Cardiac involvement in consecutive elite athletes recovered from Covid-19: A magnetic resonance study

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Magnetic resonance (MR) studies suggested cardiac involvement post-Covid-19 in a significant subset of affected individuals, including athletes. This brings serious clinical concerns regarding the potential need for in-depth cardiac screening in athletes after Covid-19 before return to play. The aim of this study was to gain further insight into the relation between Covid-19 and cardiac involvement in professional athletes. This was a retrospective cohort study, in which 26 consecutive elite athletes (national team, Olympians, top national league players; median age 24 years, interquartile range [IQR] 21–27, 81% female) were included. At 1.5 T including balanced steady-state free precession cine imaging, T1 and T2-mapping using Myomaps software (Siemens), dark-blood T2-weighted images with fat suppression, and late gadolinium enhancement (LGE) with phase-sensitive inversion recovery sequence were used. The athletes had mainly asymptomatic or mild course of the disease (77%). They were scanned after a median of 32 days (IQR 22–62 days) from the diagnosis. MR data were reviewed by three independent observers, each with >10 years cardiac MR experience. Native T1, T2, extracellular volume, and T2 signal intensity ratio were calculated. Diagnosis of acute myocarditis was based on modified Lake Louise criteria. Statistical analyses used were Pearson correlation and Bland–Altman repeatability analysis. At the time of MR the athletes had no pathologic electrocardiogram abnormalities or elevated troponin levels. MR did not reveal any case of acute myocarditis. Cardiac abnormalities were found in five (19%) athletes, including four athletes presenting borderline signs of isolated myocardial edema and one athlete showing nonischemic LGE with pleural and pericardial effusion. Another athlete had signs of persistent lung congestion without cardiac involvement. We have shown that in a small group of elite athletes with mainly asymptomatic to mild Covid-19, lack of electrocardiographic changes, and normal troponin concentration 1–2 months after the diagnosis, there were no signs of acute myocarditis, but 19% of athletes had some abnormalities as assessed by cardiac MR.
Level of Evidence: 4
Technical Efficacy Stage: 3

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been shown to affect various organs of the human body.[1] Although other coronaviruses do not typically show cardiac tropism, due to its unique structure, SARS-CoV-2 has been demonstrated to affect the heart directly and indirectly.[2] The virus can directly invade cardiomyocytes or endothelial cells leading to myocarditis, myocardial infarction, life-threatening arrhythmias, and acute and/or chronic heart failure.[1,2] SARS-CoV-2 can also indirectly injure the heart through stimulation of systemic inflammatory and immunologic reaction.[1,2] It was initially thought that the frequency of cardiac involvement resulting from SARS-CoV disease (Covid-19) correlated with the severity of the clinical course of the disease and the presence of comorbidities.[3] Supporting that, an MR study by Huang et al. in patients who reported

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cardiac symptoms disclosed abnormal findings in 58% of patients.[4] However, more recent MR studies of individuals recovered from Covid-19 have demonstrated a high frequency of cardiac involvement despite an asymptomatic or benign course of the disease.[5,6] A study by Puntmann et al. has shown that 2–3 months post infection 78% of patients, of whom 18% were asymptomatic and 49% had mild to moderate symptoms, presented abnormal cardiac MR findings and 60% demonstrated an ongoing inflammation.[5]

Myocarditis can lead to serious complications including life-threatening arrhythmias and sudden cardiac death and/or acute and chronic heart failure, with exercise being one of the factors which may worsen the course of the disease as demonstrated in animal studies.[7] Experts in sports cardiology recommend in-depth cardiac screening before returning to sport only in athletes with prolonged recovery from Covid-19, limiting testing to 12-lead electrocardiogram (ECG) and echocardiography, or even a direct return to play in asymptomatic or mildly symptomatic athletes.[8,9] Studies in athletes recovered from Covid-19 to date have demonstrated a variable frequency of cardiac involvement despite asymptomatic or mildly symptomatic course. A COVID-19 Myocardial Pathology Evaluation in AthleTEs with Cardiac Magnetic Resonance (COMPETE-CMR) study reported fibrosis (other than insertion point) in 5% of athletes, with only 3% of them meeting MR criteria for myocarditis,[10] while a study by Rajpal et al. has shown signs of myocarditis in 15% of athletes and further 30% of them presenting isolated myocardial fibrosis suggestive of previous injury.[6] In both studies there was no clear correlation between symptoms and cardiac involvement. Anxiety has been further increased by the recent death of a 27-year-old professional basketball player who suffered a sudden cardiac death during training shortly after recovery from Covid-19.[2] There are consequently serious clinical concerns regarding the potential need for in-depth cardiologic screening in all athletes after COVID-19 before they can be safely allowed to fully return to training and competitions.

Therefore, the aim of this study was to gain further insight into the relation between Covid-19 and cardiac involvement in professional athletes.

Methods

Ethical Considerations

The tests were part of a routine clinical assessment before full return to training and competition mandated by the National Centre for Sports Medicine, a partner of the Polish Olympic Team, in light of the reports showing high frequency of cardiac involvement in individuals recovering from Covid-19, including asymptomatic cases. The study received local Ethical Committee approval for retrospective analysis of clinical data (no. IK.NPIA.0021.78.1983/20).

Study Group

Twenty-six consecutive, Caucasian elite athletes who were members of the Polish National Olympic Team and top league professional volleyball and football clubs and tested positive for Covid-19 with a real-time polymerase chain reaction test between August and October 2020 were included. They represented different sport categories, including strength (wrestling, judo, sprint athletics), mixed (soccer, volleyball), and skill disciplines (fencing). All athletes underwent an MR of the heart as soon as possible in terms of safety and logistics after Covid-19 infection. Additional tests performed on the day of the MR scan were detailed physical examination, resting ECG, and laboratory tests, including whole blood count and markers of inflammation (C-reactive protein [CRP]) and cardiac injury (high-sensitive [hs] troponin T) using standardized equipment (Cobas 800, Roche, Rotkreuz, Switzerland). The local detection limit for hs-troponin T was 4 pg/ml and for CRP 0.60 mg/L. The 99th percentile upper cut-off value for hs-troponin T was 13.90 pg/ml and the upper limit of normality for CRP was 5 mg/L.

Mild Covid-19 was defined as the presence of nonspecific and self-limited fatigue, anosmia or ageusia, and/or typical mild symptoms of upper respiratory tract or gastrointestinal infection, including headache, cough, sore throat, nasopharyngeal congestion, myalgia, nausea, vomiting, and/or diarrhea. Moderate disease was defined as symptoms persisting over 7 days and including fever or chills, hypoxia or pneumonia, and/or cardiovascular symptoms such as dyspnea and/or chest pain, tightness or pressure at rest or during exertion. Severe disease was defined as one requiring hospitalization.[11]

MR Protocol and Analysis

MR imaging was performed with a Siemens Magnetom Avanto Fit 1.5 Tesla scanner (Siemens, Erlangen, Germany). The protocol included initial scout images, followed by cine balanced steady-state free precession (bSSFP) breath-hold sequences in two-, three-, and four-chamber views. Short axis was identified using the two- and four-chamber images and a stack of images was acquired which included the ventricles from the mitral and tricuspid valvular plane to the apex.

Precontrast T1-mapping with modified Look Locker sequence and T2-mapping were performed with a T2-prepared SSFP sequence immediately after acquisition of the bSSFP cine images and processed using MyoMaps software (Siemens, Erlangen, Germany). For that purpose, three short axis slices (one basal, one mid-ventricular, and one apical) and two-, three-, and four-chamber views were obtained. Subsequently an acquisition of dark-blood T2-weighted images with fat suppression in the same orientations was performed.

Following these acquisitions, 0.1 mmol/kg of a gadolinium contrast agent (gadobutrol—Gadovist, Bayer Shering

Pharma AG, Berlin, Germany) was administered and flushed with 30 ml of isotonic saline. Late gadolinium enhancement (LGE) images in three long axis and a stack of short-axis imaging planes were obtained with a breath-hold phase-sensitive inversion recovery sequence 10 min after the contrast injection. The inversion time was adjusted to null normal myocardium (typically between 250 and 350 ms as assessed by means of a TI-scout acquisition). This was followed by a postcontrast T1-mapping acquisition 15 min after the contrast injection in the same orientations as the precontrast T1-mapping.

Images were analyzed with the use of dedicated software (Syngovia, Siemens, Erlangen, Germany). All studies were assessed independently by three physicians—one cardiologist and two radiologists, each with long-lasting expertise in cardiac MR (Ł.A.M—13 years of experience, M.M. and B.M-W.—12 years of experience). End-diastolic and end-systolic endocardial and epicardial contours were drawn semi-automatically for the left ventricle (LV) and manually for the right ventricle (RV) in the short axis stack of bSSFP cine acquisitions. Delineated contours were used for the quantification of end-diastolic (LVEDVI/RVEDVI) and end-systolic volumes (LVESVI/RVESVI), stroke volumes (LVSVI/RVESVI), ejection fraction (LVEF/RVEF), and LV mass (LVMI), indexed to body surface area. We used previously published normal values of left and right ventricular volumes, systolic function and mass as a reference.[12]

Precontrast T1 and T2 relaxation times, T2 signal intensity (T2 SI) ratios and postcontrast T1 relaxation times were calculated from a 1.0 cm^2 region of interest (ROI) placed in the mid-ventricular short-axis slice in the mid-section of the interventricular septum avoiding the RV/LV insertion points. Caution was taken not to include LGE areas in the measurements and not to include blood pool in the ROI. For blood pool pre- and postcontrast T1 calculation, a ROI of the same size was placed at the same level in the ventricular cavity, but separate from the papillary muscles or trabeculations. For T2 SI ratio, a ROI in the skeletal muscles of the chest of the same size was used. Extracellular volume (ECV) was calculated using the previously validated equation: $ECV = (1 - \text{hematocrit}) \times ([1/T1myopost - 1/T1myopre]/[1/T1bloodpost - 1/T1bloodpre])$.[13]

The presence and location of LGE was assessed visually. Junction point (insertion/hinge point) LGE in isolation was not considered as pathologic and therefore was not reported.[14] Abnormal native T1 and T2 values were defined as greater than 1054 ms and greater than 50 ms, respectively, based on previously derived sequence and scanner-specific cut-offs of 2 standard deviations (SDs) above the respective means in a healthy population.[15] Increase of myocardial T2 SI ratio was defined as a signal intensity ratio of the LV myocardium to skeletal muscle ≥2.0.[16] Acute myocarditis was diagnosed according to the updated Lake Louise criteria using a T2-based criterion in combination with a T1-based criterion.[17] Abnormal ECV values were defined as >31.9%, which is 2 SDs above the mean observed in previous study of athletes.[18]

TABLE 1. Baseline characteristics of the studied group

	Study group (n = 26)
Age (years), median (IQR)	24 (21–27)
Female sex, n (%)	21 (81)
BSA (kg/m^2), median (IQR)	1.68 (1.58–1.81)
Sporting discipline, n (%)	
Wrestling	11 (42)
Sprint athletics	6 (23)
Fencing	4 (15)
Volleyball	3 (12)
Soccer	1 (4)
Judo	1 (4)
Time from diagnosis to cardiac MR, median (IQR), days	32 (22–62)
Symptoms, n (%)	
Asymptomatic	6 (23)
Mild	14 (54)
Moderate	5 (19)
Severe/hospitalization	1 (4)
hs-troponin T at the time of cardiac MR (pg/ml), median (IQR)	4 (4–5)
hs-troponin T result, n (%)	
Detectable	4 (15)
Abnormal	0 (0)
CRP at the time of cardiac MR (mg/L), median (IQR)	0.6 (0.6–0.8)
CRP result, n (%)	
Detectable	4 (15)
Abnormal	0 (0)
Resting ECG changes, n (%)	
ST-T changes	0 (0)
Q waves	0 (0)
Other	0 (0)

Abbreviations: BSA, body surface area; CRP, C-reactive protein; ECG, electrocardiogram; hs, high sensitivity; IQR, interquartile range; MR, magnetic resonance.

Statistical Methods

All results for categorical variables were presented as a number and a percentage. Continuous variables were expressed as mean and SD or median and interquartile range (IQR), depending on the normality of the distributions assessed with the use of the chi-square test. Inter-reader variability was assessed in 10 randomly chosen athletes using Pearson correlation test and Bland–Altman repeatability analysis between two readers (cardiologist and one of the radiologists). All tests were two-sided with the significance level of $p < 0.05$. Statistical analyses were performed with MedCalc statistical software 10.0.2.0 (Ostend, Belgium).

Results

Baseline Characteristics

Our study group consisted mainly of female athletes (81%) representing wrestling, sprint athletics and fencing (Table 1). Male athletes included soccer and volleyball players and one wrestler. Most of the athletes were asymptomatic (23%) or mildly symptomatic (54%) during the course of Covid-19. One female athlete with fever and myalgia was shortly hospitalized due to pulmonary changes observed in a computed tomography scan, but did not need respiratory support or have any noticeable cardiac abnormalities at that time as determined by ECG, echocardiography, and markers of myocardial injury. Other athletes spent the time of infection in self-isolation and did not train. ECG and laboratory tests performed on the day of the MR scan did not disclose any abnormalities. Detectable values of hs-troponin T and CRP were found in four (15%) of athletes. The median time between diagnosis and MR was 32 days (IQR 22–62 days).

MR Findings

Half of the studied athletes (n = 13) had a balanced enlargement of the heart chambers (Table 2). Two male athletes (8%) with enlarged LV had mildly decreased or borderline LVEF (56% and 58%, respectively), which in one was accompanied by mild LVMI increase (92 g/m^2).

None of the athletes fulfilled the original or modified criteria for the diagnosis of an active myocarditis (one T1-based criterion and one T2-based criterion).[17] Abnormalities in myocardial tissue characteristics were found in five (19%) athletes. These included: (1) borderline raised T2 SI ratio found in three female athletes—one with mild and two with moderate symptoms as demonstrated in Figure 1a; (2) signs of borderline myocardial edema by T2-mapping found in female athlete with mild COVID-19 course (T2 = 50.5 ms) as shown in Figure 1b; and (3) one case of a female athlete with moderate symptoms presenting linear mid-wall LGE in the mid-ventricular infero-lateral segment of the LV accompanied by mild pericardial and pleural effusion, but without signs of myocardial edema (Figure 1c–f). One

TABLE 2. Cardiac magnetic resonance findings

	Study group (n = 26)	Above/below reference (12, 15, 18), n (%)
LVEDVI (ml/m^2), median (IQR)	95 (84–106)	13 (50)
LVESVI (ml/m^2), median (IQR)	37 (31–42)	15 (58)
LVSVI (ml/m^2), median (IQR)	58 (53–62)	0 (0)
LVEF (%), median (IQR)	61 (60–62)	2 (8)
LVMI (kg/m^2), median (IQR)	61 (58–66)	1 (4)
RVEDVI (ml/m^2), median (IQR)	96 (85–105)	13 (50)
RVESVI (ml/m^2), median (IQR)	39 (35–45)	8 (31)
RVSVI (ml/m^2), median (IQR)	57 (50–64)	0 (0)
RVEF (%), median (IQR)	59 (57–60)	0 (0)
T1 (ms), median (IQR)	1010 (992–1028)	0 (0)
T2 (ms), median (IQR), ms	46 (45–48)	1 (4)
T2 SI, median (IQR)	1.86 (1.58–1.96)	3 (12)
LGE, n (%)		
Subendocardial	0 (0)	1 (4)
Mid-wall	1 (4)	
Subepicardial	0 (0)	
ECV (%), median (IQR)	26 (24–27)	0 (0)
Pericardial effusion, n (%)	2 (8)	2 (8)
Modified Lake Louise criteria[17] for acute myocarditis, n (%)	0 (0)	0 (0)
Pulmonary changes (pulmonary congestion, pleural effusion)	2 (8)	2 (8)

Abbreviations: ECV, extracellular volume; IQR, interquartile range; LGE, late gadolinium enhancement; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left-ventricular end-systolic volume index; LVMI, left ventricular mass index; LVSVI, left ventricular stroke volume index; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index; RVSVI, right ventricular stroke volume index; T2 SI ratio, ratio of signal intensity between myocardium and skeletal muscle on T2-weighted image.

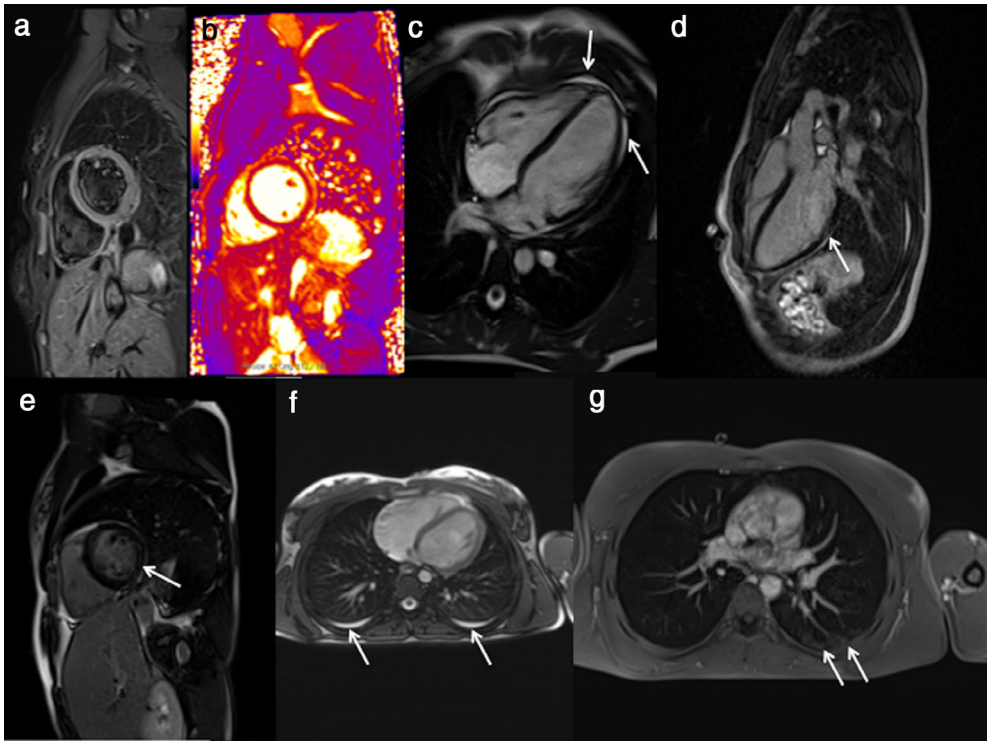

FIGURE 1: Cardiac magnetic resonance findings in studied athletes recovered from Covid-19. (a)Borderline T2 SI ratio of myocardium in comparison to skeletal muscle; (b) increased T2 of 50.5 ms; (c–f) Pericardial effusion (c, arrows), mid-wall linear fibrosis presented in two orientations (d, short axis and e, three-chamber view marked with arrows) as well as pleural effusion (f, arrows) in a 21-year-old female wrestler with moderate symptoms. (g) Lung congestion (arrows) in an athlete without any myocardial abnormalities

additional female athlete had discrete pericardial effusion (<5 mm). T1-mapping and ECV values were normal in all athletes. Importantly, we did not observe any correlation between CRP or troponin and native T1 or T2 values, T2 SI or ECV.

Additionally, in one female athlete with a completely asymptomatic course of the disease and without cardiac abnormalities, there were signs of a small subpleural pulmonary congestion in the left lung (Figure 1g).

Inter-Reader Variability

The correlation coefficients r and Bland–Altman bias were, respectively, 0.94 ($p < 0.05$) and 11.3 ± 8.3 ms for T1, 0.84 ($p < 0.05$) and 0.1 ± 1.4 for T2, and 0.87 ($p < 0.05$) and 0.05 ± 0.12 for T2 SI ratio.

Discussion

In a group of 26 elite athletes with mostly asymptomatic or mild course of Covid-19 we have demonstrated lack of criteria for an active myocarditis by MR performed after 1–2 months from the diagnosis. Abnormal cardiac MR findings, which could not be directly ascribed to physiological adaptation to exercise, were disclosed in one fifth of the athletes. These included mainly isolated signs of myocardial edema on T2-mapping or borderline raised T2 SI ratio.[16,17] Otherwise studied athletes presented changes, which could be explained by physiological adaptation to exercise (the so called athlete's heart).[19]

Isolated myocardial edema (especially borderline) without other markers of acute myocarditis or any other cardiac abnormalities on MR and with normal levels of markers of myocardial injury in an asymptomatic individual should be considered with caution in terms of its impact on management for several reasons. First of all, it has been shown that isolated myocardial edema has only a limited specificity as a marker of biopsy-proven myocarditis.[20] Second, transient myocardial edema has been previously observed shortly after running a marathon and was fully reversible at 3 months without complications and interruption of physical activity.[21] Finally, and most importantly, isolated myocardial edema without fibrosis has not been shown to independently affect prognosis in patients with suspected myocarditis.[22,23] Therefore in our opinion, in cases of asymptomatic individuals with negative troponin levels, normal ECG and normal LVEF, isolated signs of myocardial edema do not justify a change of management. In the case of an athlete recovered from Covid-19, our findings should not be used as a sole indication to withhold an athlete from training and/or competition.

On the contrary, the presence of LGE in the myocardium irrespective of its localization and pattern, except junction point fibrosis, has been persistently linked to worse prognosis.[24] In our study, only one patient with moderate

symptoms had nonischemic fibrosis, which could be linked to recent Covid-19 as supported by pericardial and pleural effusion, but could also be a marker of previous silent myocarditis or other causes. This pattern of fibrosis is not infrequently observed in asymptomatic athletes even without a history of prior myocarditis.[14,25] In any case, it should warrant further management to exclude the risk of inherited cardiomyopathy and/or arrhythmias of other origin consisting of at least detailed family history, 24-h-Holter monitoring and maximal exercise testing.

Overall, our findings, despite one suspicious case, are reassuring for athletes who have recently recovered from asymptomatic or mild Covid-19 and who have absence of increased troponin or ECG changes 1–2 months after the infection. All athletes gradually resumed training and safely returned to play. Our findings support the published American guidelines on the management of athletes post Covid-19, obviating the need for cardiac testing before return to play in asymptomatic or mild cases and limiting comprehensive cardiac evaluation, including MR, to moderate cases with signs of cardiac involvement in first-line tests (ECG, echocardiography, troponin).[9] In line with that, echocardiography performed in the athlete with LGE from our study would have also disclosed pericardial effusion and provided an indication for a cardiac MR study.

Our results are in contrast with some cardiac MR studies in the general population and athletes recovered from Covid-19. In a study by Puntmann et al. on 100 mainly asymptomatic or mildly symptomatic patients without increased troponin concentration after a mean of 2–3 months from diagnosis, cardiac abnormalities were found in over 70% of cases.[5] This could be related to the higher age of their study patients and the more frequent presence of cardiovascular and other risk factors or even to a low threshold for defining abnormality or other methodological issues raised in commentaries to the study.[26] These concerns are supported by findings on hospitalized patients with Covid-19 with significantly increased troponin who also had about 70% frequency of abnormal MR findings in the heart.[27] However, these patients represented the upper end of the Covid-19 spectrum of disease severity and not the lower end as in the study by Puntmann et al.

A study on collegiate athletes, by definition younger and healthier than the general population, has demonstrated signs of an active myocarditis in 15% of athletes and further 30% of them showing isolated myocardial fibrosis suggestive of previous injury.[6] The discrepancy between our results and the results of this study could potentially be explained by sex differences in the athletes studied (all male vs. mainly females in our study). Females have been shown to have a more benign clinical course of the disease, which may be due to females eliciting stronger immune responses to pathogens and/or the influence of sex hormones.[28] In a second American study on athletes post-Covid-19, which reported a 3% frequency of active myocarditis there was also a predominance of female athletes.[10] Finally, a difference between our results and previous cardiac MR studies on athletes post-Covid-19 could also be influenced by geographic or ethnical differences in the course of the disease.[29]

One of the athletes from our study demonstrated isolated pulmonary changes, which could potentially be linked to the Covid-19 infection. Studies with the use of computed tomography, have confirmed the risk of long-term pulmonary changes postinfection.[30] Importantly, despite this isolated extracardiac finding, we do not recommend cardiac MR to detect pulmonary changes due to much lower sensitivity than computed tomography.[31] However, we suggest that when performing a cardiac MR study on patients recovered from Covid-19, assessment for potential pulmonary changes should be given particular attention.

Limitations

First, our study was based on a relatively few subjects. However, the sample size was similar to some previously published studies with MR on athletes recovered from Covid-19[6] and data in this study group are highly needed. Second, due to time constraints and pandemic restrictions, our study lacked a matched control group. Therefore, we could not assess what percentage of elite athletes without the history of Covid-19 would also have myocardial edema or small pleural/pericardial effusions on cardiac MR. However, we report similar adaptive changes to sport in terms of ventricular enlargement, ECV, and prevalence of LGE as in a previous study on middle-age endurance athletes.[18] Last, we were also unable to present any clinical follow-up to assess the prognosis of the presented findings.

Conclusions

We have demonstrated that in elite athletes with mainly asymptomatic to mild Covid-19, lack of electrocardiographic changes and normal troponin concentration after a 1–2 months from the diagnosis there were no signs of acute myocarditis, but 19% of athletes had some abnormalities mostly nonlimiting them from return to play as assessed by cardiac magnetic resonance. Our results may support the proposed return to play guidelines recommending limited testing in this group of athletes.

Conflict of Interest

The authors declare that there is no conflict of interest.

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