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ORIGINAL PAPER

Vaccine–carditis study: Spanish multicenter registry of inflammatory heart disease after COVID-19 vaccination

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Abstract

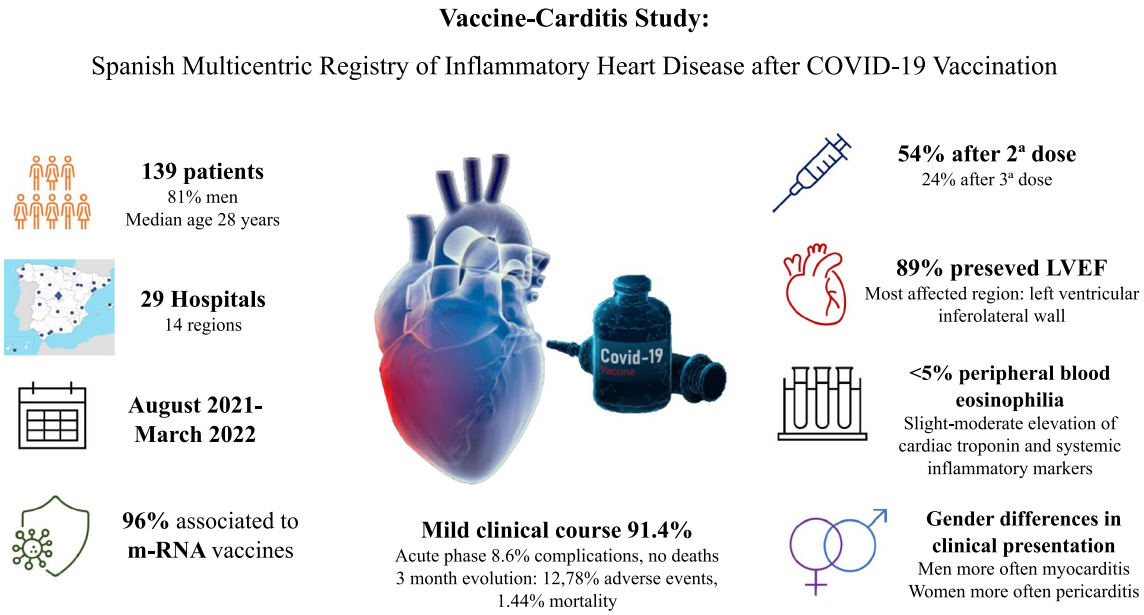
Introduction and objectives Vaccines against SARS-CoV-2 have been a major scientific and medical achievement in the control of the COVID-19 pandemic. However, very infrequent cases of inflammatory heart disease have been described as adverse events, leading to uncertainty in the scientific community and in the general population.

Methods The Vaccine–Carditis Registry has included all cases of myocarditis and pericarditis diagnosed within 30 days after COVID-19 vaccination since August 1, 2021 in 29 centers throughout the Spanish territory. The definitions of myocarditis (probable or confirmed) and pericarditis followed the consensus of the Centers for Disease Control and the Clinical Practice Guidelines of the European Society of Cardiology. A comprehensive analysis of clinical characteristics and 3-month evolution is presented.

Results From August 1, 2021, to March 10, 2022, 139 cases of myocarditis or pericarditis were recorded (81.3% male, median age 28 years). Most cases were detected in the 1st week after administration of an mRNA vaccine, the majority after the second dose. The most common presentation was mixed inflammatory disease (myocarditis and pericarditis). 11% had left ventricular systolic dysfunction, 4% had right ventricular systolic dysfunction, and 21% had pericardial effusion. In cardiac magnetic resonance studies, left ventricular inferolateral involvement was the most frequent pattern (58%). More than 90% of cases had a benign clinical course. After a 3-month follow-up, the incidence of adverse events was 12.78% (1.44% mortality).

Conclusions In our setting, inflammatory heart disease after vaccination against SARS-CoV-2 predominantly affects young men in the 1st week after the second dose of RNA-m vaccine and presents a favorable clinical course in most cases.

Graphical abstract



Keywords SARS-CoV-2: severe acute respiratory syndrome coronavirus 2 · mRNA: messenger ribonucleic acid · COVID-19: coronavirus disease 2019 · CMR: cardiac magnetic resonance · EMB: endomyocardial biopsy · ECG: electrocardiogram · LVEF: left ventricular ejection fraction

Introduction

Vaccines against SARS-CoV-2 have been a scientific and medical achievement in the control of the COVID-19 pandemic. Between 2021 and 2022, more than 95 million doses of these drugs were administered in Spain, reaching 92.8% of the population over 12 years of age vaccinated with at least two doses and 53.5% with the third booster dose [1]. Depending on their mechanism, there are several types of vaccines against COVID-19. Some of them (Vaxzevria/AZD1222 and JNJ-78436735/Ad26.COV2.S) transfer the deoxyribonucleic acid (DNA) encoding the spike protein of SARS-CoV-2 through an adenovirus vector. Other vaccines (BNT162b2/Comirnaty and mRNA-1273/Spikevax) consist of messenger ribonucleic acid (mRNA) strands encoding the SARS-CoV-2 spike protein delivered through a lipid nanoparticle capsule [2–8].

The vaccines approved by the Spanish and European health authorities were shown to reduce the severity of COVID-19 infection, as well as mortality, in their respective clinical trials published in 2020 [9–12]. Although no significant adverse cardiovascular events were observed in these studies, very rare cases of inflammatory heart disease (IHD) associated with the administration of this products were described during the population-based vaccination campaign, both in Spain and in other countries. This prompted the Centers for Disease Control and Prevention (CDC) to issue a statement on May 27, 2021, regarding a possible relationship between vaccination against SARS-CoV-2 and myocarditis, both for the BNT162b2 vaccine (Comirnaty) and for the mRNA-1273 vaccine (Spikevax) [13]. Subsequently, on June 2nd, 2021 the Israeli Ministry of Health reported for the first time 148 cases of myocarditis within 30 days of vaccination with mRNA-based vaccines, mostly in young patients after the second dose [14]. On July 19, 2021, the European Medicines Agency advised that both myocarditis and pericarditis should be added to the list of adverse effects of mRNA vaccines [15]. In December 2021, the Spanish Agecy of Medicines and Health Products published a statement regarding the risk of myocarditis and pericarditis associated with COVID-19 vaccines [16]. Since then, several series from different countries have been published, addressing this issue [17–23].

In a context of uncertainty about this adverse effect, the Vaccine–Carditis Registry was promoted as a national multicenter study with the aim of characterizing the clinical profile of inflammatory heart disease after vaccination against SARS-CoV-2 in our epidemiological setting, as well as evaluating the short- and long-term evolution. The aim of the present study is to describe the clinical picture and prognosis of patients diagnosed with myocarditis or pericarditis during the 1st month after the administration of any vaccine against SARS-CoV-2 and evaluate the occurrence of adverse events during a 3-month follow-up.

Methods

The Vaccine–Carditis Registry is a prospective multicenter observational study developed in 29 Spanish hospitals that consecutively included patients with inflammatory heart disease after vaccination against SARS-CoV-2 (Fig. 1). The study was initiated by a group of researchers and promoted by the Hospital Universitari Arnau de Vilanova (Lleida) and the IRB-Lleida (Institute for Biomedical Research Lleida), with the support of the Working Group on Myocarditis of the Spanish Society of Cardiology and the collaboration of the Spanish Agency of Medicines and Health Products. The registry was initiated in August 2021 and remains open as long as the vaccination campaign against COVID-19 continues. For the present work, a first cutoff was made in March 2022, when 39,845,453 people (85% of the population) had received two doses of vaccine and 24,114,643 people had received the booster dose (51% of the population). Currently, in addition to continuing the prospective inclusion of new patients, a medium- and long-term clinical follow-up is being performed.

This study adheres to the principles described in the Declaration of Helsinki. Approval was granted by the Ethics Committee for Research with Medicines of the Hospital Universitario Arnau de Vilanova de Lleida with registration CEIC-2546 on August 17, 2021. The patients included gave written consent.

Study population

Patients diagnosed with myocarditis, pericarditis, or both (mixed inflammatory heart disease) within 30 days after administration of any SARS-CoV-2 vaccine were prospectively included. Given the epidemiological circumstances, retrospective inclusion of those patients with a diagnosis prior to the incorporation of the corresponding center into the study was allowed. The only exclusion criterion was the patient's refusal to participate and/or to sign the informed consent form.

Myocarditis was classified as probable or confirmed according to the definitions of the Centers for Disease Control [24]. For the diagnosis of confirmed acute myocarditis, either histopathological confirmation (Dallas criteria [25]) or the combination of elevated markers of myocardial injury and consistent findings on cardiac magnetic resonance imaging (modified Lake Louise criteria [26]) were required. Pericarditis was defined on the basis of current European Society of Cardiology criteria [27]. The combination of both entities was classified as mixed inflammatory heart disease (MIHD). The detailed diagnostic criteria are shown in Fig. 2.

Characteristics assessed and data recording

Study data were collected and managed using REDCap electronic data capture tools hosted at the IRB-Lleida (Institute for Biomedical Research Lleida). Each participating center completed an anonymous, predefined electronic case report form (eCRF) developed by the investigators.

Baseline patient characteristics were recorded including sex, age, ethnicity and anthropometric data, history of confirmed infection by for SARS-CoV-2 (either with antigen testing or polymerase chain reaction), and the presence of any relevant clinical conditions. The date of administration of each dose of vaccine, the number of doses received, and the type of vaccine were recorded. The dates of onset of

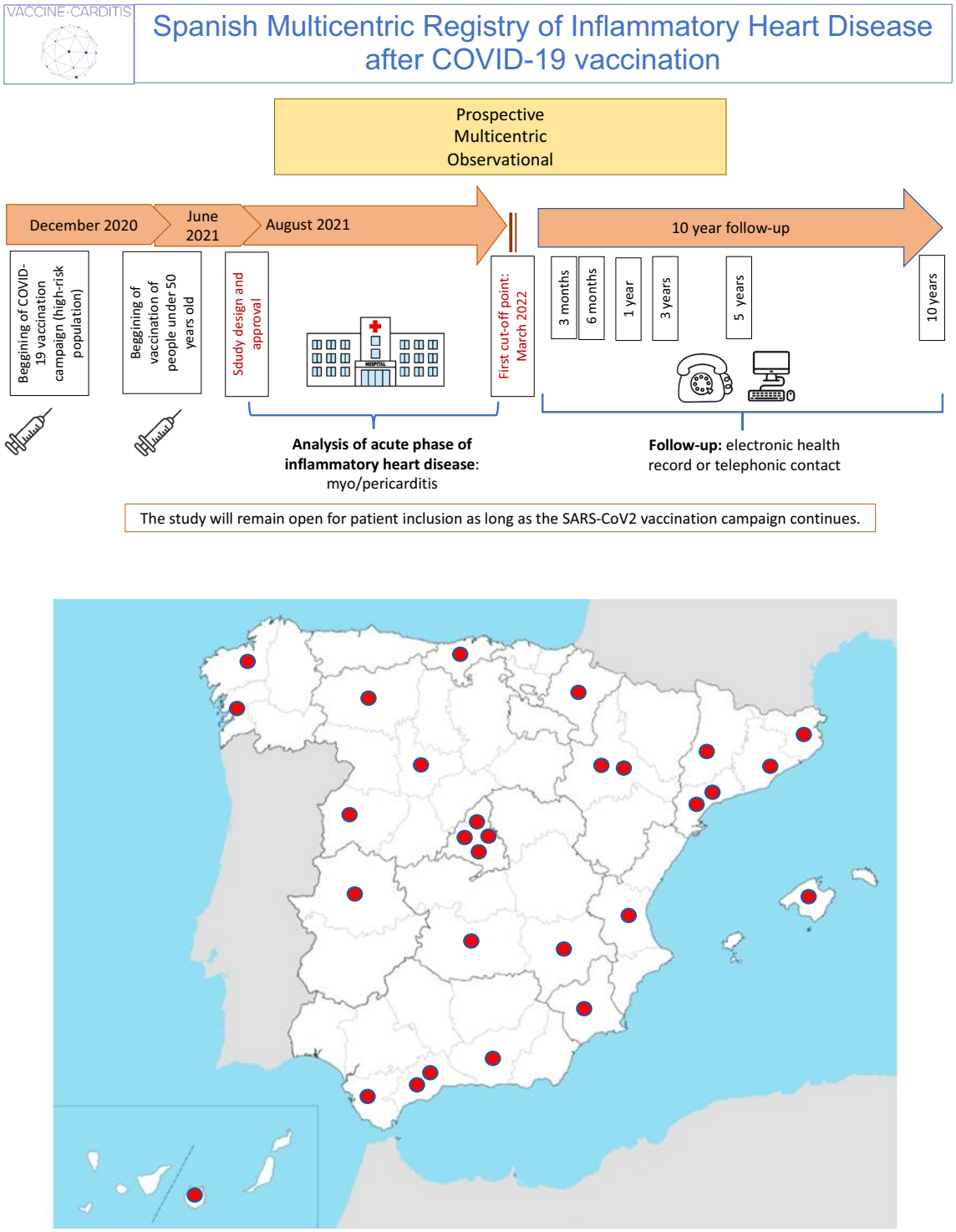


Fig. 1 Study design and geographic distribution of participating centers

symptoms and diagnosis, the form of clinical presentation, and the need for hospital admission were identified. The laboratory, electrocardiographic, echocardiographic, and cardiac magnetic resonance variables were recorded, as well as the treatment administered. In addition, a detailed analysis of those patients who suffered any serious complication during the acute phase of the disease was conducted, defining serious complications as the presence of any of the following events: mortality, acute heart failure, cardiogenic shock, severe pericardial effusion, sustained ventricular

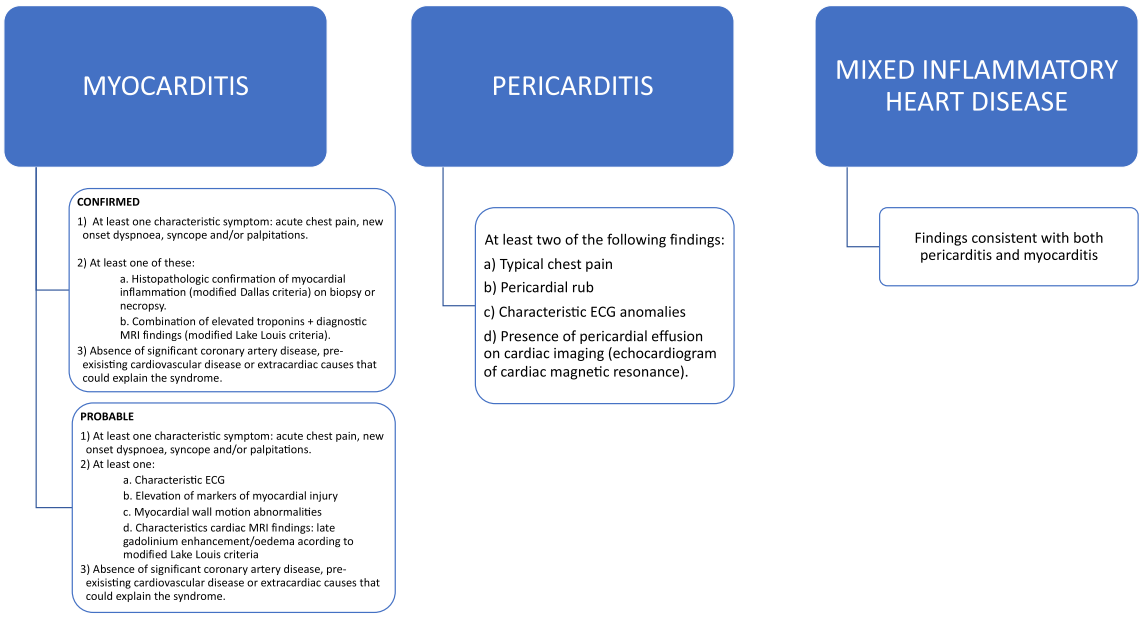


Fig. 2 Diagnostic criteria

arrhythmias, need for temporary or permanent cardiac pacing, cardiac transplantation, or the implantation of mechanic circulatory support devices. Finally, a subanalysis according to gender was designed to evaluate possible differences in disease presentation between men and women.

The following data were recorded at the 3-month follow-up: death (cardiovascular or not-cardiovascular cause), resuscitated cardiac arrest, heart failure (ambulatory, emergency room, or in-hospital management), need of pacemaker or implantable cardioverter–defibrillator (ICD), sustained ventricular tachycardia or appropriate ICD therapy, heart transplant or implantation of a ventricular assist device, recurrent myocarditis or pericarditis, incessant pericarditis or evolution to constrictive pericarditis.

Statistical analysis

Univariate analysis of both qualitative and quantitative variables was performed. Qualitative variables were described as frequency and percentage. Quantitative variables were defined as mean ± standard deviation in normal distributions, while the median and interquartile range were used in the case of non-normal distributions. For the comparison of variables according to gender, the χ^2 test or Fisher's exact test was used if the expected value of any of the cells was < 5. The Student's *t* test was used for quantitative variables, after checking normality using the Kolmogorov–Smirnov test. A value of $p < 0.05$ was considered statistically significant. The analysis was carried out with the Stata version 14 statistical program.

Results

Clinical characteristics

Up to March 2022, a total of 139 patients (18.7% women) were included. The temporal distribution of cases is shown in Fig. 3. The most frequent diagnosis was mixed inflammatory heart disease (42.4%), followed by isolated myocarditis (35.3%) and isolated pericarditis (22.3%). The median age

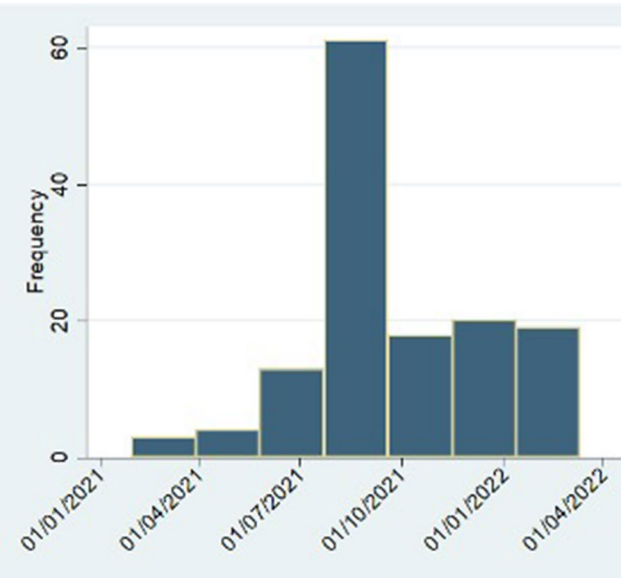


Fig. 3 Temporal distribution of cases

was 28 years (IQR 20–40). 15.1% had some relevant medical history: 6.5% previous myocarditis or pericarditis (none of them related to SARS-CoV-2), 2.2% other cardiovascular disease, 4.3% autoimmune disorder, and 2.2% immunosuppression. 10.3% had previously suffered SARS-CoV2 infection.

Type of vaccine and temporal relationship

55.4% of the cases were associated with Comirnaty vaccine (BNT162b2) and 41.0% with Spikevax vaccine (mRNA-1273), while only four cases (2.6%) were related to adenovirus-driven vaccines. The dose most frequently associated with disease was the second (54.0%), followed by the third (23.7%). The median time between the last dose and the onset of symptoms was 4 days. Baseline patient characteristics and vaccination data are shown in Table 1.

Diagnostic findings

73.4% of the cases showed elevated serum C-reactive protein (CRP), with a mean value of 13.35 g/mL (normal values 0.2–5 g/mL) and only 4.3% had eosinophilia in peripheral blood. Troponin levels were elevated in 76.3% of patients, the majority (56.6%) with values between 1 and 100 times the upper limit of normality. The most frequent electrocardiographic finding at diagnosis was ST-segment elevation (52.9%); however, 23.2% had a normal ECG. In patients with ventricular dysfunction (LVEF < 50%), the median NT-ProBNP value was 4644 pg/mL (RIQ 1548–10,195).

In cardiac imaging tests, 11.5% of patients developed left ventricular systolic dysfunction (defined as any LVEF less than 50%), 5.1% had right ventricular dysfunction, and pericardial effusion was observed in 21.0%. Eighty-nine patients (64.0%) underwent cardiac magnetic resonance (CMR) imaging during the acute phase of the disease, showing edema and late gadolinium enhancement (LGE) in the majority of cases (71.9% and 68.5%, respectively). Among patients with LGE, 90.3% had inferolateral and 35.5% anteroseptal involvement, with the following regional distribution: exclusive inferolateral involvement 58.1%, exclusive anteroseptal involvement 3.2%, mixed involvement (inferolateral and anteroseptal) 32.3%, and only apical involvement 4.8%. Figure 4 shows an example of cardiac magnetic resonance imaging.

Treatment

Most patients received nonsteroidal anti-inflammatory drugs and colchicine (73.4% and 66.9%, respectively). Four patients (2.9%) were treated with corticosteroids or other immunosuppressive therapy. 15.1% of patients received beta-blockers, 9.4% angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-II receptor blockers (ARB), 2.2% neprilysin inhibitors (ARNI), and 2.2% mineralocorticoid receptor antagonists (MRA). Among those who developed left ventricular dysfunction (LVEF < 50%), 43.8% were treated with ACEI/ARB, 18.8% with ARNI, 43.8% with beta-blockers, and 18.8% with MRA. Other data are shown in Table 2.

Table 1 Demographic and epidemiological characteristics of patients and vaccines

Basal characteristics of the patient population ($n = 139$)	
Female sex	26 (18.7%)
Age (years)	28 ± 20
Caucasian ethnicity	130 (95.6%)
Body mass index (kg/m^2)	24,2 ± 5,9
Medical background	21 (15.1%)
Previous myo/pericarditis	9 (6.5%)
Autoimmune disorder	6 (4.3%)
Immunosuppression	3 (2.2%)
Previous heart disease	3 (2.2%)
Prior COVID-19 infection	14 (10.3%)
SARS-CoV2 vaccination data ($n = 139$)	
Type of vaccine	
BNT162b2	77 (55.4%)
mRNA-1273	57 (41.0%)
AZD1222 (ChAdOx1)	1 (0.7%)
JNJ-78436735(Ad26.COV2.S)	3 (2.2%)
Unknown	1 (0.7%)
Dose related to the event	
First	31 (22.3%)
Second	75 (54.0%)
Third (booster)	33 (23.7%)

Clinical evolution and complications

81.1% of the patients required hospitalization, with a median length of stay of 5 ± 3 days. 127 patients (91.4%) had a mild clinical course and benign evolution, while 12 patients (8.6%) presented at least one serious complication during the acute phase of the disease. Among these, the most frequent event was acute heart failure (8 patients, 5.8%), of which three patients (2.2% of the total sample) developed cardiogenic shock. Six patients (4.3%) had severe pericardial effusion or cardiac tamponade, and one patient suffered an episode of sustained ventricular tachycardia requiring cardioversion. Of the 12 cases with complications, 41.6% were women and their mean age was 58 years. In all of them, the last dose of the vaccine received was mRNA (50% related to the third dose) after a median of 7.3 days. Left ventricular systolic dysfunction was present in 41.6%. Of the six patients with complications who underwent MRI, 4 had

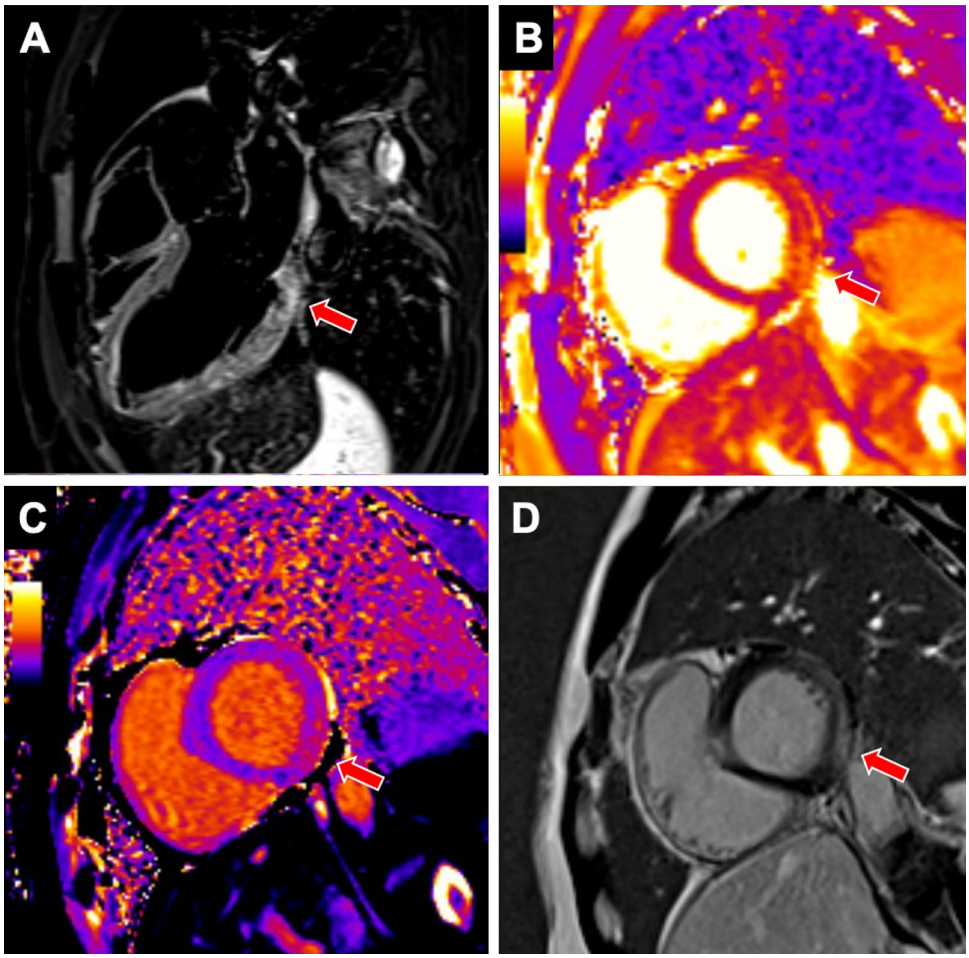


Fig. 4 Example of cardiac magnetic resonance imaging findings in post-vaccination myocarditis. Cardiac magnetic resonance images obtained on the 4th day after administration of the second dose of mRNA vaccine (Comirnaty, BioNTech/Pfizer) in a 20-year-old male. The study was compatible with the diagnosis of myocarditis according to the Lake–Louise criteria (presence of T2 and T1 criteria in a probable clinical context). The T2 criterion can be appreciated as signal hyperintensity in the TSE-T2w-STIR long-axis three-chamber sequence, located in the basal inferolateral segment (panel **a**, arrow), which is more clearly identified in the basal short-axis T2-mapping sequence over the same segment (panel **b**, arrow). The T1 criteria are visualized in the same geometry and segment in the native T1-mapping (panel **c**, arrow) and late enhancement-PSIR (panel **d**, arrow) sequences. In acute phase, T1 criteria may be increased by the presence of myocardial edema, not necessarily indicating replacement fibrosis. *mRNA* messenger ribonucleic acid, *TSE-T2w-STIR* triple-pulse inversion-recovery T2-weighted turbo spin-echo sequence, *PSIR* phase-sensitive inversion-recovery sequence

edema and one had LGE, with septal, apical, and inferior distribution. NSAIDs and colchicine were administered in most cases (75.0% and 58.3%, respectively).

Although the three patients who suffered cardiogenic shock required short-term mechanical circulatory support (one with intra-aortic balloon pump, one with a percutaneous axial Impella pump, and one with a combination of Impella and veno-arterial extracorporeal oxygenation membrane), none of them required emergent cardiac transplantation or the implantation of long-term ventricular assist devices, and no mortality was observed in the acute phase of the disease. Table 3 contains the complete description of patients with complications.

Comparison by gender

A different clinical presentation was observed between women and men. Isolated myocarditis was the predominant clinical manifestation in men, while isolated pericarditis was the predominant clinical manifestation in women ($p=0.017$). Compared to women, men more frequently presented elevation of troponins (79.7% vs 61.5%, $p=0.05$) and LGE on cardiac MRI (77.3 vs 28.6%; $p=0.001$). The risk of complications was significantly higher in women (5/26 vs 7/113, OR 3.6, $p=0.04$). Heart failure and severe pericardial effusion were the most frequent complications in both groups; however, their risk was different: 11.5% of women developed acute heart failure (vs 4.4% of men) and 11.5%

Table 2 Clinical presentation, diagnostic findings, and treatments

Clinical presentation and ECG findings ($n=139$)	
Symptoms	
Chest pain	133 (95.7%)
Dyspnea	28 (20.1%)
Syncope	2 (1.4%)
Palpitations	21 (15.1%)
Diagnosis	
Isolated myocarditis	49 (35.3%)
Isolated pericarditis	31 (22.3%)
Mixed inflammatory heart disease	59 (42.4%)
Electrocardiogram	
Normal	32 (23.2%)
ST-segment elevation	73 (52.9%)
Other abnormalities	33 (23.9%)
Diagnostic test findings	
Laboratory findings ($n=139$)	
Leucocytes (cells/mm^3)	8470 ± 5350
C-reactive protein (g/mL)	13.35 ± 40,55
Peripheral blood eosinophilia	6 (4.3%)
Troponin elevation (above the 99th percentile)	106 (76.3%)
1–100 × upper limit of normality	60 (56.6%)
100–1000 × upper limit of normality	38 (35.8%)
> 1000 × upper limit of normality	8 (7.5%)
NT-proBNP (myocarditis)	1792.8 ± 3010.9
Echocardiograms ($n=139$)	
Left ventricular dysfunction (LVEF < 50%)	16 (11.5%)
Right ventricular dysfunction	7 (5.1%)
Pericardial effusion (any degree)	29 (21.0%)
Cardiac magnetic resonance ($n=89$; 64.0%)	
Edema	64 (71.9%)
Late gadolinium enhancement	61 (68.5%)
LGE distribution patterns ($n=61$)	
Left ventricular inferolateral region	36 (58.1%)
Left ventricular anteroseptal region	2 (3.2%)
Both inferoseptal + anteroseptal regions	20 (32.3%)
Only apical region	3 (4.8%)
Treatment ($n=139$)	
Nonsteroidal anti-inflammatory drugs	102 (73.4%)
Colchicine	93 (66.9%)
Corticosteroids or other immunosupressors	4 (2.9%)
Beta-blockers	21 (15.1%)
ACE inhibitors or angiotensin-II receptor blockers	13 (9.4%)
Angiotensin-receptor neprylisin inhibitors	3 (2.2%)
Mineralocorticoid receptor blockers	3 (2.2%)

of women suffered severe pericardial effusion or cardiac tamponade (vs 2.6% of men). The summary of the results is shown in Graphical abstract.

3-Month follow-up data

Data of 3-month follow-up are available for 133 patients (95.68%). After this period of time, 17 patients (12.78%) suffered at least one of the prespecified adverse events. Two patients died, one related to nosocomial bacterial infection and another due to out-of-hospital sudden death (3-month mortality rate 1.44%). Three patients (2.25%) were diagnosed with heart failure, of which one required hospital admission and another underwent the implantation of a cardiac resincronization therapy with defibrillator (CRT-ICD). One patient had an episode of sustained ventricular tachycardia. Eleven cases of recurrent or incessant pericarditis and one case of recurrent myocarditis were observed. No patient required heart transplantation or a long-term ventricular assist device.

Regarding diagnostic tests at the 3-month follow-up, 55 patients underwent a new echocardiogram. Left ventricular ejection fraction was preserved in 54 (98.18%), with a median value of 60% (IQR 60–65%). 12 patients (9.23%) underwent a cardiac-MRI, showing persistent edema in 3 (25%) and LGE in 7 (58.33%).

Discussion

This prospective, multicenter, observational study conducted in 29 Spanish centers describes the characteristics and clinical course of patients diagnosed with inflammatory heart disease after administration of a vaccine against COVID-19, representing one of the largest series regarding this issue in Europe. In addition, the study adds information to previously reported series, incorporating prognostic data beyond the acute phase.

Although due to its nature the present registry does not allow a precise calculation of the incidence of this phenomenon in our population, our data suggest that it constitutes a very infrequent event, since during the period described a total of 139 cases were recorded in 29 hospitals with a combined population area of approximately 11.5 million inhabitants (number of cases described 11.8 cases per million inhabitants). Other series from different countries have reported a very low incidence of myocarditis and/or pericarditis after administration of SARS-CoV-2 vaccines, with notable differences depending on the sources (10–12 cases per million in the USA, 15–30 cases per million in the European Union and 48–203 cases per million in the UK) [16–22]. This discordance can be explained by the heterogeneity between the different populations and the definitions of post-vaccinal myocarditis and pericarditis used, as well as by the variability in the capacity of the health systems to detect cases.

To put into perspective the incidence of vaccine-mediated inflammatory heart disease, it should be noted that the

Table 3 Description of cases with complications

Complication	Diagnosis	Age	Sex	Previous background	Vaccine	Dose	Time vaccine symptoms (days)	Natriuretic peptide	Troponin (ULR)	CRP (mg/L)	LVEF (%)	Oedema (CMR)	Fibrosis (CMR)	Treatment
AHF and SPE	Pericarditis	81	F	No	Comirnaty	3	11	NT-proBNP: 2480 pg/mL	Normal	552	60	–	–	Colchicine and steroids
AHF and SPE	Pericarditis	79	M	No	Comirnaty	3	9	NT-proBNP: 5117 pg/mL	77 (47)	259	60	No	No	NSAID, colchicine and pericardial drainage
AHF and SPE	Pericarditis	84	F	No	Comirnaty	2	11	NT-proBNP: 1433 pg/mL	Normal	12.6	50	–	–	NSAID and colchicine
AHF	Mixed IHD (probable)	63	M	Kidney transplant, ICM	2 doses ChAdOx1 and booster Comirnaty	3	1	NT-proBNP 70.000 pg/mL	2535 (34)	273	25	–	–	NSAID, steroids, ARNI, MRA, BB
AHF	Myocarditis (probable)	41	M	No	2 Comirnaty, booster Spikevax	3	2	NT-proBNP: 4778 pg/mL	Normal	9.6	27	No	Yes (septal, apical)	ARNI, MRA, BB
SPE	Pericarditis	42	M	No	Comirnaty	2	29	NT-proBNP: 98 pg/mL	Normal	19	75	–	–	NSAID and colchicine
SPE	Mixed IHD (probable)	87	F	No	Comirnaty	2	11	NT-proBNP: 1263 pg/mL	144 (13)	224	79	Pericardic	No	NSAID and colchicine
SPE	Pericarditis	64	M	No	2 ChAdOx1, booster Spikevax	3	7	–	Normal	137	60	–	–	NSAID and colchicine
SMVT	Myocarditis (probable)	33	F	Previous myocarditis	Spikevax	2	2	–	204 (34)	90	63	–	–	NSAID and BB
Card shock (IABP)	Myocarditis (confirmed)	41	M	No	Comirnaty	1	1	BNP: 456 pg/mL	4.3 (0.1)	315	30	Apical	No	Steroids
Card shock (Impella)	Myocarditis (confirmed)	62	F	Lung malignancy	Spikevax	3	3	NT-proBNP: 8069 pg/mL	12,487 (2.5)	11.4	10	Diffuse	No	Colchicin and steroids
Card shock (Impella and VA-ECMO)	Myocarditis (confirmed)	25	M	No	Comirnaty	1	6	–	4729 (34)	18	20	Diffuse	No	ARNI, MRA, BB, SGLT-2i

F female, *M* male, *AHF* acute heart failure, *SPE* severe pericardial effusion, *NSAID* non-steroidal anti-inflammatory drugs, *BB* beta-blockers, *MRA* mineralocorticoid receptor antagonists, *ARNI* angiotensin-receptor neprilysin inhibitor, *AHF* acute heart failure, *SGLT-2i* sodium–glucose transport protein 2 inhibitors, *CRP* C-reactive protein, *SMVT* sustained monomorphic ventricular tachycardia, *CMR* cardiac magnetic resonance, *ULN* upper limit of normality, *RV* right ventricle, *ICM* ischemic cardiomyopathy, *IABP* intra-aortic balloon pump, *VA-ECMO* veno-arterial extracorporeal membrane oxigenator

burden myocardial injury related to COVID-19 infection has been found to be high, up to 25% in hospitalized patients, and is associated with a worse prognosis both in the short and long term [28].

In contrast to other previously published series [20, 29], the present study prospectively and consecutively collected all cases of inflammatory heart disease after vaccination against COVID-19, reducing the risk of underdetection and leading to higher quality data compared to those obtained in retrospective studies based on drug surveillance programs.

In agreement with other published series [20, 29], the majority of patients were young males during the 1st week after the second dose of an mRNA vaccine. Of note, 24% of cases were detected after the third dose, a finding with possible implications in the pathophysiological mechanisms underlying this disease.

The most common presentation was mixed inflammatory heart disease with concomitant diagnosis of myocarditis and pericarditis. In this regard, and as a finding not previously published in the literature, there were significant differences in the clinical presentation according to gender, with predominantly myocardial involvement in men and pericardial affectation in women. Chest pain was the most frequent symptom and ST-segment elevation was the most common electrocardiographic abnormality, in accordance with previous series [20, 29]. In most patients, a slight elevation of inflammatory markers was observed, suggesting a pathophysiological mechanism different from the systemic inflammatory syndrome observed in some cases of myocarditis associated with COVID infection. On the other hand, the infrequent detection of eosinophilia in peripheral blood points to phenomena other than hypersensitivity and/or allergy, observed as an adverse effect of other drugs. In this regard, recent studies suggest a variety of etiopathogenic theories underlying inflammatory heart disease after vaccination against COVID-19 [30], which include, among others, autoimmune disorders due to cross-reactivity caused by molecular mimicry between the SARS-CoV-2 spike glycoprotein and human proteins, as well as reactions mediated by antibodies against the interleukin-1 receptor antagonist causing a transient loss of peripheral immune tolerance [31].

Regarding cardiac biomarkers, it should be noted that cardiac troponins were found to be mild or moderately elevated in most cases. However, 7% of patients had more marked elevations of this biomarker, a finding whose prognostic implications needs to be established through prospective follow-up.

It is also relevant that most patients (89%) had preserved systolic function. In cases of myocarditis, the inflammation usually involved the inferolateral region of the left ventricle, as observed in myocarditis of other causes. However, in 35% of cases anteroseptal inflammation was present, a finding associated with a worse long-term prognosis in series of myocarditis of other origins [32] and whose impact on evolution should be established in future analyses.

In our population, more than 90% of patients had a benign evolution. However, 8.6% presented some serious complication during admission, a higher proportion than in other published series [16–22]. A possible explanation for this finding may be an overrepresentation of cases with a more severe clinical presentation, as they are easier to identify. In addition, the prospective nature of our study allows a more detailed clinical characterization, leading to the detection of some complications that may have been underdetected in studies with a retrospective design. It is also noteworthy that the subgroup of patients with severe complications was older and had a higher proportion of comorbidities than the general sample. According to previously reported data, COVID-19 vaccine-induced myocarditis has a much better prognosis, compared to classic viral myocarditis [33].

In our study, we found that although women are less frequently diagnosed with post-vaccination inflammatory heart disease, they have a higher risk of suffering severe complications than men. This is consistent with other myocarditis series, in which female sex has been associated with a worse prognosis [34].

Regarding post-admission evolution, in our study the vast majority of patients had a complete resolution of symptoms and cardiac function in a short-term follow-up. However, 12.78% of patients had an adverse event during the following 3 months, including two deaths (1.44%). This data are consistent with the prognosis reported in other series [33] and suggest the need for close follow-up after the acute phase.

The present study has several limitations. Firstly, the study describes only part of the total cases of post-vaccination myocarditis or pericarditis in Spain, and therefore does not allow to establish the exact incidence of the disease in the general population. In relation to the vaccines most frequently associated with inflammatory heart disease (Comirnaty and Spikevax), it should be taken into account that in Spain these two products have been the most widely administered [1]. Secondly, some patients might have been undiagnosed, especially those with mild symptoms and who have not required hospitalization. In addition, as in other similar series, in our study it is not possible to ensure a cause-effect relationship between the administration of the vaccine and the development of myocarditis or pericarditis, assuming causality based on the principles of biological plausibility, temporal relationship and the absence of an alternative explanation. Fourth, no histopathological samples are available, which could contribute to understand the pathophysiological mechanisms underlying this entity and help to outline the best therapeutic strategies. Finally, the present manuscript describes only the short-term evolution of patients presenting with inflammatory heart disease after COVID-19 vaccination, and a longer follow-up is needed to

assess the medium and long-term prognosis. Future updates of this registry will try to answer some of these questions.

Conclusion

Inflammatory heart disease after vaccination against COVID19 in Spain predominantly affects young males, more often after the second dose of mRNA-based vaccines, and usually manifests as a mixed cardiac inflammatory picture with myocardial and pericardial involvement. The most frequently affected myocardial region is the inferolateral left ventricular wall and the disease presents with preserved systolic function in the majority of cases. Less than 10% presented complications during the acute phase, which were more frequent after the third dose, in older patients with comorbidities and in women. In a short-term follow-up, most patients remain asymptomatic and maintain a normal systolic function. The maintenance of this registry will allow a better understanding of the evolution of these patients in the medium and long term.

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Data availability Raw data were generated and collected at Arnau de Vilanova Hospital and Institut de Reserca Biomèdica Lleida (IRB-Lleida). Derived data supporting the findings of this study are available from the corresponding author on request.

Declarations

Conflict of interest None of the authors have conflicts of interest to declare in relation to this manuscript.

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