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The role of cardiac magnetic resonance imaging in the contemporary diagnosis of acute myocarditis and myocardial injury

PhD Thesis

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2. List of Abbreviations

ACS	acute coronary syndrome
ACE 2	angiotensin-converting enzyme 2
AHA	American Heart Association
Ag	antigen
ANOVA	analysis of variance
BMI	body mass index
BNP	brain natriuretic peptide
BSA	body surface area
bSSFP	balanced steady-state sree srecession
CA	coronary angiography
CKMB	creatinine–kinase MB
CMR	cardiac magnetic resonance
COVID-19	coronavirus disease 2019
CRP	c-reactive protein
EACVI	European Association of Cardiovascular Imaging
ECV	extracellular volume
EGE	early gadolinium-enchancement
EDV	end-diastolic volume
EF	ejection fraction
ECG	electrocardiogram
EMB	endomyocardial biopsy
ESC	European Society of Cardiology
ESV	end-systolic volume

GCS	global circumferential strain
GFR	glomerular filtration rate
GLS	global longitudinal strain
GRS	global radial strain
HCM	hypertrophic cardiomyopathy
HIV	human immunodeficiency virus
HR	heart rate
i	index
IgA	immunoglobulin A
IgG	immunoglobulin G
IQR	interquartile range
M	mass
MDC	mechanical dispersion from circumferential strain
MDL	mechanical dispersion from longitudinal strain
MI	myocardial infarction
MINOCA	myocardial infarction with non-obstructed coronary arteries
LA	left atrium
LGE	late gadolinium-enhancement
LV	left ventricular
PCR	polymerase chain reaction
RV	right ventricular
SA	shor axis
SARS-CoV	severe acute respiratory syndrome coronavirus

SARS-CoV-2 severe acute respiratory syndrome coronavirus-2

SCD sudden cardiac death

SD standard deviation

SI signal intensity

SP spike protein

SV stroke volume

TLR Toll-like receptor

WMA wall motion abnormality

3. Introduction

3.1. Myocarditis

In the simplest terms, myocarditis is defined as the inflammation of myocardial tissue. Myocarditis can be determined according to phase, aetiology, disease severity, and histological findings. We can differentiate between acute (< 1 month) and chronic myocarditis (> 1 month) based on the onset of the symptoms (4). We can also classify the disease regarding the infiltrating cell types into eosinophilic, lymphocytic, giant cells, or granulomatous. Myocarditis is caused predominantly by viruses; however, the origin of myocardial inflammation is non-specific. It can be stemmed from a broad range of infections, toxic substances, drugs, and systemic immune-mediated diseases (5). The symptoms vary between mild presentation (short-term chest pain, fatigue) and high-risk cases of rapidly deteriorating cardiac function and life-threatening arrhythmias. Indeed, it is a relatively common cause of sudden cardiac death (SCD) in young people (6-10% based on autopsy series) (6, 7).

The frequency of myocarditis is influenced by several factors such as seasons, regional climate differences, the patient's age, and sex (8). Contemporary registries show that acute myocarditis is more common among relatively young patients (20-40 years), and male sex emerged as an important predisposing factor (9), although the underlying mechanism is incompletely understood. It is rather difficult to estimate the prevalence and the disease burden, as it varies over time and endemic diseases (4).

Despite the considerable scientific effort in recent years, the diagnosis of myocarditis remains a challenge due to the significant heterogeneity in clinical presentations and the wide variety of causes (5). Whilst, there is no targeted therapy for the most common, uncomplicated viral myocarditis cases, the diagnosis or the ruling out has impactful consequences for the patient. Failing to recognise the problem can lead to long-term health impairment. In contrast, falsely ordering prolonged (3-6 months) abstain from physical activity (10) might affect the life trajectory of a young individual.

Routine cardiovascular diagnostic tools, such as ECG and echocardiography, lack specificity and sensitivity to prove myocarditis (4). Cardiac troponins are very sensitive to myocardial injury, but they are not specific for the cause of the damage. The gold standard investigation technique, the endomyocardial biopsy, is very specific and can

establish the diagnosis and the underlying aetiology but has little sensitivity and is an invasive tool (11). Myocardial tissue characterisation using cardiac magnetic resonance imaging has emerged as a unique tool for the non-invasive diagnosis of myocarditis and has significantly improved the detection of the disease (12, 13). It can reveal the extent and pattern of myocardial damage and has been shown to provide prognostic information, which is essential for the long-term management of the patients.

3.2. The pathogenesis

Myocarditis has a heterogeneous aetiology: it is caused mainly by viruses but also by other infections organisms (including bacteria and protozoa). A broad range of toxic substances and drugs (most recently, immune checkpoint inhibitors), as well as systemic immune-mediated diseases can also induce myocarditis. The in-depth description of all factors and processes linked to the pathogenesis of myocarditis is beyond the limits of my PhD thesis; therefore, I refer the reader to the following reviews for further details (5, 14). Here, I summarise the leading agents and biological pathways linked to the disease.

3.2.1. Role of viruses

Myocarditis is most commonly induced by viruses, and we can classify viral agents based on the mechanism that causes myocardial inflammation. We differentiate between primary cardiotropic, vasculotropic, lymphotropic and cardiotoxic viruses, furthermore angiotensin-converting enzyme 2 (ACE2)-tropic and cardiotoxic viruses (5).

Cardiotropic viruses such as adenoviruses and enteroviruses (Coxsackie A and B, echovirus) are well-established causes of myocarditis. These viruses bind to a common transmembrane receptor of cardiomyocytes and induce direct myocardial injury (15). Vasculotropic viruses, namely parvovirus B19, can enter endothelial cells and trigger the release of proinflammatory cytokines, leading to inflammation-mediated apoptosis of the cardiomyocytes. Notably, parvovirus B19 may persist in the myocardial tissue; it was even found in autopsy samples from individuals without myocarditis (16). Members of the Herpesviridae family, such as Epstein–Barr virus, HHV6, and cytomegalovirus, are categorised as lymphotropic; these viruses can remain in the body for an extended period, with or without causing inflammation of the cardiac tissue (5). Cardiotoxic viruses, such as human immunodeficiency virus (HIV), hepatitis C virus, influenza A and B virus, can indirectly trigger myocarditis by activating uncontrolled immune responses such as

cytokine storm or a cellular immune-response by molecular mimicry. Finally, viruses belonging to the Coronaviridae family, including Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV), and SARS-CoV-2, can bind to ACE2 and potentially cause direct cardiac injury. Moreover, these viruses are suggested to induce indirect cardiac damage in an immune-mediated manner (17, 18).

Currently, the position statement on myocarditis by the European Society of Cardiology (ESC) recommends endomyocardial biopsy (EMB) and viral genome analysis using quantitative polymerase chain reaction (PCR) in all suspected acute myocarditis cases to define the underlying aetiology (11). However, it is not realistic in the clinical routine. The 2020 scientific statement by the American Heart Association (AHA) recommends a more conservative approach and reserves EMB for cases where there are diagnostic uncertainties or the histological assessment is vitally important (for instance, acute myocarditis presenting with cardiogenic shock) (4).

3.2.2. Role of the immune-response

The role of host immune response in the pathogenesis of myocarditis is still incompletely understood. Firstly, the viral infection activates the innate immune response and cardiomyocytes via pattern recognition receptors like Toll-like receptors (TLR) (19). The activated receptors then release cytokines, chemokines, interferons, and alarmins, leading to further activation of the first line of defence: mast cells, neutrophils, dendritic cells, monocytes, and macrophages (5). Notably, the antiviral effect of these cells is beneficial, whilst their excessive activation can trigger myocardial destruction and dysfunction. Secondly, danger signals, such as interleukin-1β induce haematopoiesis, leading to increased monocyte and myeloid progenitor cell generation, which might ultimately cause heart damage through the cardiosplenic axis (14). Finally, T cell activation is believed to have a critical mediating role in heart damage, especially in autoimmune myocarditis. It has also been shown that T cells drive the cardiac damage caused by viral myocarditis through different T cell subsets (5, 20).

Autoimmune myocarditis might occur as a primarily cardiac involvement or as a manifestation of a systemic immune-mediated disorder (5, 14). Heart-specific autoantibodies have been shown to recognise cardiac autoantigens, such as cardiac α- and

β-myosin heavy chains (21). Experimental models have illustrated both antibody and cell-mediated forms of autoimmune myocarditis, although mainly the humoral mechanism has been demonstrated in humans. The role of cardiac autoimmunity in disease progression depends largely on genetic factors, including the susceptibility of the host and the molecular mimicry between myocardial and microbial proteins (14).

3.3. Diagnosis and prognosis

3.3.1. The clinical spectrum of myocarditis

The symptoms of acute myocarditis include chest pain, dyspnoea, fatigue, palpitations, and syncope. The single most frequently reported sign is chest pain, followed by dyspnea (9, 22). Prodromal symptoms are rather common, including fever, chills, flu-like symptoms, gastrointestinal disorders, sore throat, or respiratory tract infection. Data from the Multicenter Lombardy Registry has shown that the majority of acute myocarditis cases presented with chest pain (97%), had no complications (73.4%), and had ST-segment elevation on the ECG (62.3%) (9). On the other hand, 26.6% of the cases were complicated by LV systolic dysfunction, ventricular arrhythmias, or cardiogenic shock. Consequently, these patients had worse short- and long-term outcomes.

The acute phase of the most common viral myocarditis lasts approximately 1 to 3 days. Exposure to intracellular antigens will trigger the cascade of immunologic processes (humoral and cellular immune response) to switch on. The main objective of this activation is to eliminate the virus; however, in some individuals, the immunologic response may persist for an extended period resulting in chronic myocarditis (14).

3.3.2. Coronary angiography

Due to its highly time-sensitive nature, coronary occlusion should be ruled out using invasive coronary angiography (CA) or computed tomography angiography as part of the diagnostic work-up of typical chest pain (4, 11). In this sense, although CA is not strictly part of the diagnostic work-up of acute myocarditis, these modalities should be in the forefront of clinical management depending on the symptoms and intitial test results of the patient.

3.3.3. Electrocardiogram

Overall, standard 12-lead ECG alterations are present in about 85% of the acute myocarditis cases (9). The most frequent ECG abnormality is ST-segment elevation mimicking acute myocardial infarctions, presenting typically in the inferior and lateral leads. Atrioventricular block, brady- or tachycardia, and ventricular arrhythmias are also reported and suggest high-risk myocarditis forms (4, 11). In fulminant myocarditis low voltage QRS might also present, due to the extensive oedema (23). Although non of these ECG abnormalities are specific to myocarditis, therefore has limited value during the diagnostic work-up.

3.3.4. Laboratory tests

A wide range of laboratory tests is recommended in patients with the suspicion of acute myocarditis (11). Biomarkers of myocardial necrosis (high-sensitivity troponins and creatinine kinase MB) are routinely measured and very sensitive at showing myocardial damage. Serum markers of inflammation (C-reactive protein and erythrocyte sedimentation rate) are often elevated but offer little help in the diagnosis making. Routine viral serology tests are rarely informative, although they might prove vital in specific cases (for instance HIV associated myocarditis).

3.3.5. Echocardiography

The main advantage of echocardiography in patients with the suspicion of myocarditis is that it helps to rule out other causes, including valvular disease or significant wall motion abnormalities (24). Acute myocarditis might present on echocardiography with impaired systolic function, increased wall thickness due to oedema, diastolic dysfunction, abnormal tissue Doppler imaging (4). Pericardial effusion might also present in the case of pericardial involvement. On the whole, echocardiography is neither sensitive nor specific to the myocardial alterations commonly present in myocarditis; therefore, its diagnostic value is limited. However, left ventricular ejection fraction (LVEF) measured at hospital admission might have incremental predictive value on patient outcome(9).

3.3.6. Cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) is the noninvasive reference standard for evaluating cardiac function, structure, and tissue composition. CMR is the most informative cardiovascular imaging modality, and a comprehensive discussion of all modalities and

applications is far beyond the limits of my PhD thesis. Here, I will focus on the CMR techniques and applications we employed during our research.

3.3.6.1. Description of the cardiac morphology and function

The high spatial resolution and tissue contrast provided by CMR techniques allow a detailed assessment of the anatomy of the heart and major blood vessels (25). To ensure consistent image quality and reproducibility, guidelines from major CMR societies aid best practices adopted by reporting centers (26, 27). Currently, the retrospectively triggered balanced steady-state free precession (bSSFP) cine sequence is the most widely used in the clinical routine to assess the cardiac morphology, volumes and function. The quantification of the left (LV) and right ventricular (RV) volumes, mass and ejection fraction is based on manual, semi-automatic or more recently, artificial intelligence-driven automatic delineation of the endocardium and epicardium on the short-axis cine images in end-systolic and end-diastolic phase (27).

CMR can be also used to measure strain, which permit a more accurate evaluation of myocardial deformation can potentially overcome the inherent limitations of ejection fraction. One major caveat is that the majority of the tissue-tracking methods proposed in CMR require additional specific sequences with their respective post–processing tools (28). CMR-based deformation imaging has been increasingly adopted since the introduction of feature-tracking analysis. This novel quantification technique enables the assessment of myocardial strain using conventional bSSFP cine images. The optimal myocardium blood contrast provides optimal definition of the endocardial layer, therefore endocardial features can be tracked through the cardiac cylcle similar to the speckle-tracking technique used in echocardiography (29). Feature-tracking enables the measurement of global and regional left and right ventricular strain parameters, mechanical dispersion and intraventricular dyssynchrony as well.

3.3.6.2. Main diagnostic targets and their pattern in myocardial inflammation

Myocardial oedema, defined as the myocardial tissue's increased water content, is represented on CMR with prolonged T1 and T2 relaxation times. T2 weighted images are more sensitive to pick up tissue oedema, which appears as regional (most commonly affecting midmyocardial or subepicardial layers) or global signal hyperintensity (30).

Parametric T2 mapping allows the direct assessment of increased relaxation time (31). T1 relaxation time is also prolonged by oedema, but it is less specific for active inflammation (32).

Inflammation also causes hyperemia and increases vascular permeability, which ultimately leads to the expansion of the extracellular space. T1-weighted spin-echo images and early gadolinium-enhanced images are targeted to visualise these alterations, although it less frequently used in clinical routine (33).

Severe inflammation induces direct myocardial damage: necrosis, fibrosis, and scarring. In CMR, this is visualised by prolonged T1 relaxation times, increased extracellular volume (ECV,) and late gadolinium enhancement (LGE). The gadolinium-based contrast material gains access to the extracellular spaces. The following common LGE patterns have been identified after nonischemic inflammatory injuries: lesions tend to be patchy, affecting the subepicardial and midmyocardial layers (in contrast to ischemic lesions that involve the subendocardium), and to favour the basal to mid-inferolateral walls (30). In extremely severe inflammation, the high–signal intensity regions may extend almost transmurally, but generally, the subendocardial layer is intact. However, in hypereosinophilia syndrome, the LGE shows a circumferential subendocardial pattern, although that does not localise to any coronary territory (34).

Pericardial involvement is sometimes accompanying myocardial inflammation, although not necessarily. Generally, pericardial abnormalities are viewed as a supportive criterion in diagnosing myocarditis. Importantly, pericardial effusion on its own does not prove pericarditis. Pericarditis is associated with thickened pericardial layers showing oedema and abnormal pericardial LGE (33).

In uncomplicated cases of myocarditis, dysfunction is focal, affecting only the injured area. Consequently, the surrounding myocardium might compensate by an increase in contractility, although the wall motion is simply unaffected in most cases. LVEF may be preserved or mildly decreased. In recent years, myocardial deformation imaging, especially CMR-based feature-tracking analysis, has been gaining recognition for its unique value in approximating myocyte metabolism and contractility more accurately than LVEF (35). Strain values, primarily global longitudinal strain (GLS), are

increasingly employed for the fine appreciation of myocardial function, although this technique is also non-specific.

3.3.6.3. Lake Louise Criteria

CMR imaging has emerged as the method of choice for the noninvasive assessment of acute myocarditis over the last decade (4, 33). In 2009, the Lake Louise Consensus Group recommended a standard protocol for assessing myocardial inflammation using CMR, which includes the visualisation of oedema, hyperemia, capillary leak, and necrosis (13). The growing evidence supporting the use of parametric mapping techniques in tissue characterisation led to the update of the criteria in 2018 (33), which is used to diagnose acute myocarditis today (**Table 1**).

Table 1: Recommendations of cardiac magnetir resonance imaging criteria of myocardial inflammation, adapted from Ferreira VM et al. (33). Abbreviations: CMR = cardiac magnetic resonance imaging; ECV = extracellular volume, EGE = early gadolinium enhancement; LV = left ventricle; LGE = late gadolinium-enhancement; SI= signal intensity; T2W = T2-weighted

Lake Louise Criteria	**Updated Lake Louise Criteria**	**Diagnostic target and example**
Main criteria		
T2-weighted imaging Regional high T2 SI OR Global T2 SI ratio ≥2.0 in T2W CMR images	T2- based imaging Regional high T2 SI OR Global T2 SI ratio ≥2.0 in T2W CMR images OR Regional or global increase of myocardial T2 relaxation time	Myocardial oedema
Early gadolinium enhancement (EGE)	T1-based imaging Regional or global increase of native	T1 –oedema (intra- or extra-cellular), hyperemia/

SI ratio myocardium/ skeletal muscle of ≥ 4 in EGE images Late gadolinium-enhancement (LGE) Areas with high SI in a nonischemic pattern in LGE images	myocardial T1 relaxation time or ECV OR Areas with high SI in a nonischemic distribution pattern in LGE images	capillary leak, necrosis, fibrosis EGE – hyperemia, capillary leak LGE – necrosis, fibrosis, (acute extracellular oedema) ECV – oedema (extracellular), hyperemia/capillary leak, necrosis, fibrosis
Supportive criteria		
Pericardial effusion in cine CMR images	Pericardial effusion in cine CMR images OR High signal intensity of the pericardium in LGE images, T1 or T2 mapping	Pericardial inflammation
Systolic LV wall motion abnormality in cine images	Systolic LV wall motion abnormality in cine images	LV dysfunction

As described above the diagnosis of acute myocarditis is based on at least one T2-based criterion (global or regional increase of myocardial T2 relaxation time or an increased signal intensity in T2-weighted CMR images) for the visualisation of oedema; with at least one T1-based criterion (increased myocardial T1, extracellular volume, or late gadolinium enhancement) to illustrate myocardial injury. Whilst the combination of positive T2-based and T1-based markers will increase specificity to establish acute myocarditis, having only one positive feature may still support a diagnosis of acute myocardial inflammation in an appropriate clinical scenario, although with less specificity.

Overall, the diagnostic accuracy of the Lake Louise Criteria to identify acute myocarditis is 83% (sensitivity, 78-80%; specificity, 87-88%) (36). CMR diagnostic accuracy is highest for infarct-like presentation; moreover, it is a particularly effective technique for excluding myocardial inflammation. Due to the course of the disease, the optimal sensitivity of diagnostic imaging is limited to a few weeks from presentation (approximately two weeks). Notably, the aetiology of myocarditis cannot be established based on the CMR presentations.

3.3.7. Endomyocardial biopsy

EMB establishes the definitive diagnosis of myocarditis and identifies the underlying aetiology, moreover the type of inflammation (lymphocytic, eosinophilic or giant cell myocarditis, cardiac sarcoidosis) present in the myocardial tissue. Therefore, EMB can provide the necessary basis for the initiation of cause-specific treatment when appropriate (11). The histopathologic assessment is based on the Dallas criteria. Immunohistochemistry and viral genome analysis using PCR are important tools to refine the diagnosis further (4, 37).

Two main limiting factors should be considered: EMB is an invasive technique, and the diagnostic accuracy is limited by sampling error. Fortunately, ample evidence supports that EMB is safe (complication rate as low as 1-2%) when performed by experienced teams (11). Early assessment (<2 weeks) and multiple samples (4-6) can improve specificity; more recently the application of CMR was also suggested to optimise EMB accuracy (4).

One major limiting factor of CMR application is haemodynamic instability, a severe presentation where the patient cannot tolerate lying flat and motionless for an extended period. Therefore, in myocarditis presenting with progressive or persistent severe cardiac dysfunction, high-grade heart block or symptomatic ventricular arrhythmias, an EMB-guided diagnostic approach is recommended by both the AHA and ESC (38).

3.4. Differential diagnostic questions

Acute myocarditis can mimic the symptoms and intitial presentation of coronary occlusion as higlighted above, in which cases the use of CA should always be considered. Furthermore, the clinical presentation of acute myocarditis and pericarditis might be

similar; and high-sensitivity troponin can aid the discrimination. In the following section, I endeavour to describe some current differential diagnostic challenges in myocarditis and myocardial injury and how CMR is employed to clarify these questions.

3.4.1. The working diagnosis of MINOCA

Myocardial infarction (MI) with non-obstructed coronary arteries (MINOCA) is an important working diagnosis subgroup among patients with signs and symptoms of acute coronary syndrome (ACS), and their prevalence is up to 10% in this cohort (39, 40). The inclusion and exclusion criteria and diagnostic methods of studies assessing patients with the working diagnosis of MINOCA varied significantly (41-45). The ESC published a position paper on MINOCA in 2017 to facilitate clinical decision-making. This paper, among others, suggests that CMR imaging should be used in patients with a working diagnosis of MINOCA due to its unique capacity to assess cardiac function, structure and tissue characteristics, including oedema and necrosis/fibrosis (39). The recent AHA scientific statement recommends the "traffic light" sequence for the clinical assessment of this patients group. This algorithm aids the establishement of "true" MINOCA diagnosis. Tamis-Holland et al. delineated the central role of CMR for the clarification of disease aetiology (**Figure 1**) (3).

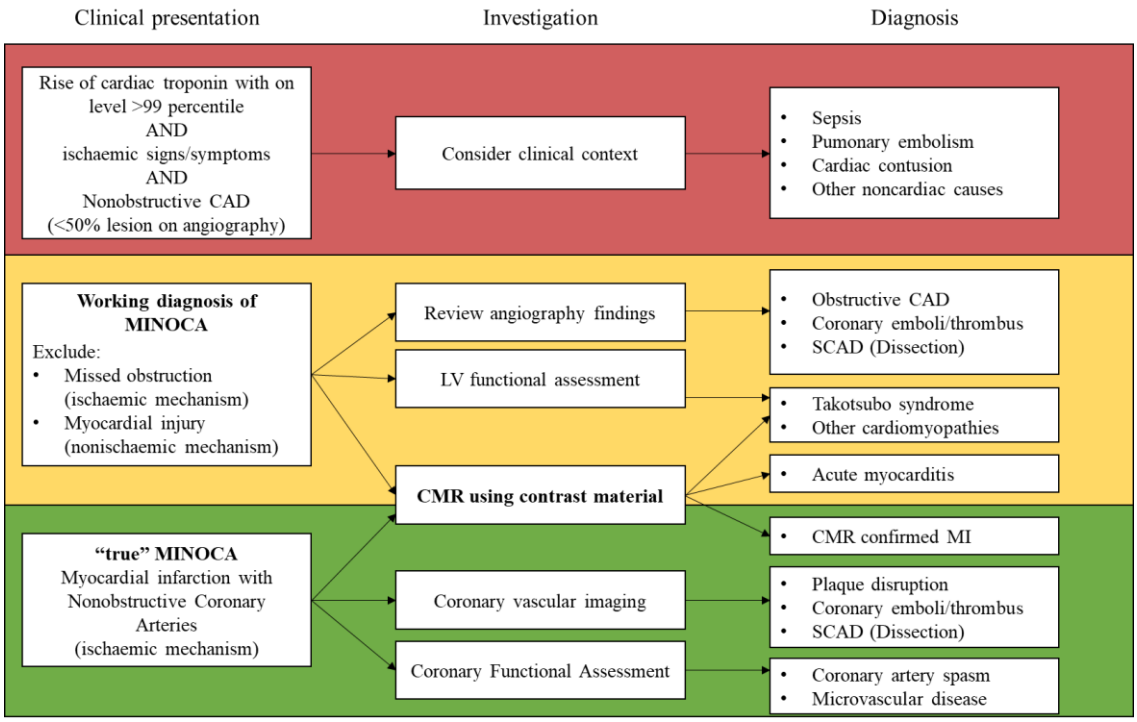

Figure 1: Proposed clinical algoritm for the diagnosis of MINOCA adapted from Tamis-Holland et al (3). Abbreviations: CAD = coronary artery disease, CMR = cardiac magnetic resonance imaging, MINOCA = myocardial infarction with non-obstructed coronary arteries; SCAD = spontan coronary artery dissection

The causes of "true" MINOCA are categorized as atherosclerotic and non-atherosclerotic. The atherosclerotic sources of MINOCA incorpotates unstable non-obstructive plaques (plaque rupture or plaque erosion) with spontaneous autolysis of the correponding intracoronary thrombus (39, 40). Non-atherosclerotic causes of MINOCA comprise of epicardial and microvascular coronary spasm, spontan coronary artery dissection (SCAD) and distal coronary embolism or thrombosis.

CMR findings in MINOCA (both atherosclerotic and non-atherosclerotic pathomechanism) are similar as those in obstructive ACS with occlusive plaque rupture: oedema depicted on T2 weighted images and necrosis on LGE images in subendocardial or transmural pattern indicates of a acute myocardial infarction. Furthermore, CMR, especially the presence and pattern of LGE, is suggested to provide incremental prognostic information (41). Notably, data is sparse regarding whether CMR-based strain parameters have additional prognostic role to other readily available imaging modalities (such as LVEF or LGE). However, some limited studies have already demonstrated the prognostic value of GLS in patients with acute MI (46, 47).

3.4.2. Cardiovascular involvement after SARS-CoV-2 infection and anti-SARS-CoV-2 vaccination

Since its beginning in March 2020, the coronavirus disease 2019 (COVID-19) pandemic has affected all areas of life from an individual level to global economic, scientific, and social trajectories. As of February 2022, the number of confirmed COVID-19 cases reached more than 400 million, with almost 6 million related deaths worldwide (48). Notably, since the end of 2020, we have administered more than 10 milliard doses of anti-SARS-CoV-2 vaccination, a step that promises to end the global pandemic.

The presence and extent of cardiac involvement in coronavirus disease 2019 (COVID-19) patients are of great interest. SARS-CoV-2 infects the epithelial cells of the respiratory tract via angiotensin-converting enzyme 2 (ACE2) receptor and may lead to

serious consequences in the respiratory system (18, 49). It has also been established that COVID-19 can induce multi-organ involvement, targetting both the heart and the vessels via the ACE2 receptor (50). Thus far older age (>60 years), male sex, and pre-existing comorbidities, such as obesity and hypertension, are proved to be the major risk factors for death in COVID-19 patients (51). Importantly, COVID-19 with myocardial injury (defined by significantly elevated troponin levels) has been linked to an increased burden of in-hospital mortality (52, 53). Previous studies has demonstrated that COVID-19 associated myocardial injury can include myocardial infarction, myocarditis, acute heart failure, and secondary organ damage due to sepsis and critical illness (54).

3.4.2.1. The role of CMR after SARS-CoV-2 infection

Emerging yet inconsistent initial findings led to greater interest in CMR imaging studies after SARS-CoV-2 infection. A German cohort study by Puntmann et al. (55) using late gadolinium enhancement (LGE) and novel T1 and T2 mapping sequences showed myocardial involvement in 78% of middle-aged patients, raising serious concerns regarding their cardiac health. Approximately one-third of the alterations were solely based on native mapping elevations, which are increasingly used in establishing myocardial tissue alterations without contrast administration. However, the exact diagnostic and prognostic impact of these novel sequences are less well known than that of widely used techniques such as LGE (26). Indeed, subsequent publications did not reiterate these findings (54, 56-58). Kotecha et al. published CMR findings from 148 hospitalised COVID-19 patients with severe infection and troponin positivity (59). They performed CMR approximately two months after discharge and found a myocarditis-like pattern of LGE in 26% (39/148) and myocardial infarction or inducible ischemia in 22% (32/148). This landmark study demonstrated that even among patients with primarly chest complains and evidence of COVID-19 associated myocardial injury, the mid-term prevalence of myocardial involvment is lower than initially reported. Overall, it seems that the study by Puntmann et al. is an outlier in a long line of investigations looking into the cardiovascular involvment after COVID-19.

3.4.2.2. The role of CMR after SARS-CoV-2 infection in athletes

The myocardial involvement among highly trained athletes returning to extreme physical activity after the infection received unprecedented attention in the last one and a half

years, with social media attention skyrocketing around positive findings (60). Case series from 2020 by Rajpal et al.(61) and Brito et al. (62) found a high prevalence of myocardial (15%) and pericardial (39.5%) inflammatory alterations among college athletes following mild and asymptomatic SARS-CoV-2 infection. In contrast, subsequent publications reported a much lower prevalence of cardiac involvement ranging from 0.7% to 3.0% in college athletes after the infection (63-65).

3.4.2.3. Myocarditis after anti-SARS-CoV-2 vaccination

Anti-SARS-CoV-2 vaccination is increasingly linked to rare cases of myocarditis and myopericarditis, primarily in the young adult and adolescent male population (66). The connection between novel mRNA vaccines and these cases has been made. However, postvaccination myocarditis may arise after different vaccinations too, including the smallpox vaccine that contains live viruses (67).

Case reports and case series has shown the potential role of CMR imaging in the verification of vaccination-related myocarditis. Myocarditis predominantly occured after the administation of the second dose of mRNA vaccines, BNT162b2 mRNA-Pfizer-BioNTech and the mRNA-1273-Moderna (68, 69). A cohort study from Israel described clinical follow-up, but they derived the data from hospital reporting systems, which precluded the characterization of cardiac function or tissue alterations (70). Therefore, we have little evidence concerning the course of myocarditis after SARS-CoV-2 vaccination and, consequently, the CMR findings.

The proposed underlying mechanisms of the evolution of vaccination-related myocarditis include molecular mimicry between the SARS-CoV-2 spike protein and self-antigens, triggers of preexisting immune pathways, and accelerated innate immunogenic reactions. However, these are primarily theoretical suggestions as the immune response of patients with myocarditis after anti-COVID-19 vaccination has not been revealed in detail (66).

4. Objectives

The main objectives of our studies were to demonstrate the benefits of deep cardiovascular phenotyping, using a wide variety of standard and novel markers of the cardiac function, morphology, and tissue composition in the diagnostic work-up of patients with suspected acute myocardial damage.

4.1. Defining the diagnostic and prognostic implications of early CMR in the workup of patients with the working diagnosis of MINOCA

The current ESC guideline on acute MI presenting with ST-segment elevation suggests the use of CMR examination in the subgroup of patients with non-obstructed coronary arteries within two weeks after the onset of symptoms to increase the diagnostic accuracy of the method (71). However, the systematic application of early CMR in the differential diagnosis of patients with a working diagnosis of MINOCA and their subsequent prognosis is less well defined.

Thus, we conducted our first study with the following two aims. First, we evaluated the diagnostic implications of early CMR (≤7 days). Second, we sought to assess the prognostic impact of conventional risk factors and CMR examination, including diagnosis, standard parameters, and strain analysis, in patients with a working diagnosis of MINOCA.

4.2. Defining the cardiac involvement after SARS-CoV-2 infections in young competitive athletes

Published studies analyzing the cardiac involvement by CMR imaging in athletes who recovered after SARS-CoV-2 illness yielded conflicting results. Whilst earlier data found a high prevalence of myocardial and pericardial inflammatory alterations among college athletes following SARS-CoV-2 infection (61, 62), novel works reported a considerably lower prevalence (63-65). The current expert consensus statements establishing the screening protocol for potential cardiac involvement in competitive athletes recovering from SARS-CoV-2 infection highlighted the need for more robust data with the inclusion of appropriate control subjects (72, 73).

Therefore, our second study aimed to evaluate the cardiac involvement after SARS-CoV-2 infection in young highly-trained athletes using a comprehensive CMR imaging study,

including tissue characterisation and strain analysis. We compared the CMR features with healthy sex- and age-matched athletes and healthy sex- and age-matched less active controls.

4.3. Defining the clinical, CMR imaging, and immunological characteristics of myocarditis after SARS-CoV-2 vaccination

Currently, clinical and imaging data are sparse regarding the course of myocarditis after anti-COVID-19 vaccination. The underlying mechanisms of the evolution of vaccination-related myocarditis are largely unclear. The proposed concepts are primarily theoretical as the immune response of myocarditis patients after anti-SARS-CoV-2 vaccination has not been reported (66).

The purpose of our third study was to delineate the clinical, CMR imaging and immunological features of myocarditis after COVID-19 immunization in the acute phase and during short term follow-up. Second, we aimed to illustrate the features of myocarditis potentially linked to the anti-SARS-CoV-2 vaccine in the context of myocarditis cases where vaccination or any contact with infection did not occur. Third, we aimed to investigate the immunological response to SARS-CoV-2 immunization in patients with myocarditis and matched controls.

5. Methods

5.1. Study design, study populations, comparator groups

5.1.1. The diagnostic and prognostic implications of early CMR in the workup of patients with the working diagnosis of MINOCA

In this retrospective longitudinal observational study we investigate consecutive patients presenting between April 2009 and April 2019 with a working diagnosis of MINOCA (troponin-positive acute chest pain and non-obstructed coronary arteries) who underwent CMR in our tertiary referral centre. The inclusion criteria for admission into the study were: 1) acute chest pain 2) a significant increase in the high-sensitive troponin T (>14 ng/l); 3) ECG changes (e.g. at least 1-mm of ST-segment elevation or ST-segment depression or negative T-waves in at least two associated leads); and 4) normal coronary arteries or coronary arteries with signs of atherosclerosis with stenosis <50% in a luminal diameter as per invasive CA. The exclusion criteria were: 1) a CMR examination conducted more than seven days after invasive CA; 2) malignant ventricular arrhythmias at presentation or having dilated cardiomyopathy with signs of severe heart failure as a primary complaint; 3) acute or chronic renal failure with a glomerular filtration rate (GFR) <30 mL/min/1.73 m2; and 4) age <18 years. Patients' referral diagnoses were provided by the referring clinician based on the initial results of the physical examination, 12-lead ECG, laboratory values, risk factors, comorbidities, CA and echocardiography. Patient data, including risk factors, laboratory values, and all CMR-based parameters, are described by the CMR-based diagnostic groups.

All-cause mortality was ascertained based on both available medical records and the National Health Insurance Fund of Hungary (Hungarian acronym: NEAK) database, which includes up-to-date information on deaths. As a central agency, the NEAK performs functions specified by legislation, maintains records and financial accounts, and fulfils reporting obligations.

5.1.2. Cardiac involvement after SARS-CoV-2 infections in young competitive athletes

Between July 2020 and February 2021, athletes recovering from SARS-CoV-2 infection who underwent CMR in our institution were consecutively included in this observational

study. SARS-CoV-2 infection was established based on PCR swab tests or serum immunoglobulin G (IgG) antibody tests. We excluded athletes 1) aged <16 years and 2) those performing <6 training hours/week. Athletes were referred for CMR by their cardiologist to investigate potential heart involvment caused by SARS-CoV-2 infection, ideally before the athlete's return to high levels of sports activity. All athletes completed a set of questionnaires regarding their sports activity and SARS-CoV-2 infection. Symptoms were evaulated using the National Institutes of Health's COVID-19 treatment guideline (74). Asymptomatic SARS-CoV-2 infection was reported in individuals who tested positive for SARS-CoV-2 and had no symptoms consistent with the disease. Mild infection was defined based on symptoms such as fever, cough, headache, loss of smell, and/or taste but not more alarming signs. Chest pain, dyspnoea, and shortness of breath were categorised as moderate symptoms. Long COVID was characterised by persistent symptoms, mostly fatigue and palpitations, extending beyond four weeks after the initial infection. Our published data in Journal of the American College of Cardiolog: Cardiovascular Imaging incorporating the first 12 athletes after SARS-CoV-2 infection were included in this study (75). To avoid duplication of results, here I will present our methods, results and conclusions combined into one based on our publication in the Brisitsh Journal of Sports Medicine (1).

Clinical assessments, including 12-lead electrocardiography (ECG) and high-sensitivity troponin T (hsTnT) were recorded at median one day (0-7 days) before the CMR examination. The local laboratory cut-off for elevated hsTnT was >13.99 ng/L. All tests were performed after an appropriate quarantine period (10 days).

We compared CMR metrics to those of sex- and age-matched healthy athletes (n=59) and healthy less active controls (n=56). All included healthy volunteers were scanned to establish normal reference ranges for the less active and athletic population without any suspicion of cardiovascular risk factors or pathology prior to the COVID-19 pandemic (59%) or who tested seronegative for the disease (41%). Athletes after SARS-CoV-2 infection and control athletes both participated in competitive sports activity, the majority of them being professional athletes competing at national or international levels in mixed or endurance sports disciplines (10). Healthy, less active controls reported <6 training hours/week. None of the participants reported consumption of illegal drugs. None of the

athletes after SARS-CoV-2 infection was administered systemic steroid treatment during their illness.

Follow-up was conducted using the institutional electronic database and via telephone. During the follow-up visit athletes completed a questionnaire regarding potential ongoing symptoms, their ability to return to sports activity, and their overall experience during the examination. We offered a comprehensive follow-up cardiological examination, including a CMR scan at our institution to all athletes reporting reinfection with SARS-CoV-2, and those with definite or possible myocardial alteration on their baseline scan.

5.1.3. The clinical, CMR imaging, and immunological characteristics of myocarditis after SARS-CoV-2 vaccination

We studied the clinical, CMR imaging features and immune response of myocarditis patients after SARS-CoV-2 vaccination in a CMR-based register between December 2020 and September 2021. We contacted all Hungarian institutions performing CMR scans (n=19), among which four institution reported eligible cases. We defined the following inclusion criteria: 1) anti-SARS-CoV-2 vaccination not more than 21 days before the acute symptoms; 2) presence of one or more of the following symptoms: new-onset chest pain, dyspnoea or palpitation or syncope; 3) troponin elevation as per the local laboratory; and 4) CMR examination confirming the clinical suspicion of acute myocarditis.

We collected information regarding the participant's acute symptoms, previous medical history, including their history of cardiovascular and immunological diseases using an in-house developped questionnaire. Cardiac biomarker levels, laboratory tests and 12-lead ECG were recorded. Echocardiography and CMR examination were performed. We carried out immunological tests in all acquiescent patients. Symptomatic patients (e.g. ongoing chest pain) were admitted to intensive/coronary care units (ICU/CCU) with continuous bedside monitoring. We performed follow-up cardiology examinations and CMR scans 3-6 months after the acute presentation in all consenting patricipants.

The laboratory test protocol included troponin, CKMB, CRP, white blood cell count, eosinophil cell count. Antinuclear antibodies (ANA), extractable nuclear antigen antibodies (ENA), antineutrophil cytoplasmic antibodies (ANCA), and serum immunoglobulin levels (IgG, IgM, IgA) were measured (n=10). A subgroup myocarditis

patients after anti-SARS-CoV-2 vaccination (n=12) and all immunisation matched controls (n=23) underwent a detailed evaluation of humoral and cellular immune response at the Semmelweis University. We stantardised the immunology test protocol and its interpretation as follows: SARS-CoV-2 specific antibodies (referred to in the text as S1 Ig) were analysed using Elecsys Anti-SARS-CoV-2 S immunoassay (Roche Diagnostics International Ltd, Switzerland) on Cobas e6000 instrument. This assay detects antibodies specific to the SARS-CoV-2 spike (S) protein receptor-binding domain (RBD) in human serum and plasma (cut-off: ≥0.8). The method uses electrochemiluminescence to determine antibodies. Immunoglobulin response was measured using ELISA test on an Elite Lite (DAS, Italy) device. We will refer to the IgG and IgA immunoglobulins against the S1 domain of the spike protein as S1 IgG and IgA for transparency. Immunoglobulin levels were quantified in quantitative (S1 IgG) or semiquantitative (S1 IgA) manner (76). The T cell response was determined via QuantiFERON SARS-CoV-2 assay, which uses interferon-gamma release assay described in detail elsewhere (77). It consists of three antigen tubes: Ag1, Ag2, and Ag3, that use a combination of proprietary antigen peptides specific to SARS-CoV-2 to stimulate lymphocytes involved in cell-mediated immunity. The Ag1 tube contains CD4+ epitopes derived from the S1 subunit RBD of the spike protein. The Ag2 tube contains CD4+ and CD8+ epitopes from the S1 and S2 subunits of the spike protein. The Ag3 tube consists of CD4+ and CD8+ epitopes from S1 and S2 and immunodominant CD8+ epitopes derived from the whole SARS-CoV-2 genome.

We considered two comparator groups during our study. Firstly, the CMR control group were sex- and age-matched from the Semmelweis Universities CMR database as per the following criteria 1) troponin elevation 2) CMR examination confirming acute myocarditis was completed <2 weeks after the acute presentation 3) CMR examination before the first reported case of SARS-CoV-2 infection in Hungary (2020.03.04.) OR negative PCR excluding the infection 4) follow-up CMR was carried out between 3-6 months after the acute scan. Secondly, the study participants' immune response was compared with 23 sex-age, and SARS-CoV-2 immunisation matched controls from the Semmelweis Universities database. We considered the time elapsed from their first COVID-19 vaccination and the type of vaccine received for the immunisation matching. Morover, we objectively quantified SARS-CoV-2 exposure using anti-nucleocapsid protein levels, which showed no difference between myocarditis patients after anti-

COVID-19 vaccination and controls. This matching step was crucial, as more participants reported prior SARS-CoV-2 infection in the control group than in the myocarditis group.

5.2. Ethical approval

Written infromed consent was obtained from all participants before inclusion in our studies. All ethical approvals are in accordance with the ethical standards laid out in the 1964 Declaration of Helsinki and its later amendments. Issuing authority and individual approval number is given below.

5.2.1. The diagnostic and prognostic implications of early CMR in the workup of patients with the working diagnosis of MINOCA

The study was approved by the Hungarian National Institute of Pharmacy and Nutrition (OGYEI/29206-4/2019).

5.2.2. Cardiac involvement after SARS-CoV-2 infections in young competitive athletes

The ethical approval was acquired from the National Public Health Center of Hungary (52001-6/2020/EÜIG).

5.2.3. The clinical, CMR imaging, and immunological characteristics of myocarditis after anti-SARS-CoV-2 vaccination

The study was approved by National Public Health Center of Hungary (15357-7/2021/EÜIG).

5.3. CMR image acquisition protocol

All CMR examinations were performed using 1.5 T scanners (Siemens Magnetom Aera, Siemens Magnetom Amira, GE SIGNA Voyager, Phillips Achieva, Phillips Ingenia). The CMR protocol contained the following sequences in all studies: cine sequence covering the whole heart, T2 weighted images depicting myocardial oedema, late gadolinium enhancement (LGE) images showing necrosis or fibrosis.

Functional imaging was performed using balanced steady-state free precession cine sequences in four-chamber, two-chamber, and three-chamber long-axis (LA) views and a short-axis (SA) stack from the cardiac base to the apex with complete coverage of the left ventricle (LV) and right ventricle (RV). T2-weighted spectral presaturation with

inversion recovery (SPIR) images for the qualitative assessment of oedema. LGE images were acquired using a segmented inversion-recovery sequence 10-15 min after administering an intravenous bolus of 0.15 mmol/kg of the gadolinium-based contrast agent gadobutrol (Gadovist, Bayer-Schering Pharma) at a rate of 2-3 ml/s through an antecubital intravenous line. The inversion time was corrected to optimize the suppression of normal myocardium.

In the assessments of SARS-CoV-2 and SARS-CoV-2 induced myocarditis, we also used parametric mapping sequences to evaluate myocardial alterations. We ascertained quantitative descriptors of oedema using T2 mapping sequence: T2-prep balanced steady-state free precession (b-SSFP). T1 mapping was performed using long-T1 5(3)3 and short-T1 5(3)3 modified look-locker inversion recovery (MOLLI).

5.4. Image analysis and interpretation protocol

Overall, CMR scans across all studies were analysed and reported under the supervision and final approval of at least one of two consultants with >10 years of experience in performing CMR with a level 3 certification in CMR reporting issued by the European Association of Cardiovascular Imaging (EACVI). Notably, we considered a wide range of cardiovascular metrics using a combination of well-established, clinical used parameters and novel features that are widely used in research settings.

All postprocessing analyses were performed using Medis Suite Software (Medis Medical Imaging Software, The Netherlands). LV and RV volumes, function, and mass were calculated from the SA stack using artificial intelligence-based automated contour detection (autoQ application) with manual adjustments if required.

Strain measurements were performed using cine images and analysed with the feature-tracking application of Medis QStrain software by an experienced reader across all studies. Endocardial segmentation was obtained manually on LA and SA cine images in end-systolic and end-diastolic phases (78). LV global strain values, including longitudinal (GLS), circumferential (GCS) and radial (GRS) strain were measured. For global dyssynchrony measurement, mechanical dispersion (MD) was determined, defined as the SD of the time-to-peak circumferential (MDC) and longitudinal (MDL) strain of the LV segments and expressed as a percent of the cardiac cycle. We could derive strain features for all participants.

In the assessments of SARS-CoV-2 and SARS-CoV-2 induced myocarditis, myocardial native T1 and T2 relaxation times were measured conservatively in the midventricular or basal septum (if the midventricular images were technically inadequate for analysis) of the myocardium using motion-corrected images (27) by an experienced investigator blinded to the clinical data of a given subject. We defined our reference ranges for native T1 and T2 values using the healthy volunteer data (athletes and less active individuals). In case of suspicion of focal T1 mapping elevation, a separate region of interest in that area was drawn.

5.4.1. The diagnostic and prognostic implications of early CMR in the workup of patients with the working diagnosis of MINOCA

We combined visual and quantitative information from cine images with qualitative information from T2-weighted and LGE images to establish the final CMR diagnosis. The patients received one of the following diagnoses: acute MI, acute myocarditis, Takotsubo syndrome or normal CMR. Acute MI diagnosis was based on an increased or decreased T2 signal, perfusion defect, microvascular obstruction, and an ischaemic LGE pattern (subendocardial to transmural) (39, 79). The definition of acute myocarditis was established as per the LLC criteria: increased T2 signal showing myocardial oedema on SPIR images and the presence of LGE in a patchy non-ischaemic pattern with a subepicardial and/or mid-myocardial extent (13). Takotsubo syndrome was diagnosed based on regional WMAs extending beyond a single coronary territory with no extensive LGE and potential myocardial oedema (80). If we did not detect any abnormalities on the CMR images, such as myocardial oedema, necrosis/fibrosis, or WMA, the patient was identified as having normal CMR. Finally, we distinguished patients with an LGE pattern not specific to any known disease as having an inconclusive CMR. We recorded the CMR diagnosis and subsequently compared it with the referring diagnosis to investigate the impact of CMR.

We tested the interobserver variability of feature-tracking strain metrics in a subgroup of randomly selected patients (n=100). Parameters with an interrater agreement (kappa) over 0.6 were accepted.

5.4.2. The cardiac involvement after SARS-CoV-2 infections in young competitive athletes

Nonischaemic LGE was defined as midmyocardial and/or subepicardial myocardial LGE confirmed in two perpendicular views. Pericardial involvement was reported if the pericardium showed definite LGE and the thickness of the pericardium was >2 mm regardless of pericardial oedema. We defined hinge point fibrosis as a small, focal LGE confined to the inferoseptal segment, where the RV attaches to the septum.

We standardised image interpretation according to the following criteria 1) visual assessment based on all CMR images was conducted by two observers blinded to the clinical data of a given subject 2) myocardial and pericardial LGE was visually confirmed by two independent observers. In case of disagreement between the observers, a third CMR specialist with an EACVI level 3 certificate was consulted for consensus.

Cardiac involvement was classified as definite in case of LGE showing pathological pattern or certain T1 abnormality, with T2 abnormality, and one or more supporting findings such as decreased LV ejection fraction or elevated troponin level. Possible peri/myocardial involvement was reported when we found: 1) mild T1 abnormality or the presence of LGE with normal T2, or 2) mildly elevated T1 and T2 mapping with no LGE or other supporting findings. We determined abnormal T1 and T2 values based on the sequence-specific cut-offs of two standard deviations (SDs) above the means of the healthy, sex- and age-matched athlete controls (male athletes: T1: 986 ms, T2: 46 ms; female athletes: T1: 1001 ms, T2 49 ms).

5.4.3. The clinical, CMR imaging, and immunological characteristics of myocarditis after SARS-CoV-2 vaccination

The CMR image acquisition protocol (described above) of the acute and follow-up CMR scans were similar in most cases. Of note, we accepted follow-up scans without T2 weighted sequences. We offered a CMR scan slot at the Semmelweis University Heart and Vascular Center (n=2) if the follow-up was not feasible in the referring hospital. Mapping sequences were available in three institutions (n=13/16). We collected raw CMR data in DICOM format, and conducted all post-processing analyses in the core CMR laboratory at Semmelweis University Heart and Vascular Center.

LGE was quantified using the 5SD technique, we kept manual adjustments to the minimum. We compared mapping values in participants who underwent CMR examination at the core laboratory (n=9) as per the international recommendation (27). Acute myocarditis was defined as per the modified Lake Louise criteria (33). The interpretation of CMR scans was standardised: the presence and pattern of myocardial oedema and LGE was visually defined independently by two EACVI certified observers. In case of disagreement between the observers, a third level 3 EACVI certified CMR specialist was consulted for consensus.

5.5. Statistical analysis

Statistical analysis and data visualisation were performed using the MedCalc software V.18.11 and RStudio in all studies. The Shapiro-Wilk test was applied to test normality. Continuous variables showing a normal distribution are presented as the mean and standard deviation (SD), and those showing a non-normal distribution are reported as medians and interquartile ranges (IQRs). Categorical variables are presented as frequencies and percentages. Comparisons between two independent groups were conducted using independent samples t-tests and Mann-Whitney U tests as appropriate. Acute and follow-up (paired samples) examinations were compared using paired sample t-tests and Wilcoxon tests. In the case of three or more groups, comparisons of the means of continuous variables with normal distribution were performed using one-way ANOVA and the Scheffe test for post hoc pairwise comparisons. The distributions of non-normal continuous variables were compared by Kruskal-Wallis tests. We applied analysis of covariance (ANCOVA) to formally test the difference between the trajectory of myocarditis after SARS-CoV2 vaccination and myocarditis unrelated to COVID-19. Khi tests were applied to compare the distributions of categorical data. Associations were assessed using Spearman's rank correlation analyses. Univariate associations of time variables with mortality were visualised using Kaplan-Meier curves and compared by the log-rank test. Univariate and multivariate associations of risk factors and covariates with mortality were assessed using Cox proportional hazard regression analyses. Variables with $p<0.05$ in univariate analyses were candidates for multivariate analysis. Probability values were 2-sided, and across all analysis $p<0.05$ were considered significant.

6. Results

6.1. The diagnostic and prognostic implications of early CMR in the workup of patients with the working diagnosis of MINOCA

6.1.1. Diagnostic impact

During the 11-year study period, we examined 255 patients (42±16 years, 165 male) with troponin-positive acute chest pain who underwent CMR within 7 days following CA with non-obstructed coronary arteries. The mean time delay between CA and CMR examinations was 2.7 days. We could establish the final diagnosis in 86% of the cases using CMR: MI (n=55), acute myocarditis (n=136), Takotsubo (n=26), and myocardial contusion (n=1) (81). CMR demonstrated a structurally normal heart in 33 patients. The remaining four patients had inconclusive CMR findings as follows: atypical sarcoidosis, atypical myocarditis, or amyloidosis. Further examinations revealed Churg-Strauss Syndrome, AL amyloidosis, an unspecified autoimmune disease affecting multiple organs or remaining inconclusive. Due to the combined small number of patients with myocardial contusion and uncertain CMR findings (n=5), these patients were excluded from the further analysis. The distributions of CMR diagnoses in patients with normal arteries and those with signs of atherosclerosis are depicted in **Table 2**. In 61% of the MI (or MINOCA), 82% of acut myocarditis, 54% of the Takotsubo and 58% of the normal CMR patients presented with completely normal CA findings.

The sankey diagram on **Figure 2.** illustrates the distributions of the referrals as they link to the CMR-based diagnosis. The referral diagnosis was confirmed in 48% and overwritten in 16% by CMR. Among those with uncertain referrals (n=71), CMR identified a diagnosis in 79%. The single most common clinical suspicion was myocarditis (n=155) in our cohort; however, CMR altered it to MI in 21%, completely changing the management and medical therapy of the patients. Overall, CMR influenced patient management in 46% of the cases. In all newly diagnosed MI patients the medication was altered, furthermore the unexpected diagnosis Takotsubo and myocarditis led to lifestyle modifications and/or close monitoring and prolonged medical surveillance.

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Table 2: Baseline characteristics from Vago et al. (2). We compared continuous variables with normal distribution using one-way ANOVA and the Scheffe post hoc test and continuous variables with non-normal distribution by Kruskal-Wallis tests and and the Dunn post hoc test. Chi-square tests were used to compare the distributions of categorical data. Abbreviations: CA = coronary angiography; CMR = cardiac magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; i = indexed to body surface area; LV = left ventricular; M = mass; MDL = mechanical dispersion from longitudinal strain; MDC = mechanical dispersion from circumferential strain; SV = stroke volume

	Total (n=250)	**Acute myocardial infarction (n=55)**	**Acute myocarditis (n=136)**	**Takotsubo syndrome (n=26)**	**Normal CMR (n=33)**	**P value**
Patient characteristics and risk factors						
Age, years	42±16	48±15	34±10	67±10	49±14	<0.001
Female, n(%)	85 (34)	27 (49)	16 (12)	26 (100)	16 (49)	<0.001
Time between CA and CMR, days	2.7±1.9	2.9±1.9	2.4±1.9	3.4±2.1	2.8±2.0	NS
Normal CA, n(%) Signs of atherosclerosis, n(%)	178 (71) 72 (29)	34 (62) 21 (38)	112 (82) 24 (18)	14 (54) 12 (46)	19 (58) 14 (42)	<0.001
Body mass index (kg/m^2)	25 (5)	25 (6)	26 (5)	24 (4)	26 (7)	NS
High cholesterol, n(%)	55 (36)	20 (49)	14 (20)	9 (60)	12 (48)	0.001
Hypertension, n(%)	67 (31)	24 (47)	15 (13)	11 (48)	17 (57)	<0.001

Diabetes mellitus, n(%)	12 (6)	3 (6)	3 (3)	4 (17)	2 (7)	0.047
Current smoking, n(%)	47 (22)	15 (31)	24 (22)	3 (13)	5 (17)	NS
Infection, fever before chest pain n(%)	77 (37)	7 (15)	64 (56)	1 (5)	5 (20)	<0.001
ST-segment elevation, n(%)	145 (61)	28 (52)	90 (69)	13 (52)	14 (44)	0.016
Laboratory values						
Hs Troponin T (ng/l)	550 (905)	954 (1990)	689 (759)	373 (872)	93 (185)	<0.001
Creatinine–kinase MB (U/L)	39 (49)	46 (52)	46 (50)	34 (22)	21 (11)	0.005
C-reactive protein (mg/L)	16 (52)	5 (10)	31 (59)	4 (22)	9 (26)	<0.001
Creatinine (mmol/L)	71 (20)	68 (20)	73 (19)	69 (27)	67 (21)	NS
Glomerular filtration rate > 60 Glomerular filtration rate < 60	149 (95) 8 (5)	35 (95) 2 (5)	85 (99) 1 (1)	9 (64) 5 (36)	20 (0) 0 (0)	<0.001
CMR characteristics						
LVEF (%)	54±8	55±8	55±7	43±9	59±9	<0.001
LVEDVi (ml/m^2)	89±14	86±15	92±13	92±13	79±12	<0.001
LVESVi (ml/m^2)	41±11	40±14	42±9	52±13	33±6	<0.001
LVSVi (ml/m^2)	48±9	47±8	50±9	39±8	46±7	<0.001
LVMi (g/m^2)	60±12	56±12	63±12	57±12	56±10	<0.001
Oedema, n(%)	199 (80)	53 (96)	130 (96)	16 (64)	0 (0)	<0.001
Late gadolinium enhancement, n(%)	196 (78)	55 (100)	136 (100)	3 (12)	0 (0)	<0.001
Global longitudinal strain (%)	-19±5	-19±4	-20±3	-11±6	-21±4	<0.001

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Global circumferential strain (%)	-24±6	-23±6	-25±5	-17±5	-29±5	<0.001
Global radial strain (%)	47±14	48±12	48±11	26±13	58±12	<0.001
MDL (%)	13±6	15±5	12±4	16±6	14±5	<0.001
MDC (%)	8±5	11±5	6±3	16±4	7±4	<0.001

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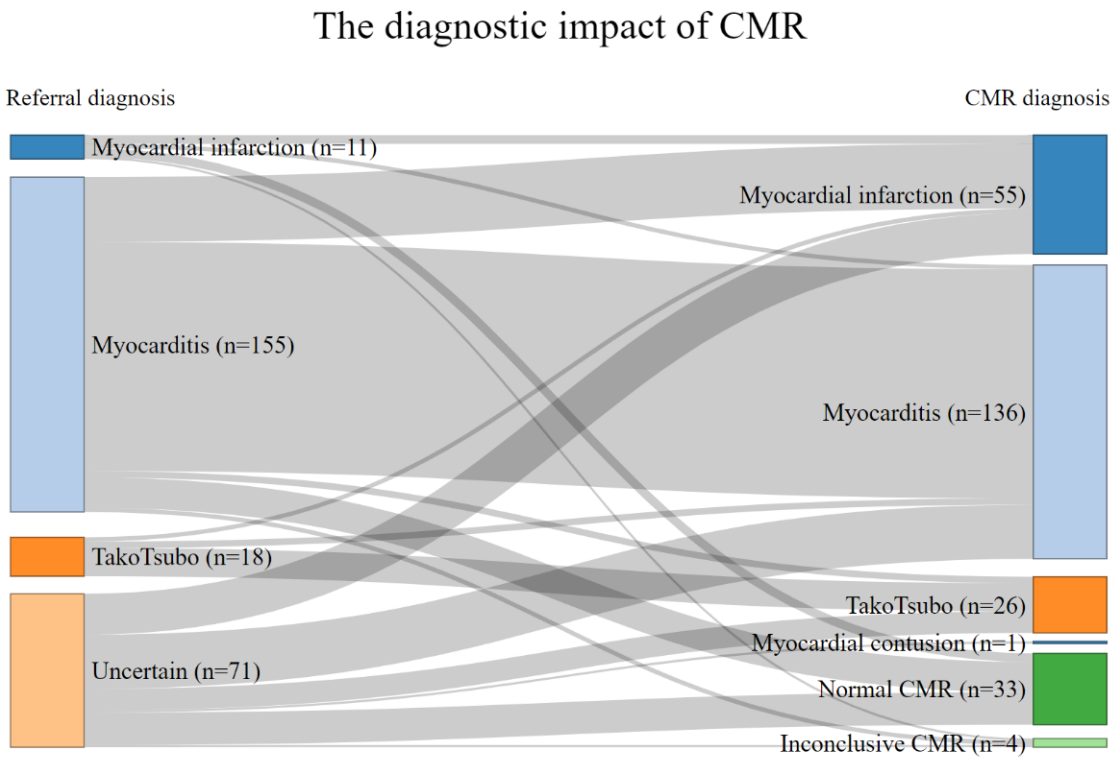

Figure 2: Sankey diagramm showing the diagnostic impact of early CMR in patients with the working diagnosis of MINOCA from Vago et al. (2). The column on the left shows the referral diagnosis and the column on the right the CMR diagnosis. In patients with troponin-positive acute chest pain and non-obstructed coronary arteries, an early CMR (≤7 days) provided a diagnosis in 86%. CMR confirmed the referral in 48% and overrode it in 16%, identified the aetiology in 22%, revealed a structurally normal heart in 13% and remained inconclusive in 1% of the patients. Abbreviations: CMR = cardiac magnetic resonance, MINOCA = myocardial infarction with non-obstructed coronary arteries.

6.1.2. Patient characteristics, laboratory values, CMR parameters, strain analysis

The comparison of baseline demographic data is shown in **Table 2**. We found low prevalence of traditional cardiovascular risk factors among myocarditis patients while MI, Takotsubo patients and those with normal CMR had higher burden of risk factors including hypertension and high cholesterol**.** LVEF was preserved for myocarditis and MI in contrast Takotsubo patients showed lower LVEF and higher LVESVi than any other group. Among strain parameters, the following differences were detected: Patients with Takotsubo syndrome showed significantly higher (thus poorer) GLS and GCS than were found in the other groups. We observed no difference in GLS and GCS values between MI and myocarditis patients; in contrast global dyssynchrony measures, specifically MDC, was significantly higher (signifying a worse contraction pattern) in the MI group. **Figure 3** illustrates the segmentation for strain analysis and the patterns of LGE in MI, myocarditis and Takotsubo patients.

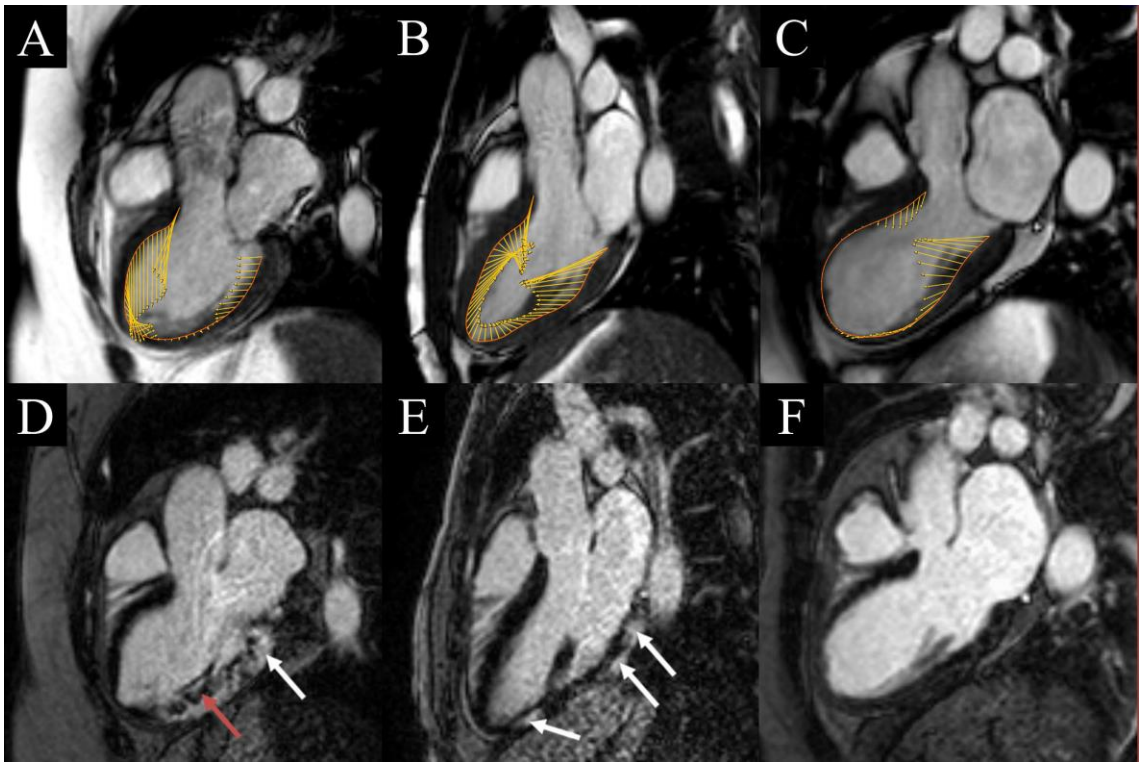

Figure 3: Cardiac magnetic resonance images of patients with myocardial infarction (A and D), myocarditis (B and E) and Takotsubo syndrome (C and F) from Vago et al. (2). Cine movie images depict endocardial segmentation and contraction pattern during strain analysis (A–C). Late gadolinium-enhanced images show transmural necrosis (white arrow) and microvascular obstruction (red arrow) in patients with acute infarction (D); patchy, midmyocardial necrosis in myocarditis (white arrows) (E); and the lack of LGE in Takotsubo syndrome (F). Abbrevations: LGE = late gadolinium enhancement.

6.1.3. Follow-up and mortality

The 30-day, one-year, and 4-year mortality rates were 0.4%, 1.8% and 5.9%, respectively (**Table 3**). The 4-year all-cause mortality rates by the diagnosis of MI, myocarditis, Takotsubo, or normal CMR in these patients were 10.2%, 1.6%, 27.3% and 0%, respectively. **Figure 4** illustrates a strong association between a CMR diagnosis and mortality (log-rank test: 24, $p<0.0001$). Finally, Takotsubo and MI as the diagnosis, older age, hypertension, diabetes, female sex, LVEF, LVSVi and strain parameters, including GLS, GCS and MDC were significant univariate predictors of mortality (**Table 4**).

Table 3: Follow-up and mortality (2) . Values are n(%) or mean values with ±SD. Abbrevations: CMR = cardiac magnetic resonance; MI = myocardial infarction

***Confidence interval for deaths per patient year**

MI: 0.008 to 0.05748

Myocarditis: 0.0004 to 0.0129

Takotsubo: 0.0234 to 0.1389

Normal CMR: 0 to 0.0373

****Pairwise comparison of death per patient-year**

MI vs Myocarditis, P=0.0073

MI vs Normal CMR, P=0.1184

MI vs Takotsubo, P=0.1025

Myocarditis vs Normal CMR, P=0.552

Myocarditis vs Takotsubo, P<0.0001

Takotsubo vs Normal CMR, P=0.0119

	Total (n=250)	**Acute MI (n=55)**	**Acute myocarditis (n=136)**	**Takotsubo syndrome (n=26)**	**Normal CMR (n=32)**	**P value**
Follow-up time (in days)	1394±985	1345±920	1503±1021	1314±1081	1090±807	NS
Early mortality (one-month)	1 (0.4)	0 (0)	0 (0)	1 (4)	0 (0)	0.0343

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One-year mortality n(%)	4 (1.8)	1 (2)	0 (0)	3 (13.6)	0 (0)	< 0.001
Four-year mortality n(%)	13 (5.9)	5 (10.2)	2 (1.6)	6 (27.3)	0 (0)	< 0.001
Deaths per patient-year (%)	1.4%	2.5%	0.4%	6.4%	0%	*, **

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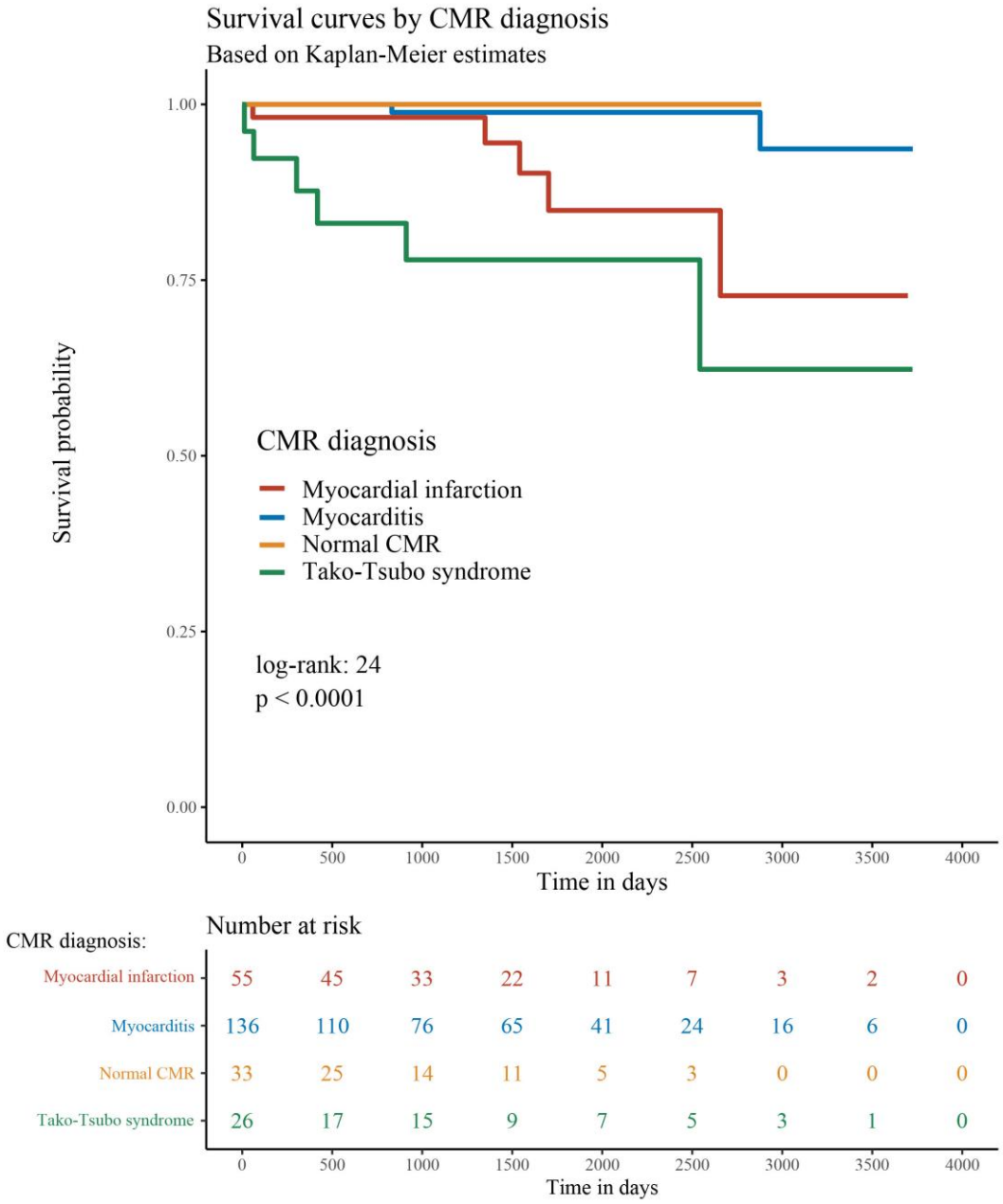

Figure 4: Kaplan-Meier survival curves showing the risk of mortality by CMR diagnosis (2). Abbreviations: CMR = cardiac magnetic resonance.

Table 4: Predictors of mortality all-cause mortality adapted from Vago et al (2). Univariate and multivariate associations of risk factors and covariates with mortality were assessed using Cox proportional hazard regression analyses. Variables with values of $p<0.05$ in univariate analyses were candidates for multivariate analysis**.** Significant values are shown in bold. Abbreviations: BMI = body mass index; CI = confidence interval CK = creatinine kinase; CMR = cardiac magnetic resonance; CRP = C reactive protein; GCS = global circumferential strain; GLS = global longitudinal strain; i = indexed to body surface area; LGE = late gadolinium enhancement; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = felt ventricular end systolic volume; LVSV = left ventricular stroke volume; MDC = mechanical dispersion from circumferential strain; MDL = mechanical dispersion from longitudinal strain; MI = myocardial infarction.

	Univariable Analysis				**Multivariable Analysis**			
			95% CI				**95% CI**	
	P	**HR**	**Lower**	**Upper**	**P**	**HR**	**Lower**	**Upper**
MI as diagnosis	**0.0190**	7.1417	1.381	36.930	0.8626	1.2445	0.104	14.830
Takotsubo as diagnosis	**0.0005**	17.5201	3.531	86.938	0.4053	5.9911	0.088	406.122
Age	**<0.0001**	1.0880	1.047	1.131	0.7570	1.0117	0.940	1.089
Sex	**0.0256**	3.6022	1.169	11.103	0.3932	0.2884	0.016	5.007
Diabetes mellitus	**0.0157**	5.0467	1.357	18.765	0.3700	2.4772	0.341	18.000
Hypertension	**0.0004**	15.630	3.451	70.792	**0.0061**	26.7828	2.552	281.058
BMI	0.2513	0.9265	0.813	1.056				

No ST-segment elevation present at admission	0.2269	1.9693	0.656	5.912				
TroponinT value	0.6159	0.9999	0.999	1.000				
CKMB value	0.8153	0.9982	0.984	1.013				
CRP value	0.4718	1.0028	0.995	1.011				
LVEF	**0.0057**	0.9332	0.898	0.982	0.5634	1.0789	0.834	1.396
LVEDVi	0.5777	0.9881	0.947	1.031				
LVESVi	0.0935	1.0350	0.994	1.076				
LVSVi	**0.0065**	0.9336	0.889	0.981	0.5258	0.9481	0.804	1.118
Oedema present on CMR	0.5548	0.6749	0.183	2.488				
LGE present on CMR	0.0964	0.3867	0.126	1.185				
GLS	**0.0020**	1.1266	1.045	1.215	0.5861	1.1257	0.735	1.724
GCS	**0.0018**	1.1356	1.048	1.230	0.2594	1.2177	0.8651	1.715
MDC	**<0.0001**	1.2141	1.109	1.329	**0.0351**	1.2542	1.0160	1.548
MDL	0.2011	1.0803	0.963	1.212				

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6.2. The cardiac involvement after SARS-CoV-2 infections in young competitive athletes

6.2.1. Baseline characteristics

We included 147 (94 male, median[IQR] 23[20-28] years) athletes with prior SARS-CoV-2 infection in this observational study. During the course of SARS-CoV-2 infection 19 athletes were asymptomatic, 80 experienced mild, 43 moderate and 5 long COVID symptoms. None of the study participants were hospitalized. CMR examination was conducted median 32 days after a positive PCR test. Overall, 4.7% (n=7) of patients showed definite or possible alterations on their CMR scans, and none of these athletes were asymptomatic during the infection (**Figure 5**).

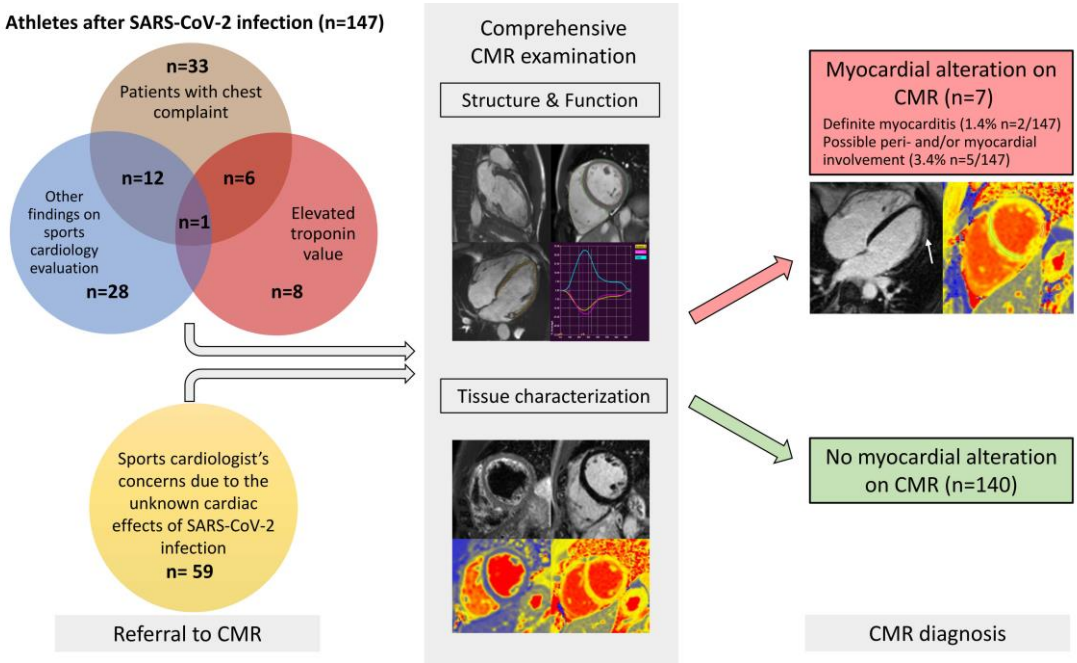

Figure 5: Summary of results as shown by Szabo et al. (1). Athletes were referred for cardiac magnetic resonance (CMR) by their cardiologists to evaluate the possible structural alterations caused by SARS-CoV-2 infection. Referrals are given on the left side of the figure. First, patients with chest complaints (brown bubble), including chest pain, dyspnoea, and palpitation. Second, patients who had to CMR due to elevated troponin levels (red bubble) with or without accompanying symptoms. Third, other findings on sports cardiology assessment (blue bubble) such as echocardiography and/or 12-lead-ECG examination. Four, athletes referred to CMR due to unknown cardiac

effects of SARS-CoV-2 (yellow bubble) despite having negative results on cardiology examination. We performed CMR examination that contained sequences to assess structure, function (long- and short-axis cine images), and tissue-specific data (T2 weight images, late gadolinium enhancement, native T2 and T1 mapping). The right column shows that definite or possible cardiac involvement was present in seven patients. We observed definite signs of myocarditis in two athletes (red box, underneath white arrow showing subepicardial enhancement). The majority of athletes had no alterations on their CMR (green box). Abbreviations: CMR = cardiac magnetic resonance; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2 .

Table 5: Clinical findings and short-term clinical outcome among athletes with CMR alterations adapted from Szabo et al. (1).
Abbreviations: CMR = cardiac magnetic resonance, ECG = electrocardiogram; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; NA = not applicable; RBBB = right bundle branch block

Athlete No.	**Sex**	**Symptoms**	**Findings on other exams**	**Summary of CMR findings**	**Certainty of cardiac involvement, clinical outcome (6 months)**
1.	Male	Moderate • chest pain • fever • headache • joint pain • diarrhoea • smell and taste disturbance	Troponin: elevated (hs Troponin T: 18 ng/L, normal: <14 ng/L) 12-lead ECG: minor repol. alteration Holter ECG: Sinus tachycardia (1 hour) Echocardiography: slightly dilated right ventricle	LVEF: 52 % GLS: -18 % Septal native T1 and T2: normal Pathological LGE / pattern: Yes - Lateral subepicardial T1 and T2 mapping value in the area corresponding with the LGE: 1016 ms and 50 ms– mildly elevated	Definitive Returned to sport, no persistent cardiac complaints at follow-up

2.	Male	Moderate • chest pain • dyspnea • fever • cough	Troponin: elevated (hs Troponin I: 198 ng/L, normal: <45 ng/L) 12-lead ECG: minor repol. alteration Holter ECG: normal Echocardiography: normal Exercise test (3 months after COVID infection): normal	LVEF: 58 % GLS: -18 % Septal native T1: elevated Septal native T2: normal Pathological LGE / pattern: Yes - Lateral subepicardial T1 and T2 mapping value in the area corresponding with the LGE: 1065 ms and 53 ms– elevated	Definitive Returned to sport, no persistent cardiac complaints at follow-up
3.	Male	Moderate • chest pain • dyspnea • fatigue • cough	Troponin: normal 12-lead ECG: RBBB (previously reported) Echocardiography: normal	LVEF: 61 % GLS: -22 % Septal native T1 and T2: normal Pathological LGE / pattern: Yes – non-specific inferior and hinge point LGE T1 and T2 mapping value in the area corresponding with the LGE: 984 ms and 41 ms– normal	Possible Returned to sport, no persistent cardiac complaints at follow-up
4.	Female	Long- COVID	Troponin: normal 12-lead ECG: normal	LVEF: 67 % GLS: - 27 %	Possible

		• palpitationlong-lastingg fatigue	Holter ECG: normal Echocardiography: normal	Septal native T1: gray zone normal/elevated Septal native T2: mildly elevated Pathological LGE / pattern: No	Returned to sport, no persistent cardiac complaints at follow-up
5.	Female	Moderate • chest pain • back pain • smell and taste disturbance	Troponin: normal 12-lead ECG: PVC Holter ECG: trigeminy PVC on exertion Echocardiography: normal	LVEF: 60 % GLS: -22 % Septal native T1 and T2 : mildly elevated Pathological LGE / pattern: No	Possible Returned to sport, no persistent cardiac complaints at follow-up
6.	Female	Mild • fever • fatigue • palpitation • smell and taste disturbance	Troponin: elevated (hs Troponin I: 28 ng/L – normal:<1,9 ng/L) 12-lead normal Echocardiography: normal	LVEF: 55 % GLS: -18 % Septal native T1: mildly elevated Septal native T2: normal Pathological LGE / pattern: No	Possible Returned to sport, no persistent cardiac complaints at follow-up
7.	Male	Moderate • chest pain • long-lasting fatigue	Troponin: elevated (hs Troponin I: 225 ng/L – normal: <45 ng/L)	LVEF: 61 % GLS: -20 % Septal native T1 and T2: normal	Possible Returned to sport, no persistent

			12-lead ECG: descending PQ depression Echocardiography: decreased longitudinal strain, mild anterior and anteroseptal wall motion abnormality	Pathological LGE / pattern: Yes – Pericardial involvement	cardiac complaints at follow-up

6.2.2. Myocardial alterations on CMR

We observed the following CMR alterations: 1) LGE showing a nonischaemic pattern and elevated native T1 mapping consistent with acute myocarditis as per the LLC (n=1); 2) LGE showing a nonischaemic pattern consistent with a prior myocarditis with mildly increased T2 (n=1); 3) nonspecific nonischaemic LGE (n=1); 4) mildly elevated T1 and T2 values with no pathological LGE (n=2); 5) isolated, slightly elevated T1 (n=1); and 4) pericardial involvement (n=1). **Table 5** describes the clinical and CMR characteristics of athletes with definite (n=2) or possible (n=5) myocardial or pericardial alterations.

HsTnT recorded at Semmelweis University Heart and Vascular Centre was elevated in 4.5% of the athletes (n=6/133); among these, only one has shown myocardial involvment on CMR. Hinge point fibrosis was observed in 32% (n=44) of the athletes after SARS-CoV-2 infection, which we reported as nonpathological. Notably, the proportion of hinge point fibrosis was similar in athletes after SARS-CoV-2 infection (44/139, 32%) and healthy control athletes (6/15, 40%; p=0.513), however only 15 healthy control athletes were administed contrast agent during their scan.

6.2.3. Comparison with matched control groups

The comparison between demographic parameters and CMR features of highly trained athletes with prior SARS-CoV-2 infection, healthy athletic controls, and healthy less active controls is depicted in **Table 6**. We observed increased cardiac volumes and myocardial mass in athletes relative to less active healthy volunteers, signifying normal sports adaptation. LV analysis showed subtle functional alterations between athletes and controls, with the former showing slightly lower strain values. Native T1 values were slightly decreased in the athletes after SARS-CoV-2 infection compared to less active volunteers. The T2 values were not different among the three groups. Age-, sex- and training load matched athletic groups showed no difference regarding any features of the cardiac phenotype considered in our study: LV and RV function, volumes, strain, native T1 or T2.

Table 6: Baseline characteristics from Szabo et al. (1). Abbreviations: CMR = cardiac magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; ESV, end-systolic volume; GLS = global longitudinal strain; GCS = global circumferential strain; i = indexed to body surface area; LV = left ventricular; M = mass; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SV = stroke volume.

	Athletes after SARS-CoV-2 infection (n=147)	**Healthy athletic controls (n=59)**	**Healthy less active controls (n=56)**	**Athletes after SARS-CoV-2 infection vs Healthy athletic controls P values**	**Athletes after SARS-CoV-2 infection vs Healthy less active controls P values**
Group characteristics					
Age, median [IQR], years	23[20, 28]	25[21, 29]	24[23, 28]	0.146	0.062
Female, n(%)	53(36)	20(34)	20(36)	0.771	0.864
Body surface area, mean±SD, m^2	2 ±0.2	2 ±0.3	1.9 ±0.2	0.413	0.003
Heart rate, median (IQR), bpm	60[53, 69]	62[56, 72]	71[63, 84]	0.067	<0.001
Degree of training, median [IQRS], hours/week	15[12, 22]	19[15, 22]		0.024	
Sports discipline, n(%)					
- Skill	2(1)	0(0)			
- Power	9(6)	9(15)		0.077	

- Mixed	108(74)	35(60)			
- Endurance	28(19)	15(25)			
Member of a national team n(%)	87(60)	52(91)		<0.001	
Olympic team member, n(%)	17(12)	15(26)		0.014	
CMR parameters					
LVEF, median [IQR], %	57[54, 60]	56[53, 60]	59[57, 62]	0.473	<0.001
LVEDVi, median [IQR], ml/m^2	111[100, 123]	111[102, 122]	91[83, 100]	0.523	<0.001
LVESVi, median [IQR], ml/m^2	48[40, 55]	47[43, 53]	38 [34, 42]	0.52	<0.001
LVSVi, median [IQR], ml/m^2	63[58, 69]	64[58, 68]	54[50, 59]	0.685	<0.001
LVMi, median [IQR], g/m^2	58[49, 65]	59[50, 73]	47[39, 51]	0.199	<0.001
RVEF, median [IQR], %	56[53, 59]	55[52, 58]	57[54, 61]	0.14	0.014
RVEDVi, median [IQR], ml/m^2	110[99, 121]	113[103, 127]	90[79, 103]	0.119	<0.001
RVESVi, median [IQR], ml/m^2	48[41, 55]	50[44, 59]	38[33, 47]	0.055	<0.001
RVSVi, median [IQR], ml/m^2	61[56, 67]	63[57, 68]	53[47, 58]	0.229	<0.001
LV-GLS median [IQR], %	-21[-23, -19]	-20[-23, -19]	-22[-24, -20]	0.942	<0.001
LV-GCS, mean±SD, %	-28±4	-28±4	-31±3	0.426	<0.001
RV GLS, mean±SD, %	-24±4	-24±3	-25±4	0.691	0.21
T1 mapping, median [IQR], ms	958[939, 970]	955[934, 973]	972[960, 987]	0.564	<0.001
T2 mapping, median [IQR], ms	45 [43, 46]	44[43, 46]	44[43, 45]	0.196	0.215

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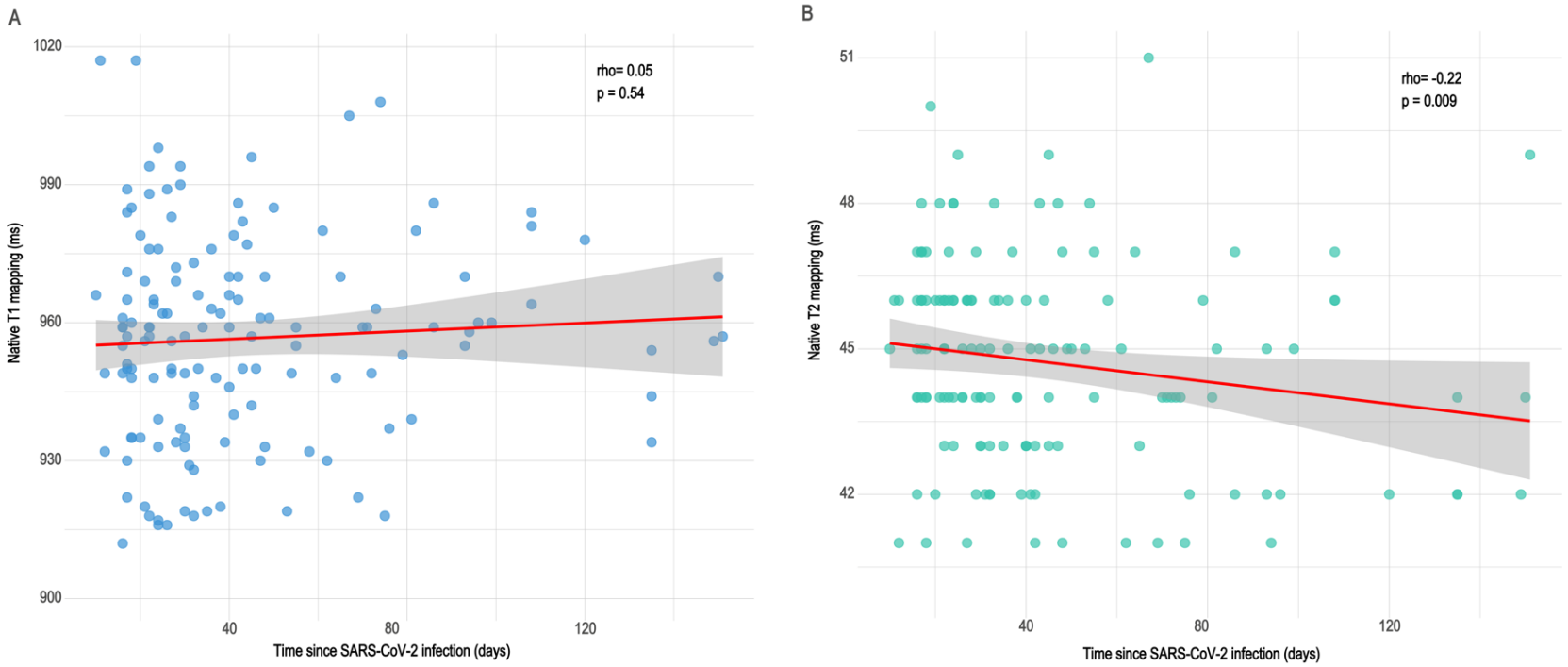

Figure 6:Associations of native T1 and T2 mapping values and the time since confirming SARS-CoV-2 infection (1). Correlations were derived using Spearman's rank correlation analyses. Abbreviations: CMR = cardiac magnetic resonance; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2

We explored the associations of native T1 and T2 mapping values with the time since confirmation of SARS-CoV-2 infection (**Figure 6**). We did not observe a correlation between native T1 and time elapsed since SARS-CoV-2 infection, whilst T2 values showed a weak negative correlation (Rho: -0.22, p=0.009) with this parameter.

T1 values were significantly lower among male participants compared to females (median[IQR]: 953[934 – 965] vs 977[959 – 987] ms, p <0.0001) in all groups (**Figure 7**).

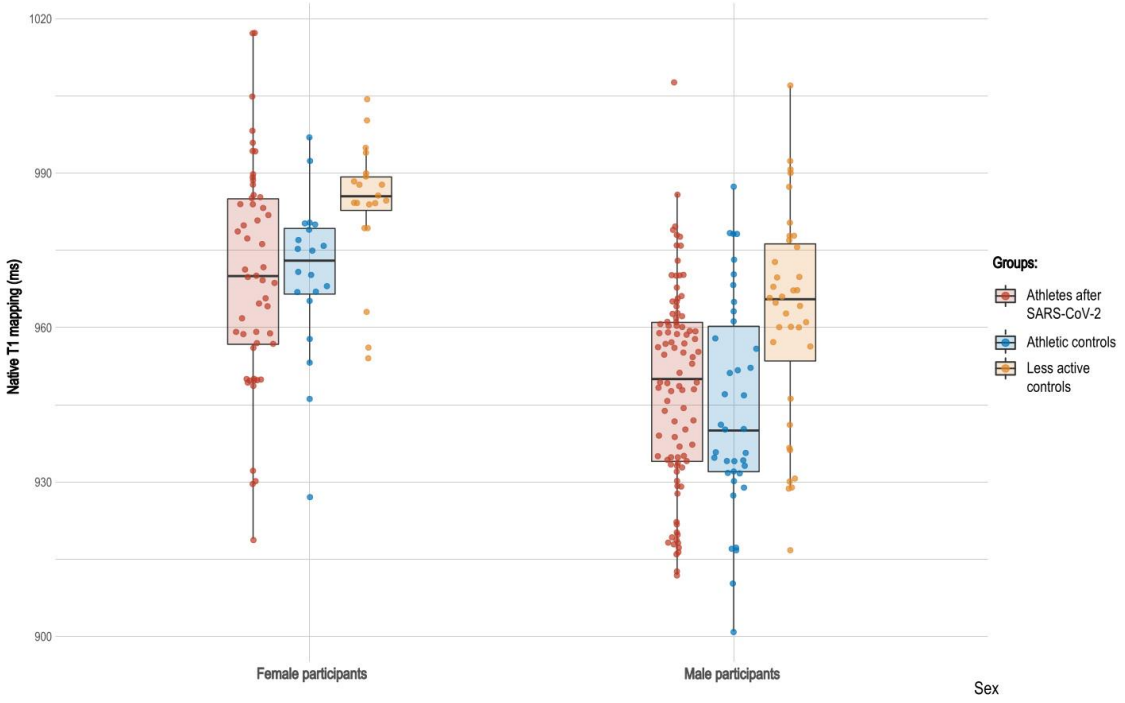

Figure 7: Comparison of native T1 values between sexes (1). Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2

Fourteen elite athletes had CMR scan in our institute prior to obtaining positive SARS-CoV-2 PCR results. The two CMR scans were performed an average of 384 days apart. We found no difference in any CMR measures before and after the infection, as shown in **Table 7**.

Table 7: Comparison between CMR examinations before and after SARS-CoV-2 infection as per Szabo et al. (1) . Abbreviations: CMR = cardiac magnetic resonance; EDV = end-diastolic volume index; EF = ejection fraction; ESV = end-systolic volume; GLS = global longitudinal strain; GCS = global circumferential strain; i = indexed to body surface area; LV = left ventricular; M = mass index; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SV = stroke volume, RV = right ventricular

	CMR scan before SARS-CoV-2 infection (n=14)	**CMR scan after SARS-CoV-2 infection (n=14)**	**P values**
LVEF, median [IQR], %	55 [53 – 58]	57 [53 – 61]	0.091
LVEDVi, median [IQR], ml/m^2	111 [103 – 120]	117 [104 – 125]	0.305
LVESVi, median [IQR], ml/m^2	47 [46 – 59]	51 [42 – 55]	0.216
LVSVi, median [IQR], ml/m^2	65 [57 – 67]	65 [60 – 75]	0.135
LVMi, median [IQR], g/m^2	63 [59 – 77]	70 [62 – 82]	0.502
RVEF, median [IQR], %	54 [52 – 56]	57 [53 - 60]	0.091
RVEDVi, median [IQR], ml/m^2	113 [107 – 120]	116 [100 – 122]	0.946
RVESVi, median [IQR], ml/m^2	53 [44 -60]	49 [45 – 57]	0.094
RVSVi, median [IQR], ml/m^2	62 [57- 69]	64 [59 – 73]	0.38
LV-GLS median [IQR], %	-20 [-22 – -19]	-20 [-21 – -18]	0.241
LV-GCS, average ±SD, %	-27 ± 3	-28 ± 5	0.883
RV GLS, average ±SD, %	-24 ± 3	-23 ± 3	0.29
T1 mapping, median [IQR], ms	947 [932 – 961]	937 [933 – 966]	0.791

We compared athletes after SARS-CoV-2 infection based on their symptoms category (**Figure 8**), which showed that athletes with moderate symptoms, had slightly elevated native T1 values relative to their asymptomatic and mildly symptomatic counterparts ($p < 0.05$). Of note, the T1 value remained below the cut-off point (male: T1: 986 ms; female: T1: 1001 ms) for the majority of study participants. Furthermore, there was no difference in the LVEF or GLS values of these groups.

6.2.4. Follow-up and clinical outcome

We conducted the follow-up visits for 122 (83%) athletes after SARS-CoV-2 infection at a median of 232 days from the infection. All but two athletes could return to sports activity. One of them did not return to sports due to the progression of his depression, and he currently receives medication. The other athlete suffered from long-COVID syndrome, including light-headedness and a long-term rapid increase in his heartbeat. At the time of the follow-up, the latter athlete had a negative exercise test and was encouraged to slowly restart sports activity. The midterm outcomes of the seven athletes showing definite or possible myocardial involvement on CMR is shown in **Table 5**, all of them could return to competitive sports activity safely and had nmo persisting cardiovascular symptoms.

Figure 9 shows the acute and follow-up CMR scans in those patients with myocardial involvement (n=4) who returned for a follow-up scan. In one athlete with LGE showing a nonischaemic pattern consistent with previous myocarditis, the follow-up CMR showed shrinkage of the LGE. Among the three patients presenting with mild, isolated mapping elevation the follow-up scan revealed that the elevated T1 and or T2 values had subsided for two patients and remained slightly elevated for the last. Three athletes asked to postpone their follow-up scans due to their lack of symptoms and their ongoing sports season.

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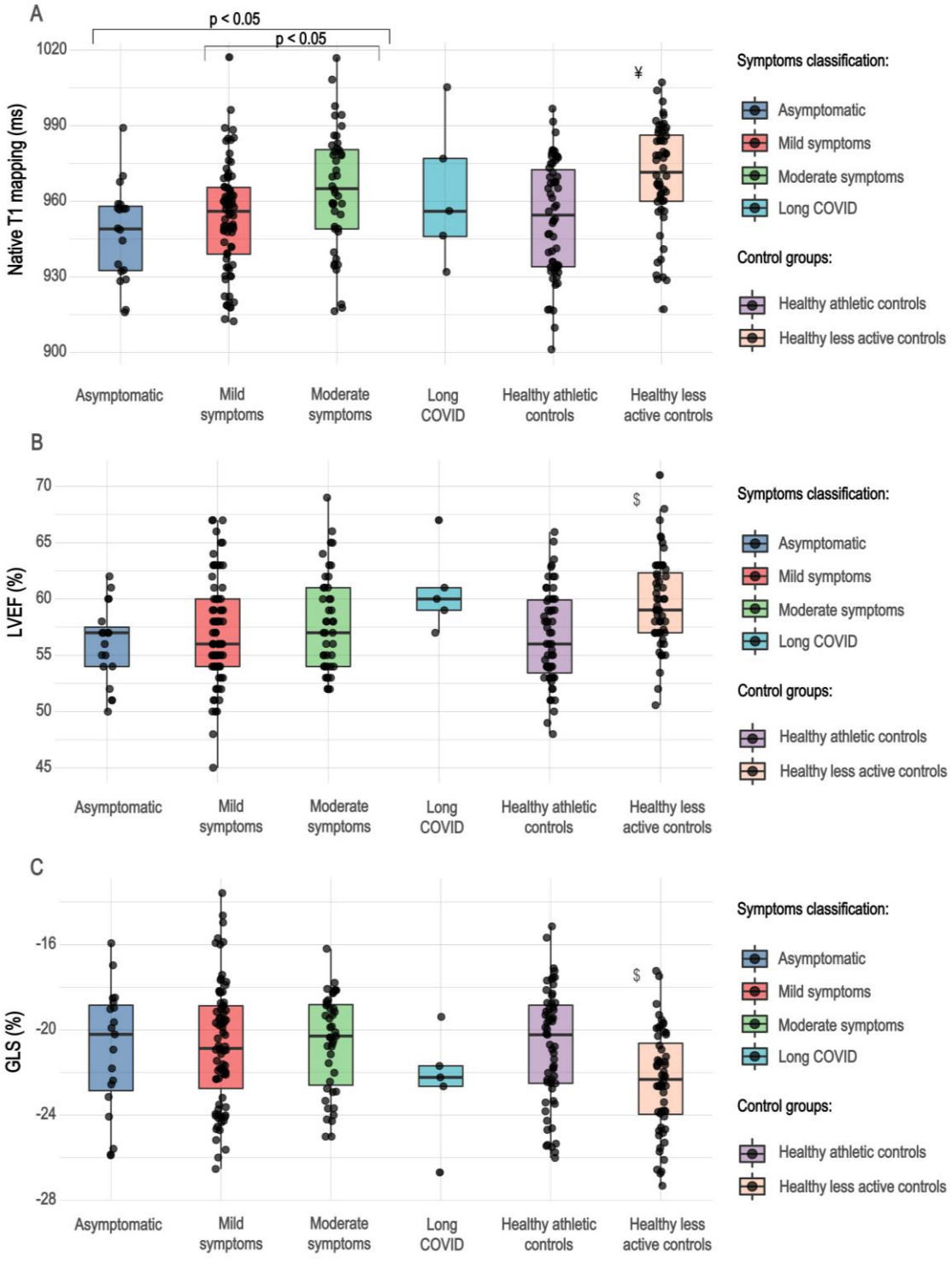

Figure 8: Boxplots of native T1, LVEF, and GLS statified by symptom groups from Szabo et al. (1). Moderately symptomatic post-COVID-19 athletes had elevated native T1 compared to asymptomatic and mildly symptomatic participants ($p < 0.05$). However, the T1 value remained below the normal cut-off point for the majority. There was no

difference in the LVEF or GLS values among these groups. The distributions of non-normal continuous variables were compared by Kruskal-Wallis tests and the Dunn test for post hoc pairwise comparisons. Abbreviations: CMR = cardiac magnetic resonance; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2

¥: Kruskal-Wallis test showing a significant difference between healthy less active controls and asymptomatic and mildly symptomatic athletes after SARS-CoV-2 infection and healthy athletic controls.

$: Kruskal-Wallis test showing a significant difference between healthy less active controls and asymptomatic, mildly and moderately symptomatic athletes after SARS-CoV-2 infection, and healthy athletic controls.

Overall, ten athletes reported a subjectively long recovery from SARS-CoV-2 infection. Furthermore three athletes disclosed that, they returned to sports activity but did not reach their peak potential at the time of their follow-up. It was due to anxiety in one case and two athletes experienced mild, long-term sinus tachycardia with no apparent structural alteration. None of the national team members (n= 71) reported significant setbacks in their performance. In all patients who reported reinfection confirmed by PCR (n=4), we performed follow-up CMR, which showed no myocardial involvement.

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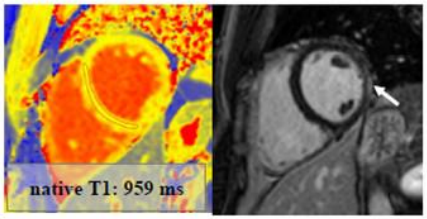
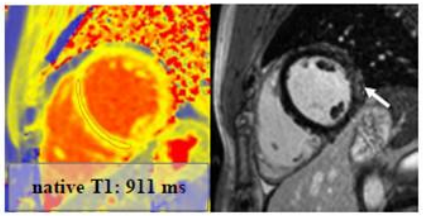
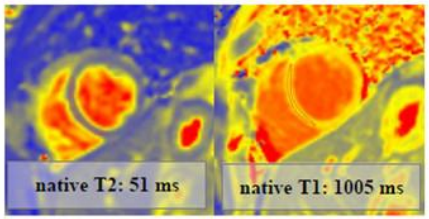
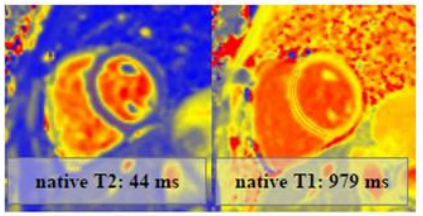
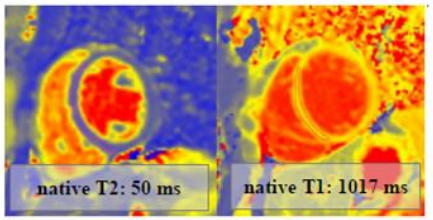
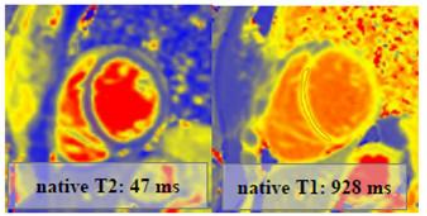
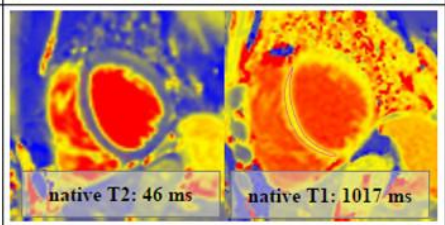
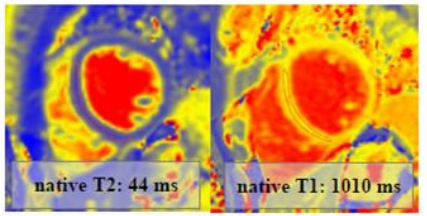
Athlete No.	Sex	*Symptoms*	CMR findings	CMR images	Time to follow-up CMR from COVID-19 (days)	Follow-up CMR findings	Follow-up CMR images
1.	Male	Moderate • headache • fever • chest pain • joint pain • diarrhea • smell and taste disturbance	LVEF: 52 % GLS: -18 % Septal native T1: normal Septal native T2: normal Pathological LGE / pattern: Yes - Lateral subepicardial LGE (5SD method): 9.3%		299	LVEF: 58 % GLS: -20 % Septal native T1: normal Septal native T2: normal Pathological LGE / pattern: Yes - Lateral subepicardial LGE (5SD method): 5.4%	
4.	Female	Long- COVID • palpitation • long lasting fatigue	LVEF: 67 % GLS: - 27 % Septal native T1: gray zone normal/elevated Septal native T2: elevated Pathological LGE / pattern: No		129	LVEF: 62 % GLS: - 27 % Septal native T1: normal Septal native T2: normal Pathological LGE / pattern: No	
5.	Female	Moderate • chest pain • back pain • smell and taste disturbance	LVEF: 60 % GLS: -22 % Septal native T1: elevated Septal native T2: elevated Pathological LGE / pattern: No		105	LVEF: 62 % GLS: -25 % Septal native T1: normal Septal native T2: normal Pathological LGE / pattern: No	
6.	Female	Mild • fever • fatigue • palpitation • smell and taste disturbance	LVEF: 55 % GLS: -18 % Septal native T1: elevated Septal native T2: normal Pathological LGE / pattern: No		81	LVEF: 57 % GLS: -21 % Septal native T1: gray zone normal/elevated Septal native T2: normal	

Figure 9: Acute and follow-up CMR scans in patients with myocardial alterations who returned to their follow-up scan (1).

Abbreviations: CMR = cardiac magnetic resonance; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction.

6.3. Myocarditis after SARS-CoV-2 vaccination

6.3.1. Clinical characteristics

A total of four centres reported 16 CMR-confirmed myocarditis cases following anti-SARS-CoV-2 vaccination, with chest pain presenting 4±2 days after vaccination. **Table 8** summarize the baseline characteristics of the sample. All myocarditis patients were young (mean age 22±7 years, between 13 and 36 years), male, and generally presented after their second dose of anti-COVID-19 immunization (13, 81%). The majority received mRNA vaccines (75%), while 25% developed myocarditis after vector vaccine administration. Prior SARS-CoV-2 infection was reported by three patients and among them one presented with acute myocarditis after the first dose of vaccine. Previous CMR confirmed myocarditis was reported by two participants, they occurred two and four years before anti-SARS-CoV-2 vaccination (**Figure 10**). The medical history of four patients revealed immune-mediated diseases, including Crohn's disease, psoriasis, asthma and allergies, but none of them was on systemic corticosteroid therapy. Overall, four participants reported intensive physical activity directly after vaccination (intensive sport activity, heavy physical labour), and one individual noted heavy alcohol consumption following immunization. Generally, fever and shivering started within two days, and chest pain developed within four days after vaccination. ECG alterations were observed in seven patients (ST elevation in 6, negative T wave in 1). The initial troponin level was elevated in all (**Table 9**), and we frequently documented increased CKMB, CRP and proBNP levels too. There were no reported new onset heart failure symptoms, syncope, or sustained brady- or tachyarrhythmias during the acute phase.

Table 8: Description of the sample from Szabo et al. (1). Abbreviations: CRP = c-reactive protein; BMI = body mass index, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2

Baseline characteristics	**Values are given in mean±SD OR median[IQR] OR n(%) as appropriate for the data**
Age, years	22 ± 7
Sex, male %	16 (100)
BMI	26 ± 4
SARS-CoV-2 vaccine type n, (%)	

mRNA - Pfizer (BNT162b2 mRNA-Pfizer-BioNTech) - Moderna (mRNA-1273-Moderna) Vector vaccine - Sputnik V (Gam-COVID-Vac)	 10 (62.5) 2 (12.5) 4 (25)
SARS-CoV-2 vaccine dose n, (%) - First dose - Second dose - Third dose	 2 (12.5) 13 (81.2) 1 (6.2)
First complaint after vaccination, days	1.8 ± 1.6
Chest pain after vaccination, days	3.8 ± 1.9
Previous SARS-CoV-2 infection yes, n %	2 (12.5)
Previous myocarditis yes, n %	2 (12.5)
Positive immunological history - Crohn's disease, n % - Asthma, n % - Psoriasis, n % - Allergy, n %	4 (25) 1 (6.2) 1 (6.2) 1 (6.2) 1 (6.2)
Cardiovascular risk factors - Hypertension, n % - Diabetes, n % - Smoking, n % - Obesity, n %	 2(12.5) 0 (0) 4 (25) 3 (18.8)
Intense physical activity after vaccination - Sport activity - Physically demanding job	4 (25) 3 (18.8) 1 (6.2)
Elevated troponin level n, %	16 (100)
Creatinine–kinase MB (U/L) Cut-off: ≥ 25 U/L	31 [26, 62]
C-reactive protein (mg/L) Cut-off: ≥ 5 mg/L	23 [13,43]
NTproBNP (pg/ml) Cut-off: ≥ 125pg/ml	351 [223, 677]
Thrombocyte count (Giga/L) Normal range: 150-400 Giga/L	214 [199, 229]
White blood cell count (Giga/L) Normal range: (4.0-10.0 Giga/L)	7.9 [5.7,9.5]
Eosinophil count (Giga/L) Cut-off: >0.5 Giga/L	0.10 [0.07, 0.17]

6.3.2. CMR features of acute myocarditis after SARS-CoV-2 vaccination

CMR examination was carried out mean 4±2 days (between 1 and 8 days) after the onset of acute chest pain showing acute myocarditis as per the LLC. Myocardial involvement has shown a focal or localised pattern in the majority of the cases (n=15), primarily affecting the lateral wall of the LV with signs of subepi-midmyocardial oedema and necrosis (**Figure 10**). Diffuse myocarditis with elevated global mapping values (T2, T1 and ECV) was documented in one patient (**Figure 11**) after mRNA vaccine. LVEF was preserved for most, except for two patients whose LVEF were mildly decreased (46% and 47%). We did not find definitive pericardial involvement in any study participants.

Table 9: Peak troponin value for myocarditis patients after COVID-19 vaccination (82). Maximal troponin values for each participants is reported according to the local laboratory. Abbreviations: hs = high-sensitive

Case No	Cardiac troponin type	Local Cut-off	Peak value
1	hs troponin T (ng/L)	>14 ng/L	1159
2	hs troponin T (ng/L)	>14 ng/L	1007
3	hs troponin T (ng/L)	>14 ng/L	376
4	hs troponin T (ng/L)	>14 ng/L	1366
5	hs troponin T (ng/L)	>14 ng/L	3018
6	hs troponin T (ng/L)	>14 ng/L	144
7	hs troponin I (pg/ml)	>19 gp/ml	11907
8	hs troponin I (µg/L)	>0.0198 µg/L	4.067
9	hs troponin T (ng/L)	>14 ng/L	2136
10	hs troponin T (ng/L)	>14 ng/L	212
11	hs Troponin I (pg/ml)	>34.2 pg/ml	7665
12	hs troponin T (ng/L)	>14 ng/L	220
13	hs troponin T (ng/L)	>14 ng/L	2431
14	Troponin I (ng/L)	>19 ng/L	4047
15	hs troponin I (pg/L)	>30 gp/ml	3976
16	hs troponin T (ng/L)	>14 ng/L	228

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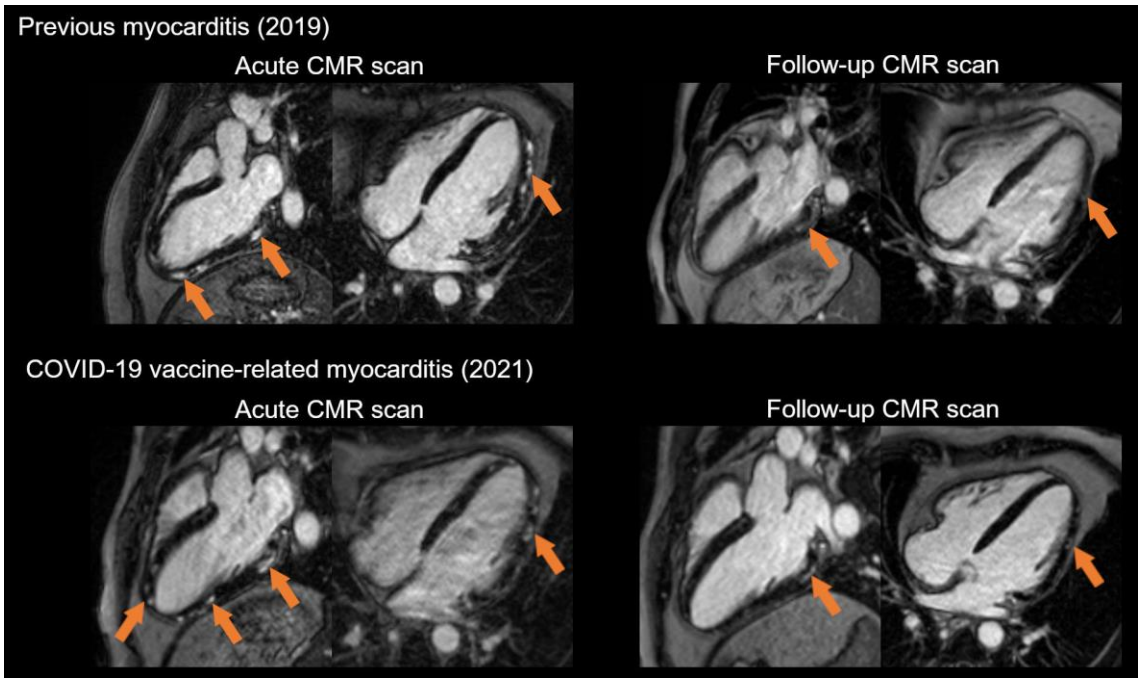

Figure 10: Recurrent myocarditis in a young male patient after the second dose of anti-SARS-CoV-2 vector vaccine, from Vago et al. (82). The patient had a previous myocarditis in 2019 (upper row). At the time, he presented with chest pain preceded by gastrointestinal infection and fever. His cardiology examination revealed elevated troponin levels, and the CT coronary angiogram was normal. The acute CMR showed patchy subepicardial oedema and late gadolinium enhancement (LGE) (orange arrows). Three months later, on his follow-up CMR scan, oedema had disappeared, and the LGE had shrunk. In 2021, the patient developed fever and recurrent chest pain two days after the second dose of his anti-SARS-CoV-2 vector vaccine (bottom row). Urgent CMR showed focal LGE in a similar pattern as the first myocarditis. On the three months follow-up the myocardial injury resolved. Abbreviations: CMR = cardiac magnetic resonance.

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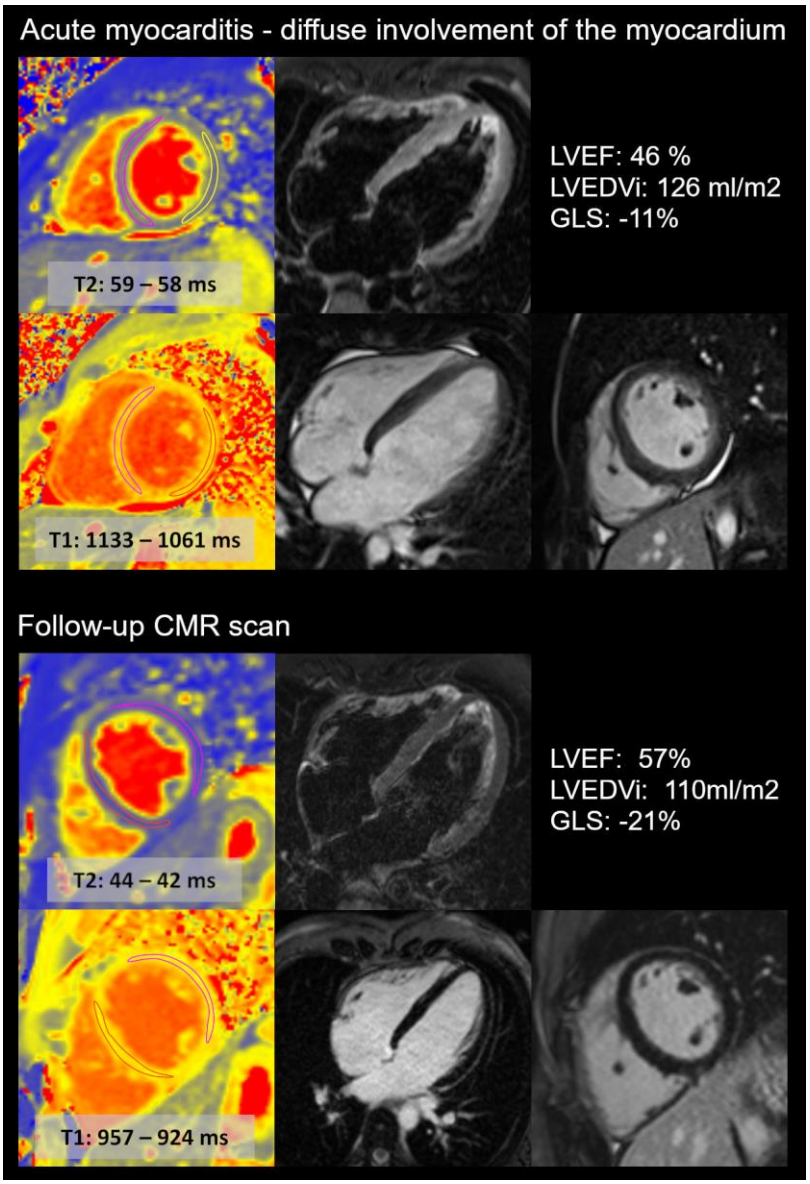

Figure 11: Diffuse acute myocarditis after the second dose of anti-COVID-19 mRNA vaccine in a young athlete (82). We present the acute (upper images) and follow-up (lower images) CMR scan of a young male athlete (national team member). The first CMR proved acute myocarditis with diffuse myocardial involvement, with elevated T2 and T1 values and diffuse myocardial oedema. Left ventricular ejection fraction and global longitudinal was mildly decreased, ventricular end-diastolic volume (LVEDVi) was within the age specific athletic normal range. The follow-up scan showed normalization of T2 and T1 and the left ventricular systolic function. The LVEDVi decreased, which is corresponding with the normal reverse remodelling expected from a highly trained athlete after the first three months of mandatory prohibition from high intesity sports activity. After the follow-up he gradually returned to the training.

Currently, the athlete performs highly level of sports activity and does not report recurrent or persisting symptoms. Abbreviations: CMR = cardiac magnetic resonance imaging; GLS = global longitudinal strain; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction

6.3.3. Clinical status and CMR changes during follow-up

One patient reported a recurrent episode of myocarditis (three months after the vaccine), preceded by gastrointestinal infection during follow-up. Other study participants did not disclose symptom recurrence. Laboratory values returned to the normal range including hs troponin T (6[4,7] ng/L) and CKMB (2[2,11] U/L). Follow-up CMR examination was performed mean 112±27 days after the baseline scan (n=14). LVEF marginally increased upon follow-up, and LVEDVi slightly decreased, remaining or returning to the normal range for all (**Table 10**). Increased T2 values showing focal oedema were resolved. The native T1 and ECV measured in the affected area also decreased; however, ECV remained marginally elevated. The LGE area (% LGE of the myocardial mass) shrank from median 7% to 3% during the follow-up, it disappeared completely in 31% (4/13) of cases. The highly trained athlete in whom all signs and symptoms of myocarditis disappeared on follow-up cardiology examination (**Figure 3**) was able to gradually return to sports activity.

6.3.4. Myocarditis after SARS-CoV-2 immunization vs. myocarditis unrelated to COVID-19:

Table 11 depicts the results from ANOCVA test considering the effect of both follow-up time and myocarditis group (myocarditis after SARS-CoV2 vaccination vs myocarditis unrelated to COVID-19 immunization or infection). The test showed no difference between the overall trajectory of cardiac volumes, function, mass, oedema and LGE between myocarditis patients after anti SARS-CoV-2 vaccine and matched myocarditis patients (male patients, 22±7 vs. 23±6 years). Notably, we found a slight difference in T1 mapping. **Figure 12** illustrates the trajectory of CMR metrics between acute and follow-up scans in the both groups.

Table 10: Comparison between acute and follow-up CMR scans of myocarditis patients after anti-SARS-CoV-2 vaccination as per Vago et al. (82). Continuous variables showing a normal distribution are presented as the mean and standard deviations (± SD), and those showing a nonnormal distribution are reported as medians and interquartile ranges [IQRs]. Acute and follow-up examinations were compared using paired sample t tests and Wilcoxon tests. Abbreviations: CMR = cardiac magnetic resonance; ECV = extracellular volume; EDV = left ventricular end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; GLS = global longitudinal strain; i = indexed to body surface area; M = mass; NA = not applicable; LGE = late gadolinium-enhancement LV = left ventricular RV = right ventricular; SV = stroke volume.

	Acute myocarditis after COVID-19 vaccination (n = 16)	**Follow-up Myocarditis after COVID-19 vaccination (n = 14)**	**Acute vs. follow-up CMR, Myocarditis after COVID-19 vaccination (P values)**
Elapsed time, days	4 ± 2	112 ± 27	NA
LVEF, %	58 ± 6	60 ± 3	0.042
LVEDVi, ml/m^2	87 ±13	83 ± 9	0.046
LVSVi, ml/m^2	50 ± 7	50 ± 6	0.961
LVMi, g	53 ± 10	51 ± 7	0.228
GLS, %	-20.5[-22.5,-19]	-21[-22, -20]	0.083
RVEF, %	58 ± 4	57 ± 5	0.559
RVEDVi, ml/m^2	83 ± 10	84 ± 9	0.722
RVSVi, ml/m^2	48 ± 6	48 ± 6	0.489
T1 mapping septal, ms	966 [951, 1016]	957 [950, 965]	0.578
T1 mapping affected area, ms	1056 [1038, 1113]	976 [953.5, 1018]	0.031
T2 mapping septal, ms	43 [43, 44]	43 [42, 43]	0.375
T2 mapping affected area, ms	51 [50, 55]	44 [43, 47.5]	0.016
ECV septal, %	26 [24, 28]	25.5 [23.5, 27.5]	0.125
ECV affected area,%	38 [35, 41.5]	30.5 [28, 35]	0.016
LGE g	6 [3, 10]	2 [0.5, 4]	0.001
LGE %	7 [3, 12]	3 [1, 4]	0.001

Table 11 Assessment of the trajectroy of myocarditis patients after SARS-CoV-2 immunization and myocarditis patients unrelated to COVID-19 immunization or infection over the acute phase and follow-up using analysis of covariance (82). Analysis of covariance (ANCOVA) test results are shown for each CMR metrics, taking into account the effect of the patient group (myocarditis patients after SARS-CoV-2 vaccination vs myocarditis not linked to SARS-COV-2 infection) and time of the CMR scan (acute vs follow-up CMR scan) and the combination of these effects. Models are unadjusted. Abbreviations: CMR = cardiac magnetic resonance; ECV = extracellular volume; EDV = left ventricular end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; GLS = global longitudinal strain; i = indexed to body surface area; M = mass; NA = not applicable; LGE = late gadolinium-enhancement LV = left ventricular RV = right ventricular; SV = stroke volume.

CMR metricss	Effects	ANCOVA test P value
LVEF, %	Group	0.476
	Group:Time	0.613
	Time	0.013
LVEDVi, ml/m2	Group	0.752
	Group:Time	0.445
	Time	0.044
LVSVi, ml/m2	Group	0.954
	Group:Time	0.599
	Time	0.641
LVMi, g	Group	0.676
	Group:Time	0.548
	Time	0.051
GLS, %	Group	0.318
	Group:Time	0.812
	Time	0.102
RVEF, %	Group	0.701
	Group:Time	0.384
	Time	0.924
RVEDVi, ml/m2	Group	0.435
	Group:Time	0.501
	Time	0.253
RVSVi, ml/m2	Group	0.601
	Group:Time	0.795
	Time	0.527
T1 mapping septal	Group	0.171
	Group:Time	0.382
	Time	0.002

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T1 mapping affected area	Group	0.513
	Group:Time	0.04
	Time	<0.001
T2 mapping septal	Group	0.278
	Group:Time	0.741
	Time	0.075
T2 mapping affected area	Group	0.467
	Group:Time	0.175
	Time	<0.001
ECV septal	Group	0.041
	Group:Time	0.852
	Time	0.112
ECV affected area	Group	0.035
	Group:Time	0.92
	Time	<0.001
LGE g	Group	0.32
	Group:Time	0.554
	Time	<0.001
LGE %	Group	0.164
	Group:Time	0.438
	Time	<0.001

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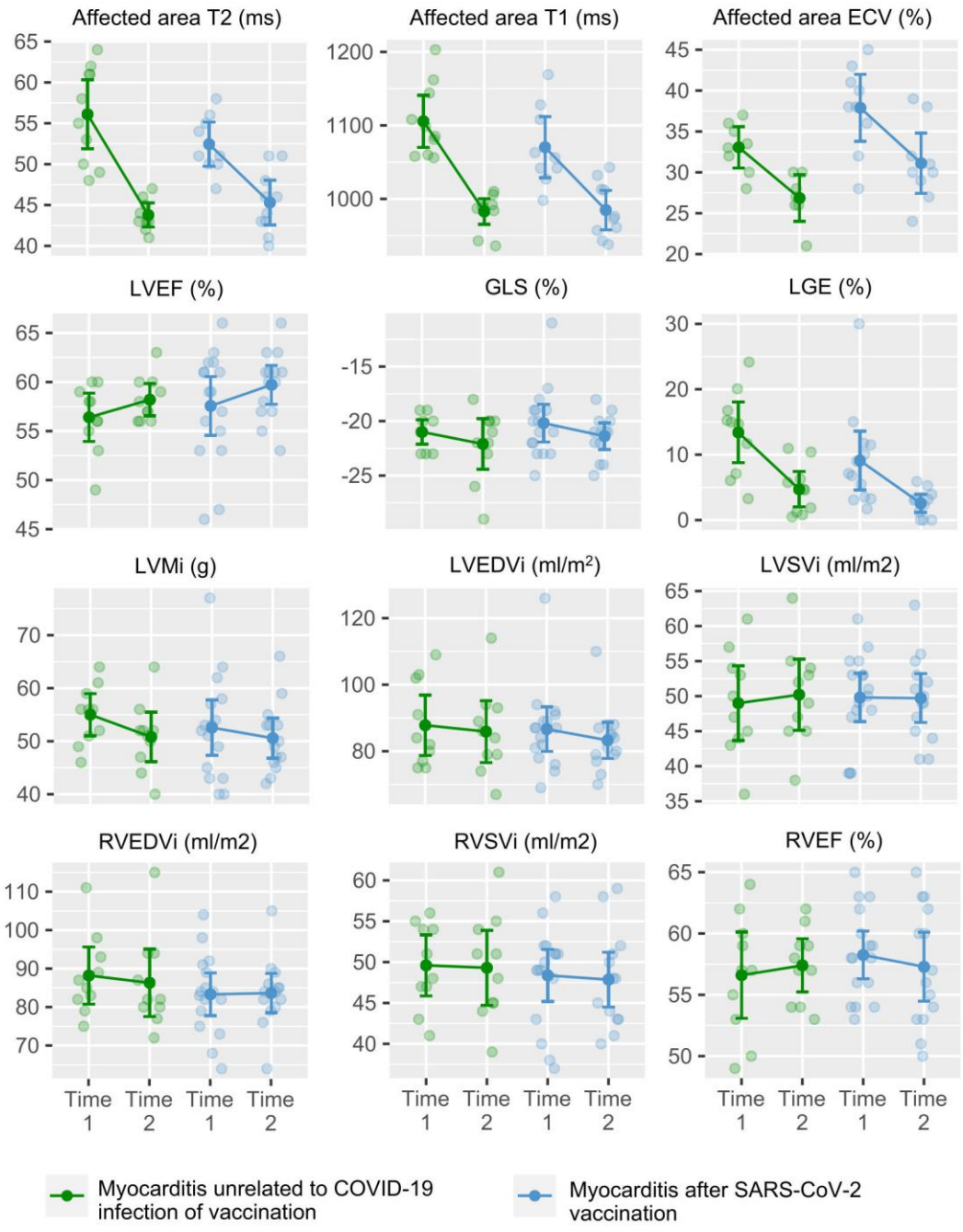

Figure 12: CMR metrics of myocarditis patients after SARS-CoV-2 immunization and myocarditis patients unrelated to COVID-19 immunization or infection over the acute phase and follow-up scan (82). Changes of CMR metrics between the acute (Time 1) and follow-up (Time 2) scans in myocarditis patients after SARS-CoV-2 immunization (in blue) and myocarditis patients unrelated to COVID-19 infection or vaccination (in green). Abbreviations: CMR = cardiac magnetic resonance; ECV = extracellular volume; EDV = left ventricular end-diastolic volume; EF = ejection fraction; ESV = end-systolic

volume; GLS = global longitudinal strain; i = indexed to body surface area; M = mass; NA = not applicable; LGE = late gadolinium-enhancement LV = left ventricular RV = right ventricular; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; SV = stroke volume.

6.3.5. Assessment of the immunological response:

SARS-CoV-2 immune response was assessed in 12 patients after anti-SARS-CoV-2 vaccination and compared with immunization-, age-, sex matched controls (n=23, male patients, mean 22±6 years). The immunological testing was performed on average three and a half months after the first dose of vaccination for both groups. The main difference between myocarditis patients and the comparator group was in terms of their history of previous SARS-CoV-2 infection (25% vs. 91%). To account for this difference we tested anti-NCP (IgG, IgM) levels, which showed no difference between the two groups. We did not find significant difference in the markers of humoral immune response (S1 Ig, SP1 IgG, SP1 IgA) between myocarditis patients after SARS-CoV-2 immunization and those matched controls (**Table 12**). In contrast, we found an increased T-cell response (Ag1, Ag2, Ag3) in myocarditis patients compared to controls ($p < 0.01$).

Table 12: Immune response in myocarditis patients after anti-SARS-CoV-2 immunization vs. age-, sex- and SARS-CoV-2 immunization-matched controls from Vago et al. (82). Abbreviations: Ag = antigen; Ig = immunglobulin; SARS-CoV-2 = severe acute respiratory syndrome

	Myocarditis after anti-SARS-CoV-2 vaccination (n=12)	**Matched controls (n=23)**	**P value**
Age, years	22 ± 7	22 ± 6	NS
Sex, male %	12 (100)	23 (100)	NS
Time from the first dose of vaccine to test, days	109 ± 57	108 ± 58	NS
Time form the second dose of vaccine to test, days	86 ± 60	81 ± 55	NS
Anti-SARS-CoV-2 vaccine			

- mRNA vaccine n(%) - vector vaccine n(%)	8 (67%) 4 (33%)	18 (78%) 5 (22%)	NS
Test after the second dose of anti-SARS-CoV-2 vaccine, yes(n%)	10 (83%)	18 (86%)	NS
Previous SARS-CoV-2 infection, yes n(%)	3 (25%)	21 (91%)	<0.001
Time from previous SARS-CoV-2 infection, days	224 ± 66	284 ± 73	NS
Anti-SARS-CoV-2 NCP-IgG (Ratio *) Cutoff: > 1.1	0.24 [0.13, 0.49]	0.32 [0.21, 1.23]	NS
Anti-SARS-CoV-2 NCP-IgM (Ratio *) Cutoff: > 1.1	0.31 [0.24, 0.48]	0.33 [0.18, 0.66]	NS
S1 Ig (U/ml) Cutoff: ≥ 0.8 U/ml	10265.5 [2232, 38327.5]	9167 [3948.5, 20050]	NS
SP1 IgG (RU/ml) Cutoff: ≥ 11 RU/ml	1155.5 [284, 1656]	627 [283, 1537.5]	NS
SP1 IgA (Ratio*) Cutoff: ≥ 1.1	11 [7, 11]	7 [6.5, 10]	NS
Ag1 – S1 CD4+ (IU/ml) Cutoff: ≥ 0.15	1.3 [0.5, 4.5]	0.5 [0.2, 1.0]	0.002
Ag2 – S1 CD4+ CD8+ (IU/ml) Cutoff: ≥ 0.15	2.0 [1.0, 4.7]	0.6 [0.2, 1.2]	0.008
Ag3 – S1 CD4+ CD8+, whole genome CD8+ (IU/ml) Cutoff: ≥ 0.15	2.4 [1.0, 6.8]	0.8 [0.6, 1.5]	<0.001

Comparison between different type of vaccines showed that markers of the humoral immune response (S1 Ig, SP1 IgG, SP1 IgA) were significantly more increased after the mRNA vaccine than after the vector vaccine. At the same time, there was no difference regarding measures of cellular immune response (Ag1, Ag2,Ag3) between the two groups (**Table 13**).

Table 13: Immune response to anti-SARS-CoV-2 mRNA vaccine compared to vector vaccine (82). Abbreviations: Ag = antigen; Ig = immunglobulin; SARS-CoV-2 = severe acute respiratory syndrome

	mRNA vaccine (n=26)	**Vector vaccine (n=9)**	**P**
Age, years	22 ± 6	22 ± 4	NS
Time from the first vaccine to test	111 ± 59	102 ± 53	NS
S1 Ig (U/ml) Cutoff: ≥ 0.8 U/ml	13252 [5848, 27727]	3127 [428.5, 8785]	0.015
SP1 IgG (RU/ml) Cutoff: ≥ 11 RU/ml	1087 [353, 2089.5]	284 [68, 507.5]	0.006
SP1 IgA (Ratio*) Cutoff: ≥ 1.1	8.6 [6.9, 11.2]	5.6 [1.9, 8.1]	0.017
Ag1 – S1 CD4+ (IU/ml) Cutoff: ≥ 0.15	0.8 [0.4, 1.4]	0.3 [0.1, 1.4]	NS
Ag2 – S1 CD4+ CD8+ (IU/ml) Cutoff: ≥ 0.15	1 [0.6, 1.7]	0.6 [0.2, 1.8]	NS
Ag3 – S1 CD4+ CD8+, whole genome CD8+ (IU/ml) Cutoff: ≥ 0.15	1.2 [0.8, 2.1]	0.7 [0.4, 2.3]	NS

Finally, there was no correlation between the humoral immune response (S1 Ig, SP1 IgG, SP1 IgA) and LVEF. In contrast, we could demonstrate a negative correlation between T-cell response and LVEF **(Figure 13).**

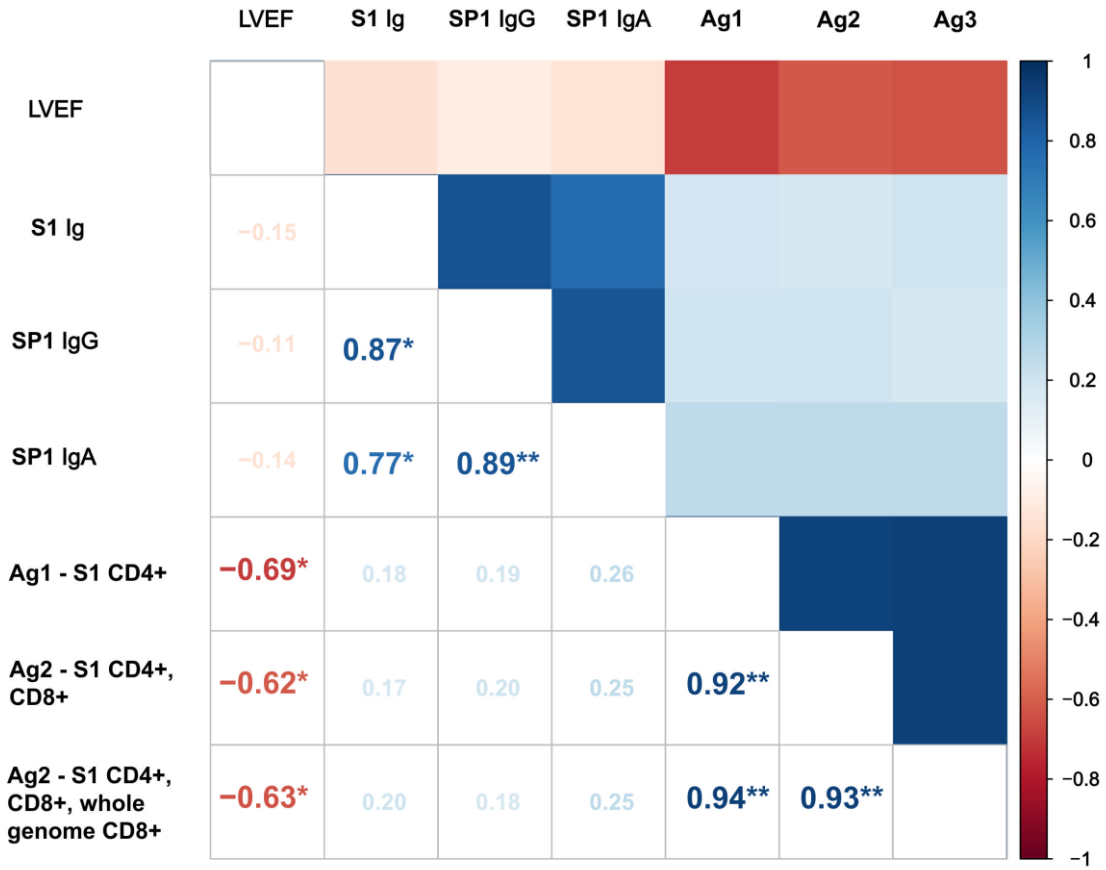

Figure 13: Correlation matrix showing the relationship between measures of the immune response to SARS-CoV-2 and LVEF (82). Associations were derived using Spearman's rank correlation analyses, correlation coefficients are reported. A positive correlation is shown in blue, negative correlation is with red. Abbreviations: Ag = antigen; Ig = immunglobulin, LVEF = left ventricular ejection fraction

* : $p<0.05$

**: $p<0.001$

7. Discussion

7.1. The diagnostic and prognostic implications of early CMR in the workup of patients with the working diagnosis of MINOCA

7.1.1. Summary of findings

In this large single-centre cohort of patients with troponin-positive acute chest pain and non-obstructed coronary arteries we report we report the following main findings using CMR imaging. First, performing CMR within a suitably narrow time frame (<7 days) can provide a diagnosis in up to 86% of the cases. Moreover, in our study it modified the patient management in 46%. Second, the underlying aetiologies differ considerably, and the prognosis of these diagnosis groups (myocarditis, MI, Takotsubo and normal CMR) may vary. Third, Takotsubo and MI as diagnosis group, older age, hypertension, diabetes, female sex, LVEF, LVSVi and most of the investigated strain features were univariate predictors of mortality.

7.1.2. Comparison with existing literature

Studies with a longer time window between CA and CMR have demonstrated inconsistent diagnostic success rates (27-74%) in patients with a working diagnosis of MINOCA. Due to the temporary nature of certain changes (such as oedema or the characteristic wall motion abnormality in Takotsubo syndrome), this may lead to the misclassification of patients (41, 83). We carried out CMR in all participants within 7 days (mean of 2.6 days) after CA, which allowed us to provide a definite diagnosis in almost 90% of the cases, similarly to what Bhatia et al. found in their study with a similar cohort size (215 patients) and mean time delay to CMR (3.68 days) (84). Here, we corroborate that early CMR has an excellent diagnostic yield in patients with the working diagnosis of MINOCA and that it leads to the reclassification of a high proportion of cases (42, 84-86). The proportion of MI (or true MINOCA) in our study (22%) was slightly higher than that reported by Kawecki et al. (9%) and some other investigations, but similar to the findings of Bhatia et al. (22%) and Dastidar et al. (25%) (41, 84, 86-88).

The mean age of our patient population is slightly lower than those in pior studies. Probably due to the high ratio of patients with a clinical suspicion of acute myocarditis;

however, among these patients, CMR indicated MI in 21%, which is not a negligible portion.

Previous reports have shown that MINOCA patients have slightly better prognoses than those with obstructive coronary artery disease. However, recent studies based on the SWEDEHEART registry demonstrated that these patients have unfavourable outcomes too (43, 44, 89). Most studies that have assessed the prognosis of MINOCA treat this group as homogenous, and this confounding factor may account for the wide variation observed in one-year mortality, which ranges from 0.6% to 12.3% (43, 90-92). There are two main sources of heterogeneity: first, patient groups are very different concerning their ages. As an example, Safdar observed low mortality (0.6%) in a younger (aged 18-55) patient population, while the high mortality (12.3%) reported by Dreyer et al. was found in patients aged >65 years. Second, the underlying aetiology (e.g. myocarditis, MI, Takotsubo syndrome) in patients with a working diagnosis of MINOCA is not homogenous, as Ferreira and Sechtem et al. underscored in their recent editorials. They concluded that the adoption of CMR in the clinical routine may refine the diagnostic labelling of such patients, thereby modiflying treatment approaches and patient prognosis (42, 45). Our finding are comparable to those of Dastidar et al., who used CMR systematically at a median of 37 days (41) after the initial presentation. Their results also reinforced the diagnostic and prognostic value of CMR in patients with working diagnosis of MINOCA. Compared to their results, the mortality was higher in the MI (or MINOCA) patients in our cohort (10% vs. 4%) over a slightly longer follow-up (3.5 vs. 4 years). Moreover, Dastidar et al. reported a heterogeneous group of cardiomyopathies, which was not present in our study. We found that the mortality rate was slightly higher per patient-year among our Takotsubo patients compared to Templin et al., who described the long-term outcomes of the Takotsubo patients included in the InterTAK registry (6.4% vs. 5.6%) (93).

In univariate analysis, Takotsubo and MI as a diagnosis, key cardiovascular risk factors (diabetes, hyptertension) and CMR parameters, including LVEF, LVSVi and most of the investigated strain parameters were predictors of mortality. However, in our multivariate analysis, only hypertension and a strain-derived dyssynchrony measure (MDC) were significant predictors of all-cause mortality. The reason for this might be confounding among the candidate predictor variables. For example, in the bivariate correlations,

hypertension showed only a marginal correlation with any other risk factors or CMR parameters. This might explain why hypertension was both a univariate and a multivariate predictor, consistent with the previous findings of large national registries that reported prognoses of MINOCA patients (43, 94). Other demographic characteristics, including older age and female sex, were significant predictors of mortality in univariate but not multivariate analysis. However, MDC was correlated with patient age, sex, Takotsubo or MI as the CMR diagnosis, and many CMR parameters, such as LVEF and LV strain features, all of which were significant univariate predictors. Our findings suggest that CMR may not only has an leading role in the differential diagnosis of patients with a working diagnosis of MINOCA but can also provide useful supplementary features for risk stratification.

7.1.3. Study limitations

This was a single-centre study with a relatively limited sample size by diagnosis group, which might restrict the generalizability of our prognostic conclusions. We excluded patients with contraindications to CMR (based on seriously impaired renal function or the lack of ability to cooperate with the examination), which might have resulted in an underestimation of our hazard ratios. Almost one-third of patients were referred to CMR from other institutions; and their laboratory and ECG test results, patient history were provided by the referring clinicians. During the data collection (2009–2019), all patients referred for CMR had one of the mentioned ECG alterations; therefore, our results are only applicable to patients with ECG changes. Finally, due to the retrospective nature of the study, blinded interpretation of the CMR images was not performed.

7.2. Cardiac involvement after SARS-CoV-2 infections in young competitive athletes

7.2.1. Summary of findings

In this large single centre study of 147 highly trained athletes we performed deep phenotyping of the athlete's heart after SARS-CoV-2 infection using CMR imaging. We also put our findings into the context of sex- and age-matched healthy athletes and less active controls. We made the following main contributions. First, only a minority of the athletes after SARS-CoV-2 infection had definite (n=2, 1.4%) or possible (n=5, 3.4%) myocardial or pericardial alterations on CMR. Second, in this group, where all athletes

were referred to the examination by a cardiologist, CMR revealed no significant differences regarding any volumetric, functional or tissue characteristics compared to matched healthy athletes. Third, comparing athletes with different symptom severities showed that athletes with moderate symptoms had slightly greater T1 values than athletes with asymptomatic and mildly symptomatic infections. However, T1 mapping values remained below the cut-off point for most patients. Finally, the majority of athletes returned to high levels of sports activity without any persisting complaint our symptom.

7.2.2. Comparison with existing literature

We found a lower frequency of myocardial alteration among young athletes than initially suggested by Rajpal and colleagues (61), who performed CMR for 26 asymptomatic or mildly symptomatic college athletes with negative troponin levels, normal ECG, and normal echocardiography. They reported that almost 50% of the athletes had LGE and 15% had myocardial alterations interpreted as acute myocarditis. In our study, only one patient had CMR findings consistent with acute myocarditis according to the LLC (33), and one had findings suggesting previous myocarditis. As per those three athletes who presented with slightly elevated T1 values with or without elevated T2, we reported possible mild diffuse myocardial involvement and performed a follow-up CMR scan, which showed the resolution of these alterations in two patients. Our results corroborate the findings by Starekova et al., Moulson et al., and Martinez et al. (64, 65, 95) signifying the modest prevalence of myocardial involvement after SARS-CoV-2 infection in young, otherwise healthy individuals. In a nationwide cohort of U.S. collegiate athletes Moulson et al. demonstrated that the cardiac involvement among athletes might be low as 0.7%. They also found that CMR scans performed on the basis of clinical symptoms were four times more likely to show myocardial alterations as opposed to those that were performed as a primary screening method (64). Overall, these results are in agreement with pathological research showing that only 1-7% of 277 autopsied hearts across 22 publications had COVID-19-related myocarditis according to histopathological findings (96), although in a different patient population. Notably, in our study only one athlete had pericardial involvement; which is in contrast with the case series of Brito et al., who found pericardial enhancement in 39.5% of athletes (62), but in line with subsequent investigations.

We did not find a difference regarding the proportion of hinge point fibrosis after SARS-CoV-2 infection in athletes and healthy control athletes; but, only a handful of healthy volunteer athletes received contrast material in our control group (n=15). We found a somewhat higher proportion of hinge point fibrosis than Clark et al. (athletes after SARS-CoV-2 infection) and a lower ratio than Domenech-Ximenos et al. in endurance athletes before the pandemic (32% vs 22% vs 38%). Of note, these groups were different from ours regarding the ratio of female participants (36% vs 63% vs 47%), sports discipline and training load, which might explain the observed discrepancies (63, 97).

Our results are in agreement with the contemporary literature with regards to athletic adaptation (98, 99). Data are scarce as to the feature-tracking strain pattern of highly trained athletes preventing direct comparison, but the overall trends observed in our cohort (slightly lower global strain values among highly trained males) are similar to those in the available publications using echocardiography (100-102). Comparing athletes with prior SARS-CoV-2 infection and matched athletes showed no difference between CMR parameters, including strain features and native T1 and T2 values. This finding confirms the observations by Clark et al. (63) who reported only a slight difference between post-COVID-19 athletes and healthy control athletes regarding their mid-septal T2 mapping values. However, the athletic groups in their investigation were matched by training load only, not age or sex, which could have contributed this finding. McDiarmid et al. (103) has shown that physiological hypertrophy may decrease T1 value in highly trained male athletic population. Our findings confirmed this observation: both male and female athletes had distinct T1 (and T2) pattern similar to other CMR parameters, which justifies the use of sex-matched control groups when interpreting mapping alterations.

In our dataset, there was no correlation between T1 mapping values and the elapsed time since SARS-CoV-2 infection, similar to what Kotecha et al. (59) found with a somewhat longer delay between infection and CMR scans (median 68 vs 32 days). In contrast, a weak but significant correlation was found between T2 mapping and time since infection. This might imply a slight reduction in subclinical oedema over time; however, we need more evidence to confirm this result.

One unique strength of this study is that 14 athletes had undergone a previous CMR scan at our institute with a standardised protocol; therefore, we could compare the results of

the two scans. This comparison, however, showed no differences between CMR parameters before and after SARS-CoV-2 infection.

Follow-up at median 232 days after COVID infections showed the majority of athletes returned to high levels of sports activity (n=120/122), although some could not reach their peak performance (n=3) and some experienced reinfection (n=4).

The comparison between athletes with different symptoms revealed slightly elevated T1 mapping values among athletes with chest complaints relative to asymptomatic and mildly symptomatic athletes; however, this did not lead to a reduction in systolic heart function. Moreover, T1 values remained in the normal range for most patients. Currently, there are no data regarding the subclinical cardiac alterations caused by mild forms of systemic viral infections such as influenza and whether they are detectable on CMR. We believe that studies investigating the long-term impact of isolated T1 and T2 mapping elevations are necessary to understand the exact prognostic significance of these alterations, and in this study, we share the concerns of Moulson and Baggish (104) regarding the use of these highly sensitive, albeit less well-understood techniques, in the screening of otherwise healthy athletes with prior SARS-CoV-2 infection. The current consensus document (72) regarding the use of CMR in athletes after SARS-CoV-2 infection highlights the importance of well-established screening methods such as troponin, ECG and echocardiography. Moreover, in suspected arrhythmias further examinations such as 24-h Holter monitoring might be beneficial, (72, 73) and premature ventricular beats on exercise test might suggest scar on CMR examination as demonstrated by recent studies, enabling a better targeting of CMR scans (105). In agreement with this, our results caution against the routine use of CMR for troponin-negative, asymptomatic, or mildly symptomatic COVID-19 patients, as it may lead to false conclusions.

7.2.3. Study limitations

This was a single-centre study performed in a major CMR referral centre. Approximately one-third of the athletes after SARS-CoV-2 infection were referred from other institutions; therefore, their clinical data were provided by the referring clinicians. All athletes included in our study were Caucasian and experienced asymptomatic, mild/moderate or long COVID; thus, our conclusions are only applicable to this specific

group. Because our study included patients referred by a cardiologist, the reported prevalence of abnormal CMR findings may be overestimated compared to a non-selected population of athletes with SARS-CoV-2 infection. In addition, the clinical implications of CMR abnormalities in the absence of cardiovascular symptoms remain unknown. Lastly, only a proportion of healthy control athletes received contrast during their CMR; thus, findings related to LGE in the athletic control group could have been missed.

7.3. The clinical, CMR imaging, and immunological characteristics of myocardtitis patietns after SARS-CoV-2 vaccination

7.3.1. Summary of finding

This study of 16 myocarditis patients after anti-SARS-CoV2-vaccination confirmed by CMR makes the following contributions. First, in a cohort of acute myocarditis presenting on average 4 days after immunization, we observed that 75% had received mRNA vaccines and 25% vector vaccines. Second, on the follow-up visit, a mean of 112 days after the acute event, CMR abnormalities showing myocardial injury, decreased or completely disappeared. Third, there was no discernible difference regarding CMR features between myocarditis cases linked to SARS-CoV-2 vaccination and myocarditis unrelated to COVID-19. Finally, we found an increased T-cell response among myocarditis patients after vaccination compared to matched controls.

7.3.2. Comparison with existing literature

All patients presented with fever, chest pain and elevated troponin levels, with no evidence of ongoing viral infection, approximately 2-4 days after the second dose of the COVID-19 vaccine. This finding is line with previous reports (106-109). Whilst the majority of our patients were administered mRNA vaccine, similar to what studies from the US and Israel found (70, 110), 25% presented after receiving the Sputnik V vaccine. In Hungary, approximately 40% of the young population (aged 16 – 35 years) obtained a vector anti-SARS-CoV-2 vaccine (111) suggesting that myocarditis presenting after COVID-19 vaccine might be less skewed towards mRNA vaccines than previously reported (112). Of note, at the time of our study, only the Pfizer-BioNTech vaccine was authorized to immunize the adolescent population (n=5 in our cohort), who seem to be more susceptible to this adverse effect (66). This might limit meaningful comparison of the risks of myocarditis associated with different type of vaccines. Interestingly, a study

derived from the Vaccine Adverse Events Reporting System (VAERS) already advised against using mRNA vaccines among those with a higher risk for myocarditis and encourages vector vaccines as a safer alternative (112). However, a reporting system such as VAERS is prone to over- or underreporting based on the awareness and attention of the reporters (67). Accordingly, VAERS should be used as a hypothesis-generating or event detection system (67, 113).

Overall, twenty-five percent of our patients reported immune-mediated diseases in our cohort. Two individuals disclosed previous acute myocarditis, and one experienced recurrent myocarditis three months after vaccination. In the latter case, acute myocarditis was linked to acute gastrointestinal infection; thus, it is unlikely that this event was associated with vaccination. These findings might propose a predisposing immune response, as described previously in acute myocarditis unrelated to immunization (11). Notably, we did not ascertain a significant difference between the immune response of participants with predisposing factors and that of those without; however, the small number of patients in each group might prevent meaningful conclusions.

The male predominance of myocarditis has been previously demonstrated, and the cause is still incompletely understood (114). One leading hypothesis is based on sex hormone disparities. Differences in sex hormone receptor expression have been observed on both immune cells and cardiac tissues (115) and the highest levels of free testosterone is reported in young males (116). Moreover, testosterone has a role in interleukin-10 upregulation and interferon-gamma downregulation. Yet, the direct relationship between testosterone levels and myocarditis has not been conclusively proven.

Five individuals disclosed possible acute triggers in our study population: physical activity (n=4) and heavy alcohol consumption (n=1) immediately after immunisation. Vigorous physical activity can trigger the onset of myocarditis and should be avoided during ongoing infection (10, 11); this might be appropriate after vaccination, too. To sum up, these results imply that the combined effect of genetic predisposition, hormonal factors and acute triggers may contribute to myocarditis after SARS-CoV-2 vaccination.

Case reports have granted a visual account of vaccine-induced myocarditis by CMR (68, 69, 117, 118), and here we demonstrate for the first time the improvement of the myocardial injury on imaging. Moreover, for context, we present a control group of

myocarditis unrelated to the anti-SARS-CoV-2 vaccination or infection. In our study, the most frequent localization of LGE was the lateral wall of the LV for all, suggesting that based on the image alone, it is unattainable to distinguish myocarditis cases post-vaccination from viral myocarditis. Our finding is similar to recent report from Fronza et al. (119). CMR is a key diagnostic method for myocardial injury; but clarifying the disease aetiology requires a holistic approach, taking into account the patient's history, symptoms and potential predisposing factors.

Myocarditis can heal over time (120), and our study support the notion that this is true for cases linked to the COVID-19 immunization, too. T2 values showing oedema normalized on follow-up for all patients. Moreover, T1 mapping, ECV, and LGE decreased. Data suggest that LGE on the acute CMR scan is not equal to irreversible myocardial damage but the result of myocardial inflammation that can decrease over time. Moreover, none of the participants had extensive (>20%) LGE during follow-up. We observed a slight improvement in LVEF during follow-up. Whilst the betterment of GLS values were not significant in our study, as expected based on the literature (121), the overall trend of GLS also suggested a marginal improvement over time. In summary, all of these imaging findings are all considered to be good prognostic markers in myocarditis (10).

SARS-CoV-2 infection leads to production of specific antibodies and CD4+ and CD8+ cells (122). Increasing evidence supports the role of the T-cell-mediated response to SARS-CoV-2 infection; which is associated with less severe disease (123, 124). Our results indicate an accelerated COVID-specific T-cell-mediated immune response in the myocarditis group compared to the age-, sex- and vaccination status-adjusted control population.

While we believe that acute myocarditis after anti-SARS-CoV-2 vaccination is an important cardiovascular adverse effect, this should not eclipse the data backing up the effectiveness of vaccines (66, 125). The question also arose if the adverse reaction to immunization (myocarditis) or the consequences of SARS-CoV-2 infection is more serious in young patients. The most severe of the latter is the multisystem inflammatory syndrome in children (MIS-C), which is characteised by systemic illness and often necessitates prolonged hospitalization. Recent evidence from France linked COVID-19 vaccination is with lower MIS-C incidence among adolescents (126). Moreover,

Zambrano et al. found that critically ill MIS-C patients requiring life support, were all unvaccinated, reinforcing the vaccination for eligible children (127). Finally, there is an urgent need for an international consensus regarding the immunization protocol for those who experienced acute myocarditis after their COVID-19 vaccine.

7.3.3. Limitations

The main limitation of our study is the small sample size, which is due to the rare occurrence of myocarditis after COVID-19 vaccination. Although we contacted all Hungarian centres reporting CMR, we could not avoid referral bias to CMR by clinicians. We compared results of mapping sequences only among those participants who were scanned at the Semmelweis University Heart and Vascular Center to avoid interscanner variability. Myocarditis control group's history was provided by the referring physician. The control group for the immunological studies did not undergo CMR examination.

8. Conclusion

Results from our cohort of patients with troponin-positive acute chest pain and non-obstructed coronary arteries indicate that early CMR has a leading role in the differential diagnosis of MINOCA. The aetiology in these patients varies considerably, and the prognosis of different diagnosis groups may differ. CMR may also provide prognostic information with the implementation of strain analysis. As such, CMR may have an important role in the risk stratification of these patients.

Our initial findings in a small group of elite athletes without comorbidities who recently recovered from COVID-19 showed no signs of cardiac involvement on CMR. We confirmed and refined this result in a much larger group of consecutively included highly trained athletes after SARS-CoV-2 infection and referred by a cardiologist. Overall, only two patients (1.4%) presented with definite signs of myocarditis. Our results suggest that cardiac involvement occurs with modest frequency among asymptomatic and mildly/moderately symptomatic SARS-CoV-2 infections in young athletes with CMR showing no evidence of systemic cardiac impairment compared. The follow-up revealed that the majority of athletes returned to high levels of sports activity without any persisting symptoms. Critically, our results do not support the use of routine CMR in troponin-negative, asymptomatic, or mildly symptomatic athletes who recover from this illness, as this might lead to false conclusions.

In this cohort of myocarditis patients after COVID-19 immunization confirmed by CMR, we found that acute myocarditis can occur after mRNA and vector vaccines, predominantly in individuals with predisposing factors. Upon mid-term follow-up, myocarditis showed improvements in CMR markers, including the LVEF and tissue-specific alterations. The T-cell response was more prominent among myocarditis patients after COVID-19 vaccination than matched controls.

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9. Summary

Cardiac magnetic resonance imaging (CMR) has a unique role in evaluating myocarditis and myocardial injury as the noninvasive reference method for assessing cardiac morphology, function, and tissue composition. Despite the considerable scientific effort in recent years, the differential diagnosis of myocardial injury remains a challenge due to the significant heterogeneity in clinical presentations and the wide variety of causes.

In a series of studies, we provided novel evidence on the clinical application of CMR in the diagnostic work-up of suspected myocarditis and myocardial injury. Firstly, we have shown that an early CMR performed within seven days of the acute presentation has a crucial diagnostic benefit in patients with the working diagnosis of myocardial infarction with non-obstructed coronary arteries (MINOCA). CMR has established the diagnosis in 86% of patients, namely acute myocarditis, acute myocardial infarction, or Takotsubo cardiomyopathy. Critically, we demonstrated that the prognosis of these different diagnosis groups differs considerably. Secondly, we reported our initial findings in a small group of elite athletes who recently recovered from COVID-19 showed no signs of cardiac involvement on CMR. We confirmed and refined this result in a much larger group of consecutively included highly trained athletes after SARS-CoV-2 infection and referred by a cardiologist. Essentially, the message remained the same: cardiac involvement occurs with modest frequency among asymptomatic and mildly/moderately symptomatic SARS-CoV-2 infections in young athletes (definitive myocarditis 1.4%). Comparing athletes after SARS-CoV-2 infection and matched healthy athletes showed no difference between CMR parameters. Therefore, our results do not support the use of routine CMR in troponin-negative, asymptomatic, or mildly symptomatic athletes who recover from this illness, as this might lead to false conclusions. Finally, in a cohort of COVID-19 vaccine-induced myocarditis confirmed by CMR, we have shown that both mRNA and vector vaccine can cause acute myocarditis in individuals with predisposing factors. We illustrated the improvement of COVID-19 vaccine-induced myocarditis over time. Crucially, in our study, the T-cell response was more prominent among vaccination-induced myocarditis patients than matched controls; furthermore, we saw a connection between the intensity of the T-cell response and the left ventricular systolic function.

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10. Összefoglalás

A szív mágneses rezonanciás vizsgálatnak (MR), mint a szív morfológiájának, funkcióinak és szöveti összetételének noninvazív megismerésére alkalmas referenciamódszernek, egyedülálló szerepe van a szívizomgyulladás és a szívizomsérülés megítélésében. Az elmúlt évek jelentős tudományos erőfeszítései ellenére a szívizomsérülés differenciáldiagnózisa továbbra is kihívást jelent a klinikai megjelenések jelentős heterogenitása és a kiváltó okok sokfélesége miatt.

Vizsgálataink során új bizonyítékokat szolgáltattunk a szív MR klinikai alkalmazásával kapcsolatban a feltételezett szívizomgyulladás és szívizomsérülés diagnosztikájában. Első vizsgálatunkban kimutattuk, hogy a panaszok megjelenését követő hét napon belül elvégzett szív MR jelentős diagnosztikai előnnyel jár az obstruktív koszorúér-betegség nélkül kialakuló akut szívizominfarktus (MINOCA) munkadiagnózisával vizsgált betegek esetén. A szív MR a betegek 86%-ánál adta meg a diagnózist, nevezetesen akut szívizomgyulladást, akut szívizominfarktust vagy Takotsubo szindrómát. Kimutattuk, hogy a különböző diagnózis csoportok prognózisa jelentősen eltér egymástól. Másodszor, beszámoltunk a COVID-19-ből felépült élsportolók egy kis csoportjában végzett kezdeti megállapításainkról, amely során a szív MR vizsgálat nem mutatott szívbetegségre utaló jeleket. Ezt az eredményt megerősítettük illetve megfigyeléseinket kibővítettük a SARS-CoV-2 fertőzés után vizsgálat nagyobb élsportolói csoport vizsgálatával. Az üzenet lényegében változatlan maradt: a szív érintettség alacsony gyakoriságot mutat a fiatal sportolók körében akik tünetmentesen vagy enyhén/közepesen tünetekkel estek át SARS-CoV-2 fertőzésen (definitív myocarditis 1,4%). Szív MR paraméterek tekintetében nem volt különbség a SARS-CoV-2 fertőzés utáni sportolók és az egészséges sportolók között. Eredményeink tehát nem támasztják alá a szív MR rutinszerű alkalmazását a troponin-negatív, tünetmentes vagy enyhén tünetmentes sportolóknál, mivel ez téves következtetésekhez vezethet. Végül a COVID-19 vakcina által kiváltott szívizomgyulladásos betegek körében kimutattuk, hogy az mRNS és a vektor vakcina is okozhat akut szívizomgyulladást hajlamosító tényezőkkel rendelkező egyénekben. Bizonyítottuk, hogy az oltásmyocarditis idővel javulását mutat. Vizsgálatunkban kulcsfontosságú, hogy a T-sejtes válasz hangsúlyosabb volt az oltásmyocarditises betegek körében, mint illesztett kontrollokban; továbbá összefüggést találtunk a T-sejtes válasz intenzitása és a bal kamra szisztolés funkciója között.

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ORIGINAL RESEARCH

Early cardiac magnetic resonance imaging in troponin-positive acute chest pain and non-obstructed coronary arteries

Hajnalka Vágó ,[1] Liliána Szabó ,[1] Zsófia Dohy,[1] Csilla Czimbalmos,[1] Attila Tóth,[1] Ferenc Imre Suhai,[1] György Bárczi,[1] V. Anna Gyarmathy,[2,3] Dávid Becker,[1] Béla Merkely[1]

ABSTRACT

Objective We assessed the diagnostic and prognostic implications of early cardiac magnetic resonance (CMR), CMR-based deformation imaging and conventional risk factors in patients with troponin-positive acute chest pain and non-obstructed coronary arteries.

Methods In total, 255 patients presenting between 2009 and 2019 with troponin-positive acute chest pain and non-obstructed coronary arteries who underwent CMR in ≤7 days were followed for a clinical endpoint of all-cause mortality. Cine movies, T2-weighted and late gadolinium-enhanced images were evaluated to establish a diagnosis of the underlying heart disease. Further CMR analysis, including left ventricular strain, was carried out.

Results CMR (performed at a mean of 2.7 days) provided the diagnosis in 86% of patients (54% myocarditis, 22% myocardial infarction (MI) and 10% Takotsubo syndrome and myocardial contusion (n=1)). The 4-year mortality for a diagnosis of MI, myocarditis, Takotsubo and normal CMR patients was 10.2%, 1.6%, 27.3% and 0%, respectively. We found a strong association between CMR diagnosis and mortality (log-rank: 24, p<0.0001). Takotsubo and MI as the diagnosis, age, hypertension, diabetes, female sex, ejection fraction, stroke volume index and most of the investigated strain parameters were univariate predictors of mortality; however, in the multivariate analysis, only hypertension and circumferential mechanical dispersion measured by strain analysis were independent predictors of mortality.

Conclusions CMR performed in the early phase establishes the proper diagnosis in patients with troponin-positive acute chest pain and non-obstructed coronary arteries and provides additional prognostic factors. This may indicate that CMR could play an additional role in risk stratification in this patient population.

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INTRODUCTION

A growing number of studies have confirmed that myocardial infarction (MI) with non-obstructed coronary arteries (MINOCA) is an important working diagnosis subgroup among patients with signs and symptoms of acute coronary syndrome (ACS). The prevalence of patients with a working diagnosis of MINOCA is up to 10% among patients with ACS.[1 2] The inclusion and exclusion criteria and diagnostic methods of studies assessing these patients have varied greatly.[3–7]

To facilitate clinical decision making, the European Society of Cardiology (ESC) published a position paper on MINOCA. This paper, among others, suggests that CMR imaging should be used in patients with a working diagnosis of MINOCA due to its unique capability to non-invasively assess cardiac function, structure and tissue characteristics, including oedema and necrosis/fibrosis.[2]

Myocardial deformation imaging modalities, especially CMR-based feature-tracking analysis in recent years, are gaining recognition for their unique value in more accurately approximating myocyte metabolism and contractility than the widely used left ventricular ejection fraction (LVEF).[8] Although limited data are available regarding whether CMR-based strain parameters have incremental prognostic roles in addition to other readily available imaging modalities, some studies have already demonstrated the prognostic value of LV strain in patients with acute MI.[9 10]

According to the current ESC guidelines on patients with acute MI presenting with ST-segment elevation, in the subgroup of patients with non-obstructed coronary arteries, performing a CMR examination within 2 weeks after the onset of symptoms should increase the diagnostic accuracy of this method.[11] However, little is known about the systematic application of early CMR in both the differential diagnosis of patients with a working diagnosis of MINOCA and their subsequent prognosis. Thus, we conducted a study with the following two aims. First, we evaluated the diagnostic implications of early CMR (≤7 days). Second, we sought to assess the prognostic impact of conventional risk factors and CMR examination, including diagnosis, standard parameters and strain analysis, in patients with a working diagnosis of MINOCA.

METHODS

Study population

Consecutive patients presenting between April 2009 and April 2019 with a working diagnosis of MINOCA (troponin-positive acute chest pain and non-obstructed coronary arteries) who underwent CMR in our tertiary referral centre were identified in our CMR database and followed up in this retrospective longitudinal observational study. The inclusion criteria for enrolment into the study were: (1) acute chest pain; (2) a significant increase in the

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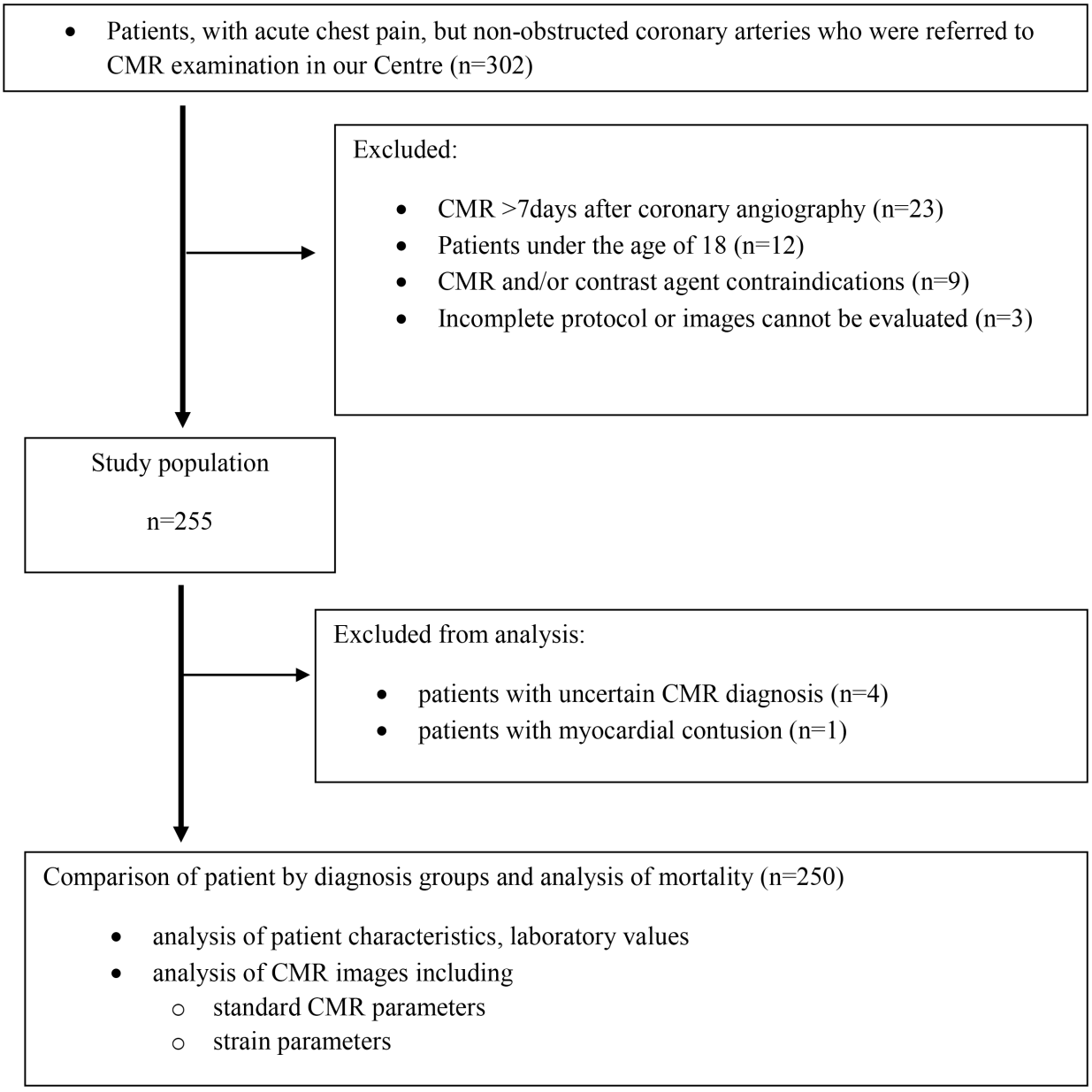

Figure 1 Study flow chart. CMR, cardiovascular magnetic resonance.

high-sensitive troponin T value (>14 ng/L); (3) ECG changes, such as at least 1 mm of ST-segment elevation or ST-segment depression or negative T-waves in at least two related leads; and (4) normal coronary arteries or coronary arteries with signs of atherosclerosis with stenosis <50% in a luminal diameter as demonstrated by invasive coronary angiography. The exclusion criteria were: (1) a CMR examination performed more than 7 days after invasive coronary angiography; (2) malignant ventricular arrhythmias at presentation or having known dilated cardiomyopathy with signs of severe heart failure as a primary complaint; (3) acute renal failure or chronic disease with a glomerular filtration rate <30 mL/min/1.73 m^2; and (4) age <18 years (figure 1). Patients' referral diagnoses were based on a physical examination, 12-lead ECG, laboratory values, comorbidities, and coronary angiography and echocardiography, and these results were provided to us by the referring physician. All patients gave their written informed consent for data collection and research purposes.

Cardiovascular magnetic resonance (CMR) protocol

CMR examinations were performed on a 1.5 Tesla MRI scanner (Achieva, Philips Medical Systems). The CMR protocol contained the following sequences: cine movie images, T2-weighted spectral inversion recovery (SPIR) images for myocardial oedema and late gadolinium enhancement (LGE) images for necrosis/fibrosis. Functional imaging was performed using balanced steady-state free precession cine sequences in four-chamber, two-chamber and three-chamber long axis (LA) views and a short axis (SA) stack from the cardiac base to apex, with full coverage of the left and right ventricle. Wall motion abnormalities (WMAs) were assessed. LGE images were acquired using a segmented inversion recovery sequence 10–15 min after the administration of an intravenous bolus of 0.15 mmol/kg of the gadolinium-based contrast agent gadobutrol (Gadovist, Bayer-Schering Pharma) at a rate of 2–3 mL/s through an antecubital intravenous line. The inversion time was adjusted to provide optimal suppression of normal myocardium.

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Image analysis

For all participating patients, the CMR studies were analysed and reported under the supervision and with the final approval of at least one of two consultants with >10 years of experience in performing CMR with a European Association of Cardiovascular Imaging CMR level 3 certification. The visual and parametric information obtained from cine movies was combined with T2-weighted and LGE images to establish the final diagnosis. Based on the CMR findings, patients received one of the following diagnoses: acute MI, acute myocarditis, Takotsubo syndrome (Takotsubo) or normal CMR. A diagnosis of MI was based on an increased or decreased T2 signal, perfusion defect, microvascular obstruction and an ischaemic LGE pattern (subendocardial to transmural).[2 12] Acute myocarditis was defined as an increased T2 signal showing myocardial oedema on SPIR images and the presence of LGE in a patchy non-ischaemic pattern with a subepicardial and/or midmyocardial extent.[13] The diagnosis of Takotsubo was established based on regional WMAs extending beyond a single coronary territory with no extensive LGE and potential myocardial oedema.[14] If we did not find any abnormalities, including myocardial oedema, necrosis/fibrosis or WMA, the patient was characterised as having normal CMR. Patients with an LGE pattern not specific to any disease were defied as inconclusive. LV functional and morphological parameters were calculated from the SA stack using MedisSuite/QMass Software (Medis Medical Imaging Software, The Netherlands). The CMR-based diagnosis was recorded and subsequently compared with the referring diagnosis to investigate the diagnostic impact of CMR. Quantitative deformation assessment was obtained using cine images and analysed with the feature-tracking application of Medis QStrain software by an experienced reader. Endocardial contour detection was performed manually on LA and SA cine images in end-systolic and end-diastolic phases as described by Pedrizzetti *et al*.[15] Global strain values, including longitudinal (GLS), circumferential (GCS) and radial (GRS) LV strain parameters, were measured. For global dyssynchrony measurement, mechanical dispersion (MD) was assessed, defined as the SD of the time-to-peak circumferential (MDC) and longitudinal (MDL) strain of the LV segments and expressed as a per cent of the cardiac cycle. No patient was excluded from the analysis because strain measurements could not be performed. Interobserver variability in strain parameters was compared in a subgroup of randomly selected patients (n=100) that included 25 patients from each diagnosis group. Only strain parameters with an inter-rater agreement (kappa) higher than 0.6 were accepted for analysis; therefore, all strain parameters concerning myocardial rotation and MD derived from radial strain were excluded.

Study endpoint

The endpoint of our study was all-cause mortality, which was ascertained based on both available medical records and the National Health Insurance Fund of Hungary (Hungarian acronym: NEAK) database, which includes up-to-date information on deaths. The NEAK, as a central agency, performs functions specified by legislation, maintains records and financial accounts and fulfils reporting obligations. As part of the core activity of the NEAK, the institute provides information on health insurance and its current status.

Data management and statistical analysis

Patient data, including risk factors, laboratory values, standard CMR and CMR-based strain parameters, are described by the CMR-based diagnostic groups. Continuous variables that had a normal distribution based on Shapiro-Wilk's test are presented as the mean and SD, and those with a non-normal distribution are presented as the median and 95% CI. Categorical variables are presented as frequencies and percentages. Comparisons of the means of continuous variables with normal distribution were performed using one-way analysis of variance and the Scheffe test for post hoc pairwise comparisons. The distributions of non-normal continuous variables were compared by Kruskal-Wallis tests. The χ^2 test was applied to compare the distributions of categorical data. Univariate associations of time variables with mortality were visualised using Kaplan-Meier curves and compared by the log-rank test. Univariate and multivariate associations of risk factors and covariates with mortality were assessed using Cox proportional hazard regression analyses. Variables with values of $p<0.05$ in univariate analyses were candidates for multivariate analysis. Probability values were two sided, and values of $p<0.05$ were considered significant. MedCalc software and R Studio were used for the statistical analysis and graph generation.

Patient and public involvement in the study

It was not possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

RESULTS

The diagnostic impact of CMR

During the 11-year study period, we analysed the data of 255 patients (42±16 years, 165 men) with troponin-positive acute chest pain who underwent CMR examination within 7 days following coronary angiography with non-obstructed coronary arteries (figure 1). The mean time delay between the coronary angiography and CMR examination was 2.7 days. CMR provided a final diagnosis in 86% of the cases: MI (n=55), acute myocarditis (n=136), Takotsubo (n=26) and myocardial contusion (n=1).[16] CMR demonstrated a structurally normal heart in 33 patients. The diagnosis of four patients remained inconclusive after CMR. In these four patients, the examination raised the suspicion of sarcoidosis, atypical myocarditis or amyloidosis. Further examinations revealed Churg-Strauss syndrome, Amyloid light-chain amyloidosis, autoimmune disease affecting multiple organs or remaining inconclusive. Given the combined small number of patients with myocardial contusion and uncertain diagnosis (n=5), these patients were excluded from the statistical analysis. The distributions of CMR diagnoses in patients with normal arteries and those with signs of atherosclerosis are shown in table 1.

In 61% of the MI (or MINOCA) patients, coronary angiography was normal. Figure 2 shows the distributions of the referral diagnoses as they relate to the CMR-based diagnosis. Overall, CMR confirmed the referral diagnosis in 48% and overrode it in 16% of the patients. CMR identified a diagnosis in 79% of those with an uncertain referral diagnosis (n=71). The most common referral diagnosis was myocarditis (n=155); however, CMR revealed MI in 21% of these patients. A comparison was performed between patients with a referral diagnosis of myocarditis in whom the CMR confirmed this suspicion (n=106) and those who were diagnosed with MI (n=32). The results showed that, compared with patients with myocarditis, patients with MI were slightly older (44±15 vs 33±9; $p<0.001$) and a higher percentage had hypertension (41% vs 14%; $p=0.002$). Takotsubo patients were referred to CMR as Takotsubo (n=13), myocarditis (n=3) or uncertain (n=10). Overall, CMR influenced patient management in 46% of the cases. Most

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Table 1 Description of the sample

	Total (n=250)	Acute myocardial infarction (n=55)	Acute myocarditis (n=136)	Takotsubo syndrome (n=26)	Normal CMR (n=33)	P value
Patient characteristics and risk factors						
Age (years)	42±16	48±15	34±10	67±10	49±14	<0.001
Gender						
Female	85 (34)	27 (49)	16 (12)	26 (100)	16 (49)	<0.001
Male	165 (66)	28 (51)	120 (88)	0 (0)	17 (51)	
Time between coronary angiography and CMR (days)	2.7±1.9	2.9±1.9	2.4±1.9	3.4±2.1	2.8±2.0	NS (0.062)
Coronary angiography						
Normal	178 (71)	34 (62)	112 (82)	14 (54)	19 (58)	<0.001
Signs of atherosclerosis	72 (29)	21 (38)	24 (18)	12 (46)	14 (42)	
BMI (ttkg/m^2)	*25 (5)*	*25 (6)*	*26 (5)*	*24 (4)*	*26 (7)*	NS (0.319)
Hypercholesterinaemia	55 (36)	20 (49)	14 (20)	9 (60)	12 (48)	0.001
Hypertension	67 (31)	24 (47)	15 (13)	11 (48)	17 (57)	<0.001
Diabetes mellitus	12 (6)	3 (6)	3 (3)	4 (17)	2 (7)	0.047
Current smoking	47 (22)	15 (31)	24 (22)	3 (13)	5 (17)	NS (0.267)
Reported infection and/or fever before the acute chest pain	77 (37)	7 (15)	64 (56)	1 (5)	5 (20)	<0.001
ST-segment elevation present	145 (61)	28 (52)	90 (69)	13 (52)	14 (44)	0.016
Laboratory values						
Hs Troponin T (ng/L)	*550 (905)*	*954 (1990)*	*689 (759)*	*373 (872)*	*93 (185)*	<0.001
CK-MB (U/L)	*39 (49)*	*46 (52)*	*46 (50)*	*34 (22)*	*21 (11)*	0.005
CRP (mg/L)	*16 (52)*	*5 (10)*	*31 (59)*	*4 (22)*	*9 (26)*	<0.001
Creatinine (mmol/L)	*71 (20)*	*68 (20)*	*73 (19)*	*69 (27)*	*67 (21)*	NS (0.573)
GFR						
>60	149 (95)	35 (95)	85 (99)	9 (64)	20 (0)	<0.001
<60	8 (5)	2 (5)	1 (1)	5 (36)	0 (0)	
CMR characteristics						
LVEF (%)	54±8	55±8	55±7	43±9	59±9	<0.001
LVEDVi (mL/m^2)	89±14	86±15	92±13	92±13	79±12	<0.001
LVESVi (ml/m^2)	41±11	40±14	42±9	52±13	33±6	<0.001
LVSVi (ml/m^2)	48±9	47±8	50±9	39±8	46±7	<0.001
LVMi (g/m^2)	60±12	56±12	63±12	57±12	56±10	<0.001
Oedema present	199 (80)	53 (96)	130 (96)	16 (64)	0 (0)	<0.001
LGE present	196 (78)	55 (100)	136 (100)	3 (12)	0 (0)	<0.001
GLS (%)	−19±5	−19±4	−20±3	−11±6	−21±4	<0.001
GCS (%)	−24±6	−23±6	−25±5	−17±5	−29±5	<0.001
GRS (%)	47±14	48±12	48±11	26±13	58±12	<0.001
MDL (%)	13±6	15±5	12±4	16±6	14±5	<0.001
MDC (%)	8±5	11±5	6±3	16±4	7±4	<0.001

Values are mean±SD, n (%) or median (IQR) in italic are provided due to considerable skewness of the given variable.

BMI, body mass index; CK-MB, creatinine kinase myocardial band; CMR, cardiac magnetic resonance; CRP, C reactive protein; GCS, global circumferential strain; GFR, glomerular filtration rate; GLS, global longitudinal strain; GRS, global radial strain; 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; MDC, mechanical dispersion from circumferential strain; MDL, mechanical dispersion from longitudinal strain.

importantly, in newly diagnosed patients with MI, the medication was changed. Based on an unexpected diagnosis of MI in 51, Takotsubo in 13 and myocarditis in 30 patients, CMR led to lifestyle changes and/or closer surveillance.

Patient characteristics, laboratory values, CMR parameters and strain analysis

While the prevalence of traditional cardiovascular risk factors was relatively low, certain significant differences in patient characteristics were observed (table 1). Overall, the mean LVEF remained preserved with normal LV volumes (table 1). Takotsubo patients showed lower LVEF and higher left ventricular end-systolic volume index than was found in any other group. Among strain parameters, the following differences were observed: Takotsubo patients had significantly higher (ie, less negative) GLS and GCS and lower GRS values than were found in the other groups (table 1, online supplementary figure 1). A comparison of MI and myocarditis patients showed there was no significant difference regarding their GLS, GCS and GRS values; however, global dyssynchrony parameters, especially MDC, were significantly higher in the MI group. Figure 3 demonstrates the strain analysis and the patterns of LGE in MI, myocarditis and Takotsubo patients.

Follow-up and mortality

Overall, the 30-day, 1-year and 4-year mortality rates were 0.4%, 1.8% and 5.9%, respectively (table 2).

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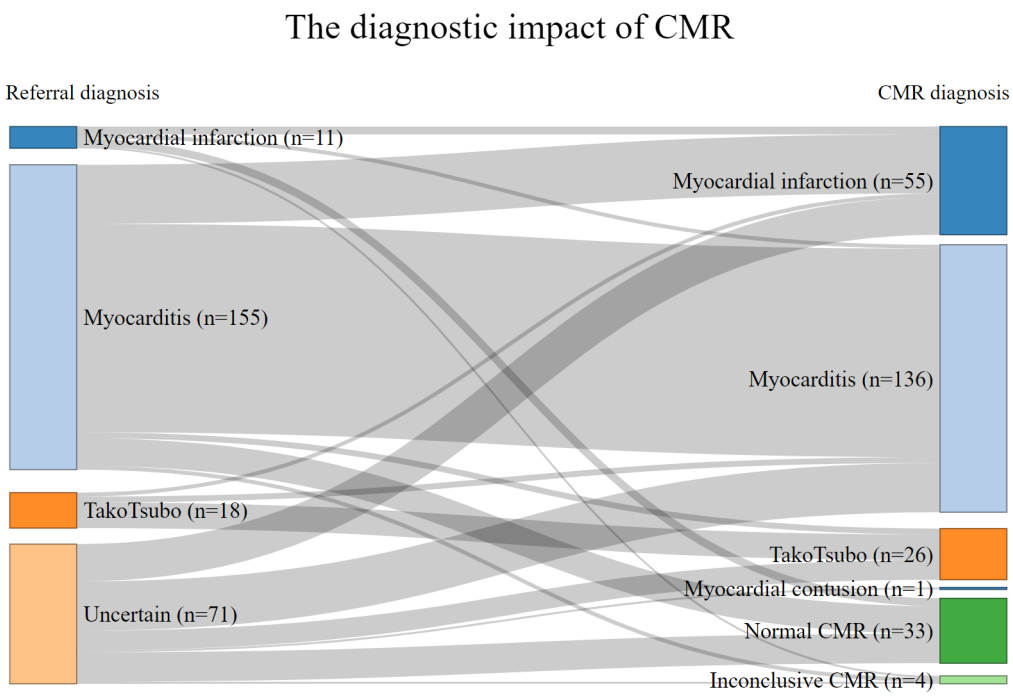

Figure 2 The diagnostic impact of early CMR. Among patients with troponin-positive acute chest pain and non-obstructed coronary arteries, an early CMR (≤7 days) established a diagnosis in 86% of the patients. CMR confirmed the referral diagnosis in 48% and overrode it in 16%, identified the aetiology in 22%, revealed a structurally normal heart in 13% and remained Inconclusive in 1% of the patients. CMR, cardiovascular magnetic resonance.

The 4-year all-cause mortality rates by the diagnosis of MI, myocarditis, Takotsubo or normal CMR in these patients were 10.2%, 1.6%, 27.3% and 0%, respectively. Figure 4 shows Kaplan-Meier survival analysis figures and the corresponding log-rank tests. There was a strong association between a CMR diagnosis and mortality (log-rank test: 24, p<0.0001). Takotsubo and MI as the diagnosis, age, history of hypertension or diabetes, female sex, LVEF, left ventricular stroke volume index

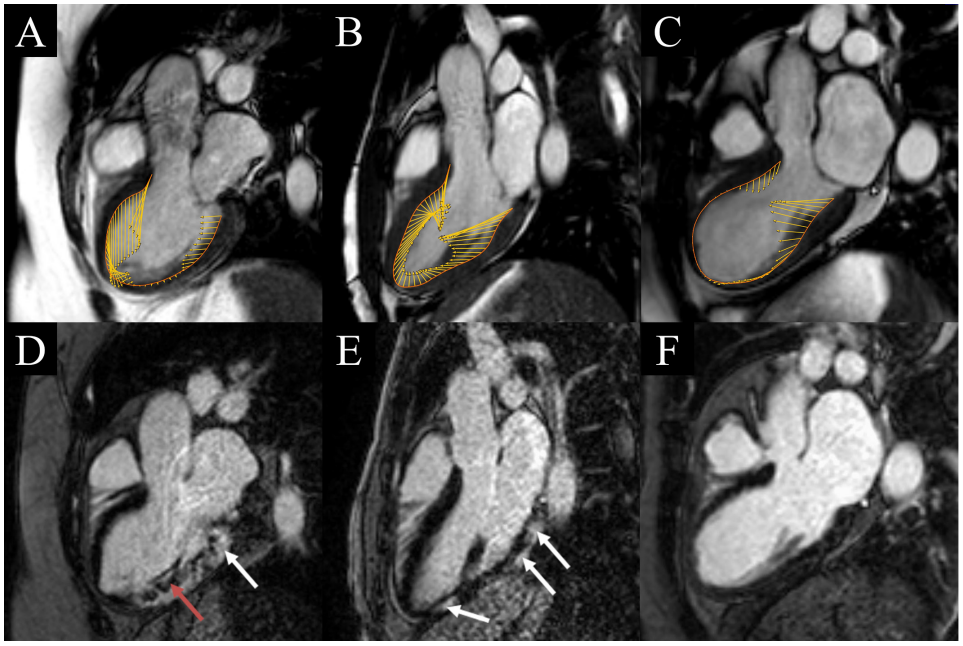

Figure 3 CMR images of patients with myocardial infarction (A and D), myocarditis (B and E) and Takotsubo syndrome (C and F). CMR cine movie images depict endocardial contours during strain analysis (A–C). Late gadolinium-enhanced images showing transmural necrosis (white arrow) and microvascular obstruction (red arrow) in patients with acute myocardial infarction (D); patchy, midmyocardial necrosis in myocarditis (white arrows) (E); and the lack of LGE in Takotsubo syndrome (F). CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement.

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Table 2 Follow-up and mortality

	Total (n=250)	Acute MI (n=55)	Acute myocarditis (n=136)	Takotsubo syndrome (n=26)	Normal CMR (n=32)	P value
Follow-up time (in days)	1394±985	1345±920	1503±1021	1314±1081	1090±807	NS (0.162)
Early mortality (1 month)	1 (0.4)	0 (0)	0 (0)	1 (4)	0 (0)	0.0343
One-year mortality	4 (1.8)	1 (2)	0 (0)	3 (13.6)	0 (0)	<0.001
Four-year mortality	13 (5.9)	5 (10.2)	2 (1.6)	6 (27.3)	0 (0)	<0.001
Deaths per patient-year (%)	1.4	2.5	0.4	6.4	0	*†

Values are n (%) or mean values with ±SD.
*CI for deaths per patient year.(MI:0.008-0.05748; Myocarditis:0.0004-0.0129; TakoTsubo:0.0234-0.1389; TakoTsubo:0.0234-0.1389)
†Pairwise comparison of death per patient (MI versus myocarditis: p=0.0073; MI versus normal CMR: p=0.1184; MI versus Takotsubo: p=0.1025; Myocarditis versus normal CMR: p=0.552; Myocarditis versus Takotsubo: p<0.0001; TakoTsubo versus normal CMR: p=0.0119)
CMR, cardiac magnetic resonance; MI, acute myocardial infarction; Myocarditis, acute myocarditis; TakoTsubo, Tako-Tsubo syndrome.

(LVSVi) and most of the investigated strain parameters, including GLS, GCS, GRS and MDC, were significant univariate predictors of mortality (table 3).

In the multivariate model, hypertension and a strain-derived dyssynchrony parameter, MDC, were independent predictors of mortality.

Correlations of the variables are shown in online supplementary 2a-c.

DISCUSSION

In our study of a large single-centre cohort of the systematic application of CMR (≤7 days) in patients with troponin-positive acute chest pain and non-obstructed coronary arteries, we found the following:

1. Performing CMR within a suitably narrow time window can provide a diagnosis in up to 86% of this patient population.

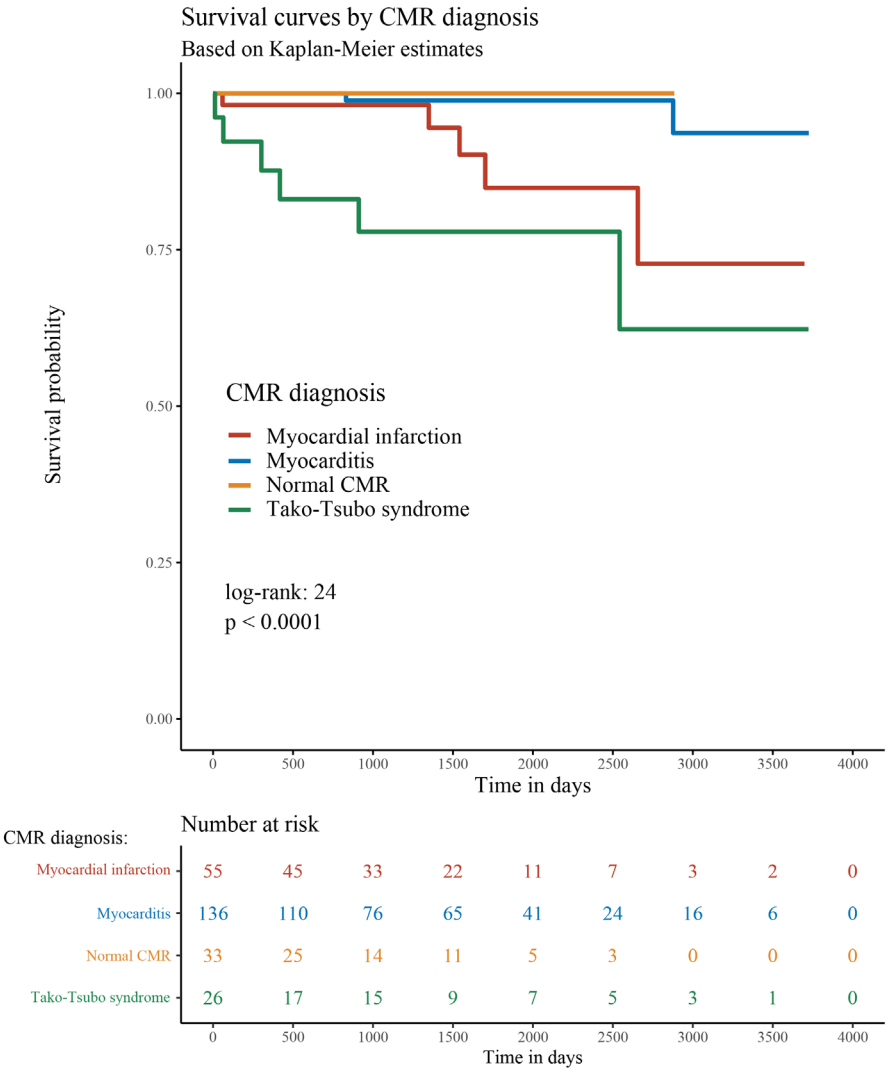

Figure 4 Kaplan-Meier curves showing the risk of mortality by CMR diagnosis. CMR, cardiovascular magnetic resonance.

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Table 3 Univariable and multivariable association for mortality

	Univariable analysis				Multivariable analysis			
			95% CI				95% CI	
	P value	HR	Lower	Upper	P value	HR	Lower	Upper
MI as diagnosis	**0.0190**	7.1417	1.381	36.930	0.8626	1.2445	0.104	14.830
Takotsubo as diagnosis	**0.0005**	17.5201	3.531	86.938	0.4053	5.9911	0.088	406.122
Age	**<0.0001**	1.0880	1.047	1.131	0.7570	1.0117	0.940	1.089
Sex	**0.0256**	3.6022	1.169	11.103	0.3932	0.2884	0.016	5.007
Diabetes mellitus	**0.0157**	5.0467	1.357	18.765	0.3700	2.4772	0.341	18.000
Hypertension	**0.0004**	15.630	3.451	70.792	**0.0061**	26.7828	2.552	281.058
BMI	0.2513	0.9265	0.813	1.056				
No ST-segment elevation present at admission	0.2269	1.9693	0.656	5.912				
Troponin T value	0.6159	0.9999	0.999	1.000				
CK-MB value	0.8153	0.9982	0.984	1.013				
CRP value	0.4718	1.0028	0.995	1.011				
LVEF	**0.0057**	0.9332	0.898	0.982	0.5634	1.0789	0.834	1.396
LVEDVi	0.5777	0.9881	0.947	1.031				
LVESVi	0.0935	1.0350	0.994	1.076				
LVSVi	**0.0065**	0.9336	0.889	0.981	0.5258	0.9481	0.804	1.118
Oedema present on CMR	0.5548	0.6749	0.183	2.488				
LGE present on CMR	0.0964	0.3867	0.126	1.185				
GLS	**0.0020**	1.1266	1.045	1.215	0.5861	1.1257	0.735	1.724
GCS	**0.0018**	1.1356	1.048	1.230	0.2594	1.2177	0.8651	1.715
GRS	**0.0039**	0.9513	0.920	0.984	0.3388	1.1038	0.902	1.351
MDC	**<0.0001**	1.2141	1.109	1.329	**0.0351**	1.2542	1.0160	1.548
MDL	0.2011	1.0803	0.963	1.212				

Significant values are shown in bold.
BMI, body mass index; CK, creatinine kinase; CMR, cardiac magnetic resonance; CRP, C reactive protein; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LGE, late gadolinium enhancement; LVEDVi, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, felt ventricular end systolic volume index; LVSVi, left ventricular stroke volume index; MDC, mechanical dispersion from circumferential strain; MDL, mechanical dispersion from longitudinal strain; MI, myocardial infarction.

2. The aetiologies in these patients differ considerably, and the prognosis of the diagnosis groups may vary.
3. Takotsubo and MI as a diagnosis, age, hypertension, diabetes, female sex, LVEF, LVSVi and most of the investigated strain parameters were univariate predictors of mortality; however, in the multivariate analysis, only hypertension and MDC remained independent predictors of mortality.

Studies with a longer delay between coronary angiography and CMR have demonstrated variable success rates (27%–74%) in identifying the diagnosis in patients with a working diagnosis of MINOCA. Due to the temporary nature of certain alterations, this may lead to the misclassification of cases.[7 17] All patients in our study underwent CMR within 7 days (mean of 2.6 days) after coronary angiography, and we were able to provide a definite diagnosis in almost 90% of these cases, akin to what Bhatia *et al*[18] found in their study with a similar cohort size (215 patients) and mean time delay to CMR (3.68 days). Our study therefore corroborates the finding that early CMR has an excellent diagnostic yield in these patients and leads to the reclassification of a high proportion of cases.[3 4 18–20] The proportion of MI (or MINOCA) patients in our study (22%) was slightly higher than that reported by Kawecki *et al* (9%) and some other studies that reported MI diagnosed by CMR in patients with a working diagnosis of MINOCA but similar to those found by Bhatia *et al* (22%) and Dastidar *et al* (25%).[7 18 19 21 22] Notably, our patient population is slightly younger than those in previous studies. This may be related to the high proportion of patients with a clinical suspicion of acute myocarditis; however, among these patients, CMR indicated MI in 21% of the patients, which is not a negligible portion.

As reported previously, MINOCA patients have slightly better prognoses than those with obstructive coronary artery disease; however, recent studies based on the SWEDEHEART registry showed that these patients have unfavourable outcomes.[5 6 23] Most studies that have assessed the prognosis of MINOCA treat this group as homogenous, and this confounding factor may account for the wide variation observed in 1-year mortality, which ranges from 0.6% to 12.3%.[5 24–26] First, patient groups are heterogeneous concerning their ages—the low mortality (0.6%) found by Safdar was observed in a younger (aged 18–55 years) patient population, while the high mortality (12.3%) observed by Dreyer *et al*[24] was found among patients aged >65 years. Second, the group of patients with a working diagnosis of MINOCA is not homogenous. Indeed, Ferreira and Sechtem *et al* emphasised the heterogeneity of the diagnoses obtained in patients with a working diagnosis of MINOCA in their recent editorials. They concluded that the use of CMR may refine the diagnostic labelling of such patients, thereby influencing treatment strategies and patient prognosis.[3 4] Our results are comparable with those presented in a recent study by Dastidar *et al*,[7] who used CMR systematically at a median of 37 days. Their findings reinforced the diagnostic and prognostic value of CMR in these patients. However, we found that mortality was higher in the MI (or MINOCA) group (10% vs 4%) over a slightly longer follow-up (3.5 vs 4 years). Additionally, they found a heterogeneous group of cardiomyopathies. We found that the mortality

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rate was slightly higher per patient-year among our Takotsubo patients than was reported in Templin *et al*,[27] who described the long-term outcomes of the Takotsubo patients included in the InterTAK registry (6.4% vs 5.6%).

In our univariate analysis, Takotsubo and MI as a diagnosis, many risk factors and CMR parameters, notably LVEF, LVSVi and most of the investigated strain parameters, were predictors of mortality. However, in our multivariate analysis, only hypertension and a strain-derived dyssynchrony parameter were significant predictors of all-cause mortality. The reason for this might be confounding among the candidate predictor variables. For example, in the bivariate correlations, hypertension showed only a marginal correlation with any other risk factors or CMR parameters. This might explain why hypertension was both a univariate and a multivariate predictor, consistent with the previous findings of large national registries that reported prognoses of MINOCA patients.[5 28] Other parameters, including older age and female sex, were significant predictors of mortality in univariate but not multivariate analysis. However, MDC was correlated with patient age, sex, Takotsubo or MI as the CMR diagnosis, and many CMR parameters, including LVEF and all of the strain parameters, all of which were significant univariate predictors. Our findings indicate that CMR has an important role in the diagnosis of patients with a working diagnosis of MINOCA and may provide useful additional parameters in the risk stratification of these patients.

CONCLUSIONS

Among patients with troponin-positive acute chest pain and non-obstructed coronary arteries, CMR performed within 7 days established a diagnosis in 86% of the patients. The aetiology in these patients varies considerably, and the prognosis of different diagnosis groups may differ. Furthermore, with the implementation of strain analysis, CMR may provide additional prognostic factors. As such, CMR may have an important role in the risk stratification of these patients.

Key messages

What is already known on this subject?

- The position paper by the European Society of Cardiology on myocardial infarction with non-obstructive coronary arteries (MINOCA) suggested the use of cardiac magnetic resonance (CMR) imaging in patients with a working diagnosis of MINOCA.

What might this study add?

- Among patients with troponin-positive acute chest pain and non-obstructed coronary arteries, CMR performed within 7 days established a diagnosis in 86% of the patients. Their aetiologies differed considerably, and the prognosis of different diagnosis groups may vary.

How might this impact on clinical practice?

- CMR may enable clinicians to establish the proper diagnosis and provide additional prognostic factors, which could enhance the personalised assessment of prognosis in patients with troponin-positive acute chest pain and non-obstructed coronary arteries.

LIMITATIONS

One limitation is that this was a single-centre study with a relatively limited sample size by diagnosis group, which might limit the generalisability of our prognostic conclusions. Although our study was designed to represent a real-world population, we excluded patients with contraindications to CMR, which might have resulted in an underestimation of our HRs. Approximately one-third of patients were referred from other hospitals; therefore, their clinical data were provided by the referring clinicians. During the data collection (2009–2019), all patients referred for CMR had one of the mentioned ECG alterations; therefore, our results are only applicable to patients with ECG changes. Due to the retrospective nature of the study, blinded interpretation of the CMR images was not performed. Moreover, although coronary vascular imaging modalities, intravascular ultrasound and optical coherence tomography can provide insight into plaque disruption or spontaneous coronary artery dissection,[2] these modalities were not included in our study.

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Contributors HV and LS: involved in data collection, study design, manuscript preparation and statistical analysis. ZD, CC, AT, FIS and GB: involved in data collection and manuscript review. VAG: involved in statistical support and manuscript preparation. DB and BM: involved in study design and manuscript review.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethical approval was obtained from the Hungarian National Institute of Pharmacy and Nutrition (OGYEI/29206-4/2019) in correspondence with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Please contact the corresponding author.

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Cardiac Magnetic Resonance Findings in Patients Recovered From COVID-19

Initial Experiences in Elite Athletes

A new study by Puntmann et al. (1) investigating an unselected group of 100 middle-aged patients who had recently recovered from coronavirus disease 2019 (COVID-19) without cardiac symptoms, suggests that an overwhelming 78% of the cases had cardiovascular involvement detectable by cardiovascular magnetic resonance (CMR) imaging. However, it is unknown if there is a cardiac involvement in otherwise healthy young patients after their recovery from COVID-19, especially in elite athletes who gradually return to vigorous exercise after the infection. Our aim was to describe the CMR results of elite athletes recently recovered from COVID-19 with mild to moderate symptoms to provide further insight into this currently very relevant topic (**Figure 1**).

A total of 12 professional, elite (>10 training h/week, participating in mixed sports) athletes (10 females and 2 males; median age: 23 years; interquartile range [IQR]: 20 to 23 years) after recovering from severe acute respiratory syndrome coronavirus 2 infection diagnosed by polymerase chain reaction on swab test, were referred to our center for CMR examination before returning to high levels of athletic performance. Patients underwent laboratory testing on the day of the CMR examination (n = 11). CMR examinations were performed on a 1.5T MR scanner (Magnetom Aera Siemens, Malvern, Pennsylvania). The protocol contained the following sequences: balanced steady-state free precession cine movie, T2-weighted spectral presaturation with inversion recovery, late gadolinium enhancement images, T1 mapping using long-T1 5(3)3 modified look locker inversion recovery, and T2 mapping using T2-prepared balanced steady-state free precession T2 mapping. Myocardial T1 and T2 relaxation times were measured conservatively in the septal midventricular myocardium using motion-corrected images. The study was approved by the Medical Research Council of Hungary. All participants gave their written informed consent for data collection and research purposes.

The median time from positive polymerase chain reaction to CMR was 17 (IQR: 17 to 19) days in 10 female athletes, and 67 and 90 days in 2 male athletes, respectively. Two athletes were asymptomatic during infection, 10 athletes had mild/moderate symptoms (e.g., taste and/or smell disturbance) (n = 7), weakness (n = 5), fever (n = 4), and sore throat and/or coughing (n = 4). Only 1 athlete had palpitation, and none had chest pain during infection. Nobody had significantly elevated C-reactive protein, N-terminal pro-B-type natriuretic protein, or high-sensitivity troponin T levels. None of the athletes showed myocardial or pericardial edema or pathological late gadolinium enhancement. We compared CMR parameters of the female athletes with age- and sex-matched healthy elite athletes (n = 15) and healthy controls (n = 15) using Kruskal-Wallis tests. There was no difference among the 3 groups (athletes recovered from COVID-19 vs. healthy athletes vs. healthy controls) regarding their left ventricular ejection fraction (58% [IQR: 55% to 61%] vs. 57% [IQR: 54% to 60%] vs. 60% [IQR: 58% to 63%]), and T2 mapping parameters (44 ms [IQR: 44 to 45 ms] vs. 44 ms [IQR: 44 to 45 ms] vs. 46 ms [IQR: 44 to 47 ms]). Left ventricular volumes (left ventricular end-diastolic volume index: 100 ml/m^2 [IQR: 95 to 110 ml/m^2] vs. 102 ml/m^2 [IQR: 98 to 109 ml/m^2] vs. 85 ml/m^2 [IQR: 80 to 89 ml/m^2]; $p < 0.001$) were elevated and T1 mapping (957 ms [IQR: 943 to 972 ms] vs. 957 ms [IQR: 951 to 976 ms] vs. 981 ms [IQR: 966 to 990 ms]; $p = 0.002$) values were lower in both groups of athletes compared to healthy controls, showing signs of cardiac remodeling in athletes, as described previously (2).

Our initial findings in a small group of elite athletes without comorbidities who recently recovered from COVID-19 showed no signs of cardiac involvement on CMR. Puntmann et al. (1) reported that CMR performed with median 71 days after COVID-19 diagnosis revealed cardiac involvement in 78% of the cases, with ongoing myocardial inflammation in 60% of patients. In their study, T1 mapping showed excellent discriminative value between COVID-19 patients and risk factor–matched controls, and a significant difference between home- and hospital-recovered patients. However, the publication by Huang et al. (3) found in a smaller sample of 26 COVID-19 patients with cardiac symptoms that patients with conventional CMR findings had higher T1 mapping compared to patients without conventional CMR findings and healthy controls, whereas there was no difference between the latter 2 groups.

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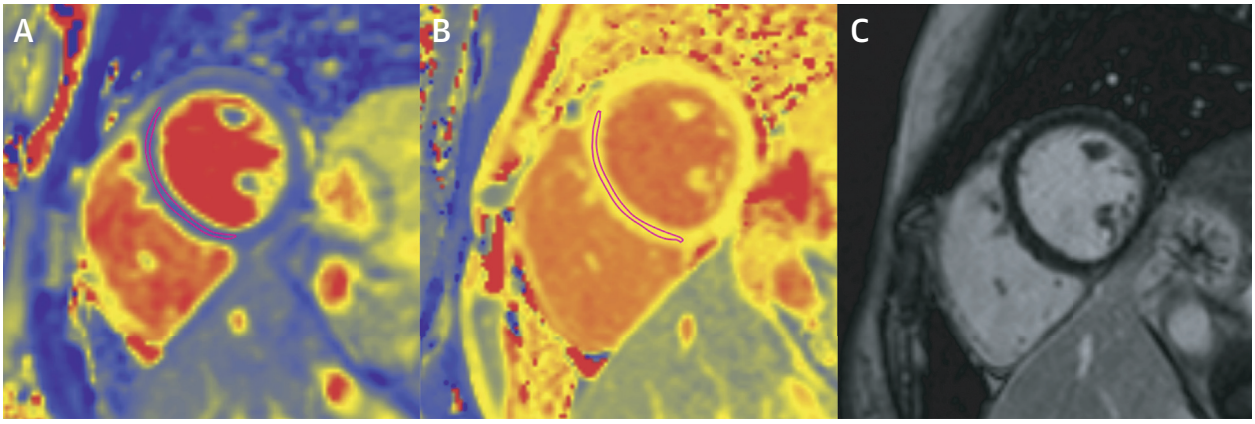
FIGURE 1 **Example of an Athlete Recovered From Coronavirus Disease 2019**



Cardiac magnetic resonance imaging showed normal T2 mapping (43 ms) **(A)** and T1 mapping (938 ms) **(B)** values and there was no pathological late gadolinium enhancement **(C)**.

As there are uncertainties regarding the cardiovascular consequences of COVID-19, our results do not support the use of routine CMR in troponin-negative, asymptomatic, or mildly symptomatic athletes who recover from this illness.

Our study is limited by the following factors: this small group of patients was younger compared to groups in previous studies and had mild symptoms. Additionally, for 2 male athletes the time from illness to CMR imaging was longer.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Is cardiac involvement prevalent in highly trained athletes after SARS-CoV-2 infection? A cardiac magnetic resonance study using sex-matched and age-matched controls

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ABSTRACT

Objectives To investigate the cardiovascular consequences of SARS-CoV-2 infection in highly trained, otherwise healthy athletes using cardiac magnetic resonance (CMR) imaging and to compare our results with sex-matched and age-matched athletes and less active controls.

Methods SARS-CoV-2 infection was diagnosed by PCR on swab tests or serum immunoglobulin G antibody tests prior to a comprehensive CMR examination. The CMR protocol contained sequences to assess structural, functional and tissue-specific data.

Results One hundred forty-seven athletes (94 male, median 23, IQR 20–28 years) after SARS-CoV-2 infection were included. Overall, 4.7% (n=7) of the athletes had alterations in their CMR as follows: late gadolinium enhancement (LGE) showing a non-ischaemic pattern with or without T2 elevation (n=3), slightly elevated native T1 values with or without elevated T2 values without pathological LGE (n=3) and pericardial involvement (n=1). Only two (1.4%) athletes presented with definite signs of myocarditis. We found pronounced sport adaptation in both athletes after SARS-CoV-2 infection and athlete controls. There was no difference between CMR parameters, including native T1 and T2 mapping, between athletes after SARS-CoV-2 infection and the matched athletic groups. Comparing athletes with different symptom severities showed that athletes with moderate symptoms had slightly greater T1 values than athletes with asymptomatic and mildly symptomatic infections ($p<0.05$). However, T1 mapping values remained below the cut-off point for most patients.

Conclusion Among 147 highly trained athletes after SARS-CoV-2 infection, cardiac involvement on CMR showed a modest frequency (4.7%), with definite signs of myocarditis present in only 1.4%. Comparing athletes after SARS-CoV-2 infection and healthy sex-matched and age-matched athletes showed no difference between CMR parameters, including native T1 and T2 values.

INTRODUCTION

The presence and extent of cardiac involvement in patients with COVID-19 are of great interest, especially among highly trained athletes returning to extreme physical activity after the infection. Emerging yet conflicting evidence has led to greater interest in cardiac magnetic resonance (CMR) imaging studies due to its ability to provide tissue-specific information non-invasively. A cohort study by Puntmann *et al*[1] using late gadolinium enhancement (LGE) and novel T1 and T2 mapping sequences showed myocardial involvement in an alarming 78% of middle-aged patients, raising serious concerns regarding their cardiac health. Approximately one-third of the alterations were solely based on mapping elevations; however, the exact diagnostic and prognostic impact of these contemporary techniques is less well understood than that of widely used techniques such as LGE.[2]

Recently published studies have evaluated cardiac involvement by CMR imaging in athletes who recovered after SARS-CoV-2 infection. Earlier data by Rajpal *et al*[3] and Brito *et al*[4] found a high prevalence of myocardial (15%) and pericardial (39.5%) inflammatory alterations among college athletes following SARS-CoV-2 infection. Subsequent publications reported a lower prevalence of cardiac involvement ranging from 0.7% to 3.0% in college athletes after SARS-CoV-2 infection.[5–7]

The most recent expert consensus statements regarding the screening of potential cardiac involvement in competitive athletes recovering from SARS-CoV-2 infection highlight the need for more robust data with the inclusion of appropriate control subjects.[8 9] Therefore, our study aimed to investigate cardiac involvement after SARS-CoV-2 infection in young competitive athletes using a comprehensive CMR imaging study, including tissue characterisation and feature-tracking strain analysis. We compared our results with those from healthy sex-matched and age-matched athletes and healthy sex-matched and age-matched less active controls.

METHODS

Study population

All athletes recovering from SARS-CoV-2 infection who were referred to our centre for CMR examination between July 2020 and February 2021 were consecutively included in this observational study (figure 1). SARS-CoV-2 infection was diagnosed by PCR on swab tests or by serum IgG antibody tests prior to CMR examination. We excluded athletes

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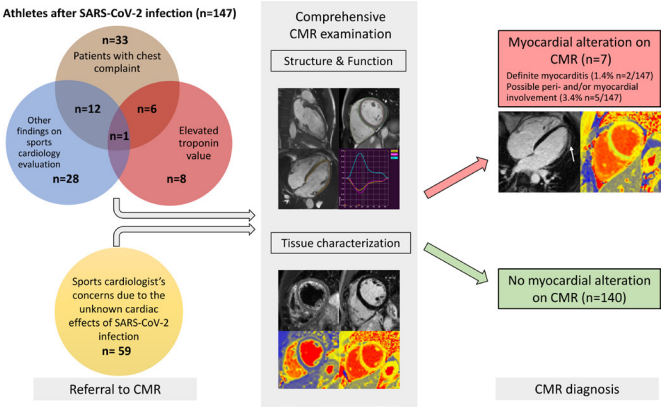

Figure 1 Central illustration. Athletes were referred for CMR by their cardiologists to evaluate the possible structural alterations caused by SARS-CoV-2 infection. CMR referral is summarised as follows: patients who had chest complaints (brown bubble), including chest pain, dyspnoea and palpitation; second, patients who had CMR due to elevated troponin levels (red bubble) with or without accompanying symptoms; third, due to other findings on sports cardiology evaluation (blue bubble) such as alterations on echocardiography and/or 12-lead-ECG examination; lastly, those referred to CMR due to the unknown cardiac effects of the infection (yellow bubble) despite having negative results on cardiology examination. All athletes underwent a comprehensive CMR examination that contained sequences to assess structural, functional (long-axis and short-axis cine images) and tissue-specific data (T2-weighted images, LGE, native T2 and T1 mappings). Overall, we found cardiac involvement on CMR in only seven patients. Only two presented with definite signs of myocarditis (red box, underneath white arrow showing subepicardial LGE). The majority of athletes had no alterations on their CMR (green box). CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement.

(1) aged <16 years and (2) performing <6 hours of training/week. Athletes were referred for CMR by their cardiologist to evaluate for possible structural alterations caused by SARS-CoV-2 infection, in most cases prior to their return to high levels of sports activity. Detailed information regarding patient referral to CMR is included in figure 1. All athletes completed a sports-specific questionnaire and a questionnaire regarding their SARS-CoV-2-related symptoms. Symptoms were assessed using the COVID-19 treatment guidelines published by the National Institutes of Health.[10] Asymptomatic SARS-CoV-2 infection was defined for individuals who tested positive for SARS-CoV-2 and had no symptoms consistent with COVID-19. Mild symptoms were defined as symptoms such as fever, cough, headache, loss of smell and/or taste but not more alarming signs, such as chest pain, dyspnoea and shortness of breath, which were categorised as moderate symptoms. Long-COVID-19 symptoms were persistent symptoms, mostly fatigue and palpitations, extending beyond 4 weeks after the initial infection. Data from the first 12 athletes with post-COVID-19 scanned in our institute published in Journal of the American College of Cardiology (JACC) imaging are incorporated in the current publication.[11]

Clinical data, including 12-lead ECG and high-sensitivity troponin T (hsTnT) were recorded a median of 1 day (0–7 days) prior to the CMR examination. The local laboratory cut-off value for detectable hsTnT was >2.99 ng/L and that for elevated hsTnT was >13.99 ng/L. All examinations were performed after an appropriate quarantine period (10 days).

CMR parameters were compared with those of sex-matched and age-matched healthy athletes (n=59) and healthy, less active controls (n=56). All healthy controls were scanned to establish normal values for the less active and athletic population without any suspicion of cardiovascular pathology prior to the COVID-19 pandemic (59%) or in athletes and volunteers who tested seronegative for the disease (41%). Athletes after SARS-CoV-2 infection and healthy control athletes both performed high levels of sport activity, the majority of them being professional athletes competing at national or international levels in mixed or endurance sports disciplines (table 1).[12] Healthy, less active controls performed <6 hours of sports activity/week. None of the participants reported a history of cardiovascular disease or consumption of illegal drugs. None of the athletes with post-COVID-19 received steroids during their illness.

CMR protocol

CMR examinations were performed on a 1.5 T MRI scanner (Magnetom Aera; Siemens Healthcare, Erlangen, Germany). A comprehensive CMR protocol was carried out, including cine movies, T2-weighted spectral presaturation with inversion recovery, T2 mapping using T2-prep balanced steady-state free precession (b-SSFP), T1 mapping using long-T1 5(3)3 and short-T1 5(3)3 modified look-locker inversion recovery and LGE imaging. Functional imaging was performed using b-SSFP cine sequences in four-chamber, two-chamber and three-chamber long-axis views and a short-axis (SA) stack from the cardiac base to apex with full coverage of the left ventricle (LV) and th right ventricle (RV). Overall, 139 athletes after SARS-CoV-2 infection and 15 healthy control athletes agreed to receive contrast agent. None of the healthy, less active controls were given contrast material. LGE images were acquired using a segmented inversion recovery sequence 10–15 min after the administration of an intravenous bolus of 0.15 mmol/kg gadolinium-based contrast agent gadobutrol (Gadovist, Bayer-Schering Pharma) at a rate of 2–3 mL/s through an antecubital intravenous line. The inversion time was adjusted to provide optimal suppression of normal myocardium.

Image analysis

All postprocessing analyses were performed using Medis Suite Software (Medis Medical Imaging Software, The Netherlands). LV and RV volumes, function and mass were calculated from the SA stack using artificial intelligence–based automated contour detection (autoQ application) with manual adjustments if required. Myocardial native T1 and T2 relaxation times were measured conservatively in the midventricular or basal septum (if the midventricular images were technically inadequate for analysis) of the myocardium using motion-corrected images[13] by an experienced observer blinded to the clinical data and group of a given subject. In case of suspicion of focal T1 mapping elevation, a separate region of interest in that area was drawn. Quantitative deformation assessment was obtained using cine images and analysed using the QStrain application. Global strain values, including LV longitudinal (global longitudinal strain (GLS)), circumferential, radial and RV longitudinal, and free wall strain, were measured. The interpretation of LGE was standardised as follows: myocardial and pericardial LGE was visually defined by two observers based on the presence and pattern. All images were visually assessed by two observers blinded to the clinical data of a given subject. In case of disagreement between the observers, a third CMR specialist with an European Association of Cardiovascular Imaging level 3 certificate was consulted for consensus. Non-ischaemic LGE was defined as midmyocardial and/or subepicardial myocardial LGE confirmed in two

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Table 1 Comparison between athletes after SARS-CoV-2 infection, healthy athlete controls and healthy, less active controls

	Athletes after SARS-CoV-2 infection (n=147)	Healthy athletic controls (n=59)	Healthy, less active controls (n=56)	Athletes after SARS-CoV-2 infection versus healthy athletic controls P values	Athletes after SARS-CoV-2 infection versus healthy, less active controls P values
Group characteristics					
Age (years), median (IQR)	23 (20–28)	25 (21–29)	24 (23–28)	0.146	0.062
Sex: female, N (%)	53 (36)	20 (34)	20 (36)	0.771	0.864
Body surface area (m^2), average ±SD	2±0.2	2±0.3	1.9±0.2	0.413	0.003
Heart rate (beats/min), median (IQR)	60 (53–69)	62 (56–72)	71 (63–84)	0.032	<0.001
Degree of training (hours/week), median (IQRS)	15 (12–22)	19 (15–22)		0.024	
Sport discipline, N (%)				0.077	
Skill	2 (1)	0 (0)			
Power	9 (6)	9 (15)			
Mixed	108 (74)	35 (60)			
Endurance	28 (19)	15 (25)			
Member of a national team, N (%)	87 (60)	52 (91)		<0.001	
Member of an Olympic team, N (%)	17 (12)	15 (26)		0.014	
CMR parameters					
Standard left and right ventricular parameters					
LVEF (%), median (IQR)	57 (54–60)	56 (53–60)	59 (57–62)	0.473	<0.001
LVEDVi (mL/m^2), median (IQR)	111 (100–123)	111 (102–122)	91 (83–100)	0.523	<0.001
LVESVi (mL/m^2), median (IQR)	48 (40–55)	47 (43–53)	38 (34–42)	0.52	<0.001
LVSVi (mL/m^2), median (IQR)	63 (58–69)	64 (58–68)	54 (50–59)	0.685	<0.001
LVMi (g/m^2) median (IQR)	58 (49–65)	59 (50–73)	47 (39–51)	0.199	<0.001
RVEF (%), median (IQR)	56 (53–59)	55 (52–58)	57 (54–61)	0.14	0.014
RVEDVi (mL/m^2), median (IQR)	110 (99–121)	113 (103–127)	90 (79–103)	0.119	<0.001
RVESVi (mL/m^2), median (IQR)	48 (41–55)	50 (44–59)	38 (33–47)	0.055	<0.001
RVSVi (mL/m^2), median (IQR)	61 (56–67)	63 (57–68)	53 (47–58)	0.229	<0.001
Global left and right ventricular strain					
LV-GLS (%) median (IQR)	−21 (−23 to −19)	−20 (−23 to 19)	−22 (−24 to −20)	0.942	<0.001
LV-GCS (%), average ±SD	−28±4	−28±4	−31±3	0.426	<0.001
LV-GRS (%), median (IQR)	52 (46–60)	50 (45–58)	56 (53–62)	0.609	<0.001
RV-GLS (%), average ±SD	−24±4	−24±3	−25±4	0.691	0.21
Parametric mapping					
T1 mapping (ms), median (IQR)	958 (939–970)	955 (934–973)	972 (960–987)	0.564	<0.001
T2 mapping (ms), median (IQR)	45 (43–46)	44 (43–46)	44 (43–45)	0.196	0.215

CMR, cardiac magnetic resonance; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LEDVi, left ventricular end diastolic volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end systolic volume index; LVMi, left ventricular mass index; RV, right ventricular; RVEDVi, right ventricular end diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end systolic volume index; RVMi, right ventricular mass index; SLVi, left ventricular stroke volume index.

perpendicular views. Pericardial involvement was reported if the pericardium showed definite LGE and the thickness of the pericardium was >2 mm regardless of pericardial oedema. Hinge point fibrosis was defined as a small volume of focal LGE confined to the inferoseptal segment, where the RV attaches to the septum. We classified cardiac involvement as definite in case of CMR T1 abnormality or LGE showing pathological pattern and CMR T2 abnormality and one or more supporting findings such as decreased LV ejection fraction or elevated troponin level. Possible pericardial/myocardial involvement was reported when we found (1) mild CMR T1 abnormality or the presence of LGE with normal T2, or (2) mildly elevated T1 and T2 mapping with no LGE or other supporting findings.

Follow-up

We performed midterm follow-up using the institutional electronic database for the patients who returned to our clinic, and we contacted the other athletes via telephone. Athletes completed a questionnaire regarding any ongoing symptoms, their ability to return to high sports activity levels, and their overall experience during the CMR examination. We offered a follow-up cardiological examination, including a CMR scan at our institution, to all athletes reporting reinfection with SARS-CoV-2. All athletes with definite or possible myocardial alteration on their baseline scan were contacted and offered a follow-up CMR examination.

Data management and statistical analysis

The Shapiro-Wilk test was applied to test the normality of our data. Continuous variables showing a normal distribution are presented as the mean and SD, and those showing a non-normal distribution are reported as medians and IQRs. Categorical variables are presented as frequencies and percentages. Comparisons between participant groups were conducted using independent samples t-tests and Mann-Whitney U tests as appropriate. Non-normal continuous variables were compared by the Kruskal-Wallis test. χ^2 tests were applied to compare the distributions

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of categorical data. Associations were assessed using Spearman's rank correlation analyses. Probability values were two-sided, and p values of <0.05 were considered significant. Elevated T1 and T2 values were defined based on the sequence-specific cut-offs of 2 SDs above the respective means of the healthy, sex-matched and age-matched athlete controls (male athletes: T1: 986 ms, T2: 46 ms; female athletes: T1: 1001 ms, T2: 49 ms). MedCalc software V.18.11 (Belgium) and RStudio V.1.3.1.093 (RFoundation, Austria) were used for statistical analysis and graph generation. All data are available on reasonable request.

RESULTS

Overall, 147 (94 male, median 23, IQR 20–28 years) athletes with prior SARS-CoV-2 infection were included in our study. They were asymptomatic (n=19) or experienced mild (n=80), moderate (n=43) or long-COVID-19 (n=5) symptoms, and none of them required hospital treatment. CMR imaging was performed at a median of 32 days after a positive PCR test. Overall, 4.7% (n=7) of patients had alterations in their CMR scans, and none of these athletes were asymptomatic. The CMR findings were as follows: LGE showing a non-ischaemic pattern and elevated native T1 mapping consistent with acute myocarditis as per the Lake Louise criteria (n=1); LGE showing a nonischaemic pattern consistent with previous myocarditis with only mildly elevated T2 values (n=1); non-specific nonischaemic LGE (n=1); slightly elevated T1 and T2 values with no pathological LGE (n=2); isolated, slightly elevated T1 value (n=1); and pericardial involvement (n=1). All athletes with definite (n=2) or possible (n=5) myocardial or pericardial alterations were referred to CMR examination based on the clinical suspicion of myocardial involvement as detailed in table 2. HsTnT recorded in our institute was elevated in 4.5% of the cases (n=6/133); among these patients, only one had myocardial alteration on CMR.

We found hinge point fibrosis in 32% (n=44) of the athletes after SARS-CoV-2 infection, which we reported as non-pathological. Fifteen healthy control athletes received contrast material. The proportion of hinge point fibrosis was similar in athletes after SARS-CoV-2 infection (44/139, 32%) and healthy control athletes (6/15, 40%; p=0.513).

Table 1 shows the comparison between highly trained athletes with prior SARS-CoV-2 infection, healthy athletic controls and healthy less active controls. We found elevated cardiac volumes and myocardial mass in athletes relative to less active controls, signifying normal sport adaptation. There were no differences between the matched athletic groups regarding their LV and RV functional and volumetric parameters. LV analysis showed subtle functional alterations between athletes and controls, with the former showing slightly lower strain values. There was no difference regarding any strain parameters between athletes after SARS-CoV-2 infection and healthy control athletes. Native T1 values were slightly lower in the athletes after SARS-CoV-2 infection than in the controls, but there was no difference between athletic groups. The T2 values were not different among the three groups.

We explored the associations of native T1 and T2 mapping values with the time since confirmation of SARS-CoV-2 infection (figure 2). We did not find a correlation between T1 values and time since the infection, while T2 values showed a weak negative correlation (Rho: −0.22, p=0.009) with this parameter.

Comparison of native T1 mapping values between sexes revealed that men (median 953, IQR 934–965 ms) had significantly lower T1 values than women (median 977, IQR 959–987 ms), regardless of whether they were healthy controls or athletes after SARS-CoV-2 infection (p<0.0001) (online supplemental file 1).

Fourteen elite athletes had previously undergone CMR imaging in our institute prior to obtaining positive SARS-CoV-2 PCR results (table 3). The two CMR scans for this group were performed an average of 384 days apart. Comparing examinations before and after the infection revealed no differences regarding any CMR parameters, as shown in table 3.

We compared athletes with prior SARS-CoV-2 infection regarding their symptoms (figure 3), which showed that athletes with moderate symptoms, mainly chest pain and dyspnoea, had slightly elevated native T1 values relative to their asymptomatic and mildly symptomatic counterparts (p<0.05). However, the T1 value remained below the cut-off point for the majority of patients. Furthermore, there was no difference in the LV ejection fraction or GLS values among these groups.

We obtained follow-up in 122 (83%) athletes after SARS-CoV-2 infection at a median of 232 days after the infection. All but two athletes could return to sports activity safely. One of them did not return to sports due to the progression of his depression, and he currently receives medication. The other athlete experienced long-COVID syndrome, including lightheadedness and long-term rapid increase in his heartbeat. At the time of our follow-up, this athlete had a negative exercise test and was advised to restart sports activity. The outcomes of the seven athletes with CMR alteration are shown in table 2.

Online supplemental file 2 shows the acute and follow-up CMR scans in those patients with myocardial alteration (n=4) who returned for a follow-up scan. In one athlete with LGE showing a non-ischaemic pattern consistent with previous myocarditis, the follow-up CMR showed slightly elevated systolic function and the shrinkage of the LGE. Among the three patients presenting with mild, isolated mapping elevation, the follow-up scan revealed that the elevated mapping values had subsided for two patients and remained slightly elevated for the last. Three athletes asked to postpone their follow-up scans due to their lack of symptoms and their ongoing sports season.

Overall, 10 athletes reported a subjectively long recovery from COVID-19. Three additional athletes said that, although they returned to sports activity, they did not reach their peak potential at the time of their follow-up. It was due to anxiety in one case and two athletes experienced mild, long-term sinus tachycardia with no apparent structural alteration. None of the national team members (n=71) reported significant setbacks in their performance. In all patients who reported reinfection confirmed by PCR (n=4), we performed follow-up CMR without definite alteration (online supplemental file 3).

DISCUSSION

The current study presents a comprehensive analysis of the CMR findings of 147 highly trained athletes following SARS-CoV-2 infection and compares them to sex-matched and age-matched healthy athletes and less active controls. In this group, where all athletes were referred to the examination by a cardiologist, CMR revealed no overall differences regarding any volumetric, functional or tissue characteristics between athletes with prior SARS-CoV-2 infection and matched healthy athletes. However, a minority of the athletes had definite (n=2, 1.4%) or possible (n=5, 3.4%) myocardial or pericardial alterations on CMR. Four of these athletes were moderately symptomatic; two of them had long COVID; and one had mild symptoms.

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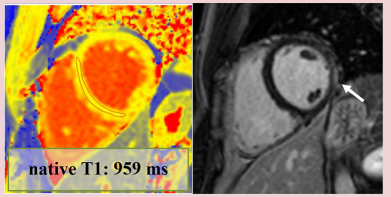
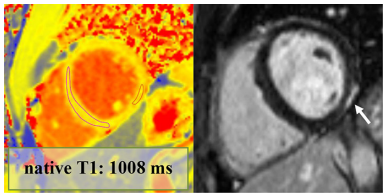
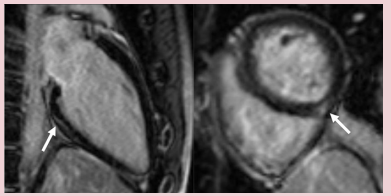
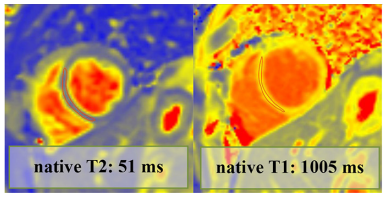
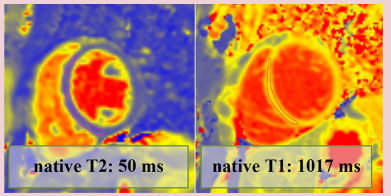
Table 2 Detailed information regarding athetes with post-COVID-19 with myocardial or pericardial alterations on cardiac MRI

Athlete no	Sex	Symptoms	Findings on other exams	Time to CMR after positive test results (days)	hsTnT recorded prior to CMR (ng/L)	CMR findings	Pathological alteration	Certainty of cardiac involvement	Clinical outcome (6 months)
1.	Male	Moderate ► Chest pain. ► Fever. ► Headache. ► Joint pain. ► Diarrhoea. ► Smell and taste disturbance.	Troponin: elevated (hsTnT: 18 ng/L, normal: <14 ng/L) 12-lead ECG: minor repolarisation. alteration Holter ECG: sinus tachycardia (1 hour) Echocardiography: slightly dilated RV Exercise test (4 months after COVID-19 infection): normal	70	18	LVEF: 52% GLS: −18% Septal native T1: normal Septal native T2: normal Pathological LGE/pattern: yes—lateral subepicardial T1 and T2 mapping value in the area corresponding with the LGE: 1016 and 50 ms—mildly elevated		Definite	Returned to sport, no persistent cardiac complaints at follow-up
2.	Male	Moderate ► Chest pain. ► Dyspnoea. ► Fever. ► Cough.	Troponin: elevated (hs troponin I: 198 ng/L, normal: <45 ng/L) 12-lead ECG: minor repol. alteration Holter ECG: normal Echocardiography: normal Exercise test (3 months after COVID-19 infection): normal	74	NA	LVEF: 58% GLS: −18% Septal native T1: elevated Septal native T2: normal Pathological LGE/pattern: Yes—lateral subepicardial T1 and T2 mapping value in the area corresponding with the LGE: 1065 and 53 ms—elevated		Definite	Returned to sport, no persistent cardiac complaints at follow-up
3.	Male	Moderate ► Chest pain. ► Dyspnoea. ► Fatigue. ► Cough.	Troponin: normal 12-lead ECG: RBBB (previously reported) Holter ECG: not performed Echocardiography: normal Exercise test (5 months after COVID-19 infection): normal	27	4	LVEF: 61% GLS: −22% Septal native T1: normal Septal native T2: normal Pathological LGE/pattern: Yes—non-specific inferior and hinge point LGE T1 and T2 mapping value in the area corresponding with the LGE: 984 and 41 ms—normal		Possible	Returned to sport, no persistent cardiac complaints at follow-up
4.	Female	Long COVID-19 ► Palpitation. ► Long-lasting fatigue.	Troponin: normal 12-lead ECG: normal Holter ECG: normal Echocardiography: normal Exercise test (5 months after COVID-19 infection): normal	67	<3	LVEF: 67% GLS: −27% Septal native T1: grey zone normal/elevated Septal native T2: mildly elevated Pathological LGE/pattern: no		Possible	Returned to sport, no persistent cardiac complaints at follow-up
5.	Female	Moderate ► Chest pain. ► Back pain. ► Smell and taste disturbance.	Troponin: normal 12-lead ECG: PVC Holter ECG: trigeminy PVC on exertion Echocardiography: normal Exercise test (4 months after COVID-19 infection): normal	19	<3	LVEF: 60% GLS: −22% Septal native T1: mildly elevated Septal native T2: mildly elevated Pathological LGE/pattern: No		Possible	Returned to sport, no ongoing cardiac complaints.

Continued

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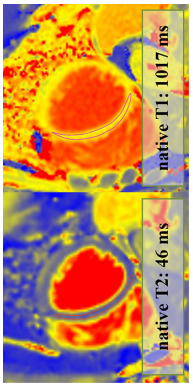
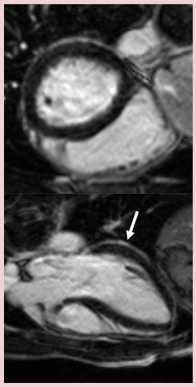
Table 2 Continued

Athlete no	Sex	Symptoms	Findings on other exams	Time to CMR after positive test results (days)	hsTnT recorded prior to CMR (ng/L)	CMR findings	Pathological alteration	Certainty of cardiac involvement	Clinical outcome (6 months)
6.	Female	Mild ▲ Fever. ▲ Fatigue. ▲ Palpitation. ▲ Smell and taste disturbance.	Troponin: elevated (hs troponin I: 28 ng/L—normal: <1.9 ng/L) 12-lead normal Holter ECG: NA Echocardiography: normal Exercise test: NA	11	<3	LVEF: 55% GLS: −18% Septal native T1: mildly elevated Septal native T2: normal Pathological LGE/pattern: no		Possible	Returned to sport, no ongoing cardiac complaints
7.	Male	Moderate ▲ Chest pain. ▲ Long-lasting fatigue.	Troponin: elevated (hs troponin I: 225 ng/L—normal: <45 ng/L) 12-lead ECG: descending PQ segment depression Holter ECG: NA Echocardiography: decreased longitudinal strain, mild anterior and anteroseptal wall motion abnormality Holter ECG: NA	120	10	LVEF: 61% GLS: −20% Septal native T1: normal Septal native T2: normal Pathological LGE/pattern: Yes—pericardial involvement		Possible	Returned to sport, no ongoing cardiac complaints

CMR, cardiac magnetic resonance; GLS, global longitudinal strain; hsTnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; NA, not applicable; PVC, premature ventricular complex.

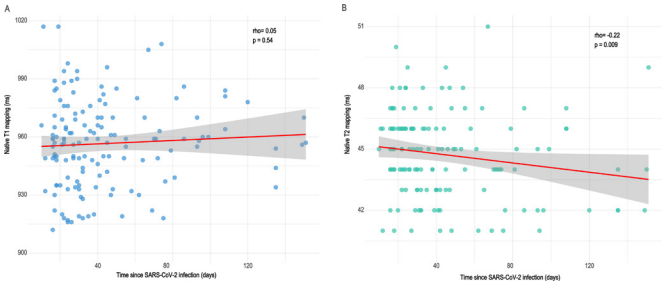


Figure 2 Associations of native T1 and T2 mapping values and the time from confirmation of SARS-CoV-2 infection. We did not find a correlation between T1 values and time since SARS-CoV-2 infection, while T2 values showed a weak negative correlation with this parameter.

Among young highly trained athletes, we found a lower frequency of myocardial alteration than previously reported by Rajpal and colleagues,[3] who performed CMR for 26 asymptomatic or mildly symptomatic collage athletes with negative troponin levels and normal ECG and echocardiography. They found that 46% of the athletes had LGE and 15% had myocardial alterations interpreted as acute myocarditis. In our study, only one patient had CMR findings consistent with acute myocarditis as per the Lake Louise criteria,[14] and one had findings suggesting previous myocarditis. As per those three athletes who presented with slightly elevated T1 values with or without elevated T2 values, we reported possible mild diffuse myocardial involvement and performed a follow-up CMR scan, which showed the resolution of these alterations in two patients. Our results are quite similar to those found by Starekova *et al*, Moulson *et al* and Martinez *et al*,[5 7 15] signifying the modest prevalence of

Table 3 Comparison between CMR examinations before and after SARS-CoV-2 infection

	CMR scan before SARS-CoV-2 infection (n=14)	CMR scan after SARS-CoV-2 infection (n=14)	P values
Standard left and right ventricular CMR parameters			
LVEF (%), median (IQR)	55 (53–58)	57 (53–61)	0.091
LVEDVi (mL/m^2), median (IQR)	111 (103–120)	117 (104–125)	0.305
LVESVi (mL/m^2), median (IQR)	47 (46–59)	51 (42–55)	0.216
LVSVi (mL/m^2), median (IQR)	65 (57–67)	65 (60–75)	0.135
LVMi (g/m^2), median (IQR)	63 (59–77)	70 (62–82)	0.502
RVEF (%), median (IQR)	54 (52–56)	57 (53–60)	0.091
RVEDVi (mL/m^2), median (IQR)	113 (107–120)	116 (100–122)	0.946
RVESVi (mL/m^2), median (IQR)	53 (44–60)	49 (45–57)	0.094
RVSVi (mL/m^2), median (IQR)	62 (57–69)	64 (59–73)	0.38
Global left and right ventricular strain			
LV-GLS (%), median (IQR)	−20 (−22 to −19)	−20 (−21 to −18)	0.241
LV-GCS (%), average ±SD	−27±3	−28±5	0.883
LV-GRS (%), median (IQR)	50 (45–55)	49 (45–53)	0.715
RV-GLS (%), average ±SD	−24±3	−23±3	0.29
Parametric mapping			
T1 mapping, median (IQR), ms	947 (932–961)	937 (933–966)	0.791
T2 mapping, median (IQR), ms	43 (43–45)	44 (42–46)	0.32

CMR, cardiac magnetic resonance; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LV, left ventricular; 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; RV, right ventricular; 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.

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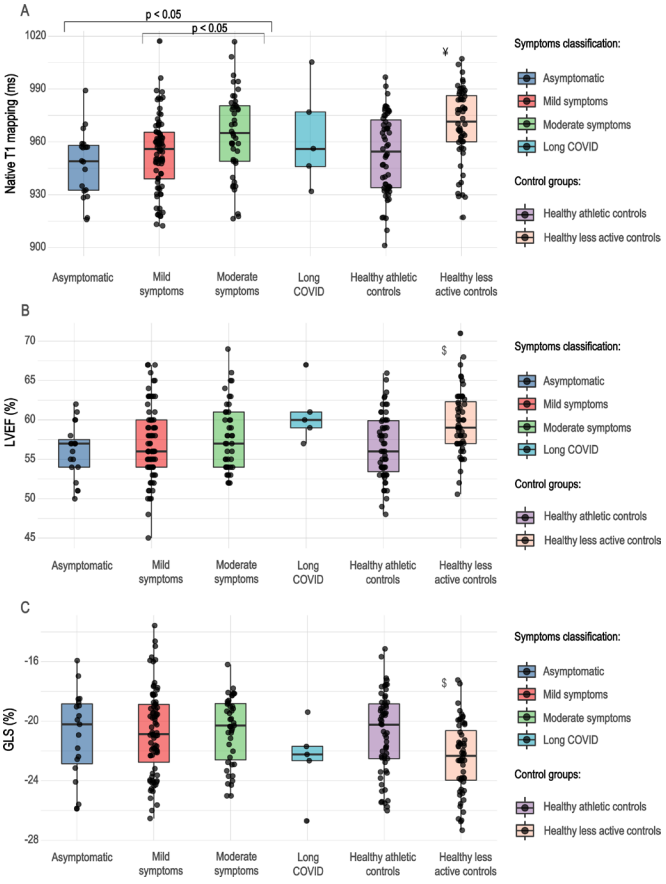

Figure 3 Boxplots of native T1 mapping, LVEF and GLS values by symptom group. Moderately symptomatic athletes with post-COVID-19 had elevated native T1 values relative to asymptomatic and mildly symptomatic infections (p<0.05). However, the T1 value remained below the normal cut-off point for the majority of patients. There was no difference in the LVEF or GLS values among these groups. ¥, Kruskal-Wallis test showing a significant difference between healthy, less active controls and asymptomatic and mildly symptomatic athletes after SARS-CoV-2 infection and healthy athletic controls; $, Kruskal-Wallis test showing a significant difference between healthy, less active controls and asymptomatic, mildly and moderately symptomatic athletes after SARS-CoV-2 infection, and healthy athletic controls. GLS, global longitudinal strain; LVEF, left ventricular ejection fraction.

myocardial involvement after SARS-CoV-2 in young, otherwise healthy individuals. In a nationwide research study among US collegiate athletes conducted by Moulson and colleagues, they also found the cardiac involvement among athletes as low as 0.7%, and interestingly, they found that CMR scans performed on the basis of clinical symptoms were four times more likely to show myocardial alterations as opposed to those that were performed as a primary screening method.[7] Overall, these findings are in line with pathological reports showing that only 1%–7% of 277 autopsied hearts across 22 publications had COVID-19-related myocarditis according to histopathological findings,[16] although in a different patient population. In our cohort, only one athlete presented with pericardial involvement; this finding is in contrast with the case series of Brito and colleagues, who found pericardial enhancement in 39.5% of athletes.[4]

We did not find a difference regarding the proportion of hinge point fibrosis after SARS-CoV-2 infection in athletes and healthy control athletes; however, only a relatively small number of control athletes received contrast material (n=15). We found a slightly higher proportion of hinge point fibrosis than Clark *et al* (athletes after SARS-CoV-2 infection) and a lower ratio than Domenech-Ximenos *et al* in endurance athletes before the pandemic (32% vs 22% vs 38%). Of note, these athletic groups were different from ours in some respects, including the ratio of female athletes (36% vs 63% vs 47%), sports discipline and training hours, which might account for the differences.[6 17]

Our findings regarding sport adaptation are in line with the current literature.[18 19] Data are scarce regarding the feature-tracking strain analysis of highly trained athletes, and the tendencies described in our study (slightly lower global strain values among highly trained men) are similar to those in the currently available publications using echocardiography.[20–22] Comparing athletes with prior SARS-CoV-2 infection and matched athletes showed no difference between CMR parameters, including strain parameters and native T1 and T2 mapping values. This finding confirms the results of the recent research letter by Clark *et al*,[6] who reported only a small difference between athletes post-COVID-19 and healthy control athletes regarding their mid-septal T2 mapping values. However, the groups in their study were matched by training load, not age or sex, which could have contributed to differences. While the cohort study by Puntmann *et al*[1] reported a higher prevalence of findings, new studies have shown similar results to ours, although in very different populations.[23 24] McDiarmid *et al*[25] previously demonstrated that physiological hypertrophy slightly decreased the T1 value among highly trained athletes. We also found that, similar to other CMR parameters, men and women have distinct native T1 and T2 values, which justifies the use of sex-matched control groups when interpreting mapping alterations.

We did not find a correlation between T1 mapping values and the time passed since SARS-CoV-2 infection, similar to what Knight *et al*[24] found in their study with a somewhat longer delay between SARS-CoV-2 infection and CMR examination (median 68 vs 32 days). A weak but significant correlation was found between T2 mapping and time since infection. This might suggest a reduction in subclinical oedema over time; however, we need more information to confirm this finding.

One unique strength of this study is that 14 athletes had undergone a previous CMR scan at our institute with a standardised protocol; therefore, we were able to compare the results of the two scans. This comparison, however, showed no differences between CMR parameters before and after SARS-CoV-2 infection.

Follow-up at median 232 days after COVID-19 infections showed the majority of athletes returned to high levels of sports activity (n=120/122), although some could not reach their peak performance (n=3) and some experienced reinfection (n=4).

The comparison between athletes with different symptoms revealed slightly elevated T1 mapping values among athletes with chest complaints relative to asymptomatic and mildly symptomatic athletes; however, this did not lead to a reduction in systolic heart function. Moreover, T1 values remained in the normal range for most patients. Currently, there are no data regarding the subclinical cardiac alterations caused by mild forms of systemic viral infections such as influenza and whether they are detectable on CMR. We believe that studies investigating the long-term impact of isolated T1 and T2 mapping elevations are necessary to understand the exact prognostic significance of these alterations, and in this study, we share the concerns of Moulson and Baggish[26] regarding the use of these highly sensitive, although less well-understood techniques, in the screening of otherwise healthy athletes with prior SARS-CoV-2 infection.

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The current consensus document[9] regarding the use of CMR in athletes after SARS-CoV-2 infection highlights the importance of well-established screening methods such as troponin, ECG and echocardiography. Moreover, in suspected arrhythmias, further examinations such as 24-hour Holter monitoring might be beneficial,[8 9] and premature ventricular beats on exercise test might suggest scar on CMR examination as demonstrated by recent studies, enabling a better targeting of CMR scans.[27] In agreement with this, our results caution against the routine use of CMR for troponin-negative, asymptomatic, or mildly symptomatic patients with COVID-19, as it may lead to false conclusions.

LIMITATIONS

This was a single-centre study performed in a major CMR referral centre. Approximately one-third of the athletes after SARS-CoV-2 infection were referred from other institutions; therefore, their clinical data were provided by the referring clinicians. All athletes included in our study were Caucasian and experienced asymptomatic, mild/moderate or long COVID-19; thus, our conclusions are only applicable to this specific group. Because our study included patients referred by a cardiologist, the reported prevalence of abnormal CMR findings may be overestimated compared with a non-selected population of athletes with SARS-CoV-2 infection. In addition, the clinical implications of CMR abnormalities in the absence of cardiovascular symptoms remains unknown. Lastly, only a proportion of healthy control athletes received contrast agent during their CMR; thus, findings related to LGE in the athletic control group could have been missed.

What are the new findings?

- Among 147 highly trained athletes after SARS-CoV-2 infection, we found that cardiac involvement on cardiac magnetic resonance (CMR) was present in only seven (4.8%) patients, among whom only two (1.4%) presented with definite signs of myocarditis.
- Comparing athletes after SARS-CoV-2 infection and healthy sex-matched and age-matched athletes showed no difference between CMR parameters, including strain and native T1 and T2 mapping values.
- Comparison between CMR examinations before and after the infection (n=14) revealed no differences regarding any CMR parameters.
- Follow-up at a median of 232 days after the infections showed the majority of athletes returned to high levels of sports activity (n=120/122, 98.4%).

How might it impact on clinical practice in the future?

- Cardiac involvement has a low prevalence among highly trained athletes after SARS-CoV-2 infection.
- Matched control groups are essential for the interpretation of isolated T1 or T2 mapping alterations.
- Our results caution against the routine use of CMR for troponin-negative, asymptomatic or mildly symptomatic patients after SARS-CoV-2 infection.

CONCLUSION

Among 147 consecutively included highly trained athletes after SARS-CoV-2 infection and referred by a cardiologist, we found cardiac involvement in 4.7% using CMR, among whom only two (1.4%) presented with definite signs of myocarditis. Our results suggest that cardiac involvement occurs with modest frequency among asymptomatic and mildly/moderately symptomatic SARS-CoV-2 infections in young athletes. Comparisons between athletes after SARS-CoV-2 infection and matched healthy athletes showed no difference between CMR parameters, including strain parameters and T1 and T2 mapping values. Moreover, there was no difference in CMR parameters among athletes examined before and after the infection. The follow-up revealed that the majority of athletes returned to high levels of sports activity without any persisting symptoms.

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Contributors LS contributed to the conception of the study, investigation, analysis, interpretation of the data and writing the original draft. VJ, CF, OK, NS and EC contributed to the formal analysis of the data, investigation, and project administration. ZD, AK, BL, HK and FIS contributed to the investigation and methodology of the study and edited the manuscript. DB and BM contributed to the conceptualisation, interpretation of the data, funding acquisition, supervision and editing of the manuscript. HV contributed to the conceptualisation, investigation, interpretation of the data, funding acquisition, supervision, writing and editing of the manuscript. All authors gave their final approval to the manuscript. LS and HV are responsible for the overall content as guarantors.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was obtained from the National Public Health Center in accordance with the ethical standards laid out in the 1964 Declaration of Helsinki and its later amendments. IV/9697-1/2020/EKU. All participants gave their written informed consent. It was not possible to involve patients in the design or reporting of our current study. Athletes with post-COVID-19 are currently involved in the 'return-to-play practices' and dissemination plans of our ongoing research.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data are available upon reasonable request.

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Immunological response and temporal associations in myocarditis after COVID-19 vaccination using cardiac magnetic resonance imaging: An amplified T-cell response at the heart of it?

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Introduction: Although myocarditis after anti-SARS-CoV-2 vaccination is increasingly recognized, we have little data regarding the course of the disease and, consequently, the imaging findings, including the tissue-specific features. The purpose of this study is to describe the clinical, immunological, and cardiac magnetic resonance (CMR) features of myocarditis after COVID-19 immunization in the acute phase and during follow-up. We aimed to compare the trajectory of the disease to myocarditis cases unrelated to COVID-19.

Methods: We assembled a CMR-based registry of potentially COVID-19 vaccination-related myocarditis cases. All patients who experienced new-onset chest pain and troponin elevation after COVID-19 vaccination and imaging confirming the clinical suspicion of acute myocarditis were enrolled in our study. Participants underwent routine laboratory testing and testing of their humoral and cellular immune response to COVID-19 vaccination. Clinical and CMR follow-up was performed after 3–6 months. We included two separate, sex- and age-matched control groups: (1) individuals with myocarditis unrelated to COVID-19 infection or vaccination confirmed by CMR and (2) volunteers with similar immunological exposure to SARS-CoV-2 compared to our group of interest (no difference in the number of doses,

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types and the time since anti-SARS-CoV-2 vaccination and no difference in anti-nucleocapsid levels).

Results: We report 16 CMR-confirmed cases of myocarditis presenting (mean ± *SD*) 4 ± 2 days after administration of the anti-SARS-CoV-2 vaccine (male patients, 22 ± 7 years), frequently with predisposing factors such as immune-mediated disease and previous myocarditis. We found that 75% received mRNA vaccines, and 25% received vector vaccines. During follow-up, CMR metrics depicting myocardial injury, including oedema and necrosis, decreased or completely disappeared. There was no difference regarding the CMR metrics between myocarditis after immunization and myocarditis unrelated to COVID-19. We found an increased T-cell response among myocarditis patients compared to matched controls ($p < 0.01$), while there was no difference in the humoral immune response.

Conclusion: In our cohort, myocarditis occurred after both mRNA and vector anti-SARS-CoV-2 vaccination, frequently in individuals with predisposing factors. Upon follow-up, the myocardial injury had healed. Notably, an amplified cellular immune response was found in acute myocarditis cases occurring 4 days after COVID-19 vaccination.

KEYWORDS

myocarditis, SARS-CoV-2 immunization, cardiovascular magnetic resonance, immunological response, vaccination, inflammation

Introduction

Increasing evidence links coronavirus disease 2019 (COVID-19) vaccination to rare cases of myocarditis and myopericarditis, primarily in the young adult (1) and adolescent (2) male population (3, 4). The connection between novel mRNA vaccines and these cases has been made. However, earlier data show that post-vaccination myocarditis may occur after a variety of vaccinations, including the smallpox vaccine that contains live virus (5).

Cardiac magnetic resonance (CMR) imaging is the method of choice for noninvasive visualization of myocardial injury (6–8). Case reports and case series demonstrated the role of CMR in the confirmation of myocarditis after anti-SARS-CoV-2 immunization. Importantly, these cases describe vaccine-induced myocarditis associated with mRNA vaccines, particularly after the second dose of the BNT162b2 mRNA-Pfizer-BioNTech and mRNA-1273-Moderna vaccines (9–12). An extensive cohort study from Israel based on hospital reporting systems described clinical follow-up data, but measures of cardiac function were not available (13). Therefore, we have little data regarding the course of the disease and, consequently, the CMR findings, including the tissue-specific features of myocarditis.

The underlying mechanism of the evolution of vaccination-related myocarditis is largely unclear. The proposed concepts include triggering of preexisting immune pathways and accelerated innate immunogenic reactions (4). Previously, it was also suspected that spike reactive mimicry might also play a role; however, this hypothesis has since been refuted by Marram et al. (14). However, these are primarily theoretical notions, as the immune response of myocarditis patients after COVID-19 vaccination has not been described (4).

The purpose of this study was to describe the clinical, CMR imaging and immunological features of different types of myocarditis after COVID-19 immunization in the acute phase and during follow-up. Second, we aimed to illustrate the features of myocarditis potentially linked to the COVID-19 vaccine in the context of myocarditis cases where vaccination or any contact with COVID-19 disease did not occur. Third, we describe the immunological response to COVID-19 immunization in patients with myocarditis and matched controls.

Methods

Study population

This is a retrospective CMR-based registry of myocarditis cases following COVID-19 immunization. We contacted all Hungarian institutions performing CMR scans ($n = 19$) between December 2020 and September 2021. All participants must exhibit the following inclusion criteria, to be admitted to the study: (1) COVID-19 vaccination not more than 21 days before the acute presentation; (2) presence of one or more of the following symptoms: new-onset chest pain, dyspnea,

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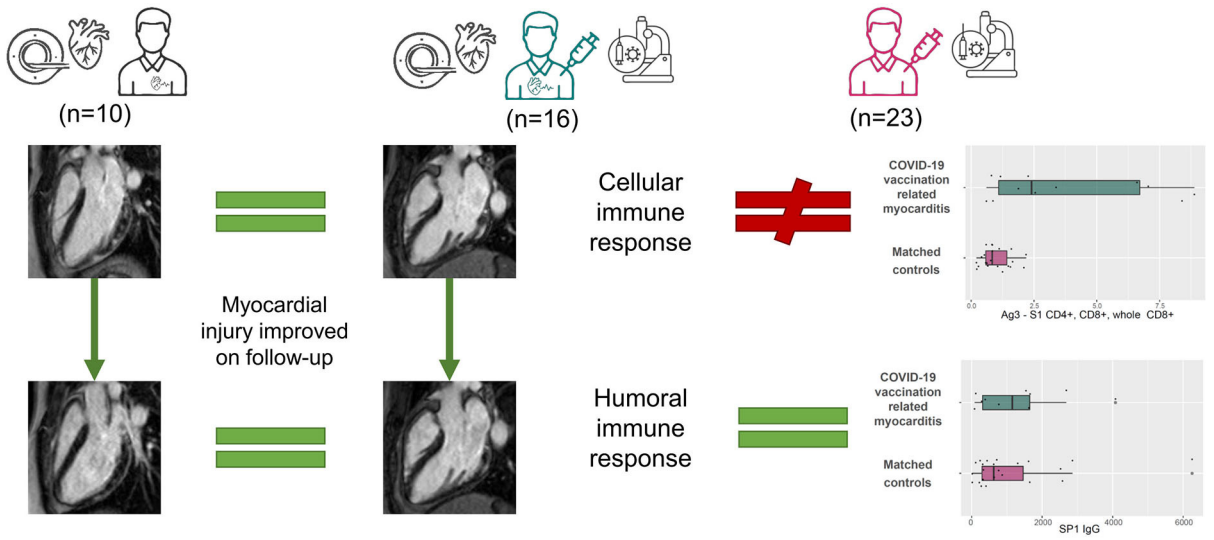

FIGURE 1
Visual abstract. We compared the CMR findings of myocarditis patients after COVID-19 vaccination (middle) to those of patients with myocarditis unrelated to COVID-19 immunization or infection (left). We did not find a difference between the groups in the acute (upper images) or follow-up (lower images) scans, but the myocardial injury improved. We compared the immune response of myocarditis patients after COVID-19 vaccination to COVID-19 immunization status-matched controls (right). There was no difference regarding the humoral immune response. In contrast, the cellular immune response was amplified in the myocarditis group.

or palpitation or syncope; (3) troponin elevation as per the local laboratory; and (4) CMR imaging confirming the clinical suspicion of acute myocarditis. Based on our criteria, four centers reported myocarditis cases after COVID-19 vaccination.

Study protocol

All participants completed a questionnaire regarding their acute symptoms and previous medical history, including their history of cardiovascular and immunological diseases. Cardiac biomarker levels, laboratory test results and 12-lead ECG results were recorded. Echocardiography and CMR examination were performed. Immunological tests were carried out in all acquiescent participants. Symptomatic patients (e.g., ongoing chest pain) were admitted to intensive/coronary care units (ICU/CCU) with continuous bedside monitoring. Asymptomatic patients with elevated cardiac troponin or patients discharged from ICU/CCU to general wards were monitored using telemetry. Follow-up examinations and CMR scans were carried out 3–6 months after the acute presentation in patients who consented. The study design is shown on Figure 1.

Ethical approval

Ethical approval was obtained from the National Public Health Center under the ethical standards laid out in the 1964 Declaration of Helsinki and its later amendments. IV/2568-1/2021/EKU. All participants or their legal guardian gave their written informed consent for the analysis.

Myocarditis comparator group

We included a group of myocarditis patients confirmed by CMR to illustrate the potential similarities and differences from the myocarditis patients after COVID-19 vaccination. The CMR comparator group was sex- and age-matched, retrospectively selected from the Semmelweis University CMR database according to the following criteria: (1) troponin elevation, (2) CMR examination confirming acute myocarditis was completed <2 weeks after the acute presentation, (3) CMR examination before the first reported case of SARS-CoV-2 infection in Hungary (2020.03.04.) OR negative PCR excluding the infection, and (4) follow-up CMR was carried out between 3 and 6 months after the acute scan. All control CMR scans were performed using a Siemens Magnetom Aera 1.5 T scanner. A comprehensive CMR protocol was carried out, including cine movies, T2-weighted spectral presaturation with inversion recovery (SPIR), T2 mapping using T2-prep balanced steady-state free precession (b-SSFP), T1 mapping using long-T1 5(3)3 and short-T1 5(3)3 modified look-locker inversion recovery (MOLLI) and late gadolinium enhancement (LGE) imaging. Functional evaluation was performed using b-SSFP cine sequences in four-chamber, two-chamber, and three-chamber long-axis views and a short-axis stack from the cardiac

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base to apex with full coverage of the left ventricle and right ventricle. None of the myocarditis patients had a history of immune checkpoint inhibitor treatment.

CMR protocol

Overall, four Hungarian centers reported myocarditis cases after SARS-CoV-2 vaccination. CMR scans were performed on 1.5 T scanners (Siemens Magnetom Aera, Siemens Magnetom Amira, GE SIGNA Voyager, Phillips Ingenia). The CMR protocol had to include the following sequences regardless of the institution: cine sequence covering the whole heart for functional assessment, T2 weighted images or T1 mapping depicting myocardial oedema and LGE or T1 mapping showing necrosis or fibrosis. The protocol of the acute and control CMR scans was similar in most cases, although we accepted control CMR scans without T2-weighted images. If a control CMR scan was not possible in the original institution, the participant was offered a CMR scan slot at the Semmelweis University Heart and Vascular Center ($n = 2$). Mapping sequences were available from 3 institutions ($n = 13/16$). LGE images were acquired using segmented inversion recovery sequences 10–15 min after administration of an intravenous bolus of gadolinium-based contrast agent (gadobutrol in 0.15 ml/kg, or gadoteric acid in 0.4 ml/kg) at a rate of 2–3 ml/s through an antecubital intravenous line. The inversion time was adjusted to provide optimal suppression of normal myocardium.

CMR analysis

CMR scans were collected in raw DICOM format, and all post-processing analyses were conducted in a core CMR laboratory using the Medis Suite Software (Medis Medical Imaging Software, The Netherlands) to minimize observer-related variance. LV and RV volumes, function and mass were calculated from the SA stack using artificial intelligence-based automated contour detection (autoQ module) with manual adjustments if necessary. Short-axis LGE images were contoured manually, and then the LGE mass and LGE% were quantified using the 5SD technique with manual adjustments if required in the Medis QMass module. Myocardial native T1 and T2 relaxation times were consequently measured in the midventricular or basal septum (15) (if the midventricular images were technically inadequate for analysis) of the myocardium using motion-corrected images. One further ROI was manually drawn to the affected area guided by visual inspection (15). The comparison regarding mapping values was carried out in participants who underwent their CMR examination and at Semmelweis University Heart and Vascular Center ($n = 9$). Elevated T1 and T2 values were defined based on sequence-specific cut-offs of 2 standard deviations (SDs) above the respective means of the healthy male controls (T1: 1,000 ms, T2: 49 ms).

Acute myocarditis was defined as per the modified Lake Louise criteria (LLC) (7). Specifically, at least two positive main LLC criteria in corresponding locations were necessary for the diagnosis. At least one positive criteria for oedema visualization (T2-weighted images, T2 mapping or T1 mapping) and at least one positive criteria for necrosis visualization

TABLE 1 Baseline characteristics.

Age, years	22 ± 7
Sex, male %	16 (100)
BMI	26 ± 4
SARS-CoV-2 vaccine type *n*, (%)	
mRNA	
- Pfizer (BNT162b2 mRNA-Pfizer- BioNTech)	10 (62.5)
- Moderna (mRNA-1273-Moderna)	2 (12.5)
Vector vaccine	
- Sputnik V (Gam-COVID-Vac)	4 (25)
SARS-CoV-2 vaccine dose *n*, (%)	
- First dose	2 (12.5)
- Second dose	13 (81.2)
- Third dose	1 (6.2)
First complaint after vaccination, days	1.8 ± 1.6
Chest pain after vaccination, days	3.8 ± 1.9
Previous SARS-CoV-2 infection yes, *n* %	2 (12.5)
Previous myocarditis yes, *n* %	2 (12.5)
Positive immunological history	4 (25)
- Crohn's disease, *n* %	1 (6.2)
- Asthma, *n* %	1 (6.2)
- Psoriasis, *n* %	1 (6.2)
- Allergy, *n* %	1 (6.2)
Cardiovascular risk factors	
- Hypertension, *n* %	2 (12.5)
- Diabetes, *n* %	0 (0)
- Smoking, *n* %	4 (25)
- Obesity, *n* %	3 (18.8)
Intense physical activity after vaccination	4 (25)
- Sport activity	3 (18.8)
- Physically demanding job	1 (6.2)
Elevated troponin level *n*, %	16 (100)
CKMB (U/L) *Cut-off: ≥ 25 U/L*	31 [26, 62]
C-reactive protein (mg/L) *Cut-off: ≥ 5 mg/L*	23 [13, 43]
NTproBNP (pg/ml) *Cut-off: ≥ 125 pg/ml*	351 [223, 677]
Thrombocyte count (Giga/L) *Normal range: 150–400 Giga/L*	214 [199, 229]
White blood cell count (Giga/L) *Normal range: 4.0–10.0 Giga/L*	7.9 [5.7, 9.5]
Eosinophil count (Giga/L) *Cut-off: >0.5 Giga/L*	0.10 [0.07, 0.17]

Baseline characteristics.
CKMB, Creatine kinase-MB; NTproBNP, N-terminal pro B-type natriuretic peptide; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

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(LGE or T1 mapping). The interpretation of CMR scans was standardized: the presence and pattern of myocardial oedema and LGE was visually defined independently by two EACVI certified observers (VH EACVI level 3-certified CMR specialists with more than 15 years of experience in CMR reporting and LS completed her EACVI written certification and has 3.5 years of experience reporting CMR). In case of disagreement between the observers, a third level 3 EACVI-certified CMR specialist (AT) with more than 15 years of experience in CMR reporting was consulted for consensus. Non-ischaemic LGE was defined as midmyocardial and/or subepicardial myocardial LGE confirmed in two perpendicular views.

Control group for immunological studies

The immune response of the study participants was compared with that of 23 sex- and age-matched controls from the Semmelweis University database. Subjects included in the control group were comparable to the myocarditis group regarding the doses and type of anti-SARS-CoV-2 vaccine they received and the time elapsed since their vaccination. We objectively quantified SARS-CoV-2 exposure using anti-nucleocapsid protein levels, which showed no difference between myocarditis patients after COVID-19 vaccination and controls. This matching step was crucial, as more participants reported previous SARS-CoV-2 infection in the control group than in the myocarditis group.

Laboratory protocol

Participants underwent routine laboratory testing for biomarkers including troponin, CKMB, CRP, white blood cell count, and eosinophil cell count. Antinuclear antibodies (ANAs), extractable nuclear antigen antibodies (ENAs), antineutrophil cytoplasmic antibodies (ANCAs) and serum immunoglobulin (IgG, IgM, IgA) levels were also measured from myocarditis samples ($n = 10$). A subgroup of myocarditis patients after COVID-19 vaccination ($n = 12$) and all immunization-matched controls ($n = 23$) underwent an evaluation of humoral and cellular immune responses at Semmelweis University. The immunology protocol and their interpretation were standardized to allow meaningful comparisons. Enzyme immunoassay providing semiquantitative *in vitro* determination of human antibodies of the immunoglobulin class IgG and IgM against modified nucleocapsid protein (NCP) of SARS-CoV-2 in serum or plasma has been obtained (referred to in the text as NCP-IgG and NCP-IgM). The results are given as a ratio (extinction of the sample/extinction of calibrator). The results below 0.8 are considered negative, the results equal to or above 0.8 and below 1.1 are considered borderline, and the results equal to or above 1.1 are considered positive due to the test description. SARS-CoV-2-specific antibodies (referred to in the text as S1 Ig) were analyzed using an Elecsys Anti-SARS-CoV-2 S immunoassay (Roche Diagnostics International Ltd, Switzerland) on a Cobas e6000 machine. The test detects antibodies specific to the SARS-CoV-2 spike (S) protein receptor-binding domain (RBD) in human serum and plasma. The method uses electrochemiluminescence to quantitatively determine antibodies based on the double-antigen sandwich principle. The test cut-off was $\geq$0.8 as per the manufacturer. The detailed immunoglobulin response was determined using the ELISA test, and the sample dilution was performed manually; further steps were carried out automatically using an Elite Lite (DAS, Italy) device. We will refer to the IgG and IgA immunoglobulins recognizing the S1 domain of the spike protein determined by ELISA as SP1 IgG and IgA for transparency. We quantified immunoglobulin levels in a quantitative (SP1 IgG) or semiquantitative (SP1 IgA) manner (16). The T-cell response was assessed via the QuantiFERON SARS-CoV-2 assay, an interferon-gamma release assay described in detail elsewhere (17). In short, this assay consists of three antigen tubes, SARS-CoV-2 Ag1, Ag2 and Ag3, that use a combination of proprietary antigen peptides specific to SARS-CoV-2 to stimulate lymphocytes involved in cell-mediated immunity in heparinized whole blood. The Ag1 tube contains CD4+ epitopes derived from the S1 subunit RBD of the spike protein. The Ag2 tube contains CD4+ and CD8+ epitopes from the S1 and S2 subunits of the spike protein. The Ag3 tube consists of CD4+ and CD8+ epitopes from S1 and S2 and immunodominant CD8+ epitopes derived from the whole SARS-CoV-2 genome.

Data management and statistical analysis

Statistical analysis and data visualization were performed using MedCalc software V.18.11 (Belgium) and RStudio (Version 1.3.1.093, RFoundation, Austria). The Shapiro–Wilk test was applied to test the normality of our data. Continuous variables showing a normal distribution are presented as the mean and SD, and those showing a non-normal distribution are reported as medians and IQRs. Categorical variables are presented as frequencies and percentages. Acute and follow-up examinations were compared using paired sample *t* tests and Wilcoxon tests. We applied analysis of covariance (ANCOVA) to formally test the difference between the trajectory of myocarditis after SARS-CoV-2 vaccination and myocarditis unrelated to COVID-19. Chi tests were applied to compare the distributions of categorical data. Comparisons between the immunological response of myocarditis patients after SARS-CoV-2 vaccine and the comparator group were conducted using independent samples *t* tests and Mann–Whitney *U* tests as appropriate. Associations were assessed using Spearman's rank correlation

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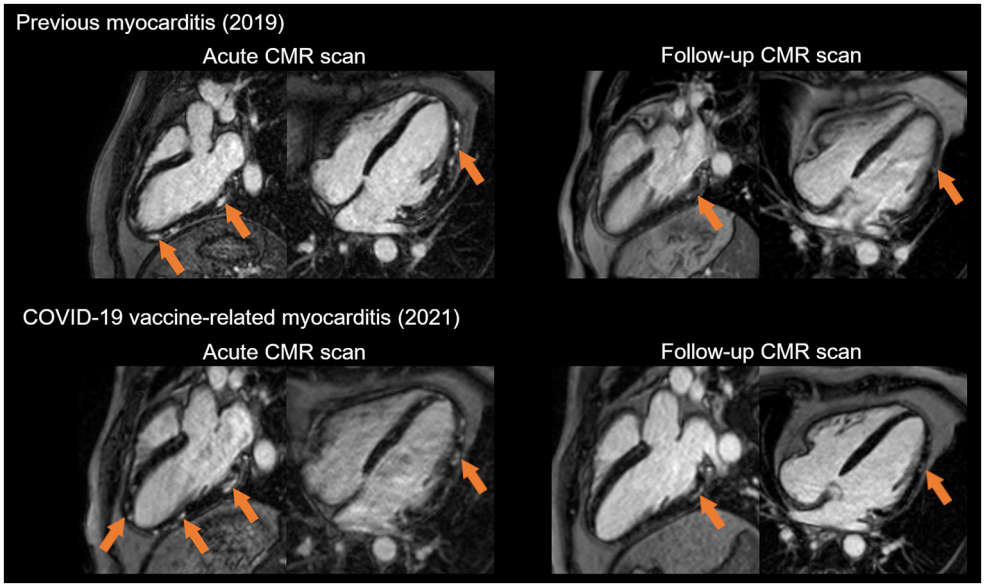

FIGURE 2
Recurrent myocarditis in a young male patient after the second dose of anti-COVID-19 vector vaccine. Our patient had prior myocarditis in 2019. At the time, he presented with chest pain preceded by gastrointestinal infection and fever. He had elevated troponin levels, and the CT coronary angiogram was negative. The acute CMR showed patchy subepicardial oedema and late gadolinium enhancement (LGE) (orange arrows). Three months later, on his follow-up scan, the oedema disappeared, and the LGE shrank. In 2021, the patient experienced fever and recurrent chest pain 2 days after the second dose of the COVID-19 vaccine. His acute CMR imaging showed LGE in a similar pattern as during the first acute myocarditis episode. Notably, signs of myocardial injury resolved on the follow-up scan.

analyses. Probability values were two-sided, and p values of <0.05 were considered significant. All data are available on reasonable request.

Results

Description of clinical characteristics

A total of four centers reported 16 CMR-confirmed cases of myocarditis following SARS-CoV-2 immunization, with chest pain presenting a mean of 4 ± 2 days after vaccination. Patient characteristics are included in Table 1. All of them were young (five were <18 years, mean age 22 ± 7 years, between 13 and 36 years) male patients and generally presented after their second dose of COVID-19 immunization (13, 81%). Most of them received mRNA vaccines (75%), while 25% presented with myocarditis after receiving a vector vaccine. Three patients reported prior SARS-CoV-2 infection, and one of them developed acute myocarditis after the first dose of vaccine. Two participants had acute myocarditis in their previous medical history confirmed by CMR imaging (Figure 2). In these cases, the time elapsed from the prior myocarditis to vaccination was 2 and 4 years, respectively. Four patients reported immune-mediated diseases, including Crohn's disease, psoriasis, asthma and allergies. None of the patients received systemic corticosteroid therapy. Overall, four participants reported intensive physical activity directly after vaccination (intensive sport activity, heavy physical labor), and

TABLE 2 Peak troponin value for myocarditis patients after COVID-19 vaccination.

Case no	Cardiac troponin type	Local cut-off	Peak value
1	hs troponin T (ng/L)	>14 ng/L	1,159
2	hs troponin T (ng/L)	>14 ng/L	1,007
3	hs troponin T (ng/L)	>14 ng/L	376
4	hs troponin T (ng/L)	>14 ng/L	1,366
5	hs troponin T (ng/L)	>14 ng/L	3,018
6	hs troponin T (ng/L)	>14 ng/L	144
7	hs troponin I (pg/ml)	>19 gp/ml	11,907
8	hs troponin I (μg/L)	>0.0198 μg/L	4.067
9	hs troponin T (ng/L)	>14 ng/L	2,136
10	hs troponin T (ng/L)	>14 ng/L	212
11	hs Troponin I (pg/ml)	>34.2 pg/ml	7,665
12	hs troponin T (ng/L)	>14 ng/L	220
13	hs troponin T (ng/L)	>14 ng/L	2,431
14	Troponin I (ng/L)	>19 ng/L	4,047
15	hs troponin I (pg/L)	>30 gp/ml	3,976
16	hs troponin T (ng/L)	>14 ng/L	228

Maximal troponin values for each participants is reported according to the local laboratory. hs, high-sensitive.

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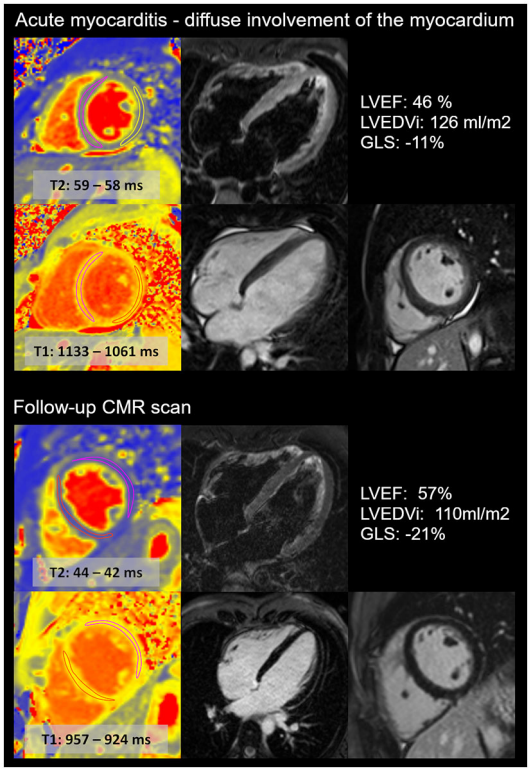

FIGURE 3
Diffuse acute myocarditis after the second dose of anti-COVID-19 mRNA vaccine in a young athlete. CMR images show the acute (upper images) and follow-up (lower images) scans of a young, highly trained athlete (national team member). The first CMR scan confirmed acute myocarditis with diffuse involvement of the myocardium, with elevated T2 and T1 mapping and diffuse myocardial oedema. The left ventricular ejection fraction (LVEF) was mildly decreased, and global longitudinal (GLS) strain was decreased during the acute scan. The follow-up scan revealed the normalization of T2 and T1 mapping values and left ventricular systolic function. The LVEDVi decreased. No LGE was present. The patient was prohibited from participation in sports activity for the first 3 months, and then he gradually returned to sports activity. Currently, the athlete performs a high level of sports activity and does not report recurrent or persisting symptoms.

one individual noted heavy alcohol consumption following immunization. The first systemic symptoms (fever, shivering) developed within 2 days, and chest pain presented a mean of 4 days after vaccination in all patients. ECG alterations were documented in seven patients (ST elevation in 6, negative T wave in 1). The initial troponin level was elevated in all study participants (Table 2), and we frequently noted CKMB, CRP and proBNP elevation as well. The white blood cell count, eosinophil count, and other markers remained in the normal range. During the acute phase, there were no heart failure symptoms, syncope, or documented sustained brady- or tachyarrhythmias.

CMR features of acute myocarditis after COVID-19 immunization

CMR was performed on average 4 ± 2 days (between 1 and 8 days) after the onset of acute chest pain. The majority of the cases showed a localized pattern of myocarditis, mainly affecting the lateral wall of the left ventricle with signs of subepi-midmyocardial oedema and necrosis (Figure 2). In one case, we found diffuse myocarditis with elevated T2, T1 and ECV values (Figure 3) caused by the mRNA vaccine. The left ventricular ejection fraction (LVEF) was in the normal range for most cases, except for two patients whose LVEF was mildly decreased (46 and 47%). Notably, these two patients had no previous history of acute myocarditis. There was no definitive pericardial involvement in any patients.

Clinical status and CMR changes during follow-up

During our follow-up, one patient experienced a recurrent episode of acute myocarditis (3 months after the vaccine), preceded by gastrointestinal infection. Other patients did not report symptom recurrence. The hs Troponin T (6[4, 7] ng/L), CKMB (2[2, 11] U/L), CRP (2[1, 3] mg/L) and proBNP (29[12,49] pg/ml) values returned to the normal range. Follow-up CMR was carried out 112 ± 27 days after the baseline scan ($n = 14$). We found that the LVEF marginally increased upon follow-up, and LVEDVi slightly decreased, both remaining in the normal range (Table 3). Elevated T2 values depicting local oedema in the affected area were resolved. The native T1 value and ECV measured in the affected area also decreased; however, ECV remained slightly elevated. The LGE area shrank in all participants and disappeared completely in 31% (4/13) of cases. The highly trained athlete in whom all signs of acute myocarditis disappeared on follow-up (Figure 3) was able to gradually return to sports activity. He restarted exercising 3 months ago and did not experience recurrent or persisting symptoms.

Myocarditis after SARS-CoV-2 immunization vs. myocarditis unrelated to COVID-19

The considering the effect of both follow-up time and myocarditis group, the ANCOVA test showed no difference between the trajectory of cardiac volumes, function, mass, oedema and LGE between myocarditis patients immunization and age- and sex-matched myocarditis patients unrelated to COVID-19 vaccination or infection (male patients, 22 ± 7 vs. 23 ± 6 years). Notably, we found a marginal difference between

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TABLE 3 Comparison between acute and follow-up CMR scans of myocarditis patients after COVID-19 vaccination.

	Acute myocarditis after COVID-19 vaccination ($n = 16$)	Follow-up myocarditis after COVID-19 vaccination ($n = 14$)	Acute *vs.* follow-up CMR, myocarditis after COVID-19 vaccination (P values)
Elapsed time, days	4 ± 2	112 ± 27	NA
LVEF, %	58 ± 6	60 ± 3	0.042
LVEDVi, ml/m^2	87 ±13	83 ± 9	0.046
LVSVi, ml/m^2	50 ± 7	50 ± 6	0.961
LVMi, g	53 ± 10	51 ± 7	0.228
GLS, %	−20.5 [−22.5, −19]	−21 [−22, −20]	0.083
RVEF, %	58 ± 4	57 ± 5	0.559
RVEDVi, ml/m^2	83 ± 10	84 ± 9	0.722
RVSVi, ml/m^2	48 ± 6	48 ± 6	0.489
T1 mapping septal, ms	966 [951, 1,016]	957 [950, 965]	0.578
T1 mapping affected area, ms	1,056 [1,038, 1,113]	976 [953.5, 1,018]	0.031
T2 mapping septal, ms	43 [43, 44]	43 [42, 43]	0.375
T2 mapping affected area, ms	51 [50, 55]	44 [43, 47.5]	0.016
ECV septal, %	26 [24, 28]	25.5 [23.5, 27.5]	0.125
ECV affected area,%	38 [35, 41.5]	30.5 [28, 35]	0.016
LGE g	6 [3, 10]	2 [0.5, 4]	0.001
LGE %	7 [3, 12]	3 [1, 4]	0.001

Comparison between acute and follow-up CMR scans myocarditis after COVID-19 immunization. Continuous variables showing a normal distribution are presented as the mean and standard deviations (± SD), and those showing a non-normal distribution are reported as medians and interquartile ranges [IQRs]. Acute and follow-up examinations were compared using paired sample t tests and Wilcoxon tests.
CMR, cardiac magnetic resonance; ECV, extracellular volume; EDVi, left ventricular end diastolic volume index; EF, ejection fraction; ESVi, end systolic volume index; GLS, global longitudinal strain; Mi, mass index; NA, not applicable; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; SVi, left ventricular stroke volume index.

T1 mapping (Table 4). Figure 4 illustrates the trajectory of CMR metrics between acute and follow-up scans in the both groups.

Assessment of the immunological response

Markers of the SARS-CoV-2 immune response were obtained for 12 patients. The test was performed a mean of 109 and 86 days after the first and second doses, respectively. Similarly, immunological testing was ascertained for the control group at a mean of 108 and 81 days after the first and second doses of anti-SARS-CoV-2 vaccine. The main difference between myocarditis patients and the comparator population was in terms of their history of previous SARS-CoV-2 infection (25 vs. 91%); however, anti-NCP (IgG, IgM) testing showed no difference between the two groups. There was no significant difference in the humoral immune response of myocarditis patients after SARS-CoV-2 immunization and those of sex- and age-matched controls (male patients, 22 ± 7 vs. 22 ± 6 years) (Table 5). In contrast, we found an increased T-cell response in myocarditis patients compared to controls ($P < 0.01$). We found that S1 IgG and IgA values negatively correlated with the time elapsed since the first vaccination (Supplementary Figure 1). Markers of the humoral immune response showed higher values after the mRNA vaccine than after the vector vaccine. At the same time, there was no difference regarding the cellular immune response between the two groups (Supplementary Table 1).

Notably, there was no difference in the immune response of myocarditis patients with or without predisposing factors (Supplementary Table 2).

Finally, there was no correlation between the humoral immune response (S Ig, SP1 IgG, SP1 IgA) and LVEF. In contrast, we found that the T-cell response parameters showed a negative correlation with the marker of systolic function (Figure 5).

Discussion

Summary of findings

The present data confirm and extend previous observations regarding the association of COVID-19 vaccination with myocarditis. This study of myocarditis patients after COVID-19 immunization confirmed by CMR makes the following contributions. First, in a cohort of acute myocarditis presenting a mean of 4 days after COVID-19 vaccination, we found

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TABLE 4 Assessment of the trajectory of myocarditis patients after SARS-CoV-2 immunization and myocarditis patients unrelated to COVID-19 immunization or infection over the acute phase and follow-up using analysis of covariance.

CMR metricss	Effects	ANCOVA test *P*
LVEF, %	Group	0.476
	Group:Time	0.613
	Time	0.013
LVEDVi, ml/m2	Group	0.752
	Group:Time	0.445
	Time	0.044
LVSVi, ml/m2	Group	0.954
	Group:Time	0.599
	Time	0.641
LVMi, g	Group	0.676
	Group:Time	0.548
	Time	0.051
GLS, %	Group	0.318
	Group:Time	0.812
	Time	0.102
RVEF, %	Group	0.701
	Group:Time	0.384
	Time	0.924
RVEDVi, ml/m2	Group	0.435
	Group:Time	0.501
	Time	0.253
RVSVi, ml/m2	Group	0.601
	Group:Time	0.795
	Time	0.527
T1 mapping septal	Group	0.171
	Group:Time	0.382
	Time	0.002
T1 mapping affected area	Group	0.513
	Group:Time	0.04
	Time	<0.001
T2 mapping septal	Group	0.278
	Group:Time	0.741
	Time	0.075
T2 mapping affected area	Group	0.467
	Group:Time	0.175
	Time	<0.001
ECV septal	Group	0.041
	Group:Time	0.852
	Time	0.112
ECV affected area	Group	0.035
	Group:Time	0.92
	Time	<0.001
LGE g	Group	0.32
	Group:Time	0.554
	Time	<0.001
LGE %	Group	0.164
	Group:Time	0.438
	Time	<0.001

Analysis of covariance (ANCOVA) test results are shown for each CMR metrics, taking into account the effect of the patient group (myocarditis patients after SARS-CoV-2 vaccination vs. myocarditis not linked to SARS-CoV-2 infection) and time of the CMR scan (acute vs. follow-up CMR scan) and the combination of these effects. Models are unadjusted.

CMR, cardiac magnetic resonance; ECV, extracellular volume; EDVi, left ventricular end diastolic volume index; EF, ejection fraction; ESVi, end systolic volume index; GLS, global longitudinal strain; Mi, mass index; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; SVi, left ventricular stroke volume index.

that 75% had received mRNA vaccines and 25% vector vaccines. Second, on the follow-up visit, a mean of 112 days after the acute presentation, CMR abnormalities depicting myocardial injury, decreased, or completely disappeared. Third, there was no apparent difference regarding CMR metrics between myocarditis cases potentially associated with COVID-19 vaccination and myocarditis unrelated to COVID-19. Finally, we found an increased T-cell response among myocarditis patients after vaccination compared to matched controls.

Comparison with existing literature

Our patients invariably presented with fever followed by chest pain and elevated troponin levels, typically 2–4 days after the second dose of the COVID-19 vaccine. This finding is consistent with previous reports (1, 12, 18). There was no evidence of ongoing SARS-CoV-2 infection or other viral infection in any of the participants. While most of our patients presented after the mRNA vaccine, similar to what studies from the US and Israel found (1, 13), 25% of all cases presented after receiving the Sputnik V vaccine. In Hungary, ∼40% of the population between the ages of 16 and 35 received a vector anti-SARS-CoV-2 vaccine (19), suggesting that myocarditis after COVID-19 vaccine might be less skewed toward mRNA vaccines than previously reported (20). Notably, at the time of our study, only the Pfizer-BioNTech vaccine was authorized to immunize the adolescent population ($n = 5$ in our cohort), who seem to be more prone to this adverse effect (4). This might limit meaningful comparison of the risk of myocarditis associated with different COVID-19 vaccines. Interestingly, a study based on the Vaccine Adverse Events Reporting System (VAERS) already cautioned against using mRNA vaccines among those with a higher risk for myocarditis and encourages vector vaccines as a safer alternative (20). However, a passive reporting

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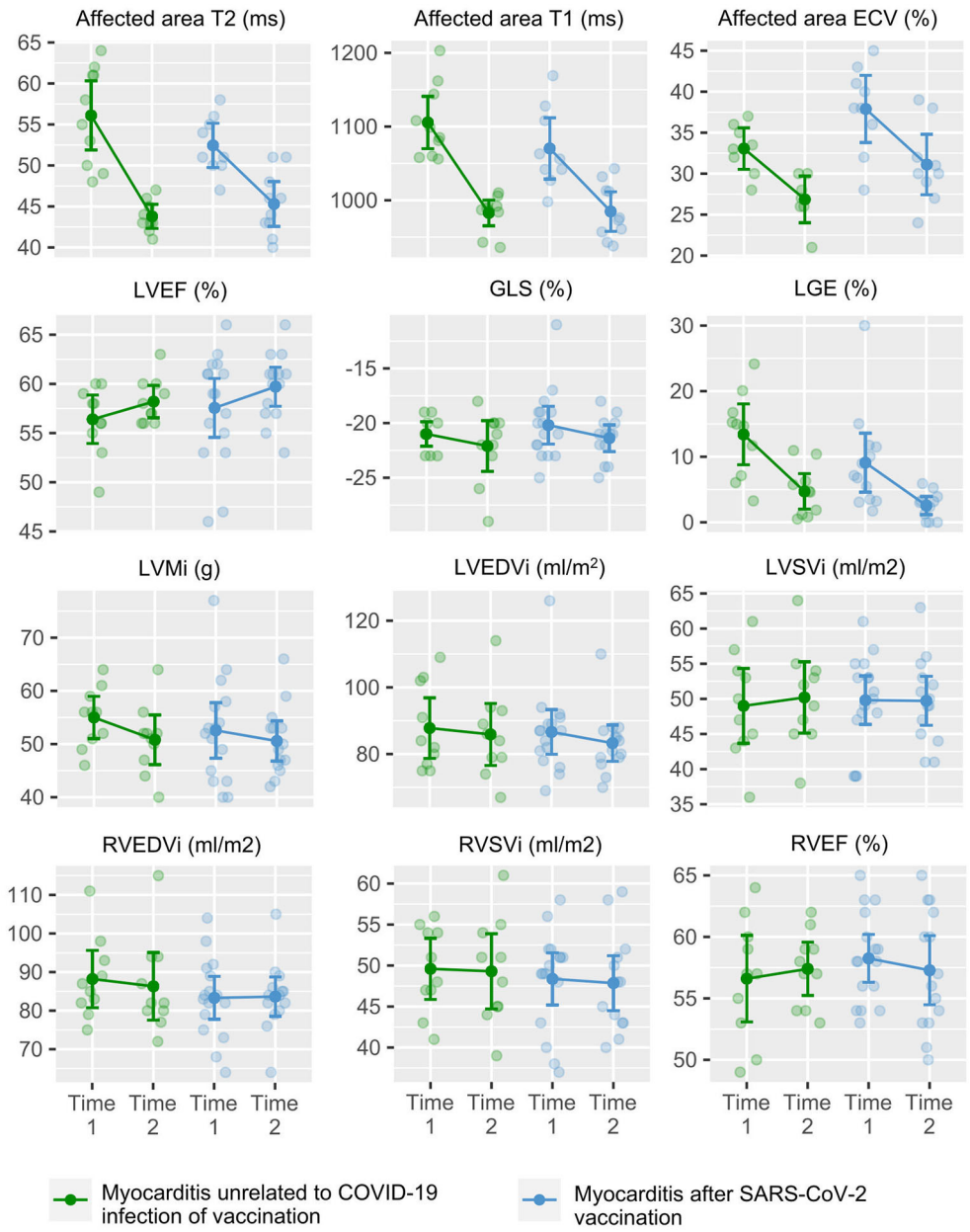

FIGURE 4
CMR metrics of myocarditis patients after SARS-CoV-2 immunization and myocarditis patients unrelated to COVID-19 immunization or infection over the acute phase and follow-up scan. Graphs show the trajectory of CMR metrics between the acute (T1) and follow-up (T2) CMR scans in myocarditis patients after SARS-CoV-2 immunization (in blue) and myocarditis patients unrelated to COVID-19 infection or vaccination (in green). CMR, cardiac magnetic resonance; ECV, extracellular volume; EDVi, left ventricular end diastolic volume index; EF, ejection fraction; ESVi, end systolic volume index; GLS, global longitudinal strain; Mi, mass index; LGE, late gadolinium enhancement; LV, left ventricular; RV, right ventricular; SVi, left ventricular stroke volume index.

system such as VAERS is prone to over- or underreporting based on the knowledge and attention of the reporters (5). Therefore, it should be used as a hypothesis-generating or event detection system (5, 21). Moreover, participants in our study received Gam-COVID-Vac (two doses required) as opposed to the Janssen vaccine (one dose required), which is approved by the Food and Drug Administration for use in the US and is therefore reported in the VAERS.

There are several aspects of the history of our patients that are worth noting. Twenty-five percent of our patients reported immune-mediated diseases. Furthermore, two individuals reported prior acute myocarditis, and one experienced

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TABLE 5 Immune response in myocarditis patients after COVID-19 immunization vs. age-, sex- and COVID-19 immunization-matched controls.

	Myocarditis patients after COVID-19 vaccination ($n = 12$)	Age- sex- and immunization-matched controls ($n = 23$)	*P*
Age, years	22 ± 7	22 ± 6	0.924
Sex, male %	12 (100)	23 (100)	NA
Time from the first dose of vaccine to test, days	109 ± 57	108 ± 58	0.983
Time form the second dose of vaccine to test, days	86 ± 60	81 ± 55	0.907
COVID-19 vaccine			
- mRNA vaccine *n* (%)	8 (67%)	18 (78%)	0.814
- vector vaccine *n* (%)	4 (33%)	5 (22%)	
Test after the second dose of COVID-19 vaccine, yes (*n* %)	10 (83%)	18 (86%)	0.432
Previous SARS-CoV-2 infection, yes *n* (%)	3 (25%)	21 (91%)	<0.001
Time from previous SARS-CoV-2 infection, days	224 ± 66	284 ± 73	0.206
Anti-SARS-CoV-2 NCP-IgG (Ratio*) *Cutoff: > 1.1*	0.24 [0.13, 0.49]	0.32 [0.21, 1.23]	0.198
Anti-SARS-CoV-2 NCP-IgM (Ratio*) *Cutoff: > 1.1*	0.31 [0.24, 0.48]	0.33 [0.18, 0.66]	0.715
S1 Ig (U/ml) *Cutoff: ≥ 0.8 U/ml*	10265.5 [2,232, 38327.5]	9,167 [3948.5, 20,050]	0.881
SP1 IgG (RU/ml) *Cutoff: ≥ 11 RU/ml*	1155.5 [284, 1,656]	627 [283, 1537.5]	0.505
SP1 IgA (Ratio*) *Cutoff: ≥ 1.1*	11 [7, 11]	7 [6.5, 10]	0.095
Ag1 – S1 CD4+ (IU/ml) *Cutoff: ≥ 0.15*	1.3 [0.5, 4.5]	0.5 [0.2, 1.0]	0.002
Ag2 – S1 CD4+ CD8+ (IU/ml) *Cutoff: ≥ 0.15*	2.0 [1.0, 4.7]	0.6 [0.2, 1.2]	0.008
Ag3 – S1 CD4+ CD8+, whole genome CD8+ (IU/ml) *Cutoff: ≥ 0.15*	2.4 [1.0, 6.8]	0.8 [0.6, 1.5]	<0.001

Immune response to myocarditis after COVID-19 vaccination vs. age-, sex- and COVID-19 immunization-matched controls. Continuous variables showing a normal distribution are presented as the mean and standard deviations (± SD), and those showing a non-normal distribution are reported as medians and interquartile ranges [IQRs]. Comparisons between participant groups were conducted using independent samples t tests and Mann–Whitney U tests as appropriate.
*Ratio, extinction of the sample/extinction of calibrator; Ag, Antigen; CD, Cluster of differentiation; NA, Not applicable; NCP, Nucleocapsid protein; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SP1, Spike protein 1.

recurrent myocarditis 3 months after vaccination. In the latter case, acute myocarditis was linked to acute gastrointestinal infection; thus, it seems unlikely that this event was associated with vaccination. These findings might suggest a predisposing immune system response, as described previously in the etiology of acute myocarditis unrelated to vaccination (22). We did not find a statistically significant difference between the immune response of participants with predisposing factors and that of those without predisposing factors; however, the limited number of patients in each group precludes meaningful conclusions.

The male predominance of myocarditis after vaccination and myocarditis unrelated to vaccination has been previously described, and the cause is still unknown (23). One leading hypothesis is based on sex hormone disparities. It has been proven that there are differences in sex hormone receptor expression on both immune cells and cardiac tissues (24). The highest free testosterone levels have been described in males aged 12–24 years (25). Moreover, testosterone has a role in interleukin-10 upregulation and interferon-gamma downregulation. However, the direct relationship between testosterone levels and myocarditis has not been conclusively proven. Finally, experimental data demonstrate that Y chromosome-associated genetic factors are also responsible for the higher prevalence of myocarditis among males (26). Vigorous sports activity can trigger the onset of acute myocarditis and should be avoided during ongoing infection (22, 27); this might also be applicable after immunization, especially among young males. Five individuals reported possible acute triggers in our cohort: vigorous physical activity ($n = 4$) and heavy alcohol consumption ($n = 1$) immediately after immunization. In summary, our current findings suggest that the combined effect of genetic predisposition, hormonal factors and acute triggers may contribute to the pathomechanism of myocarditis after COVID-19 vaccination.

Several case reports have provided a visual account of myocarditis after COVID-19 immunization using CMR imaging (28–31), and this is the first study to show the improvement of myocardial injury. Moreover, for context, we provided a control group of myocarditis unrelated to the COVID-19 vaccine or SARS-CoV-2 infection. In our study, the most frequent localization of LGE was the lateral wall of the left ventricle in both myocarditis patients after COVID-19 vaccination and patients with myocarditis unrelated to COVID-19 infection or vaccination. This suggests that based on the CMR image, it

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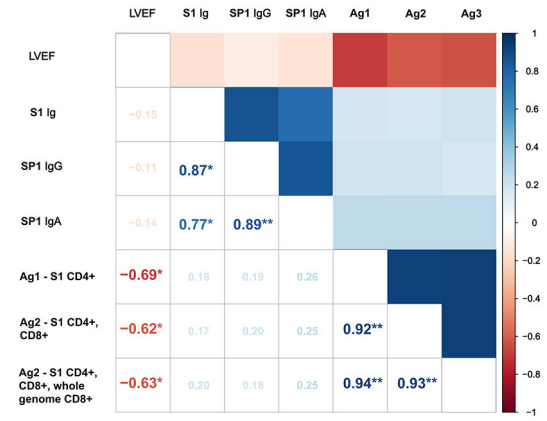

FIGURE 5
Correlation matrix showing the associations between SARS-CoV-2 immune response and LVEF. Positive correlations are shown in blue, and negative correlations are shown in red. Ag, Antigen; CD, Cluster of differentiation; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SP1, Spike protein 1; *$p < 0.05$; **$p < 0.001$.

is impossible to distinguish myocarditis cases post-vaccination from viral myocarditis. Our finding is in line with the recent report from Fronza et al. (32). CMR is a crucial diagnostic tool for myocardial injury. However, clarifying the disease etiology requires a holistic approach, taking into account the patient's history, symptoms and potential predisposing factors.

It has been shown, that acute myocarditis can heal or completely resolve over time (33), and our results support the notion that this is also true for cases potentially linked to the COVID-19 vaccine. We found that T2 mapping returned to the normal range on follow-up for all patients. Moreover, T1 mapping, ECV, and LGE decreased. Data suggest that LGE on the acute CMR scan is not equal to irreversible myocardial damage but the result of myocardial inflammation that can decrease over time and suggests a better prognosis over more extended follow-up periods. Additionally, none of the participants had extensive (>20%) LGE during follow-up, which is also considered a better prognostic marker (27). We found a slight improvement in LVEF during follow-up. Whilst the betterment of GLS values were not significant in our study, as expected based on the literature (34), the overall trend of GLS also suggested a marginal improvement over time when looking at individual data points.

In addition to the production of SARS-CoV-2-specific antibodies, COVID infection also leads to the generation of specific CD4+ and CD8+ cells (35). Increasing evidence supports the essential role of the T-cell-mediated response to SARS-CoV-2 infection; the COVID-specific T-cell response is associated with less severe disease (36, 37). Thereafter, to obtain a comprehensive view regarding the COVID-specific adaptive immune response, it is essential to measure specific antibodies and CD4+ and CD8+ cells from the same individual. Our current data indicate a substantially accelerated COVID-specific T-cell-mediated immune response in the myocarditis group compared to the age-, sex-, and vaccination status-adjusted control population. It is noteworthy that a larger proportion of controls than myocarditis patients had previously had COVID infections.

The rapid onset of symptoms after vaccination is an intriguing phenomenon and might be connected with immune response-mediated pathomechanisms. Reports all over the globe agree that myocarditis starts ∼2–4 days after vaccination. Although data regarding long-term immunity are scarce, it seems that a T-cell response is sustained for several months after infection and appears to be more prolonged than the antibody response. It has also been suggested that the T-cell response to different COVID-19 vaccines differs among age groups (17).

While we believe that acute myocarditis after COVID-19 vaccination is an important cardiovascular adverse effect that may occur after both mRNA and vector vaccines, this should not overshadow the ample evidence that clearly supports the effectiveness of vaccines (38, 39). The question also arose if young patients with COVID-19 are more likely to develop acute myocarditis or other adverse events than individuals after SARS-CoV-2 immunization. The most serious of which is the multisystem inflammatory syndrome in children (MIS-C). Recent evidence from France suggests that COVID-19 vaccination is associated with lower MIS-C incidence among adolescents (40). Moreover, in a new report by Zambrano et al. critically ill MIS-C patients requiring life support, all were unvaccinated, reinforcing the COVID-19 vaccination recommendation for eligible children (41). Therefore, there is an urgent need for an international consensus recommendation regarding an immunization protocol for those who experienced acute myocarditis after their COVID-19 vaccine.

Limitations

The main limitation of our study is the small sample size, which is mainly due to the rare occurrence of myocarditis after COVID-19 vaccination. Although we contacted all Hungarian centers reporting CMR, we could not avoid referral bias to CMR by clinicians. Mapping sequences were available in three institutes out of four. Similarly to other reports of myocarditis after COVID-19 vaccination, we report myocarditis cases of young, male patients. This prevents generalizability of our results to the female or older male population. In the institute where the parametric T2 mapping sequence was not available, oedema was characterized by T2-weighted black blood images alone. Mapping sequences were compared only among those participants who were scanned at the Semmelweis University Heart and Vascular Center (using a Siemens Magnetom Aera

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1.5 T scanner) to avoid inter scanner variability. Importantly, our myocarditis control group's history was provided by the referring physician. The control group for the immunological studies did not undergo CMR examination.

Conclusions

In this cohort of myocarditis patients after COVID-19 immunization confirmed by CMR, we found that acute myocarditis can occur after mRNA and vector vaccines, predominantly in individuals with predisposing factors. Upon mid-term follow-up, myocarditis showed improvements in CMR markers, including the LVEF and tissue-specific alterations. The T-cell response was more prominent among myocarditis patients after COVID-19 vaccination than matched controls.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by National Public Health Center of Hungary. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HV, LS, GN, BM, RK, and DB contributed to the conception and design of the study. HV, LS, AT, VJ, ZD, GB, ES, ZU, ZS, and GGN contributed to the data acquisition and curation. LS performed the statistical analysis and wrote the first draft of the manuscript. HV refined the manuscript. GN, GGN, ZU, and ZS wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.961031/full#supplementary-material

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