Noninvasive Assessment of Cardiac Changes in Patients with Coronavirus Disease-19 (COVID-19) by Bedside Ultrasound

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Abstract

PURPOSE: This study was conducted to explore the value of noninvasive assessment of bedside ultrasound in diagnosing cardiac changes of COVID-19. METHODS: We performed a retrospective study in 34 patients with COVID-19 and analyzed their clinical data, biochemistry test results (creatine kinase-MB [CK-MB], cardiac troponin I [cTnI] and C-reactive protein [CRP]), and parameters of cardiac ultrasound (left atrium [LA], left ventricular end-diastolic dimensions [LVDD], right atrium [RA], right ventricle [RV], main pulmonary artery [MPA], left ventricular ejection fraction [LVEF], tricuspid valve [TV], pulmonic valve [PV] and pulmonary artery systolic pressure [PASP]). We classified the patients based on their clinical symptoms: mild, moderate, severe, and critical groups, and compared the parameters. RESULTS: As the disease progressed, the parameters of both biochemical blood tests and cardiac ultrasound changed regularly, manifested as enlargement of LA, LVDD, RA, RV, and MPA and increase of PASP, CRP, CK-MB, and cTnI. Of these parameters, CRP, LA, LVDD, MPA, and PASP of the severe group were more notably elevated than those of the mild and the moderate groups ($p<0.05$). The critical group increased more markedly in CK-MB, cTnI, and RA than the other groups ($p<0.05$), and rose more sharply in CRP, LA, LVDD, RV, MPA, and PASP than the mild and the moderate groups ($p<0.05$). CONCLUSION: As the disease progressed, the patients had the enlarged heart with expanded pulmonary arteries and elevated PASP. Bedside ultrasound can be a noninvasive assessment of the above changes and a guidance of clinical treatment.

Introduction

Since its outbreak in December 2019, Coronavirus Disease 2019 (COVID-19) has quickly spread through over 200 countries and regions worldwide and has become the public health emergency of international concern. The pathogen of COVID-19 is a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is highly pathogenic and contagious. Clinical characteristics of SARS-CoV-2 infection typically include fever and respiratory symptoms. Furthermore, a significant proportion of patients presented with cardiac symptoms. Recent reports suggest that cardiac complications not only are common ([?]20%–25%) in COVID-19 infection but also are associated with increased mortality [1], such as arrhythmia (16.7%) and acute myocardial damage (7.2%), and death can occur in severe cases (10.5%) [2]. However, in those reports, cardiac complications were defined according to clinical and laboratory parameters (troponin levels), without any systematic cardiac imaging. Echocardiography is the mainstay of cardiac imaging, used to diagnose different causes of heart failure and to assist in patient hemodynamic evaluation, risk assessment, and therapy of patients hospitalized in intensive care unit [3]. With myocardial enzymes and other biochemical blood parameters, this study summarizes cardiac ultrasound characteristics of patients with COVID-19 and explores the clinical value of assessment of cardiac damage in patients with COVID-19 by cardiac ultrasound.

Materials and Methods

Our institutional review board (IRB) approved this retrospective study that evaluated de-identified data and involved no potential risk to patients. Written informed consent was waived. No link between the patients and the researchers was made available to avert any potential breach of confidentiality. This study was conducted in accordance with the current version of the Declaration of Helsinki.

Participants

In this retrospective study, patients with COVID-19 admitted to our hospital were selected as research subjects. Based on their clinical symptoms, all the selected patients were classified as mild (with mild symptoms and no signs of pneumonia on imaging), moderate (showing fever and respiratory symptoms with radiological findings of pneumonia), severe (adult cases meeting any of the following criteria: [1] respiratory distress [[?]30 breaths/ min]; [2] pulse oxygen saturation [?]93% at resting state; [3] alveolar oxygen partial pressure [PaO2]/ fraction of inspired oxygen [FiO2] [?]300mmHg [1mmHg=0.133kPa]. Patients whose chest imaging show obvious lesion progression within 24-48 hours >50% shall be managed as severe cases.), and critical cases (meeting any of the following criteria: [1] respiratory failure and requiring mechanical ventilation; [2] shock; [3] with other organ failures that require intensive care unit [ICU] care). After confirmation of COVID-19 and clinical classification, patients underwent biochemical blood tests and bedside echocardiography immediately. Inclusion criteria: patients with positive results for the COVID-19 nucleic acid tests (RT-PCR method), in accordance with definitions of confirmed cases in *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)* [4] released by National Health Commission of the People's Republic of China. Exclusion criteria: (1) patients who lacked biochemical blood tests or bedside cardiac ultrasound examination; (2) patients whose bedside echocardiography images were of poor quality and could not be used for image analysis; (3) patients who suffered an acute myocardial infarction, rheumatic heart disease (acute), or other cardiac diseases, or underwent cardiac surgery within one month; (4) patients with chronic obstructive pulmonary disease, cor pulmonale, or other pulmonary diseases.

Methods

Biochemical blood test: The serum markers of myocardial damage and inflammation were collected from the patients, including creatine kinase-MB (CK-MB), cardiac troponin I (cTnI), and C-reactive protein (CRP).

Echocardiography: Philips Affinity 50 Color Doppler Diagnostic Ultrasound System (Philips, Bothell, WA, USA) equipped with an S4-2 phased array transducer (bandwidth: 2-4Mhz) was used. The examinations at the bedside were all performed by the same ultrasound physician with more than ten years of clinical ultrasound experience. Patients were placed under resting state in left lateral decubitus and supine positions and observed mainly in the parasternal long-axis, aorta, and apical four-chamber view. The M-mode and two-dimensional images were recorded to measure the volumes of the left atrium (LA), left ventricular end-diastolic dimension (LVDD), right atrium (RA), right ventricle (RV), and main pulmonary artery (MPA). The left ventricular ejection fraction (LVEF) was measured by the M-mode ultrasound. The velocity of the tricuspid valve (TV) and pulmonary valve (PV), TR velocity (TR_{max}), and other data were measured by the continuous wave Doppler ultrasound. PASP values were calculated from TR velocity (TR_{max}), and the formula was $PASP = 4(TR_{max})^2 + RAP$. The diagnostic criteria for pulmonary hypertension were PASP [?]35 mmHg[3]. The criteria for abnormal ultrasound findings were based on the *Consensus for Standard Assessment by Echocardiography in Chinese Adults with Heart Failure*[5].

Statistical Analysis

The statistical analysis of this study was performed using SPSS (version 24; IBM, New York, USA). Enumeration data were presented with counts (percentages), and differences among groups were compared using the X^2 test. Measurement data were presented as mean ± standard deviation and compared using the one-way ANOVA. *[M (P_{25}, P_{75})]* (median [interquartile range]) was given and compared using the nonparametric tests (Kruskal-Wallis test) when the data were not normally distributed. $P<0.05$ was considered statistically significant.

Results

Clinical Features

34 patients with COVID-19 (25 male and 9 female patients, age range: 18-80 years) were included in this study. The procedure for selection is shown in Figure 1. Patients in the mild group were significantly younger than those in the other three groups (p¡0.05). There was no statistical difference in underlying diseases among the patients with COVID-19 (p¿0.05). The clinical characteristics are shown in Table 1.

Parameters of Cardiac Enzyme (CK-MB and cTnI) and CRP

The critical group showed a significant increase in the level of CK-MB and cTnI compared with the other three groups (p¡0.05), among which there were no statistical differences (p¿0.05). The severe and critical group showed a significant elevation in the level of CRP compared with the mild and moderate groups, as shown in Table 2.

Cardiac Ultrasound Findings

The severe and critical group showed an increase in LA, LVDD, MPA, and PASP compared with the mild and moderate groups (p¡0.05). The critical group showed a marked enlargement in RA compared with the other three groups (p¡0.05). The critical group showed an increase in RV compared with the mild and moderate groups, which demonstrated statistically significant differences (p¡0.05), as shown in Table 3.

Discussion

COVID-19 can not only cause severe damage to the lungs as the target organs but also induce damage to multiple organs[2,4], including heart, liver, kidney, and so on. Especially in critically ill patients, COVID-19 with comorbid cardiovascular disease is not clinically rare[6-8]. Data from 1216 patients scanned in 69 countries across six continents demonstrated left or right ventricular abnormalities in half of all patients with COVID-19 undergoing echocardiography, and that these abnormalities were severe in 1 in 7 patients. The majority had non-specific patterns of ventricular dysfunction, although new myocardial infarction, myocarditis, and takotsubo cardiomyopathy were observed in a minority of patients[9]. COVID-19 may aggravate pre-existing cardiovascular disease and trigger new and more serious heart damage, which may cause heart failure, cardiogenic shock, and even death in severe and critical cases [4]. Therefore, such indicators, including cardiac morphology and function as well as myocardial enzymes, are closely monitored clinically and timely treatment is also given according to their changes to reduce myocardial damage, lower mortality rate and improve prognosis.

Given that CK-MB and cTnI exhibit a relatively strong sensitivity and specificity in the diagnosis of myocardial damage[10], the results of this study that CK-MB and cTnI in the critical group were significantly higher than those in the other groups ($p<0.05$) indicate that patients in the critical group had the most significant myocardial damage. This may be caused by the fact that in critically ill patients, abnormally elevated inflammatory cytokines and overactivated immune cells enter the bloodstream and invade the vascular endothelial cells of the heart, resulting in the damage to vascular endothelial cells and the increase of vascular permeability, and thus making it possible for inflammatory cells to penetrate the endodermis, infiltrate the myocardial tissue and directly lead to the damage of myocardial cells. Meanwhile, endothelial cell damage causes vascular diastolic dysfunction and decreased coronary flow reserve, limiting the myocardial blood supply under the high load and thus bringing about myocardial ischemia [11], which further aggravates the myocardial damage. In this situation, CK-MB and cTnI significantly increase, which eventually leads to secondary cardiac enlargement in critically ill patients. However, it is still unclear whether SARS-CoV-2 can directly attack the myocardium. According to the autopsy result reported by Wang Fusheng, the academician of the China Scientific Academy, and his team [12], the pathological changes in the lungs of the deceased patients were obvious, but no significant histological changes were observed in heart tissues, which indicates that SARS-CoV-2 may not directly damage the heart.

In addition, the results of this study display that with disease severity progresses, RA, RV, and MPA of the patients with COVID-19 tend to expand, and their PASP increases gradually. This may be caused by the large amounts of cytokines in patients with COVID-19, which even causes an "inflammatory cytokine storm" [13]. It causes inflammatory response edema in the bronchus and alveolus, as well as inflammatory exudation, thereby resulting in obstruction of ventilation and gas exchange, ventilation-perfusion imbalance, hypoxemia, carbon dioxide retention, and other symptoms. These symptoms reflexively provoke vasoconstriction of pulmonary small vessels and increase resistance. Besides, the hypoxia in the lung tissue and acidosis induced by the infection causes increased synthesis and secretion such as endotheliogenic contraction/diastolization factors, prostaglandins. These further aggravate pulmonary small vessel contraction and spasm. The persistence of the above changes leads to long-term contraction of pulmonary arterioles, which progresses with the severity of the disease aggravates, and ultimately leads to increased pulmonary arterial pressure [14] as well as pulmonary artery dilatation. Persistent pulmonary hypertension also further worsens the right heart enlargement. During hospitalization, 20% of patients experienced clinical deterioration, and in these patients, a second echocardiogram showed further deterioration of RV parameters, probably related to increased pulmonary pressures [15].

As for the increase of CK-MB and cTnI in critically ill patients, we believe it is related to the following reasons. On the one hand, the infiltration of inflammatory cytokines and immune cells after a pulmonary infection causes damage to myocardial cells. On the other hand, the increase of pulmonary arterial pressure leads to increased right heart afterload and aggravated myocardial oxygen consumption. Given that the myocardium is extremely sensitive to hypoxia, this can directly lead to myocardial energy metabolism disorders, and further aggravates myocardial damage. Therefore, the prognosis of myocardial damage may depend more on the control of pulmonary inflammation and the degree of decrease in pulmonary arterial pressure. According to the inference, active treatment of pulmonary infection and monitoring of pulmonary arterial pressure may play an important role in promoting the outcome of myocardial damage.

Cardiac ultrasound is the preferred method for clinical cardiac structure and function assessment and pulmonary arterial pressure monitoring. Also, our previous study showed that bedside ultrasound has important clinical significance in the assessment and dynamic observation of pulmonary lesions in patients with COVID-19[16]. In a third of patients who underwent echocardiography on clinical indication, imaging was reported to result in an immediate change in patient management. This included changes in disease-specific therapies, such as pericardiocentesis or therapy for heart failure, pulmonary embolism, or acute coronary syndromes. It also contributed to decisions regarding the level of patient care, such as the admission of patients to critical care, and the need for titration of haemodynamic support [9]. Among patients with COVID-19 who underwent echocardiography, cardiac structural abnormalities were present in nearly two-thirds of patients with myocardial injury. Myocardial injury was associated with increased in-hospital mortality particularly if echocardiographic abnormalities were present [17]. Therefore, for those infected patients with myocardial damage, bedside ultrasound can be used for combined detection of heart and lungs and dynamic monitoring of changes in the condition, providing a reference for clinical treatment. Moreover, critically ill patients with COVID-19 are often associated with multiple organ involvement, and bedside ultrasound facilitates the immediate systemic assessment of the patient.

This study has several limitations. Firstly, the sample size was small. Therefore, the possible confounding factors that affect the results may occur, and expansion of the sample size and a multicenter study is needed. Secondly, this study was a retrospective analysis, lacking indicators related to the evaluation of right ventricular systolic and diastolic function, and no evaluation of right heart function. Thirdly, this study did not perform dynamic cardiac ultrasound monitoring in patients with COVID-19. Therefore, follow-up examinations are required to illustrate the ultrasound manifestations in the whole course of COVID-19.

In summary, the patients with COVID-19 had the gradually enlarged heart with enlarged pulmonary arteries and elevated PASP as the disease progressed. Bedside ultrasound can be used for a noninvasive assessment of the above changes, which may be helpful as a clinical guide to treatment.

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Table 1

Clinical Characteristics of Patients with COVID-19

Parameter	Mild (n=5)	Moderate (n=12)	Severe (n=12)	Critical (n=5)	P-value
Age (year)	32.00±15.12	50.33±12.24[a]	60.15±13.52[a]	61.17±11.34[a]	<0.01
Male	5（100%）	8（66.66%）	7（58.33%）	5（100%）	0.150
BMI (kg/m^2)	23.78±4.89	24.11±2.83	24.47±3.69	27.09±3.60	0.357
Recent travel to Wuhan	1（20%）	12（100%）[a]	6（50.00%）[b]	3（60.00%）[b]	<0.01
Close contact with infected patients	1（20%）	0	2（16.66%）[b]	1（20.00%）[b]	<0.05
Symptom					
Fever (>37.5°C)	3（60%）	8（66.66%）	11（91.66%）	5（100%）	0.192
Cough	3（60%）	5（41.66%）	10（83.33%）	5（100%）	0.056
Fatigue	0	1（8.33%）	6（50.00%）[ab]	4（80.00%）[ab]	<0.01
Muscle soreness	0	2（16.66%）	5（41.66%）	1（20.00%）	0.253
Underlying disease					
Hypertension	0	1（8.33%）	2（16.66%）	2（40.00%）	0.280
Diabetes	0	1（8.33%）	2（16.66%）	1（20.00%）	0.704
Tuberculosis	0	0	1（8.33%）	1（20.00%）	0.393

Note: Mark ([a]), ([b]), and ([c]) to indicate a significant difference (p＜0.05) compared with the mild group, moderate and severe group, respectively.

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Table 2

Comparison of CK-MB, cTnI and CRP in Patients with COVID-19

Parameter	Mild (n=5)	Moderate (n=12)	Severe (n=12)	Critical (n=5)	P-value
CK-MB（U/L）	10.73±3.01	12.45±4.77	12.73±14.06	19.36±8.69[abc]	<0.05
cTnI	0	0	1（8.33%）	5(100%)[abc]	<0.01
CRP [M (P_{25}, P_{75}) mg/L]	3.36(0.71,16.93)	1.38(0.55,16.10)	29.52(10.31,74.33)[ab]	58.01(34.51,85.36)[ab]	<0.01

Note: **A.** Mark ([a]), ([b]), and ([c]) to indicate a significant difference (p＜0.05) compared with the mild group, moderate and severe group, respectively. **B.** Abnormal levels of cTnI were presented with counts (percentages).

Table 3

Results of Cardiac Ultrasound in Patients with COVID-19

Parameter	Mild (n=5)	Moderate (n=12)	Severe (n=12)	Critical (n=5)	P-value
LA (mm)	31.50±2.42	33.42±2.50	36.77±5.16[ab]	40.00±4.56[ab]	<0.01
LVDD (mm)	43.66±4.22	44.50±3.26	48.53±3.77[ab]	52.00±7.37[ab]	<0.01
RA (mm)	32.66±2.33	34.58±1.24	35.92±1.55[a]	38.16±4.21[abc]	<0.01
RV (mm)	32.83±3.31	33.83±1.19	35.15±1.90	36.66±3.82[ab]	<0.05
MPA (mm)	22.33±0.51	23.25±2.26	24.92±2.10[ab]	26.16±0.75[ab]	<0.01
LVEF (%)	67.33±5.16	67.41±5.53	66.61±3.57	65.00±3.74	0.745
TV (m/s)	0.60±0.12	0.62±0.12	0.65±0.15	0.62±0.13	0.882
PV (m/s)	0.88±0.15	0.91±0.13	0.87±0.13	0.91±0.68	0.848
PASP (mmHg)	26.00±2.82	26.50±4.42	36.60±7.55[ab]	39.50±9.60[ab]	<0.01

Note: Mark ([a]), ([b]), and ([c]) to indicate a significant difference ($p < 0.05$) compared with the mild group, moderate and severe group, respectively.

Figure

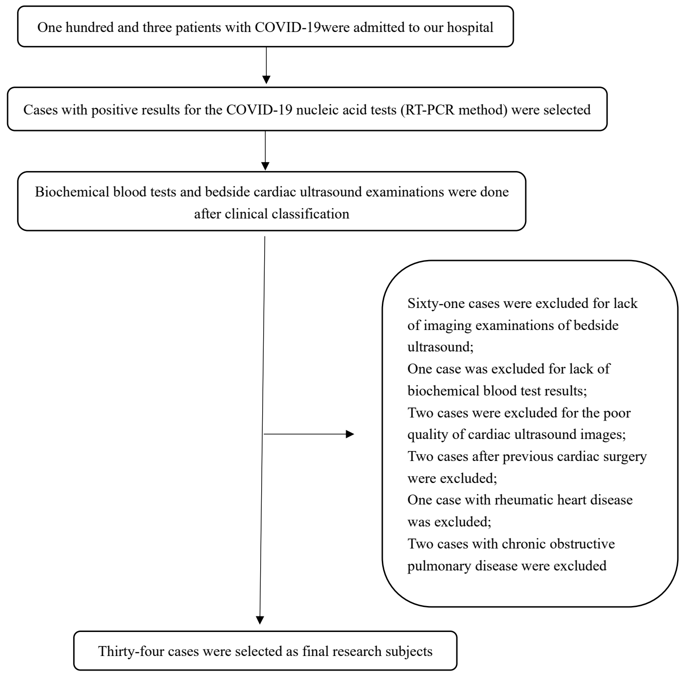

Fig. 1. Procedure for Patient Inclusion.

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