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Myocarditis and pericarditis risk with mRNA COVID-19 vaccination compared to unvaccinated individuals: A retrospective cohort study in a Spanish Tertiary Hospital

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ABSTRACT

Objective: This study compared the incidence of pericarditis and myocarditis in patients exposed to mRNA COVID-19 vaccines to the incidence in those who were not vaccinated, considering the incidence of these conditions resulting from COVID-19 infection.
Methods: This was a retrospective cohort study of individuals assigned to health area of La Paz University Hospital in Spain. The exposure factor was vaccination with mRNA COVID-19 vaccines between December 27th, 2020 and January 9th, 2022 with a minimum follow-up of one month. The outcome was the incidence of pericarditis or myocarditis in these individuals.
Results: The incidence of pericarditis and myocarditis in the total population exposed to at least one dose of mRNA COVID-19 vaccines was 5/100,000 (CI95%:3 to 8 per 100,000), compared to 70/100,000 (CI95%: 66 to 92 per 100,000) in those who were not vaccinated. In the adolescent population (aged 12–17), the incidence was 10/100,000 in vaccinated population (CI95%: 5 to 45 per 100,000) compared to 20/100,000 in unvaccinated (CI95%: 6 to 79 per 100,000). The incidence of pericarditis or myocarditis in patients with COVID-19 infection was 200/100,000 people (CI95%: 114 to 306 per 100,000). The most common cause of pericarditis and myocarditis in the cohort was idiopathic/infectious (74 cases). Cases of myocarditis attributed to COVID-19 infection were more severe and had higher mortality rates compared to cases with other causes.
Conclusion: The incidence of pericarditis and myocarditis in patients exposed to mRNA COVID-19 vaccines was lower than in those who were not vaccinated, especially in adults.The most common cause of pericarditis and myocarditis was idiopathic/infectious, but the most frequent cause in adolescent patients was mRNA COVID-19 vaccination. Cases of myocarditis due to COVID-19 infection were more severe and had greater mortality.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), was first identified in December 2019 [1]. The World Health Organization (WHO) declared the COVID-19 pandemic on March 11th, 2020, when 4,291 deaths and 118,000 cases across 114 countries had already been reported [2]. Since then, a great deal of effort has been dedicated worldwide to developing vaccines and antiviral drugs. On December 27th, 2020, the vaccination campaign against COVID-19 began in Spain [3], providing free vaccinations to all residents.

1.1. First COVID-19 vaccines to be licensed

The first COVID-19 vaccine authorized by both the European Medicines Agency (EMA) and the European Commission (EC) was the BNT162b2 mRNA vaccine (trade name Comirnaty, marketed by Pfizer-BioNTech), which received approval on December 21st, 2020 [4].

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Subsequently, three new vaccines were licensed: mRNA-1273 mRNA vaccine (trade name Spikevax, marketed by Moderna) [5], ChAdOx1-SARS-COV-2 adenovirus vaccine (trade name Vaxzevria, marketed by AstraZeneca) [6], and Ad26.COV2.S adenovirus vaccine (marketed by Janssen) [7]. The Pfizer-BioNTech and Moderna vaccines were developed using modified messenger RNA encoding the S protein of the SARS-CoV-2 virus [4,5]. In contrast, the Janssen and AstraZeneca vaccines against COVID-19 are composed of an adenovirus vector that codes for the S protein of the SARS-CoV-2 virus [6,7].

The complete primary vaccination scheme with BNT162b2 mRNA (Pfizer-BioNTech), mRNA-1273 (Moderna) and ChAdOx1-SARS-COV-2 (AstraZeneca) comprises 2 separate doses administered at different times. In contrast, the complete primary vaccination scheme with Ad26.COV2.S (Janssen) consists of a single dose [4–7].

Safety is a determining factor for population confidence in vaccines. The prevalence of adverse effects, although mostly non-severe, creates wariness in a significant proportion of the population towards vaccination [8]. In terms of the safety of COVID-19 vaccines, an increasing number of cases of severe but rare myocarditis and pericarditis have been reported following mRNA COVID-19 vaccination, particularly in adolescents and young adults [9], [10].

1.2. Pharmacovigilance of COVID-19 vaccines

In July 2021, the EMA safety committee (Pharmacovigilance Risk Assessment Committee) concluded that myocarditis and pericarditis can occur in very rare cases following administration of the Pfizer-BioNTech and Moderna COVID-19 vaccines [11]. As a result, the committee recommended listing myocarditis and pericarditis as new side effects in the product information for these vaccines.

Subsequently, two large European pharmacoepidemiological studies that included children and adolescents provided further evidence on the risk of myocarditis and pericarditis following administration of mRNA vaccines: a cohort study based on Nordic registry data [12] and a case-control study based on French national health data [13].

In addition, the consortium coordinated by University Medical Centre Utrecht in partnership with VAC4EU conducted a pharmacoepidemiological study using a large amount of healthcare data from four European countries: the Netherlands, the United Kingdom, Italy and Spain. The study cohort comprised 35,369,669 individuals (49.2% women) with a median age of 39–49 years across the four countries. Across data sources, the 2020 background incidence of myocarditis in individuals without COVID-19 was 0.5–2.9 per 100,000 person-years in children aged 5–11 years, 1.2–9.9 in individuals aged 12–17 years, 2.8–6.4 for those aged 18–29 years, and 2.7–4.5 for those 30 years and older. For pericarditis, these incidence was 0.6–5.2 per 100,000 person-years in children aged 5–11 years, 2.8–12.6 in individuals aged 12–17 years, 10.0–21.9 for those aged 18–29 years, and 11.6–29.7 for those 30 years and older. The results confirmed the findings from independent research in France and Nordic countries and revealed that COVID-19 itself increased the incidence of these events [14].

1.3. Clinical characteristics and diagnosis of myocarditis and its complications (perimyocarditis)

The frequency of myocarditis is not well defined, its clinical presentation varies, and there is no sensitive and specific non-invasive diagnostic test to confirm the disease. According to the 2019 Global Burden of Disease report, the incidence rate of myocarditis was 6.1 per 100,000 men (with a 95% uncertainty interval [UI] of 4.2–8.7 per 100,000) and 4.4 per 100,000 women aged 35–39 years (with a 95% UI of 3.0–6.3 per 100,000) [15].

The aetiology of myocarditis is often difficult to identify. However, the patient's history and clinical presentation might suggest specific aetiologies including infectious agents (viruses, bacteria, fungi, and parasites) and non-infectious causes such as toxins, drugs, hypersensitivity reactions, systemic diseases (autoimmune), and radiation exposure [16].

The clinical manifestations of myocarditis are highly variable, ranging from subclinical disease to symptoms such as asthenia, chest pain, heart failure, cardiogenic shock, arrhythmias, and even sudden death [17].

The definitive diagnosis of myocarditis is established through endomyocardial biopsy, which is considered the gold standard method. The World Health Organization/International System and Federation of Cardiology definition specifies diagnosis using established histological (Dallas criteria), immunological, and immunohistochemical criteria [18]. Endomyocardial biopsy is performed only in cases in which it is clinically indicated [19].

The prognosis of myocarditis varies widely and depends on the underlying cause and the severity of the presenting symptoms.

The treatment for myocarditis includes general measures such as avoiding nonsteroidal anti-inflammatory drugs (NSAIDs), excessive alcohol consumption, and strenuous exercise. Immunosuppressive therapy is recommended in specific autoimmune disorders such as giant cell myocarditis, sarcoidosis, non-infectious eosinophilic myocarditis, and autoimmune myocarditis in the setting of known extracardiac autoimmune disease (e.g., lupus myocarditis) [20].

1.4. Clinical characteristics and diagnosis of pericarditis and its complications (myopericarditis)

Pericarditis refers to inflammation of the pericardial layers, with or without pericardial effusion, and is the most common form of pericardial disease [21]. According to an observational study conducted in Finland over a 9.5-year period, the incidence of pericarditis requiring hospitalization was 3.3 per 100,000 person-years [22].

The pericardium can be affected by various factors including infectious agents (viruses, bacteria, fungi, and parasites) and non-infectious causes (autoimmune diseases, neoplasms, metabolic diseases, trauma, drugs, and other factors) [21].

The clinical diagnosis can be reached based on established clinical criteria [21]. Pericardial biopsy is generally performed as part of a therapeutic procedure, such as surgical drainage, in patients with recurrent pericardial effusions and cardiac tamponade after prior pericardiocentesis (therapeutic biopsy). Additionally, the biopsy can be conducted as a diagnostic procedure in patients with disease that persists longer than three weeks despite treatment without a definitive diagnosis [23].

The treatment of acute pericarditis should target the underlying cause. In developed countries, however, most cases of acute pericarditis in immunocompetent patients are either due to a viral infection or are idiopathic. The therapeutic goals for treating acute pericarditis are pain relief, resolution of the inflammation (and, if present, pericardial effusion), and prevention of recurrence. The most commonly employed drugs in its treatment are NSAIDs and colchicine (in those with a suspected viral cause). Physical activity should also be restricted. Most patients with low-risk acute pericarditis can be effectively managed in an outpatient setting, while high-risk patients should be admitted for treatment initiation and further diagnostic evaluation [24].

Features of acute pericarditis associated with increased risk include fever (>38 ºC), subacute course (without the acute onset of chest pain), signs suggesting cardiac tamponade (e.g., haemodynamic involvement), the presence of major pericardial effusion, immunosuppression, a history of vitamin K antagonist therapy or new anticoagulants, acute trauma, no clinical improvement after 7 days of treatment with NSAIDs and colchicine at the appropriate dosage, and elevated cardiac troponin levels [25].

Patients with acute idiopathic or viral pericarditis have a good long-term prognosis. Cardiac tamponade rarely occurs in patients with acute idiopathic pericarditis but is more common in patients with a specific underlying aetiology such as malignancy, tuberculosis, and purulent

pericarditis. Constrictive pericarditis can occur in approximately 1% of patients with acute idiopathic pericarditis and is more common in patients with specific aetiologies [24].

1.5. Need for the current study: a retrospective cohort study in a tertiary hospital

There is growing evidence of an association between myocarditis and pericarditis as rare adverse effects of mRNA COVID-19 vaccines, especially among adolescent and young adult men.

This study aims to provide a better understanding of the cases of myocarditis and pericarditis linked to COVID-19 vaccines that use messenger RNA technology. The knowledge that can be provided by this retrospective cohort study at a tertiary hospital (La Paz Hospital, Madrid, Spain) includes determining the incidence of these cases in those exposed to mRNA COVID-19 vaccines and comparing the clinical characteristics of myocarditis and pericarditis not related to the vaccines. The study also aims to investigate the demographic features, clinical characteristics, and outcomes of these cases, as well as those related to other drugs and other non-drug entities.

The availability of an electronic medical record at La Paz Hospital, implemented there in June 2018, enables the systematic search for patients across hospital departments, including the emergency department, hospitalization wards, intensive care units, and outpatient clinics.

1.6. Implications for healthcare

Knowledge of the incidence of pericarditis and myocarditis cases, as well as the characteristics of these entities in patients with a possible causal relationship with mRNA vaccines, can provide useful insight for managing these diseases.

1.7. Objectives of the study

The main objective of the study was to compare the incidence of pericarditis and myocarditis among patients exposed to mRNA COVID-19 vaccines compared with those not exposed to them at La Paz Hospital (Madrid, Spain). In addition, we aimed to calculate the incidence within specific age subgroups and vaccination regimens (full regimen with two doses or at least one dose of the vaccine).

Secondary Objectives included: Characterizing cases of pericarditis and myocarditis associated with SARS-CoV-2 infection and other causes; describing cases of drug-induced pericarditis and myocarditis, including instances related to COVID-19 vaccines, comparing the incidence of pericarditis and myocarditis in patients exposed to COVID-19 vaccines with that associated with COVID-19 infection; and providing a detailed description of the clinical characteristics of pericarditis or myocarditis cases.

2. Material and methods

2.1. Design

The study was designed as a retrospective cohort of patients of all ages. The selection period lasted from December 27th, 2020 to January 9th, 2022, with a minimum follow-up of one month. The exposure of interest was the administration of the mRNA vaccine prophylaxis against COVID-19. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

2.2. Study population

The total population registered in the Community of Madrid in 2021 was 6,751,251 [26]. Additional data on the population of the Community of Madrid can be obtained from the National Institute of Statistics of Spain [27]. Of this population, 536,448 are assigned to La Paz University Hospital [28]. In Spain, the population is allocated to a designated health area that encompasses a designated referral hospital, determined by the administration based on the physical proximity of the population's residence. Consequently, individuals residing within a particular health area typically receive care at the corresponding referral hospital. However, patients residing outside their assigned health area or from other regions of Spain may seek treatment at a non-corresponding hospital if they are traveling through, but this is uncommon. Regardless, all treated patients have their corresponding health area recorded in their administrative data within the electronic medical record.

2.3. Exposure factor

On January 10th, 2022, the Spanish Ministry of Health published an activity report on the comprehensive management of COVID-19 vaccination [29]. The activity period ran from December 27th, 2020 to January 9th, 2022. The report contains data on the population that received doses of the various vaccines available in that period, stratified by region (including the Autonomous Community of Madrid) and age. Due to limited data availability for specific healthcare areas within the Autonomous Community of Madrid, we projected vaccination data from the entire Autonomous Community to the healthcare area of La Paz Hospital, assuming that vaccination rates were consistent across all areas. The data obtained from the estimation are shown in Tables 1s to 4s of supplementary material. The percentage of the designated population vaccinated during the study period, from December 27th, 2020 to January 9th, 2022 extrapolated to the hospital, was 83.7% with at least one dose of vaccine and 79.2% with full vaccination [29]. Detailed data on the vaccinated population can be found in Annex I (Material and Methods supplementary content).

On December 20th, 2021, a new vaccine was authorized in the European Union: NVX-CoV2373 (trade name Nuvaxovid, marketed by Novavax) [30]. As of January 9th, 2022, this vaccine was not available in Spain for administration to the general population [29].

2.4. Outcome

The study included patients admitted to the emergency room or hospital with the outcomes of interest (myocarditis or pericarditis) from December 27th, 2020 to January 9th, 2022 in La Paz University Hospital. The attending physician made the diagnosis of myocarditis and pericarditis based on their clinical judgment. All reports of patients seen at the hospital during the study period with a diagnosis of pericarditis or myocarditis were identified. Therefore, the diagnosis had already been established by the attending physician, who generated a report documenting the diagnosis. All cases were reviewed in the patient's clinical history by study investigators J.G., A.L.G.d.l.H., and M.U. to confirm they met the inclusion criteria for the study. The investigators assessed whether the diagnoses of pericarditis and myocarditis made by the attending physicians aligned with the criteria outlined by the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases [16] and the European Society of Cardiology Guidelines for the diagnosis and management of pericardial diseases [21]. Only newly diagnosed episodes of pericarditis and myocarditis that occurred during the study period were included, regardless of whether the patient had a history of prior episodes, as long as those previous episodes had resolved. Doubtful cases were reviewed by researcher E.R.

Incident outcome events were defined as the date of first care for myocarditis or pericarditis during the study period (from December 27th, 2020 to January 9th, 2022). The reports from the electronic medical records were downloaded by a researcher on February 24th, 2022. A second researcher then reviewed the reports, correcting any data entry errors. Once this initial verification was completed, the reports, along with any necessary corrections, underwent a thorough

review by three of the study researchers. The comprehensive review confirmed that the reports indeed pertained to cases of pericarditis or myocarditis diagnosed within the study period. Each possible case was assigned a study identification number in the case report form, and all study variables were collected. The study collected data on demographic characteristics, aetiology of pericarditis or myocarditis, previous medications, vaccine type exposure and date of dose, clinical symptoms and onset, analytical parameters, electrocardiography and other imaging tests, length of stay in the hospital, and outcome (See detailed study variables in supplementary material).

The inclusion criteria encompassed cases with a diagnosis of myocarditis or pericarditis that treated in the hospital during the study period. Cases without an episode of myocarditis or pericarditis or insufficient information for diagnostic evaluation at the time of the study were excluded.

Cases of myocarditis or pericarditis were classified according to their aetiology. Cases with aetiologies other than the COVID-19 mRNA vaccine involved individuals who had not received the vaccine (unexposed). In case of a suspected pharmacological aetiology, the drug causality was carried out using the Spanish pharmacovigilance system algorithm [31]. The algorithm assigns a score to each of seven factors that are considered to be relevant in determining whether an adverse drug reaction (ADR) is causally related to a medication. The factors are: chronology, literature, withdrawal, rechallenge, alternative causes, contributing factors, complementary explorations. The chronology was considered compatible between 1 and 7 days or up to 21 days later. In rare cases, symptoms can appear up to 21 days later, but it was considered not fully compatible. The final score classifies the causal relationship into 5 categories: < 0 unrelated, 1–3 conditional, 4–5 possible, 6–7 probable, and 8 definite. Cases falling into the "unrelated" and "conditional" categories were considered unrelated to the drug, while those categorized as "possible", "probable", and "definite" were considered related to the drug. Cases related to the COVID-19 mRNA vaccine were in individual who had received at least one dose of the vaccine (exposed). In cases where non-vaccine drug-related causes were suspected, the algorithm was also employed to verify the association. The algorithm can be found in Table 5s of supplementary material). For all patients initially categorized as having a pharmacological aetiology, a complete report was submitted to the pharmacovigilance centre in Madrid, Spain (accessible at https://www.notificaram.es).

2.5. Statistical analysis

A descriptive, univariate analysis was conducted. Quantitative variables are presented as median and standard deviation, and qualitative variables are presented as absolute and relative values. The normality of the data distribution was studied using the Kolmogorov-Smirnov test.

The analysis of intergroup differences was performed using the Mann–Whitney U test and the Kruskal-Wallis test for quantitative variables and using Pearson's chi-squared test (or Fisher's exact test, when necessary) for qualitative variables. In cases involving multiple comparisons, the p-values were adjusted using Holm's post-hoc method. All data analysis was performed using RStudio (Integrated Development for R. RStudio, PBC, Boston, MA; http://www.rstudio.com).

We estimated the incidence rate with 95% confidence intervals of pericarditis and myocarditis associated with mRNA COVID-19 vaccination in adults and adolescents (12–17 years), alongside the overall incidence of pericarditis and myocarditis in the hospitalized individuals, and the incidence of pericarditis and myocarditis in individuals with COVID-19 infection. Additionally, we calculated the incidence of pericarditis and myocarditis in the population with at least one dose and with a complete regimen. The denominator was different for each subgroup of the population (total population, adult population, and adolescent population) due to the differential number of individuals exposed to the risk factor in each group. The relative risk of incidence between exposed and non-exposed individuals was also estimated. To estimate the incidence of pericarditis/myocarditis in the population with COVID-19 infection, we utilized the COVID@HULP cohort study (COVID@HULP Working Group) [32] as the source of denominator data. This study provided information on the number of COVID-19 cases within the population assigned to La Paz Hospital and, consequently, treated at our institution during the study period.

3. Results

A total of 351 possible cases of pericarditis or myocarditis were identified, 157 of which were confirmed cases of pericarditis and myocarditis diagnosed during the study period (118 cases of pericarditis and 39 of myocarditis). The remaining 194 cases were excluded for the following reasons: 38 suspected cases of pericarditis or myocarditis on admission to the emergency department were not confirmed after completing the patients' study, and 156 cases were diagnosed prior to the study period (subsequent hospital control visits during the study period were downloaded). Fig 1.

Of the 157 cases of pericarditis and myocarditis identified during the study period, 3 cases of pericarditis and 1 case of myocarditis with idiopathic/viral aetiology did not belong to the hospital's designated population (3 of these cases were from other autonomous communities and one was from another country). The overall incidence of pericarditis and myocarditis in the entire population assigned to La Paz Hospital was 28.5 per 100,000 individuals. The incidence varied from 15.3 in children (5–11 years) to 20.7 per 100,000 in adolescents (12–17 years), and reached 31.7 per 100,000 in adults. The incidence of pericarditis and myocarditis was 21.4 and 7.1 per 100,000 people, respectively.

The aetiologies of the cases of pericarditis and myocarditis were categorized into two main groups: unexposed individuals and exposed individuals. Within the unexposed group, four subgroups were identified: cardiac, COVID-19 infection, idiopathic/infectious, and other aetiologies. These subgroups represent organically or physiologically related entities (Table 1). The category of 'other aetiologies' encompasses autoimmune disorders, drugs other than vaccines, and uremic pericarditis. Among all detected cases, the most common aetiological category was idiopathic/infectious, which mainly included idiopathic aetiology after a negative causality study or suspected viral cause in

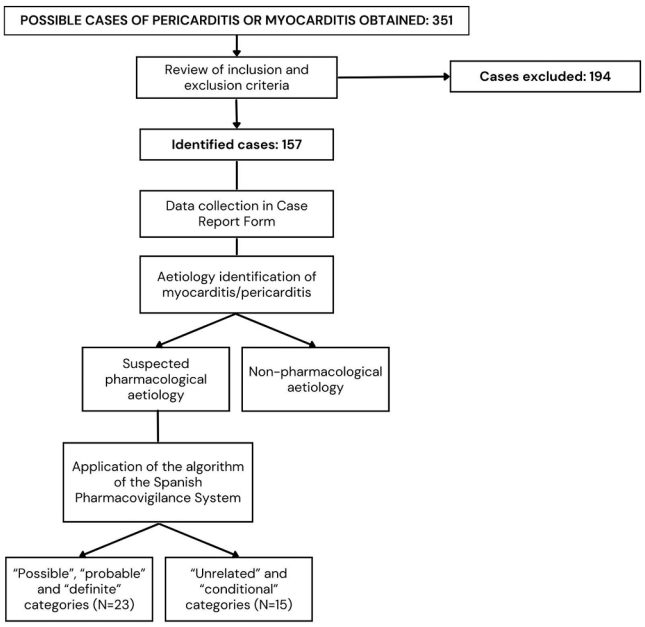

Figure 1. Study flowchart

Fig. 1. Study flowchart.

Table 1
Aetiologies of the cases of pericarditis and myocarditis.

Aetiological category	Aetiology identified in cases of pericarditis or myocarditis	No. of cases
UNEXPOSED individuals		
Cardiac	Heart surgery	9
	Post-infarction	19
	Total in the category	**28**
COVID-19		**18**
Idiopathic/ infectious	Idiopathic	35
	Idiopathic/viral suspicion	32
	Bacterial	5
	Viral	2
	Total in the category	**74**
Other aetiologies	Autoimmune	12
	Pharmacological (others than mRNA COVID-19 vaccines)*	3
	Uremic	2
	Total in the category	**17**
EXPOSED individuals		
mRNA COVID-19 vaccines		**20**
Total cases detected		**157**

N.A., Does not apply, there is no grouping of different entities in the category. *Three cases were identified with pharmacological causes other than mRNA COVID-19 vaccines, "possible" for enoxaparin, amoxicillin/clavulanate and doxorubicin.

patients with mild clinical symptoms and a history of recent mild respiratory infection (47.1%).

In the adult patients, the idiopathic/infectious aetiology was the most frequently observed. In contrast, the most frequent aetiology in the adolescent patients was the mRNA COVID-19 vaccine. The Table 2 summarized the distribution of pericarditis and myocarditis by age group. The paediatric population (5–11 years) assigned to La Paz University Hospital and administered 1 dose of mRNA vaccine was 13,471. However, there were no cases of pericarditis or myocarditis observed in our cohort for this age group (Table 2).

Twenty of these cases were associated with mRNA COVID-19 vaccines (19 with the Pfizer-BioNTech vaccine and 1 with the Moderna vaccine). Of these 20 cases, 14 were pericarditis and 6 were myocarditis. The median time between vaccination and symptom onset was 6 days. The majority of cases of pericarditis and myocarditis after vaccination with mRNA COVID-19 vaccine were of young men, with 18 cases in men and 2 in women, typically occurring after the second dose. (Table 3).

Table 4 details the demographic, clinical, and analytical characteristics and data of the patients diagnosed with pericarditis and/or myocarditis, classified according to the previously defined aetiological group. The patients with COVID-19 aetiology had a significantly higher median age and a longer median hospital stay compared with those with other aetiologies. Three of the adult patients with myocarditis died; two of them had COVID-19 infection while the third had idiopathic myocarditis with cardiogenic shock. The patients with pericarditis and myocarditis related to mRNA vaccines were younger and had fewer comorbidities compared with the patients with other aetiologies. The median period between the administration of a dose of mRNA vaccine and the onset of the first symptoms of pericarditis and myocarditis was 6 days (range 0–18 days).

Table 3
Description of the 19 cases after administration of the BNT162b2 mRNA vaccine (Pfizer-BioNTech) and mRNA-1273 vaccine (Moderna).

Dose after which symptom onset occurred	Total cases	Cases by sex	Age range (years)	Median (years)
BNT162b2 mRNA vaccine (Pfizer-BioNTech)				
First dose	8	Male, 8	16–51	40
		Female, 0	n/a	n/a
Second dose	11	Male, 9	13–74	34
		Female, 2	27–57	42
mRNA-1273 vaccine (Moderna)				
First dose	1	Male, 1	27	27

n/a, not applicable

The most common aetiology of pericarditis was idiopathic/viral (n = 61), followed by cardiac (n = 28) and secondary to mRNA COVID-19 vaccines (n = 14), and all cases of pericarditis of cardiac aetiology were due to post-infarction (19/28) or postcardiac surgery (9/28). The most frequent cause of myocarditis was COVID-19 infection (n = 14), followed by idiopathic/viral infection (n = 13); no myocarditis of cardiologic origin was detected in the cohort. Tables 4A and 4B show the characteristics of pericarditis and myocarditis cases respectively. Cases of myocarditis due to COVID-19 infection had a significantly higher median age, a longer median hospitalization stay, and a higher mortality compared with other aetiologies.

3.1. Main objective: Incidence of pericarditis/myocarditis in patients exposed to mRNA COVID-19 vaccines compared with those not exposed

We calculated the incidence rate in the population with at least one dose of mRNA vaccine, the incidence rate in the population with a complete vaccination regimen (2 doses of mRNA vaccine), and the incidence of pericarditis and myocarditis in both the adult and adolescent (12–17 years) subgroups. In both age groups, we calculated the incidence for those exposed to at least one dose or two doses of the mRNA vaccine (full vaccination). There were no cases of pericarditis or myocarditis associated with COVID-19 vaccines in the paediatric population (<11 years) during the study period, and therefore the incidence for this age group could not be determined.

The majority of the population completed the full vaccination regimen (two doses) during the study period. However, all those exposed to a dose of mRNA vaccine would be at risk of pericarditis and myocarditis; we therefore calculated the incidence for the population that was administered at least one dose.

3.1.1. Incidence in the population with at least one dose of vaccine and complete dose vaccination

The incidence of pericarditis and myocarditis in the total population exposed to at least 1 dose of mRNA COVID-19 vaccine was 5 per 100,000 people. The incidence of pericarditis and myocarditis in the total population exposed to complete vaccination (2 doses of mRNA COVID-19 vaccines) was 4 per 100,000 people (Table 5).

Table 2
Distribution of pericarditis and myocarditis by age group.

	Cases of myocarditis/pericarditis	Cardiac	COVID-19	Idiopathic/Viral	Vaccine-associated (SARS-COV-2 mRNA)	Others
Total	157	28	18	74	20	17
	100%	(17.8%)	(11.5%)	(47.1%)	(12.7%)	(10.8%)
Adults (≥18 y)	144	27	17	69	16	15
	92%	18.75%	11.81%	47.92%	11.11%	10.42%
Adolescents (12–17 y)	7	0	0	2	4	1
	4%	0.00%	0.00%	28.57%	57.14%	14.29%
Children (5–11 y)	6	1	1	3	0	1
	4%	16.67%	16.67%	50.00%	0.00%	16.67%

Table 4
Demographic characteristics of the patients with pericarditis and myocarditis according to aetiology. *Due to the main variable (aetiology of pericarditis/myocarditis) having more than 2 levels, a post-hoc Tukey test was performed for the variables that yielded significant results, generating the following outcomes.*

	Cardiac	COVID-19	Idiopathic/Viral	Vaccine-induced (SARS-COV-2 mRNA)	Other aetiologies	p
Number of cases	28	18	74	20	17	
Age (median [IQR]), years	59.00 [53.00, 69.25]	61.50 [32.00, 80.50]	45.00 [23.25, 61.75]	36.00 [27.00, 42.75]	46.00 [23.00, 63.00]	0.002 *
Sex (%) Male	22 (78.6)	13 (72.2)	53 (71.6)	18 (90.0)	8 (47.1)	0.057
Female	6 (21.4)	5 (27.8)	21 (28.4)	2 (10.0)	9 (52.9)	
ER stay (median [IQR]), days	1.00 [0.00, 1.00]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	1.00 [0.50, 1.00]	0.071
Hospital ward stay (median [IQR]), days	3.50 [1.00, 6.25]	11.00 [5.00, 15.00]	0.00 [0.00, 3.00]	3.00 [0.50, 4.00]	0.00 [0.00, 11.50]	< 0.001 *
ICU stay (median [IQR]), days	2.00 [0.00, 3.00]	0.00 [0.00, 2.75]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	< 0.001 *
Comorbidities (%) No	4 (14.3)	4 (22.2)	42 (56.8)	14 (70.0)	1 (6.2)	< 0.001 *
Yes	24 (85.7)	14 (77.8)	32 (43.2)	6 (30.0)	15 (93.8)	
Leukocyte count (median [IQR]), (per μL)	13,700.00 [9220.00, 15,540.00]	7740.00 [6120.00, 11,490.00]	9570.00 [7055.00, 11,960.00]	8910.00 [7380.00, 10,920.00]	10,545.00 [8717.50, 12,442.50]	0.008 *
Hb (median [IQR]), (g/dL),	14.00 [12.50, 15.00]	14.60 [12.60, 15.50]	15.00 [13.65, 15.75]	15.00 [14.35, 15.90]	13.30 [12.42, 15.35]	0.106
Urea (median [IQR]), (mg/dL)	38.00 [29.50, 50.00]	42.00 [29.00, 70.50]	29.50 [24.25, 34.75]	24.50 [22.50, 36.50]	41.00 [21.55, 73.50]	0.062
Creatinine (median [IQR]), (mg/dL)	0.86 [0.76, 1.11]	0.96 [0.82, 1.22]	0.83 [0.69, 0.94]	0.82 [0.73, 0.95]	0.97 [0.78, 1.25]	0.057
Na^+ (median [IQR]), (mmol/L)	139.00 [136.00, 140.00]	138.00 [137.00, 139.00]	139.00 [137.25, 140.00]	139.00 [138.00, 140.50]	139.00 [137.50, 141.00]	0.657
K^+ (median [IQR]), (mmol/L)	4.00 [3.70, 4.20]	4.10 [3.80, 4.40]	4.10 [3.80, 4.40]	3.95 [3.80, 4.27]	4.30 [4.05, 4.55]	0.342
Bicarbonate (median [IQR]), (mmol/L)	27.20 [24.40, 29.30]	24.35 [23.98, 25.15]	25.15 [24.18, 27.70]	25.00 [24.80, 27.00]	28.60 [26.80, 29.40]	0.504
Troponin I (median [IQR]), (ng/L)	4123.40 [240.20, 16,466.50]	338.90 [118.20, 3549.00]	6.45 [2.50, 86.82]	125.70 [4.35, 8410.00]	24.80 [2.50, 53.80]	0.136

**Statistically significant p-value. ER, emergency room; ICU, intensive care unit; Hb, haemoglobin; Na^+, sodium; K^+, potassium; μL, microliter; g/dL, grams per decilitre; mg/dL, milligrams per decilitre; mmol/L, millimole per liter; ng/L, nanogram per liter.*

3.1.2. Incidence in the adult population (≥18 years) with at least one dose of vaccine and complete dose vaccination

The incidence of pericarditis and myocarditis in the adult population (≥18 years) exposed to at least one dose of mRNA COVID-19 vaccine was 5 per 100,000 adult population. The incidence of pericarditis and myocarditis in the adult population exposed to the complete regimen of mRNA COVID-19 vaccines was 3 per 100,000 adult population (Table 6).

3.1.3. Incidence in the adolescent population (12–17 years) with at least one dose of vaccine and complete dose vaccination

The incidence of pericarditis and myocarditis in the adolescent population (12–17 years) exposed to at least one dose of mRNA COVID-19 vaccine was 10 per 100,000 adolescent population. The incidence of pericarditis and myocarditis in the adolescent population (12–17 years) exposed to a complete regimen of mRNA COVID-19 vaccines was 10 per 100,000 adolescent population (Table 7).

3.2. Secondary objectives

3.2.1. Description of the drug-induced pericarditis and myocarditis cases, including COVID-19 vaccine-related cases

Of the cases of pericarditis and myocarditis with a known pharmacological aetiology, 20 were related to mRNA COVID-19 vaccines, and 3 were related to other drugs (enoxaparin, amoxicillin/clavulanate, and doxorubicin). The comparative analysis of the characteristics between the two groups of pharmacological causes can be found in Table 8.

3.2.2. Incidence of pericarditis and myocarditis cases in the patients exposed to COVID-19 vaccines compared with those associated with COVID-19 infection

The incidence of pericarditis/myocarditis in the patients exposed to at least one dose of mRNA COVID-19 vaccine was 5 per 100,000 population, and the incidence in the patients with COVID-19 infection was 200 per 100,000 population (Table 9). This results in a ratio of 200 cases of pericarditis and myocarditis due to COVID-19 infection for every 5 caused by mRNA COVID-19 vaccines.

4. Discussion and conclusions

4.1. Summary of the results and discussion

This cohort study of patients exposed to COVID-19 vaccines and admitted to the emergency room or hospital ward with pericarditis or myocarditis between December 27th, 2020 and January 9th, 2022, in a population of 536,448 people assigned to the hospital, found an incidence of pericarditis and myocarditis of 21.4 and 7.1 per 100,000 people, respectively. The incidence of pericarditis and myocarditis in the total and adult population (≥18 years) exposed to at least one dose of mRNA COVID-19 vaccine was 5 per 100,000 individuals for both diseases. The incidence of pericarditis and myocarditis in the total and adult population exposed to a full vaccination regimen was 4 per 100,000 individuals and 3 per 100,000 individuals, respectively. In this study, most cases of pericarditis and myocarditis following administration of mRNA COVID-19 vaccines consisted of young men who had been administered 2 doses, with a median time to onset of 6 days after administration of a dose of mRNA vaccine. Most of the adolescent population completed the full vaccination regimen (2 doses) during the study period. Consequently, the incidence of myocarditis and

Table 4A
Demographic characteristics of the patients with pericarditis (n = 118) according to aetiology category. *Due to the main variable (aetiology of pericarditis) having more than 2 levels, a post-hoc Tukey test was performed for the variables that yielded significant results, generating the following outcomes.*

	Cardiac (n = 28)	COVID-19 (n = 4)	Idiopathic /Viral (n = 61)	Vaccine-induced (SARS-COV-2 mRNA) (n = 14)	Other aetiologies (n = 11)	p
Age (median [IQR]), years	59.00 [53.00, 69.25]	35.50 [25.00, 42.00]	41.00 [23.00, 68.00]	37.50 [19.50, 46.25]	41.00 [22.50, 62.00]	0.006 *
Sex (%) Male	22 (78.6)	3 (75.0)	43 (70.5)	13 (92.9)	4 (36.4)	0.031 *
Female	6 (21.4)	1 (25.0)	18 (29.5)	1 (7.1)	7 (63.6)	
ER stay (median [IQR]), days	1.00 [0.00, 1.00]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]	0.054
Hospital ward stay (median [IQR]), days	3.50 [1.00, 6.25]	6.00 [4.50, 9.50]	0.00 [0.00, 2.00]	3.00 [0.00, 5.00]	0.00 [0.00, 7.75]	< 0.001 *
ICU stay (median [IQR]), days	2.00 [0.00, 3.00]	5.00 [1.50, 8.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	< 0.001 *
Comorbidities (%) No	4 (14.3)	2 (50.0)	37 (60.7)	11 (78.6)	0 (0.0)	< 0.001 *
Yes	24 (85.7)	2 (50.0)	24 (39.3)	3 (21.4)	11 (100.0)	
Leukocyte count (median [IQR]), (per μL)	13,700.00 [9220.00, 15,540.00]	5940.00 [3200.00, 11,065.00]	9680.00 [7110.00, 11,990.00]	10,280.00 [7850.00, 11,820.00]	11,090.00 [9285.00, 13,157.50]	0.026 *
Hb (median [IQR]), (g/dL)	14.00 [12.50, 15.00]	14.60 [12.25, 15.00]	14.95 [13.60, 15.78]	15.10 [14.60, 15.90]	13.95 [12.60, 15.45]	0.134
Urea (median [IQR]), (mg/dL)	38.00 [29.50, 50.00]	26.00 [21.00, 31.50]	29.50 [24.75, 34.25]	23.00 [21.25, 35.25]	44.00 [41.00, 103.00]	0.011 *
Creatinine (median [IQR]), (mg/dL)	0.86 [0.76, 1.11]	0.87 [0.82, 0.92]	0.82 [0.66, 0.92]	0.77 [0.70, 0.88]	0.99 [0.87, 1.34]	0.103
Na^+ (median [IQR]), (mmol/L)	139.00 [136.00, 140.00]	136.00 [135.00, 137.00]	139.00 [138.00, 141.00]	139.00 [138.00, 141.00]	138.50 [137.25, 139.75]	0.218
K^+ (median [IQR]), (mmol/L)	4.00 [3.70, 4.20]	3.60 [3.50, 3.75]	4.10 [3.90, 4.50]	4.10 [3.88, 4.30]	4.35 [4.10, 4.57]	0.035
Bicarbonate (median [IQR]), (mmol/L)	27.20 [24.40, 29.30]	24.40 [24.40, 24.40]	25.55 [24.72, 28.25]	24.80 [14.35, 27.10]	28.60 [26.80, 29.40]	0.637
Troponin I (median [IQR]), (ng/L)	4123.40 [240.20, 16,466.50]	254.00 [130.45, 16,783.30]	4.00 [2.50, 15.15]	18.10 [2.80, 6824.00]	2.50 [2.50, 44.10]	< 0.001 *

**Statistically significant p-value. ER, emergency room; ICU, intensive care unit; Hb, haemoglobin; Na^+, sodium; K^+, potassium; μL, microliter; g/dL, grams per decilitre; mg/dL, milligrams per decilitre; mmol/L, millimole per liter; ng/L, nanogram per liter.*

pericarditis was the same in those exposed to 1 dose as in those exposed to 2 doses (10 per 100,000).

Similar results with the incidence of pericarditis and myocarditis in the total and adult population have been published in the literature. In a population-based cohort study, 4,931,775 individuals aged 12 years or older were followed from October 1st, 2020 to October 5th, 2021. Of those vaccinated with BNT162b2 (Pfizer-BioNTech), an absolute rate of 1.4 per 100,000 vaccinated individuals developed myocarditis or myopericarditis within 28 days of vaccination. Among the population vaccinated with mRNA-1273 (Moderna), an absolute rate of 4.2 per 100,000 vaccinated individuals developed myocarditis or myopericarditis within 28 days of vaccination [33]. Unfortunately, the incidence by type of mRNA vaccine cannot be estimated due to the low number of mRNA-1273 (Moderna) cases (n = 1).

In our cohort, we found that most cases of pericarditis and myocarditis following administration of mRNA COVID-19 vaccines consisted of young men who had been administered two doses. These findings agree with those published in the literature. In a retrospective cohort study conducted in the U.S. that examined the primary outcome of myocarditis/pericarditis among men aged 18–25 years who were administered mRNA COVID-19 vaccines, the pooled incidence rate was the highest after the second dose: 1.71 (95% CI 1.31–2.23) per 100,000 person-days for BNT162b2 and 2.17 (1.55–3.04) per 100,000 person-days for mRNA-1273 (Moderna). The authors concluded that these results did not indicate a statistically significant difference in risk between mRNA-1273 and BNT162b2 [34].

Our results in the incidence of pericarditis and myocarditis in adolescent population agree with those published for the population in the U.S. The published incidence of myocarditis/pericarditis within 7 days following mRNA COVID-19 vaccination among children and younger adults in the U.S. was 15 per 100,000 for those aged 12–15 years and 13.7 per 100,000 for those aged 16–17 years [35]. However, the published incidence for myocarditis in the years prior to the COVID-19 pandemic was lower. A study conducted in Finland reported an incidence rate for myocarditis of 1.95 per 100,000 person-years, calculating the incidence using data from all hospital admissions for myocarditis in patients aged ≤ 15 years from 2004 to 2014, along with the corresponding population data [36].

In our study, the incidence of pericarditis/myocarditis in the patients with COVID-19 infection was 200 per 100,000 people, a ratio of 200 cases of pericarditis and myocarditis due to COVID-19 infection for every 5 caused by the mRNA COVID-19 vaccine. Similar data on the incidence of myocarditis in patients with COVID-19 have been published. A study conducted in the U.S. from March 2020 to January 2021 found that the risk for myocarditis was 0.146% among patients with COVID-19 [37]. Therefore, the incidence of pericarditis and myocarditis appears to be 40-fold higher in patients with COVID-19 than in patients exposed to the mRNA COVID-19 vaccine. On the other hand, patients with a COVID-19 aetiology had a significantly higher median age, a longer median stay, and higher mortality compared with patient with any other aetiology.

4.2. Strengths and limitations

Evaluating the causality of an ADR identified during drug exposure is critically important due to its implications for patient safety and the overall risk-benefit assessment of medications. The WHO global introspection method, despite its usefulness, has faced criticism for its subjectivity and imprecision, as it primarily relies on expert clinical judgment [38,39]. In response to this, several decision algorithms have been developed since 1977, which combine and score various criteria in a structured manner to minimize subjective biases. These algorithms exhibit high sensitivity (approaching 100%) and positive predictive value [40]. The use of causality algorithms is crucial for establishing a

Table 4B
Demographic characteristics of patients with myocarditis (n = 39) according to aetiology category. *Due to the main variable (aetiology of myocarditis) having more than 2 levels, a post-hoc Tukey test was performed for the variables that yielded significant results, generating the following outcomes.*

	Cardiac (n = 0)	COVID-19 (n = 14)	Idiopathic /Viral (n = 13)	Vaccine-induced (SARS-COV-2 mRNA) (n = 6)	Other aetiologies (n = 6)	p
Age (median [IQR]), years	-	73.00 [43.50, 81.00]	46.00 [26.00, 49.00]	33.50 [28.00, 37.50]	50.00 [30.50, 68.75]	0.006 *
Sex (%) Male	-	10 (71.4)	10 (76.9)	5 (83.3)	4 (66.7)	0.031 *
Female	-	4 (28.6)	3 (23.1)	1 (16.7)	2 (33.3)	
ER stay (median [IQR]), days	-	1.00 [1.00, 1.00]	1.00 [0.50, 1.00]	1.00 [1.00, 1.00]	0.00 [0.00, 1.00]	0.054
Hospital ward stay (median [IQR]), days	-	11.50 [5.25, 16.50]	3.00 [0.50, 5.00]	3.00 [2.25, 3.00]	0.00 [0.00, 15.00]	< 0.001 *
ICU stay (median [IQR]), days	-	0.00 [0.00, 0.00]	0.00 [0.00, 2.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	< 0.001 *
Comorbidities (%) No	-	2 (14.3)	5 (38.5)	3 (50.0)	1 (20.0)	< 0.001 *
Yes	-	12 (85.7)	8 (61.5)	3 (50.0)	4 (80.0)	
Leukocyte count (median [IQR]), (per μL)	-	8240.00 [6745.00, 11,162.50]	8960.00 [5670.00, 11,960.00]	8120.00 [6082.50, 9227.50]	9895.00 [7537.50, 11,712.50]	0.026 *
Hb (median [IQR]), (g/dL)	-	14.30 [12.70, 15.73]	15.00 [13.90, 15.30]	14.75 [13.52, 15.90]	13.30 [10.20, 14.90]	0.134
Urea (median [IQR]), (mg/dL)	-	48.00 [31.25, 76.25]	29.50 [19.25, 35.25]	27.00 [24.75, 33.75]	5.70 [5.00, 6.40]	0.011 *
Creatinine (median [IQR]), (mg/dL)	-	1.00 [0.84, 1.29]	0.87 [0.80, 1.11]	0.91 [0.82, 0.97]	0.84 [0.72, 0.99]	0.103
Na^+ (median [IQR]), (mmol/L)	-	138.50 [137.25, 139.75]	138.00 [136.00, 139.00]	139.00 [139.00, 139.75]	142.00 [139.00, 142.00]	0.218
K^+ (median [IQR]), (mmol/L)	-	4.20 [3.82, 4.40]	3.80 [3.70, 4.10]	3.85 [3.65, 3.98]	4.30 [3.50, 4.30]	0.035
Bicarbonate (median [IQR]), (mmol/L)	-	24.30 [23.85, 25.90]	24.10 [20.70, 25.40]	26.00 [25.50, 26.50]	No data[$]	0.637
Troponin I (median [IQR]), (ng/L)	-	412.55 [139.55, 3072.68]	2690.55 [336.28, 15,041.00]	2557.00 [663.12, 8747.25]	1657.65 [40.85, 7290.82]	< 0.001 *

**Statistically significant p-value. ER, emergency room; ICU, intensive care unit; Hb, haemoglobin; Na^+, sodium; K^+, potassium; μL, microliter; g/dL, grams per decilitre; mg/dL, milligrams per decilitre; mmol/L, millimole per liter; ng/L, nanogram per liter.*
[$]No data in 5 cases due to autoimmune aetiology and 1 due to pharmacological aetiology

Table 5
Incidence in the total population with at least one dose of vaccine and complete dose vaccination.

	Cases of myocarditis/ pericarditis	Individuals	Incidence (CI95%)	Risk Ratio
Individuals with at least one dose	20	361,244	5 per 100,000 (3 to 8 per 100,000)	0.0714
Unvaccinated	137	175,204	70 per 100,000 (66 to 92 per 100,000)	
Individuals with full vaccination	13	351,534	4 per 100,000 (2 to 6 per 100,000)	0.0571
Unvaccinated	137	184,914	70 per 100,000 (62 to 87 per 100,000)	

Table 6
Incidence in the adult population (≥18 years) with at least one dose of vaccine and complete dose vaccination.

	Cases of myocarditis/ pericarditis	Individuals	Incidence (CI95%)	Risk Ratio
Individuals with at least one dose	16	296,943	5 per 100,000 (3 to 8 per 100,000)	0.0625
Unvaccinated	128	144,018	80 per 100,000 (74 to 106 per 100,000)	
Individuals with full vaccination	10	288,962	3 per 100,000 (2 to 6 per 100,000)	0.0375
Unvaccinated	128	151,999	80 per 100,000 (70 to 100 per 100,000)	

causal link between an ADR and a specific medication. These algorithms provide a structured and objective approach to evaluating the evidence, especially in cases where the ADR is rare or has a long latency period. It is a significant strength of this study that case evaluation was conducted using a standardized causality algorithm that assigns scores to each of the seven factors considered relevant to determining causality [31].

The actual number of individuals that are vaccinated within the population designated to La Paz Hospital is not available but has been estimated to be similar to the vaccination percentages of the Community of Madrid to which it belongs, given that they are part of the same healthcare system.

The cases of pericarditis and myocarditis detected were based on the diagnoses of the physicians who treated the patients in the emergency room, hospital ward or intensive care unit. The emergence of COVID-19 and COVID-19 vaccines has impacted the increase in the incidence of pericarditis and myocarditis treated in the hospital. However, it is possible that the incidence is being overestimated, as cases that were previously managed on an outpatient basis might now be referred to hospital care due to the uncertainty of the cardiovascular impact of SARS-CoV-2. On the other hand, it has been possible not to detect outpatient settings (primary care centres for the population assigned to our hospital) and that cases of myocarditis or pericarditis might have been misdiagnosed (which would underestimate the incidence).

In certain cases, the causality (drug or not) was identified during the patient's evaluation; however, in the doubtful cases but with possible drug causality, the causality algorithm of the Spanish

Table 7
Incidence in the adolescent population (12–17 years) with at least one dose of vaccine and complete dose vaccination.

	Cases of myocarditis/ pericarditis	Individuals	Incidence (CI95%)	Risk Ratio
Individuals with at least one dose	4	22,759	10 per 100,000 (5 to 45 per 100,000)	0.5
Unvaccinated	3	11,038	20 per 100,000 (6 to 79 per 100,000)	
Individuals with full vaccination	3	22,147	10 per 100,000 (3 to 39 per 100,000)	0.5
Unvaccinated	3	11,038	20 per 100,000 (6 to 80 per 100,000)	

Table 8
Characteristics of the patients with drug-induced pericarditis or myocarditis, including COVID-19 vaccine-related cases.

	Drug-induced (N = 3)	Vaccine-related (SARS-CoV-2 mRNA) (N = 20)	p
Age (median [IQR]), years	53.00 [37.50, 60.00]	36.00 [27.00, 42.75]	0.411
Sex (%) Male	3 (100.0)	18 (90.0)	1.000
Female	0 (0.0)	2 (10.0)	
ER stay (median [IQR]), days	1.50 [1.25, 1.75]	1.00 [1.00, 1.00]	0.172
Hospital ward stay (median [IQR]), days	3.50 [1.75, 5.25]	3.00 [0.50, 4.00]	0.951
ICU stay (median [IQR]), days	0.00 [0.00, 5.00]	0.00 [0.00, 0.00]	0.355
Comorbidities (%) No	0 (0.0)	14 (70.0)	0.093
Yes	3 (100.0)	6 (30.0)	
Leukocyte count (median [IQR]), (per μL)	9150.00 [8425.00, 9630.00]	8910.00 [7380.00, 10,920.00]	0.886
Hb (median [IQR]), (g/dL)	15.10 [11.60, 15.30]	15.00 [14.35, 15.90]	0.534
Urea (median [IQR]), (mg/dL)	44.00 [44.00, 44.00]	24.50 [22.50, 36.50]	0.342
Creatinine (median [IQR]), (mg/dL)	0.97 [0.84, 0.99]	0.82 [0.73, 0.95]	0.339
Na^+ (median [IQR]), (mmol/L)	138.00 [137.50, 139.00]	139.00 [138.00, 140.50]	0.410
K^+ (median [IQR]), (mmol/L)	4.00 [3.90, 4.15]	3.95 [3.80, 4.27]	0.879
Bicarbonate (median [IQR]), (mmol/L)	25.00 [25.00, 25.00]	25.00 [24.80, 27.00]	1.000
Troponin I (median [IQR]), (ng/L)	2.50 [2.50, 2.50]	125.70 [4.35, 8410.00]	0.057

**Statistically significant p-value. ER, emergency room; ICU, intensive care unit; Hb, haemoglobin; Na^+, sodium; K^+, potassium; μL, microliter; g/dL, grams per decilitre; mg/dL, milligrams per decilitre; mmol/L, millimole per liter; ng/L, nanogram per liter.*

Pharmacovigilance System was applied to determine drug causality.

4.3. Conclusions

The incidence of pericarditis and myocarditis in patients exposed to mRNA COVID-19 vaccines was lower than in those who were not vaccinated, especially in adults. The most common cause of pericarditis and myocarditis was idiopathic/infectious, but the most frequent cause in adolescent patients was mRNA COVID-19 vaccination. Cases of myocarditis due to COVID-19 infection were more severe and had greater mortality.

Table 9
Incidence of pericarditis and myocarditis in patients with full mRNA COVID-19 vaccine regimen.

	Cases of myocarditis/ pericarditis	Individuals	Incidence (CI95%)	Risk Ratio
mRNA vaccine-related	20	361,244[a]	5 per 100,000 (CI95%: 3 to 8 per 100,000)	0.025
COVID-19 infection-related	18	9292[b]	200 per 100,000 (CI95%: 114 to 306 per 100,000)	

[a] Number of individuals exposed to at least one dose (Table 5).
[b] Data from patients categorized as having COVID-19 in La Paz Hospital during the study period

Graphical abstract.

Ethical aspects

This study was conducted in accordance with the Declaration of Helsinki and approved by the La Paz Hospital Ethics Committee, Madrid, Spain.

Institutional review board statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the La Paz Hospital Ethics Committee, Madrid, Spain (protocol code PI-5138, January 17, 2022).

Informed consent statement

Patient consent was waived due to the study's retrospective nature, in accordance with the national legislation and the institutional requirements.

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CRediT authorship contribution statement

Ramírez Elena: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Gómez López de las Huertas Arturo:** Investigation, Writing – original draft. **Jiménez-González María:** Formal analysis, Methodology, Writing – original draft. **Urroz Elizalde Mikel:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **Guijarro Eguinoa Francisco Javier:** Investigation, Writing – original draft.

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2024.116181.

References

[1] World Health Organisation. WHO Director-General's Remarks at the Media Briefing on 2019-nCoV on 11 February 2020. Available at: ⟨https://www.who.in

t/director-general/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020⟩ [Accessed September 1, 2023].
[2] WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020" World Health Organization (WHO). March 11, 2020] Available at ⟨https://www.who.int/es/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020⟩ [Accessed September 1, 2023].
[3] Nota de prensa, Ministerio de Sanidad y Consumo del Gobierno de España. Available at [Press release, Ministry of Health and Consumer Affairs of the Government of Spain]. Available at ⟨https://www.sanidad.gob.es/gabinete/notasPrensa.do?id=5182⟩ [Accessed September 1, 2023].
[4] Comirnaty. Summary of Product Characteristics. Available at: ⟨https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf⟩ [Accessed September 1, 2023].
[5] Spikevax. Summary of Product Characteristics. Available at: ⟨https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf⟩ [Accessed September 1, 2023].
[6] Vaxzevria, Summary of Product Characteristics. Available at: ⟨https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf⟩ [Accessed September 1, 2023].
[7] COVID-19 Janssen vaccine. Summary of Product Characteristics. Available at:: ⟨https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-janssen-epar-product-information_en.pdf⟩ [Accessed September 1, 2023].
[8] S.B. Black, B. Law, R.T. Chen, C.L. Dekker, M. Sturkenboom, W.T. Huang, M. Gurwith, G. Poland, The critical role of background rates of possible adverse events in the assessment of COVID-19 vaccine safety, Vaccine 39 (19) (2021) 2712–2718, https://doi.org/10.1016/j.vaccine.2021.03.016.
[9] H.W. Kim, E.R. Jenista, D.C. Wendell, C.F. Azevedo, M.J. Campbell, S.N. Darty, M. A. Parker, R.J. Kim, Patients with acute myocarditis following mRNA COVID-19 vaccination, JAMA Cardiol. 6 (10) (2021) 1196–1201, https://doi.org/10.1001/jamacardio.2021.2828.
[10] J. Montgomery, M. Ryan, R. Engler, D. Hoffman, B. McClenathan, L. Collins, D. Loran, D. Hrncir, K. Herring, M. Platzer, N. Adams, A. Sanou, L.T. Cooper Jr., Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military, JAMA Cardiol. 6 (10) (2021) 1202–1206, https://doi.org/10.1001/jamacardio.2021.2833.
[11] Comirnaty and spikevax: Possible link to very rare cases of myocarditis and pericarditis. (EMA press office (2021). [cited 2021 Dec 15]. Available at: ⟨https://www.ema.europa.eu/en/news/comirnaty-spikevax-possible-link-very-rare-cases-myocarditis-pericarditis⟩ [Accessed September 1, 2023].
[12] Ø. Karlstad, P. Hovi, A. Husby, T. Härkänen, R.M. Selmer, N. Pihlström, J. V. Hansen, H. Nohynek, N. Gunnes, A. Sundström, J. Wohlfahrt, T.A. Nieminen, M. Grünewald, H.L. Gulseth, A. Hviid, R. Ljung, SARS-CoV-2 vaccination and myocarditis in a nordic cohort study of 23 million residents, JAMA Cardiol. 7 (6) (2022) 600–612, https://doi.org/10.1001/jamacardio.2022.0583.
[13] S. Le Vu, M. Bertrand, M.J. Jabagi, J. Botton, J. Drouin, B. Baricault, A. Weill, R. Dray-Spira, M. Zureik, Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines, Nat. Commun. 13 (1) (2022 25) 3633, https://doi.org/10.1038/s41467-022-31401-5.
[14] S.H. Bots, J. Riera-Arnau, S.V. Belitser, et al., Myocarditis and pericarditis associated with SARS-CoV-2 vaccines: A population-based descriptive cohort and a nested self-controlled risk interval study using electronic health care data from four European countries, Front Pharm. 13 (2022) 1038043, https://doi.org/10.3389/fphar.2022.1038043.
[15] Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. Roth Journal of the American College of Cardiology;76 (25);2982–3021. Available in: https://doi.org/10.1016/j.jacc.2020.11.010.
[16] A.L. Caforio, S. Pankuweit, E. Arbustini, C. Basso, J. Gimeno-Blanes, S.B. Felix, M. Fu, T. Heliö, S. Heymans, R. Jahns, K. Klingel, A. Linhart, B. Maisch, W. McKenna, J. Mogensen, Y.M. Pinto, A. Ristic, H.P. Schultheiss, H. Seggewiss, L. Tavazzi, G. Thiene, A. Yilmaz, P. Charron, P.M. Elliott, European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, , 2648a-2648d, Eur. Heart J. 34 (33) (2013) 2636–2648, https://doi.org/10.1093/eurheartj/eht210.
[17] E. Ammirati, M. Cipriani, C. Moro, C. Raineri, D. Pini, P. Sormani, R. Mantovani, M. Varrenti, P. Pedrotti, C. Conca, A. Mafrici, A. Grosu, D. Briguglia, S. Guglielmetto, G.B. Perego, S. Colombo, S.I. Caico, C. Giannattasio, A. Maestroni, V. Carubelli, M. Metra, C. Lombardi, J. Campodonico, P. Agostoni, G. Peretto, L. Scelsi, A. Turco, G. Di Tano, C. Campana, A. Belloni, F. Morandi, A. Mortara, A. Cirò, M. Senni, A. Gavazzi, M. Frigerio, F. Oliva, P.G. Camici, Registro Lombardo delle Miocarditi. Clinical Presentation and Outcome in a Contemporary Cohort of Patients With Acute Myocarditis: Multicenter Lombardy Registry, Circulation 138 (11) (2018) 1088–1099, https://doi.org/10.1161/CIRCULATIONAHA.118.035319.
[18] C. Tschöpe, E. Ammirati, B. Bozkurt, A.L.P. Caforio, L.T. Cooper, S.B. Felix, J. M. Hare, B. Heidecker, S. Heymans, N. Hübner, S. Kelle, K. Klingel, H. Maatz, A. S. Parwani, F. Spillmann, R.C. Starling, H. Tsutsui, P. Seferovic, S. Van Linthout, Myocarditis and inflammatory cardiomyopathy: current evidence and future directions, Nat. Rev. Cardiol. 18 (3) (2021) 169–193, https://doi.org/10.1038/s41569-020-00435-x. Epub 2020 Oct 12.
[19] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey Jr, M.H. Drazner, G. C. Fonarow, S.A. Geraci, T. Horwich, J.L. Januzzi, M.R. Johnson, E.K. Kasper, W. C. Levy, F.A. Masoudi, P.E. McBride, J.J. McMurray, J.E. Mitchell, P.N. Peterson, B. Riegel, F. Sam, L.W. Stevenson, W.H. Tang, E.J. Tsai, B.L. Wilkoff, 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, Circulation 128 (16) (2013) 1810–1852, https://doi.org/10.1161/CIR.0b013e31829e8807. Epub 2013 Jun 5.
[20] Cooper L.T. Treatment and prognosis of myocarditis in adults. Uptotade.com. Acceso el 21/12/2021. Available at ⟨https://www.uptodate.com/contents/treatment-and-prognosis-of-myocarditis-in-adults?search=micarditis&topicRef=4939&source=see_link⟩ [Accessed September 1, 2023].
[21] Y. Adler, P. Charron, M. Imazio, L. Badano, G. Barón-Esquivias, J. Bogaert, A. Brucato, P. Gueret, K. Klingel, C. Lionis, B. Maisch, B. Mayosi, A. Pavie, A. D. Ristic, M. Sabaté Tenas, P. Seferovic, K. Swedberg, W. Tomkowski, ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS), Eur. Heart J. 36 (42) (2015) 2921–2964, https://doi.org/10.1093/eurheartj/ehv318. Epub 2015 Aug 29.
[22] V. Kytö, J. Sipilä, P. Rautava, Clinical profile and influences on outcomes in patients hospitalized for acute pericarditis, Circulation 130 (18) (2014) 1601–1606, https://doi.org/10.1161/CIRCULATIONAHA.114.010376.
[23] Imazio, M. Acute pericarditis: Clinical presentation, diagnostic evaluation, and diagnosis. Uptodate.com. Available at: ⟨https://www.uptodate.com/contents/acute-pericarditis-clinical-presentation-and-diagnosis⟩ [Accessed September 1, 2023].
[24] Imazio, M. Acute pericarditis: Treatment and prognosis. Uptodate.com. Available at: ⟨https://www.uptodate.com/contents/acute-pericarditis-treatment-and-prognosis⟩ [Accessed September 1, 2023].
[25] M. Imazio, E. Cecchi, B. Demichelis, S. Ierna, D. Demarie, A. Ghisio, F. Pomari, L. Coda, R. Belli, R. Trinchero, Indicators of poor prognosis of acute pericarditis, Circulation 115 (21) (2007) 2739–2744, https://doi.org/10.1161/CIRCULATIONAHA.106.662114.
[26] Evolution of the registered population. Madrid's community statistical institute. Accesed on May 22, 2023. Available at: ⟨http://www.madrid.org/iestadis/fijas/estructu/general/anuario/ianucap02.htm⟩ [Accessed September 1, 2023].
[27] Instituto Nacional de Estadística (INE). Principales series de población desde 1998. [National Institute of Statistics (INE). Main population series since 1998.]. Aviablable at: ⟨https://www.ine.es/jaxi/Tabla.htm?path=/t20/e245/p08/l0/&file=02003.px&L=0⟩ [Accessed September 1, 2023].
[28] Total population assigned to the La Paz Hospital. Madrid's community statistical institute. Accesed on May 22, 2023. Available at: ⟨https://gestiona.comunidad.madrid/desvan/desvan/AccionDatosUnaSerie.icm?codSerie=1146199⟩ [Accessed September 1, 2023].
[29] GIV COVID-19, Comprehensive management of COVID-19 vaccination. Spanish Ministry of Health. Accesed on May 22, 2023. Available in: ⟨https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Informe_GIV_comunicacion_20220110.pdf⟩ [Accessed September 1, 2023].
[30] Nuvaxovid. Summary of Product Characteristics. Available at: ⟨https://www.ema.europa.eu/en/documents/product-information/nuvaxovid-epar-product-information_en.pdf⟩ [Accessed September 1, 2023].
[31] C. Aguirre, M. García, Evaluación de la causalidad en las comunicaciones de reacciones adversas a medicamentos. Algoritmo del Sistema Español de Farmacovigilancia Causality assessment in reports on adverse drug reactions. Algorithm of Spanish pharmacovigilance system, Med Clin. 147 (10) (2016) 461–464, https://doi.org/10.1016/j.medcli.2016.06.012.
[32] A.M. Borobia, A.J. Carcas, F. Arnalich, R. Álvarez-Sala, J. Monserrat-Villatoro, M. Quintana, J.C. Figueira, R.M. Torres Santos-Olmo, J. García-Rodríguez, A. Martín-Vega, A. Buño, E. Ramírez, G. Martínez-Alés, N. García-Arenzana, M. C. Núñez, M. Martí-de-Gracia, F. Moreno Ramos, F. Reinoso-Barbero, A. Martin-Quiros, A. Rivera Núñez, J. Mingorance, C.J. Carpio Segura, D. Prieto Arribas, E. Rey Cuevas, C. Prados Sánchez, J.J. Rios, M.A. Hernán, J. Frías, J.R. Arribas, On Behalf Of The Covid Hulp Working Group, A cohort of patients with COVID-19 in a major teaching hospital in Europe, J. Clin. Med 9 (6) (2020) 1733, https://doi.org/10.3390/jcm9061733.
[33] A. Husby, J.V. Hansen, E. Fosbøl, E.M. Thiesson, M. Madsen, R.W. Thomsen, H. T. Sørensen, M. Andersen, J. Wohlfahrt, G. Gislason, C. Torp-Pedersen, L. Køber, A. Hviid, SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study, BMJ 375 (2021) e068665, https://doi.org/10.1136/bmj-2021-068665.
[34] H.L. Wong, M. Hu, C.K. Zhou, P.C. Lloyd, K.L. Amend, D.C. Beachler, A. Secora, C. N. McMahill-Walraven, Y. Lu, Y. Wu, R.P. Ogilvie, C. Reich, D.A. Djibo, Z. Wan, J. D. Seeger, S. Akhtar, Y. Jiao, Y. Chillarige, R. Do, J. Hornberger, J. Obidi, R. Forshee, A. Shoaibi, S.A. Anderson, Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases, Lancet 399 (10342) (2022) 2191–2199, https://doi.org/10.1016/S0140-6736(22)00791-7.
[35] K. Goddard, K.E. Hanson, N. Lewis, E. Weintraub, B. Fireman, N.P. Klein, Incidence of myocarditis/pericarditis following mRNA COVID-19 vaccination among children and younger adults in the United States, Ann. Intern Med 175 (12) (2022) 1169–1771, https://doi.org/10.7326/M22-2274. Epub 2022 Oct 4.
[36] A. Arola, E. Pikkarainen, J.O. Sipilä, J. Pykäri, P. Rautava, V. Kytö, Occurrence and features of childhood myocarditis: a nationwide study in Finland, J. Am. Heart Assoc. 6 (11) (2017) e005306, https://doi.org/10.1161/JAHA.116.005306.
[37] T.K. Boehmer, L. Kompaniyets, A.M. Lavery, J. Hsu, J.Y. Ko, H. Yusuf, S. D. Romano, A.V. Gundlapalli, M.E. Oster, A.M. Harris, Association between COVID-19 and myocarditis using hospital-based administrative data - United

States, March 2020-January 2021, MMWR Morb. Mortal. Wkly Rep. 70 (35) (2021) 1228–1232, https://doi.org/10.15585/mmwr.mm7035e5.
[38] F.E. Karch, C.L. Smith, B. Kerzner, et al., Adverse drug reactions-a matter of opinion, Clin. Pharm. Ther. 19 (5 Pt 1) (1976) 489–492.
[39] S. Blanc, P. Leuenberger, J.P. Berger, et al., Judgments of trained observers on adverse drug reactions, Clin. Pharm. Ther. 25 (5 Pt 1) (1979) 493–498.
[40] A.F. Macedo, F.B. Marques, C.F. Ribeiro, Can decisional algorithms replace global introspection in the individual causality assessment of spontaneously reported ADRs? Drug Saf. 29 (2006) 697–702.