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Combined Heart Injuries on the Data of Contrast-Enhanced Cardiac Magnetic Resonance Imaging in Patients With Post-Covid Syndrome

Aim	Prospective assessment of the nature of cardiac injury in patients with post-COVID syndrome according to contrast-enhanced MRI in routine clinical practice.
Material and methods	106 previously unvaccinated patients were evaluated. 62 (58.5%) of them were women with complaints that persisted after COVID-19 (median age, 57.5 [49; 64] years). In addition to standard indexes, markers of inflammation and myocardial injury were determined, and cardiac contrast-enhanced MRI was performed in each patient.
Results	The median time from the onset of COVID-19 to cardiac MRI was 112.5 [75; 151] days. The nature of cardiac injury according to MRI in patients with post-COVID syndrome was complex and included a decrease in left ventricular (LV) and right ventricular ejection fraction, pericardial effusion, and pathological foci of late and early contrast enhancement at various locations. In 29 (27.4%) cases, there was a combination of any two signs of heart injury. In 28 (26.4%) patients with focal myocardial injury during the acute phase of COVID-19, hydroxychloroquine and tocilizumab were administered significantly more frequently, but antiviral drugs were administered less frequently. The presence of focal myocardial injury was associated with pathological LV remodeling.
Conclusion	According to contrast-enhanced cardiac MRI, at least 27.4% of patients with post-COVID syndrome may have signs of cardiac injury in various combinations, and in 26.4% of cases, foci of myocardial injury accompanied by LV remodeling are detected. The nature of heart injury after COVID-19 depends on the premorbid background, characteristics of the course of the infectious process, and the type of prescribed therapy. An algorithm for evaluating patients with post-COVID syndrome is proposed.

Keywords	COVID-19; COVID-19 complications; post-COVID syndrome; myocarditis; magnetic resonance imaging
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COVID-19 pandemic has shown undisputedly the involvement of the cardiovascular system in the pathogenesis of this disease and the occurrence of specific disorders that can persist for a long time in the so-called long COVID [1–8]. As well as the quality of life reduces after COVID-19, the risks of developing thrombosis, coronary artery disease (CAD), arrhythmias, and inflammatory heart diseases significantly increase [5–8]. The term "COVID heart" has been introduced into scientific use to draw attention to this problem [9].

The signs of myocardial injury that persist after COVID-19 are of particular interest. Magnetic resonance imaging (MRI) of the heart detects them in 10–49% of cases and even in apparently healthy people with a mild course of the infection [10–19]. On the top of myocardial injury, systolic or diastolic ventricular dysfunction and pericarditis may occur after COVID-19 [12, 15, 20–24]. The question remains how the resulting injury affects the development of arrhythmias, heart failure (HF), and clinical prognosis [15, 16, 18, 19].

Objective

Conduct prospective assessment of the nature of heart damage in patients with long COVID using contrast-enhanced MRI in routine clinical practice.

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Material and Methods

From October 2020 to June 2021, 1,157 patients with history COVID-19 were referred by outpatient physicians to the Department of Post-COVID Complications of the Voronezh Regional Clinical Consultative and Diagnostic Center. Dyspnea and palpitations during exercise, irregular heartbeat, chest pains that appeared after COVID-19 were the reason for the cardiac examination. The study included patients above 18 years old who signed the informed consent and were in a stable condition, and whose diagnosis was confirmed by the isolation of SARS-CoV-2 RNA. The study protocol was approved by the local ethics committee (No.145 dated September 16, 2020) and registered in ClinicalTrials.gov (NCT04794062).

A total of 119 non-vaccinated patients who had had COVID-19 for the first time were included in the study. By the time of inclusion in the study, 103 (97.2%) patients had a more than 1-month history of COVID-19. The most common symptoms were dyspnea in 84 (79%) cases, palpitations during exercise in 80 (75%), severe fatigue in 80 (75%), and irregular heartbeat in 66 (62%) cases.

C-reactive protein (CRP), ferritin, N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity troponin I were estimated in addition to the common indicators, and contrast-enhanced MRI of the heart was performed.

Of the 119 patients selected at baseline, 13 patients did not have separate cardiac tests or MRI, and 106 patients from 27 to 80 years old (median age 57.5 [49; 64] years), including 62 (58.5%) female patients, completed the study.

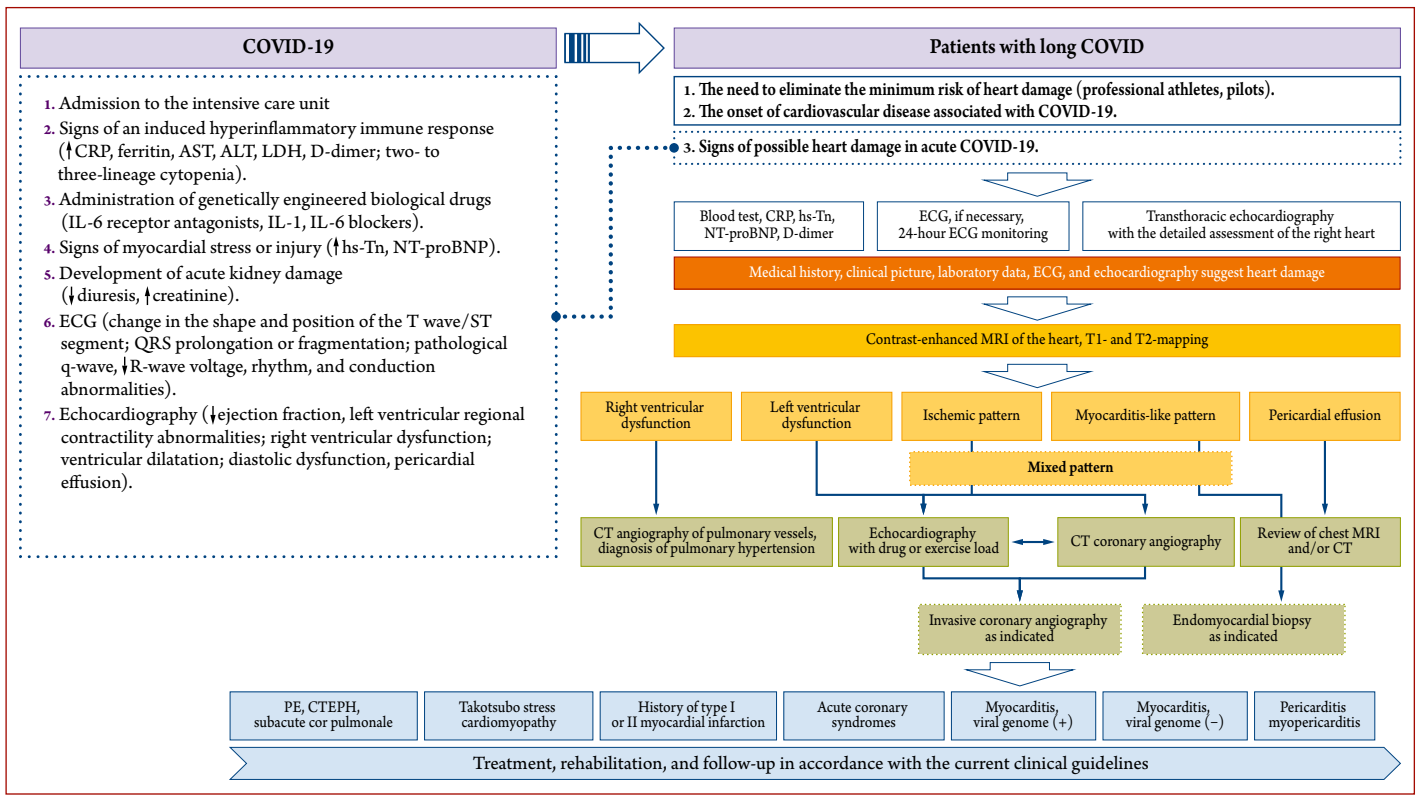
Elevated levels of CRP (>5 mg/L), ferritin (females >120 μg/L, males >250 μg/L), NT-proBNP (>125 pg/mL), and high-sensitivity troponin I (females >15.6 ng/L, males >34.2 ng/L) were reported in 20 (18.9%), 15 (14.1%), 14 (13.2%), and 3 (2.8%) subjects, respectively.

Electrocardiography showed bundle branch block in 12 (11.3%) cases, an abnormality of the polarity and/or shape of the T wave in 10 (9.4%) cases, an increase or decrease in the ST segment in 8 (7.5%) cases, and an intraventricular conduction abnormality with a QRS complex duration of < 100 ms in 6 (5.7%) cases.

Transthoracic echocardiography revealed reduced left ventricular ejection fraction (LVEF) to 40–59%, impaired regional contractility, diastolic dysfunction, and pericardial effusion in 20 (18.8%), 4 (3.8%), 9 (8.5%), and 10 (9.4%) patients, respectively.

The median time from the onset of COVID-19 to MRI of the heart was 112.5 [75; 151] days. The examination was performed using the 1.5 T Optima MR 450 W GE Healthcare scanner. Data were

Central Illustration. Examination algorithm for patients with long COVID using multimodal imaging



LDH, lactate dehydrogenase; IL, interleukin; hs-Tn, high-sensitivity troponin; NT-proBNP, N-terminal pro-brain natriuretic peptide; ECG, electrocardiogram; CTEPH, chronic thromboembolic pulmonary hypertension.

collected using ECG synchronization. Conventional signs of myocarditis (Lake Louise Consensus Criteria, 2009) were used to assess inflammatory myocardial injury: focal or global increased intensity of the MRI signal in T2 weighted images (myocardial edema), increased T1 signal of the myocardium during early contrast enhancement (myocardial hyperemia), areas of delayed contrast enhancement in the myocardium (necrosis and/or fibrosis) [24]. Contrast enhancement was performed immediately after the MR sequences by intravenous administration of gadobutrol at a dose of 0.1 mmol/kg. T1 weighted images were obtained in 1–3 minutes after the administration of the contrast agent to assess early contrast enhancement (ECE) and in 10 minutes to assess the phenomenon of delayed contrast enhancement (DCE). The presence of myocardial edema and the ECE and DCE phenomena was determined by myocardial segments in three short-axis sections of the left ventricle. Dimensions of the heart and ejection fractions were estimated based on the reference ranges provided in the 2019 EACI guidelines [25].

The data obtained were processed in Python and Statistica 12.0. The quantitative variables were compared using the Mann-Whitney U-test, and the qualitative variables were compared using Fisher's exact test and chi-squared test. The analysis of associations was based on the calculation of Pearson correlation coefficients. Quantitative variables were represented as the medians and quartiles, and qualitative variables were expressed as the absolute numbers and percentages. Differences were statistically significant with p less than 0.05.

Results

MRI of the heart revealed a decrease in global LV contractility in 19 (17.9%) of cases and in global right ventricular (RV) contractility in 39 (36.8%) cases. Pericardial effusion was found in 27 (25.5%) patients. There were no cases of myocardial edema. The phenomenon of ECE or DCE occurred in 28 (26.4%) patients, with ECE detected in 5 (5.7%) cases and DCE in 26 (24.5%) cases. At least one sign of heart damage was found in 72 (67.9%) patients examined and at least two signs in 29 (27.4%) subjects. The most common were a decrease in RVEF and LVEF in 15 (14.1%) patients, a decrease in RVEF and DCE in 11 (10.4%) patients, and a decrease in RVEF and pericardial effusion in 10 (9.4%) patients. Combinations of three signs such as a decrease in RVEF and LVEF and DCE and a decrease in RVEF and LVEF and pericardial effusion were observed in 7 (6.6%) and 6 (5.6%) patients, respectively. The combination of RV and LV dysfunction, DCE, and pericardial effusion occurred in 3 (2.8%) cases.

The analysis of associations between different types of heart damage showed that there is a significant weak correlation between the decrease in RVEF and LVEF ($r=0.41$; $p<0.0001$), and the ECE and DCE phenomena ($r=0.18$; $p=0.0598$). The results of the cluster analysis showed that among the 16 combinations of MRI signs of heart damage, there were stable correlations between reduced RVEF and LVEF, as well as the ECE and DCE phenomena. The pattern of post-COVID heart damages in the form of a Venn diagram with the allocation of the most typical combinations based on a tree-like clustering structure is presented in Figure 1.

ECE was observed in total of 9 LV segments, and DCE in 100 LV segments, and the median number of damaged segments with DCE was 3 [1; 5]. DCE foci were located intramyocardially in the form of multiple dashed, spotted, or diffuse areas in 15 (58%) cases, subepicardially in 1 (4%) case, subendocardially in 3 (11.5%) cases, and transmurally in 4 (15%) cases, and 3 (11.5%) patients had a combination of various types of contrast agent distribution in the myocardium. There was no history of CAD in all cases of transmural or subendocardial DCE. Examples of post-COVID heart damage are presented in Figure 2.

A search was performed to see whether the development of post-COVID myocardial injury depends on the baseline patient characteristics. The data are presented in Table 1.

There were no differences between patients with and without myocardial injuries in sex, age, type of comorbidity, severity of the disease, CRP, ferritin, high-sensitivity troponin I, and NT-proBNP, and the main ECG and echocardiography parameters. However, the presence of ECE and DCE foci in the myocardium was associated with significantly more frequent use of hydroxychloroquine and tocilizumab in the acute phase of COVID-19 and less often used of antiviral and antibacterial agents. More, this was associated with increased LV end-diastolic and end-systolic volumes.

Discussion

Heart damage in patients with a history of COVID-19 is an urgent problem caused by the pandemic. Due to known limitations of endomyocardial biopsy, MRI of the heart remains the main technique for diagnosing inflammatory myocardial injury [6, 24].

Our study included middle-aged and older patients with a typical premorbid background irrespective of

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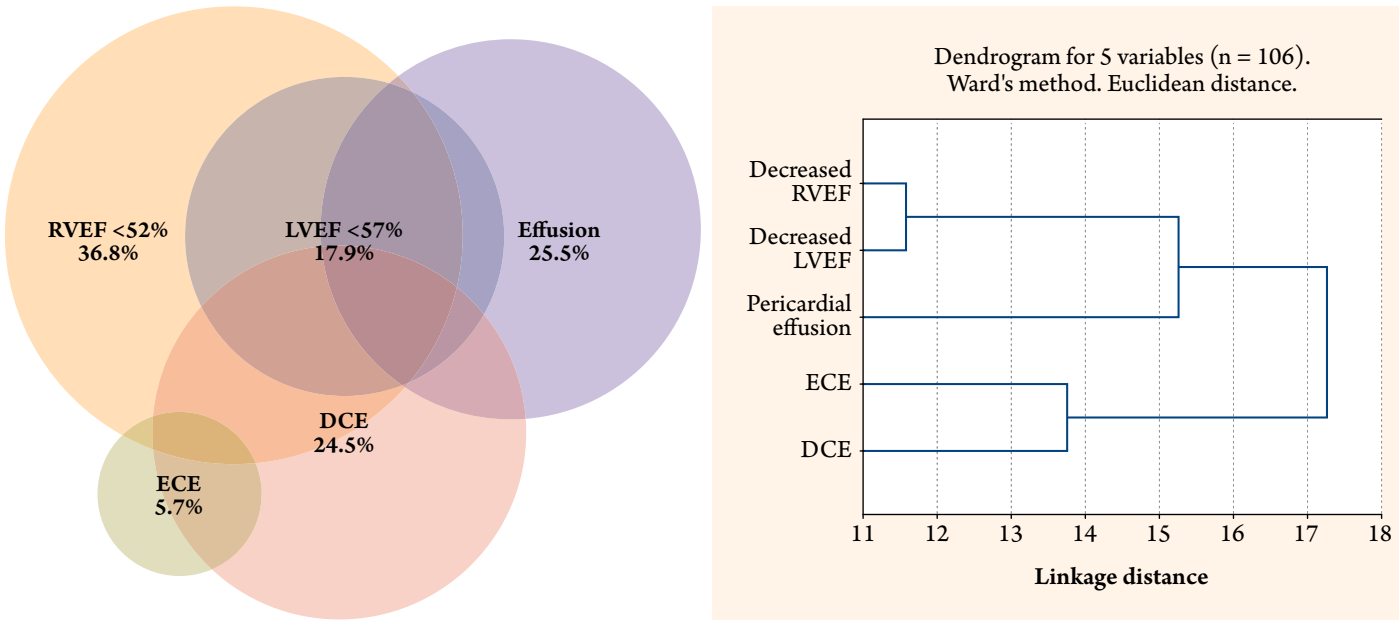
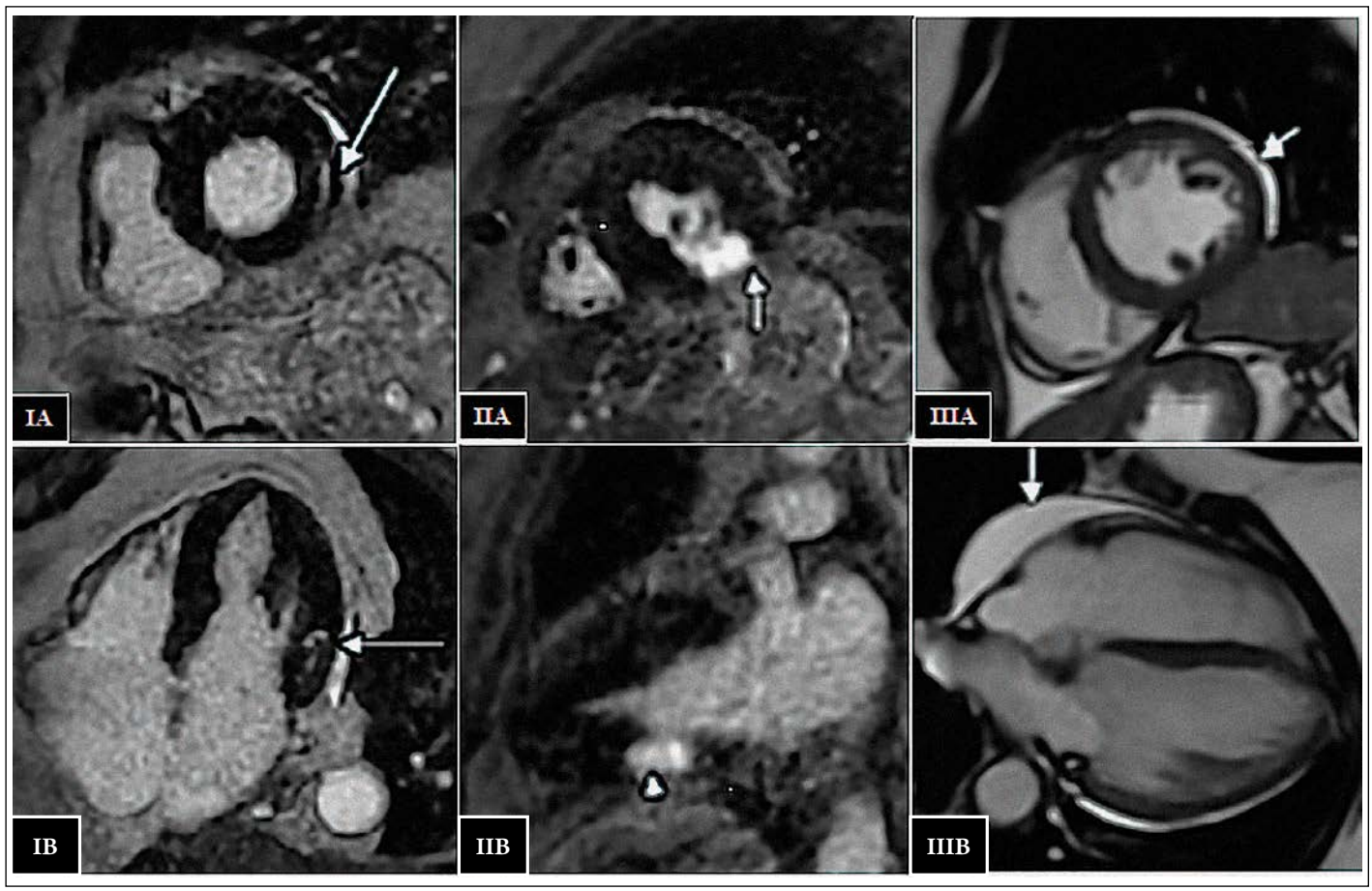
Figure 1. Heart damage pattern in contrast-enhanced MRI in patients with a history of COVID-19 – a Venn diagram highlighting the most typical feature clusters



RVEF, right ventricular ejection fraction; LVEF, left ventricular ejection fraction; ECE, early contrast enhancement; DCE, delayed contrast enhancement.

Figure 2. Examples of heart damage in contrast-enhanced MRI



A – a short-axis view; **B** – a long-axis view; I – a male patient, 65 years old, day 94 after the onset of COVID-19: subepicardial and intramyocardial contras agent retention in anterolateral basal segments of the left ventricle (↑); II – a female patient, 64 years old, day 156 after the onset of COVID-19: transmural contras agent retention in inferior and inferolateral middle segments of the left ventricle (↑); III – a female patient, 55 years old, day 104 after the onset of COVID-19: pericardial effusion up to 16mm along the lateral wall of the left ventricle increasing along the free wall of the right ventricle (↑).

Table 1. Characteristics of patients included in the study and cardiac MRI data

Parameter	All patients (n = 106)	Early or delayed contrast retention (n = 28)	No contrast retention (n = 78)	p
Age, years	57.5 [49; 64]	55.5 [45; 66.5]	58 [51; 63]	0.6334
Female, n (%)	62 (58.5)	13 (46)	49 (63)	0.1310
Systolic BP / diastolic BP, mm Hg	140 [124; 148] / 85 [80; 92]	132 [120; 147] / 79 [75.5; 91]	140 [126; 148] / 87.5 [80; 92]	0.3816 / 0.0867
Body mass index, kg/m²	29.8 [26.4; 32.9]	29.3 [26.4; 32.9]	30.5 [26.3; 32.8]	0.6542
Smokers, n (%)	11 (10.4)	4 (14)	7 (9)	0.4757
Arterial hypertension, n (%)	95 (89.6)	25 (89)	70 (90)	0.9456
Obesity, n (%)	33 (31.1)	7 (25)	26 (33)	0.4139
Diabetes mellitus, n (%)	15 (14.2)	5 (18)	10 (13)	0.5349
Coronary artery disease, n (%)	13 (12.6)	5 (18)	8 (10)	0.3215
History of stroke, n (%)	8 (7.5)	3 (11)	5 (6)	0.4327
Mean number of symptoms	6 [4; 8]	6 [3; 8]	6 [4; 8]	0.9742
Mild COVID-19*, n (%)	28 (26.4)	9 (32)	19 (24)	0.7896
Moderate, n (%)	33 (31.3)	7 (25)	26 (33)	
Severe, n (%)	36 (33.9)	10 (36)	26 (33)	
Extremely severe, n (%)	9 (8.5)	2 (7)	7 (9)	
Referred to hospital, n (%)	76 (71.7)	19 (68)	57 (73)	0.6296
Length of hospital stay, days	16 [12; 20]	16 [10; 20]	15 [12.5; 19.5]	0.7789
Hydroxychloroquine**, n (%)	26 (24.5)	11 (39)	15 (19)	0.0343
Antiviral drugs, n (%)	27 (25.5)	3 (11)	24 (31)	0.0438
Interferon-α, n (%)	21 (19.8)	4 (14)	17 (22)	0.5811
Antibacterial drugs, n (%)	95 (89.6)	21 (75)	74 (95)	0.0070
Glucocorticoids, n (%)	62 (58.5)	18 (64)	44 (56)	0.4681
IL-6 receptor inhibitor, n (%)	6 (5.7)	4 (14)	2 (3)	0.0407
Anticoagulants, n (%)	80 (75.5)	23 (82)	57 (73)	0.4456
Mean number of drugs*	4 [3; 6]	4 [3; 6]	4 [3; 6]	0.7498
Time to MRI from the onset of COVID-19, days	112.5 [75; 151]	112.5 [77; 145]	114 [70; 159]	0.7716
LVEDV, mL	118 [100; 139]	127 [113.5; 141]	113.5 [98; 138]	0.0455
LVESV, mL	42 [33; 54]	47.5 [40; 62.5]	40 [33; 51]	0.0205
LVSV, mL	73.5 [63; 85]	70 [70.5; 84]	71 [61; 85]	0.2727
LVEF, %	63 [58; 68]	62.5 [56.6; 66]	63 [58; 69]	0.2481
LV mass, g	108 [92; 127]	110 [99; 136]	107 [90; 125]	0.1351
LVEDVI, mL/m²	61.5 [51; 68]	66 [56; 70.5]	59.5 [51; 65]	0.0356
LVESVI, mL/m²	22 [18; 26]	25 [21.5; 29.5]	21 [18; 25]	0.0080
LVSVI, mL/m²	37.6 [32.8; 42.8]	38.4 [34.6; 43.3]	36.9 [30.9; 42.8]	0.3280
LVMI, g/m²	54 [48; 63]	56 [51; 68]	53.6 [47.7; 62.0]	0.0820
LVEF < 57 %, n (%)	19 (17.9)	7 (25)	12 (15)	0.2630
RVEDV, mL	116 [96.5; 138.5]	113 [101; 148]	116 [94; 132]	0.6140
RVESV, mL	50.5 [42; 65]	57 [45; 66]	49 [41; 64]	0.1598
RVSV, mL	62.5 [50; 78.5]	62 [50; 75]	63 [52; 80]	0.7302
RVEF, %	55 [47; 62]	53 [45.5; 60]	55.5 [49; 62]	0.2381
RVEDVI, mL/m²	58.5 [52; 67.5]	60 [52; 75]	58 [52; 66]	0.3403
RVESVI, mL/m²	26 [22; 31.5]	29 [22; 44]	25 [22; 31]	0.0728
RVSVI, mL/m²	31.5 [25.5; 38.2]	31.1 [24.1; 41.3]	32 [25.5; 37.7]	0.5237
RVEF < 52 %, n (%)	39 (36.8)	11 (39)	28 (36)	0.8206
Pleural effusion, n (%)	27 (25.5)	6 (21)	21 (27)	0.6234

The quantitative variables are expressed as the medians and interquartile ranges (Me [Q1; Q3]) and qualitative variables are presented as the absolute numbers and percentages (%). * – in accordance with the temporary guidelines of the Ministry of Health of the Russian Federation; ** – specific therapy for COVID-19; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index ; LVSVI, left ventricular stroke volume index; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction; RVEDVI, right ventricular end-diastolic volume index; RVESVI, right ventricular end-systolic volume index; RVSVI, right ventricular stroke volume index.

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the severity and treatment of COVID-19. MRI findings showed that long COVID is often accompanied by heart damage of a complex nature, including foci of myocardial injury, pericardial effusion, LV and RV dysfunction, or a combination thereof. There is regularity in simultaneous occurrence of RV and LV dysfunctions, and ECE and DCE, which reflects the common pathogenesis of these phenomena in COVID-19 [1–3, 26, 27].

The results obtained are consistent with other studies in which foci of post-COVID myocardial injury were detected in 10–35% and even 49% of cases, and T1- and T2 mapping allows confirming the presence of active myocarditis in 19.4–60% of such cases [10–17, 19]. However, pathomorphological examinations detect the development of typical myocarditis only in 4.5–14% of cases, which is less than the frequency of detecting myocarditis by MRI of the heart [1, 4, 26, 27]. Myocarditis caused by SARS-CoV-2 is characterized by a remarkable macrophage infiltration. however, it is unknown whether this is important for increased time of contrast transit through the myocardium, and this issue requires separate study [1, 2, 26–28].

The association of long COVID in general with persistent visceral inflammation, including the heart, was confirmed in the recent studies CISCO-19 and COVERSCAN [14, 19]. The role of autoimmune mechanisms was also shown in the development of heart damage in COVID-19 in response to specific anticardial antibodies [27, 29].

As in other studies including patients with burdened premorbid condition, we observed, in addition to the DCE phenomenon characteristic of myocarditis, ischemic and even mixed variants of contras agent retention, and the presence of myocardial injury was associated with LV remodeling [10, 11, 15, 17–19].

Post-COVID ischemic myocardial injury is noted in 17–23% of cases, and it is unclear whether it depends on the severity of the infection or is determined by premorbid status [11, 12, 15–19]. Kotecha et al. [15] detected MRI signs of ischemic injury in patients with a history of COVID-19 with increased troponin levels, and an adenosine stress test also detected transient ischemia, although most of the subjects did not have CAD. Ischemic injury could be caused by type I or type II myocardial infarction [15]. Therefore, an DCE pattern typical of CAD in post-COVID MRI of the heart may be an indication for an additional examination of coronary circulation.

COVID-19 can be accompanied by impaired global ventricular contractility and pericardial effusion, and RV damage is an independent predictor of poor prognosis [10–12, 15–18, 20–23]. Frequent involvement of the RV is due to characteristic lung damage with microcirculatory thrombosis or acute pulmonary embolism (PE) [1–4, 22, 23]. Thus, post-COVID RV dysfunction can be considered as subacute cor pulmonale subject to mandatory ruling out of non-massive PE.

As in other studies, it was shown in our work that the evaluation of high-sensitivity troponins and NT-proBNP is of limited significance in long COVID but is extremely important for the early diagnosis of heart damage in acute COVID-19 [10, 12, 15, 18, 19].

Several studies noted the effect of drugs used in acute COVID-19 directly on the development of myocarditis and other long-term consequences, but this requires special verification [12, 19].

In the recent expert consensus opinion of the American College of Cardiology, it was proposed to use the term "myocardial involvement" in the absence of complete criteria for myocarditis, but the presence of ECG, echocardiography, and MRI signs of heart damage. This broad term includes type I and type II myocardial infarction, multisystem inflammatory syndrome, stress cardiomyopathy, cytokine storm, acute cor pulmonale, exacerbation of CH, the onset of previously silent cardiac disease. At the same time, the term "myocardial injury" means an increase, for various reasons, only in cardiospecific troponin levels, which is more characteristic of the acute phase of the infection [7]. Thus, further research is required to clarify the specific mechanism of post-COVID heart damage. The central figure presents a possible examination algorithm for patients with long COVID using multimodal imaging.

Limitations

This study was a prospective single-center non-comparative study. The sample was formed based on patient encounters, which did not completely exclude bias. Focal and other changes in the heart detected by MRI could be a consequence not only of COVID-19, but also of the underlying diseases. T1- and T2 mapping was not used.

A cross-sectional data analysis is presented, which does not reveal the natural course of changes that occurred after COVID-19. The relatively small sample size made it difficult to compare individual subgroups and could prevent the identification of factors associated with heart damage.

At the same time, given the presence of types of heart damage caused by one pathogenic factor – SARS-CoV-2 virus – similar to the results of other studies, including in patients without a burdened premorbid condition, the results can be considered correct.

Conclusion

In our work, contrast-enhanced magnetic resonance imaging of the heart made it possible for the first time in everyday clinical practice to detect silent and various types of heart damage in patients with long COVID and nonspecific complaints.

The nature of heart damage in long COVID depends on the premorbid condition, the course and treatment of COVID-19. Changes typical of both inflammatory and ischemic myocardial injury are observed in some cases. The occurrence of myocardial injury is accompanied by left ventricular remodeling.

Early detection of post-COVID cardiac disorders, their differential diagnosis and the administration of the best possible therapy are a serious challenge and require active research in this area, given the widespread prevalence of COVID-19 and its consequences.

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