

# Cardiovascular Involvement in Patients Recovered from COVID-19: Reality or Fantasy?

*Compromiso cardiovascular en pacientes recuperados de COVID-19: ¿realidad o fantasía?*

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## ABSTRACT

**Background:** COVID-19 infection has been associated with cardiovascular complications in 7-28% of hospitalized patients, with the diagnosis based on biomarkers elevation. Subclinical cardiac involvement in outpatients recovered from COVID-19 represents a growing concern, as well as mid- or long-term cardiovascular effects.

**Objective:** The aim of the present study was to determine the usefulness of detecting cardiovascular involvement in outpatients recovered from COVID-19, and its association with symptoms and risk factors.

**Methods:** Between September 2020 and March 2021, 668 patients >18 years were prospectively included. All the patients had to have COVID-19 confirmed diagnosis by a positive reverse transcription-polymerase chain reaction (RT-PCR) test in a respiratory tract sample COVID-19. They were evaluated with physical examination, electrocardiogram (ECG) and Doppler echocardiography. Patients with symptoms suggestive of risk or abnormal findings on ECG or echocardiogram underwent cardiac magnetic resonance imaging (CMRI) with gadolinium-based contrast agent.

**Results:** Mean age was  $42.9 \pm 14.9$  years and 56.9% were women; 12.9% were hypertensive, 4.3% were diabetic and 6.9% obese. Overall, 57.6% had no cardiovascular risk factors and only 4.2% had a history of cardiovascular disease. The disease was mild in 73.2%; 16.3% required hospitalization and 1.05% needed mechanical ventilation. Only 5 patients had myocarditis diagnosed by CMRI, and both pericardial effusion and abnormal repolarization were significantly associated with myocarditis ( $p < 0.0001$ ).

**Conclusions:** Abnormal ECG or echocardiographic findings were uncommon in our cohort. The diagnosis of viral myocarditis was made in 5 cases with clinical signs and symptoms, and was confirmed by CMRI.

**Key words:** Coronavirus Infections/complications – Cardiovascular Diseases – Risk Factors

## RESUMEN

**Introducción:** Se ha descrito que la infección por COVID-19 se asocia a complicaciones cardiovasculares en pacientes hospitalizados en 7-28% de los casos, con diagnóstico basado en elevación de biomarcadores. La afección cardíaca subclínica post COVID-19 en pacientes ambulatorios representa una preocupación creciente, así como las secuelas cardiovasculares a mediano y largo plazo. El objetivo del presente trabajo fue determinar la utilidad de la detección de compromiso cardiovascular en pacientes post COVID-19 ambulatorios, y su asociación con síntomas y factores de riesgo.

**Material y métodos:** Se incluyeron 668 pacientes de manera prospectiva, >18 años entre septiembre de 2020 y marzo de 2021. Debían tener polimerasa de transcriptasa inversa (PCR) positiva en una muestra del tracto respiratorio positiva para COVID-19, y se les realizó evaluación con examen físico, electrocardiograma (ECG) y eco Doppler cardíaco. A quienes presentaban síntomas de riesgo o anomalías en el ECG o el eco Doppler, se les solicitó resonancia cardíaca (RMC) con contraste endovenoso.

**Resultados:** La edad media fue de  $42,9 \pm 14,9$  años; el 56,9% fueron mujeres. El 12,9% eran hipertensos, el 4,3% diabéticos y el 6,9% obesos. El 57,6% no tenía factores de riesgo cardiovascular y solo el 4,2% contaba con antecedentes cardiovasculares. El 73,2% presentó enfermedad leve, un 16,3% requirió internación y el 1,05% asistencia ventilatoria mecánica. Solo 5 pacientes tuvieron diagnóstico por RMC de miocarditis, y tanto el derrame pericárdico como la presencia de trastornos de la repolarización se asociaron significativamente con la misma ( $p < 0,0001$ ).

**Conclusiones:** La presencia de alteraciones en el ECG o el eco Doppler cardíaco en nuestra cohorte fue infrecuente. Se diagnosticaron 5 casos de miocarditis viral con clínica compatible y confirmación por RMC.

**Palabras clave:** xx

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has affected millions of people since its onset by the end of 2019. COVID-19 has been associated with several direct and indirect cardiovascular complications, and some studies have reported that between 7-28% of the patients hospitalized had acute myocardial injury. (1-3)

The etiology of this myocardial injury is not entirely clear but could be related with microvascular damage, myocarditis, hypoxemia, cytokine-mediated tissue damage or even stress cardiomyopathy. (3,4) The diagnosis of myocardial injury was mostly based on biomarker elevation, without the use of cardiac imaging tests. (1, 3)

Arrhythmias and conduction disorders have been reported in patients with COVID-19. Arrhythmias are not an uncommon manifestation of infections, and could be related with viral involvement of the cardiac conduction system. (5,6)

Transthoracic echocardiography (TTE) is a useful tool for the evaluation of these patients since it provides complete information about the heart structure in a short time and can be performed either in patients hospitalized or outpatients. Likewise, the electrocardiogram (ECG) can provide relevant information in patients with suspected arrhythmias, myocarditis, or myocardial injury, which have been reported in association with COVID-19. (4,5-7)

As our understanding of COVID-19-related complications evolves, subclinical heart disease, as myocarditis, pericarditis, and right ventricular dysfunction in the absence of significant clinical symptoms, represents a growing concern. (8) There is little information about the cardiovascular involvement in outpatients recovered from COVID-19 and the possibility of mid- or long-term cardiovascular effects. In turn, the prevalence of cardiovascular complications after the acute infection is unknown. As a result of the large number of patients affected by this disease, it is important to know the association between COVID-19 and cardiovascular abnormalities after the infection. Although the potential implications of these findings in the general population are important, they become particularly relevant in athletes because during the acute phase of viral myocarditis exercise can exacerbate the myocardial injury and trigger malignant ventricular arrhythmias. (5,9) The role of multimodality imaging for the detection and clinical assessment of patients recovered from COVID-19 has been scarcely evaluated.

The aim of this study was to determine the usefulness of a comprehensive cardiovascular evaluation for detecting cardiovascular involvement in patients recovered from COVID-19. We sought to determine the prevalence of abnormal findings in the electrocardiogram, echocardiogram, and cardiac magnetic resonance imaging (CMRI) in patients recovered from COVID-19 and its association with the symptoms and risk factors described for an adverse outcome.

## METHODS

We prospectively included 668 consecutive patients  $\geq$  18 years who voluntarily attended the post-COVID-19 cardiology clinic at our institution between September 2020 and March 2021.

To be included, all the patients should give informed consent and present a diagnosis of COVID-19 infection confirmed by a positive reverse transcription-polymerase chain reaction (RT-PCR) test in a respiratory tract sample. (10) During the acute phase, 72% of the patients underwent a computed tomography scan of the thorax without contrast media.

Upon giving informed consent, a systematic cardiology evaluation was performed for the purposes of this study which included history taking, physical examination, 12-lead ECG and complete Doppler echocardiography.

Demographic data, comorbidities, usual medication, and physical examination and laboratory findings (including troponin-I levels) were analyzed. Hypertension was defined if the patient was receiving antihypertensive treatment or as systolic blood pressure  $\geq$  140 mm Hg or diastolic blood pressure  $\geq$  90 mm Hg; diabetes was defined based on the patients' previous diagnosis, or use of insulin or oral hypoglycemic agent; smoking was defined as tobacco use in the last 30 days; and dyslipidemia was defined as the use of oral lipid-lowering agents without a history of known cardiovascular disease or based on a previous diagnosis. The symptoms analyzed included dyspnea (according to the New York Heart Association classification), palpitations, angina, or syncope. Body surface area (BSA) was calculated using the DuBois method ( $m^2 = 0.007184 \times \text{height (cm)}^0.725 \times \text{weight (Kg)}^0.425$ ). (11)

Patients with high-risk symptoms or with abnormal findings on echocardiogram or ECG underwent CMRI with gadolinium-based contrast agent.

Data supporting the findings of this study are available upon reasonable request.

### Echocardiography

All the patients underwent complete and conventional transthoracic color-Doppler echocardiography using a Vivid S5 ultrasound machine with 2-4 MHz transducer (GE® Vingmed Ultrasound, Israel and Vivid T8, GE® Medical Systems, China). The procedures were performed by a team made up of 5 cardiologists specialized in echocardiography (Level III).

The routine echocardiographic variables [left ventricular dimension, left ventricular ejection fraction (LVEF), left atrial volume, aortic velocity and left ventricular outflow tract velocity, and pulmonary systolic pressure estimation] were measured in all the patients. Left ventricular mass index, relative wall thickness, left atrial volume indexed by CS, and E/A ratio were calculated. The presence of segmental wall motion abnormalities, coronary or non-coronary distribution pattern, and pericardial effusion were also evaluated. The images were recorded in DICOM format for off-line auditing by 2 experienced cardiologists (MCC and PS), masked to previous measurements and patient data.

### Statistical analysis

Continuous variables were expressed as mean  $\pm$  standard deviation or median and interquartile range (IQR), as appropriate, and categorical variables as a percentage. Continuous variables were compared with the Student's t test (2 tails) or with the Mann-Whitney U test, depending on the distribution of the data. Categorical variables were analyzed with the chi-square test with Yates correction or Fisher's exact

test. The clinical and risk parameters underwent univariate analysis to predict the development of electrocardiographic and echocardiographic abnormalities during follow-up. Those variables with clinical relevance and statistical significance on univariate analysis underwent multivariate analysis. A *p* value < 0.05 was considered statistically significant.

#### Ethical considerations

The study protocol was approved by the Institutional Review Board. The investigation was conducted following the recommendations of the Declaration of Helsinki. All patients gave their informed consent before participating in the study.

#### RESULTS

A total of 668 patients were included. Mean age was  $42.9 \pm 14.9$  years and 380 (56.9%) were women. Hypertension was found in 12.9% (*n*=86) of the patients, diabetes in 4.3% (*n*=29) and obesity in 6.9% (*n*=46). The characteristics of the population are detailed in Table 1.

Cardiovascular risk factors were not present in 57.6% (*n*=385) of the patients and 31% (*n*=209) had at least one risk factor. The clinical presentation during the disease is shown in Figure 1. Only 4.2% (*n*=28) had a history of cardiovascular disease, and significant coronary artery disease was the most common (1.8%).

In most cases, the disease was mild (73.2%, 489 patients). Pneumonia was observed in 25.1% (*n*=168) of the patients and confirmed by computed tomography scan and clinical findings. Hospitalization was necessary in 16.3% (*n*=109) of the patients, with a median length of hospital stay of 6 days (IQR 1-75). Seven patients (1.05%) were admitted in the intensive care unit and required mechanical ventilation (MV). Patients with pneumonia were older (51.4 vs. 40.8 years, *p* < 0.0001), as well as those who required hospitalization (52.1 vs. 41.2 years, *p* < 0.0001) and intensive care/MV (53.2 vs. 42.8 years, *p* < 0.00001). Figure 2 shows the clinical course by age ranges. Pneumonia was more common in men (OR 1.81, 95% CI 1.27-2.58, *p* = 0.0008). Male sex was also associated with a higher rate of hospitalization (OR 1.7, 95% CI 1.2-2.4, *p* = 0.004) and an 8-fold increased risk of admission to intensive care unit/MV (OR 8.06, 95% CI 1.43-45.4, *p* = 0.02), after adjusting for age. Hospitalization was more common in obese patients, although this association was lost when age was considered (OR 1.6, 95% CI 0.86-3.13, *p* = 0.7).

During convalescence from COVID-19, 5.9% (*n*=40) of the patients presented persistent palpitations and 27.9% (*n*=187) persistent dyspnea (Table 2).

The ECG was normal in 92.8% (*n*=620) of the patients, 3.6% (*n*=24) had previous conduction disorders, 1.8% (*n*=12) presented arrhythmias, and 1.8% (*n*=12) had abnormal repolarization. The echocardiogram was normal in 85% (*n*=567). Five patients had new wall motion abnormalities and 3 patients presented pericardial effusion; 93 patients had other

**Table 1.** Demographic and clinical characteristics of COVID-19 patients (*n* = 668)

Characteristics	( <i>n</i> = %)
Women	380 (56.8%)
Age, mean (SD)	42.9 (14.9)
Risk factors	
Hypertension	86 (12.9%)
Diabetes	29 (4.3%)
Dyslipemia	130 (19.5%)
Smoking habit	64 (9.6%)
Obesity	46 (6.9%)
Previous cardiovascular disease	
Congenital heart defect	5 (0.75%)
Significant coronary artery disease	12 (1.8%)
Arrhythmias	7 (1.05%)
Signs and symptoms	
Fever	383 (57%)
Cough	326 (48.8%)
Asthenia	522 (78%)
Headache	302 (45%)
Anosmia/ageusia	357 (53.4%)
Diarrhea	63 (9.4%)
Pleuritic pain	17 (2.5%)
Disease severity	
Mild symptoms	489 (73.2%)
Pneumonia	168 (25.1%)
Hospitalization	109 (16.3%)
Days of hospitalization, mean (IQR)	6 (1-75)
MV	7 (1.05%)

D: standard deviation. IQR: interquartile range. MV: mechanical ventilation

findings not related with myocarditis. These findings are shown in Figure 3 and 4.

Twelve patients reported chest pain during the evaluation; 4 had abnormal ventricular repolarization, 1 had pericardial effusion, and in 4 the CMRI showed findings consistent with post-COVID-19-related myocarditis. In another patient CMRI was requested due to frequent arrhythmia and positive cardiac enzymes, and the diagnosis of myocarditis was confirmed. Abnormal repolarization on ECG and pericardial effusion on echocardiogram were significantly associated with myocarditis (*p* < 0.0001).

In conclusion, COVID-19-associated myocarditis was diagnosed in 5 outpatients during convalescence, was suspected by clinical findings, ECG, echocardiogram and/or enzymes, and confirmed by CMRI. The clinical course was mild in all the cases, without complications.

#### DISCUSSION

Our study presents one of the first and largest cohorts with analysis of the risk of cardiovascular involvement in patients recovered from COVID-19.

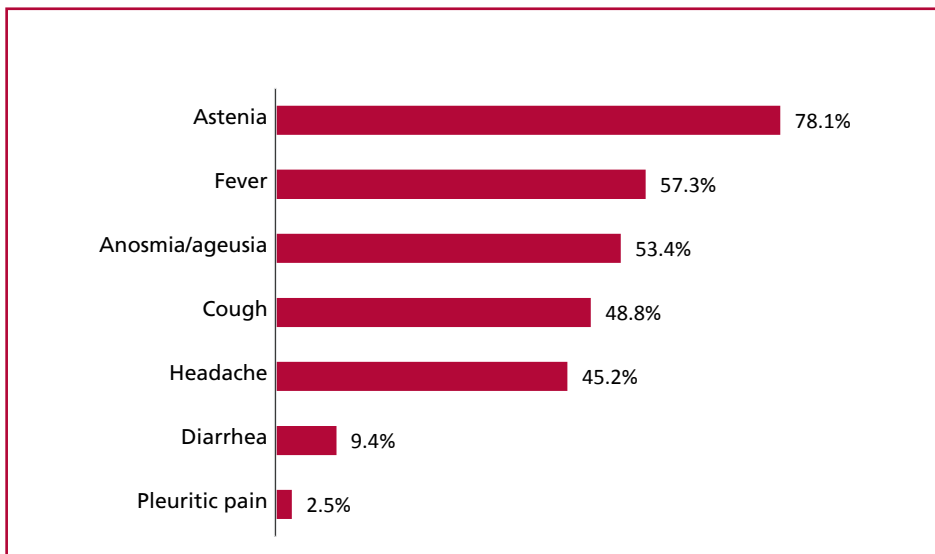


Fig. 1. Signs and symptoms.

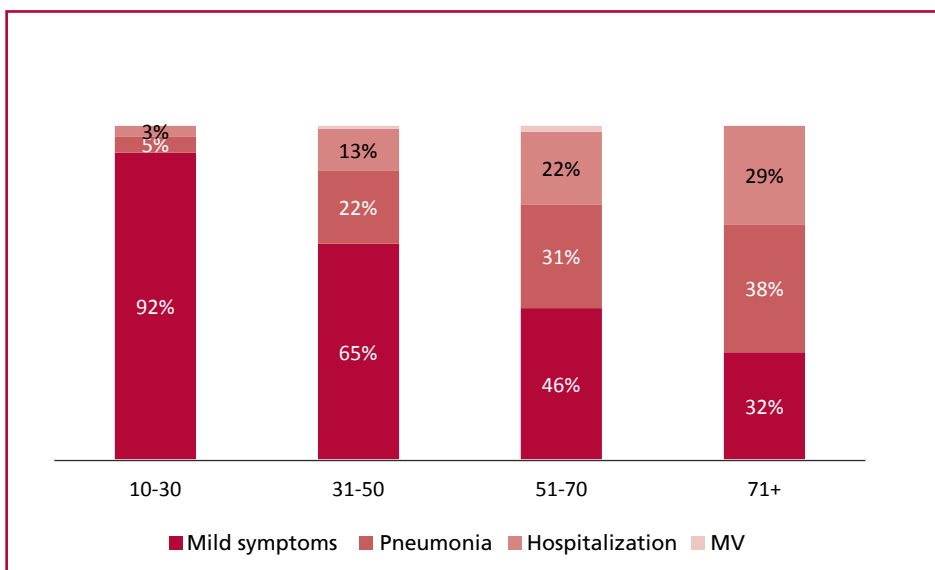


Fig. 2. Evolution of the clinical picture by age range.

MV: Mechanical ventilation

Table 2. Convalescence findings

Findings (n=668)	(n = %)
Symptoms during convalescence	
Palpitations	40 (5.9%)
Dyspnea	187 (27.9%)
Chest pain	12 (1.8%)
ECG findings	
Normal	617 (92.4%)
Previous conduction disorders	24 (3.6%)
Abnormal repolarization	12 (1.8%)
TTE findings	
Normal	567 (84.9%)
New wall motion abnormalities	5 (0.75%)
Pericardial effusion	3 (0.45%)

ECG: electrocardiogram. TTE: transthoracic echocardiography.

The relationship of acute COVID-19 infection with direct and indirect cardiovascular complications has been established. (1,7,8,12) In a retrospective study of 138 patients hospitalized in Wuhan, almost 17% of patients had arrhythmias and about 7% had acute myocardial injury. (12) However, the prevalence of cardiovascular complications after the infection has not been established.

Myocarditis is caused by many etiologies, including different infectious agents, drugs, systemic diseases and toxins, (4,5) with an estimated incidence of 22 per 100,000 persons. (13,14) Viral infections are the most important cause. (4,5,15)

In a review by Castiello et al. published in March 2021, the authors mentioned the difficulty of establishing the incidence of COVID-19-related myocarditis, since despite the analysis of the 38 cases reported

Fig. 3. ECG findings.

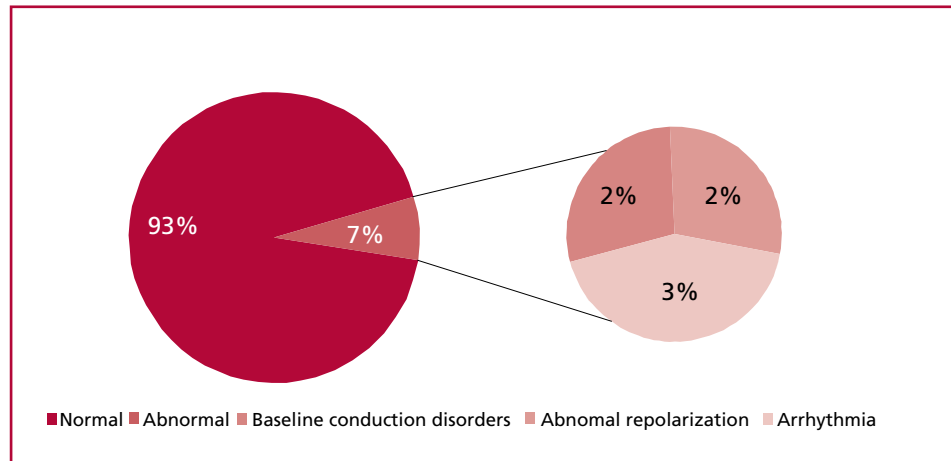
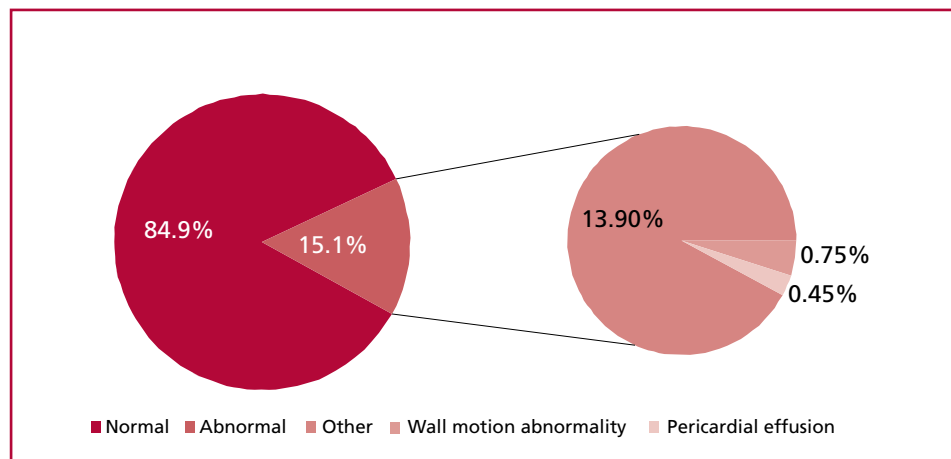


Fig. 4. Echocardiographic findings.



in the study, the true incidence is estimated to be higher. The low number of case reports and the difficult access to specific diagnostic methods such as biomarkers and CMRI are the main reasons for not achieving an accurate final diagnosis. (14,16)

Although the course of the disease is most often oligosymptomatic or asymptomatic, myocarditis is a frequent cause of arrhythmias and sudden death in the young population. (5, 9)

In our cohort of COVID-19 survivors, the parameters suggestive of myocarditis were rare and the diagnosis was made in less than 1% of cases. In all the cases the disease was suspected by the clinical characteristics of the patients and ECG, echocardiogram or biomarker findings, and was confirmed by CMRI. Abnormal repolarization on ECG and pericardial effusion on echocardiogram were significantly associated with myocarditis.

In 2021, Parodi et al. stated that, given the incidence of COVID-19 infection, it is necessary to perform a systematic evaluation of patients recovered from COVID-19 infection, and this should always include TTE as the main tool for the early detection of cardiovascular complications after the infection. (17)

The present study demonstrates the importance

of performing a comprehensive evaluation, including complete history taking, physical examination, ECG, TTE and laboratory tests in all the patients. Depending on the case, further evaluation with cardiac biomarkers should be performed to rule out the presence of predictors of myocarditis, and in such cases it is advisable to perform CMRI to confirm the diagnosis, based on the Lake Louise criteria. (18)

Although in some studies CMRI was systematically performed in patients recovered from COVID-19 with rates of myocardial injury close to 30%, its prognostic value could not be established. (19) These results could be explained by the frequent detection of mild fibrosis not related with ventricular dysfunction or wall motion abnormalities, and the presence of unspecific findings. (17,20)

The RACCOVID-19 registry showed a high incidence of cardiovascular complications (15.3%) in patients hospitalized for COVID-19, the most common being heart failure, myocardial injury determined by increased blood troponins, and atrial fibrillation. Patients with pre-existing diseases or cardiovascular risk factors were more likely to present complications, with higher levels of systemic inflammation markers. (21) However, this population is different from that

of our study, with cases of COVID-19 patients requiring hospitalization, older patients ( $57 \pm 18$  years) and higher prevalence of comorbidities.

In terms of cost-effectiveness of health resources in convalescent outpatients with COVID-19, we believe that the indication of more complex and expensive studies in selected patients should be guided by clinical suspicion.

In our series, myocarditis was mild in all the cases, with no impact on survival or new cardiovascular events in the short term. A priori, the presence of post-COVID-19 myocarditis does not represent an adverse prognosis, although long-term follow-up is required to make such a determination.

### Study limitations

This is a single-center study, with low event rate and short follow-up.

Moreover, in line with standard clinical practice, CMRI was not performed in asymptomatic patients or in those who had no abnormal findings in the complementary tests (due to cost-effectiveness reasons), so we ignore whether asymptomatic patients or patients with no other findings could have presented signs of myocarditis in the CMRI.

### CONCLUSIONS

In our cohort of COVID-19 survivors, abnormal findings on ECG or echocardiogram after viral infection were rare. Palpitations and dyspnea were the most frequent cardiovascular symptoms during convalescence. The diagnosis of viral myocarditis was made in 5 cases with clinical signs and symptoms and was confirmed by CMRI.

### Conflicts of interest

None declared.

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

### Sources of funding:

None.

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