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Comparison of clinical and echocardiographic parameters of patients with COVID-19 pneumonia three months and one year after discharge

Aim	To study changes in clinical and echocardiographic parameters in patients after documented COVID-19 pneumonia at 3 months and one year following discharge from the hospital.
Material and methods	The study included 116 patients who have had documented COVID-19 pneumonia. Patients underwent a comprehensive clinical evaluation at 3 months ± 2 weeks (visit 1) and at one year ± 3 weeks after discharge from the hospital (visit 2). Mean age of the patients was 49.0±14.4 years (from 19 to 84 years); 49.6% were women. Parameters of global and segmentary longitudinal left ventricular (LV) myocardial strain were studied with the optimal quality of visualization during visit 1 in 99 patients and during visit 2 in 80 patients.
Results	During the follow-up period, the incidence rate of cardiovascular diseases (CVD) increased primarily due to development of arterial hypertension (AH) (58.6 vs. 64.7%, p=0.039) and chronic heart failure (CHF) (35.3% vs. 40.5%, p=0.031). Echocardiography (EchoCG) showed decreases in values of end-diastolic dimension and volume, LV end-systolic and stroke volumes (25.1±2.6 vs. 24.5±2.2 mm/m^2, p<0.001; 49.3±11.3 vs. 46.9±9.9 ml/m^2, p=0.008; 16.0±5.6 vs. 14.4±4.1 ml/m^2, p=0.001; 36.7±12.8 vs. 30.8±8.1 ml/m^2, p<0.001, respectively). LV external short-axis area (37.1 [36.6–42.0] vs. 38.7 [35.2–43.1] cm^2, p=0.001) and LV myocardial mass index calculated with the area-length formula (70.0 [60.8–84.0] vs. 75.4 [68.2–84.9] g/m^2, p=0.024) increased. LV early diastolic filling velocity (76.7±17.9 vs. 72.3±16.0 cm/sec, p=0.001) and lateral and septal early diastolic mitral annular velocities decreased (12,10±3,9 vs. 11.5±4.1 cm/sec, p=0.004 and 9.9±3.3 vs. 8.6±3.0 cm/sec, p<0.001, respectively). The following parameters of LV global longitudinal (– 20.3±2.2 vs. –19.4±2.7%, p=0.001) and segmental strain were impaired: apical segments (anterior, from –22.3±5.0 to –20.8±5.2%, p=0.006; inferior, from –24.6±4.9 to –22.7±4.6, p=0.003; lateral, from –22.7±4.5 to –20.4±4.8%, p<0.001; septal, from –25.3±4.2 to –23.1±4.4%, p<0.001; apical, from –23.7±4.1 to –21.8±4.1%, p<0.001), mid-cavity (anteroseptal, from –21.1±3.3 to –20.4±4.1%, p=0.039; inferior, from –21.0±2.7 to –20.0±2.9%, p=0.039; lateral, from –18.4±3.7 to –17.6±4.4%, p=0.021). RV basal and mid-cavity sphericity indexes increased (0.44±0.07 vs. 0.49±0.07 and 0.37±0.07 vs. 0.41±0.07, respectively, p<0.001 for both). A tendency for increased calculated pulmonary arterial systolic pressure (22.5±7.1 and 23.3±6.3 mm Hg, p=0.076) was observed. Right ventricular outflow tract velocity integral decreased (18.1±4.0 vs. 16.4±3.7 cm, p<0.001).
Conclusion	Patients after COVID-19 pneumonia one year after discharge from the hospital, compared to the follow-up data 3 months after the discharge, had an increased incidence of CVD, primarily due to the development of AH and CHF. EchoCG revealed changes in ventricular geometry associated with impairment of LV diastolic and systolic function evident as decreases in LV global longitudinal strain and LV myocardial apical and partially mid-cavity strain.

Keywords	COVID-19; pneumonia; cardiovascular diseases; echocardiography; myocardial strain; strain
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The National Institute for Health and Care (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) identify in the COVID-19 rapid guideline the following forms of the novel coronavirus disease: acute COVID-19 (complaints and symptoms

last for up to 4 weeks); ongoing symptomatic COVID-19 (complaints and symptoms last for 4–12 weeks); post-COVID-19 syndrome (complaints and symptoms develop during or after COVID-19, last for more than 12 weeks, and do not result from some other disease)

Full scope of long-term effects of COVID-19 is still to be determined. Acute myocardial involvement is relatively well described, but the frequency and severity of myocardial abnormalities in the long term are not yet known. According to the published data, a significant number of patients continue to have inflammatory process after the discharge. We have suggested that COVID-19 associated pneumonia initiates or exacerbates structural and functional myocardial remodeling in the long term after the discharge. It is necessary to study the cardiovascular status of patients with history of COVID-19 over time to develop the best possible management strategy and rehabilitation methods for patient at risk of post-COVID-19 syndrome, as well as to understand the pathogenesis of COVID-19 and predict the sequelae of the pandemic.

Objective

To study the dynamics of clinical and echocardiographic parameters in persons who had documented history of COVID-19 associated pneumonia in 3 and 12 months after the discharge.

Material and Methods

The study provides provisional results of «Prospective follow-up of patients with history of COVID-19 associated pneumonia». It was conducted following the Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the local ethics committee (No. 159 dated July 23, 2020). The study is included in the International Register of the National Institute of Health (ClinicalTrials.gov ID NCT04501822). Patients were identified by the data from the 1C health information system of an infectious disease hospital from April 2020 to July 2021. Inclusion criteria were as follows: laboratory confirmed diagnosis of COVID-19 associated pneumonia and the patient's willingness to be followed up. Exclusion criteria: exacerbated chronic diseases, less than 5-year history of cancer, tuberculosis and other diseases associated with pneumofibrosis, HIV, heart defects, chronic hepatitis; low-quality echocardiographic image, pregnancy, cancer, refusal to participate. A total of 13 patients were excluded due to pregnancy (n=3), travel to another region for shift (n=2), cancer diagnosed after visit 1 (n=2), refusal to participate due to unwillingness to undergo lung computed tomography (CT) over time (n=6). The study included 116 patients with documented history of COVID-19 associated pneumonia, in 3 months±2 weeks and 12 months±3 weeks after the discharge, at the age of 19–84 years (mean age 49±14.4 years); 49.6% of patients were female.

Diagnoses and results of the examinations at admission were derived from discharge summaries. The severity of lung involvement was assessed during hospital stay in accordance with the current guidelines [2]. According to chest X-ray, 31.3%, 33.3%, 29.3%, and 6.1% of hospitalized patients had mild, moderate, severe, critical damage, respectively. 14.2% of patients were treated in intensive care units. At the follow-up visits, all subjects underwent lung CT, echocardiography using an expert-grade ultrasound diagnostic system Vivid S70, a matrix sensor M5Sc-D (1.5–4.6 MHz) with data stored and processed in DICOM format. Echocardiographic data were analyzed on an IntelliSpace Cardiovascular workstation and the TomTec software (Philips, USA), and a video archive was created for data storage and post-processing. Linear dimensions of the cavities and thickness of the heart walls, the presence of left ventricular hypertrophy (LVH), volumes of the heart chambers, and systolic ventricular function were evaluated following the guidelines and considering sex-associated differences. Tricuspid annular plane systolic excursion (TAPSE) was evaluated in the M-mode from the apical four-chamber view; the tricuspid annular velocity S' was assessed in the tissue Doppler mode; the right ventricular (RV) fractional area change was calculated as a relation of the difference in the end-diastolic and end-systolic RV areas to the end-diastolic RV area, per cent [3]. Peak pulmonary artery systolic pressure (ePASP) was calculated as the sum of the peak tricuspid regurgitation pressure gradient and the right atrial pressure. The latter was evaluated using the method developed by Otto et al. [4, 5]. The stroke volume was calculated as the product of the LV outflow tract cross-sectional area (LVOT diameter 2/4) and the LVOT linear velocity integral. Parameters of global and segmental longitudinal LV strain were estimated on Visit 1 and Visit 2 in 99 and 80 patients with adequate image quality, respectively. Ventricular longitudinal strains were estimated in the AFI (Automatic Functional Imaging) mode based on the 2D strain function from the apical view and frame rate >60 fps [3, 6].

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Table 1. Changes in clinical characteristics of patients with history of COVID-19 associated pneumonia, in 3 and 12 months after the discharge

Parameter		General group (n=116)		p
		3 months	12 months	
Body mass index, kg/m²		28.7±5.8	29.4±6.1	<0.001
Body surface area, m²		1.9±0.2	2.0±0.2	<0.001
Overweight, n (%)		39 (33.6)	46 (39.7)	0.189
Obesity, n (%)		42 (36.2)	44 (37.9)	0.754
Cardiovascular diseases, n (%)		68 (58.6)	75 (64.7)	0.039
Heart rhythm disorders, n (%)		38 (32.8)	46 (40.0)	0.215
CHF, n (%)		41 (35.3)	47 (40.5)	0.031
CHF (NYHA), n (%)	FC I	27 (57.4)	29 (61.7)	0.754
	FC II	10 (21.3)	14 (29.8)	0.219
	FC III	4 (8.5)	4 (8.5)	1.000
AH, n (%)		65 (56.0)	72 (62.1)	0.016
Arterial hypertension grade, n (%)	1	10 (15.4)	10 (13.9)	0.625
	2	26 (40.0)	32 (44.4)	0.109
	3	29 (44.6)	30 (41.7)	1.000
CAD, n (%)		18 (15.5)	20 (17.2)	0.261
CAD combined with AH, n (%)		17 (14.7)	19 (16.4)	0.688
Glycemic abnormalities, n (%)		11 (9.5)	12 (10.3)	1.000
Diabetes mellitus type 2, n (%)		9 (7.8)	10 (8.6)	0.250
Impaired glucose tolerance, n (%)		2 (1.7)	2 (1.7)	1.000
Improvements in lung CT, n (%)		55 (49.1)	57 (55.9)	0.112

The data are expressed as the mean and the standard deviation (M±SD) or the number of patients (n (%));
CHF, chronic heart failure; NYHA, New York Heart Association; FC, functional class; CAD, coronary artery disease; AH, arterial hypertension; CT, computed tomography.

Chronic heart failure (CHF) was diagnosed following the current clinical guidelines [7].

Statistical analysis was performed using SPSS 21 (SPSS Inc., Chicago, IL, USA) and Statistica 12.0. The distribution of variables was assessed using the Kolmogorov-Smirnov test. The variables are presented as the mean and standard deviation (M±SD) in the normal distribution of quantitative data and the median and interquartile range (Me [Q1 – Q3]) in the non-normal distribution. The significance of differences between continuous variables was assessed depending on the distribution based on the Student's t-test for dependent samples or the Wilcoxon signed-rank test. McNemar's test was used to compare qualitative variables. The results were estimated as significant at $p<0.05$.

Results

CT signs of pneumonia resolved in nearly half of the subjects (n=55, 49%) in 3 months after the discharge, and these data did not change significantly during the follow-up. The others had residual fibrous and interstitial abnormalities of different severity, such as pleuropulmonary adhesions, ground glass opacities, areas of interlobular interstitial thickening, consolidation, single moderately enlarged mediastinal lymph nodes.

The main clinical characteristics of patients are provided in Table 1. During the follow-up, the mean body mass index increased, but the incidence of obesity and overweight remained the same. Cardiovascular diseases (CVDs) were diagnosed at Visit 1 in more than half of patients, and the prevalence increased by 6.1% by Visit 2. Arterial hypertension (AH) was the most common, it was diagnosed in most patients at Visit 1, and its frequency increased by 6.1% at Visit 2. The incidence of glycemic abnormalities and coronary artery disease (CAD) did not change significantly. CAD was accompanied by AH in most cases. The incidence of irregular heart rhythm and conduction disorders, including sinus arrhythmias, extra heartbeats, atrial fibrillation, and atrial flutter, intracardiac blocks, did not increase significantly. Severe CHF (NYHA FC III) was determined in four patients on Visit 1 and Visit 2. The overall incidence of CHF NYHA FC I and II increased by 5.2%.

There were no patients with reduced left ventricular ejection fraction (LVEF) included at this stage. The following trends were observed in the mean values of echocardiographic parameters of the left heart in the follow-up period (Table 2). Maximum left atrial (LA) volume index decreased, and minimum LA volume index increased, total LA ejection volume index and LA ejection fraction decreased. Anteroposterior LA dimension tended to decrease. LV end-diastolic diameter index and LV end-diastolic volume index, LV end-systolic volume and LV end-systolic stroke volume, and cardiac minute volume and cardiac index decreased. LV short-axis external and internal surface areas, and LV mass index (area-length) increased. Normal LV geometry recovered by Visit 2 in ten patients, nine of them had eccentric LV hypertrophy at Visit 1. LVOT flow time and integral and early LV diastolic filling velocity decreased. Systolic velocity in the orifice of the right superior pulmonary vein (S wave) increased. Tissue Doppler echocardiography showed a significant decrease in the early diastolic lateral and septal mitral valve annular velocities (e' later and e' sept, Table 2).

Table 2. Changes in echocardiographic parameters of the left heart of patients with history of COVID-19 associated pneumonia, in 3 and 12 months after the discharge

Parameter		General group (n=116)		p
		3 months	12 months	
Heart rate, bpm		67.3±11.9	66.3±12.0	0.311
LV outflow tract	mm	32 [30–34]	32 [29–34]	0.033
	mm/m²	16.8±2.1	16.4±1.9	<0.001
Interventricular septum	mm	10 [9–11]	10 [9–11]	0.389
	mm/m²	5.2 [4.8–5.8]	5.2 [4.8–5.8]	0.199
LV inferior wall	mm	9 [9–10]	9 [9–10]	1.000
	mm/m²	4.9±0.6	4.9±0.6	0.106
Left ventricular end-diastolic diameter (LVEDD)	mm	48.1±3.7	47.3±3.1	0.010
	mm/m²	25.1±2.6	24.5±2.2	<0.001
Left ventricular end-diastolic length	mm	81.5±7.6	82.3±7.1	0.228
	mm/m²	42.6±4.5	42.5±4.2	0.811
Left ventricular end-diastolic volume (LVEDV)	mm	96.0±28.1	92.1±24.9	0.035
	mm/m²	49.3±11.3	46.9±9.9	0.008
Increased LVEDV, n (%)		11 (9.5)	8 (6.9)	0.508
Left ventricular end-systolic volume (LVESV)	mL	31.2±12.4	28.3±10.0	0.003
	mL/m²	16.0±5.6	14.4±4.1	0.001
Increased LVESV, n (%)		5 (4.3)	2 (1.7)	0.375
Left ventricular stroke volume (LVSV)	mL	70.6±24.1	59.8±15.1	<0.001
Left ventricular stroke index (LVSI)	mL/m²	36.7±12.8	30.8±8.1	<0.001
Cardiac minute volume	L/min	4.2 [3.7–5.3]	3.8 [3.2–4.6]	<0.001
Cardiac index	L/min/m²	2.2 [1.9–2.7]	1.9 [1.6–2.3]	<0.001
LV myocardial external surface	cm²	37.1 [36.6–42.0]	38.7 [35.2–43.1]	0.001
LV myocardial internal surface	cm²	21.4 [17.5–23.7]	22.2 [20.0–24.5]	0.003
Left ventricular mass (area-length)	g	141.4±38.7	152.7±41.1	0.004
	g/m²	70.0 [60.8–84.0]	75.4 [68.2–84.9]	0.024
Frequency of detecting LV hypertrophy, n (%)		18 (18.8)	27 (23.5)	0.607
LV geometry, n (%)	Normal	89 (77.4)	99 (85.3)	0.035
	Concentric remodeling	8 (7.0)	7 (6.0)	1.000
	Concentric LVH	2 (1.7)	3 (2.6)	1.000
	Eccentric LVH	16 (13.9)	7 (6.0)	0.022
LVEF (Simpson 2D), %		68.1±5.3	69.7±4.6	0.013
Reduced LVEF, n (%)		0 (0)	0 (0)	–
Mitral regurgitation grade ≥2, n (%)		2 (1.7)	0 (0)	–
LVOT flow time, ms		305.1±30.5	290.0±30.7	<0.001
LVOT acceleration time, ms		90±22	82±12	0.004
LVOT deceleration time, ms		214±31	208±30	0.039
LVOT time-velocity integral, ms		20.0 [18.0–23.6]	19.3 [17.1–21.7]	0.002
IVRT, ms		98.1±24.9	102.4±25.7	0.167
IVCT, ms		70.8±22.6	67.9±18.3	0.312
DT, ms		197.0 [165.0–241.0]	191.0 [170.0–220.0]	0.404
E, cm/s		76.7±17.9	72.3±16.0	0.001
A, cm/s		68.5±20.1	68.0418.6	0.889
e' later, cm/s		12.103.9	11.5±4.1	0.004
e' sept, cm/s		9.9±3.3	8.6±3.0	<0.001
Left atrial anteroposterior dimension	mm	36.0 [32.0–38.0]	35.0 [33.0–39.0]	0.719
	mm/m²	18.8±2.2	18.6±2.1	0.086
Left atrial maximum volume	mL	46.0 [38.5–59.0]	46.0 [39.5–56.0]	0.106
	mL/m²	26.0±7.2	25.3±7.4	0.015
Left atrial minimum volume	mL	16.5 [12.0–23.0]	18.0 [14.0–24.0]	0.004
	mL/m²	9.9±5.4	10.8±5.6	0.011
Left atrial total ejection volume	mL	31.1±8.9	28.4±8.5	<0.001
	mL/m²	16.1±4.3	14.5±3.8	<0.001

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Table 2 (continued). Changes in echocardiographic parameters of the left heart of patients with history of COVID-19 associated pneumonia, in 3 and 12 months after the discharge

Parameter	General group (n=116)		p
	3 months	12 months	
Left atrial ejection fraction, n (%)	62.9±9.8	58.4±9.6	< 0.001
Epicardial fat thickness, mm	7.0 [6.0–8.0]	7.0 [6.0–8.0]	0.918

The data are expressed as the median and interquartile range (Me [Q1–Q3], the mean and standard deviation (M±SD), the number of patients (n (%)); LV, left ventricle; LVSV, left ventricular stroke volume; LVSI, left ventricular stroke index; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; IVRT, isovolumetric relaxation time; IVCT, isovolumetric contraction time; DT, deceleration time; E, early left ventricular filling velocity; A, late left ventricular filling velocity; e' later, peak lateral mitral annular velocity; e' sept, peak septal mitral annular velocity.

Table 3. Changes in echocardiographic parameters of the right heart of patients with history of COVID-19 associated pneumonia, in 3 and 12 months after the discharge

Parameter		General group (n=116)		p
		3 months	12 months	
Right atrial maximum volume	mL	33.0 [25.0–40.0]	33.0 [26.0–39.0]	0.761
	mL/m²	16.4 [13.6–20.3]	16.6 [14.3–19.5]	0.833
Right atrial maximum length	mm	48.7±6.5	49.5±6.3	0.074
	mm/m²	25.4±3.2	25.5±3.0	0.576
Right atrial maximum width	mm	35.4±6.3	35.3±5.5	0.862
	mm/m²	18.5±3.1	18.2±2.7	0.501
RV anteroposterior dimension	mm	26.0 [24.0–28.0]	26.0 [24.0–27.0]	0.007
	mm/m²	13.5±1.9	13.0±1.5	<0.001
Increased RV anteroposterior dimension, n (%)		7 (6.0)	2 (1.7)	0.125
RV diastolic area	cm²	15.4±4.1	14.5±3.2	0.001
	cm²/m²	8.0±1.8	7.5±1.5	<0.001
RV systolic area	cm²	7.3±2.5	6.5±1.8	<0.001
	cm²/m²	3.8±1.1	3.3±0.8	<0.001
RV fractional area change (RVFAC)		52.55±8.17	55.0±8.9	0.019
TAPSE, mm		22.68±3.22	22.8±2.3	0.637
Decreased TAPSE, n (%)		8 (7.0)	2 (1.7)	0.070
RV basal transverse dimension, mm		30.41±5.42	31.1±4.1	0.045
Increased RV basal transverse dimension, n (%)		2 (1.7)	1 (0.9)	1.000
RV middle transverse dimension, mm		25.75±5.42	25.8±4.2	0.852
Increased RV middle transverse dimension, n (%)		2 (1.7)	3 (2.6)	1.000
RV longitudinal dimension, cm		69.50±8.80	63.9±8.3	<0.001
Increased RV longitudinal dimension, n (%)		6 (5.2)	2 (1.7)	0.289
RV sphericity index, basal		0.44±0.07	0.49±0.07	<0.001
RV sphericity index, middle		0.37±0.07	0.41±0.07	<0.001
RVOT short-axis proximal dimension (RVOT Prox), mm		28.0 [26.0–30.0]	28.0 [26.0–20.0]	0.357
Increased RVOT Prox, n (%)		2 (1.7)	1 (0.9)	1.000
RVOT short-axis distal dimension (RVOT Distal), mm		20.0 [19.0–22.0]	21.0 [20.0–23.0]	0.006
Increased RVOT Distal, n (%)		4 (3.5)	5 (4.3)	1.000
RV free wall thickness, mm		4.1±0.9	4.4±0.6	<0.001
RV hypertrophy, n (%)		7 (6.0)	4 (3.4)	0.508
Pulmonary artery diameter, mm		18.0 [17.0–20.0]	19.0 [17.0–20.0]	0.001
Tricuspid regurgitation grade ≥2, n (%)		2 (1.7)	3 (2.6)	0.723
ePASP (Otto), mm Hg		22.5±7.1	23.3±6.3	0.076
Tricuspid annular S' velocity, cm/s		10.4±2.6	10.1±3.0	0.289
Pulmonary artery acceleration time, ms		116.2±26.6	112.2±20.0	0.190
RVOT flow integral, cm		18.1±4.0	16.4±3.7	<0.001

The data are expressed as the median and interquartile range (Me [Q1–Q3]), the mean and standard deviation (M±SD), number of patients (n (%)); RV, right ventricle; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; RVOT Prox, short-axis proximal right ventricular outflow tract; RVOT Distal, short-axis distal right ventricular outflow tract; ePASP, estimated pulmonary artery systolic pressure.

Echocardiographic characteristics of the right heart are presented in Table 3. Maximum right atrial length tended to increase. Mean RV anteroposterior dimension index and RV longitudinal dimension decreased during the follow-up period, RV middle transverse dimension and RV outflow tract (RVOT) proximal short-axis dimension did not change, RV basal transverse dimension, and RVOT distal short-axis dimension increased. Pulmonary artery diameter increased. Basal and middle RV sphericity indices increased. Tricuspid annular plane systolic excursion (TAPSE) and S' tricuspid annular velocity did not change significantly, but the frequency of TAPSE reduction tended to decrease. RV end-diastolic and end-systolic area indices decreased; RV area change fraction increased. Estimated pulmonary artery systolic pressure (ePASP) and RV free wall thickness tended to increase. RVOT flow integral decreased.

LV longitudinal strain are given in Table 4. Global and segmental strain of all apical and partially middle segments of the LV (anteroseptal, inferior, and lateral) worsened significantly during the follow-up.

Discussion

The main challenge in treating a disease caused by SARS-CoV-2 is the unpredictability of its acute course associated with rapid deterioration of the patient condition and death. It is necessary to identify predictors of the unfavorable long-term course of the disease for more effective treatment, which would help classify patients and identify risk groups.

Mean body mass index of the subjects corresponded to overweight both at Visit 1 and Visit 2. It increased during the follow-up, however, the frequency of detecting overweight and obesity did not change significantly. Nevertheless, the incidence of CVDs increased significantly, mainly due to higher prevalence of AH and CHF. During the follow-up, seven patients developed de novo AH. It should be noted that these changes occurred notwithstanding the fact that all patients received recommendations for healthy lifestyle and nutrition at Visit 1. Increased mean body mass index also influenced the quality of echocardiographic imaging, specifically, 100 and 80 patients had optimal image quality of myocardial strain at Visit 1 and Visit 2, respectively. Attention is drawn to a significant decrease in the frequency of eccentric LV remodeling due to the normalization of its geometry. This finding is consistent with reduced end-diastolic diameter index and LV volumes (similar trends were observed for our patients and when compared with hospitalization data [8]).

Table 4. Mean left ventricular longitudinal strain in patients with history of COVID-19 associated pneumonia, in 3 and 12 months after the discharge, %

LV longitudinal strain	Satisfactory image in 3 months (n=99)	Satisfactory image in 12 months (n=80)	p
Global	–20,3±2,2	–19,4±2,7	0,001
Global strain<-19%, n (%)	28 (28,3)	34 (57,5)	0,011
LV basal anterior segment	–17 [16–20]	–17 [14–19,5]	0,736
Basal anteroseptal segment	–16,8±3,1	–16,7±3,6	0,888
Basal inferoseptal segment	–19,9±3,7	–19,5±4,0	0,701
Basal inferior segment	–17,0±2,8	–16,7±3,1	0,491
Basal lateral segment	–17,2±3,7	–17,4±4,1	0,575
Basal posterior segment	–17,9±4,7	–18,5±4,4	0,783
Middle anterior segment	–18,1±4,0	–17,7±4,5	0,465
Middle anteroseptal segment	–21,1±3,3	–20,4±4,1	0,039
Middle inferoseptal segment	–22 [20–24]	–22 [20–24]	0,928
Middle anterior segment	–18,1±4,0	–17,7±4,5	0,465
Middle anteroseptal segment	–21,1±3,3	–20,4±4,1	0,039
Middle inferoseptal segment	–22 [20–24]	–22 [20–24]	0,928
LV apical anterior segment	–22,3±5,0	–20,8±5,2	0,006
LV apical septal segment	–25,3±4,2	–23,1±4,4	<0,001
LV apical inferior segment	–24,6±4,9	–22,7±4,6	0,003
LV apical lateral segment	–22,7±4,5	–20,4±4,8	<0,001
LV apex	–23,7±4,1	–21,8±4,1	<0,001

The data are expressed as the median and interquartile range (Me [Q1–Q3]), the mean and standard deviation (M±SD), number of patients (n (%)); LV, left ventricle.

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On the other hand, the short-axis external and internal areas of the LV myocardium and, as a result, the LV mass increased (of note, the prevalence of LV hypertrophy did not increase at this stage of the follow-up). In the absence of significant trends in the LV length, thickness of the walls and interventricular septum, these changes could only be a consequence of the increased LV transverse (frontal) dimension. Thus, the LV geometry changes by the anteroposterior flattening and the transverse (or frontal) stretching.

Our findings suggest that these changes in the LV geometry and the increased LV mass were associated with a deteriorating functional state.

Worsening of LV diastolic function is evidenced by lower velocity of early diastolic LV filling, early diastolic lateral mitral annular velocity, and septal mitral annular velocity (e' later and e' sept) without any significant differences in HR at the visits. These data are consistent with the meta-analysis that showed the presence of diastolic LV dysfunction in 40% of cases in 3–6 months after the recovery from COVID-19 [9].

In our study, mean global longitudinal LV strain significantly decreased during the follow-up period, and the percentage of patients with global longitudinal LV strain<–19% increased from 28.3% to 42.5%. At the same time, LVEF, which is commonly estimated in routine echocardiography and mainly used by clinicians to assess LV function, increased. The discord can be explained by the fact that LVEF does not fully reflect the LV functional state. It will be more informative to assess these indicators by more observations.

The published data on myocardial strain in patients with COVID-19 mainly refer to the period of hospital stay. A small retrospective study including 12 patients with COVID-19 demonstrated a decrease in LV global (–11.95±4.5%) and segmental longitudinal strain irrespective of the disease outcome. The decrease was understandably more significant than in our patients, however, LVEF remain normal as it did in our patients. A retrospective analysis of 40 patients hospitalized with COVID-19 showed that LV global longitudinal strain worsened (>–15.9%) in the majority patients (80%) [11], which also exceeds our findings and is explained by the acute stage of the disease. A single-center study of 100 hospitalized patients with COVID-19, global longitudinal strain was –16.7±1.3% and –14.5±1.8% in mild and severe patients, respectively, and it was –19.4±1.6% in those who were not affected [12]. In 12 months, LV global longitudinal strain was closer to the values in those who were not affected, but lower than the values obtained in 3 months after the discharge.

There are not much prospective observations in the recovery period, and they are consistent with our findings. The examination of patients with preserved LVEF in 30–45 days after the disease, including 50 patients with moderate form and 10 patients with severe form, showed that global longitudinal strain decreased was observed in 44% and 90%, respectively, comparable by sex and age with the control group of unaffected individuals (≥19.2±1.5%) [13]. According to a meta-analysis, which included fifteen studies using echocardiography, LV global longitudinal strain abnormalities were detected in 30% of patients in 3–6 months after the discharge [9]. Number of patients with LV global longitudinal strain less than –19% in 3 months (28.3%) is comparable with the results of the meta-analysis. However, the number of such patients increased to 42.5% in 12 months, which indicates a progressive impairment of myocardial function in some patients long after the disease.

Finally, there is evidence that MRI reveal myocardial strain even in individuals who had neither CVDs nor any relevant symptoms after COVID-19 associated pneumonia. In 124 ±17 days after the discharge, there were no significant differences between the patients with moderate and severe pneumonia and the control group in the ventricular dimensions and function, but LV global longitudinal strain was reduced. This confirms that some individuals may have subclinical myocardial dysfunction a few months after the discharge [14].

The negative trends in segmental LV strain in our patients also draw attention: the indicators of all apical and partially middle LV segments became worse. Since the normal ranges of segmental LV strain are being developed, the obtained absolute values of myocardial strain cannot be clearly interpreted, but the negative trends of the LV function indicators are alarming.

Despite the lack of statistical significance of the trends, the parameters of basal LV strain are also alarming: except for the basal inferior septal strain, all were less than –18.5%. According to the results of the Russian study in 23–48-year-old individuals, who were apparently healthy before COVID-19, those who had severe pneumonia (CT 3–4) had a decrease in global LV strain up to –17.75 [14.6;19.4] % in 3 months after diagnosing COVID-19 compared with the control group of healthy individuals. A significant decrease in segmental strain in the LV basal (septal, anteroseptal, and posterior) segments was observed

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in all patients, including those with mild disease, compared to the control group. However, patients with pneumonia had more severe abnormalities. Given the fact that this study was conducted using an ultrasound scanner of the same manufacturer as we used, it seems interesting that basal anterior strain (– 16.8 [15.3; 20] %), anteroseptal strain (– 16.3 [15.1; 21.7] %), and inferior strain (– 17 [14; 19] %) of the LV in patients with history of severe pneumonia were similar to our findings [15].

The parameters of the RV also changed. On the one hand, the planimetric and some linear dimensions of the RV (anteroposterior and longitudinal) decreased. On the other hand, other RV dimensions significantly increased, such as the basal transverse diameter. These changes explain the increase in the RV sphericity indices. That is, changes in the RV geometry are similar to that of the LV: both ventricles decreased in the anteroposterior direction and extended in the frontal direction. At the same time, the thickness of the RV free wall increased (but not as much as hypertrophy); the RVOT short-axis distal dimension, the pulmonary artery diameter, and hemodynamic characteristics worsened: the RVOT flow integral decreased, and ePASP tended to increase.

Let us discuss trends of the RV function parameters. The most common and well-reproduced parameter of the RV systolic function TAPSE was higher than the normal threshold (16 mm [16]) at both Visit 1 and Visit 2 and did not change significantly. However, the frequency of detecting decreased TAPSE decreased significantly during the follow-up, which may be indicative of the normalization of pancreatic function. In the previous study including fewer observations, we did not find any correlation between TAPSE and the RV strain parameters [17], which is probably due to potential disadvantages of this method (such as, the dependence of TAPSE on the scanning angle). Interestingly, a foreign observation of ninety-one patients showed an improvement in the RV function, such as increased TAPSE and RV global longitudinal strain, in 77 days after the discharge compared with the hospital data. However, the decreased LV global longitudinal strain did not improve in this observation (– 17.4±2.9 vs. –17.6±3.3%, p=0.6) [18], just as in our study.

According to our data, tricuspid annular velocity S' measured in the tissue Doppler mapping mode also exceeded the normal threshold at both visits (10 cm/s) [16] but was lower than that obtained by our Russian colleagues in the acute period of the disease (13.5±3.0 cm/s) [19]. This may result from the overestimation of tricuspid annular velocity S' in the presence of pronounced tricuspid regurgitation, since hemodynamically significant tricuspid regurgitation was detected in our study much less often.

The mean fractional area change (RVFAC) was within the normal range and increased by Visit 2 during the follow-up. This indicator does not fully reflect the RV functional state since it is the result of only a planimetric estimation of the chamber. In our previous study, RVFAC correlated with only global longitudinal strain of the RV endocardium, and the correlation was weak [17]. Anyway, conclusions on the changes in the RV functional state should only be made after analyzing the strain parameters.

Given the increased LVOT distal diameter and diameter of the pulmonary artery, the increased RV sphericity indices, as well as the decreased LVOT flow integral and the tendency for increased ePASP, it is too early to talk about normalization of the right heart parameters. Since the frequency of detecting abnormalities using lung CT scanning did not change significantly, the detected changes in the right heart may be due to restructuring of hemodynamics in the long-term period after COVID-19.

Our findings do not reflect the cardiovascular health of all patients with history of COVID-19 associated pneumonia, since the sample included only patients who agreed to undergo the examination, i.e., people who are concerned about their health and mainly who have CVDs. People in satisfactory condition were less interested in the examination and less likely to agree, which is why the percentage of favorable outcomes may be lower in our study than in the general population. Since patients were hospitalized at various times from the disease onset, the study is limited by different periods of diagnosis. It should be taken into consideration that changes in the left heart can be caused by the indirect as well as direct action of the virus through the development of de novo disease and the aggravation of the manifestations of AH existing before COVID-19. The correlations between COVID-19, AH, and changes in the left heart will be assessed at the next stages of the study. Subgroup analysis should also be conducted to identify predictors of the myocardial strain abnormalities considering the severity of lung damage in the acute period of the disease, treatment results, and the presence of CVDs (primarily AH).

Conclusion

In 12 months after the discharge, compared to the examination results obtained in 3 months after

the discharge, the prevalence of CVDs was higher in patients with history of COVID-19 associated pneumonia mainly due to arterial hypertension and chronic heart failure; echocardiography showed ventricular geometry abnormalities accompanied by deteriorated diastolic and systolic LV functions, namely, a decrease in the left ventricular global longitudinal strain and strain of the apical and partially middle LV segments.

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