CFR Cardiac Failure Review

ORIGINAL RESEARCH

Diagnosis

Cardiac Dysfunction and Subclinical Atherosclerosis in Post-COVID-19 Patients

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Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is still a burden for healthcare systems worldwide. Now, the focus is not only on acute infections, but also on the long-term effects of COVID-19. The present study aimed to evaluate the impact of SARS-CoV-2 infection on the cardiovascular system, and determine the evolution of these changes over 6 months in patients with mild and moderate COVID-19. **Methods:** The prospective observational study included 103 patients with mild and moderate COVID-19. The patients underwent an echocardiography and a measurement of the arterial stiffness parameters at baseline and 6 months from the initial assessment. **Results:** The diastolic dysfunction (the left atrium volume) was statistically significant at baseline and at the 6-month follow-up in men with moderate COVID-19. The ejection fraction presented significant differences globally in mild versus moderate COVID-19 (p=0.043) that disappeared at 6-month follow-up. Global longitudinal strain alterations were also found in both mild and moderate COVID-19 cases. Regarding the aortic pulse wave velocity, the SARS-CoV-2 infection did not influence the arterial stiffness. Ventricular arterial coupling was significantly altered in moderate COVID-19 at the 6-month evaluation (p=0.0218). Male patients presented a lower tricuspid annular plane systolic excursion at baseline. Right ventricular systolic dysfunction was more frequent among men. Systolic pulmonary arterial pressure increased significantly only in men with moderate disease. Additionally, statistically significant changes at baseline and at 6 months were found regarding the intima-media thickness. **Conclusion:** This study shows the cardiovascular long-term sequelae associated with COVID-19 in mild and moderate cases, and emphasises the appropriate investigations for their diagnosis and follow-up.

Keywords

Long COVID, systolic function, left atrium volume, atherosclerosis

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Ethics: This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Clinical Hospital of Infectious Diseases No. 3895/2022, on 4 March 2022.

Consent: All patients have given written informed consent.

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic still challenges healthcare systems worldwide. Currently, the focus is not only on acute infections, but also on the long-term effects of COVID-19, as some patients remain symptomatic for an extended period regardless of the infection severity.[1]

Post-COVID-19 syndrome, or long COVID-19, is the term used to describe the plethora of symptoms that occur weeks and even years following a COVID-19 diagnosis.[2]

The Centers for Disease Control definition of long COVID-19 is 'a chronic

condition that occurs after SARS-CoV-2 infection and is present for at least 3 months'. It includes a broad spectrum of manifestations with an unpredictable evolution.[3]

The WHO defined the post-COVID-19 syndrome as 'the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation'.[4]

The most common manifestations of long COVID-19 are neurological symptoms, cognitive impairment, headaches, fatigue, chronic pain, cardiovascular and pulmonary symptoms, anosmia, and dysgeusia.[2] Additionally, long COVID-19 comprises several new-onset disorders, such as cardiovascular and cerebrovascular diseases, thromboembolic events, type 2 diabetes, myalgic encephalomyelitis, chronic fatigue syndrome, and postural orthostatic tachycardia syndrome.[5]

One-third of the long COVID-19 patients do not present any pre-existing diseases. However, patients with a higher risk for developing long COVID-19 are women or are diagnosed with type 2 diabetes, Epstein–Barr virus reactivation, autoimmune disorders, connective tissue diseases and allergies.[5]

Post-Covid-19 Cardiovascular Manifestations

COVID-19 myocarditis, associated with SARS-Cov-2 acute infection, has a significantly elevated mortality rate, in comparison with patients without myocarditis.[6]

The clinical picture of COVID-19-related myocarditis is polymorphous, with a wide range of symptoms with variable severity. Thus, some patients may experience minor fatigue and dyspnoea, while others have more severe manifestations, such as angina and fulminant myocarditis leading to heart failure and cardiogenic shock.[7,8]

A study that included electronic health records from 40 healthcare systems showed that the risk of myocarditis was higher in unvaccinated patients, with a higher risk in boys aged between 12 and 17 years. Additionally, the risk of developing myocarditis was lower after the first dose of messenger RNA COVID-19 vaccination, but increased after the second dose. However, the cardiac outcomes were significantly higher after SARS-Cov-2 infections than after messenger RNA COVID-19 vaccination, regardless of the number of doses.[9]

Myocardial injury can also be part of the clinical picture of long COVID-19, together with pericarditis, ischaemic heart disease, heart failure, dysrhythmias, dysautonomia and thromboembolic events, and the patients experiencing chest pain, palpitations, fainting, dyspnoea, fatigue and lower limb oedema.[8,10]

Roca-Fernandez et al. investigated the myocardial injury associated with SARS-Cov-2 infection through cardiac MRI.[11] The results showed that the myocardial injury associated with long COVID-19 was still present 12 months after the acute disease diagnosis, not only in patients hospitalised with acute COVID-19, but also in patients that did not require hospitalisation, with low cardiovascular risk factors and with no prior history of cardiovascular disease.[11,12]

COVID-19-associated myocarditis can cause secondary left ventricular dysfunction. While some cardiac abnormalities resolve with time, left ventricular dysfunction assessed by 3D and strain echocardiography and right ventricular dysfunction resolved only partly at 2-month follow-up.[12,13]

A plausible explanation for the long COVID-19-associated cardiac injury is the chronic inflammation maintained by persistent viral reservoirs associated with chronic immune system stimulation caused by the viral antigens. Another feasible hypothesis is the development of an autoimmune response against cardiac antigens via molecular mimicry.[14]

T-cell dysfunctions, namely reduced $CD4^+$ and $CD8^+$ memory cell counts, and increased PD1 expression, together with autoantibodies against angiotensin-converting enzyme 2, β2 adrenoreceptor, muscarinic M2 receptor and angiotensin receptor are also implicated in the long COVID-19 pathogenesis.[5,15–17]

The long COVID-19 manifestations extend beyond myocardial afflictions. Endothelial dysfunction, and haemorrhagic and thrombotic events are also present in these patients. The persistent microthrombi, which are resistant to fibrinolysis, cause a blockage in the microcirculation and, together with the capillary rarefaction, can explain not only the myocardial injury associated with long COVID-19, but also the sustained neuropsychiatric damage.[18]

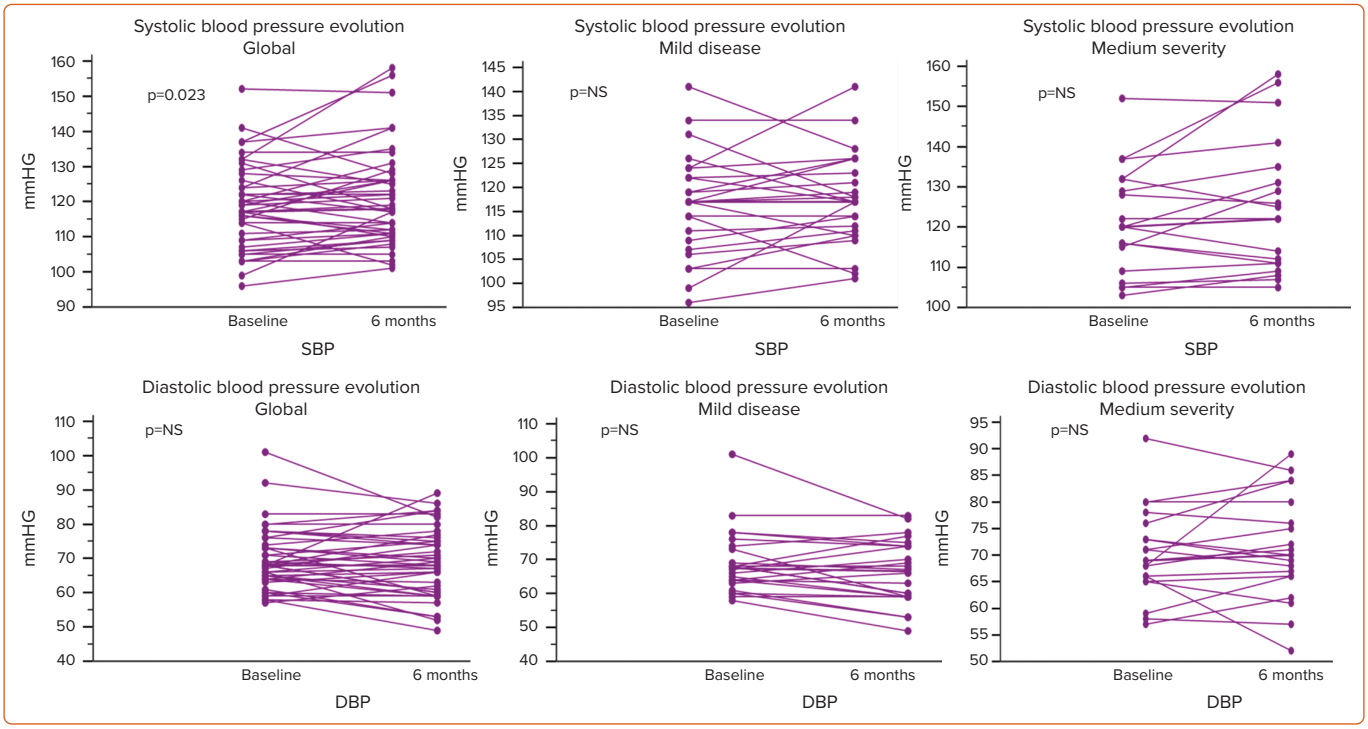
The present study aimed to determine changes in cardiac dysfunction and subclinical atherosclerosis in post-COVID-19 patients. The detection of specific changes in patients with long-term COVID-19 and newly diagnosed cardiac abnormalities or worsening of pre-existing cardiac pathologies emphasises the importance of long-term follow-up and appropriate management of these patients.

Methods

This prospective observational study included 103 patients diagnosed with mild and moderate COVID-19, based on positive SARS-CoV-2 molecular testing or rapid antigen test and severity by definition at the Clinical Hospital of Infectious Diseases, Cluj-Napoca, Romania.[19] Based on the patients' COVID-19 diagnosis timeframe (April 2022 to October 2022) and the national data regarding the circulating SARS-CoV-2 variants of concern, the patients were classified as infected with the omicron variant of concern.[20] Inclusion criteria for the present study were age between 18 and 75 years and a positive polymerase chain reaction test for SARS-CoV-2 or a SARS-CoV-2 rapid antigen test within 30 days of the baseline evaluation. Exclusion criteria were the presence of prior uncontrolled hypertension, ischaemic heart disease, arrhythmias, decompensated heart failure or diabetes and severe forms of COVID-19. The patients were assigned into groups (mild or moderate disease) according to the first WHO classification and adopted by a Romania Health Ministry Order on COVID-19 management.[19] The patients included in the study underwent two cardiovascular evaluations. The first evaluation was within 30 days of the COVID-19 diagnosis, and the second after 6 months from the initial assessment.

Demographic data and information regarding medical history and cardiovascular risk factors, including smoker/non-smoker status and COVID-19 vaccination status, were collected for all the patients included in the study. A cardiologist performed an ECG registration and transthoracic echocardiographic evaluation, including speckle tracking evaluation, and determined the arterial parameters (intima-media thickness, aortic pulse wave velocity; PWVAo, and aortic augmentation index) and ventricular–arterial coupling (VAC) for all the patients. The aforementioned investigations were carried out at the 4th Medical Clinic, Cluj-Napoca, Romania. The echocardiography, together with the left ventricle global

Figure 1: Systolic and Diastolic Blood Pressure at Baseline and at 6 Months in Mild and Moderate Disease Severity



DBP = diastolic blood pressure; SBP = systolic blood pressure.

longitudinal strain (GLS) and the intima-media thickness measurements were performed using Vivid™ T8 (GE Healthcare). Arterial blood pressure was measured in a supine position after 5 min of rest, together with the aortic pulse pressure, aortic augmentation index and PWVao using the TensioMed arteriograph.

All the parameters were determined at baseline at the 6-month follow-up.

All patients included in the study gave written informed consent. The study has the approval of the Ethics Committee, and complies with the recommendations of the Declaration of Helsinki for medical research involving human subjects.

Results

A total of 103 COVID-19 patients, with a mean age of 41.56 ± 11.77 years were included in the prospective observational study, including 35.9% men and 66 64.1% women. Of the total number of patients, 65.04% presented mild forms of COVID-19, while 34.95% presented medium disease severity. No patient included in the study presented severe SARS-Cov-2 infections. Among the patients, 43.1% were obese/overweight. Regarding smoking status, 26 (25.2%) smoked cigarettes. The vaccination status showed that 86 (83.5%) were vaccinated against SARS-Cov-2. Additionally, one (1%) had diabetes, four (3.9%) had cancer, 17 (16.5%) had autoimmune diseases (i.e. Hashimoto's thyroiditis), five (4.9%) had immunosuppression, four (3.9%) had chronic kidney disease, four (13.6%) had chronic lung diseases and eight (7.8%) had chronic liver diseases, but none suffered from cerebrovascular or cardiovascular diseases. Women with a medium form of COVID-19 were older than those with a mild form of the disease. There were no differences in disease severity regarding vaccination status, weight or comorbidities.

The evolution of systolic and diastolic blood pressure at baseline and at 6 months in mild and moderate disease severity is presented in *Figure 1*. Both systolic (SBP) and diastolic blood pressure values were followed. Significant differences were found regarding SBP baseline versus 6 months at the global level (p=0.023), but not particularly in men or women. The disease severity did not significantly influence SBP evolution (neither globally, nor in men or women).

Regarding diastolic blood pressure, differences were found in the relationship with disease severity (mild versus medium) at baseline (median values 64 mmHg versus 69 mmHg; p=0.037) and 6 months (66 mmHg versus 70 mmHg, p=0.073). The significant differences were found partially when the statistical analysis was performed in relation to patients' sex (baseline for men p=0.06, for women at 6 months p=0.02).

Left Ventricular Dysfunction

The echocardiographic examination revealed, by assessing all parameters of diastolic function of the left ventricle, a statistically significant difference at baseline between men and women (p=−0.023) regarding E/A, as shown in *Table 1*. The changes in the volume of the left atrium measured at baseline and at 6 months from the COVID-19 diagnosis were also statistically significant (p=−0.0304). Also, the left atrium volume increased significantly at 6 months in men with a moderate form of COVID-19. The parameters of diastolic dysfunction did not differ significantly regarding the disease severity: mild versus medium (globally). Complete data are also presented in *Supplementary Figure 1 and Supplementary Table 1*.

Left ventricular systolic function was evaluated at baseline and at 6 months; data are presented in *Figure 2 and Supplementary Table 2*. At baseline, significant differences in ejection fraction were found in the mild versus moderate disease forms (p=0.043), just globally, not depending on patients' sex. The differences disappeared at 6 months.

Globally, ejection fraction decreased from baseline at 6 months at the limit of statistical significance, but only in mild forms. Taking into consideration

Table 1: Left Ventricle Diastolic Function at Baseline and at 6 Months

Diastolic Dysfunction	Global				Men				Women				p-value Global Men and Women
	Global	Mild	Medium	p-value	Global	Mild	Medium	p-value Mild–Medium Men	Global	Mild	Medium	p-value Mild–Medium Women	
E/A													
Baseline	1.27 (1.13–1.37)	1.37 (1.18–1.73)	1.26 (1.17–1.4)	NS	1.27 (1.11–1.4)	1.15 (0.99–1.41)	1.26 (1.16–1.33)	0.45	1.37 (1.2–1.75)	1.4 (1.25–1.8)	1.26 (1.17–1.54)	0.19	**0.02**
6 months	1.29 (1.14–1.4)	1.29 (1.14–1.4)	1.17 (1.14–1.5)	NS	1.23 (1.16–1.35)	1.23 (1.16–1.33)	1.26 (1.16–1.33)	0.75	1.24 (1.13–1.5)	1.33 (1.14–1.50)	1.14 (1.11–1.35)	0.81	0.92
p-value	NS	NS	NS		NS	NS	NS		**0.02**	NS	NS		
E/E prim													
Baseline	6.84 (5.55–8.34)	6.37 (5.59–7.6)	7 (5.94–8.21)	NS	5.94 (5.07–7.4)	5.55 (5–6.88)	6.67 (5.8–7.6)	0.1185	6.92 (6–8.13)	6.73 (5.8–8)	7.32 (6.61–8.8)	0.11	0.06
6 months	6.8 (6.09–8.21)	6.43 (6.15–8.18)	6.97 (5.85–8)	NS	6.67 (5.42–7.64)	6.36 (4.8–7.12)	7.27 (4.6–8.2)	0.6389	6.62 (5.98–8.13)	6.43 (5.9–8.2)	7.78 (6.1–9.6)	0.36	0.82
p-value	NS	NS	NS	–	NS	NS	NS	–	NS	NS	NS	–	–
Left Atrium Volume (cm^3)													
Baseline	27.65 (22–33)	29 (21.25–31)	28 (23.25–36.75)	NS	27.5 (23–33)	26.5 (20–33)	29.5 (25–34)	0.5148	29 (21.5–32)	29 (21.75–31)	26 (21–37.5)	0.71	0.55
6 months	31.5 (26–37)	30.5 (22.5–34.5)	33.5 (30–42)	**0.03**	33 (30.75–35.25)	31 (24–35)	33.5 (33–36)	0.2343	31 (23.75–40)	30 (22.5–31.75)	35.5 (27.5–44)	0.13	0.19
p-value	**0.03**	NS	NS		NS	NS	**0.08**		NS	NS	NS		

Data are presented at median (interquartile range).

GLS, significant alterations in time were found globally (p<0.0001), both in mild and moderate disease (p=0.0003 and p=0.0201, respectively); the negative evolution was present in both men and women. A statistically significant difference of GLS in mild versus medium forms of COVID-19 at baseline (p=0.059) was not found at the 6-month follow-up (p=0.668).

Regarding the independent factors for GLS, on multivariate analysis, neither disease severity nor vaccination status were independent predictors.

Additionally, the left atrium volume was influenced by the vaccination status. Thus, a statistically significant increase in left atrium volume was noticed at the 6-month follow-up versus baseline in vaccinated versus unvaccinated patients without statistically significant differences between men and women. The aforementioned data are presented in *Supplementary Table 1*.

Subclinical Atherosclerosis in Post-COVID-19

Arterial stiffness parameters were also evaluated at baseline and the 6-month follow-up, in relation to the COVID-19 severity and sex. *Figure 3* presents the evolution of the pulse wave velocity and the VAC (pulse wave velocity:GLS ratio) at baseline and 6 months in mild and moderate COVID-19.

Taking into consideration just PWVAo, COVID-19 infection did not have any significant influence above the arterial stiffness. In contrast, the pulse wave velocity:GLS ratio was significantly altered in moderate COVID-19 infection (globally −0.41 at baseline versus −0.52 at 6 months; p=0.0218; in men p=0.0082; in women p=NS).

To emphasise the independent predictor factors for PWVAo at baseline and 6 months, univariate and multivariate analyses were performed. At baseline age (p<0.001), BMI (p<0.001), GLS (p<0.001) and central SBP (SBP p<0.001) were independent factors; at 6 months, the same persisted to be independent factors.

In multivariate analysis, age, GLS (just for PWVAo at 6 months) and central SBP were found to be independent factors for PWVAo – complete data are presented in *Supplementary Tables 3 and 4*.

The differences in intima-media thickness measurements were statistically significant both at baseline (p<0.001) and at 6 months (p=0.039) in relation to the disease severity.

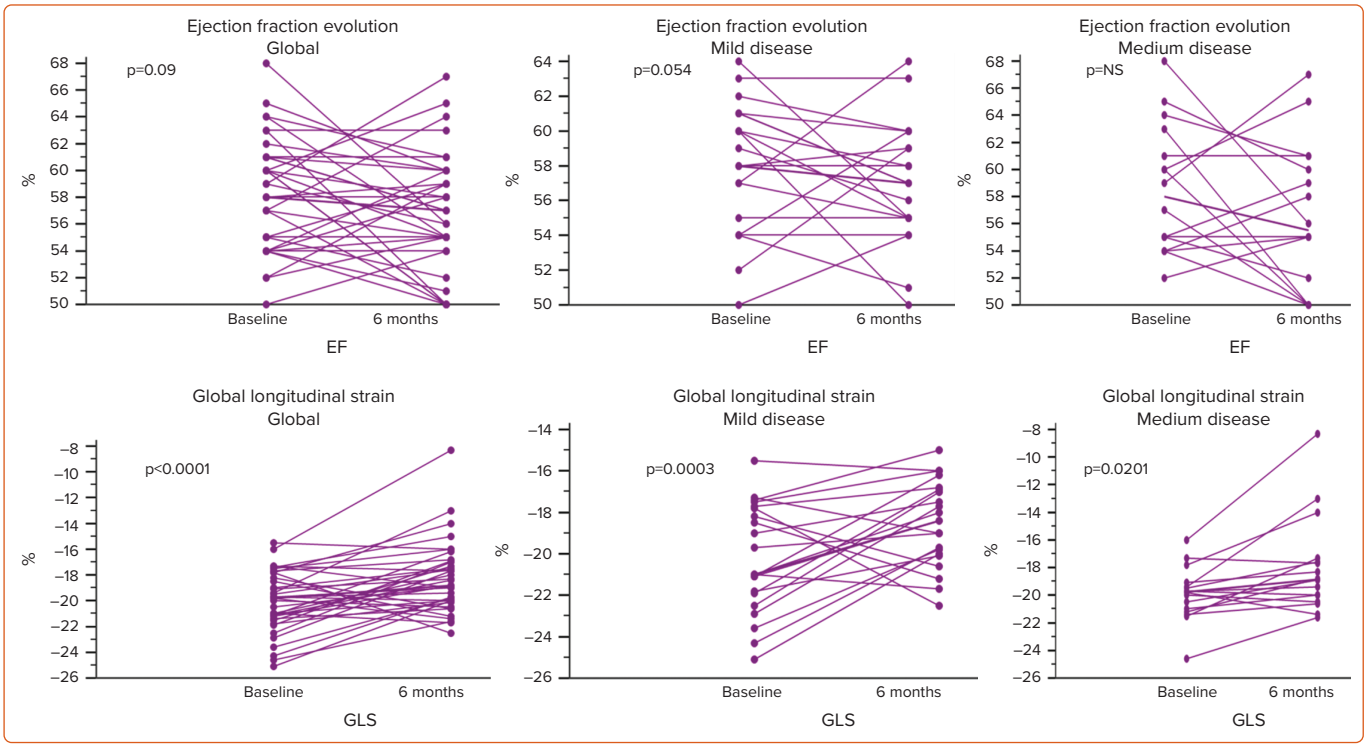
Right Ventricular Dysfunction:

Table 2 presents the right ventricle systolic function at baseline and at 6-month reassessment. Male patients with a moderate form of the disease presented a lower tricuspid annular plane systolic excursion value at baseline that later improved at the 6-month re-evaluation. In addition, there is a statistically significant difference regarding the systolic function of the right ventricle; the right ventricular systolic dysfunction was more frequent among men than women (p=−0.021). In contrast, tricuspid annular plane systolic excursion was not influenced by the severity of the disease.

Regarding the systolic pulmonary arterial pressure, it was significantly increased only in men, at 6 months in the medium form of COVID-19 (p=−0.07), and globally, only in moderate forms of the disease (p=−0.02), without a statistically significant difference in those with mild forms of the disease.

Additionally, the right ventricular systolic function and the right atrium-right ventricle gradient at baseline and the 6-month follow-up

Figure 2: Left Ventricular Systolic Function at Baseline and at 6 Months in Mild and Moderate COVID-19



EF = ejection fraction; GLS = global longitudinal strain.

are presented in *Supplementary Figure 2 and Supplementary Table 5*. The unvaccinated patients presented better right ventricular function at 6 months in comparison with the vaccinated individuals. The difference reached statistical significance globally and in female patients.

Discussion

SARS-Cov-2 causes primarily respiratory symptoms; however, the cardiomyocyte tropism of the virus was demonstrated, as the genome of the virus has been found through polymerase chain reaction testing in cardiac tissue.[21]

The cardiac complications associated with COVID-19 represent not only a secondary event to the pulmonary injury, but can be the result of direct infection of the myocardial tissue causing myocarditis, pericarditis, acute myocardial infarction, acute heart failure and thromboembolic events. Studies have demonstrated the persistence of myocardial inflammation, even in patients who have made an apparent recovery from the acute stage of the disease.[21,22]

The objective of our study was to evaluate the persistence of cardiovascular damage in post-COVID-19 patients. Currently, cardiac function has been assessed in a few studies at the time of diagnosis and afterwards at different time intervals, ranging from weeks to 12 months, in patients with mild and moderate forms of the disease.[11]

In our study, there was no statistically significant difference between the mild or moderate forms of COVID-19 in relation to the vaccination status. However, the data from the literature support the importance of vaccination for long-COVID-19 prevention.[23,24]

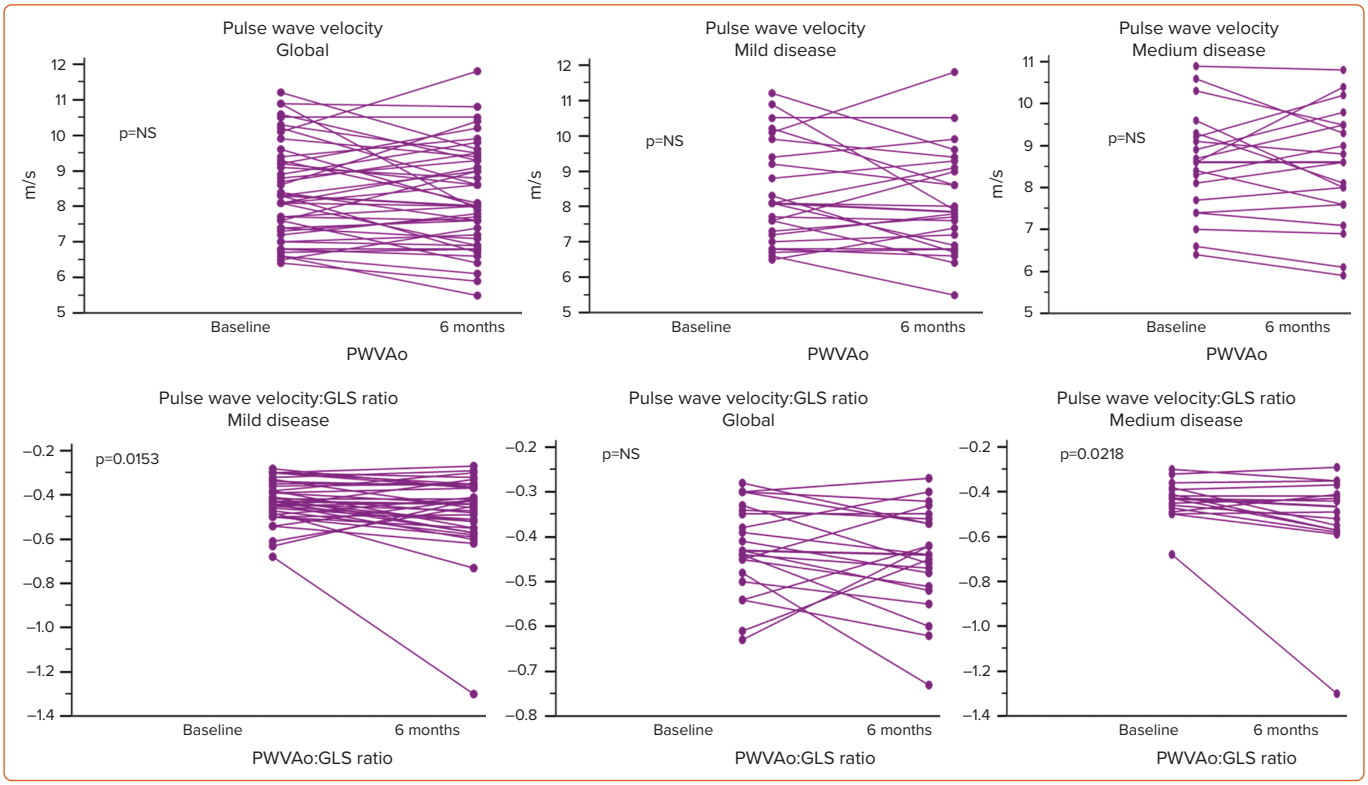
Now, the majority of the studies are focused on the persistence of respiratory symptoms, neuropsychiatric symptoms, anxiety, depression and quality of life in long COVID-19 patients, while prospective studies that focus on cardiovascular damage as part of the clinical picture of long-term COVID-19 are few.[24–26] Therefore, in our study, every patient underwent echocardiography. Men with moderate forms of disease more frequently presented right ventricular dysfunction identified at baseline, which later improved at the 6-month re-examination. Persistent right ventricular damage after SARS-Cov-2 infection was also demonstrated in other studies, such as the one conducted by Ilardi et al.[27] In that study, right ventricular GLS and right ventricular free-wall longitudinal strain were significantly reduced in patients with COVID-19 and pulmonary embolism compared with patients without pulmonary embolism.[27]

Furthermore, right ventricular dysfunction is common among hospitalised patients with SARS-Cov-2 infection and is a predictor of mortality at 1-year post-COVID-19.[28]

Studies that evaluate cardiac changes in patients with mild and moderate forms of COVID-19 are few, and even more so are those that follow their persistence among these patients. Fernandez et al. showed that cardiac changes can persist for >6 months and are present even 12 months post-COVID-19.[11] We also identified an increased volume of the left atrium at 6 months in the case of male patients with moderate forms of the disease.

Changes in the left atrium were also identified in other studies, such as the one conducted by ZeinElabdeen et al.[29] They observed impaired left atrium parameters (left atrium reservoir strain and left atrium stiffness) in the case of patients who developed dyspnoea and exercise intolerance as long COVID-19 symptoms. It is important to mention that before the infection with SARS-Cov-2, these patients did not present these symptoms.[29]

Figure 3: Pulse Wave Velocity and Pulse Wave Velocity:Global Longitudinal Strain Ratio at Baseline and at 6 Months in Mild and Moderate COVID-19



GLS = global longitudinal strain; NS = not significant; PWVAo = aortic pulse wave velocity.

Table 2: Right Ventricle Systolic Function at Baseline and at 6 Months

Right Ventricle Function	Global				Men				Women				
	Global	Mild	Medium	p	Global	Mild	Medium	p Mild–Medium Men	Global	Mild	Medium	p Mild–Medium Women	p Global Men and Women
RA-RV Gradient (mmHg)													
Baseline	21.5 (18–27.62)	20 (18–25)	22 (16–27.25)	0.77	21 (15.75–25)	20.5 (17.5–25)	22 (15–26.8)	0.82	20.5 (18–26)	20 (18-25)	22 (18–27.31)	0.71	0.74
6 months	25 (17.75–29)	18 (15–29)	26 (22–29.7)	**0.07**	25 (17.25–29.75)	20.5 (15–27)	28 (23.7–34.7)	**0.09**	23 (17–29)	18 (12–29)	25.5 (22–28.5)	0.21	0.53
p-value	NS	NS	**0.02**		NS	NS	**0.07**		NS	NS	NS		
TAPSE (mm)													
Baseline	23 (22.3–25)	24 (22.75–26.25)	23.5 (21–24.8)	0.32	23 (20.75–24.5)	23.5 (21–27)	22 (20.5–24)	0.33	24 (23–26)	24 (23–26)	24.4 (23.5–25)	0.79	**0.02**
6 months	25 (23–27)	24 (22–25.75)	25 (23–27)	0.57	24 (23–26)	23.5 (22.5–24)	25 (23–30)	0.20	24 (22–26.75)	24 (22–26.75)	24 (21.5–26.5)	0.92	0.79
p-value	NS	NS	NS		NS	NS	**0.03**		NS	NS	NS		

Data are presented as median (interquartile range). RA-RV = right atrium-right ventricle; TAPSE = tricuspid annular plane systolic excursion.

Regarding clinical and subclinical left ventricular dysfunction, Cannata et al. followed the patients at 7 months via speckle tracking, and clinically at 21 months post-COVID-19. They identified a subclinical systolic dysfunction in 27% of patients who had normal 2D left ventricular ejection fraction values, and in 34% of all patients included in the study. In addition, left ventricular GLS values ≥–18 were associated with an increased risk of major adverse cardiovascular events. In addition, long COVID-19 was diagnosed in 44% of the patients included in the study at 7-month follow-up.[30]

VAC is defined as the relationship between ventricular and arterial elastance, indicating myocardial efficiency and haemodynamic status.[31] Thus, it is a critical parameter that reflects the interaction between the heart and the vascular system. It is an important prognostic marker, and studies show that patients with inadequate VAC have significantly higher mortality rates, emphasising the need for monitoring this parameter in critical care.[32] In our study, the VAC values were significantly altered in moderate forms of COVID-19.

A strength of this study is that it emphasises the long-term cardiovascular effects of COVID-19 through a comprehensive cardiovascular evaluation. The study's limitations are the small number of patients and the absence of a control group.

Conclusion

Post-COVID-19 patients present left ventricular dysfunction, especially subclinical (GLS versus FE). Regarding the diastolic dysfunction parameters, statistically significant differences exist in the volume of the left atrium at 6-month follow-up. The right ventricular dysfunction is statistically significant only in men. Subclinical forms of atherosclerosis develop early post-COVID-19, and manifest by an increase in the intima-media thickness, without affecting other arterial stiffness parameters (PWVAo). Additionally, ventricular–arterial coupling was significantly altered in moderate COVID-19 infection at the 6-month evaluation. Further research is needed to investigate whether these changes are permanent or transient. ❑

Clinical Perspective

- The study shows the cardiovascular long-term sequelae associated with COVID-19 after mild and moderate cases of COVID-19.
- The study proves the importance of screening for cardiovascular alterations in post-COVID-19 syndrome.
- The study emphasises the importance of follow-up of COVID-19 patients, even for periods >6 months, to monitor the evolution of cardiovascular changes over time.

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