Magnetic Resonance Letters 1 (2021) 2–10

Contents lists available at ScienceDirect

Magnetic Resonance Letters

journal homepage: www.keaipublishing.com/MRL

Review Article

Evaluation of injuries caused by coronavirus disease 2019 using multi-nuclei magnetic resonance imaging

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A R T I C L E I N F O

Article history:
Received 24 June 2021
Received in revised form 6 July 2021
Accepted 19 July 2021
Available online 8 August 2021

Keywords:
COVID-19
Multi-nuclei
MRI
Hyperpolarized ^{129}Xe
Lung
Brain
Heart

A B S T R A C T

The ongoing pandemic of coronavirus disease 2019 (COVID-19) has been a great burden for the healthcare system in many countries because of its high transmissibility, severity, and fatality. Chest radiography and computed tomography (CT) play a vital role in the diagnosis, detection of complications, and prognostication of COVID-19. Additionally, magnetic resonance imaging (MRI), especially multi-nuclei MRI, is another important imaging technique for disease diagnosis because of its good soft tissue contrast and the ability to conduct structural and functional imaging, which has also been used to evaluate COVID-19-related organ injuries in previous studies. Herein, we briefly reviewed the recent research on multi-nuclei MRI for evaluating injuries caused by COVID-19 and the clinical ^{1}H MRI techniques and their applications for assessing injuries in lungs, brain, and heart. Moreover, the emerging hyperpolarized ^{129}Xe gas MRI and its applications in the evaluation of pulmonary structures and functional abnormalities caused by COVID-19 were also reviewed.

1. Introduction of coronavirus disease 2019 (COVID-19)

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Since the first known case was reported in December 2019 in Wuhan, China, the disease has rapidly spread worldwide. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak as a pandemic. To date, more than 182 million confirmed cases and 3.95 million deaths have been reported worldwide [2]. The ongoing pandemic of COVID-19 has been a great burden for the national healthcare system in many countries because of its high transmissibility, severity, and fatality.

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Peer review under responsibility of Innovation Academy for Precision Measurement Science and Technology (APM), CAS.

https://doi.org/10.1016/j.mrl.2021.100009

COVID-19 is mainly transmitted via respiratory droplets [3] and close contact, and other transmissions [4] include contacting with contaminated objects and aerosol transmission in relatively closed environments. Patients with COVID-19, including asymptomatic patients, are the main source of infection. Some immunity can be obtained after infection or vaccination; however, the duration of immunity remains unknown.

The severity of COVID-19 could be classified as asymptomatic, mild, moderate, or severe according to the clinical symptoms. Most symptomatic patients with COVID-19 have mild to moderate symptoms [5]. The most common symptoms are fever, dry cough, and fatigue. While other symptoms, including sore throat, nasal congestion, muscle or joint pain, headache, loss of smell and taste, and diarrhoea [6,7], are less common but would also affect some patients. The clinical symptoms of COVID-19 are summarized in Table 1. Multiple organs, including lungs, brain, kidneys, and heart, can be affected by COVID-19, and pneumonia is one of the most common clinical manifestations [8]. Some critically ill patients would eventually develop acute respiratory distress syndrome (ARDS), multiple organ failure, or septic shock [9]. Moreover, a severe disease onset may lead to death due to massive alveolar damage and progressive respiratory failure [6]. Fortunately, most patients recover from the acute phase of COVID-19. However, some discharged patients may have some sequelae.

The clinical symptoms of COVID-19 are the first and most accessible information [12] for diagnosis and are used for severity classification but cannot be used for definite diagnosis, because common symptoms, such as fever and dry cough, are also typical symptoms of the common cold. The diagnosis of COVID-19 is generally confirmed using viral tests, including nucleic acid amplification tests (NAATs) and antigen tests. NAATs with reverse transcription-polymerase chain reaction (RT-PCR) are currently the most widely used diagnostic methods for COVID-19 testing worldwide [4]. Moreover, chest imaging, such as chest radiography and computed tomography (CT), is also advised by the WHO for diagnostic purposes in symptomatic patients when RT-PCR is not available or its result is negative with the presence of a high clinical suspicion of COVID-19 [13].

Chest imaging is a crucial element for patient management and plays a vital role in the diagnosis, detection of complications, and prognostication of COVID-19 [12,14]. Among chest imaging modalities, CT is the most widely used modality for COVID-19 owing to its high resolution and scanning speed, and typical features, such as ground-glass opacities (GGOs), consolidation, and crazy-paving [15], could be found among patients with COVID-19. Chest CT has shown a high sensitivity for COVID-19 pneumonia diagnosis [16], and some patients have early typical lung consolidation on CT when RT-PCR yields negative findings [17]. Significant destruction of the lung parenchyma, including interstitial inflammation and extensive consolidation [18], is the typical radiographic manifestation of COVID-19 pneumonia. Extensive GGOs and pulmonary consolidation may suggest ARDS and massive lung infections with alveolar damage [19]. Chest CT could also be used to evaluate the lesion absorption of residual GGOs and subpleural parenchymal bands (Fig. 1) [14,15]. In addition, it has also been used to evaluate the short-term and long-term health consequences among discharged patients with COVID-19. According to a retrospective study, chest imaging abnormalities were found in more than half of the discharged patients in the early convalescence phase [20]. Moreover, significant radiological and physiological abnormalities were still observed in a considerable proportion of COVID-19 survivors without critical illness at 3 months after discharge [21]. Meanwhile, more abnormal chest imaging manifestations were found in COVID-19 survivors with more severe illness during hospitalization at 6 months after discharge from the hospital [22].

In addition to CT, MRI is another important clinical imaging technique for disease diagnosis because of its good soft tissue contrast and the ability to conduct structural and functional imaging. It is more suitable for long-term evaluation of diseases because it is free of ionizing radiation. Although many nuclei, including ^{1}H, ^{13}C, ^{23}Na, ^{31}P, ^{35}Cl, ^{17}O, and ^{129}Xe, can be used for MRI, clinical MRI generally utilizes the nucleus of ^{1}H as the signal source for its abundance in the body and inherently high magnetic resonance (MR) signal sensitivity. With the development of MRI techniques, multi-nuclei MRI has been developing rapidly and shown feasibility and potential in clinical practice because the MR signal sensitivity can be enhanced enormously by cutting-edge MRI acquisition and reconstruction techniques, hardware, and hyperpolarization (HP) techniques, such as spin exchange optical pumping (SEOP) and dynamic nuclear polarization. Herein, we reviewed the recent research on multi-nuclei MRI for evaluating injuries caused by COVID-19, including the techniques of ^{1}H MRI and the emerging HP ^{129}Xe gas MRI and their applications for assessing abnormalities in lungs, brain, heart, and other organs caused by this disease.

Table 1
Symptoms and signs of coronavirus disease 2019.

Symptoms and signs	Frequency range	Reference
Fever	83%–99 %	[10]
Dry cough	59%–82 %	[10]
Fatigue	44%–70 %	[10]
Shortness of breath	31%–40 %	[10]
Muscle pain	11%–35 %	[10]
Sore throat	13.9 %	[11]
Headache	13.6 %	[11]

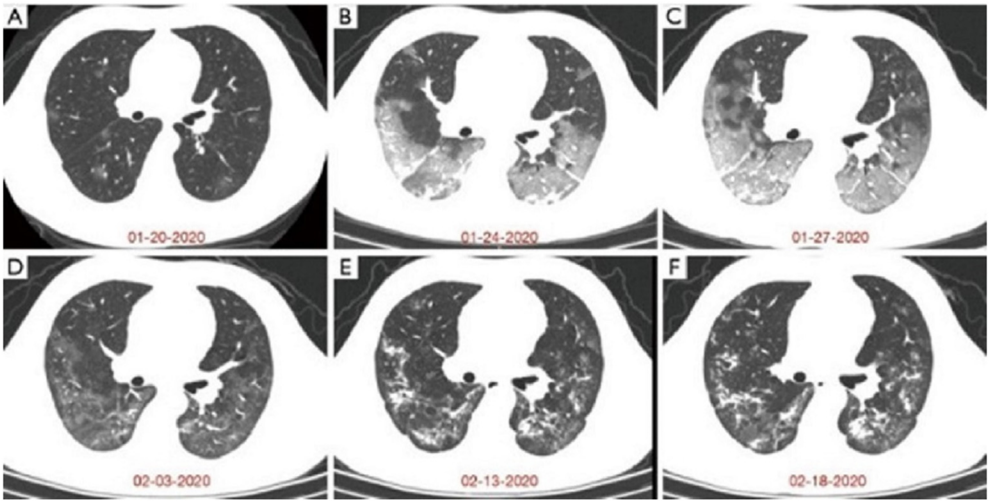

Fig. 1. Typical chest computed tomographic images of recovering and discharged patients. Reproduced with permission [14].

2. Evaluation of COVID-19 using ^{1}H MRI

2.1. Evaluation of COVID-19-related pulmonary damage using ^{1}H MRI

Compared with CT, ^{1}H MRI has good soft tissue contrast and is free of ionizing radiation and radioactivity, which allows its use in lung imaging, though it is also confronted with great challenges because of low proton density and short T_2* in lung parenchyma. With the aid of the ultrashort echo time (UTE) technique, clinical ^{1}H MRI could be used to evaluate COVID-19 (Fig. 2). And the results are considered in concordance with those of CT [23]. In addition, pulmonary MRI techniques, such as oxygen-enhanced (OE)-MRI [24] and high-performance low-field MRI with periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) [25], have been used to evaluate lung damage caused by COVID-19.

OE-MRI was first proposed by Edelman in 1996. It has the ability to assess pulmonary regional oxygen delivery and uptake [26]. OE-MRI is mainly based on the relaxation effect of protons caused by oxygen, which is a paramagnetic substance that can reduce the T_1 values of protons. In this imaging technique, the longitudinal relaxation rate of protons changes in proportion to the concentration of molecular oxygen dissolved in the interstitial tissue. Two scans should be performed under the conditions of breathing pure oxygen (100 % oxygen) and room air (21 % oxygen) to obtain the OE-MR images. Thereafter, hyperoxic and normoxic images and corresponding signal intensities ($S_{100\ \%}$ and $S_{21\ \%}$) could be obtained. By subtracting normoxic from hyperoxic images ($S_{100\%}$–$S_{21\ \%}$), the distribution of lung ventilation function, that is, OE-MR images, could be obtained. UTE sequences are frequently used to improve the signal to noise ratio (SNR) of OE-MR images. Recently, OE-MRI has also been used to investigate pulmonary ventilation in discharged patients with COVID-19 of different severities [24]. The sequence of respiratory-gated three-dimensional (3D) UTE-MRI was used to obtain the OE-MRI data from 49 discharged patients with COVID-19, and regional abnormalities were calculated by measuring the ventilation defects using the percent signal enhancement (PSE) map, which was calculated using the following equation: PSE = ($S_{100\ \%}$ - $S_{21\ \%}$)/$S_{21\ \%}$. The analysis showed that the detection of lesions using chest CT and OE-MRI was in good agreement. Moreover, the severity of COVID-19 could be well determined using PSE derived from OE-MRI, and lesion and normal areas of the lungs could also be clearly

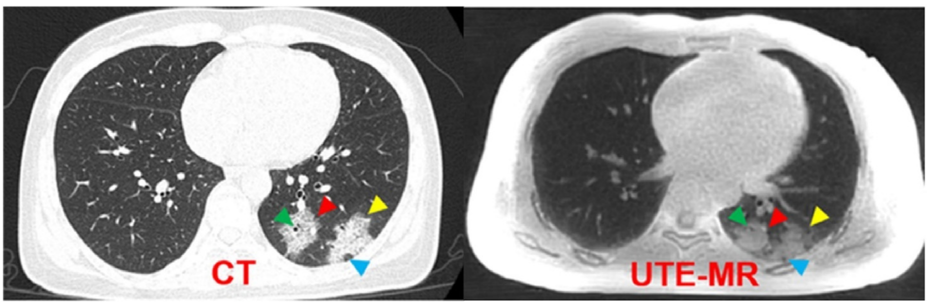

Fig. 2. Representative CT and UTE-MR images of a female patient with coronavirus disease 2019. Reproduced with permission [23]. CT, computed tomography; UTE, ultrashort echo time; MR, magnetic resonance.

distinguished. However, the measurement of the lesion type and size was still beyond the ability of OE-MRI. OE-MRI might be helpful for stratifying the severity of COVID-19, guiding the treatment, evaluating the treatment response, predicting the prognosis, and identifying patients who require earlier intervention.

In addition to OE-MRI, high-performance low-field MRI can also be used to detect pneumonia. To resolve the low MR image quality owing to the low water density and air-tissue interfaces causing local magnetic susceptibility gradients [27], researchers have developed a high-performance low-field MRI system integrating modern technology at 0.55 T [28]. The system has a lower and more uniform field to reduce magnetic susceptibility gradients caused by air-tissue interface and reduce image distortion caused by field inhomogeneity. To overcome the motion artifacts and short T_2* of the lung parenchyma, researchers have also developed PROPELLER based on fast spin echo (FSE) and UTE radial MRI, which could correct the artifacts without additional acquisitions by taking advantage of oversampling at the center of the *k*-space used as inherent navigator information. Because this technique is based on FSE, the obtained images have fewer artifacts resulting from B_0 inhomogeneity and are not affected by image warping owing to eddy currents [29]. With the aid of high-performance low-field MRI with PROPELLER, a precise visualization of persistent pulmonary changes was achieved, including GGOs caused by COVID-19 [25]. With this method, patchy GGOs could be easily measured, and the measured GGOs agree well with those obtained by CT. In a previous longitudinal study, follow-up MRI was performed 2 weeks later, and the imaging results were almost unchanged, which demonstrated its potential for repetitive monitoring of morphological changes in patients with COVID-19. The results indicated that high-performance low-field MRI with PROPELLER could detect lung impairments in patients with COVID-19 and is suitable for long-term longitudinal evaluation.

2.2. Evaluation of COVID-19-related brain injuries using ^{1}H MRI

COVID-19 is essentially a multisystem disease, and brain injuries caused by this disease have also been observed by doctors and researchers [30]. Physicians around the world have also conducted numerous investigations to evaluate neurological performance in patients with COVID-19. Among the techniques for brain examination, ^{1}H MRI has been widely used for clinical diagnosis because it is free of ionizing radiation and radioactivity and has high soft tissue contrast.

Generally, the common neurological manifestations caused by COVID-19 include altered consciousness, pathological wakefulness upon cessation of sedation, confusion, agitation [30], and skeletal muscle damage [31]. With the aid of clinical MRI techniques, intracranial hemorrhagic lesions, acute thrombosis [30], encephalitis, cytotoxic edema, abnormal blood perfusion, and multifocal white matter lesions can be observed in some patients with COVID-19. The identified cerebral diseases among affected patients mainly include acute ischemic stroke, acute necrotizing encephalopathy (ANE), acute disseminated encephalomyelitis, parkinsonism, edema-associated brain infection, and COVID-19-related disseminated leukoencephalopathy (CRDL).

Acute stroke is a cerebrovascular disease that is generally caused by sudden rupture or obstruction of the cerebrovascular system, resulting in damage to the brain tissue. Helms and colleagues found acute and subacute ischemic strokes in patients with COVID-19 using diffusion-weighted imaging (DWI). Moreover, enhancement in leptomeningeal spaces and bilateral hypoperfusion in the frontotemporal lobes could be found in some patients using brain MRI [32].

COVID-19 is considered likely to represent an immune-mediated phenomenon and is associated with acute severe encephalopathy, such as ANE. ANE is a complication of influenza and other viral infections associated with intracranial cytokine storms, which can cause blood-brain barrier breakdown with no symptoms of direct viral invasion or parainfectious demyelination [33]. In a previous study by Dixon et al. increased brainstem swelling was observed on T_1/T_2-weighted images (T1WIs/T2WIs), diffusion-weighted images, and susceptibility-weighted images in a patient on day 6, and hemorrhagic lesions in the brainstem, amygdala, putaminal, and thalamic nuclei were also observed (Fig. 3) [34].

COVID-19-associated parkinsonism was also found in some patients using clinical imaging techniques, including fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT, MRI, and single-photon emission computed tomography [35]. In the studies by Morassi et al. two patients with COVID-19, who had no history of Parkinson's disease and prodromal features of parkinsonism, developed a rapidly progressing form of atypical Parkinson's disease with encephalitis. Increased cortical thickness was found in the cerebral cortical thickness map obtained on 3D gradient echo MRI, and the abnormal regions of cortical thickness associated with the high metabolic regions were also observed on FDG-PET/CT, which indicated regions involved in the inflammatory process. Moreover, Freeman and colleagues evaluated brain injuries caused by COVID-19 using fluid-attenuated inversion recovery (FLAIR) MRI and found that some patients with COVID-19 (6/59) were suspected to have CRDL [36]. The features, including extensive confluent or multifocal white matter lesions, microhemorrhages, and diffusion restriction or enhancement, were found on the brain images.

Some researchers also conducted follow-up studies to evaluate the brain recovery of discharged patients with COVID-19 using FLAIR MRI, diffusion tensor imaging, and arterial spin labeling [37]. Preliminary results showed that indirect damage associated with an inflammatory storm would cause brain injuries and increased brain volume, cerebral blood flow, and white matter tracts. COVID-19-related hypoxemia and vascular endothelial dysfunction might contribute to neurological changes, and the abnormalities in these brain regions need to be monitored during rehabilitation to help understand the potential neurological sequelae of COVID-19.

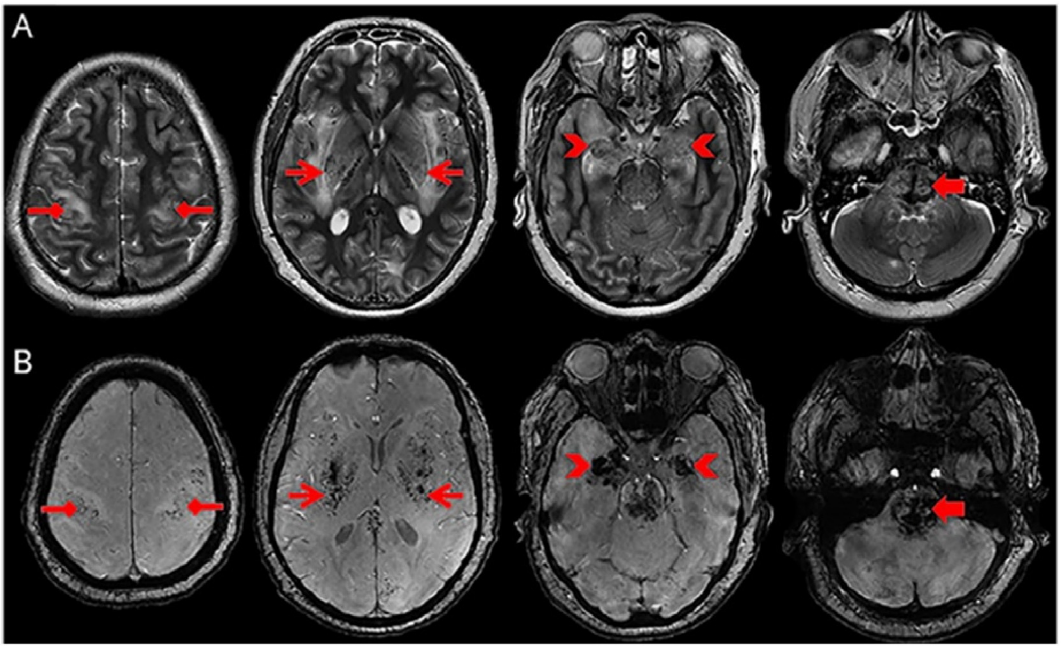

Fig. 3. (A) T_2-weighted and (B) susceptibility-weighted brain images of a patient with acute necrotizing encephalopathy on day 6. Reproduced with permission [34].

2.3. Evaluation of COVID-19-related cardiac involvement using ^{1}H MRI

Several investigators have also conducted cardio-related MRI studies on COVID-19 [38–40]. Xia et al. evaluated cardiac involvement related to COVID-19 in 26 discharged patients using cardiac magnetic resonance (CMR) [38]. CMR protocols consisted of conventional sequences (cine, T2WI, and late gadolinium enhancement (LGE)) and quantitative mapping sequences (T1WI, T2WI, and extracellular volume (ECV) mapping). Abnormal CMR results were found in 15 patients, 14 of whom had myocardial edema and 8 had LGE. Compared with those of the controls, the overall T_1, T_2, and ECV of the patients with positive conventional CMR findings significantly increased. The study showed that some patients with COVID-19

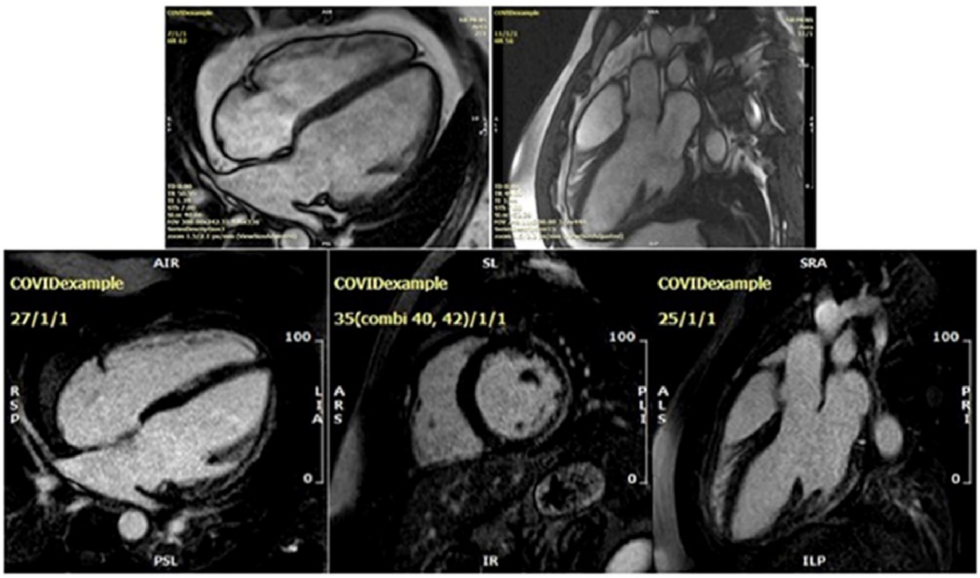

Fig. 4. Cardiac magnetic resonance findings of a male patient at 6 months after the diagnosis of severe coronavirus disease pneumonia. Reproduced with permission [39].

developed cardiac involvement during rehabilitation. CMR revealed myocardial edema, fibrosis, and impaired ventricular function [39] (Fig. 4).

3. Evaluation of COVID-19-related pulmonary damage using ^{129}Xe gas MRI

HP ^{129}Xe gas MRI is an emerging technique for pulmonary function and microstructure evaluation and has developed rapidly in recent years. The technique utilizes HP ^{129}Xe as an inhalation gas contrast agent, whose MR signal could be enhanced by more than 50,000 times than that in thermal equilibrium via the technique of rubidium-vapor SEOP [41]. With the HP ^{129}Xe gas MRI technique, high-resolution lung gas images could be obtained [42]. Owing to its good solubility and chemical shift sensitivity to the surrounding environment, HP ^{129}Xe gas MRI has unique advantages for probing the gas exchange function of the lung globally and regionally. It has been widely used for evaluating lung injuries caused by diseases, such as chronic obstructive pulmonary disease [43], asthma [44], cystic fibrosis [45], idiopathic pulmonary fibrosis [46], and other lung diseases [47], including COVID-19 [48]. Moreover, ^{129}Xe gas MRI offers unique advantages for longitudinal studies, especially those involving children, owing to the absence of ionizing radiation [49]. The feasibility and safety of HP ^{129}Xe gas MRI have been demonstrated in numerous clinical trials in China, the United States, the United Kingdom, Canada, and other countries [50].

HP ^{129}Xe gas MRI was first used to evaluate pulmonary ventilation, gas exchange function, and microstructure changes caused by COVID-19 by Li et al. [48]. In their study, quantitative physiological parameters derived from HP ^{129}Xe gas MRI were analyzed between discharged patients with COVID-19 and healthy volunteers, and a higher ventilation defect percent (VDP) was found in the former (5.5 %) than in the latter (3.7 %). Moreover, morphological parameters derived from ^{129}Xe gas MRI showed no significant difference between the groups; however, an impaired pulmonary gas exchange function, that is, longer gas exchange time constant, was found in the patients with COVID-19. These findings suggested that regional ventilation and alveolar airspace dimensions were relatively normal after the patients were discharged, while the gas exchange function diminished (Fig. 5). As reported in previous studies, pulmonary fibrosis might be a sequela of SARS infection, and the pathological features of COVID-19 are similar to those of SARS. These results suggest that alveolar interstitial thickening and perfusion deficits might exist in the lungs of discharged patients with COVID-19, which might be caused by inflammation and possible fibrosis. This study demonstrated the feasibility of HP ^{129}Xe gas MRI in evaluating localized pulmonary function damage caused by COVID-19, which could be useful for the long-term evaluation of this disease.

As previously reported, fatigue and breathlessness still existed in some patients after long-term infection, although they have no significant abnormality in pulmonary function tests (PFTs), imaging, or clinical tests [51]. Recently, HP ^{129}Xe gas MRI has also been used to identify the possible causes of breathlessness in patients with COVID-19 at 3 months after discharge [52]. Ventilation and dissolved-phase ^{129}Xe gas MRI were performed in patients and healthy volunteers, and abnormalities of gas transfer were found in patients with post-COVID-19 pneumonia. These results might explain the possible etiology of the breathlessness symptom lasting for months after discharge and indicate that HP ^{129}Xe gas MRI might be a useful technique for the diagnosis of dyspneic patients with COVID-19.

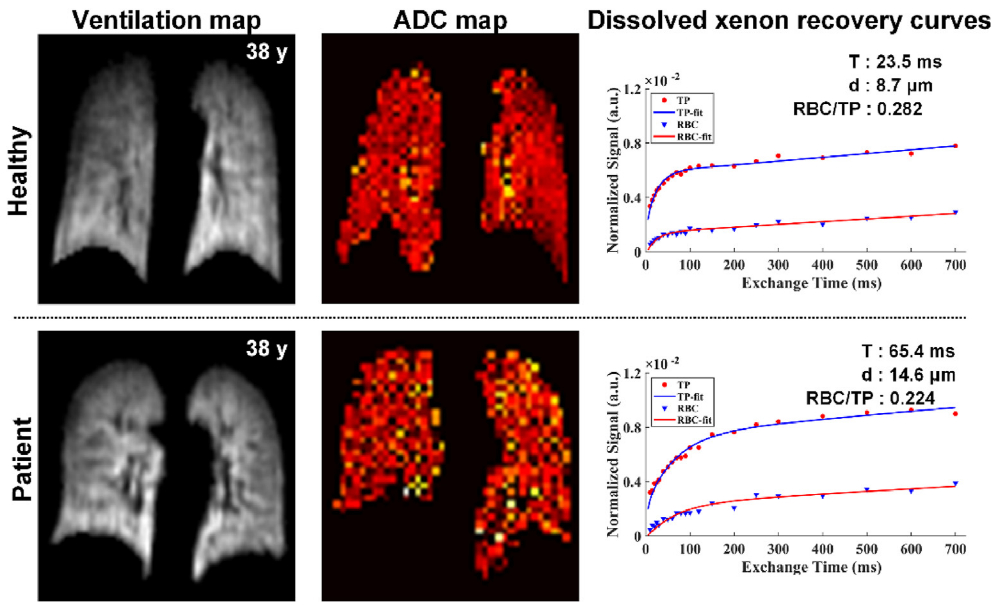

Fig. 5. Hyperpolarized ^{129}Xe gas magnetic resonance imaging/spectroscopy (MRS) results of a healthy subject and a discharged patient with coronavirus disease 2019. Reproduced with permission [48].

4. Conclusion

COVID-19 is a multisystem disease, and some patients could experience long-term COVID as reported. Clinical imaging techniques play an important role in COVID-19 diagnosis as well as in the assessment of injuries caused by the disease. Apart from chest CT, multi-nuclei MRI also has potential in COVID-19 diagnosis and long-term COVID evaluation because it is free of ionizing radiation and has good soft tissue contrast. With the use of multi-nuclei MRI techniques, especially the emerging HP ^{129}Xe gas MRI technique, the pulmonary structural and functional changes caused by COVID-19 could be quantified. Moreover, combined with the accelerated acquisition techniques and emerging reconstruction method based on artificial intelligence, MRI with ^{13}C, ^{23}Na, ^{17}O and ^{31}P, could also be used for evaluating brain, heart, liver, and other organ injuries caused by COVID-19, especially the functional injuries. Previous studies have demonstrated the feasibility and potential of multi-nuclei MRI techniques in the evaluation of injuries caused by COVID-19. The preliminary results indicate that it is a promising imaging modality for long-term COVID evaluation and management, which might make it a helpful tool for the evaluation in the post-COVID-19 course.

Declaration of conflict of interest

Q Zhou disclosed no relevant relationships. **Q. C. Rao** disclosed no relevant relationships. **H. D. Li** disclosed no relevant relationships. **M. Zhang** disclosed no relevant relationships. **X. C. Zhao** disclosed no relevant relationships. **L. Shi** disclosed no relevant relationships. **C. H. Ye** disclosed no relevant relationships. **X. Zhou** disclosed no relevant relationships.

Acknowledgement

This work is supported by National key Research and Development Project of China (grant no. 2018YFA0704000), National Natural Science Foundation of China (grant no. 91859206, 81625011, 21921004), Scientific Instrument Developing Project of the Chinese Academy of Sciences (grant no. GJJSTD20200002, YJKYYQ20200067), Key Research Program of Frontier Sciences, CAS (grant no. ZDBS-LY-JSC004). Haidong Li acknowledges the support from Youth Innovation Promotion Association, CAS (grant no. 2020330). Xin Zhou acknowledges the support from the Tencent Foundation through the XPLORER PRIZE.

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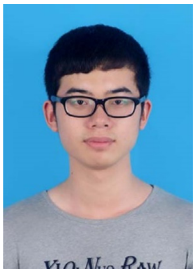

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