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MINIREVIEWS

## Role of cardiac magnetic resonance imaging in the diagnosis and management of COVID-19 related myocarditis: Clinical and imaging considerations

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## Abstract

There is a growing evidence of cardiovascular complications in coronavirus disease 2019 (COVID-19) patients. As evidence accumulated of COVID-19 mediated inflammatory effects on the myocardium, substantial attention has been directed towards cardiovascular imaging modalities that facilitate this diagnosis. Cardiac magnetic resonance imaging (CMRI) is the gold standard for the detection of structural and functional myocardial alterations and its role in identifying patients with COVID-19 mediated cardiac injury is growing. Despite its utility in the diagnosis of myocardial injury in this population, CMRI's impact on patient management is still evolving. This review provides a framework for the use of CMRI in diagnosis and management of COVID-19 patients from the perspective of a cardiologist. We review the role of CMRI in the management of both the acutely and remotely COVID-19 infected patient. We discuss patient selection for this imaging modality; T1, T2, and late gadolinium enhancement imaging techniques; and previously described CMRI findings in other cardiomyopathies with potential implications in COVID-19 recovered patients.

Key Words: Cardiac magnetic resonance imaging; COVID-19; Cardiovascular magnetic resonance; Myocarditis; Coronavirus; Cardiovascular complications

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**Core Tip:** Cardiovascular magnetic resonance imaging (CMRI) is a powerful imaging modality used in defining cardiac tissue characterization. As the prevalence and incidence of coronavirus disease 2019 (COVID-19) continues to rise, the utility of CMRI in defining COVID-19 related myocardial damage is growing. This review discusses the impact of CMRI in diagnosing myocardial involvement in acutely ill and recovered COVID-19 patients as well as its implications for patient management.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus responsible for the coronavirus disease 2019 (COVID-19) pandemic, continues to spread across the United States (US) and globally. As of January 21, 2021, the US reported over 23 million confirmed cases of COVID-19 as well as over 400000 COVID-19 related mortalities[1]. It has been previously reported that COVID-19 patients often have complications involving acute myocardial injury. These injuries are the most frequently reported cardiovascular abnormality in COVID-19, and occur in approximately 8%-12% of all patients[2]. Other cardiovascular effects of COVID-19 include endothelial damage, systolic heart failure, and arrhythmias[3]. Proposed mechanisms for cardiac injury include those mediated by systemic inflammation, direct viral attack on cardiomyocytes, myocardial interstitial fibrosis, overactive cytokine and interferon immune response, coronary plaque destabilization, and hypoxia[4,5].

Myocarditis is an increasingly recognized complication of COVID-19[6]. While endomyocardial biopsy remains the gold standard for tissue diagnosis, this procedure is invasive, characterized by potential serious complications and may be impractical in certain patient populations. Non-invasive imaging modalities, however, provide a safe alternative to aid in the diagnosis and management of myocarditis. While echocardiography possesses distinct advantages including low cost, accessibility, and faster interpretation times that may be beneficial in resource-scarce settings, many patients with early or mild myocarditis may have a normal echocardiogram [7]. Computed tomography (CT) modalities lack high quality myocardial tissue characterization that is essential for the diagnosis of myocarditis while exposing patients to significant amounts of radiation and contrast materials. Nuclear imaging is another potential modality to aid in the diagnosis of myocarditis, but lacks the spatial resolution to distinguish mid or epicardial myocardial perfusion defects (myocarditis) from subendocardial perfusion defects (ischemic) with significant partial volume effect and hence limited diagnostic accuracy[7].

Cardiovascular magnetic resonance imaging (CMRI) techniques remain the preferred modality for assessing patients with suspected myocarditis. CMRI provides detailed anatomical visualization, tissue-level analysis, safety, quantitative accuracy, and inter-observer consistency [7,8]. CMRI techniques are not without their limitations. These include higher cost when compared to echocardiography, longer exam times, and reliance on imaging interpretation by readers specifically trained in this discipline. Despite these limitations, CMRI remains the preferred imaging modality in the assessment of COVID-19 patients suspected of myocarditis and has the potential of playing a pivotal role in early diagnosis COVID-19-related cardiac injury. Finally, CMRI has the unique ability to evaluate subclinical and chronic cardiac involvement following COVID-19 infection.

## **CMRI AND CARDIAC TISSUE CHARACTERIZATION**

CMRI represents the gold standard for the noninvasive cardiac tissue characterization, detection of acute and chronic myocardial changes, and myocardial viability [9-12].



This volumetric and functional assessment utility has expanded its indications for not only diagnostic purposes, but also treatment guidance and patient follow-up as is currently being investigated in those patients with COVID-19 related acute myocarditis[13]. CMRI is also currently used to risk stratify patients with ischemic heart disease and myocarditis, assess precise ejection fraction, quantify scar tissue, and predict location of re-entrant circuits within the scar to guide catheter ablation<sup>[14]</sup>. The future of CMRI continues to grow with the incorporation of artificial intelligence, postprocessing techniques and development of new MR sequences such as T1 and T2 mapping[13].

#### T1 mapping

Non-ischemic cardiomyopathies may present with acute edema and diffuse tissue fibrosis that is captured well using T1 mapping[15]. T1 mapping techniques may identify the heterogeneity of damaged cardiac tissue without the use of contrast. The native T1 values increase in areas of edema and fibrosis as seen in acute myocarditis (including the acute phase of COVID-19) and the T1 values decrease in areas of lipid overload as seen in Anderson-Fabry diseases[13,16]. These elevated T1 values can also be seen early amyloid deposition, aortic stenosis, and dilated cardiomyopathy<sup>[13]</sup>.

#### T2 mapping

T2 mapping technique is similar to T1 imaging as it also identifies areas of inflammation and edema. Being highly sensitive to the water content of myocardial tissue, T2 can reliably identify patients with inflammatory cardiomyopathies and is indicated to detect inflammation associated with viral myocardial damage, myocardial infarction, sarcoidosis, toxicity from chemotherapeutic drugs, transplant rejection as well as detection of iron overload[13,16,17].

#### Late gadolinium enhancement

Late gadolinium enhancement (LGE) imaging techniques involves the use of gadolinium as a contrast agent to identify heterogeneity within myocardial tissue. LGE imaging represents a cornerstone of CMRI as it is used to define chronic myocardial fibrosis and necrosis caused by ischemia as well as myocardial fibrosis frequently present in non-ischemic dilated cardiomyopathy. Damaged cardiac tissue has a slower gadolinium washout time than healthy tissue, which allows for not only identification of myocardial scarring, but also its quantification[11,12,18]. LGE images of COVID-19 patients suspected of myocardial involvement revealed enhancement at the left ventricular base, suggestive of myocarditis (Figure 1).

Renal function should be assessed prior to the use of LGE as its use is relatively contraindicated for patients with significant renal impairment, although new generation Gadolinium agents seem to be safer to use[14,16,19]. Current guidelines proposed by the European Society of Cardiology, American Heart Association (AHA) and American College of Cardiology indicate the use of CMRI for diagnosis and management of coronary artery disease and cardiomyopathies, with a class I recommendation for suspected infiltrative causes[13,14,20].

Although data regarding CMRI characteristics of COVID-19 myocarditis is limited to case reports and series, a small study did compare 8 patients with COVID-19 myocarditis to 8 patients with non-COVID-19 myocarditis and 12 healthy patients<sup>[21]</sup>. Patients with suspected acute COVID-19 myocarditis (with elevated troponin and CRP) were found to have a pattern of diffuse myocardial edema detected as diffuse globally higher T1 and T2 myocardial relaxation times. Comparatively1, the patients with non-COVID-19 myocarditis had a more focal disease with prolonged T1 and T2 relaxation times and more visible myocardial edema and LGE lesions. It was also noted that skeletal muscle T1 was elevated in COVID-19 myocarditis patients, which impacted the T2 ratio to not be elevated significantly. Severe wall-motion abnormalities due to stress-induced cardiomyopathy and small pericardial effusions were also detected as CMRI enhancements in the COVID-19 myocarditis group[21].

### **ROLE OF CMRI IN PATIENTS INFECTED WITH COVID-19**

#### A review of the literature

An increased prevalence of myocardial injury has been reported in patients affected by COVID-19. As described above, these findings may range from evidence of acute myocarditis to fibrosis remote from time of infection. Given these considerations,





Figure 1 Delayed cardiac magnetic resonance image obtained after Gd administration showing patchy late Gd enhancement in the midmyocardium of the basal inferolateral and mid anteroseptal walls consistent with prior myocarditis in patient who recovered from coronavirus disease 2019.

CMRI has played an important role (Table 1) in non-invasive cardiac evaluations in COVID-19 populations<sup>[16]</sup>. Despite this growing understanding of COVID-19 myocardial involvement, cases of COVID-19 myocarditis are likely underreported due to lack of imaging to reduce viral spread<sup>[22]</sup>. As a result, data at the population level regarding COVID-19 myocarditis is currently lacking. One recent study from Annie et al<sup>[23]</sup> showed the prevalence of COVID-19 myocarditis across a large multi-national registry to be 0.01% (256 patients). Despite this small prevalence, these patients were associated with increased mortality, underscoring the importance of diagnosing patients with myocarditis<sup>[23]</sup>. Due to the limitation of available large-scale data, however, our literature review is primarily centered around case-control studies. Kariyanna *et al*[24] performed a systematic review of myocarditis in COVID-19. Global case reports and retrospective studies were included in an effort to better describe trends exhibited by COVID-19 patients suspected of having myocarditis. It was determined that absence of troponin elevation was insufficient to exclude myocarditis. The most consistent findings in patients with suspected myocarditis were bilateral ground glass opacities detected on chest CT and late gadolinium enhancement from CMRI, both of which findings were observed in all patients in the study. Myocardial edema was reported in more than half of these patients, and it appears as though tissue characterization through the use of LGE and T1/T2 mapping is more useful at detecting myocardial damage than assessing ventricular function[25,26].

Understanding the complications that follow COVID-19 infection is an evolving area of research. Currently, there are several studies reporting CMRI findings in convalescent COVID-19 patients. In the largest prospective CMRI study performed to date examining 100 recovered COVID-19 positive patients, Puntmann et al[25] found that 78% of the patients had abnormal CMRI findings. These findings suggested ongoing cardiac inflammation independent of the severity of initial COVID-19 clinical presentation. Of the 78 patients diagnosed with COVID-19 related myocardial involvement, raised T1 was found in 73, raised T2 in 60, and abnormal LGE findings in 32. The elevated T1 Levels indicated diffuse myocardial fibrosis, while the elevated T2 Levels represented edema. The patients with both T1 and T2 elevated relaxation times reflected active myocardial edema that may have resulted from virus-mediated acute cardiac injury or dysregulation of an innate inflammatory immune response, whereas the patients with increased T1 but normal T2 Levels were felt to demonstrate healed residual diffuse myocardial injury[25,27]. These values were confirmed with the use of histological findings in severe cases. Furthermore, the abnormal pericardial LGE reflected cardiac tissue injury due to myocardial inflammation that was further supported by the pericardial effusion and active pericarditis<sup>[25]</sup>. It was also found that left and right ventricular ejection fraction represents a suboptimal marker of early disease detection and outcomes prediction as compared to direct tissue characterization by CMRI.



Table 1 Summary of existing data surrounding the use of cardiac magnetic resonance imaging use in coronavirus disease 2019 patients

| Ref.   | Study design   | Sample size  | CMRI findings   | Other diagnostic findings   |
|--|--|--|---|---|
| Kariyanna<br>et al <mark>[24]</mark> ,<br>2020 | Systematic review<br>of 9 case reports<br>and 2 retrospective<br>studies | 11 COVID-19 patients<br>with reported<br>myocardial<br>inflammation or<br>myocarditis                    | LGE highlighted in 100% of the patients   | Elevated cardiac markers (Troponin, CK-MB, BNP) in 9 cases. Bilateral ground glass opacities seen in all patients with CT (6 cases). ECG abnormalities (ST-elevation and T-wave inversion) in 7 cases, and decreased LVEF in 6 cases. Active inflammation reported in the all biopsies performed (2 cases) and cardiomegaly reported in 7 cases |
| Puntmann<br>et al[ <mark>25</mark> ],<br>2020  | Prospective<br>observational<br>cohort study                             | 100 recovered COVID-<br>19 patients  | Raised T1 in 73% of patients,<br>raised T2 in 60%, LGE findings in<br>32%, and pericardial enhancement<br>in 22%  | Elevated troponin in 71% of patients, and significantly<br>elevated Troponin in 5%. Endomyocardial biopsy<br>revealed active lymphocytic inflammation. Lower<br>LVEF and RVEF noted   |
| Huang <i>et al</i><br>[26], 2020               | Retrospective<br>study   | 26 recovered COVID-19<br>patients who reported<br>cardiac symptoms and<br>underwent CMRI                 | Elevated T2 and/or LGE in 58%<br>(15 patients) with 14 patients<br>having myocardial edema and 8<br>LGE +. Global T1, T2, and<br>extracellular volume were<br>elevated in patients with abnormal<br>CMRIs | Decreased RVEF, cardiac index, and stroke volume found in patients with positive CMRI findings  |
| Clark <i>et al</i><br>[27], 2020               | Retrospective cohort analysis  | 22 collegiate athletes<br>with prior COVID-19<br>infection   | LGE found in 9% (2 athletes)  | All patients had normal Troponin, normal ECG,<br>normal LVEF. LV mass was higher and RVEF was<br>lower in athletes compared to control group  |
| Li et al[28],<br>2021                          | Prospective<br>observational<br>cohort study                             | 40 COVID-19 patients<br>with moderate to severe<br>pneumonia and no<br>cardiovascular medical<br>history | LGE findings in 3% (1 patient),<br>elevated extracellular volume<br>values in 60% (24 patients)   | Normal LV and RV size and function. 70% (24 patients)<br>had lower LV 2D-global longitudinal strain with<br>subclinical changes of myocardial dysfunction   |

CMRI: Cardiac magnetic resonance imaging; COVID-19: Coronavirus disease 2019; LGE: Late gadolinium enhancement; CK-MB: Creatine kinase-MB; BNP: B-type natriuretic peptide; CT: Computed tomography; ECG: Electrocardiogram; LVEF: Left ventricular ejection fraction; RVEF: Right ventricular ejection fraction LV: Left ventricular; RV: Right ventricular.

> This study highlights the considerable potential for cardiac involvement even in COVID-19 patients who had a milder presentation or those without cardiovascular comorbidities. The persistence of myocardial damage beyond the acute phase of infection was illustrated, but the extent of this potentially chronic injury is yet to be determined and requires further investigation.

> Huang et al[26] reported a single-center retrospective study from China and found that out of 26 patients who reported cardiac symptoms during COVID-19 recovery, 15 of them had evidence of myocardial abnormalities on CMRI evaluation. Major findings included myocardial edema, fibrosis, and right ventricular impairment through the use of T1, T2, and LGE imaging. Of note, all patients had no previous history of myocardial injury. This, taken with the fact that the median length of time between symptom onset and CMRI scan was 50 days, suggests persistent COVID-19 cardiac involvement in a majority of this patient cohort. Further follow-up of patients with CMR abnormalities is necessary to confirm long-lasting myocardial involvement following resolution of COVID-19 infection.

> While the detection of abnormal CMRI findings in patients with presenting true cardiac symptoms may seem intuitive, the necessity of excluding cardiac involvement in asymptomatic or minimally symptomatic represents an evolving concept amongst the global cardiovascular community. Subclinical myocardial involvement remains a common finding among COVID-19 patients who had a CMRI performed[25,28]. Indeed, Li et al[28] identified 28 out of 40 COVID-19 patients with myocardial dysfunction based upon reduced left ventricular 2D-global longitudinal strain when compared to healthy controls. In addition, 24 of the 40 patients showed elevated extracellular volume fraction compared to healthy controls indicating diffuse interstitial fibrosis in a majority of these patients. Interestingly, only one patient in this study demonstrated the presence of LGE. This reduced percentage of patients with LGE compared to findings from other studies could be a result of differing inclusion and exclusion criteria. Regardless, these findings indicate the appreciable prevalence of subclinical cardiac abnormalities recognized by CMRI months after COVID-19 recovery.

Owing to concern for the potential development of ventricular arrhythmias and sudden cardiac death (SCD) secondary to myocarditis in general, and expected similarly with COVID-19 myocarditis specifically, it is important to assess the extent of myocardial damage[29-32]. The first sign of underlying cardiac disease is oftentimes SCD in patients with ventricular arrhythmias[31]. This is especially true of patient populations that are at increased risk for arrhythmia development such as competitive athletes[30,32]. In light of the still unknown prevalence of COVID-19 related chronic cardiovascular sequelae, the question may be raised as to when a clinician should screen patients using CMRI. Phelan et al[30] provide recommendations on how to manage high risk recovering COVID-19 athletes. Initial restriction from play for 3 to 6 mo is recommended to allow for resolution of active inflammation[30]. Athletics can be resumed upon normalization of left ventricular function and cardiac biomarkers and absence of arrhythmias[30].

CMRI can reproducibly and accurately localize tissue injury, and thus has the ability to play an important role in fatal arrhythmia risk stratification along with prediction of reentrant circuits to guide ablation procedures[14]. LGE in particular has been shown to be the best predictor of all-cause mortality in biopsy-proven viral myocarditis, emphasizing the utility of CMR in COVID-19 patients[31,33].

While myocarditis appears to be the main form of cardiac involvement in COVID-19 patients, other forms of myocardial injury have also been observed to a smaller extent. These include but are not limited to myocardial infarction, pulmonary embolism, and Takotsubo cardiomyopathy[34-37]. These cardiovascular conditions may present similarly with chest pain, dyspnea, and positive troponin; however, they may be distinguished with CMRI[38], which further emphasizes the utility of CMRI in COVID-19 patients with signs of cardiac involvement.

#### MANAGEMENT RECOMMENDATIONS/GUIDELINES

Although the role of CMRI in the diagnosis of COVID-19 related cardiac injury is accepted, its practical utilization in both the inpatient and outpatient venues faces challenges in this continuously expanding patient population. In an effort to address these concerns, the Society of Cardiovascular Magnetic Resonance (SCMR) created specific guidelines treating the use of CMRI in COVID-19 patients[39,40]. These treatment guidelines cover a variety of imaging settings, including the acutely ill patient suspected of having acute COVID-19 related myocardial injury. In these instances, the SCMR recommends a short imaging protocol of 10-15 minutes for patients with active COVID-19 infection and a poor functional status[16]. CMRI can be performed on ventilated patients through special guidelines but is highly discouraged unless absolutely clinically necessary[39]. A holistic approach is recommended with the safety of patients and healthcare workers in mind and the use of clinical judgement to suspect acute myocardial injury[39]. If used in an inpatient setting, a dedicated CMRI scanner should be established when possible to limit the spread of COVID-19 [16]. In most circumstances, CMRI should be postponed until after resolution of the patient's contagious state and performed in an outpatient setting[27,39]. Once completed, further cardiovascular recommendations may be made based upon imaging findings. Given the breadth of patients affected by COVID-19, it is possible to detect preexisting and undiagnosed cardiac abnormalities and/or true COVID-19 related injury. Consequently, cardiovascular specialists must adopt a tailored approach to the treatment of these patients in light of their clinical circumstances. For example, patients with cardiomyopathy detected on CMRI may be candidates for consultation by a dedicated congestive heart failure treatment team[41].

#### APPROACHES TO THE ROLE OF CMRI IN THE COVID-19 ERA

Due to the novelty of the COVID-19 pandemic, there is a lack of consensus on how to manage the long-term cardiac effects of COVID-19. The high prevalence and disease burden of the COVID-19 pandemic and the constraints it's placed on healthcare resources make the determination of CMRI guidelines a difficult healthcare decision with ethical dimensions. Our center recommends using a risk stratification method to determine if a CMRI is needed for each individual patient (Table 2). High risk individuals include patients who have an abnormal echocardiogram, abnormal electrocardiogram (EKG), positive troponin levels, or history of myocarditis, myocardial infarction, or non-obstructive coronary artery disease. These patients should



| Table 2 Proposed indications for cardiac magnetic resonance imaging in coronavirus disease 2019 patients |  |  |  |  |
|--|--|--|--|--|
| CMRI is indicated  | CMRI not indicated                                   |  |  |  |
| High risk patients with 2 or more of the following criteria  | Low risk patients with all of the following criteria |  |  |  |
| Symptomatic  | Asymptomatic   |  |  |  |
| Elevated troponin  | Negative troponin                                    |  |  |  |
| Abnormal echocardiogram  | Normal echocardiogram                                |  |  |  |
| Abnormal EKG   |  |  |  |  |
| High risk for ventricular arrhythmia or sudden death   |  |  |  |  |
| Myocardial infarction  |  |  |  |  |
| Clinical suspicion for myocardial injury   |  |  |  |  |

CMRI: Cardiac magnetic resonance imaging; EKG: Echocardiogram.

receive a CMRI if available.

While suspicion of myocarditis can be determined based on biomarkers, EKG, and echocardiography, these tests may not be sufficient to determine the true etiology of cardiac involvement. EKG manifestations of myocarditis vary considerably and most commonly involve sinus tachycardia and nonspecific T wave and ST segment changes [42]. Echocardiography may demonstrate increased wall thickness and hyperechogenicity but more often than not provide inconclusive findings[43]. These tests provide little use in differentiating myocarditis from similarly presenting processes such as myocardial infarction or pulmonary embolus. If the aforementioned workup does not point towards a definitive diagnosis of myocarditis, CMRI may be indicated to provide direct tissue characterization, assess cardiac function indirectly based on the degree of inflammation present, and produce the confidence necessary to establish the diagnosis of myocarditis[42,44,45]. In addition, contrast-enhanced MRI may be a useful, noninvasive tool for long-term follow-up of patients with acute myocarditis and provide more accurate data on predicting outcome. A small study of 16 patients with myocarditis found that contrast enhancement ratio at 4 wk after disease onset was predictive of long-term outcomes[12].

Patients who are asymptomatic or have negative labs or normal echocardiogram findings are low priority for receiving CMRI. While post-COVID-19 asymptomatic myocardial involvement has been documented in the literature as mentioned above, this group of individuals with no symptoms should forgo CMRI at this time unless symptoms arise due to constraints on healthcare resources amidst the pandemic.

There is, however, a large gray area between these patient extremes. Athletes, for example, are a unique patient population as they are at higher risk of sudden cardiac death if they resume vigorous exercise with signs of myocarditis[32]. While there is disagreement in the approach of these patients, we believe clinicians should defer to the 2015 AHA Return to Play guidelines[32]. If there are any abnormalities on imaging, athletes should sit out from play with repeat imaging likely warranted in three to six months[32]. Reintroduction to play can take place gradually if biomarkers and EKG findings normalize and imaging shows no active inflammation[32]. At this time, it is unclear if resolution of myocarditis-related LGE is necessary for athletes to resume competition, so physicians should continue to use clinical judgment in their assessment of these patients. The Big Ten Athletics organization has taken the lead on evaluating their collegiate athletes following COVID-19 infection by creating a Big Ten Cardiac Registry<sup>[46]</sup>. Every student-athlete who tests positive undergoes cardiac testing involving EKG, biomarkers, echocardiogram, and CMRI to thoroughly evaluate cardiac structure and function<sup>[46]</sup>. This cautious approach is ideal but may not be practical for resource-scarce areas across the country, highlighting the importance of center-specific guidelines. It should be emphasized that determining appropriate imaging guidelines is an ongoing process that should utilize new findings as they are brought forward.

While athletes make up a unique subset of patients, the general public also stands to benefit from CMR imaging as indicated in Table 2.

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### LIMITATIONS OF THE USE CMRI IN PATIENTS WITH COVID-19

There are significant practical limitations regarding the use of CMRI in COVID-19 patients. In addition to limited availability at the global scale, CMRI represents a more expensive and time-consuming imaging modality when compared to conventional alternatives such as echocardiography. Additionally, consistent interpretation of CMRI images is vital to the widespread applicability of CMRI prognostic data[30]. This may be difficult to achieve considering many medical providers do not have access to the imaging modality itself or to cardiac imaging specialists who can accurately interpret the acquired images<sup>[47]</sup>. The lack of easy access to CMRI imaging creates the potential for selection bias in studies reporting CMRI results. These limitations must be taken into consideration during the creation of imaging guidelines of COVID-19 patients worldwide. Actively contagious COVID-19 patients with suspected cardiac involvement pose a unique challenge to clinicians. In order to reduce COVID-19 spread, CMR imaging may not be appropriate in COVID-19 patients who are actively contagious, thus placing a limitation on CMRI use in the early stage of COVID-19 infection[16]. Finally, it should also be noted that the CMRI studies conducted on COVID-19 patients discussed above all lack a pre-infection CMRI for comparison. Therefore, although unlikely, it is feasible that some included patients may have had preexisting changes detectable by CMRI following an unrelated COVID-19 infection. The lack of internal control limits the applicability of these research findings; nevertheless, the reported prevalence of myocardial abnormalities detected in these studies appears higher than that encountered both in clinical practice and the literature and thus deserves consideration.

## FUTURE DIRECTION

The COVID-19 pandemic has created an unprecedented quest to obtain and synthesize data in a brief amount of time. A major topic, and one that is of particular concern, is the cardiovascular effects seen both acutely and in the chronic setting. Myocardial injury secondary to COVID-19 and the use of CMRI is an evolving subject. A systematic review of the literature, while limited, yields important insights into the use of CMRI.

In regards to active COVID-19 infection with concern for acute myocardial injury, CMRI has a more limited role. CMRI should be used in the acute setting when the findings will alter management and treatment strategies. Additionally, CMRI is able to aid in the diagnosis of myocardial infarction, RV strain in pulmonary embolism, and Takatsubo cardiomyopathy[34]. Given the infectious nature of the coronavirus, the risk of exposure and transmission of COVID-19 to healthcare workers should be kept in mind. CMRI should be performed cautiously or postponed unless they alter the treatment and management of patients in a time-critical manner.

Although CMRI usage will be constricted the general population vastly due to cost and availability limitations, we suspect a major use of CMRI moving forward will be in athletes who have recovered from COVID-19. This is due to the increased risk of adverse events including sudden cardiac death for this specific population. As demonstrated by Phelan et al[30], CMRI is recommended in athletes if clinical concern is elevated, despite normal or unremarkable biomarkers and/or Echocardiogram and EKG. Additionally, Rink et al[46] has created an athlete registry and will be performing CMRI on every student athlete that has recovered from COVID-19. As high school, collegiate, and professional sports begin their seasons, much consideration and caution will be present in those athletes who have recovered from COVID-19. Given what we know about evidence of LGE and associated ventricular events, indications for withholding athletes from competitive sport may certainly arise.

### CONCLUSION

As a relatively new imaging modality with ongoing research, guidelines regarding CMRI use continue to evolve as new techniques and advances emerge. The role of CMRI in the diagnosis of COVID-19 related illness is evolving as well. Small studies have demonstrated the presence of cardiac injury even in minimally or asymptomatic COVID-19 patients. While the long-term sequelae of COVID-19 mediated cardiac disease is unknown, the diagnostic yield of CMRI places it squarely in the forefront of imaging strategies for this growing patient population. While factors such as



availability and cost may limit the widespread adoption of CMRI, its use in selected populations such as competitive athletes remain important. Further studies examining the prognostic utility of CMRI findings in the recovered COVID-19 population appears warranted.

### REFERENCES

- 1 Center for Disease Control and Prevention. CDC COVID Data Tracker, 2021. Available from: https://covid.cdc.gov/covid-data-tracker/#cases\_casesper100klast7days
- 2 Paramasivam A, Priyadharsini JV, Raghunandhakumar S, Elumalai P. A novel COVID-19 and its effects on cardiovascular disease. Hypertens Res 2020; 43: 729-730 [PMID: 32355222 DOI: 10.1038/s41440-020-0461-x]
- Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the 3 Cardiovascular System: A Review. JAMA Cardiol 2020; 5: 831-840 [PMID: 32219363 DOI: 10.1001/jamacardio.2020.1286
- Bansal M. Cardiovascular disease and COVID-19. Diabetes Metab Syndr 2020; 14: 247-250 [PMID: 32247212 DOI: 10.1016/j.dsx.2020.03.013]
- 5 Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: Possible mechanisms. Life Sci 2020; 253: 117723 [PMID: 32360126 DOI: 10.1016/i.lfs.2020.117723
- Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol 2020; 5: 802-810 [PMID: 32211816 DOI: 10.1001/jamacardio.2020.0950]
- Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, White JA, Abdel-Aty H, Gutberlet M, Prasad S, Aletras A, Laissy JP, Paterson I, Filipchuk NG, Kumar A, Pauschinger M, Liu P; International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol 2009; 53: 1475-1487 [PMID: 19389557 DOI: 10.1016/j.jacc.2009.02.007]
- Agdamag ACC, Edmiston JB, Charpentier V, Chowdhury M, Fraser M, Maharaj VR, Francis GS, Alexy T. Update on COVID-19 Myocarditis. Medicina (Kaunas) 2020; 56 [PMID: 33317101 DOI: 10.3390/medicina56120678]
- Ferreira VM, Piechnik SK, Robson MD, Neubauer S, Karamitsos TD. Myocardial tissue characterization by magnetic resonance imaging: novel applications of T1 and T2 mapping. J Thorac Imaging 2014; 29: 147-154 [PMID: 24576837 DOI: 10.1097/RTI.000000000000077]
- 10 Mather AN, Fairbairn TA, Artis NJ, Greenwood JP, Plein S. Timing of cardiovascular MR imaging after acute myocardial infarction: effect on estimates of infarct characteristics and prediction of late ventricular remodeling. Radiology 2011; 261: 116-126 [PMID: 21828188 DOI: 10.1148/radiol.11110228
- 11 Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000; 343: 1445-1453 [PMID: 11078769 DOI: 10.1056/NEJM200011163432003]
- Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, Klocke FJ, Bonow RO, Kim 12 RJ, Judd RM. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. Lancet 2003; 361: 374-379 [PMID: 12573373 DOI: 10.1016/S0140-6736(03)12389-6]
- Busse A, Rajagopal R, Yücel S, Beller E, Öner A, Streckenbach F, Cantré D, Ince H, Weber MA, 13 Meinel FG. Cardiac MRI-Update 2020. Radiologe 2020; 60: 33-40 [PMID: 32385547 DOI: 10.1007/s00117-020-00687-1]
- 14 Nelson T, Garg P, Clayton RH, Lee J. The Role of Cardiac MRI in the Management of Ventricular Arrhythmias in Ischaemic and Non-ischaemic Dilated Cardiomyopathy. Arrhythm Electrophysiol Rev 2019; 8: 191-201 [PMID: 31463057 DOI: 10.15420/aer.2019.5.1]
- Nakamori S, Bui AH, Jang J, El-Rewaidy HA, Kato S, Ngo LH, Josephson ME, Manning WJ, 15 Nezafat R. Increased myocardial native T<sub>1</sub> relaxation time in patients with nonischemic dilated cardiomyopathy with complex ventricular arrhythmia. J Magn Reson Imaging 2018; 47: 779-786 [PMID: 28737018 DOI: 10.1002/jmri.25811]
- 16 Kelle S, Bucciarelli-Ducci C, Judd RM, Kwong RY, Simonetti O, Plein S, Raimondi F, Weinsaft JW, Wong TC, Carr J. Society for Cardiovascular Magnetic Resonance (SCMR) recommended CMR protocols for scanning patients with active or convalescent phase COVID-19 infection. J Cardiovasc Magn Reson 2020; 22: 61 [PMID: 32878639 DOI: 10.1186/s12968-020-00656-6]
- 17 Wheen P, Armstrong R, Daly CA. Recent Advances in T1 and T2 Mapping in the Assessment of Fulminant Myocarditis by Cardiac Magnetic Resonance. Curr Cardiol Rep 2020; 22: 47 [PMID: 32472218 DOI: 10.1007/s11886-020-01295-0]
- Neilan TG, Coelho-Filho OR, Danik SB, Shah RV, Dodson JA, Verdini DJ, Tokuda M, Daly CA, 18 Tedrow UB, Stevenson WG, Jerosch-Herold M, Ghoshhajra BB, Kwong RY. CMR quantification of myocardial scar provides additive prognostic information in nonischemic cardiomyopathy. JACC Cardiovasc Imaging 2013; 6: 944-954 [PMID: 23932642 DOI: 10.1016/j.jcmg.2013.05.013]



- 19 Schieda N, Blaichman JI, Costa AF, Glikstein R, Hurrell C, James M, Jabehdar Maralani P, Shabana W, Tang A, Tsampalieros A, van der Pol CB, Hiremath S. Gadolinium-Based Contrast Agents in Kidney Disease: A Comprehensive Review and Clinical Practice Guideline Issued by the Canadian Association of Radiologists. Can J Kidney Health Dis 2018; 5: 2054358118778573 [PMID: 29977584 DOI: 10.1177/2054358118778573]
- 20 von Knobelsdorff-Brenkenhoff F, Pilz G, Schulz-Menger J. Representation of cardiovascular magnetic resonance in the AHA / ACC guidelines. J Cardiovasc Magn Reson 2017; 19: 70 [PMID: 28942735 DOI: 10.1186/s12968-017-0385-z]
- Luetkens JA, Isaak A, Öztürk C, Mesropyan N, Monin M, Schlabe S, Reinert M, Faron A, Heine A, 21 Velten M, Dabir D, Boesecke C, Strassburg CP, Attenberger U, Zimmer S, Duerr GD, Nattermann J. Cardiac MRI in Suspected Acute COVID-19 Myocarditis. Radiol Cardiothorac Imaging 2021; 3: e200628 [PMID: 33969316 DOI: 10.1148/ryct.2021200628]
- Panchal A, Kyvernitakis A, Mikolich JR, Biederman RWW. Contemporary use of cardiac imaging 22 for COVID-19 patients: a three center experience defining a potential role for cardiac MRI. Int J Cardiovasc Imaging 2021; 37: 1721-1733 [PMID: 33559800 DOI: 10.1007/s10554-020-02139-2]
- 23 Annie FH, Embrey S, Alkhaimy H, Elashery AR, Nanjundappa A. association between myocarditis and mortality in COVID-19 patients in a large registry. J Am Coll Cardiol 2021; 77: 3037 [DOI: 10.1016/S0735-1097(21)04392-8]
- Kariyanna PT, Sutarjono B, Grewal E, Singh KP, Aurora L, Smith L, Chandrakumar HP, 24 Jayarangaiah A, Goldman SA, Salifu MO, McFarlane IM. A Systematic Review of COVID-19 and Myocarditis. Am J Med Case Rep 2020; 8: 299-305 [PMID: 32747875]
- Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, 25 Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol 2020; 5: 1265-1273 [PMID: 32730619 DOI: 10.1001/jamacardio.2020.3557]
- 26 Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q, Xia L. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC Cardiovasc Imaging 2020; 13: 2330-2339 [PMID: 32763118 DOI: 10.1016/j.jcmg.2020.05.004]
- 27 Clark DE, Parikh A, Dendy JM, Diamond AB, George-Durrett K, Fish FA, Fitch W, Hughes SG, Soslow JH. COVID-19 Myocardial Pathology Evaluated Through scrEening Cardiac Magnetic Resonance (COMPETE CMR). medRxiv 2020 [PMID: 32908996 DOI: 10.1101/2020.08.31.20185140
- 28 Li X, Wang H, Zhao R, Wang T, Zhu Y, Qian Y, Liu B, Yu Y, Han Y. Elevated Extracellular Volume Fraction and Reduced Global Longitudinal Strains in Participants Recovered from COVID-19 without Clinical Cardiac Findings. Radiology 2021; 299: E230-E240 [PMID: 33434112 DOI: 10.1148/radiol.2021203998]
- Schumm J, Greulich S, Wagner A, Grün S, Ong P, Bentz K, Klingel K, Kandolf R, Bruder O, Schneider S, Sechtem U, Mahrholdt H. Cardiovascular magnetic resonance risk stratification in patients with clinically suspected myocarditis. J Cardiovasc Magn Reson 2014; 16: 14 [PMID: 24461053 DOI: 10.1186/1532-429X-16-14]
- 30 Phelan D, Kim JH, Elliott MD, Wasfy MM, Cremer P, Johri AM, Emery MS, Sengupta PP, Sharma S, Martinez MW, La Gerche A. Screening of Potential Cardiac Involvement in Competitive Athletes Recovering From COVID-19: An Expert Consensus Statement. JACC Cardiovasc Imaging 2020; 13: 2635-2652 [PMID: 33303102 DOI: 10.1016/j.jcmg.2020.10.005]
- 31 Mavrogeni S, Petrou E, Kolovou G, Theodorakis G, Iliodromitis E. Prediction of ventricular arrhythmias using cardiovascular magnetic resonance. Eur Heart J Cardiovasc Imaging 2013; 14: 518-525 [PMID: 23324829 DOI: 10.1093/ehjci/jes302]
- 32 Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NA 3rd, Cooper LT Jr, Link MS, Maron MS; American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and American College of Cardiology. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 3: Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy and Other Cardiomyopathies, and Myocarditis: A Scientific Statement From the American Heart Association and American College of Cardiology. Circulation 2015; 132: e273-e280 [PMID: 26621644 DOI: 10.1161/CIR.00000000000239]
- 33 Grün S, Schumm J, Greulich S, Wagner A, Schneider S, Bruder O, Kispert EM, Hill S, Ong P, Klingel K, Kandolf R, Sechtem U, Mahrholdt H. Long-term follow-up of biopsy-proven viral myocarditis: predictors of mortality and incomplete recovery. J Am Coll Cardiol 2012; 59: 1604-1615 [PMID: 22365425 DOI: 10.1016/j.jacc.2012.01.007]
- Giustino G, Croft LB, Oates CP, Rahman K, Lerakis S, Reddy VY, Goldman M. Takotsubo 34 Cardiomyopathy in COVID-19. J Am Coll Cardiol 2020; 76: 628-629 [PMID: 32517962 DOI: 10.1016/j.jacc.2020.05.068]
- Modin D, Claggett B, Sindet-Pedersen C, Lassen MCH, Skaarup KG, Jensen JUS, Fralick M, Schou 35 M, Lamberts M, Gerds T, Fosbøl EL, Phelps M, Kragholm KH, Andersen MP, Køber L, Torp-Pedersen C, Solomon SD, Gislason G, Biering-Sørensen T. Acute COVID-19 and the Incidence of Ischemic Stroke and Acute Myocardial Infarction. Circulation 2020; 142: 2080-2082 [PMID: 33054349 DOI: 10.1161/CIRCULATIONAHA.120.050809]



- Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in 36 Hospitalized Patients With COVID-19 in a New York City Health System. JAMA 2020; 324: 799-801 [PMID: 32702090 DOI: 10.1001/jama.2020.13372]
- 37 Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S; Lille ICU Haemostasis COVID-19 Group. Pulmonary Embolism in Patients With COVID-19: Awareness of an Increased Prevalence. Circulation 2020; 142: 184-186 [PMID: 32330083 DOI: 10.1161/CIRCULATIONAHA.120.047430]
- Doltra A, Amundsen BH, Gebker R, Fleck E, Kelle S. Emerging concepts for myocardial late 38 gadolinium enhancement MRI. Curr Cardiol Rev 2013; 9: 185-190 [PMID: 23909638 DOI: 10.2174/1573403x113099990030]
- 39 Han Y, Chen T, Bryant J, Bucciarelli-Ducci C, Dyke C, Elliott MD, Ferrari VA, Friedrich MG, Lawton C, Manning WJ, Ordovas K, Plein S, Powell AJ, Raman SV, Carr J. Society for Cardiovascular Magnetic Resonance (SCMR) guidance for the practice of cardiovascular magnetic resonance during the COVID-19 pandemic. J Cardiovasc Magn Reson 2020; 22: 26 [PMID: 32340614 DOI: 10.1186/s12968-020-00628-w]
- Allen BD, Wong TC, Bucciarelli-Ducci C, Bryant J, Chen T, Dall'Armellina E, Finn JP, Fontana M, 40Francone M, Han Y, Hays AG, Jacob R, Lawton C, Manning WJ, Ordovas K, Parwani P, Plein S, Powell AJ, Raman SV, Salerno M, Carr JC. Society for Cardiovascular Magnetic Resonance (SCMR) guidance for re-activation of cardiovascular magnetic resonance practice after peak phase of the COVID-19 pandemic. J Cardiovasc Magn Reson 2020; 22: 58 [PMID: 32772930 DOI: 10.1186/s12968-020-00654-8]
- 41 Friedrich MG. Cardiac MR in Times of COVID. 2020 Mar 24. In: JCMR Journal Club. Available from: https://scmr.org/resource/dynamic/blogs/20200414 133132 16845.pdf
- Basman C, Agrawal PR, McRee C, Saravolatz L, Chen-Scarabelli C, Scarabelli TM. Diagnostic 42 Approach to Myocarditis Mimicking Myocardial Infarction at Initial Presentation. Cardiol Res 2016; 7: 209-213 [PMID: 28197294 DOI: 10.14740/cr485w]
- 43 Friedrich MG, Marcotte F. Cardiac magnetic resonance assessment of myocarditis. Circ Cardiovasc Imaging 2013; 6: 833-839 [PMID: 24046380 DOI: 10.1161/CIRCIMAGING.113.000416]
- Puntmann VO, Valbuena S, Hinojar R, Petersen SE, Greenwood JP, Kramer CM, Kwong RY, 44 McCann GP, Berry C, Nagel E; SCMR Clinical Trial Writing Group. Society for Cardiovascular Magnetic Resonance (SCMR) expert consensus for CMR imaging endpoints in clinical research: part I - analytical validation and clinical qualification. J Cardiovasc Magn Reson 2018; 20: 67 [PMID: 30231886 DOI: 10.1186/s12968-018-0484-5]
- 45 Olimulder MA, van Es J, Galjee MA. The importance of cardiac MRI as a diagnostic tool in viral myocarditis-induced cardiomyopathy. Neth Heart J 2009; 17: 481-486 [PMID: 20087452 DOI: 10.1007/BF03086308]
- 46 Big Ten Cardiac Registry Steering Committee, Rink LD, Daniels CJ, Boersma D, Borchers J, Busch J, Kovan J, Kratochvil CJ, Rifat S, Rosenthal G, Chung EH. Competitive Sports, the Coronavirus Disease 2019 Pandemic, and Big Ten Athletics. Circ Cardiovasc Qual Outcomes 2020; 13: e007608 [PMID: 33125280 DOI: 10.1161/CIRCOUTCOMES.120.007608]
- Pfeiffer MP, Biederman RW. Cardiac MRI: A General Overview with Emphasis on Current Use and 47 Indications. Med Clin North Am 2015; 99: 849-861 [PMID: 26042886 DOI: 10.1016/j.mcna.2015.02.011]





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