospital)	Yes	*Imaging:* CMR, and MRI of the brain, lung, kidneys, and liver at 3, 6, and 12 months after first onset of COVID-19 symptoms. Subsets are planned to have CT lungs and TTE *Non-imaging:* pulmonary function, exercise capacity, cognition, and mental health	Recruiting	May 2023
COVERSCAN (UK)(21)	Prospective observational cohort study	507	Adults (>18 years) with PCR confirmed SARS-CoV-2 infection, ≥7 days after discharge from hospital	No	*Imaging:* CMR and MRI of the lungs, kidneys, liver, pancreas, and spleen– three scans to be performed over 12 months	Recruiting	May 2023
COVID-HEART (UK)(22)	Prospective observational cohort study	370	Adults (≥18 years) hospitalized with COVID-19 and elevated troponin during the acute illness	No	*Imaging:* CMR *Non-imaging:* ECG, 6MWT, quality of life questionnaire, blood sample for genetic and immunologic testing Assessment made at baseline and repeated at 6 months	Recruiting	Aug. 2021
UK Biobank COVID-19 Repeat Imaging Study (UK)(23)	Prospective observational cohort study	3,000	UK Biobank participants (50-83 years) who have previously completed the UK Biobank Imaging protocol and have evidence of previous SARS-CoV-2 infection	Yes	*Imaging:* CMR, MRI of the brain and liver, carotid ultrasound, and whole body DXA. Imaging will be linked with scans previously performed at the UK Biobank imaging visit (2015-2020); thus, all study participants will have imaging available at two-time intervals (before and after COVID-19)	Recruiting	June 2021
MEMORY-COVID (UK)(24)	Retrospective observational case control study	53	Adults (≥18 years) recovered from severe COVID-19 requiring hospitalization with/without evidence of myocardial injury (biochemical, electrographic, imaging)	Yes	*Imaging:* gadolinium- and manganese-enhanced CMR and coronary CT angiography. *Non-imaging:* 12 lead ECG, blood biomarkers, hematology	Recruiting	June 2022
MOIST (Canada)(25)	Prospective observational cohort study	228	1) Adults (>18 years) with acute COVID-19 and positive high sensitivity troponin will have investigations at baseline and recovery (12 weeks post diagnosis) 2) Adults (≥18 years) recovered from COVID-19 in last 3 months.	No	*Imaging:* MRI heart, brain, lungs, and liver *Non-imaging:* blood biomarkers, spirometry, olfaction testing, exercise capacity	Recruiting	Sept. 2021
CARDOVID (France)(26)	Prospective observational cohort study	80	Pediatric patients (<20 years old) with a probable or a proven diagnosis of COVID 19 admitted to hospital with systemic acute inflammation	No	*Imaging:* at least one of - CMR, cardiac CT, CT thorax	Recruiting	June 2022

			and cardiac symptoms (cardiogenic shock or chest pain or clinical suspicion of acute myocarditis or left ventricular ejection fraction <55%)				
MYOCOVID (France)(27)	Prospective observational cohort study	400	Adult or pediatric patients with confirmed COVID-19 treated in intensive coronary care unit or intensive care unit for symptoms of acute myocarditis confirmed by CMR, CT scan or myocardial biopsy	No	*Imaging:* TTE ± CMR 12 months after acute illness. *Non-imaging:* clinical review	Recruiting	Oct. 2021
Patterns of Arrhythmias and Conduction Block in COVID-19 Patients and Its Relation to Myocardial Injury Detected by Cardiac Magnetic Resonance (Egypt)(28)	Prospective observational cohort study	50	Adults (18-80) hospitalized with COVID-19 and arrhythmias/heart block within 6 months after acute infection and with new ECG changes (LBBB, PVCs, ventricular tachycardia, AF, atrial flutter, ST-T changes, and conduction defects)	No	*Imaging:* CMR	Not yet recruiting	Jan. 2024
MIIC-MI (UK)(29)	Prospective observational study	20	Adults (18-99 years) hospitalized with acute COVID-19 and troponin elevation	No	*Imaging:* CMR ± coronary CT angiography ± Cardiac PET/MRI (68Ga-DOTATATE or 18F-FDG) *Non-imaging:* blood biomarkers, immune phenotyping, coagulation profile	Not yet recruiting	June 2021
Cardiovascular Implications of COVID-19 (USA)(30)	Cross-sectional observational study	70	Adults (18-80 years) at least 4-6 weeks after hospitalization for COVID-19 and elevated troponin during hospitalization	No	*Imaging:* CMR *Non-imaging:* blood biomarkers, hematology, autoantibodies, genomics	Recruiting	Dec. 2020
COLUMBIA CARDS (USA)(31)	Prospective observational cohort study	70	Adults (>18 years) who are at least 4 weeks from positive SARS-COV-2 test or, if hospitalized, at least 2 weeks from discharge	Yes	*Imaging:* CMR, TTE *Non-imaging:* clinical examination, blood biochemistry	Recruiting	Sept. 2022
Cardio-pulmonary Inflammation and Multi-System Imaging During the Clinical Course of COVID-19 Infection in Asymptomatic and Symptomatic Persons (USA)(32)	Prospective observational cohort study	180	Cases: adults (18-80 years) with PCR confirmed Sars-CoV-2 infection: 1) during acute phase of COVID-19 (within 14-28 days of admission) or 2) after recovery from COVID-19 (>28 days after infection)	No	*Imaging:* CMR, cardiac CT, TTE, MRI and CT scans of the brain and lungs, and ultrasound kidneys. *Non-imaging:* blood and urine samples, nasal swabs, bronchoscopy, participants may provide a spinal fluid sample	Recruiting	May 2024

CISCO-19 (UK)(33)	Prospective observational cohort study	180	Adults (>18 years) attended or admitted to hospital with COVID-19 (diagnoses by laboratory, clinical, or radiographic criteria) at least 28 days after discharge from hospital	No	*Imaging:* CMR, cardiac CT *Non-imaging:* blood biomarkers, patient reported measures of health status, well-being and functional capacity	Recruiting	Aug. 2021
COVID-CMR (France)(34)	Prospective observational cohort study	240	Adults (≥ 18 years) with history of laboratory-proven symptomatic COVID-19 infection managed without hospitalization (120 cases and 120 controls)	Yes	*Imaging:* CMR *Non-imaging:* 12 lead ECG, blood biomarkers, SARS-CoV-2 serology, 24-hour Holter ECG	Recruiting	Apr. 2021
COSMIC-19 (Kenya) (35)	Cross-sectional observational study	50	Adults (≥ 18 years) within 2-4 weeks of confirmed SARS-COV-2 infection	No	*Imaging:* CMR, combined CTCA/FDG PET *Non-imaging:* blood biomarkers	Recruiting	Feb. 2021
CMR Findings in COVID-19 Patients Presenting With Myocardial Infarction (Egypt)(36)	Cross-sectional observational study	60	Adults (aged 18-80 years) with COVID-19 presenting with AMI	Yes	*Imaging:* CMR	Not yet recruiting	Oct. 2023
COVIDsortium CMR Substudy (UK)(37)	Nested case-control study	149	Healthcare workers PCR and serology confirmed mild/asymptomatic SARS-CoV-2 infection, assessed within 6 months of acute infection	Yes	*Imaging:* CMR *Non-imaging:* serial weekly SARS-CoV-2 PCR and serology testing over 16 weeks	Completed-under peer review	Nov. 2020
COVIDsortium CMR Substudy (USA)(37)	Nested case-control study	100	Healthcare workers PCR and serology confirmed mild/asymptomatic SARS-CoV-2 infection, assessed within 6 months of acute infection	Yes	*Imaging:* CMR *Non-imaging:* serial monthly SARS-CoV-2 PCR and serology testing.	Recruiting	July 2021
Collaborative Cohort of Cohorts for COVID-19 Research (C4R) (USA)(38)	Nested longitudinal case-control study	1200	Study participants with confirmed SARS-CoV-2 infection	Yes	*Imaging:* CMR, TTE, CT thorax, MRI brain *Non-imaging:* clinical phenotyping	Under review	Mar. 2021
Etiology of increased TnT levels post-covid-19 - a cardiac magnetic resonance study (Sweden)(39)	Prospective observational cohort study	150	Patients hospitalized for COVID-19 in need of oxygen-therapy with and without respirator, assessed 6 months after discharge	No	*Imaging:* CMR, TTE *Non-imaging:* biochemical markers, gender-aspects and comorbidity	Recruiting	Dec. 2021
IMPRoving Cardiovascular RiSk Stratification Using T1	Prospective longitudinal case-control study	300	Patients with new or ongoing symptoms after acute COVID-19	Yes	*Imaging:* CMR, TTE *Non-imaging:* biochemical markers, gender aspects, long term follow up	Recruiting	Dec. 2021

Mapping in General populatION (IMPRESSION) COVID19 substudy (Germany)(40)							
NAPKON-HAP (Nationales Pandemie Kohorten Netz – Hochauflösende Plattform) (Germany)(41)	Observational cohort study	750	Study participants with confirmed SARS-CoV-2 infection	No	*Imaging:* CMR, TTE, lung imaging *Non-imaging:* biochemical markers, microbiome, single cell and bulk transcriptomics, genomic, proteomic, flow cytometry, flow mass spectrometry,	Recruiting	Ongoing
Oxford Acute Myocardial Infarction (OXAMI)-COVID (UK)(42)	Prospective observational cohort study	60	Hospitalized adult patients (18-90) with confirmed SARS-COV-2 infection with and without myocardial injury, defined as rise in high sensitive Troponin. CMR before hospital discharge.	Yes	*Imaging: CMR, CT thorax,* *Non imaging:* blood biomarkers	Recruiting	May 2021
Clinical Significance of Subclinical Myocardial Involvement in Recovered COVID-19 Patients using Cardiovascular Magnetic Resonance (Hong Kong SAR, China)(43)	Prospective longitudinal cohort study	70	Recovered COVID-19 patients with RT-PCR confirmation of SARS-CoV2. Scans will take place (i) within 2 weeks of confirmed recovery, (ii) 3 months after recovery and (iii) 1 year after recovery.	Yes	*Imaging:* CMR *Non-imaging:* 12 lead ECG, SARS-CoV-2 serology, 6MWT, blood biomarkers	Not yet recruiting	June 2023
SCMR COVID-19 Registry (international)(44)	Prospective registry	unlimited	Adults (≥ 18 years) with history of laboratory-proven asymptomatic and symptomatic COVID-19 infection managed with and without hospitalization	No	*Imaging:* CMR	Recruiting	Dec. 2022
Pa-COVID-19 substudy to test for microvascular disease (Germany)	Prospective observational cohort study	100	Adults (≥ 18 years) with history of laboratory-proven symptomatic COVID-19 infection	No	*Imaging:* CMR (6 weeks and 6 months post COVID-19), TTE. *Non-imaging:* blood and urine samples, nasal swabs, pulmonary function, exercise capacity, cognition, and mental health.	Recruiting	June 2021
Detection of Myocarditis in Patients post COVID-19 vs. healthy controls vs. classical viral Myocarditis	Retrospective observational case control study	75	Adults (≥ 18 years) with history of laboratory-proven symptomatic COVID-19 infection managed with and without hospitalization and endomyocardial biopsy; healthy	Yes	*Imaging:* CMR, TTE. *Non-imaging:* Blood and urine samples, nasal swabs, pulmonary function, exercise capacity, cognition, and mental health, endomyocardial biopsy	Completed-under peer review	Jan. 2021

(Germany)			controls and patients with classical viral myocarditis				
Evaluation of cardiac damage post COVID-19 in pediatric patients (Germany)	Prospective observational cohort study	50	Pediatric patients (<18 years old) with a proven diagnosis of COVID 19, controls are pediatric patients with acute classical viral myocarditis	Yes	*Imaging:* CMR *Non-imaging:* blood and urine samples, nasal swabs.	Recruiting	June 2021
Long-TerM OUtcomes after the Multisystem Inflammatory Syndrome In Children: MUSIC (USA, Canada)(45)	Prospective observational cohort study	600	Pediatric patients recovered from Multisystem Inflammatory Syndrome in Children	No	*Imaging:* medical charts will be reviewed to obtain information during the hospital course and outpatient clinic visits related to the study, including review of heart imaging tests performed as part of medical care *Non-imaging:* clinical follow up visits – typically at 2 weeks, 6 weeks, 6 months, 1 years and annually until 5 years after hospital discharge. Blood or saliva samples from participants and their parents for DNA testing	Recruiting	2026
CONVALESCENCE Long COVID (UK)	Prospective observational cohort study	800	Adults (>18 years) with probable or proven diagnosis (PCR or Antibody positive) of COVID-19 with and without long COVID symptoms	Yes	*Imaging:* CMR, and MRI of the brain, lung, kidneys, and liver *Non-imaging:* exercise capacity, heart rate variability, respiratory function, mental health and cognitive function, wearables, blood biomarkers – genetics and immunology	Not yet recruiting	Feb. 2024

Supplemental Table 3. CMR sequences and parameters for acute and convalescent COVID-19 patients.

CMR sequence/technique*(46)	**Diagnostic target**	**CMR parameters**	**Notes**
Cine images (b-SSFP)	LV and RV volumes and function, wall motion abnormality	LV and RV end-diastolic, end-systolic, stroke volume, cardiac index, cardiac output, LV mass, strain- global longitudinal (circumferential strain-optional)	Values interpreted using latest reference standards(47)
T1 mapping (MOLLI, ShMOLLI)	Myocardial injury/fibrosis	Global, segmental and selected regional values	Values interpreted as compared to local institutional reference standards or converted to z-scores
T2 mapping (T2-TSE, T2p-SSFP, T2- GraSE)	Myocardial edema	Global, segmental and selected regional values	Values interpreted as compared to local institutional reference standards or converted to z-scores
T2-weighted imaging (STIR)	Myocardial edema	Increased signal intensity ratio	
Late gadolinium enhancement (IR-GRE, PSIR-GRE, single shot bSSFP)	Myocardial injury, necrosis/scar	Presence, location, extent, pattern of enhancement	
Post-contrast T1 map	Myocardial injury/fibrosis	Extra-cellular volume (ECV)	Requires hematocrit at the time of the CMR
Coronal T2-weighted images for lungs (optional) (HASTE, TSE) including localizer images	COVID-related lung pathology, pericardial pathology	Pulmonary infiltrates Pericardial enhancement and effusion, pulmonary infiltrates	Report ground glass opacities, nodules, consolidation, pericardial effusion >5 mm

Notes.– b-SSRP, balanced steady state free precession; MOLLI, modified Look-Locker; ShMOLLI, short MOLLI; TSE, turbo spin echo; GraSE, gradient and spin echo; STIR, short tau inversion recovery; GRE, gradient recalled echo; PSIR, phase sensitive inversion recovery; T2p-SSFP, T2 prepared SSFP

*General imaging principles and techniques to be followed according to 'SCMR imaging protocol:2020 update'(46).
See also Kelle, S. et al. (48) and (49) for SCMR protocol recommendations and resources.

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