Original Article

Serial Echocardiographic Assessment of Right Ventricular Function and Its Association With Functional Capacity, Dyspnea, and Pulmonary Diffusion in Post-COVID-19 Survivors

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Abstract

Background: **Survivors of post-COVID-19 may experience persistent functional impairment and late cardiopulmonary sequelae. The right ventricle (RV) is particularly susceptible to injury, and RV free wall longitudinal strain (RVFWLS), measured by 2D speckle-tracking echocardiography (2D-STE), can detect subclinical RV systolic dysfunction.**

Objective: **To evaluate longitudinal changes in RV systolic function, assessed by RVFWLS, tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and tricuspid annular systolic velocity (S′), and to investigate their associations with functional capacity (30-second sit-to-stand test [30STS]), functional status (Post-COVID-19 Functional Status Scale [PCFS]), dyspnea (modified Medical Research Council [mMRC] scale), and carbon monoxide transfer coefficient (KCO) in post-COVID-19 survivors.**

Methods: **This observational analysis included participants from a prospective post-COVID-19 cohort evaluated at two follow-up visits (AV1 and AV2), approximately 4 and 13 months after the acute infection. Adults with confirmed SARS-CoV-2 infection and analyzable transthoracic echocardiography using 2D-STE were included. Statistical significance was defined as a two-sided $p < 0.05$.**

Results: **A total of 49 patients were included; 55.1% were women, the mean age was 50.7 ± 10.3 years, 63.3% had obesity, 77.6% required intensive care unit admission, and 67.3% underwent invasive mechanical ventilation. Performance on the 30STS improved (10.1 ± 3.3 vs 11.6 ± 3.1 repetitions; $p = 0.004$), and KCO increased (4.1 ± 0.7 vs 4.3 ± 0.8 mL/min/mmHg/L; $p = 0.002$), whereas mMRC scores ($p = 0.43$) and median PCFS scores ($p = 0.11$) remained unchanged. TAPSE decreased modestly but remained within the normal reference range (2.2 ± 0.3 vs 2.1 ± 0.2 cm; $p = 0.03$), while RVFWLS, FAC, and S′ showed no significant changes over time. Cross-sectional correlations between RV systolic indices and clinical outcomes were weak and nonsignificant at both AV1 and AV2 ($|r| < 0.30$; $p > 0.05$). Longitudinally, changes in RVFWLS were positively correlated with changes in KCO ($r = 0.33$; $p = 0.05$), whereas changes in FAC were inversely correlated with changes in PCFS scores ($r = -0.35$; $p = 0.02$).**

Conclusion: **In this cohort of post-COVID-19 survivors, functional capacity and pulmonary diffusing capacity improved over time, whereas RVFWLS remained persistently reduced without significant longitudinal change. These exploratory findings suggest that RV systolic indices should not be interpreted in isolation as markers of functional limitation during the late post-COVID-19 period and support the use of an integrated, multiparametric approach to patient assessment.**

Keywords: **Post-Acute COVID-19 Syndrome; Right Ventricular Dysfunction; Echocardiography; Global Longitudinal Strain.**

Introduction

Post-COVID-19 is characterized by new or persistent symptoms that typically develop within 3 months after acute SARS-CoV-2 infection, persist for at least 2 months, and substantially affect daily functioning.[1] Dyspnea, reduced exercise tolerance, and fatigue are among the most common manifestations, suggesting that persistent cardiopulmonary abnormalities may contribute to long-term functional impairment.[1,2] However, these symptoms are multifactorial and are often inadequately explained by abnormalities within a single organ system, which underscores the need for integrated phenotyping encompassing cardiac, pulmonary, and functional domains.[2,3]

Cardiac involvement in COVID-19 ranges from overt myocardial injury to subclinical myocardial dysfunction. The right ventricle (RV) is particularly vulnerable because of its sensitivity to acute increases in pulmonary vascular load resulting from hypoxic pulmonary vasoconstriction,

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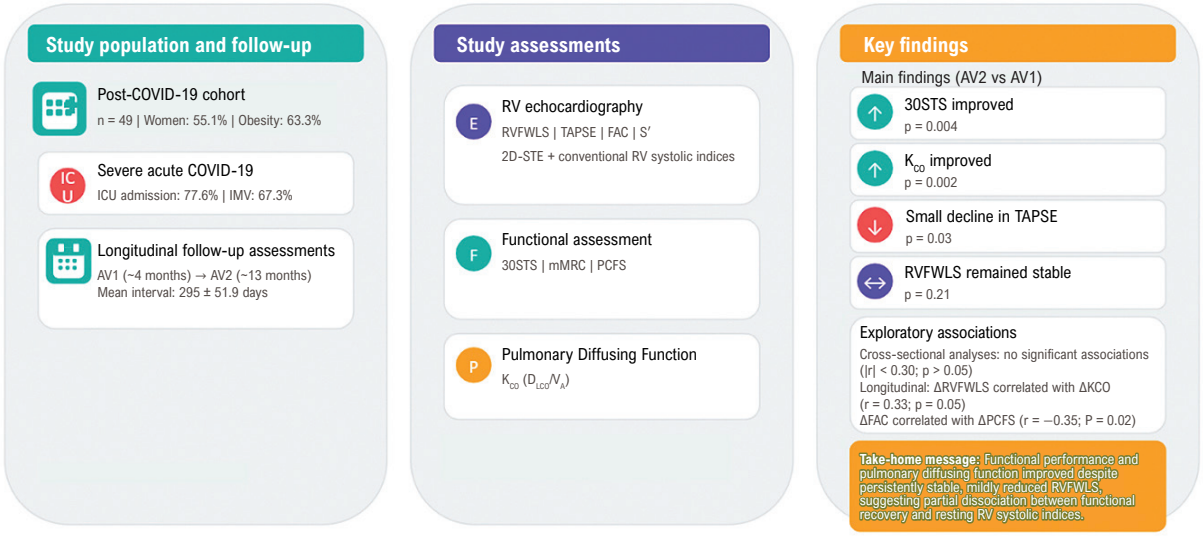
Manuscript received April 6, 2026; revised June 25, 2026; accepted July 7, 2026
Editor responsible for the review: Marcelo Tavares

DOI: https://doi.org/10.36660/abcimg.20260051i

Central Illustration: Serial Echocardiographic Assessment of Right Ventricular Function and Its Association With Functional Capacity, Dyspnea, and Pulmonary Diffusion in Post-COVID-19 Survivors



Arq Bras Cardiol: Imagem cardiovasc. 2026;39(3):e20260051

Serial Echocardiographic Assessment of Right Ventricular Function and Its Association With Functional Capacity, Dyspnea, and Pulmonary Diffusion in Post-COVID-19 Survivors. 2D-STE: 2D speckle-tracking echocardiography; 30STS: 30-second sit-to-stand test; AV1: first post-acute evaluation; AV2: second post-acute evaluation; DLCO: diffusing capacity of the lung for carbon monoxide; FAC: fractional area change; ICU: intensive care unit; IMV: invasive mechanical ventilation; KCO: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RV: right ventricle; RVFWLS: RV free wall longitudinal strain; S′: tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion; VA: alveolar volume.

thromboinflammation, microvascular dysfunction, the effects of invasive mechanical ventilation (IMV), and acute respiratory distress syndrome. During the acute phase of COVID-19, RV dysfunction — including abnormalities identified by 2D speckle-tracking echocardiography (2D-STE)-derived RV longitudinal strain — has consistently been associated with adverse clinical outcomes and mortality.[4,5] A Brazilian systematic review with meta-analysis of hospitalized patients with COVID-19 reported a high prevalence of echocardiographic abnormalities, with pooled estimates of left ventricular and RV systolic dysfunction of 25% and 17%, respectively, highlighting the clinical value of cardiac imaging during the acute phase.[6] 2D-STE provides a sensitive, reproducible assessment of RV mechanics, and RV free wall longitudinal strain (RVFWLS) can identify subtle systolic dysfunction even when conventional indices, such as tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and tricuspid annular systolic velocity (S′), remain within normal reference ranges.[7] Furthermore, normative data demonstrate clinically meaningful variation in RVFWLS according to age and sex, emphasizing the importance of contextual interpretation and longitudinal assessment.[8]

Despite accumulating evidence of RV abnormalities during the acute phase of COVID-19, longitudinal data on RVFWLS in patients with post-COVID-19 and its relationship with functional capacity, patient-reported functional status, dyspnea severity, and pulmonary diffusing capacity remain limited. Follow-up studies have yielded heterogeneous results and have generally focused on imaging outcomes alone, with limited integration of functional testing and pulmonary physiological measures, particularly in cohorts characterized by severe acute illness and a high burden of cardiometabolic comorbidities.[9,10] Consequently, it remains unclear whether longitudinal changes in RV mechanics parallel, or diverge from, recovery in functional performance and pulmonary diffusing capacity.

Accordingly, the primary aim of this study was to characterize the longitudinal trajectory of RVFWLS and conventional RV systolic indices (TAPSE, FAC, and S′) between approximately 4 and 13 months after acute COVID-19. Secondary aims were to investigate the cross-sectional and longitudinal associations of RV systolic function with functional capacity assessed by the 30-second sit-to-stand test (30STS), functional status measured by the Post-COVID-19 Functional Status (PCFS) Scale, dyspnea severity assessed using the modified Medical Research Council (mMRC) scale, and pulmonary diffusing capacity measured by the carbon monoxide transfer coefficient (K_{CO}). We

also explored whether baseline functional and pulmonary measures independently predicted follow-up RVFWLS after adjustment for baseline RVFWLS.

Methods

Study design and setting

This observational study represents an analysis of a prospective cohort of post-COVID-19 survivors followed at a dedicated post-COVID outpatient research clinic within a tertiary university hospital in southern Brazil. For the present analysis, participants underwent two standardized follow-up evaluations: AV1 (first post-acute evaluation), performed approximately 4 months after the acute phase of COVID-19, and AV2 (second post-acute evaluation), performed approximately 13 months after the acute illness. Medical records from the index hospitalization were reviewed to obtain clinical characteristics and markers of disease severity during the acute phase.

Participants

Eligible participants were adults (≥ 18 years) with SARS-CoV-2 infection confirmed by reverse transcription polymerase chain reaction using nasopharyngeal and/or oropharyngeal swab specimens, who received care during the acute phase and subsequently attended outpatient follow-up. The parent prospective cohort comprised 124 post-COVID-19 survivors. For the present paired longitudinal analysis, participants were eligible if they completed both follow-up assessments and had analyzable transthoracic echocardiography (TTE), including RVFWLS, at both AV1 and AV2. Accordingly, no formal prospective sample size calculation was performed for this secondary analysis.

Exclusion criteria were cognitive or psychiatric impairment precluding the provision of informed consent or completion of study questionnaires; missing required measurements or non-analyzable echocardiographic examinations at AV1 and/or AV2; terminal illness or receipt of palliative care; pregnancy; and age < 18 years.

Study procedures and data collection

At both AV1 and AV2, participants underwent the following assessments, according to their availability at each visit: i) TTE; ii) pulmonary function testing, including spirometry and pulmonary diffusing capacity testing, when applicable; iii) assessment of dyspnea and functional status using the mMRC and the PCFS; iv) anthropometric measurements; and v) evaluation of functional capacity using the 30STS. Vital signs, including systolic and diastolic blood pressure, heart rate, and SpO_2, were recorded at each visit.

Demographic and clinical variables

Age and sex were recorded for all participants. Body mass index was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and classified according to World Health Organization criteria.[11] Pre-existing comorbidities, including hypertension, diabetes mellitus, chronic lung disease (asthma or chronic obstructive pulmonary disease [COPD]), heart failure, and coronary artery disease, were collected for descriptive purposes and were not considered primary analytical variables.

Severity of acute COVID-19

The severity of acute COVID-19 was classified according to the highest level of care required during hospitalization: mild (no hospitalization), moderate (hospital ward admission), or severe (intensive care unit [ICU] admission, with or without IMV). Indicators of respiratory support and other markers of disease severity, including oxygen therapy, IMV, and SpO_2, were extracted from medical records when available.

Assessment of functional capacity

Functional capacity was assessed using the 30STS according to the Senior Fitness Test protocol.[12] Age- and sex-specific normative values were used solely to provide clinical context and were not applied as diagnostic cutoffs.

Assessment of dyspnea and functional status

Dyspnea severity was assessed using the mMRC (score range, 0-4).[13] Functional status was evaluated using the PCFS (grades 0-4), based on the validated Brazilian Portuguese version.[14]

Acquisition of echocardiographic images

TTE was performed using a Vivid S6 ultrasound system (GE HealthCare, Tirat Carmel, Israel) equipped with an M4S phased-array transducer, allowing acquisition of 2D, M-mode, Doppler, and myocardial strain images. Image acquisition and quantitative measurements were performed in accordance with contemporary international recommendations for echocardiographic assessment of the right heart.[8]

Echocardiographic measurements

Right ventricular free wall longitudinal strain

RVFWLS was measured using 2D-STE from an RV-focused apical four-chamber view. Images were optimized for myocardial tracking, with a target frame rate of 50-80 frames/s. Analyses were performed using three consecutive cardiac cycles. RVFWLS was calculated as the arithmetic mean of the peak systolic longitudinal strain values obtained from the basal, midventricular, and apical segments of the RV free wall.[8]

Definition of right ventricular systolic dysfunction

For categorical analyses, RV systolic dysfunction was defined according to prespecified thresholds consistent with contemporary international recommendations: TAPSE < 1.7 cm, FAC < 35%, S′ < 9.5 cm/s, and RVFWLS > −20% (ie, less negative than −20%).[8]

Pulmonary function testing

Pulmonary function testing was performed at the study clinic and included spirometry and measurement of diffusing capacity using the single-breath technique. All tests were conducted by trained personnel in accordance with current American Thoracic Society/European Respiratory Society standards for acceptability and reproducibility.[15]

Pulmonary diffusing capacity was measured as the diffusing capacity of the lung for carbon monoxide (D_{LCO}) using the single-breath method. Alveolar volume (V_A) was measured concurrently, and the carbon monoxide transfer coefficient (K_{CO}) was calculated as D_{LCO}/V_A. For the purposes of this study, pulmonary diffusing function was primarily represented by K_{CO} (mL/min/mmHg/L).[16]

Study variables and analytical strategy

The primary echocardiographic outcomes were RVFWLS, TAPSE, FAC, and S′ measured at AV1 and AV2. Functional and pulmonary outcomes included performance on the 30STS, PCFS scale grade, mMRC dyspnea score, and K_{CO}.

Analyses were conducted using three complementary approaches. First, cross-sectional analyses examined the associations between RV echocardiographic parameters and functional or pulmonary outcomes separately at AV1 and AV2. Second, longitudinal analyses evaluated within-participant changes over time, with change scores (Δ) calculated as the value at AV2 minus the value at AV1. These analyses were restricted to participants with complete paired measurements for the variable of interest. Third, categorical analyses classified participants as improved, stable, or worsened according to prespecified criteria. For RV systolic indices, the predefined thresholds for RV systolic dysfunction were used to facilitate clinically meaningful categorization.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). Figures were generated using R, version 4.5.2 (R Foundation for Statistical Computing), with the "tidyverse" package. Selected stratified analyses, including comparisons according to ICU admission and sex, as well as adjusted models when applicable, were performed in R.

The distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables are presented as mean ± SD or median (IQR) as appropriate, whereas categorical variables are presented as absolute and relative frequencies. Comparisons between AV1 and AV2 were performed using paired *t* tests or Wilcoxon signed-rank tests according to data distribution. Between-group comparisons in stratified analyses were conducted using Student's *t* tests or Mann-Whitney *U* tests, as appropriate. Categorical variables were compared using Fisher's exact test.

Associations between echocardiographic parameters and functional or pulmonary outcomes were assessed using Pearson or Spearman correlation coefficients according to the distributional characteristics of data. Correlation strength was interpreted using prespecified thresholds based on the absolute correlation coefficient: weak (< 0.30), moderate (0.30-0.49), and strong (≥ 0.50).[17]

A sensitivity power analysis for correlation coefficients was performed to contextualize the absence of a prospective sample size calculation. Assuming a two-sided significance level of $\alpha = 0.05$ ($p < 0.05$) and 80% statistical power, the minimum detectable correlation coefficients were approximately $|r| = 0.39$ for $n = 49$, $|r| = 0.40$ for $n = 46$, $|r| = 0.42$ for $n = 43$, and $|r| = 0.46$ for $n = 35$. Accordingly, weaker associations may not have been detected. Because no formal adjustment for multiple comparisons was applied, analyses involving multiple correlations and subgroup comparisons should be considered exploratory. 95%CIs are reported where appropriate, and effect sizes are presented as Cohen's *d* or rank-biserial correlation coefficients, as applicable.

Ethical considerations

The study was approved by the institutional Human Research Ethics Committee in accordance with Brazilian National Health Council Resolution 466/2012 (protocol no. 4.290.578). Written informed consent was obtained from all participants before study enrollment.

Results

Participants and follow-up

Among the 124 participants enrolled in the parent prospective cohort, 49 completed both follow-up visits and had analyzable paired echocardiographic examinations. Women comprised 55.1% (27/49) of the cohort, and obesity was present in 63.3% (31/49). Pre-existing comorbidities included hypertension in 33 participants (67.3%), diabetes mellitus in 15 (30.6%), chronic lung disease (asthma or COPD) in two (4.1%), and heart failure with reduced ejection fraction in one (2.0%).

Most participants required hospitalization during the acute phase of COVID-19, with 38 (77.6%) admitted to the ICU and 33 (67.3%) requiring IMV (Table 1).

The AV1 was performed a mean of 122.6 ± 52.8 days (4.0 ± 1.7 months) after the acute illness, whereas the AV2 occurred after a mean of 417.4 ± 24.5 days (13.7 ± 0.8 months). The mean interval between assessments was 295.0 ± 51.9 days. The study design and principal findings are summarized in Central Illustration.

Functional capacity, dyspnea, functional status, and pulmonary diffusion

Between AV1 and AV2, functional capacity as assessed by the 30STS and K_{CO} improved significantly. In contrast, dyspnea severity (mMRC) and functional status (PCFS) remained unchanged (Table 2).

Longitudinal changes in right ventricular function

Among the RV systolic indices, TAPSE showed a modest decline between AV1 and AV2, although values remained within the normal reference range. No significant longitudinal changes were observed in RVFWLS, FAC, or S′ (Table 3).

Cross-sectional associations between right ventricular function and clinical outcomes

Cross-sectional analyses performed separately at AV1 and AV2 revealed no significant associations between RV systolic indices and functional or pulmonary outcomes (all $p > 0.05$) (Table S1; Table S2).

Table 1 – Baseline characteristics and acute-phase severity of the study participants (n = 49)

Variable	Overall
Age, years	50.7 ± 10.3
Sex	
Male	22 (44.9)
Female	27 (55.1)
BMI, kg/m²	32.1 ± 5.8
BMI category	
Normal weight (18.5-24.9 kg/m²)	1 (2.0)
Overweight (25.0-29.9 kg/m²)	17 (34.7)
Obesity (≥ 30.0 kg/m²)	31 (63.3)
Hospitalization during acute COVID-19	
No	5 (10.2)
Yes	44 (89.8)
Severity of acute COVID-19	
Mild	5 (10.2)
Moderate	6 (12.2)
Severe	38 (77.6)
ICU admission	
No	11 (22.4)
Yes	38 (77.6)
IMV	
No	16 (32.7)
Yes	33 (67.3)

Data are presented as mean ± SD or n (%) as appropriate. BMI: body mass index; ICU: intensive care unit; IMV: invasive mechanical ventilation.

Longitudinal associations

In analyses based on within-participant changes (Δ = AV2 − AV1), changes in RVFWLS were positively correlated with changes in K_{CO} ($r = 0.33$; $p = 0.05$), whereas changes in FAC were inversely correlated with changes in PCFS scores ($r = -0.35$; $p = 0.02$). No other longitudinal correlations reached statistical significance (Table 4).

In analyses based on categorical trajectories (improved, stable, or worsened), changes in TAPSE were inversely correlated with the trajectory of 30STS performance ($\rho = -0.37$; $p = 0.01$), whereas all other associations were nonsignificant (Table S3).

Stratified analyses by acute-phase severity and sex

When participants were stratified according to ICU admission during the acute phase, RVFWLS at AV1 showed a nonsignificant trend toward less favorable values among patients requiring ICU care than among those who did not (−16.8 ± 4.7% vs −19.3 ± 3.4%; $p = 0.07$). No significant between-group differences were observed for the remaining RV systolic indices or for functional and pulmonary measures (Table 5). At AV2, RV echocardiographic parameters, functional outcomes, and K_{CO} were comparable between the ICU and non-ICU groups (Table 6).

Sex-stratified analyses demonstrated no significant differences in RV echocardiographic parameters or functional and pulmonary outcomes at AV1. At AV2, men exhibited lower TAPSE and FAC values than women, whereas RVFWLS and S′ remained comparable between sexes. PCFS scores showed a borderline difference between men and women (Table 7).

Table 2 – Functional status, dyspnea, functional capacity, and pulmonary diffusion at AV1 and AV2

Variable	AV1	AV2	p-value
mMRC	1.0 (0.0-2.0)	1.0 (0.0-2.0)	0.430
PCFS	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.110
30STS	10.1 ± 3.3	11.6 ± 3.1	0.004
K_{CO}, mL/min/mmHg/L	4.1 ± 0.7	4.3 ± 0.8	0.002

p-values were calculated using the Wilcoxon signed-rank test for ordinal variables (mMRC and PCFS) and the paired t test for continuous variables (30STS and KCO). Data are presented as mean ± SD or median (IQR) as appropriate. 30STS: 30-second sit-to-stand test; AV1: first post-acute evaluation; AV2: second post-acute evaluation; K_{CO}: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status.

Table 3 – Longitudinal changes in right ventricular echocardiographic measures between AV1 and AV2

Variable	AV1	AV2	MD*	95% CI	p-value
TAPSE, cm	2.2 ± 0.3	2.1 ± 0.2	−0.09	−0.17 to −0.01	0.03
RVFWLS, %	−17.4 ± 4.5	−18.4 ± 3.5	−0.99	−2.53 to 0.56	0.21
FAC, %	46.8 ± 7.4	44.6 ± 11.2	−2.26	−5.75 to 1.23	0.20
S′, cm/s	12.6 ± 2.4	12.2 ± 2.0	−0.45	−1.02 to 0.12	0.12

**MD was calculated as AV2 − AV1. Data are presented as mean ± SD. AV1: first post-acute evaluation; AV2: second post-acute evaluation; FAC: fractional area change; MD: mean difference; RVFWLS: right ventricular free wall longitudinal strain; S′: tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion.*

Table 4 – Correlations between longitudinal changes in RV echocardiographic measures and clinical outcomes

RV parameter ΔRV*	mMRC	PCFS	30STS	KCO
RVFWLS	−0.16 (p = 0.28)	−0.06 (p = 0.71)	0.007 (p = 0.96)	0.33 (p = 0.05)
TAPSE	−0.12 (p = 0.43)	−0.01 (p = 0.92)	−0.19 (p = 0.21)	0.003 (p = 0.99)
FAC	−0.17 (p = 0.25)	−0.35 (p = 0.02)	0.07 (p = 0.67)	−0.06 (p = 0.73)
S′	0.02 (p = 0.89)	0.02 (p = 0.89)	−0.21 (p = 0.17)	−0.28 (p = 0.11)

*Values are correlation coefficients (r or ρ) with corresponding p-values. Pearson or Spearman correlation coefficients were used as appropriate. *ΔRV was calculated as AV2 − AV1. 30STS: 30-second sit-to-stand test; AV1: first post-acute evaluation; AV2: second post-acute evaluation; FAC: fractional area change; K_{CO}: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RV: right ventricle; RVFWLS: RV free-wall longitudinal strain; S′: tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion.*

Table 5 – Right ventricular echocardiographic measures and clinical outcomes at AV1 according to ICU admission

Variable	Non-ICU (n = 11)	ICU (n = 38)	p-value	Effect size*
RVFWLS, %	−19.3 ± 3.4	−16.8 ± 4.7	0.07	0.55
TAPSE, cm	2.2 ± 0.3	2.2 ± 0.3	0.81	0.08
FAC, %	49.2 ± 7.4	46.1 ± 7.3	0.25	0.40
S′, cm/s	12.4 ± 2.3	12.7 ± 2.4	0.71	−0.12
30STS, repetitions	11.3 ± 1.6	10.0 ± 3.6	0.36	0.38
K_{CO}, mL/min/mmHg/L	4.0 ± 0.5	4.2 ± 0.8	0.32	−0.30
mMRC, median (IQR)	1.0 (0.0-3.0)	1.0 (0.0-2.0)	0.09	−0.06
PCFS, median (IQR)	2.0 (0.5-2.5)	2.0 (2.0-3.0)	0.65	0.27

*p-values were calculated using the Student's t test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed or ordinal variables. Data are presented as mean ± SD or median (IQR) as appropriate. *Effect size is presented as Cohen's d for independent-samples t tests and rank-biserial correlation for Mann-Whitney U tests. 30STS: 30-second sit-to-stand test; AV1: first post-acute evaluation; FAC: fractional area change; ICU: intensive care unit; K_{CO}: carbon monoxide transfer coefficient; mMRC; modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RVFWLS: right ventricular free wall longitudinal strain; S′: tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion.*

In analysis of covariance models with RVFWLS at AV2 as the dependent variable, baseline RVFWLS as a covariate, and each baseline functional or pulmonary measure entered individually as the predictor of interest, none of the baseline functional or pulmonary measures independently predicted follow-up RVFWLS after adjustment for baseline RVFWLS (Table 8).

Discussion

This study provides a longitudinal assessment of post-COVID-19 survivors from a cohort characterized by severe acute illness and a high burden of cardiometabolic comorbidities. Over a mean follow-up interval of approximately 10 months, objective measures of functional performance, assessed by the 30STS, and pulmonary

Table 6 – Right ventricular echocardiographic measures and clinical outcomes at AV2 according to ICU admission

Variable	Non-ICU (n = 11)	ICU (n = 38)	p-value	Effect size*
RVFWLS, %	−18.1 ± 2.7	−18.5 ± 3.7	0.69	0.12
TAPSE, cm	2.2 ± 0.2	2.1 ± 0.3	0.38	0.29
FAC, %	43.4 ± 15.7	45.4 ± 9.9	0.97	−0.18
S□, cm/s	12.3 ± 1.6	12.2 ± 2.1	0.89	0.04
30STS, repetitions	11.9 ± 2.4	11.5 ± 3.1	0.89	0.13
K_{CO}, mL/min/mmHg/L	4.1 ± 0.7	4.3 ± 0.8	0.51	−0.23
mMRC, median (IQR)	1.0 (0.2-1.0)	1.0 (0.0-2.0)	0.40	0.05
PCFS, median (IQR)	2.0 (1.0-2.0)	2.0 (1.0-3.0)	0.50	0.22

*p-values were calculated using the Student's t test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed or ordinal variables. Data are presented as mean ± SD or median (IQR) as appropriate. *Effect size is presented as Cohen's d for independent-samples t tests and rank-biserial correlation for Mann-Whitney U tests. 30STS: 30-second sit-to-stand test; AV2: second post-acute evaluation; FAC: fractional area change; ICU: intensive care unit; K_{CO}: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RVFWLS: right ventricular free wall longitudinal strain; S': tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion.*

Table 7 – Right ventricular echocardiographic measures and clinical outcomes at AV2 according to sex

Variable	Male (n = 22)	Female (n = 27)	p-value	Effect size*
RVFWLS, %	−18.0 ± 3.3	−18.7 ± 3.7	0.47	−0.20
TAPSE, cm	2.0 ± 0.2	2.2 ± 0.3	0.01	−0.71
FAC, %	43.5 ± 5.8	46.1 ± 14.3	0.04	0.34
S', cm/s	12.0 ± 2.1	12.4 ± 2.0	0.46	−0.21
30STS, repetitions	12.3 ± 3.2	11.1 ± 2.8	0.19	−0.23
K_{CO}, mL/min/mmHg/L	4.4 ± 0.9	4.1 ± 0.7	0.36	0.30
mMRC, median (IQR)	0.5 (0.0-1.2)	1.0 (0.0-2.0)	0.66	0.18
PCFS, median (IQR)	1.5 (0.0-2.2)	2.0 (2.0-3.0)	0.05	0.22

*p-values were calculated using the Student's t test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed or ordinal variables. Data are presented as mean ± SD or median (IQR) as appropriate. *Effect size is presented as Cohen's d for independent-samples t tests and rank-biserial correlation for Mann-Whitney U tests. 30STS: 30-second sit-to-stand test; AV2: second post-acute evaluation; FAC: fractional area change; K_{CO}: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RVFWLS: right ventricular free wall longitudinal strain; S': tricuspid annular systolic velocity; TAPSE: tricuspid annular plane systolic excursion.*

Table 8 – ANCOVA models evaluating baseline functional and pulmonary measures as predictors of RVFWLS at AV2 after adjustment for baseline RVFWLS

Model (predictor at AV1)	F (df1, df2)	p-value	Partial η^2
mMRC	1.930 (1. 47)	0.17	0.039
PCFS	0.180 (1. 47)	0.67	0.004
30STS	1.345 (1. 45)	0.25	0.029
K_{CO}	0.225 (1. 39)	0.64	0.006

The dependent variable was RVFWLS at AV2. Baseline RVFWLS (AV1) was included as a covariate. Each model included a single baseline functional or pulmonary measure as the predictor of interest. 30STS: 30-second sit-to-stand test; ANCOVA: analysis of covariance; AV1: first post-acute evaluation; AV2: second post-acute evaluation; df: degrees of freedom; K_{CO}: carbon monoxide transfer coefficient; mMRC: modified Medical Research Council; PCFS: Post-COVID-19 Functional Status; RVFWLS: right ventricular free wall longitudinal strain.

diffusing function, indexed by the K_{CO}, improved significantly. In contrast, dyspnea severity and self-reported functional status, assessed using the mMRC and the PCFS, respectively, remained unchanged despite a favorable descriptive trend. From a cardiovascular perspective, conventional RV systolic indices remained largely preserved, with the exception of a modest but statistically significant decline in TAPSE, which nevertheless remained within the normal reference range. Likewise, RVFWLS remained mildly reduced without significant longitudinal change, consistent with persistent subclinical RV systolic involvement.[8]

The susceptibility of the RV to injury during acute COVID-19 is well established. Pulmonary vascular abnormalities and thrombo-inflammatory processes increase RV afterload and may precipitate RV systolic dysfunction.[5] In 2022, investigators at the Mayo Clinic compared pre-COVID-19 echocardiograms with the first outpatient post-COVID-19 examination using blinded core laboratory strain analysis and a stringent definition of clinically meaningful deterioration. Overall, they found no clinically meaningful change in mean RV free wall strain, although a subset of patients experienced significant worsening, particularly those with new cardiopulmonary symptoms and pre-existing cardiovascular disease.[7] Longitudinal studies from other cohorts have likewise suggested that RV remodeling and dysfunction improve in most survivors but persist in clinically important subgroups, potentially attenuating linear associations when analyses are performed across the entire cohort.[18] Consistent with this heterogeneity, studies focusing on ICU survivors have reported more persistent impairment in RV strain and conventional RV systolic indices than in control populations,[19] whereas other longitudinal cohorts have demonstrated statistically significant improvements in RV strain over approximately 1 year despite minimal absolute changes.[20] Conversely, large cohorts with longer follow-up have reported RV strain values comparable to those of control participants in some settings,[10] supporting the concept that post-COVID-19 RV mechanical abnormalities are generally subtle, heterogeneous across clinical phenotypes, and not consistently reflected by symptom burden.[19,21] The present findings, which are characterized by preserved conventional RV systolic indices together with persistently but mildly reduced RVFWLS, fit within this heterogeneous body of evidence and underscore the importance of considering both clinical phenotype and methodological differences when interpreting results across studies.

The substantial cardiometabolic burden of our cohort also warrants consideration when interpreting the persistently reduced RVFWLS values. Although guideline-recommended thresholds are useful for categorical classification, they were not developed specifically for post-COVID-19 populations with a high prevalence of obesity, hypertension, and diabetes mellitus. Accordingly, in the absence of a non-COVID control group and pre-infection echocardiographic data, residual abnormalities in RVFWLS should be interpreted with caution and should not be attributed solely to prior SARS-CoV-2 infection.

Cross-sectional analyses performed at both follow-up visits demonstrated weak and nonsignificant correlations ($|r| < 0.30$; $p > 0.05$) between RV systolic indices (RVFWLS, TAPSE, FAC, and S′) and clinical outcomes, including dyspnea (mMRC), functional status (PCFS), functional capacity (30STS), and pulmonary diffusing function (K_{CO}). These findings suggest that, at a single time point during the late post-COVID-19 period, resting RV systolic performance, whether assessed by conventional echocardiographic parameters or myocardial deformation imaging, does not exhibit a linear relationship with dyspnea severity, self-reported functional limitation, objective functional performance, or pulmonary diffusing capacity.[22,23] This observation is consistent with the multifactorial pathophysiology of post-COVID-19, in which persistent symptoms and perceived functional limitation likely reflect the combined effects of residual pulmonary disease, cardiovascular abnormalities, peripheral deconditioning, autonomic dysfunction, and psychosocial factors. These interacting mechanisms may contribute to the frequently observed dissociation between objective cardiopulmonary measurements and patient-reported outcomes.[3]

When longitudinal changes (Δ) were analyzed, two modest but biologically plausible associations emerged. Changes in RVFWLS were positively correlated with changes in K_{CO} ($r = 0.33$; $p = 0.05$), whereas changes in FAC were inversely correlated with changes in PCFS scores ($r = -0.35$; $p = 0.02$). The association between improvements in pulmonary gas transfer and RV mechanics is physiologically plausible given the sensitivity of RV performance to changes in pulmonary vascular afterload.[23] However, the association between ΔRVFWLS and ΔK_{CO} reached only the conventional threshold for statistical significance and should therefore be considered hypothesis-generating, particularly because no adjustment for multiple comparisons was performed. Partial recovery of the alveolar-capillary interface may be accompanied by parallel, albeit modest, improvement in RV mechanical function.[24,25] Similarly, FAC — which is

generally considered a more global measure of RV systolic performance than annular indices alone — may capture clinically meaningful changes associated with patients' perceived functional trajectory in selected individuals.[8,26,27]

Using the categorical trajectory approach, the inverse correlation between changes in TAPSE and the trajectory of 30STS performance ($\rho = -0.37$; $p = 0.01$) indicates that greater longitudinal reductions in TAPSE were associated with greater improvement in 30STS performance categories. TAPSE is highly load dependent, reflects only the longitudinal excursion of the tricuspid annulus, and is susceptible to measurement variability. Consequently, current guidelines recommend a multiparametric assessment of RV systolic function rather than reliance on TAPSE as a standalone measure.[8] Although reduced TAPSE during acute COVID-19 hospitalization has consistently been associated with adverse outcomes, including mortality, in meta-analyses,[28] a small isolated decline during the late post-COVID-19 period, in the absence of concordant changes in FAC, S′, or RVFWLS, is more likely to reflect hemodynamic variation, measurement variability, or selective changes in longitudinal annular motion than a true deterioration in global RV systolic function.[8,19] The stability of FAC and S′ observed in our cohort further supports this interpretation.

The significant improvement in 30STS performance together with the increase in K_{CO} suggests objective recovery in both functional performance and pulmonary diffusing capacity, which may not be proportionately reflected by symptom-based or patient-reported functional measures. One plausible explanation is that improvements in 30STS performance partly reflect peripheral reconditioning, including gains in lower-extremity strength and endurance, enhanced tolerance to submaximal exercise, and/or participation in rehabilitation programs, all of which may improve functional performance despite stable echocardiographic findings.[29,30] Systematic reviews and meta-analyses of rehabilitation interventions in post-COVID-19 populations have consistently demonstrated improvements in functional outcomes, including sit-to-stand performance.[31] Likewise, longitudinal studies of survivors of COVID-19 hospitalization have frequently reported progressive improvement in pulmonary diffusing capacity (D_{LCO} and K_{CO}) over time, although residual impairment may persist in some individuals and recovery may eventually plateau, providing context for the modest increase in K_{CO} observed in our cohort.[32] Despite these objective improvements, the stability of median mMRC and PCFS scores is consistent with evidence from cardiopulmonary exercise testing (CPET) studies and systematic reviews indicating that exertional intolerance and persistent dyspnea in post-COVID-19 arise from multiple interacting mechanisms (eg, ventilatory, perfusion-related, circulatory, peripheral, and autonomic abnormalities) making it unlikely that any single resting physiological marker adequately explains symptom severity or functional limitation.[33,34]

Stratified analyses yielded additional findings that should be regarded as hypothesis-generating. When participants were stratified according to acute-phase severity, RVFWLS showed a nonsignificant trend toward more impaired values among patients requiring ICU admission at AV1, whereas values converged by AV2, a pattern consistent with greater early RV vulnerability in severe COVID-19 followed by partial recovery or physiological adaptation over time.[5,18] Sex-stratified analyses showed that men had lower TAPSE and FAC values at AV2 and experienced greater longitudinal reductions in TAPSE and S′, whereas women tended to report greater functional limitation on the PCFS. These observations should be interpreted cautiously because RV systolic indices are influenced by loading conditions and are subject to both biological and technical variability.[8] Nevertheless, the greater symptom burden reported by women is consistent with previous studies of post-COVID-19 populations using functional status instruments and rehabilitation cohorts.[35-37] Finally, analysis of covariance demonstrated that baseline mMRC, PCFS, 30STS, and K_{CO} were not independently associated with RVFWLS at follow-up after adjustment for baseline RVFWLS, suggesting that the initial severity of symptoms, functional impairment, or pulmonary dysfunction did not robustly predict subsequent RV myocardial deformation in this cohort.

Clinical implications

Our findings have three main clinical implications. First, neither RVFWLS nor conventional RV systolic indices emerged as robust standalone markers of late functional impairment or its longitudinal trajectory, supporting the use of an integrated assessment that combines echocardiography with functional testing and pulmonary evaluation, as advocated by recent post-COVID-19 phenotyping studies.[21]

Second, the modest associations observed in longitudinal (Δ-based) analyses suggest that temporal changes may be more informative than isolated measurements obtained at a single time point. However, the observed effect sizes were small and lacked consistent replication across analyses, indicating that noncardiac factors (eg, peripheral deconditioning, residual pulmonary disease, autonomic dysfunction, and psychosocial influences) are likely to play a predominant role in determining functional recovery in many patients.[38,39]

Third, the optimal timing of cardiopulmonary assessment after COVID-19 remains uncertain. Earlier evaluations, including those performed during the acute phase of illness, may provide greater prognostic value than later assessments and warrant further investigation.

Study limitations

This study has several limitations. First, the relatively small sample size limited statistical power for correlation analyses, particularly after stratification and categorical trajectory classification, increasing the risk of type II error and reducing the precision of effect estimates. Sensitivity power analysis indicated that the available sample size was sufficient to detect correlations of at least moderate magnitude; therefore, weaker associations may have gone undetected. Consequently, nonsignificant findings should not be interpreted as definitive evidence of the absence of an association, and the results should be regarded as exploratory and hypothesis-generating.

Second, the limited sample size precluded meaningful subgroup analyses according to important cardiometabolic conditions, such as obesity and hypertension, because these would have resulted in small subgroup sizes and unstable estimates.

Third, no formal adjustment for multiple comparisons was performed; therefore, isolated findings with borderline statistical significance should be interpreted cautiously. Fourth, the absence of both a non-COVID control group and pre-infection echocardiographic data limits attribution of the observed abnormalities specifically to post-COVID-19 sequelae in this cohort with a high burden of pre-existing comorbidities.

Fifth, the availability of only two follow-up assessments precluded characterization of intermediate recovery trajectories, including the possibility of early improvement followed by a later plateau. Moreover, because the first follow-up assessment occurred approximately 4 months after the acute illness, RV abnormalities present during hospitalization or in the early post-discharge period may already have partially resolved, limiting characterization of the complete course of RV recovery.

Sixth, mechanistic interpretation is limited by the absence of invasive hemodynamic assessment by right heart catheterization and CPET, both of which could have better distinguished the relative contributions of ventilatory, circulatory, peripheral, and autonomic mechanisms to persistent exercise intolerance. In addition, potentially important confounding factors (eg, pre-COVID-19 physical activity, participation in rehabilitation programs, medical therapies, infecting viral variants, and socioeconomic characteristics) could not be comprehensively accounted for.

Finally, intraobserver and interobserver reproducibility of RVFWLS measurements was not formally assessed. Therefore, the contribution of measurement variability to the small longitudinal changes observed cannot be excluded. Moreover, 2D-STE-derived RV strain is intrinsically influenced by image quality, frame rate, tracking performance, observer variability, and vendor- or software-specific algorithms, while standardization of RV strain cutoff values remains incomplete .[8]

Conclusions

Among post-COVID-19 survivors with severe acute illness and a high burden of cardiometabolic comorbidities, functional capacity and pulmonary diffusing function improved during follow-up, whereas RVFWLS remained mildly reduced without significant longitudinal change. Conventional RV systolic indices remained largely preserved, with the exception of a modest decline in TAPSE that remained within the normal reference range. These exploratory findings suggest a partial dissociation between recovery of functional and pulmonary performance and resting echocardiographic markers of RV systolic function during the late post-COVID-19 period, reinforcing the importance of an integrated, multiparametric, and individualized approach to patient assessment.

Author Contributions

Conception and design of the research: Rogelin M, Fonseca FR, Silva RM, Fialho GL; acquisition of data: Rogelin M, Aranha AFMG, Fonseca FR, Silva RM, Fialho GL; analysis and interpretation of the data, statistical analysis and writing of the manuscript: Rogelin M; obtaining financing: Silva RM; critical revision of the manuscript for intellectual content: Aranha AFMG, Fialho GL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study was funded by CNPq – MCTIC/CNPq/FNDCT/MS/SCTIE/Decit No. 07/2020.

Study Association

This article is part of the master's thesis in Medical Sciences submitted by Rogelin M, from the Graduate Program in Medical Sciences of the Universidade Federal de Santa Catarina.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee for Human Subjects under approval number 4,290,578, dated 09/21/2020. All procedures involved in this study were in accordance with the 1975 Declaration of Helsinki and its subsequent amendments. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The data supporting the results of this study are available from the corresponding author upon reasonable request.

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***Supplemental Materials**

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