

Elevated Extracellular Volume Fraction and Reduced Global Longitudinal Strains in Patients Recovered from COVID-19 without Clinical Cardiac Findings

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Manuscript Type: Original Research

Author contributions: Guarantors of integrity of entire study, Y.Y.,X.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research X.L.,Y.Z.,Z.R.,Y.Q.,B.L.; clinical studies, all authors; statistical analysis, X.L.,R.Z.,H.W,Y.Z.; and manuscript editing, X.L.,Y.H.,Y.Y.

Disclosures of Conflicts of Interest: X.L. disclosed no relevant relationships. H.W. disclosed no relevant relationships. R.Z. disclosed no relevant relationships. T.W. disclosed no relevant relationships. Y.Z. disclosed no relevant relationships. Y.Q. disclosed no relevant relationships. B.L. disclosed no relevant relationships. Y.Y. disclosed no relevant relationships. Y.H. disclosed no relevant relationships.

Supported in part by the Anhui Natural Science Foundation (202004a0702003, 201904a07020060). Fuyang Natural Science Foundation (FK20202815-3). National Natural Science Foundation of China (82071897,81970446).

Abbreviations

2D = 2 dimensional

COVID-19 = coronavirus disease 2019

ECV = extracellular volume fraction

GLS = global longitudinal strain

IQR = interquartile range

LGE = late gadolinium enhancement

LV = left ventricle

RV = right ventricle

MRI = magnetic resonance imaging

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

Summary

MRI-derived extracellular volume fraction and 2D global longitudinal strain could serve as markers of cardiac involvement in participants recovered from COVID-19 without cardiac symptoms or clinical findings of myocardial injury.

Key Results

- In a prospective, single-center study, cardiac MRI revealed extracellular volume fraction (ECV) was elevated in 24 of 40 participants recovered from moderate or severe COVID-19 and without cardiac symptoms or structural cardiac abnormalities compared to healthy controls [29.7% vs 25.0%, respectively, $p < .001$].
- 28 of 40 participants recovered from COVID-19 had subclinical changes of myocardial dysfunction with lower left ventricular 2D-global longitudinal strain (GLS) compared to healthy controls (-12.5% vs. -15.4%, respectively, $p = .002$) regardless of the severity of pneumonia.

Abstract

Background

It is unknown if there are cardiac abnormalities in participants recovered from COVID-19 without cardiac symptoms and those who have normal biomarkers and normal ECGs.

Purpose

To evaluate cardiac involvement in participants recovered from COVID-19 without clinical evidence of cardiac involvement using cardiac MRI

Materials and methods

In this prospective observational cohort study, 40 participants recovered from COVID-19 with moderate(n=24) or severe(n=16) pneumonia and no cardiovascular medical history, without cardiac symptoms, with normal ECG, normal serological cardiac enzyme levels, and discharged > 90 days between May and September 2020. Demographic characteristics, serum cardiac enzymes, and cardiac MRI were obtained. Cardiac function, native T1, ECV and Two-dimensional (2D) strain were quantitatively evaluated and compared with controls (n = 25).The Comparison among the 3 groups were performed using one-way analysis of variance (ANOVA) with Bonferroni corrected post-hoc comparisons(for normal distribution) or Kruskal-Wallis tests with post-hoc pairwise comparisons(for non-normal distribution).

Results

Forty participants (54±12 years; 24 men) enrolled with a mean time between admission and CMR of 158 ±18 days and discharge and CMR examination of 124 ±17 days. There was no LV and RV size or functional differences among participants recovered from COVID-19 and healthy controls. Only one (3%) participants had positive LGE located at the mid inferior wall. Global ECV values were elevated in both participants recovered from COVID-19 with moderate or severe pneumonia, compared to the healthy controls [median ECV (IQR)], [29.7% (28.0%-32.9%), versus 31.4% (29.3%-34.0%), versus 25.0% (23.7%-26.0%); both p<.001].The 2D-global LV longitudinal strains (GLS) were reduced in both groups of participants [COVID-19 moderate group,-

12.5%(-10.7%--15.5%), COVID-19 severe group, -12.5%(-8.7%--15.4%) compared to healthy control group -15.4%(-14.6%-17.6%), $p=.002$ and $p=.001$, respectively].

Conclusion

CMR myocardial tissue and strain imaging parameters suggest that a proportion of participants recovered from COVID-19 had subclinical myocardial abnormalities detectable months after recovery.

Introduction

The global pandemic of coronavirus disease 2019 (COVID-19) continues to cause considerable morbidity and mortality worldwide (1). As of November 23, 2020, there has been over 58 million confirmed cases globally with over 1.3 million deaths. Initially recognized as a respiratory illness, there has been a growing body of evidence of cardiovascular complications of this disease (2-7). Multiple data sets now confirm the increased risk for morbid and mortal complications due to COVID-19 in individuals with preexisting cardiovascular diseases or risk factors (8, 9). Among hospitalized patients, 7%-15% patients with COVID-19 had increased cardiac troponins indicating myocardial injury, which was associated with worse outcomes (10, 11).

The exact mechanism of cardiac injury due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been difficult to confirm (7, 12), although some autopsy studies have showed direct myocyte involvement or secondary injury from the profound inflammatory response invoked by SARS-CoV-2 (7, 13, 14).

Cardiac MRI provides tissue characterization in addition to anatomical and functional assessment of the heart and vascular system, which has now become a “one-stop shop” for diagnostic and prognostic imaging to investigate myocardial injury (15). To date, there has been limited evaluation in participants recovered from COVID-19 who reported cardiac symptoms or had abnormal serological markers of cardiac injury (4, 5). These studies demonstrated myocardial edema, fibrosis, and impaired RV function (4) in patients recovered from COVID-19 with more than 50% having ongoing myocardial inflammation (5).

There remains limited understanding of the cardiovascular sequelae in participants recovered from COVID-19 without cardiac symptoms, with normal cardiac markers and normal ECG. The purpose of our study is to evaluate cardiac involvement in participants recovered from COVID-19 without clinical evidence of cardiac involvement using cardiac MRI.

Materials and Methods

Study Participants

This single-center, prospective, observational study was performed at No. 2 People's Hospital of Fuyang City, Anhui, China. Consecutive participants recovered from COVID-19 who were seen in follow-up clinics between May and September 2020 and met the following inclusion criteria were invited to participate: (1) Participants with confirmed SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) swab test; (2) Hospitalized participants who were considered recovered and met the guideline discharge criteria (16) (a. normal temperature lasting longer than 3 days; b. resolved respiratory symptoms; c. substantially improved acute exudative lesions on chest CT images; d. two consecutive negative RT-PCR test results separated by at least 24 hours) and were isolated for 14 days; (3) Participants discharged from the hospital > 90 days (4) Participants without any cardiac symptoms at any time prior to enrollment, including chest pain, chest pressure, palpitation, or syncope who also had no shortness of breath since discharge from the hospital; (5) Participants with normal serological markers of cardiac injury: creatine kinase (CK), creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), cardiac troponin I (TnTI), and brain natriuretic peptide (BNP); (6) Participants with normal ECG. Exclusion criteria for participants were as follows: (1) A history of cardiovascular disease including coronary artery disease, myocardial infarction, diabetes, hypertension, stroke, vascular disease, or myocarditis; (2) Absolute contraindications for a contrast-enhanced MRI study such as anaphylaxis to contrast agent, brain aneurysm clips, or shrapnel injury; (3) cardiac MRI quality not sufficient for analysis. Hematocrit (Hct) and serum creatinine of all participants were determined within 24 hours prior to cardiac MRI. The baseline disease severity was determined according to the National Health Commission of the People's Republic of China's Diagnosis and Treatment Protocol of Novel Coronavirus (Version 7) in Appendix E1. Briefly, a moderate case is defined as a confirmed case with fever, respiratory symptoms, and radiographic evidence of pneumonia, while a severe case is defined as a moderate case with dyspnea or respiratory failure(16). This prospective study was approved by our local ethic institutional review board (PJ2020-02-10) and

all participants gave written consent.

Healthy controls of similar age and sex distributions was selected from a database (August 2017 to October 2019) of healthy individuals who previously underwent the MRI exams with the same protocol in our hospital without history of cardiovascular diseases or systemic inflammation or other co-morbidities. Healthy candidates were included as controls after they demonstrated normal electrocardiographic and echocardiographic results and normal CMR findings.

Cardiac MRI Imaging

Cardiac MRI were performed on a clinical 3T scanner (Skyra, Siemens Healthineers, Germany). For morphologic and functional analysis, steady-state free precession (SSFP) with breath-hold were performed, comprising a stack of contiguous parallel short-axis slices covering the entire left ventricle (LV) and right ventricle (RV) from base to apex and three LV long-axis slice (2-, 3-, and 4-chamber views) image was used for cardiac cine imaging with following parameters: field of view (FOV), 340-380 mm; repetition time (TR)/echo time (TE), 3.4/1.4 ms; matrix size, 202×182 mm; voxel size, 1.6×1.6×8.0 mm; bandwidth, 962 Hz/Px; flip angle (FA), 47°; slice thickness, 8 mm; and inter slice gap, 2 mm.

LGE images were performed approximately 10-15 minutes after intravenous administration of gadolinium-DTPA (Omniscan, GE Health Care, Ireland) at a dose of 0.15 mmol/kg in short-axis stack using a phase-sensitive inversion-recovery (PSIR) gradient echo sequence. Inversion times were adjusted to null the signal from normal myocardium (FOV, 340-380 mm; matrix size, 256×224 mm; voxel size, 1.3×1.3×8.0 mm; bandwidth, 781 Hz/Px; TR, 5.2 ms; TE, 1.24 ms; FA, 55°).

Native and post-contrast T1 mapping was acquired at the basal, mid and apical level of LV short-axis using a motion corrected Modified Look-Locker inversion-recovery (MOLLI) sequence with protocol 5(3)3 and 4(1)3(1)2, respectively during a breath hold before and 15-20 min after intravenous contrast (Omniscan, GE Health Care, Ireland)

injection. Scanning parameters were as follows: FOV, 340-380 mm; matrix size, 192×172 mm; voxel size, 1.3×1.3×8.0 mm; bandwidth, 1085 Hz/Px; TR/TE, 3.8/1.2 ms; and FA, 35°; slice thickness, 8mm. Inversion time was individually adjusted for complete nulling of the myocardium.

Cardiac MRI Imaging Analysis

MRI data were analyzed using commercially available postprocessing software (CVI42, v.5.1, Circle Cardiovascular Imaging, Calgary, Canada). Two radiologists (H.T.W with 20 years of MRI diagnostic experience and X.H.L with 15 years of MRI diagnostic experience) evaluated all cardiac MRI independently blinded to all identifying information. LV and right ventricular (RV) functional parameters were automatically processed including the trabeculations in the ventricular volume with manual adjustments.

LGE images were reviewed by the same two observers independently. The location (16 segments of AHA), and pattern (epicardial, mid-wall, or transmural) of LGE lesions were assessed by automatically delineating endo- and epicardial contours of myocardium in LGE images with manual adjustments, and LGE lesion was defined as $SI > 5SD$ above the mean SI of the remote reference myocardium(4). A senior observer (Y.Q.Y, with 30 years' experience in MRI) were designated to adjudicate any discrepancies between the two observers.

Global T1 values were derived with automated contouring of the LV myocardium (including regions of LGE lesion) on the T1 map with manual adjustments as needed to exclude cavity blood pool and epicardial fat. The global T1 values were the average of the three short axis slices. Native T1 and post-contrast T1 of myocardium and blood pool were used to derive Global ECV as described (17). Hematocrit level was determined for each individual from a venous blood sample drawn less than 24 hours prior to the cardiac MRI examination.

Cardiac MRI feature tracking (FT) was measured using voxel-tracking post-

processing software (CVI42, v.5.1, Circle Cardiovascular Imaging, Calgary, Canada). Two-dimensional (2D) global peak LV strain from feature tracking were assessed as previously described (18, 19).

Using extracellular volume fraction and myocardial mass, the composition of the myocardium volume can be further divided into cell and matrix components. The cell volume represents intact myocardial cellular components, providing a method to measure myocyte volume (20). The myocardial matrix volume= left ventricular mass (LVM)/1.05 g/ml \times ECV. The myocardial cell volume= LVM/1.05 g/ml \times [1 – ECV].

Inter-and Intra-observer Reproducibility

Intra-and inter-observer reliability of 2D strain and T1 values was assessed in 15 participants randomly selected from 65 subjects using Bland-Altman plots. Intra-observer reliability was derived from the repeated measurement by one radiologist (X.H.L) after at least a one-month interval blinded to the previous results. Inter-observer reliability was independently assessed by another radiologists (T.T.W) blinded to the first radiologist's measurements.

Statistical analysis

All statistical analysis was performed using SPSS (version 22.0, IBM statistics, Armonk, NY) and GraphPad Prism(Version7.04, GraphPad Software Inc.). Categorical variables were expressed as counts (percentage), and continuous variable as mean \pm standard deviation (SD) or median (interquartile range). Normality of distribution was tested using Shapiro-Wilk test. Comparison between two groups were performed by unpaired Student's t-test (for normal distribution) or Mann-Whitney U test (for non-normal distribution) with continuous variables, or Chi-squared test with categorical variable. The Comparison among the 3 groups were performed using one-way analysis of variance (ANOVA) with Bonferroni corrected post-hoc comparisons (for normal distribution) or Kruskal-Wallis tests with post-hoc pairwise comparisons (for non-normal distribution). To assess the qualitative data, comparisons of the three groups

were performed using Pearson's chi-square test or Fisher's exact test. Two-tailed $p < 0.05$ was considered to be statistically significant. Because 27 cardiac MRI parameters were compared within the three groups, we used the Bonferroni correction with a significance level of $P = 0.002 (0.05/27)$ to adjust for multiplicity.

Results

Participant characteristics

78 participants were screened from the COVID-19 clinic and 35 were excluded due to discharge < 90 days ($n = 5$), abnormal serological markers of cardiac injury ($n = 3$), abnormal ECG findings ($n = 4$), not underwent Cardiac MRI ($n=16$), a history of coronary artery disease($n=2$), a history of hypertension($n=5$). (Fig.1). 43 participants were enrolled in the study and 1 patient was excluded due to contrast allergy and 2 were excluded due to image quality. The final analysis cohort consisted of 40 participants (54 ± 12 years; 24 men). Twenty-five healthy controls matched for age (50 ± 15 years, $p=.23$) and sex (16 men, $p=.75$). Twenty-four COVID-19 participants (60%) were diagnosed as moderate pneumonia and 16 (40%) as severe.

Clinical characteristics and laboratory testing results of participants recovered from COVID-19 are reported in Table 1. During hospitalization, all participants were administered antiviral and antibiotic therapy including lopinavir / ritonavir and umifenovir, and moxifloxacin and cefoperazone sulbactam according to the treatment protocol(16). The mean duration from admission and discharge to cardiac MRI examination were 158 ± 18 days and 124 ± 17 days, respectively. The laboratory testing results within 24 hours of cardiac MRI were in the normal range (Table1).

Cardiac MRI parameters

Cardiac morphological and functional parameters are summarized in Table 2. There was no differences of LV or RV size and function among participants with COVID-19 and healthy controls. Only one participant with COVID-19 had positive LGE located at the mid inferior wall (Fig 2). Global ECV values was elevated in participants recovered from COVID-19 in both moderate and severe disease groups, compared with

the healthy controls [median ECV (IQR) COVID-19 moderate group, 29.7% (28.0%-32.9%), COVID-19 severe group, 31.4% (29.3%-34.0%), healthy control group, 25.0% (23.7%-26.0%); $p < .001$ for both moderate and severe disease groups compared to control] (Fig 3) (Table 3). 24 of 40 participants (60%) were above the top normal ECV cutoff of 29%.

The myocardial matrix volume showed no difference in participants recovered from COVID-19 who had severe pneumonia, compared with the healthy controls (28.2(22.5-34.8) versus 22.1(18.3-26.8), $p = .009$ ($p < .002$ is considered to indicate statistical significance). There were no differences between the moderate disease group and the healthy controls or between the two groups of participants recovered from COVID-19 ($p = .09$, $p = .99$, respectively). The myocardial cell volume showed no differences among these three groups ($p = .06$) (Fig 4).

The 2D-global LV longitudinal strains (GLS) demonstrated reduction in participants recovered from COVID-19 in both moderate and severe disease groups, compared with the healthy controls [COVID-19 moderate group, -12.5%(-10.7%--15.5%), COVID-19 severe group, -12.5%(-8.7%--15.4%), healthy control group, -15.4%(-14.6%--17.6%), $p = .002$ and $p = .001$, respectively](Table 3). 28 of 40 participants (70%) were below the normal GLS cutoff (-15%). 2D global radial strain (GRS) and 2D global circumferential strain (GCS) showed no differences among these groups ($p = .11$ and $p = .49$, respectively) (Fig5).

Intra-and Inter-observer Reliability

Global native T1 had an intra-observer reliability of $0.3 \text{ ms} \pm 1.9 \text{ ms}$ and an interobserver reliability of $-0.3 \text{ ms} \pm 2.9 \text{ ms}$. Global post T1 had an intra-observer reliability of $-0.8 \text{ ms} \pm 1.9 \text{ ms}$ and an inter-observer reliability of $-0.4 \text{ ms} \pm 1.9 \text{ ms}$. Global ECV had an intra-observer reliability of $-0.31\% \pm 0.35\%$ and an inter-observer reliability of $-0.35\% \pm 0.39\%$. 2D GLS had an intra-observer reliability of $0.23\% \pm 0.40\%$ and an inter-observer reliability of $0.09\% \pm 0.42\%$. The Bland-Altman plots are presented in Figure 6.

Discussion

We found extracellular volume fraction (ECV) elevation $>29\%$ in 24 of 40 participants (60%) recovered from moderate or severe COVID-19 discharged from the hospital for more than 90 days, showing no cardiac symptoms or clinical findings of myocardial injury, and without functional or structural cardiac impairment (LV ejection fraction was within normal range $62.6\% \pm 5.2\%$). We also found 28 of these 40 participants (70%) had subclinical changes of myocardial function demonstrated by a reduction in LV 2D-global longitudinal strain (GLS) $[-13\%(-10\%--15\%)]$ compared with healthy controls regardless of pneumonia severity. Only one of the forty participants (3%) had positive late gadolinium enhancement (LGE) positive, located at the mid inferior wall. In addition, we found that the both cell volumes and matrix volume were not different in the participants recovered from COVID-19 and control groups ($p=.06$ and $p=.01$, respectively).

Our understanding of COVID-19 involvement in the myocardium continue to evolve. The pathological evidence for acute myocarditis was reported in a patient with COVID-19 who presented with typical manifestations of fulminant myocarditis (21). Myocardial inflammation was confirmed, and coronavirus particles were detected in macrophages but not in myocardial or endothelial cells (7). Another autopsy study reported infiltration of myocardial tissue by mononuclear inflammatory cells in a postmortem of a patient with COVID-19(22).

A few studies have reported cardiac MRI findings on patients recovered from COVID-19. Huang(4) described 26 patients in a single-center retrospective cohort study demonstrating abnormal cardiac MRI findings in patients recovered from COVID-19 without evidence of cardiac involvement during their initial treatments, but presented one to three months after discharge with chest discomfort or palpitations, and other non-specific cardiac symptoms. This study found 14 (54%) of participants with evidence of myocardial edema using T2 weighted imaging. In the acute phase of myocardial inflammatory injury, LGE represents myocardial edema and necrosis, and in the chronic phase, LGE represents the formation of myocardial fibrosis (6). Huang et al showed in symptomatic patients, 31% of patients and 4% segments had evidence of small focal

subepicardial and patchy mid-wall LGE (4). The median time between onset of cardiac symptoms and cardiac MRI was 47 days (4). These findings support previous reports of COVID-19 related myocarditis (23-25), and demonstrated that cardiac MRI abnormalities of active inflammation/edema may extend into the convalescent phase of COVID-19 in individuals with cardiac symptoms. The first prospective report on a cohort of unselected 100 recently recovered patients with COVID-19 also found evidence for myocardial inflammation in 60% patients, positive LGE findings in 41% patients with 38% demonstrating an ischemic pattern of myocardial LGE (5). Overall, some form of cardiac abnormalities were present in 78% of patients at a median of 71 days (IQR of 64-92 days) post diagnosis (5). In our study, only one of the forty participants (3%) was LGE positive. Nonetheless, our study demonstrated a high prevalence of subclinical cardiac abnormalities in participants recovered from COVID-19 in a convalescent phase later than both of these studies.

Abnormal native T1 and ECV can be found in diffuse myocardial fibrosis (26, 27). ECV, which quantifies the relative expansion of the extracellular matrix as a result of diffuse reactive fibrosis in multiple cardiac pathologies, can be used as a noninvasive alternative to myocardial biopsies and histochemical analysis (17). Our findings showed in both moderate and severe pneumonia groups, there was increased global ECV compared with healthy controls, which suggests that diffuse interstitial fibrosis may be present in 60% participants recovered from COVID-19 who had ECV elevation higher than the healthy cutoff previously reported by Gottbrecht *et al* (28). However, we saw no difference on native T1 in COVID-19 recovered participants and controls ($P=.48$), which is not consistent with the findings of increased T1 values from Puntmann *et al* (5) or Huang *et al* (4). This difference may reflect different patient populations dictated by the inclusion and exclusion criteria. We have a more homogenous population with participants hospitalized for pneumonia without cardiac symptoms or clinical findings, as compared to Puntmann's mixture of hospitalized and ambulatory patients with a number of cardiovascular risk factors, or Huang's patients with cardiac symptoms. Our patient cohort with increased ECV but no difference in native T1 is consistent with previous observations in non-ischemic cardiomyopathy

(29) and in the MESA cohort (30). The significance of these results is unknown, which highlights the need for long-term follow-up.

Combining extracellular volume fraction and myocardial volume, it is possible to examine the changes of the two components of myocardium volume, which are the myocardial cell volume and the matrix volume. The cell volume represents intact myocardial cellular component, providing a way to measure the myocyte volume. In diseases with simultaneous cellular hypertrophy and extracellular matrix expansion, the ECV fraction may not change because it depicts the ratio between cell and matrix volumes(20). Although there were no statistical significant difference among the groups when a P value of 0.002 was used, separating into cell and matrix volumes allow us to gain insight into how each component of the myocardium change in the COVID-19 disease.

Feature-tracking technology is a post-processing method applied to routinely acquired cine cardiac MRI to study myocardial strain. Global longitudinal strain (GLS) is more sensitive than LV ejection fraction (EF) as a measure of systolic function and may identify subclinical LV dysfunction in cardiomyopathies (31, 32). Our study demonstrated that subclinical LV dysfunction was prevalent in participants recovered from COVID-19 and the impact of this finding on long-term outcome remains unknown.

Our study has limitations. First, the sample size is small, limited by the reduction of advanced cardiac MRI utilization and resources in the region during the early phase of the epidemic. Second, we did not perform T2 imaging. In our study, the median time between admission and cardiac MRI examination was 159 days with IQR (145-170days). At the time of study design, according to the pathogenesis and acute versus chronic phase of myocarditis and the enrollment criteria of this study, we anticipated that edema would no longer be present during this time period (33, 34). Therefore, T2 weighted imaging or T2 mapping were not performed in this study.

In conclusion, we demonstrated subclinical functional and myocardial tissue characteristic abnormalities in individuals recovered from moderate or severe COVID-

19 without cardiac symptoms or clinical findings of myocardial injury three months after recovery from SARS-CoV-2 infection. Given the pressing burden of the ongoing COVID-19 pandemic, long-term cardiovascular consequences of COVID-19 need to be investigated. Cardiac MRI can be a sensitive imaging tool for identifying cardiac involvement in COVID-19. The clinical significance of our results is unknown, and this work highlights the need for longitudinal follow-up to understand the importance and progression of subclinical myocardial findings in participants with COVID-19.

Acknowledgements

We thank all colleagues who contributed to the present study. We are especially grateful to our front-line medical staff for their professionalism, dedication, and courage in the face of the COVID-19 outbreak.

Impress

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Table 1. Clinical Characteristics of the Study Participants

Characteristics	Healthy Controls(n=25)	All COVID-19 Participants (n=40)	COVID-19 Moderate(n=24)	COVID-19 Severe(n=16)	P value ^a	P value ^b
Median Age, y	50±15	54±12	52±10	57±15	.23	.18
Men, No.(%)	16(64)	24(60)	12(50)	12(75)	.75	.11
BMI (kg/m ²)	24.0±2.7	25.2±2.5	25.2±2.2	25.1±2.2	.09	.97
BSA (m ²)	1.8±0.2	1.8±0.2	1.8±0.1	1.8±0.2	.66	.81
Heart rate (bpm)	71±6	71±9	70±10	72±9	.84	.65
Systolic blood pressure (mmHg)	127±6	127±5	128±5	126±6	.88	.41
Diastolic blood pressure (mmHg)	84±5	83±8	84±7	82±8	.39	.46
Confirmed SARS-CoV-2 PCR	0	40(100)	24(100)	16(100)	NA	NA
Duration between discharge to cardiac MRI (day)	0	124±17	121±17	129±16	NA	.07
Duration between admission to cardiac MRI (day)	0	158±18	154±20	164±12	NA	.13
Comorbidities, No.(%)						
Hypertension	0	0	0	0	NA	NA
Diabetes	0	0	0	0	NA	NA
Coronary artery disease	0	0	0	0	NA	NA
Chronic obstructive pulmonary diseases	0	0	0	0	NA	NA
Cerebrovascular disease	0	0	0	0	NA	NA
Chronic renal diseases	0	0	0	0	NA	NA
Chronic liver diseases	0	0	0	0	NA	NA
Laboratory results						
White blood cell count (×10 ⁹ /L) [§]	NA	6.0(5.6-6.5)	5.9(5.6-6.5)	6.3(5.6-6.7)	NA	.43
cTnI, ng/mL	NA	<0.01	<0.01	<0.01	NA	NA
BNP, pg/mL [§]	NA	32.5(20-36.0)	33.6(24.2-42.7)	25.1(14.5-34.6)	NA	.03 [#]

LDH (U/L) [§]	NA	210(168.5-226.5)	214(174.8-230.3)	199.5(156.0-214.8)	NA	.18
CK-MB(U/L) [§]	NA	11(8.3-14.0)	11.0(8.0-14.8)	11.5(9.0-14.0)	NA	.92
CK(U/L) [§]	NA	85.5(65.0-115.5)	88.0(65.8-119.8)	80.5(65.0-110.0)	NA	.78
Treatment before discharge						
Antiviral therapy	NA	40(100)	24(100)	16(100)	NA	NA
Antibiotic therapy	NA	40(100)	24(100)	16(100)	NA	NA

Abbreviations:

Unless otherwise specified, Data are means \pm standard deviation and n (%) for categorical variables.

[§] Data are expressed as median (IQR) for continuous variables.

BMI=body mass index; BSA= body surface area; HR=heart rate; PCR = polymerase chain reaction; LDH= lactate dehydrogenase; cTnI= cardiac troponin I; BNP= brain natriuretic peptide; NA=not apply; CK-MB= Creatine kinase-MB; CK= Creatine kinase; IQR=interquartile range

P value^a between participants with all COVID-19 participants and healthy Controls performed by unpaired Student's t-test (for normal distribution) or Mann-Whitney U test (for non-normal distribution) with continuous variables, or Chi-squared test with categorical variable

P value^b between moderate COVID-19 and severe COVID-19 performed by unpaired Student's t-test (for normal distribution) or Mann-Whitney U test (for non-normal distribution) with continuous variables, or Chi-squared test with categorical variable

P<.05 is considered to indicate statistical significance

[#]BNP normal value ranges < 100 pg/mL in our laboratory

Table 2: Cardiac MRI Parameters of Participants Recovered from COVID-19 and Controls

Cardiac MRI Findings	Healthy Controls (n=25)	ALL COVID-19 Participants (n=40)	COVID-19 Moderate (n=24)	COVID-19 Severe (n=16)	P value ^a	P value ^b
LVEF (%)	63.9±5.0	62.6±5.2	61.7±4.9	63.9±5.7	.32	.29
LVEDV (ml)	125.3±28.1	119.8±28.0	113.7±29.3	129.0±24.1	.45	.16
Indexed LVEDV(ml/m ²)	66.7±12.1	63.0±14.2	60.2±13.4	67.3±14.8	.29	.13
LVESV (ml)	51.2±11.2	44.1±13.5	42.9±11.9	45.8±15.8	.03	.32
Indexed LVESV(ml/m ²)	26.9±5.9	24.8±6.5	24.0±5.6	25.9±7.6	.20	.21
LVSV (ml)	73.0±14.9	66.8±16.6	65.3±18.5	69.2±13.5	.13	.09
Indexed LVSV (ml/m ²)	45.7±7.3	41.9±10.1	40.8±9.5	43.5±10.9	.54	.09
LVM ED (g) [§]	102.7(76.7-117.3)	87.8(71.4-105.2)	86.1(68.8-105.2)	92.9(71.4-110.4)	.09	.54
LVM SD(g) [§]	107.6(74.9-123.1)	94.0(78.3-108.9)	91.4(76.8-107.5)	97.6(80.3-114.3)	.34	.54
Indexed LVM (g/m ²) [§]	53.6(44.7-66.9)	52.8(48.0-61.3)	51.8(45.8-60.3)	58.0(51.6-64.4)	.57	.27
CO (l/min) [§]	5.8(4.9-6.1)	4.4(4.1-6.0)	4.2(4.1-4.8)	5.2(3.8-6.1)	.03	.25
CI(l/min/m ²) [§]	3.2(2.8-3.4)	2.5(2.2-2.9)	2.5(2.2-2.7)	2.6(2.1-3.4)	.14	.55
Global Native T1(ms) [§]	1138.1(1092.9-1166.2)	1137.5(1099.3-1195.3)	1134.5(1114.0-1210.0)	1140.0(1062.8-1183.8)	.48	.54
Global Post T1(ms) [§]	495.6(475.2-513.3)	641.5(599.8-689.0)	638.5(609.8-699.3)	649.0(595.3-679.8)	<.001	<.001
Global ECV (%) [§]	25.0(23.7-26.0)	30.0(28.0-33.0)	29.7(28.0-32.9)	31.4(29.3-34.0)	<.001	<.001
Matrix volume [§]	22.1(18.3-26.8)	26.1(20.9-31.8)	24.8(18.9-29.3)	28.2(22.5-34.8)	.16	.01
Cell volume [§]	69.3(52.8-84.7)	58.1(46.1-71.3)	56.1(44.5-70.4)	58.5(45.7-72.5)	.003	.06
2D-GLS (%) [§]	-15.4(-14.6--17.6)	-12.5(-9.6--15.4)	-12.5(-10.7--15.5)	-12.5(-8.7--15.4)	<.001	<.001
2D-GRS (%) [§]	30.4(25.0-35.8)	28.1(11.4-41.2)	29.8(9.8-40.6)	20.5(11.4-41.3)	.07	.11
2D-GCS (%) [§]	-22.4(-20.4--23.4)	-21.4(-16.7--23.7)	-20.8(-16.9--22.7)	-22.7(-14.5--24.7)	.15	.49
LGE, No.(%)	0	1(3)	0	1(6)	NA	NA
RVEF (%)	56.2±3.0	54.7±5.8	53.9±4.5	55.8±7.2	.17	.39

RVEDV (ml)	140.0±25.6	125.4±30.4	121.8±29.7	130.7±31.7	.05	.15
Indexed RVEDV(ml/m ²)	76.3±11.0	69.6±16.2	67.1±15.0	73.3±17.7	.05	.06
RVESV (ml)	62.2±11.7	58.1±14.9	57.5±13.6	58.9±17.1	.24	.47
Indexed RVESV(ml/m ²)	36.4±5.5	32.9±7.4	32.8±6.8	33.2±8.6	.04	.54
RVSV (ml)	76.5±16.4	69.3±18.1	66.0±18.4	74.3±17.1	.11	.12
Indexed RVSV(ml/m ²)	43.8±7.9	38.9±11.5	36.6±10.2	42.5±12.7	.07	.09

Unless otherwise specified, Data are means ± standard deviation and n (%) for categorical variables.

‡ Data are expressed as median (IQR) for continuous variables.

Abbreviations:

BSA= body surface area; LV= left ventricular; EF=Ejection Fraction; EDV = End diastolic volume; ESV = End systolic volume; SV = Stroke volume; CO= Cardiac output; LVM= left ventricular mass; CI= Cardiac index; IQR=interquartile range; LGE=late gadolinium enhancement; NA=not apply; RVEF=right ventricular ejection fraction; RVESV= right ventricular end systolic volume; GLS =global longitudinal strain; GRS= global radial strain; GCS= global circumferential strain

P value^a between participants with all COVID-19 participants and healthy Controls performed by unpaired Student's t-test (for normal distribution) or Mann-Whitney U test (for non-normal distribution) with continuous variables, or Chi-squared test with categorical variable

P value^b is for comparison of all three groups (healthy Controls, moderate COVID-19, severe COVID-19) performed by analysis of variance (ANOVA) with Bonferroni corrected post-hoc comparisons (for normal distribution) or Kruskal-Wallis tests with post-hoc pairwise comparisons (for non-normal distribution)

P<.002 (0.05/27) is considered to indicate statistical significance.

Table 3: Subgroups Comparisons with Cardiac MRI Parameters of Participants Recovered from COVID-19 Compared with Controls

Cardiac MRI Findings	Healthy Controls (n=25)	COVID-19 Moderate (n=24)	COVID-19 Severe (n=16)	P value ^a	P value ^b	P value ^c
Global ECV (%)	25.0(23.7-26.0)	29.7(28.0-32.9)	31.4(29.3-34.0)	<.001	<.001	0.33
2D-GLS (%)	-15.4(-14.6--17.6)	-12.5(-10.7--15.5)	-12.5(-8.7--15.4)	0.002	0.001	>.99

Data are medians, with interquartile range (IQR) in parentheses for continuous variables

Abbreviations:

ECV = extracellular volume fraction; GLS =global longitudinal strain

^a Statistical difference between participants with moderate COVID-19 and healthy Controls

^b Statistical difference between participants with severe COVID-19 and healthy Controls

^c Statistical difference between participants with moderate COVID-19 and participants with severe COVID-19.

P<.002 (0.05/27) is considered to indicate statistical significance

Figures

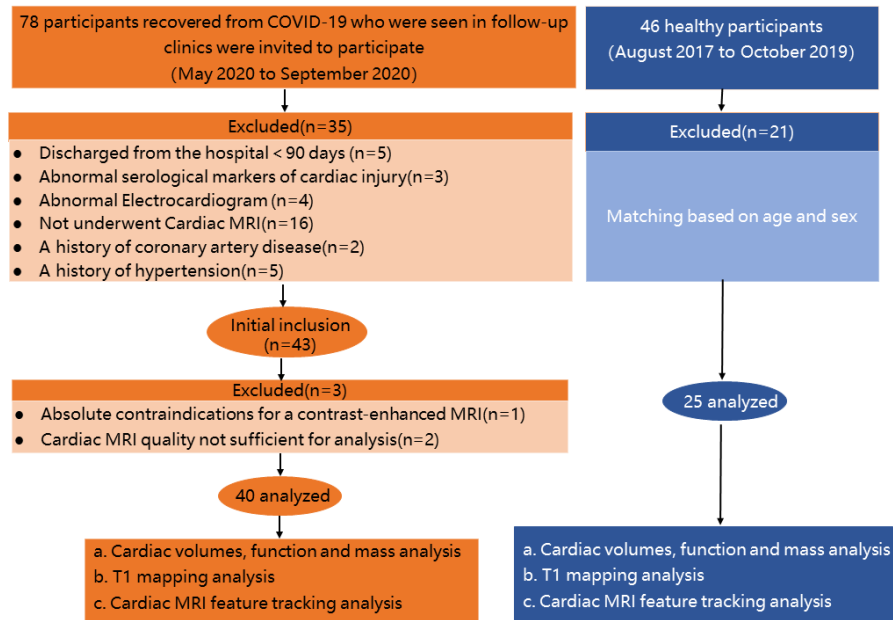


Figure 1: Flowchart of participant enrollment. COVID-19 = coronavirus disease 2019

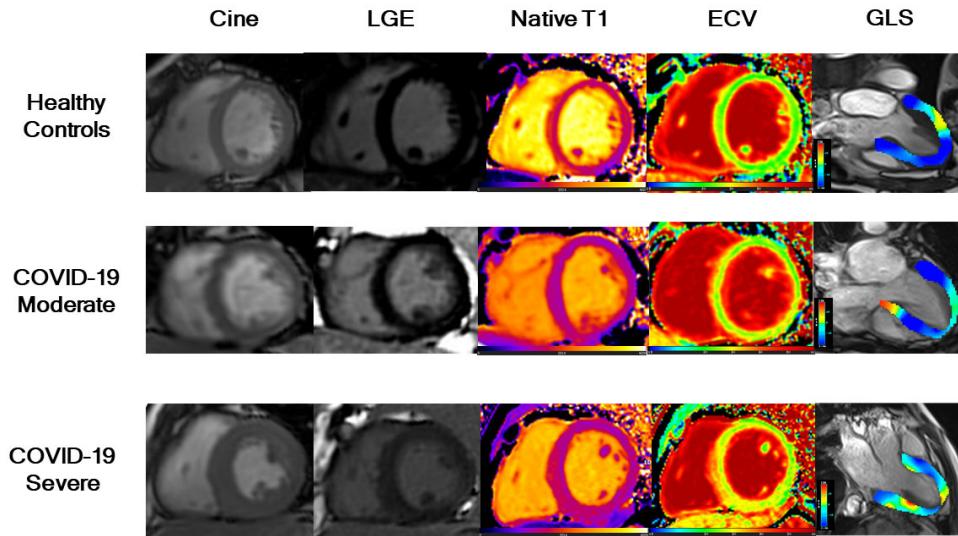


Figure 2: Examples of cardiac MRI in participants recovered from COVID-19 and healthy controls. Short-axis SSFP cine, corresponding phase sensitive inversion recovery (PSIR) late gadolinium enhancement (LGE), native T1 maps, extracellular volume (ECV) maps, and global longitudinal strain (GLS) of three groups (Healthy Control, participants with moderate COVID-19, and participants with severe COVID-19). A 41-year-old healthy man (control) (first row) with negative LGE, normal global native T1 (1161ms), global ECV (27%), and GLS (-17.2%). A 66-year-old woman (second row) with moderate COVID-19 and negative LGE, normal global native T1 (1139 ms), elevated global ECV (31%) and reduced GLS (-12.6%). A 44-year-old man (third row) with severe COVID-19 and focal LGE in the left ventricular septal segment. Native T1 (1216 ms) was increased, ECV values were elevated (34%) and LGS was lower (-9.1%). A moderate case is defined as a confirmed case with fever, respiratory symptoms, and radiographic evidence of pneumonia, while a severe case is defined as a moderate case with dyspnea or respiratory failure.

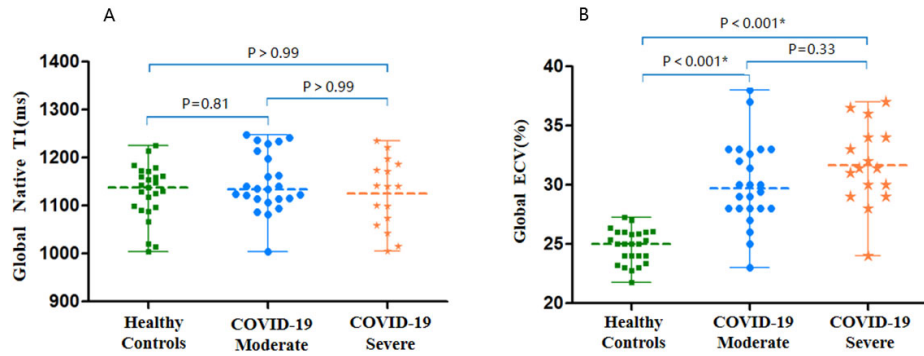


Figure 3: Native T1 and ECV scatterplots by group. There were no differences in, *A*, global native T1. There was, *B*, global ECV difference in participants with COVID-19 compared with the controls. Scatter dot plot with midlines indicate medians and whiskers indicate interquartile ranges.

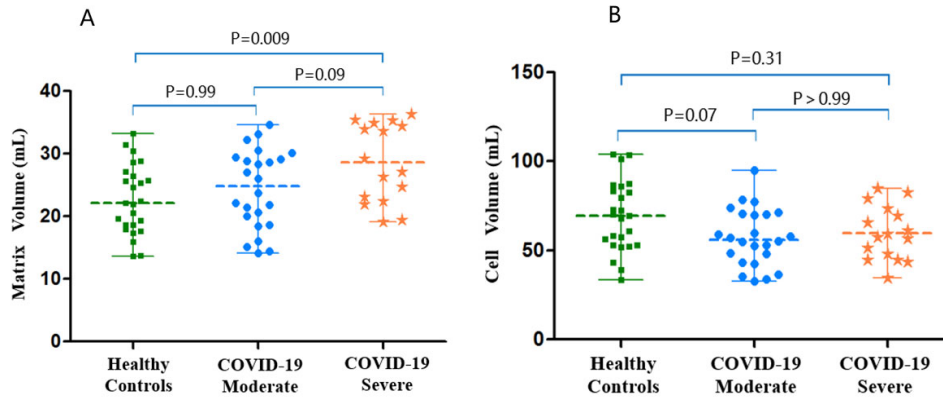


Figure 4: LV matrix volume and cell volume scatterplots by group. *A*, The left ventricular matrix volumes and, *B*, cell volumes of all study participants (healthy controls, participants with moderate COVID-19, and participants with severe COVID-19). Scatter dot plot with midlines indicate medians and whiskers indicate interquartile ranges. A moderate case is defined as a confirmed case with fever, respiratory symptoms, and radiographic evidence of pneumonia, while a severe case is defined as a moderate case with dyspnea or respiratory failure.

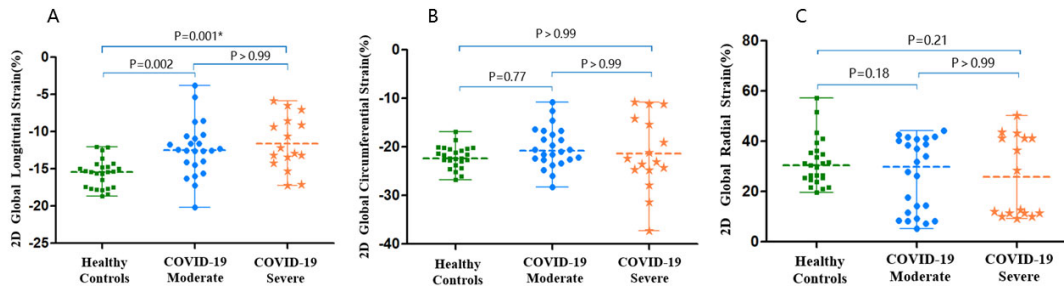


Figure 5: Cardiac MRI Feature-tracking LV strain scatterplots by group. *A*, Two-dimensional global longitudinal strain, *B*, global circumferential strain, *C*, global radial strain in the left ventricle (LV) of all study participants (healthy controls, participants with moderate COVID-19, and participants with severe COVID-19). Scatter dot plot, midlines indicate medians, and whiskers indicate interquartile ranges. A moderate case is defined as a confirmed case with fever, respiratory symptoms, and radiographic evidence of pneumonia, while a severe case is defined as a moderate case with dyspnea or respiratory failure.

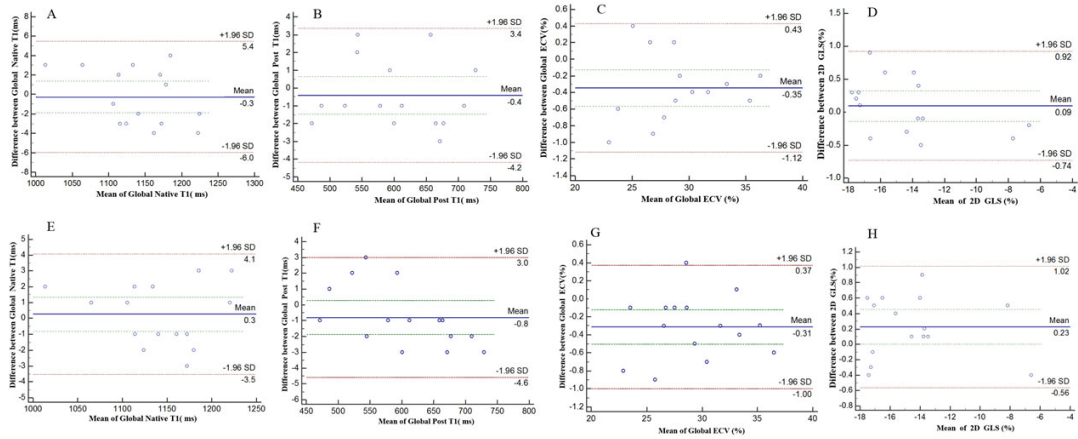


Figure 6: Bland-Altman analysis for *A-D*, interobserver reproducibility of global native T1, global post T1, global extracellular volume (ECV) and 2D global longitudinal strain (GLS). *E-H*, Intra-observer reproducibility of global native T1, global post T1, global extracellular volume (ECV) and 2D global longitudinal strain (GLS). The blue line indicates the mean value; the dashed red line indicates 95% confidence interval. A moderate case is defined as a confirmed case with fever, respiratory symptoms, and radiographic evidence of pneumonia, while a severe case is defined as a moderate case with dyspnea or respiratory failure.

Appendix E1: Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition) (published by China National Health Commission on March 4, 2020)

Impress

Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition) (published by China

National Health Commission on March 4, 2020)

中国国家卫生健康委《新型冠状病毒肺炎诊疗方案（第七版）》，发布时间：2020年3月4日

Since December 2019, a novel coronavirus pneumonia epidemic has appeared in Wuhan City, Hubei Province. With the spread of the epidemic, other cities in China and many countries abroad have also found such cases. As an acute respiratory infectious disease, the disease has been included in the Class B infectious diseases stipulated in the Law of the People's Republic of China on the Prevention and Control of Infectious Diseases, and is managed as a Class A infectious disease. Through the adoption of a series of preventive control and medical treatment measures, the upward trend of the epidemic situation in China has been contained to a certain extent. The epidemic situation in most provinces has eased, but the number of outbreaks abroad is on the rise. With the deepen understanding of the clinical manifestations, pathological features of this disease and the accumulation of experience in diagnosis and treatment, in order to further strengthen the early diagnosis and early treatment of the disease, improve the cure rate, reduce the mortality rate, and avoid in-hospital infection, and alert for the disease transmission caused by overseas input cases, we revised the previous clinical guidance to form this 7th version.

1. Etiology

The novel coronavirus (termed as COVID-19 by World Health Organization) belongs to the coronavirus β genus, which is encapsulated in round or oval shape, and 60-140nm in diameter. The genetic characteristics of COVID-19 are significantly different from SARS-CoV and MERS-CoV. It shares more than 85% homology with SARS-like coronavirus isolated from bat (bat-SL-CoVZC45). The COVID-19 can be detected in human respiratory epithelial cells for about 96 hours *in vitro*, but it takes about 6 days to isolate and culture in Vero E6 and Huh-7 cell lines.

Our current understandings on the biochemical features of COVID-19 are mostly derived from previous studies on SARS-CoV and MERS-CoV. COVID-19 is fragile to ultraviolet and heat (56 °C for 30 minutes). It can also be inactivated by liposoluble solvents, such as ether, 75% ethanol (w/v), chlorine-containing disinfectant and chloroform. However, chlorhexidine has been proved generally ineffective.

2. Epidemiology

a) Source of infection

Infected patients (symptomatic or asymptomatic) are the main source of infection.

b) **Route of transmission**

COVID-19 is transmitted through respiratory droplets and close contact. Aerosol transmission is plausible when patients are exposed to high concentration virus-containing aerosols for a long period of time and in a relatively closed environment. In addition, because COVID-19 has been isolated from stool and urine specimens, special attention should be paid to human waste disposal to avoid direct contact and/or environment contamination.

c) **Susceptible population**

Human beings are generally susceptible to COVID-19.

3. Pathology

The following summary is based on limited numbers of autopsy and biopsy findings.

a) **Lungs**

Lung consolidation was observed in various degrees.

Fibrinous exudation and hyaline membrane formation were filled in alveolar cavity. Exudative cells mainly consist of mononuclear cells and macrophages. Polynuclear giant cells were prominent. Type II alveolar epithelial cells were markedly proliferated, and some were detached into alveolar cavity. Inclusion bodies were found in type II alveolar epithelial cells and macrophages. Hyperemia and edema were apparent in alveolar septal areas. Mononuclear cell and lymphocyte infiltration, intravascular hyaline thrombosis, focal hemorrhage and necrosis of lung tissue could be seen, and hemorrhagic infarction occurred. Pathological features of organizing pneumonia and pulmonary interstitial fibrosis could be observed in pulmonary parenchyma.

Intrapulmonary bronchial epithelial cells were detached, and bronchial cavity was filled with mucus plugs. In some area, pulmonary alveoli were hyperinflated, alveolar septa fractured, and cystic cavities formed.

Coronavirus particles were found in the cytoplasm of bronchial epithelium and type II alveolar epithelial cells under electron microscope. Immunohistochemical staining showed that some alveolar epithelial cells and macrophages were positive for COVID-19 antigens. COVID-19 nuclear acids were detected through RT-PCR.

b) **Spleen, hilar lymph nodes, and bone marrow**

Spleen was markedly shrunk, in which lymphocytes were significantly reduced in numbers, with apparent focal hemorrhage and necrosis. Macrophage proliferation and phagocytosis were also observed. In lymph nodes, lymphocytes were also depleted and necrotized. In addition, immunohistochemical staining showed that the number of CD4⁺ T and CD8⁺ T cells in both spleen and lymph nodes were significantly decreased. All hematopoietic cell lineages were reduced in bone marrow.

c) **Cardiovascular system**

It was found that some cardiomyocytes were degenerated and necrotized, and a small number of monocytes, lymphocytes and/or neutrophils are infiltrated in the myocardium. In some areas, vascular endothelial cells were detached where inflammation and thrombosis occurred.

d) Liver and gallbladder

Liver was characterized by increased volume, dark red color, hepatocyte degeneration, focal necrosis with neutrophil infiltration, hepatic sinus congestion, infiltration of lymphocytes and monocytes in the portal area, and microthrombus formation. Gallbladder was also significantly increased in size.

e) Kidney

Protein exudate was found in Bowman's capsules. Renal tubular epithelium was denatured and exfoliated, and hyaline cast was formed. Interstitial hyperemia, micro thrombus and focal fibrosis could be seen.

f) Other organs

The brain tissue was congested and edematous, and some neurons were degenerated. Focal necrosis was observed in the adrenal gland. The epithelium of esophagus, stomach and intestines were denatured, necrotic and exfoliated with different degrees.

4. Clinical features

a) Clinical manifestation

Based on the current epidemiological survey, the incubation period of COVID-19 is 1-14 days. Most patients show clinical symptoms in 3-7 days.

Fever, dry cough, and fatigue are the main manifestations. Other symptoms include nasal obstruction, runny nose, sore throat, myalgia and diarrhea. In severe cases, patients presented dyspnea and/or hypoxemia within one week after onset. Some of them rapidly deteriorated to acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, coagulation dysfunction, and multiple organ failure. Notably, some severe patients only presented mild- to moderate-grade fever in their entire course of disease, and some even did not show fever at all.

Some children and newborns presented atypical symptoms, such as vomiting, diarrhea and other gastrointestinal discomfort, or only exhibited drowsiness and shortness of breath.

In mild cases, patients only presented low-grade fever and slight fatigue, without evident pneumonia.

From our current observation, most patients have a good prognosis, and only a few patients are critically ill. The prognosis for the elderly and those with chronic comorbidities is relatively worse. The clinical course of COVID-19 pneumonia in pregnant women is similar to that of the same age group. The severity of symptoms in children is relatively mild.

b) Laboratory examination

i. Routine examination

In the early stage of the disease, the total count of peripheral leukocytes could be normal or decreased, and the lymphocyte decreased. In some patients, liver transaminases, lactate dehydrogenase (LDH), creatine kinase and myoglobin were elevated. In some critically severe patients, troponins were also increased. In most patients, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were increased, while procalcitonin generally remains in normal range. Notably, D-dimer was significantly increased in severe patients, and peripheral lymphocytes were progressively decreased. Inflammatory biomarkers are often elevated in severe and critically severe patients.

ii. Etiological and serological examination

- (1) Etiological examination: COVID-19 nucleic acids can be detected in nasopharyngeal swabs, sputum and other lower respiratory tract secretions, blood and feces by using RT-PCR and next generation sequencing technology (NGS). It is more accurate to detect the lower respiratory tract specimen (sputum or airway extract). Once collected, specimen examination should be performed as soon as possible.
- (2) Serological examination: the COVID-19-specific IgM antibody starts to show positive after 3-5 days from onset. In comparison, the titer of COVID-19-specific IgG antibody is 4 times higher in recovery period than that in acute phase.

iii. Chest imaging

At the early stage of the disease, multiple small patchy shadows and interstitial changes appear, which are more obvious in the periphery of the lung. Then it developed into multiple ground-glass shadows and infiltrates shadows. In severe cases, pulmonary consolidation may occur. Pleural effusion is rare.

5. Diagnostic criteria

a) Suspected cases

Comprehensive analysis of the following epidemiological history and clinical manifestations:

i. Epidemiological history

- (1) Travel or residence history of Wuhan and surrounding areas, or other communities with documented COVID-19 positive cases within 14 days before the onset of illness.
- (2) History of contact with COVID-19-infected persons (positive for nucleic acid detection) within 14 days before the onset of illness.
- (3) History of contact with the patients presenting fever or respiratory symptoms, who travel to or reside in Wuhan and surrounding areas, or in other communities with documented COVID-19 positive cases within 14 days

before the onset of illness.

- (4) Clustering onset (2 or more cases of fever and/or respiratory symptoms within 2 weeks in small areas such as home, office, school class, *etc.*)

ii. Clinical manifestation

- (1) Presenting with fever and/or respiratory symptoms.
- (2) With imaging features of above mentioned COVID-19 pneumonia.
- (3) In the early stage of the disease, the total number of leukocytes was normal or decreased, and the lymphocyte count was normal or decreased.

A case that meets any one of the epidemiological history criteria and any two of the clinical manifestations can be identified as a suspected case. If there is no clear epidemiological history, 3 of the clinical manifestations is required.

b) Confirmed cases

Suspected cases with one of the following etiology or serological evidence can be identified as confirmed cases:

- (1) Real-time RT-PCR detection is positive for COVID-19 nucleic acid.
- (2) The viral gene identified by gene sequencing is highly homologous with known COVID-19;
- (3) The COVID-19-specific IgM and IgG antibodies are tested positive. The titer of COVID-19-specific IgG antibody is 4 times higher in recovery period than that in acute phase.

6. Clinical classification

a) Mild type

The clinical symptoms are mild, and there was no sign of pneumonia on chest imaging.

b) Moderate type

These patients had fever and respiratory symptoms. Radiologic assessments found signs of pneumonia.

c) Severe type

Adults meet any of the following criteria:

- (1) Shortness of breath, $RR \geq 30$ times/min;
- (2) Oxygen saturation $\leq 93\%$ at rest;
- (3) Alveolar oxygen partial pressure/fraction of inspiration O_2 (PaO_2/FiO_2) ≤ 300 mmHg (1mmHg=0.133 kPa).

At high altitudes (above 1000 meters), PaO_2/FiO_2 should be corrected according to the following formula: $PaO_2/FiO_2 \times [\text{Atmospheric Pressure (mmHg)}/760]$.

Patients whose pulmonary imaging showed significant progression of lesion $> 50\%$ within 24-48 hours should be treated as severe type.

Children meet any of the following criteria:

- (1) Shortness of breath (<2 months of age, $RR \geq 60$ beats/min; 2 to 12 months of age, $RR \geq 50$ beats/min; 1 to 5 years old, $RR \geq 40$ beats/min; > 5 years old, $RR \geq 30$ beats/min), excluding the effects of fever and crying;
- (2) In the resting state, the oxygen saturation is $\leq 92\%$;
- (3) Assisted breathing (groaning, wing flaps, tri-retraction sign), cyanosis, intermittent apnea;
- (4) Lethargy and convulsions;
- (5) Refuse to feed, and have signs of dehydration.

d) Critically severe type

Patients meet any of the following conditions:

- (1) Respiratory failure requiring mechanical ventilation;
- (2) Shock;
- (3) Patients combined with other organ failure needed ICU monitoring and treatment.

7. Warning signals for severe and critically severe types

a) Adults

- (1) Progressive decline in the number of peripheral lymphocytes;
- (2) Progressive increase in the levels of peripheral inflammatory biomarkers, such as IL-6 and CRP;
- (1) Progressive increase in lactic acid concentration;
- (2) Pulmonary lesions progress rapidly in a short time.

b) Children

- (1) Increased respiration rate;
- (2) Poor mental responsiveness and drowsiness;
- (3) Progressive increase in lactic acid concentration;
- (4) Imaging showed bilateral or multilobes infiltration and pleural effusion; or pulmonary lesions progress rapidly in a short time;
- (5) Infants under 3 months of age, or children having coexisting conditions (congenital heart disease, bronchopulmonary dysplasia, respiratory deformity, abnormal hemoglobin, severe malnutrition, *etc.*), or children with immunodeficiency or under immunosuppressive state (long-term use of immunosuppressants).

8. Differential diagnosis

- a) The mild manifestations of COVID-19 infections need to be distinguished from upper respiratory tract infections caused by other viruses.
- b) The COVID-19 pneumonia needs to be distinguished from other known viral pneumonia or mycoplasma pneumoniae infections, such as influenza virus, adenovirus and respiratory syncytial virus. For suspected cases, technique such as rapid antigen

detection and multiplex PCR nucleic acid detection should be taken to detect common respiratory pathogens.

- c) It should also be distinguished from non-infectious diseases such as vasculitis, dermatomyositis, and organizing pneumonia.

9. Identifying cases and filing reports

When a COVID-19 suspected case is found by any medical practitioners, it is critical to immediately isolate the suspected person in a solitary cell for further monitoring and treatment. If COVID-19 infection is still suspected after comprehensive evaluation by medical experts and/or physicians, a case report should be submitted through internet to Centers for Disease Control (CDC) within 2 hours after the initial suspicion. In addition, specimens should be collected for COVID-19 nucleic acid test. Meanwhile, the suspected person should be immediately transferred to a pre-designated hospital with secured transportation modalities. If the suspected person has a close contact history with patient(s) already diagnosed with COVID-19 pneumonia, COVID-19 nucleic acid test should be performed, even if his or her common respiratory pathogen detection test has shown positive result(s).

If COVID-19 nucleic acid tests are negative for two consecutive times (with at least 24 hours interval between each test), and if COVID-19-specific IgM and IgG antibodies remain negative after 7 days from onset, the suspected diagnosis of COVID-19 can be ruled out.

10. Treatment

a) Determine the treatment place according to patients' condition.

- (1) Suspected and confirmed cases should be isolated and treated in designated hospitals with effective isolation and protection conditions. Suspected cases should be isolated in a single ward, while confirmed cases can be admitted to multiple bedded ward.
- (2) Critically severe cases should be admitted to ICU as soon as possible.

b) General treatment.

- (1) Rest in bed with supportive treatment to ensure sufficient energy supply. The water and electrolyte balance should be noticed to maintain internal environment stability. Vital signs and oxygen saturation should be closely monitored.
- (2) Monitor the blood routine, urine routine, CRP, biochemical indicators (liver enzyme, myocardial enzyme, renal function, *etc.*), coagulation function, arterial blood gas analysis, chest imaging according to the condition. If possible, cytokine test should be performed.
- (3) Effective oxygen therapy measures should be given in time, including nasal cannula, mask oxygen and high-flow nasal cannula oxygen therapy. Hydrogen-oxygen inhalation (H_2/O_2 : 66.6%/33.3%) treatment can be considered for use.

- (4) Antiviral therapy: α -interferon (5 million U or equivalent for adult, add 2ml of sterile water, 2 times daily inhalation), lopinavir/ritonavir (200 mg/50 mg/capsule, 2 capsules each time for adults, twice a day, the course of treatment should not exceed 10 days). Ribavirin (combination with interferon or lopinavir/ritonavir is recommended, 500 mg each time for adults, 2 to 3 times intravenous infusions per day, the course of treatment should not exceed 10 days), chloroquine phosphate (for adults whose weigh over 50 kg, 500 mg each time, twice daily for 7 days; for those whose weigh less than 50 kg, 500 mg each time, twice daily for day 1 and day 2, once daily for day 3- day 7), Abidol (200 mg each time, three times a day for adults, the course of treatment should not exceed 10 days) can be tried. Attention should be paid to the adverse reactions of the above drugs, contraindications (such as chloroquine should not be used in patients with heart disease), and interaction with other drugs. It is not recommended to use 3 or more antiviral drugs at the same time. The use of related drugs should be stopped when intolerable side effects occur. The treatment of pregnant women should consider the number of weeks of gestation and choose drugs that have less impact on the fetus.
- (5) Antibacterial drug treatment: inappropriate use of antibacterial drugs should be avoided, especially the broad-spectrum antibacterial drugs.

c) Treatment of severe and critically severe cases.

(1) Principles of treatment:

In addition to symptom treatments, it is important to actively prevent complications, treat underlying diseases, prevent secondary infections, and provide organ function support.

(2) Respiratory support:

- a) Oxygen therapy: Severe patients should receive nasal cannula or mask to inhale oxygen, and evaluate in time whether respiratory distress and/or hypoxemia is relieved.
- b) High-flow nasal cannula oxygen therapy or non-invasive mechanical ventilation: When patients with respiratory distress and / or hypoxemia cannot be relieved after receiving standard oxygen therapy, high-flow nasal cannula oxygen therapy or non-invasive ventilation can be considered. If the condition does not improve or worsens within a short time (1-2 hours), tracheal intubation and invasive mechanical ventilation should be performed in time.
- c) Invasive mechanical ventilation: Using lung protective ventilation strategy, that is, small tidal volume (6-8 mL/kg ideal body weight) and low level of airway plateau pressure (≤ 30 cm H₂O) for mechanical ventilation to reduce ventilator-related lung injury. When the airway plateau pressure is ≤ 35 cm H₂O, high PEEP can be appropriately used. Keep the airway warm and humid, avoid prolonged sedation, and awaken patients early and perform pulmonary

rehabilitation treatment. For those patients with problem of man-machine synchronization, sedation and muscle relaxants should be used in time. According to the airway secretions, closed sputum suction should be considered, and bronchoscopy should be performed if necessary.

- d) Salvage treatment: For patients with severe ARDS, it is recommended to perform lung expansion. Prone ventilation should be performed for more than 12 hours per day. When prone position mechanical ventilation is not effective, if conditions permit, extracorporeal membrane pulmonary oxygenation (ECMO) should be considered as soon as possible. Related indications: ① When $FiO_2 > 90\%$, the oxygenation index is less than 80mmHg, which lasts more than 3-4 hours; ② Patients with simple respiratory failure with airway plateau pressure ≥ 35 cm H₂O, the VV-ECMO mode is preferred; if circulatory support is needed, then VA-ECMO mode will be selected. When the underlying disease is under control and cardiopulmonary function shows signs of recovery, weaning trials should be considered to begin.

(3) Circulation support:

Based on adequate fluid resuscitation, improvement of microcirculation and use of vasoactive drugs may be considered. Changes in patients' blood pressure, heart rate, and urine output, as well as lactic acid and alkali residuals in arterial blood gas analysis should be closely monitored. Noninvasive or invasive hemodynamic monitoring, such as Doppler echocardiography, echocardiography, invasive blood pressure or continuous cardiac output (PiCCO) monitoring, is necessary. In the process of treatment, attention should be paid to the liquid balance to avoid excess and deficiency.

When the patient's heart rate suddenly increases over 20% of the baseline value or the blood pressure has dropped by more than 20% of the baseline value, accompanying symptoms such as poor skin perfusion and decreased urine output, it should be alert whether patients have septic shock, gastrointestinal bleeding, or severe heart failure.

(4) Renal failure and renal replacement therapy:

When renal insufficiency occurs in critically severe patients, the causes of renal function insufficiency, such as hypoperfusion and drugs, should be analyzed. The treatment of patients with renal failure should pay attention to fluid balance, acid-base balance and electrolyte balance. For nutrition support treatment, attention should be paid to nitrogen balance, and supplement of calorie and minerals. Renal replacement therapy (CRRT) can be considered in severe patients. The indications include: ① hyperkalemia; ② acidosis; ③ pulmonary edema or excessive water load; ④ fluid management when multiple organ dysfunction occurs.

(5) Recovered patients' plasma therapy:

It is suitable for severe and critically severe patients with rapid disease progression.

(6) Blood purification treatment:

The blood purification system includes plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., which can remove inflammatory factors and stop the "cytokine storm", thereby reducing the damage to the body caused by the inflammatory response. It can be used for treatment of early and mid-term cytokine storms in severe and critically severe patients

(7) Immunotherapy:

For patients with extensive lung lesion and severe patients with elevated IL-6 levels, tocilizumab treatment can be tried. The first dose is 4-8mg/kg, the recommended dose is 400mg with dilution of 0.9% physiological saline to 100ml, and the infusion time should be more than 1 hour. If the first medication is not effective, it can be applied once more after 12 hours (the dose is the same as before), cumulative number of administrations should not be more than 2 times, and the maximum single dose should not exceed 800 mg. Pay attention to allergic reactions. It is not recommended for people with active infections such as tuberculosis.

(8) Other treatment measures

For patients with progressive deterioration of oxygenation indicators, rapid imaging progress, and excessive activation of inflammatory response, the use of glucocorticoids in the short term (3 to 5 days) should be considered. The dosage of methylprednisolone should not be over 1-2mg/kg/day. It should be noted that large doses of glucocorticoids will delay the removal of coronavirus due to immunosuppressive effects. Intestinal microecological regulators can be used to maintain intestinal microecological balance and prevent secondary bacterial infections.

For severe and critically severe children patients, intravenous gamma globulin should be considered.

Pregnant women with severe or critically severe COVID-19 pneumonia should consider pregnancy termination, and cesarean delivery is preferred.

Psychological counseling should be strengthened in patients with anxiety and fear.

d) Traditional Chinese medicine treatment

According to the local climate characteristics, patients' illness states and physical conditions, traditional Chinese medicine treatments can be used under the guidance of doctors. Huoxiang Zhengqi Capsules, *ect.* are recommended for patients with asthenia and gastrointestinal discomfort. Jinhua Qinggan granules, Lianhua Qingwen capsules

and Shufeng Jiedu Capsules, *ect.* are recommended for patients with asthenia and fever.

11. Discharge criteria and precautions after discharge

a) Discharge criteria.

- (1) The body temperature returns to normal for more than 3 days;
- (2) Significant improvement in respiratory symptoms;
- (3) Pulmonary imaging shows a marked improvement in acute exudative lesions;
- (4) Negative nucleic acid test for sputum, nasopharyngeal swabs and other respiratory specimens for two consecutive times (at least 24 hours interval between each test).

Those who meet all the above conditions can be discharged.

b) Precautions after discharge.

- (1) The hospital should make good contact with the basic medical and health institutions where the patients live, share the medical records, and timely send the discharged patients' information to the residential committee and the basic medical and health institutions.
- (2) After the patient is discharged from the hospital, it is recommended to continue the isolation management and health monitoring for 14 days, wear a mask, and live in a well-ventilated single room, reduce close contact with family members, wash hands frequently, and avoid going out.
- (3) It is recommended to follow up and return to the hospital in the 2nd and 4th week after discharge.

Translated by Chinese Society of Cardiology

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March 15, 2020, Sunday

翻译单位：中华医学会心血管病学分会

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2020年3月15日星期日