

Cardiac Injury after COVID-19 and its Association with the Severity of the Acute Presentation, Persistent Symptoms and Vaccination

Injuria cardíaca post- COVID19 y su relación con la gravedad del cuadro agudo, los síntomas persistentes y la vacunación

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ABSTRACT

Background: COVID-19 is associated with cardiovascular involvement in the acute phase. The information about cardiac involvement after COVID-19 is heterogeneous, and the indication to routinely perform cardiac imaging tests is still controversial. There is no updated information on the effect mass vaccination has on the incidence of cardiac injury after COVID-19.

Objectives: The primary objective of this study was to evaluate the prevalence of cardiac injury after COVID-19 by transthoracic echocardiography and its association with the severity of the acute phase and with persistent symptoms after recovery. The secondary objective was to explore the association of the prevalence of cardiac injury with the beginning of the vaccination campaign against COVID-19 in Argentina.

Methods: We conducted an observational, single-center, and retrospective study. All the consecutive patients who consulted for post-COVID-19 evaluation were included. All the patients underwent transthoracic echocardiography. The date the vaccination campaign started (12/29/2020) was considered the cut-off point for the analysis of the pre-vaccination and post-vaccination subgroups.

Results: The first 1000 patients who consulted in our center between 09/01/2020 and 09/01/2021 were included. Thirty-nine patients (3.9%) had new abnormal echocardiographic findings suggestive of cardiac injury after COVID-19, including left ventricular dysfunction (2.8%), pericardial effusion (0.5%), and wall motion abnormalities (0.6%). Patients with moderate or severe acute COVID-19 presented a higher prevalence of wall motion abnormalities (2.9% versus 0.3%, $p = 0.001$) and pericardial effusion (2.9% versus 0.14%, $p = 0.001$) compared to those with asymptomatic or mild COVID-19 and this association remained after adjusting for cardiovascular risk factors and age (OR 6.7, 95% CI 1.05-4.2, $p = 0.04$, and OR 25.1, 95% CI 2.1-304.9, $p = 0.01$ respectively). The percentage of patients who reported persistent symptoms during consultation after COVID-19 was 19.3%, and they had higher evidence of new left ventricular dysfunction (8.3% vs. 2.4%, $p < 0.005$); however, this association lost significance on multivariate analysis. When the association of cardiac injury with the start of vaccination was considered, the 330 patients who underwent post-COVID assessment before the vaccination campaign started had a higher prevalence of injury than the 670 patients evaluated after this date (6.3% vs. 2.7%, $p = 0.006$), and this association persisted on multivariate analysis (OR 0.35; 95% CI 0.17-0.69).

Conclusion: The prevalence of cardiac injury assessed by echocardiography after COVID-19 was 3.9%. There was a significant and independent association between the severe initial presentations and the abnormal echocardiographic findings after COVID-19, but not with persistent symptoms. Patients who consulted after the vaccination campaign started in Argentina had a lower prevalence of cardiac injury compared with those patients in the first wave.

Key words: COVID-19, SARS-CoV-2, Post-acute COVID-19 syndrome, Myocarditis, Cardiomyopathy, Echocardiography, Vaccination

RESUMEN

Introducción: La infección por COVID-19 se asocia a compromiso cardiovascular en su etapa aguda. La información sobre el compromiso cardíaco post-COVID es muy heterogénea, y la indicación de realizar estudios de imágenes cardíacas de forma rutinaria es aún controvertida. Asimismo, no existe información actualizada sobre el efecto que produjo la vacunación masiva en la incidencia de la injuria cardíaca post-COVID.

Objetivos: Analizar la prevalencia de injuria cardíaca mediante ecocardiograma luego de la infección por COVID-19 y su asociación con la gravedad del cuadro agudo y con los síntomas persistentes post-COVID. Como objetivo secundario se exploró la relación de la prevalencia de injuria cardíaca con el inicio de la campaña de vacunación contra COVID-19 en la República Argentina.

Material y métodos: Estudio analítico, observacional, prospectivo y unicéntrico. Se incluyeron todos los pacientes consecutivos que consultaron para realizar evaluación post-COVID. Se realizó ecocardiograma transtorácico en todos los pacientes. Se consideró la fecha de inicio de la campaña de vacunación (29/12/2020) para el análisis de los subgrupos pre y post vacunación.

Resultados: Se incluyeron los primeros 1000 pacientes que consultaron al centro desde el 01/09/2020 al 01/09/2021. Treinta y nueve

REV ARGENT CARDIOL 2022;90:406-412. <http://dx.doi.org/10.7775/rac.v90.i6.20567>

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Received: 09/21/2022 – Accepted: 10/28/2022

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(3,9%) presentaron hallazgos patológicos en el ecocardiograma compatibles con injuria post-COVID, incluyendo disfunción ventricular izquierda (2,8%), derrame pericárdico (0,5%) y trastorno de motilidad parietal (0,6%), no conocidos previamente. Los pacientes que padecieron cuadros de COVID-19 agudo moderados o graves presentaron mayor prevalencia de trastornos de motilidad parietal (2,9% versus 0,3%, $p = 0,001$) y derrame pericárdico (2,9% versus 0,14%, $p = 0,001$) en comparación con aquellos con cuadros asintomáticos o leves, y esta asociación se mantuvo al ajustar por factores de riesgo cardiovascular y edad (OR 6,7; IC 95% 1,05-42,2, $p = 0,04$ y OR 25,1; IC 95% 2,1-304,9, $p = 0,01$ respectivamente). El 19,3% de los pacientes referían síntomas persistentes en la consulta post-COVID; en estos pacientes se observó mayor evidencia de disfunción ventricular izquierda nueva (8,3% vs 2,4%, $p < 0,005$); no obstante, dicha asociación perdió significancia en el análisis multivariado. Respecto a la relación de la injuria cardíaca con el inicio de la vacunación, los 330 pacientes que se realizaron estudios de control post-COVID previamente al inicio de la campaña presentaron mayor prevalencia de injuria que los 670 pacientes luego de esta fecha (6,3% vs 2,7%, $p = 0,006$). Esta relación se mantuvo en el análisis multivariado (OR 0,35; IC95% 0,17-0,69).

Conclusión: La prevalencia de injuria cardíaca evaluada mediante ecocardiograma luego de la infección por COVID-19 fue de 3,9%. Se observó una asociación significativa e independiente entre cuadros iniciales de mayor gravedad y hallazgos patológicos en el ecocardiograma en la etapa post-COVID, no así con los síntomas persistentes. Los pacientes que consultaron luego del inicio de la campaña de vacunación en Argentina presentaron menos prevalencia de injuria cardíaca en comparación con los pacientes de la primera ola.

Palabras clave: COVID-19/complicaciones - SARS-CoV-2 - Síndrome post-agudo COVID-19 - Miocarditis - Cardiomiopatía - Ecocardiografía - Vacunación - Vacunas para COVID-19

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), one of the seven members of the CoV family that infect humans, (1) has resulted in more than 6.4 million deaths to date, with about 586 million cases worldwide. (2) The clinical manifestations of COVID-19 range from mild respiratory symptoms to severe pulmonary and systemic involvement. (3) Cardiovascular risk factors, advanced age and preexisting conditions increase the risk of adverse disease progression, intensive care unit (ICU) admission and mortality. (4,5) Unlike other respiratory viral infections, convalescence from COVID-19 is associated with a high incidence of persistent symptoms or respiratory, cardiovascular or neurological sequelae, and sequelae in other organs. (6) Although the reported prevalence of post-COVID-19 syndrome, also known as long COVID, is highly variable, some publications reported up to 90% of persistent symptoms for up to 6 months after the acute infection. (7) Post-COVID-19 syndrome is defined by the CDC as "signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 4 weeks and are not explained by an alternative diagnosis". (8) Several studies have demonstrated that the virus can cause indirect and direct cardiovascular involvement, but the indirect mechanisms are not entirely clear. (9) In addition to cardiovascular complications in the acute stage, (10,11) there is a clearly higher incidence of cardiovascular injury during convalescence or after COVID-19. (12,13) For this reason, over the past two years post-COVID consultations have represented a very important part of outpatient care, requiring the cardiologist to become familiar with this new disease. In a study recently published, our working group demonstrated a prevalence of post-COVID cardiac injury of 4.8% in our setting. (14) Fortunately, a clear reduction in both mortality and ICU admissions has been observed since the start of mass vaccination against the SARS-CoV-2. (15,16) However, so far there

is very little information available in the literature on whether this reduction in severe events associated with vaccination has been accompanied by a reduction in the prevalence of cardiovascular injury and persistent symptoms in the post-COVID stage.

OBJECTIVES

The primary objective of this study was to evaluate the prevalence of cardiovascular injury by transthoracic echocardiography (TTE) in the convalescence phase of COVID-19 and its association with the severity of the acute phase and with persistent post-COVID symptoms. The secondary objective was to explore the association of such prevalence of cardiovascular injury with the beginning of the vaccination campaign against COVID-19 in Argentina.

METHODS

We conducted an analytical, observational, and prospective study in an outpatient center in the province of Buenos Aires, Argentina.

All the consecutive patients who consulted for post-COVID assessment at least 15 days after they had recovered from the acute illness were included in the study. Patients with another known or possible cause of heart disease, as ischemic cardiomyopathy, hypertrophic cardiomyopathy, restrictive or dilated cardiomyopathy, severe valvular heart disease, or any other relevant heart disease were excluded.

The assessment included medical history with information about cardiovascular risk factors, severity of the acute phase of COVID-19, and presence of persistent cardiac symptoms during the convalescence such as exercise-induced dyspnea, palpitations, chest discomfort or asthenia that had not previously been reported. All the patients underwent TTE, electrocardiogram (ECG) and laboratory tests. In patients with persistent symptoms or with abnormal findings in the complementary tests, biomarkers of myocardial injury and inflammation were measured, and other tests as 24-hour Holter monitoring, exercise stress test or cardiac magnetic resonance imaging (CMRI) with gadolinium-based contrast agent were performed according to the discretion of the treating physician.

Operative definitions

The diagnosis of COVID-19 was based on the case definition of the Ministry of Health of Argentina. (17)

The following new echocardiographic findings were considered consistent with post-COVID-19 cardiac injury: left ventricular ejection fraction (LVEF) \leq 52% in men or \leq 54% in women, wall motion abnormalities, or pericardial effusion.

Mild COVID-19 was considered in case of symptoms but no evidence of pneumonia. Moderate COVID-19 was defined as clinical and radiological evidence of pneumonia with or without need for admission to a general ward. Severe COVID-19 was considered in patients admitted to the ICU with or without need for mechanical ventilation (MV).

Finally, to analyze the association between the prevalence of echocardiographic findings and the possible effect of vaccination, the date the vaccination campaign started in Argentina (12/29/2020) was considered the cut-off point for the analysis of the pre-vaccination and post-vaccination subgroups.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (SD) and categorical variables as percentages and were compared using the Student's t test or Wilcoxon test, as applicable. Categorical variables were analyzed with the chi-square test or Fisher's exact test. \rightarrow

The association between the severity of COVID-19 and abnormal echocardiographic findings was assessed with multivariate analysis, adjusting for clinical variables that showed significant differences in the univariate analysis. Patients were divided into two groups: asymptomatic or mild COVID-19, and moderate and severe COVID-19. Multivariate analysis was not performed to analyze the association between persistent symptoms and echocardiographic findings, since there were no significant differences in the echocardiographic variables of interest in univariate analysis. \rightarrow

The prevalence of the echocardiographic findings before and after vaccination against COVID-19 started was also compared by multivariate analysis with adjustment for the significant clinical variables detected on univariate analysis.

A two-tailed P value $<$ 0.05 was considered statistically significant. All the statistical calculations were performed using STATA 13 software package (Stata Corp, College Station, TX).

Ethical considerations

The study protocol was reviewed and approved by the Committee on Ethics of our institution. The investigation was conducted following the recommendations of the Declaration of Helsinki. All the patients gave their informed consent before participating in the study and anonymity was ensured.

RESULTS

We included the first 1000 patients who consulted our healthcare center from 09/01/2020 to 09/01/2021 for post-COVID evaluation. Mean age was 42 ± 13.9 years and 48% were men. The median time between diagnosis of COVID-19 and consultation was 62 days (range 16-330 days). The characteristics of the study population are described in Table 1. Of the 1000 patients, 3.1% had asymptomatic acute COVID-19, 80.2% had mild disease, 14.8% moderate disease, and 1.8% severe disease, and requirement of MV was 0.3%.

Thirty-nine patients (3.9%) had new abnormal TTE findings suggestive of post-COVID injury, including left ventricular dysfunction (2.8%), pericardial effusion (0.5%), and wall motility abnormalities (0.6%). Patients with moderate or severe acute COVID-19 presented a higher prevalence of wall motion abnormalities (2.9% versus 0.3%, $p=0.001$) and pericardial effusion (2.9% versus 0.14%, $p = 0.001$) compared to those with asymptomatic or mild COVID-19 (Figure 1). This association remained on multivariate analysis after adjusting for risk factors (diabetes, dyslipidemia, hypertension and body mass index) and age (OR 6.7, 95% CI 1.05-4.2, $p = 0.04$ and OR 25.1, 95% 2.1-304.9, $p = 0.01$, respectively). The most relevant clinical and echocardiographic data of each group are described in Table 2.

Persistent symptoms were reported by 19.3% of patients at the time of post-COVID assessment, palpitations by 4.2%, dyspnea by 9.3%, asthenia by 10.8% and chest discomfort by 2.7%. Patients with persistent post-COVID symptoms had higher evidence of left ventricular dysfunction (8.3% vs. 2.4%, $p < 0.005$) (Figure 1); however, this association lost significance on multivariate analysis.

Finally, when the association of cardiac injury with the start of vaccination was considered, the 330 patients who underwent post-COVID assessment before the vaccination campaign started had a higher prevalence of abnormal echocardiographic findings than the 670 patients evaluated after this date (6.3% vs. 2.7%, $p = 0.006$). This relationship persisted on multivariate analysis (OR 0.35; 95% CI 0.17-0.69) adjusted for age, sex, and cardiovascular risk factors (Figure 2).

Table 1. Baseline characteristics of the population

	N = 1000
Age, years, mean (SD)	42.02 (13.9)
Male gender (%)	48.1
BMI, kg/m ² mean (SD)	26.2 (5)
Total cholesterol, mg/dL, mean (SD)	194 (38.1)
LDL-cholesterol, mg/dL, mean (SD)	116 (33.1)
HDL-cholesterol, mg/dL, mean (SD)	54 (14.7)
Systolic BP, mm Hg, mean (SD)	121 (14.9)
Diastolic BP, mm Hg, mean (SD)	73 (9.5)
Hypertension (%)	18.7
Diabetes (%)	5.3
Dyslipidemia (%)	21.1
Current smoker (%)	6.7
Former smoker (%)	10.3
Obesity (BMI > 30) (%)	16.8
Use of ACEI/ARB (%)	10
Use of aspirin (%)	2.8

ARB: angiotensin II receptor blocker; SD: standard deviation. ACEI: Angiotensin-converting enzyme inhibitor; BMI: body mass index; BP: Blood pressure

DISCUSSION

Cardiac cellular tropism of SARS-CoV-2 has been widely demonstrated. (9-12,18,19) The most common mechanisms are direct virus-mediated cytotoxicity, down-regulation of ACE2 receptors, hypercoagulability, endothelial damage and immune-mediated inflammation, which may result in heart failure, myocarditis, pericarditis, myocardial infarction secondary to thrombosis or hypoxia, autonomic dysfunction, and arrhythmias, among others. (20,21) These cardiovascular manifestations may occur in the acute phase of the disease or during convalescence. Although the mechanisms and risk factors for cardiovascular involvement during the acute phase have been better studied, it

is still not clear which patients are at greatest risk of developing cardiac injury during convalescence and require further evaluation. The initial studies possibly demonstrated an overestimated incidence of cardiovascular involvement after COVID-19, and some studies using CMRI revealed cardiac involvement in up to 78% of patients. (22) These initial results were questioned after more than two years of experience and a clearly lower prevalence in daily practice. More recent studies, as the systematic review by Barssoum et al., have shown a much lower prevalence of abnormal findings, around 3 to 5% including other diagnoses other than myocarditis. (23) These results are similar to those found by our group, both in the first

Table 2. Clinical and echocardiographic findings according to the severity of acute COVID-19

	Asymptomatic-mild COVID-19 (n = 804)	Moderate-severe COVID-19 (n = 196)	p value
Age, years, mean (SD)	40.1 (13.7)	47.9 (13.9)	<0.001
Male gender (%)	53	46	0.13
BMI, mean (SD)	25.8 (4.8)	28.7 (5.4)	<0.001
Hypertension (%)	15.4	34.4	<0.001
Current smoker (%)	7.1	3.7	0.3
Diabetes (%)	4.3	11.7	0.001
Dyslipidemia (%)	18.4	35	<0.001
ECHOCARDIOGRAPHIC DATA			
LVDD, mm, mean (SD)	46.0 (4.8)	46.4 (4.7)	0.370
LVSD, mm, mean (SD)	27.8 (4.5)	27.6 (4.9)	0.621
Fractional shortening, mean (SD)	0.40 (0.07)	0.41 (0.08)	0.131
Interventricular septum, mm, mean (SD)	9.0 (1.6)	10.0 (1.8)	<0.005
Posterior wall, mm, mean (SD)	8.2 (1.3)	8.6 (1.3)	0.002
Left atrial area, cm ² , mean (SD)	16.8 (3.3)	17.8 (3.2)	<0.005
LV ejection fraction, %, mean (SD)	63.9 (5.4)	64.0 (6.5)	0.826
Mitral E-wave, m/s, mean (SD)	0.81 (0.19)	0.71 (0.20)	<0.005
Mitral A-wave, m/s, mean (SD)	0.59 (0.16)	0.69 (0.19)	<0.005
Septal S', cm/s, mean (SD)	9.8 (2.3)	9.5 (1.5)	0.387
Septal e', cm/s, mean (SD)	12.4 (3.7)	10.8 (2.9)	<0.005
Septal a', cm/s, mean (SD)	9.2 (2.8)	10.0 (2.7)	0.064
Lateral S', cm/s, mean (SD)	11.8 (2.9)	12.1 (2.6)	0.534
Anterior S', cm/s, mean (SD)	10.7 (2.2)	11.9 (2.6)	0.021
Inferior S', cm/s, mean (SD)	9.8 (1.8)	10.6 (1.7)	0.075
E/e' ratio, mean (SD)	7.2 (2.3)	7.0 (2.5)	0.561
RV S', cm/s, mean (SD)	14.4 (3.0)	14.5 (2.8)	0.761
TAPSE, mm, mean (SD)	25.5 (3.7)	24.6 (3.9)	0.131
LVDD, mm, mean (SD)	24.1 (5.2)	24.1 (3.8)	0.964
Systolic blood pressure, mm Hg, mean (SD)	21.2 (5.3)	23.3 (5.0)	0.006
RV Tei index, mean (SD)	0.41 (0.06)	0.48 (0.04)	0.055
RV FAC, mean (SD)	0.48 (0.06)	0.47 (0.06)	0.501
Aortic regurgitation, %, (n)	5.3 (42)	8.6 (16)	0.238
Mitral regurgitation, %, (n)	32.6 (262)	41.7 (81)	0.173
LV diastolic dysfunction, % (n)	4.08 (28)	6.5 (9)	0.202
Pericardial effusion, % (n)	0.14 (1)	2.9 (4)	0.001
LV systolic dysfunction, % (n)	3.2 (22)	4.3 (6)	0.494
Wall motion abnormalities, % (n)	0.3 (2)	2.9 (4)	0.001

DD = diastolic dimension; SD = systolic dimension; FAC= fractional area change; BMI = body mass index; TAPSE = tricuspid annulus plane systolic excursion; RV = right ventricular; LV = left ventricular

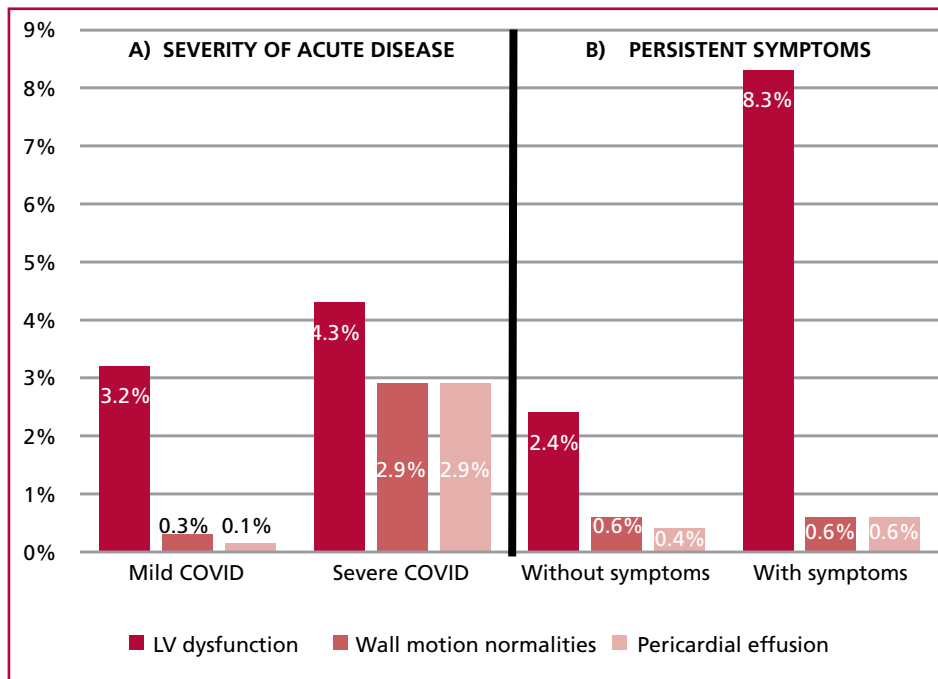


Fig. 1. Prevalence of echocardiographic findings of cardiac injury. A) Related to the severity of the acute disease. B) Related to persistent post-COVID-19 symptoms

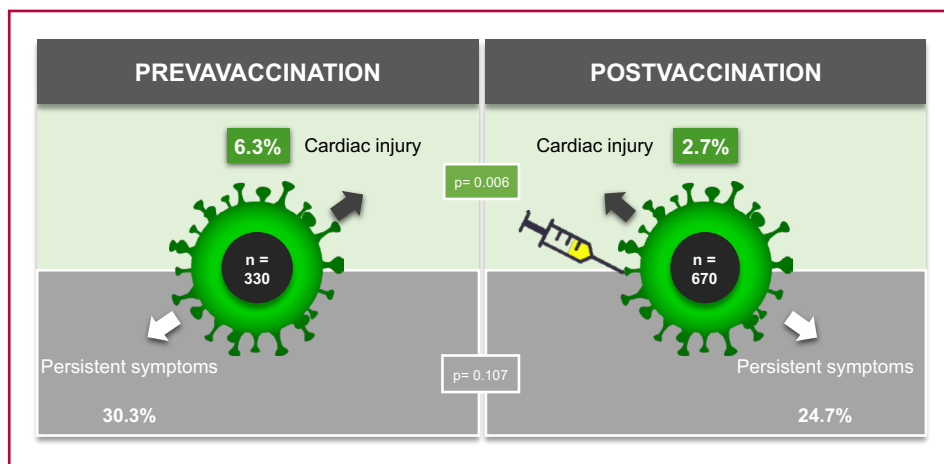


Fig. 2. Association between findings of cardiac injury and persistent symptoms with the beginning of the vaccination campaign

study before the vaccination campaign started (4.8% of cardiac injury) (14) and in this study, where 3.9% of patients presented findings suggestive of cardiac injury, particularly in patients with more severe acute COVID-19, independently of their baseline characteristics and cardiovascular risk.

Although 19.3% of patients reported persistent symptoms at the time of post-COVID assessment, these symptoms were not associated with evidence of injury on multivariate analysis. This is one of the main difficulties when evaluating a patient in the clinic, since there is no clear association between the clinical and abnormal findings in imaging tests. The definition of post-COVID-19 syndrome precisely refers to persistent symptoms independently of evidence of organ injury. (8) The mechanisms responsible for prolonged recovery in some patients are unknown,

but this is not necessarily associated with the severity of the initial symptoms but mainly with patients' cardiovascular risk factors, sex and age, among others. (24,25) This is consistent with the findings of our study, in which despite 83% of the initial COVID cases were asymptomatic or mild, a high percentage of patients reported persistent symptoms. Some mechanisms hypothesized are viral persistence due to weak immune activation, relapse or reinfection, inflammatory and immune reactions, deconditioning, and post-traumatic stress disorder. (24)

Most published studies that evaluated post-COVID patients with TTE considered the acute stage of the disease or follow-up of critically ill patients after hospital discharge. In this context, there is an urgent need for a large-scale study to routinely evaluate post-COVID patients with no selection bias using TTE, a

tool more readily available and less expensive in clinical practice than CMRI. (26) Although the sensitivity of TTE is lower, one publication reported that abnormal TTE is one of the best tools to predict cardiac involvement in CMRI, with an OR of 37. (27) In our study, TTE identified those patients requiring further investigation and who need greater care before resuming intense physical activity in the context of a disease with a high rate of persistent symptoms.

Nevertheless, although scientific societies still recommend clinical evaluation, electrocardiogram and echocardiogram in post-COVID patients visiting the outpatient clinic, (28,29) the need for routine imaging tests is debated nowadays. This discussion is largely due to an apparent reduction in the prevalence of cardiac involvement in recent months driven by vaccination, emergence of less virulent strains, and development of natural immunity. In our study, patients undergoing post-COVID assessment before the vaccination campaign started had a higher prevalence of echocardiographic involvement compared with patients after this date, and this association was independent of other baseline characteristics. A recent systematic review demonstrated a positive association between vaccination and reduction in the prevalence of post-COVID symptoms, despite great heterogeneity. (30) However, other studies did not find any association and even reported that vaccination increased the symptoms. (31,32) On the other hand, a large-scale multicenter retrospective study concluded that vaccination for COVID-19 results in a reduction of "new cardiovascular events", that is any type of cardiovascular condition as infarction or hypertension, and diabetes and thyroid disease. (33). To our understanding, there has not been yet any study directly associating vaccination with a reduction in the incidence of cardiac injury on imaging tests, which, as we have previously pointed out, is not strictly related to the presence of symptoms. Finally, there is even some evidence of myocarditis secondary to vaccination in the real world, although this was not an adverse event reported in the pivotal randomized studies involving the respective vaccines. (34-37). Large-scale studies have already demonstrated that the incidence of myocarditis and pericarditis secondary to COVID-19 is higher than that secondary to vaccination (38), thus the benefits of vaccination far outweigh the risks.

This is the first study in our environment evaluating the association of cardiac injury post-COVID-19 in the outpatient setting with the severity of the acute presentation, persistent symptoms, and vaccination, using echocardiography.

Study limitations

Our study has some limitations. Firstly, the observational design is associated with biases and confounder factors. Secondly, because of the socioeconomic characteristics of the population that usually attends our center, these patients could have better control of

their health status, which could have contributed to select a healthier population.

Finally, although we chose the date the vaccination campaign started in Argentina as the cut-off point for comparing the pre- and post-vaccination groups to avoid including vaccinated patients with at least one dose in the unvaccinated group, probably many patients in the vaccinated group lacked complete vaccination schedule at the time of the study. Also, although the number is very low, some patients enrolled in vaccine research protocols who received a dose before the national campaign began, could be erroneously included in the unvaccinated group.

CONCLUSIONS

The prevalence of cardiac injury assessed by echocardiography after COVID-19 was 3.9%. There was a significant association between the initial severe presentations and findings suggestive of injury, but not with persistent post-COVID-19 symptoms. Patients who consulted after the vaccination campaign started had a lower prevalence of cardiac injury compared with those patients in the first wave before vaccination. This may suggest that routine echocardiography after COVID-19 is the best way to monitor these patients to detect cardiac involvement irrespective of symptoms, particularly in those with more severe acute illnesses and who have not been vaccinated.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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