

Dear Editors,

On behalf of my co-authors, I would like to thank the editor and reviewers for reviewing our manuscript “Role of Cardiac MRI in the Diagnosis and Management of COVID-19 Related Myocarditis: Clinical and Imaging Considerations”. We have kindly addressed your questions and comments in a point-to-point manner as detailed below. We hope you find our manuscript suitable for publication in its latest edited form to the World Journal of Radiology. Looking forward to hearing from you soon.

Sincerely,

Lavannya Atri on behalf of Dr. Adam Berman

**Reviewer #1:**

**Specific Comments to Authors:**

The impact of the new coronavirus infection on the heart leads mainly to the development of viral myocarditis, so it is better to rename the article “Role of Cardiac MRI in the Diagnosis and Management of COVID-19 Related Myocarditis”.

**Thank you for this suggestion, we agree and have revised the title from “Cardiovascular Disease” to “Myocarditis”.**

As for the organization of the article, the authors slightly violated the classical design of the article and combined the review, case and hypothesis.

**Thank you for pointing this out, we have eliminated the case to adhere to the classical design of the review article.**

One gets the impression that the clinical case is presented somewhat incorrectly.

Echocardiography would also reveal enlarged cardiac cavities and hydropericardium. With such changes and the clinical picture, one could probably expect ECG changes typical of myocarditis / pericarditis, which would most likely be detected by an experienced clinician, especially in comparison with previous archived ECGs. However, ECHO-CG and ECG images are not included in the case description. In addition, the authors mention that troponin and NTproBNP were negative, but in such cases it is guided not only on these markers, but on the complex of laboratory markers such as myoglobin, myocardium antibodies, CRP, detection of antibodies to viruses and others.

**These are valid points and we thank the reviewer for raising these issues. The clinical case used was a real representation of the unique cases that have been clinically silent with**

**negative EKG and troponin findings but have been diagnosed via CMRI to have myocarditis. However, we have removed this case study from the manuscript as suggested to adhere to the guidelines of a review article.**

The main question that needs to be answered in this article (after all, a review article?): If the diagnosis of myocarditis could have been made to the patient without MRI on the basis of the aforementioned signs, then what additional will MRI bring in relation to the tactics of managing this patient?

**We thank the reviewer for their comment. We have added to our discussion the following in response: "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 (Basman et al, 2016). Echocardiography may demonstrate increased wall thickness and hyperechogenicity but more often than not provide inconclusive findings (Friedrich et al, 2013). 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 (Puntmann et al, 2018, Basman, et al, 2016, Olimulder et al, 2009). 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 weeks after disease onset was predictive of long-term outcomes (Wagner et al, 2003)."**

It is also worth reflecting in detail what are the diagnostic differences and features of the T1 and T2 modes in the diagnosis of COVID myocarditis (in the first half of the article, when the first mention of T1, T2, GLE occurs).

**Thank you for making this recommendation, we agree and have expanded of the diagnostic differences and features of T1 and T2 modes in the diagnosis of COVID-19 myocarditis. Our additions are as follows: "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 (Leutkens et al. 2021). 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. Comparatively, 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 (Leutkens et al. 2021)."**

In the article, it is desirable to indicate the data of population statistics of the detection of cases of myocarditis in COVID-19 disease in the United States and the use of MRI studies in these patients based on data from Medicare, CDC, electronic databases of the US health system, or other sources, and not only from the small "case-control" studies.

**We were unable to find any population statistics on myocarditis in COVID-19 patients from CDC or Medicare databases but have included data from a large multi-national registry found in a recently published study. We also stated our review of the literature was limited to case-control studies, and we acknowledged the lack of population statistics in our review. Our addition is as follows: "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 (Panchal et al, 2021). As a result, data at the population level regarding COVID-19 myocarditis is currently lacking. One recent study from Annie et al. showed the prevalence of COVID-19 myocarditis across a large multi-national registry to be .01% (256 patients). Despite this small prevalence, these patients were associated with increased mortality, underscoring the importance of diagnosing patients with myocarditis (Annie et al, 2021). Due to the limitation of available large-scale data, however, our literature review is primarily centered around case-control studies."**

In the conclusion of the article, the authors focus on the prospects of using MRI in the diagnosis of myocarditis and their subsequent observation in athletes who have undergone COVID (who represent a specific and limited category of patients). At a time when there is not enough observation data and interpretation of their results in general on the population, which seems to be more important.

**We thank the reviewer for this comment. We wanted to highlight this subset of the population due to their increased risk of adverse events including sudden cardiac death. Your point is well taken and we have redirected the emphasis to the general population.**

As for the limitations for the use of cardiac MRI, they are clearly greater than the authors mention, especially for patients with COVID.

**Thank you for this comment. We have expanded upon the limitations of CMRI generally, including limited access to CMR specialist interpretation, and with respect to COVID-19 patients, who are oftentimes unable to be imaged in the infected stage of their disease. The addition to our paper is as follows: "[CMRI interpretation] 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 (Pfeiffer,**

**2015)... 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 (Kelle et al, 2020).”**

Turning to the Algorithm for prescribing / not prescribing CMRT, proposed by the authors, I would like to note that the list of criteria (CMRI is indicated) already indicates the diagnosis of myocarditis. And then the main question, mentioned above, arises again. In this regard, the algorithm of cardiac MRI application recommended by the authors in this context should be changed and optimized.

**We thank the reviewer for this comment. We agree that the diagnosis of myocarditis may be achieved when these factors are present but many of these criteria are nonspecific. CMRI’s value lies in the ability to confirm this diagnosis and exclude other mimickers such as MI or PE along with providing prognostic information that may alter the management of the patient. Granted, we believe it is important to use clinical judgment and only proceed with CMRI if diagnosis cannot be achieved from the preceding workup.**

**Reviewer #2:**

**Specific Comments to Authors:**

The authors reporting a nice review article entitled: "Role of Cardiac MRI in the Diagnosis and Management of COVID-19 Related Cardiovascular Disease: Clinical and Imaging Considerations." I have only minor points to add:

**We thank this reviewer; however, we did not find the comments, could you kindly resend them to us please?**

**Science editor:**

**Issues raised:**

The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor

**Thank you for this comment, the figure has now been properly prepared using PowerPoint and uploaded.**

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**The picture used in this manuscript is an original CMRI scan of Dr. Adam Berman’s patient that has not been published elsewhere. Therefore, this figure is not copyrighted and does not need obtaining of permission for use.**