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Frontiers of COVID-19-related myocarditis as assessed by cardiovascular magnetic resonance

Luo Y *et al.* Frontiers of COVID-19-Related Myocarditis by CMR

Yi Luo, Ben-Tian Liu, Wei-Feng Yuan, Can-Xian Zhao

Abstract

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In some patients, COVID-19 is complicated with myocarditis. Early detection of myocardial injury and timely intervention can significantly improve the clinical outcomes of COVID-19 patients. Although endomyocardial biopsy (EMB) is currently recognized as the 'gold standard' for the diagnosis of myocarditis, there are large sampling errors, many complications and a lack of unified diagnostic criteria. In addition, the clinical methods of treating acute and chronic COVID-19-related myocarditis are different. Cardiac magnetic resonance (CMR) can evaluate the morphology of the heart, left and right ventricular functions, myocardial perfusion, capillary leakage and myocardial interstitial fibrosis to provide a noninvasive and radiation-free diagnostic basis for the clinical detection, efficacy and risk assessment, and follow-up observation of COVID-19-related myocarditis. However, for the diagnosis of COVID-19-related myocarditis, the Lake Louise Consensus Criteria may not be fully applicable. COVID-19-related myocarditis is different from myocarditis related to other viral infections in terms of signal intensity and lesion location as assessed by CMR, which is used

to visualize myocardial damage, locate lesions and quantify pathological changes based on various sequences. Therefore, the standardized application of CMR to timely and accurately evaluate heart injury in COVID-19-related myocarditis and develop rational treatment strategies could be quite effective in improving the prognosis of patients and preventing potential late-onset effects in convalescent patients with COVID-19.

Key words: COVID-19; Myocarditis; Cardiovascular magnetic resonance; Inflammation; Diagnosis; Infection

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Core tip: This review aims to explore the frontiers of Coronavirus disease 2019 (COVID-19)-related myocarditis as assessed by Cardiac magnetic resonance (CMR) and compare the similarities and differences in CMR signs between COVID-19-related myocarditis and myocarditis related to other viral infections. COVID-19-related myocarditis is different from myocarditis related to other viral infections in SI and lesion location as assessed by CMR. The Lake Louise Consensus Criteria are not fully applicable to COVID-19-related myocarditis. CMR is expected to visualize myocardial damage, locate lesions and quantify pathological changes based on various sequences with the benefit of staged diagnosis and treatment in COVID-19-related myocarditis.

INTRODUCTION

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In patients with coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the main clinical manifestations of patients are fever and cough. In patients with severe cases of COVID-19, acute respiratory distress syndrome and respiratory failure can occur^[1,2]. In some patients, COVID-19 is often complicated with myocarditis^[3]. In general, the severity of COVID-19 is proportional to the degree of cardiac injury. Early detection of myocardial injury and timely intervention can significantly improve the clinical outcomes of COVID-19 patients^[4,5]. Although endomyocardial biopsy (EMB) is currently recognized as the 'gold standard' for the diagnosis of myocarditis, there are large sampling errors, many complications and a lack of unified diagnostic criteria^[6,7]. In addition, the clinical methods of treating acute and chronic COVID-19-related myocarditis are different^[8,9]. Cardiac magnetic resonance (CMR) can evaluate the morphology of the heart, left and right ventricular functions, myocardial perfusion, capillary leakage and myocardial interstitial fibrosis to provide a noninvasive and radiation-free diagnostic basis for the clinical detection, efficacy and risk assessment, and follow-up observation in COVID-19-related myocarditis in one step^[10-14]. The Lake Louise Consensus Criteria (2009) have been widely used in the CMR diagnosis of myocarditis^[15]. The new guidelines (2018) updated and supplemented the imaging techniques and parameters to improve the accuracy of CMR in the diagnosis of myocarditis^[16]. The pathological changes in myocarditis as assessed by CMR are depicted in Figure 1. However, for the diagnosis of COVID-19-related myocarditis, the Lake Louise Consensus Criteria may not be fully applicable. This review aims to explore the frontiers of COVID-19-related myocarditis as assessed by CMR and compare the similarities and differences in CMR signs between COVID-19-related myocarditis and myocarditis related to other viral infections. We used ['COVID-19' or 'SARS-CoV-2'] and ['myocarditis' or 'myocardial inflammation']

and ['MR' or 'MRI' or 'magnetic resonance'] as the search terms and mainly searched the relevant academic articles included in PubMed.

COVID-19 RELATED MYOCARDITIS

Pathological mechanism

Compared with other viral infection-related diseases, COVID-19 is associated with a high risk of death from cardiovascular complications, with an unclear pathophysiological mechanism^[17,18]. Current studies^[18-20] propose that the potential pathogenesis of cardiovascular injury mainly includes: (1) direct virus damage; (2) hypoxia and an imbalance of myocardial oxygen supply and demand; (3) cytokine storms; and (4) abnormal coagulation. COVID-19-related cardiac injury may involve many pathways^[21], among which immune response disorder, microcirculation disorder and the side effects of antiviral drugs may be the main causes of COVID-19 myocardial injury. SARS-CoV-2 can lead to a systemic inflammatory response and immune and coagulation dysfunction after host infection. Angiotensin-converting enzyme-2 is widely distributed in the heart; however, SARS-CoV-2 can still enter host cardiomyocytes. Although studies have shown that virus particles can be observed in cardiomyocytes, there is no evidence of virus particle or SARS-CoV-2 gene expression in cardiomyocytes^[22,23]. Thus, whether SARS-CoV-2 directly damages cardiomyocytes is still controversial. Immune response disorders and cytokine storms may be the main mechanisms of heart injury in COVID-19^[24]. Infection with SARS-CoV-2 causes a systemic inflammatory response and the activation of the sympathetic adrenal system, which then causes a cytokine storm to attack cardiomyocytes and coronary arteries. In addition, SARS-CoV-2 may increase the expression of inflammatory factors, enhance the coagulation cascade, disrupt the physiological balance between coagulation and fibrinolysis, and cause the body to enter a hypercoagulable state to promote the formation of thrombosis.

Clinical staging and treatment

For acute and chronic COVID-19-related myocarditis, the clinical applications of specific remedies and symptomatic treatments are different^[25]. Determining how to accurately stage COVID-19-related myocarditis is essential. According to the pathological development and outcomes, COVID-19-related myocarditis involves an acute stage, a subacute stage, a recovery stage, a chronic stage and a sequelae stage^[26-29]. However, in the choice of treatment plans for patients with viral myocarditis, COVID-19-related myocarditis is often reducible to just an acute stage and a chronic stage for symptomatic treatment. To alleviate cardiac insufficiency and improve the survival rate, intravenous gamma globulin can be used in the treatment of acute viral myocarditis, especially in children^[30]. Immunosuppressants cannot be prescribed for patients with myocarditis not confirmed by pathology, and routine use of immunosuppressants in patients with acute myocarditis is not advocated. However, for patients with chronic myocarditis complicated with complete atrioventricular block or cardiogenic shock, immunosuppressants can be used in sufficient amounts^[31]. In addition, for patients with chronic myocarditis complicated with heart failure, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, β receptor blockers and diuretics are recommended to be used reasonably to reduce inflammatory reactions and prevent ventricular remodelling^[32]. Therefore, CMR not only can reflect the histopathological characteristics of myocardial injury but also is the most promising technical method to determine the clinical stage of COVID-19-related myocarditis.

Acute myocarditis as assessed by CMR

The main pathological changes in COVID-19-related acute myocarditis include capillary congestion and leakage, cardiomyocyte oedema and necrosis.

Myocardial oedema and decreased systolic function in early myocarditis are reversible injuries^[16]. Thus, timely intervention contributes to significantly reducing mortality in acute myocarditis. T2 weighted imaging (T2WI) is sensitive to oedema, which shows high signal intensity (SI). Short time of inversion recovery in T2WI (T2-STIR) is often used to improve the contrast between the oedematous area and the normal myocardium. Oedema is a specific marker of reversible injury in acute myocarditis and usually occurs 2-3 weeks before severe cardiomyocyte damage^[33]. Therefore, the presence of oedema is helpful to distinguish between acute and chronic COVID-19-related myocarditis. T2WI is recommended as a characteristic index to describe focal and diffuse oedema in COVID-19-related myocarditis^[34]. During the treatment of acute myocarditis, the decrease in T2WI SI can be applied as a marker of oedema remission to achieve the purpose of monitoring the condition. However, other diseases, such as sarcomatosis and immune rejection of a heart transplant, also show similar T2WI SI, and the evaluation is subjective; therefore, the high T2WISI may be not specific. T2 mapping generates different T2WI scans based on different T2 relaxation times by steady-state free precession (SSFP) and then calculates the corresponding pixels of each image by fitting the parameter equation. Therefore, the SI of each image can reflect different echo times to realize the quantification and analysis of T2 values. It is worth mentioning that the SSFP sequence can reduce various unstable factors, such as the long T2 signals generated by slow blood flow during scanning and motion artefacts caused by poor breath holding. T2 mapping is a more accurate, rapid and quantitative method for detecting myocardial oedema to compensate for the defects of traditional T2-STIR. The detection rate of myocardial oedema by T2 mapping is much higher than that by T2-STIR. T2 mapping is quite accurate for defining the scope of myocardium infection and reflecting myocardial oedema and is positively correlated with high-sensitivity troponin in the acute stage of COVID-19-related myocarditis^[35]. In addition, scanning

methods of gadolinium contrast enhancement in CMR include ³ early gadolinium enhancement (EGE) and late gadolinium enhancement (LGE). Because gadolinium contrast agent is an extracellular contrast agent that cannot pass through the complete biofilm, the two techniques are applied to detect the different characteristics of myocardial injury of COVID-19-related myocarditis: EGE is mostly used to reflect tissue congestion, which is the characteristic of an active inflammatory reaction; LGE indicates irreversible heart injury, such as myocardial necrosis and interstitial fibrosis^[36]. The acute course of COVID-19-related myocarditis is approximately 4 weeks, mainly including myocardial cell membrane rupture and myocardial tissue dissolution. With the increase in capillary blood flow and vascular leakage, gadolinium contrast agent quickly distributes to the intercellular space. Generally, at 3-5 min after injection, EGE is shown as high SI with a rapid increase in gadolinium contrast agent concentration in myocardial tissue. In the early stage of acute COVID-19-related myocarditis, a single inflammatory lesion gradually develops and spreads into multiple lesions, and the accurate application of EGE contributes to a sensitive diagnosis within the first 2 weeks after infection. A return to normal of EGE within 1 month after acute myocardial inflammatory injury indicates that left ventricular function has recovered well. ² Myocardial perfusion imaging after severe COVID-19 also demonstrates regional ischaemia rather than global blood flow reduction^[37]. Nevertheless, the biggest limitation of EGE is that it is unable to quantify SI accurately. Arrhythmia, motion artefacts caused by poor breath holding, and fast heart rate in infants may lead to failure to evaluate EGE SI. Thus, quantitative techniques such as T1 mapping and extracellular volume (ECV) analysis are recommended to evaluate COVID-19-related myocarditis. Image acquisition of T1 mapping occurs at different inversion times of the same phase of multiple cardiac cycles to directly and quantitatively measure the T1 value of each voxel of the myocardium and display the difference in the T1 value of the myocardium.

Compared with T1-weighted imaging, the application of T1 mapping is expected to reduce the subjectivity of traditional qualitative evaluation and increase the repeatability of CMR evaluation^[38]. Similar to the T2 mapping value, the native T1 mapping value also increases in acute myocarditis. It has been reported that children with COVID-19-related myocarditis show mild subepicardial LGE, suggesting diffuse interstitial oedema and myocardial injury; after immunomodulatory treatment, the oedema is relieved, and the corresponding native T1 value decreases^[39,40].

Chronic myocarditis as assessed by CMR

LGE is expected to evaluate cardiomyocyte necrosis and fibrosis in irreversible myocardial damage caused by myocarditis after SARS-CoV-2 infection^[41-43]. The content of free water is relatively low in cardiomyocytes, so oedema is not obvious, and the detection rate of T2WI is not high in chronic COVID-19-related myocarditis. Because gadolinium contrast agent can significantly reduce the T1 relaxation time and increase the SI in the myocardial injured area, LGE is more sensitive for detecting oedema than T2WI^[44]. Due to their broken cell membranes, necrotic cardiomyocytes absorb gadolinium contrast agent and show a higher SI than normal cardiomyocytes. Gadolinium contrast agent accumulates in necrotic cardiomyocytes (early stage of necrosis) and myocardium affected by interstitial fibrosis (late stage of necrosis) within a few minutes after intravenous injection, and its content exceeds that of normal myocardial tissue. Thus, LGE indicates typical "delayed enhancement" in the early and late stages of myocardial necrosis, respectively, with characteristic significance in the detection of cardiomyocyte necrosis. The LGE-positive location in COVID-19-related myocarditis is not only similar to that in myocarditis related to other viral infections, often involving the inferior wall and lateral wall of the left ventricle, but also appears in the ventricular septum and free wall at the base and middle of the left ventricle^[45-50]. Importantly,

compared with other viral infections, the area of LGE caused by SARS-CoV-2 infection of the myocardium is more extensive, but the SI of T2WI and LGE may not be obviously high^[51]. Moreover, Eiros *et al*^[52] and Inciardi *et al*^[53] evaluated COVID-19-related myocarditis through CMR, and they found that the patients had not only myocardial interstitial oedema and diffuse LGE but also ventricular dysfunction, pericarditis and pericardial effusion; CMR in a male patient with COVID-19 mild pericarditis showed focal oedema in the lateral, anterior, inferior and apical wall of the left ventricle with epicardial involvement^[54]; and a female patient with acute COVID-19-related pericarditis and cardiac tamponade presented in CMR with subepicardial LGE of the anterolateral wall of the left ventricle^[55]. Interestingly, adolescents and children infected with SARS-CoV-2 may present the clinical characteristics of Kawasaki disease and multisystem inflammatory syndrome (MIS)^[56,57]. Most children with MIS showed no obvious LGE but myocardial oedema strain and an abnormal myocardium, suggesting that focal myocardial necrosis or fibrosis was rare, but there was a lack of research for long-term follow-up and re-examination^[40,58]. Therefore, whether the prognosis of children and adolescents infected with SARS-CoV-2 is favourable needs further multicentre and big-data research. However, due to the correlation between the detection rate of LGE and the severity of myocardial damage, the sensitivity of COVID-19-related myocarditis detection is limited by the area of myocarditis. The smaller the area of myocarditis, the less likely it is to be detected by LGE. In addition, LGE also shows high SI in certain cardiomyopathies and myocardial amyloidosis, so its diagnostic specificity for COVID-19-related myocarditis is not high. COVID-19-related myocarditis needs to be comprehensively analysed by combining T2WI, EGE, T1 mapping, ECV analysis, diffusion tensor imaging (DTI) and other quantitative parameters. At present, the clinical diagnosis of myocardial fibrosis often depends on EMB, and T1 mapping has been gradually popularized and applied to reduce the potential risks associated with EMB. T1

mapping is expected to evaluate the prognosis of COVID-19-related myocarditis, and ECV analysis is an important technical method in coordination with T1 mapping^[59]. Myocardial fibrosis is the main feature of COVID-19-related myocarditis in the chronic stage and one of the pathological mechanisms leading to ventricular remodelling. Fortunately, the expansion of the myocardial extracellular matrix is reversible, and early clinical medication is expected to prevent the proliferation of fibrosis. Therefore, T1 mapping and ECV analysis not only help to determine the clinical stage of COVID-19-related myocarditis but also provide the necessary diagnostic basis for guiding treatment through quantitative analysis of myocardial extracellular matrix volume^[60]. It is worth mentioning that DTI is a technology based on DWI to quantify the anisotropy of water molecules and measure the degree and direction of water molecule diffusion^[61]. DTI is expected to analyse the data of water molecular diffusion in three-dimensional space to noninvasively observe the damage severity of myocardial tissue infected by SARS-CoV-2 and evaluate whether the myocardial structure integrity has been lost^[62]. Clinicians should be vigilant against the possible late-onset effects of convalescent patients with COVID-19 and use the CMR multiparameter model to dynamically and quantitatively evaluate myocardial fibrosis in follow-up.

Secondary myocardial infarction and cardiac dysfunction

In approximately 31% of patients, COVID-19-related myocarditis can be complicated with secondary myocardial ischaemia^[63]. SARS-CoV-2 first damages the endothelial cells of blood vessels in different human tissues and organs. Diffuse endothelial inflammation causes endothelial dysfunction and microvascular dysfunction and then leads to vasoconstriction, blood hypercoagulability and thrombosis, resulting in secondary myocardial ischaemia and myocardial infarction^[64]. Different from computed tomography angiography and echocardiography to evaluate coronary artery dilatation and

rupture in COVID-19, CMR is mainly used to evaluate the severity of myocardial injury and detect the thrombus at the apex^[45,65]. Interestingly, LGE of certain patients infected with SARS-CoV-2 showed that the infarct area was 3/4 the area of the anterior wall, and T2WI-STIR showed cardiomyocyte oedema in the corresponding location, suggesting acute myocardial infarction, but the patients had no symptoms^[26]. Secondary myocardial infarction caused by SARS-CoV-2 infection in children is often accompanied by cardiomyocyte oedema and coronary artery dilatation, which is difficult to distinguish from acute Kawasaki disease. This indicates a poor prognosis if LGE becomes positive in the follow-up. Furthermore, unlike myocarditis related to other viral infections, COVID-19-related myocarditis is often secondary to right ventricular enlargement and dysfunction, which may be related to pulmonary hypertension and acute pulmonary embolism caused by SARS-CoV-2 infection^[66]. Right ventricular dysfunction was independently associated with all-cause mortality in patients with COVID-19-related myocarditis^[67]. Ventricular remodelling may gradually induce heart failure and related complications, resulting in a poor prognosis and significantly increased mortality. Huang *et al*^[48] found that a long-term decline in right ventricular function parameters, such as the right ventricular ejection fraction, lasted in patients with COVID-19-related myocarditis. Some studies have also found that left ventricular dilation and decreased left ventricular ejection fraction occurred in convalescent patients with COVID-19^[23,68]. Although SARS-CoV-2 appears to cause less damage to the left ventricle, there may be sustained damage, so its long-term results need to be followed up.

Limitations and Prospects

T1 mapping is not recommended to be independently applied in the diagnosis of COVID-19-related myocarditis because several factors probably cause changes in the T1 value. In addition, DTI is prone to errors in tracking crossed

myocardium fibres in chronic myocarditis. Moreover, artificial intelligence techniques have relatively matured in assisting in the diagnosis and prognosis analysis of COVID-19, including COVID-19-related pneumonia, but not in COVID-19-related myocarditis. In this mini-review, the majority of the available data were from case reports and observational studies that focused on CMRI performed in the setting of acute COVID-19-related myocarditis. We need more data from cohort studies to support the findings in the setting of chronic COVID-19-related myocarditis. Findings from multicentre and large-scale research projects on COVID-19, such as CISCO-19, will contribute to guiding the clinical application of CMR in COVID-19-related myocarditis and heart injury^[12,69].

CONCLUSION

COVID-19-related myocarditis is different from myocarditis related to other viral infections in SI and lesion location as assessed by CMR. Although the Lake Louise Consensus Criteria are not fully applicable to COVID-19-related myocarditis, they are still the most authoritative diagnostic guidelines and need to be further supplemented. CMR is expected to visualize myocardial damage, locate lesions and quantify pathological changes based on various sequences with the benefit of staged diagnosis and treatment. Therefore, the standardized application of CMR to timely and accurately evaluate heart injury in COVID-19-related myocarditis and develop rational treatment strategies could be quite effective in improving the prognosis of patients and preventing potential late-onset effects in convalescent patients with COVID-19.

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