Coronavirus disease 2019 vaccination-related pericarditis: a single tertiary-center experience

Valentino Collini[a,b], Massimo Imazio[b], Marzia De Biasio[b] and Gianfranco Sinagra[a]

Aims **Vaccination represents a cornerstone of prevention in the COVID-19 pandemic. Rare adverse events including acute pericarditis and myopericarditis have been reported.**

Methods **All consecutive patients referred to our referral center for pericardial diseases following COVID-19 vaccination from 1 April 2021 to 15 April 2022 were included. Acute pericarditis and myopericarditis were diagnosed according to ESC guidelines. Patients with SARS-CoV-2 infection were excluded from the study.**

Results **Twenty-four patients (79% men) aged 39.7 ± 19.8 years were referred to our center with pericarditis after receiving COVID-19 vaccination. Thirteen (54%) patients were diagnosed with myopericarditis. The mean time between vaccination and symptoms onset was 7.0 ± 4.9 days, and the most frequent symptom was pericarditic chest pain (83%). Respectively, 50 and 33% of patients presented after the second and the third dose of the vaccine. Almost all patients were treated with both nonsteroidal anti-inflammatory drugs and colchicine. Five patients (21%) experienced a recurrence of pericarditis. No patient died or developed constrictive pericarditis. Mean follow-up was 8.0 ± 3.2 months.**

Conclusion **COVID-19 vaccine-related pericarditis typically manifest with mild clinical signs, in young male individuals, a few days after the second or third vaccine dose and are commonly characterized by a rapid complete recovery.**

J Cardiovasc Med 2022, **23**:779–783

Keywords: coronavirus disease 2019, pericarditis, vaccination

[a]Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste and [b]Cardiology, Cardiothoracic Department, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Udine, Italy

Correspondence to Massimo Imazio, MD, FESC, Cardiology, Cardiothoracic Department, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Piazzale Santa Maria della Misericordia 15, 33100 Udine, Italy
E-mail: massimo_imazio@yahoo.it

Introduction

Acute pericarditis is an inflammatory pericardial syndrome defined by the presence of two or more of the following features: chest pain, pericardial friction rub, diffuse concave upward ST-elevation or PR depression on ECG and new or worsening pericardial effusion. Myopericarditis is defined as the presence of acute pericarditis with elevation of troponin and/or new or presumed new focal or global left ventricular systolic dysfunction. Myocardial involvement is usually confirmed noninvasively by cardiac magnetic resonance.[1] The incidence of acute pericarditis has been reported as 27.7 cases per 100 000 population per year and is responsible for 0.1% of all hospital admissions.[2]

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic that has affected the lives of billions of individuals worldwide. In the absence of effective therapies against SARS-CoV-2, vaccination is crucial to limit the pandemic spread of COVID-19 and reduce mortality. Clinical trials demonstrated that the COVID-19 vaccines are both well tolerated and effective and no clinical trial has reported major cardiovascular events, including pericarditis.[3,4] Due to these findings, the European Medical Agency has authorized four vaccines to prevent COVID-19 [Comirnaty (BNT162b2), Jcovden (Ad26.COV2-S), Spikevax (mRNA-1273), Vaxzevria (AZD1222)] and the vaccination campaign began in Italy, as in all Europe on the 27 December 2020.

Several cases of vaccine-related myocarditis have been reported in literature; however, there is a paucity of information regarding pericarditis and events after the third vaccination dose.

Methods

We included all consecutive patients admitted with pericarditis following SARS-CoV-2 vaccination to the Cardiology Department of the University Hospital of Udine, between 1 April 2021 and 15 April 2022. The time interval between vaccination and the onset of pericarditis symptoms had to be less than 15 days (independently from the dose).[5]

Acute pericarditis and myopericarditis were diagnosed by the 2015 European Society of Cardiology guidelines for the diagnosis and management of pericardial diseases[1] and all patients had negative reverse transcription–PCR of nasopharyngeal swabs for SARS-CoV-2.

Baseline characteristics of study patients were summarized as frequencies and percentages for categorical variables and median ± range/interquartile range (IQR) for continuous variables. As an exploratory analysis, we compared clinical characteristics between patients with acute pericarditis and myopericarditis.

Fisher's exact test was used for categorical variables and unpaired Student's *t*-test or Mann–Whitney *U* test for continuous variables. A two-tailed *P* less than 0.05 was considered statistically significant.

Results

Details are provided in Table 1. Nineteen (79%) male and five (21%) female patients diagnosed with pericarditis after receiving COVID-19 vaccination were included. The mean age was 39.7 ± 19.8 years. Eleven (46%) patients had acute pericarditis and 13 patients had myopericarditis. Patients who developed myopericarditis were younger (26 vs. 55 years, $P < 0.001$), had fewer comorbidities (no comorbidities in 92 vs. 45%, $P = 0.02$) and more frequently had a history of previous pericarditis (38 vs. 0%) than those who developed acute pericarditis. Overall, four were active or former smokers, and the most common comorbidity was hypertension (25% of patients). One patient experienced a recurrence 11 months after mild pericarditis related to SARS-CoV-2 infection; four patients relapsed after previous idiopathic pericarditis (mean time 21.2 ± 7.3 months). One patient developed pericarditis after AZD1222 vaccination, all others (96%) after mRNA vaccines. Most patients developed pericarditis after the second or the third dose of vaccine (50 and 33%, respectively). The mean time between vaccination and symptoms onset was 7.0 ± 4.9 days and the most frequent symptom was pericarditic chest pain (83%) followed by fever and dyspnea. The most common abnormal ECG finding was diffuse ST-elevation and PR depression (63%, most frequent in acute pericarditis). All patients with definitive myopericarditis underwent cardiac magnetic resonance within 15 days from clinical presentation, which confirmed the clinical diagnosis. No patient underwent endomyocardial biopsy because of stable and uncomplicated cases with myocardial involvement. Pericardial effusion was found in 11 (46%) patients and was reported as mild in 8 patients. No patient needed pericardial drainage. Four patients with myopericarditis had mild reduction of LVEF at presentation and during follow-up. The median values of C-reactive protein were 60 mg/l. Most patients (75%) were treated with dual therapy, and the most used drugs were colchicine and ibuprofen (88 and 83% of patients, respectively). All patients with myopericarditis and six patients with acute pericarditis were hospitalized with a median length of stay of 4.2 ± 2.6 days. Four patients developed a recurrence of pericarditis and one received anakinra after failure of therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and prednisone. Mean follow-up was 8.0 ± 3.2 months.

Discussion

Historically, postvaccination myocarditis and pericarditis have been reported as a rare adverse event, especially after live-attenuated smallpox vaccine[6] and less frequently for diphtheria, poliomyelitis, tetanus, influenza and hepatitis B.[7,8]

Although acute pericarditis and myopericarditis were not observed as adverse events in coronavirus disease 2019 vaccine trials,[3] suspected cases have been reported following vaccination, particularly in adolescents and young adults.[9,10]

In this article, we summarize 24 cases of COVID-19 vaccine-related pericarditis and discuss their association with the vaccination.

The average number of pericarditis observed every 3 months during the vaccine period was significantly higher than during the prevaccination period (12.3 ± 0.8 vs. 6.2 ± 1.9, $P < 0.001$) (Fig. 1).

In our cases, young healthy men (<40 years old) were at higher risk of developing pericardial and myocardial inflammation after COVID-19 vaccination, and this was consistent with the literature.[11,12]

This result could be because of increased levels of inflammatory cytokines at puberty, and the sex difference may be explained by the pro-inflammatory role of testosterone in male individuals, as opposed to the anti-inflammatory role of estrogen in female individuals.[13]

This pro-inflammatory state also appears to be the cause of the severe hyper-inflammation condition (i.e. Multisystem Inflammatory Syndrome in Children), which has been described in children, within 2–4 weeks of SARS-CoV-2 infection. This syndrome can result in a severe clinical course requiring intensive care management with a mortality rate of 1–2%.[14]

The typical onset of symptoms, usually after the second or third dose of the vaccine (83% of our patients), suggests an immune-mediated mechanism because of an important cytokine activation of preexisting autoreactive immune cells.[15] In this regard, it could be interesting to consider an assessment of serological evidence for prior SARS-CoV2 infection, especially in young subjects with pericarditis after the first dose. Furthermore, in our patients, the average time between the second and third dose of vaccine was less than 6 months (5.3 ± 0.8), and this short time between doses, in susceptible individuals, may have promoted the above exaggerated autoreactive response.

As for idiopathic or virus-related pericarditis, the common clinical presentation was chest pain[16] and the most frequent ECG abnormality was widespread ST-segment elevation with PR depression. ECG changes were not associated with a worse prognosis.[17]

Table 1 Main data from the studied population

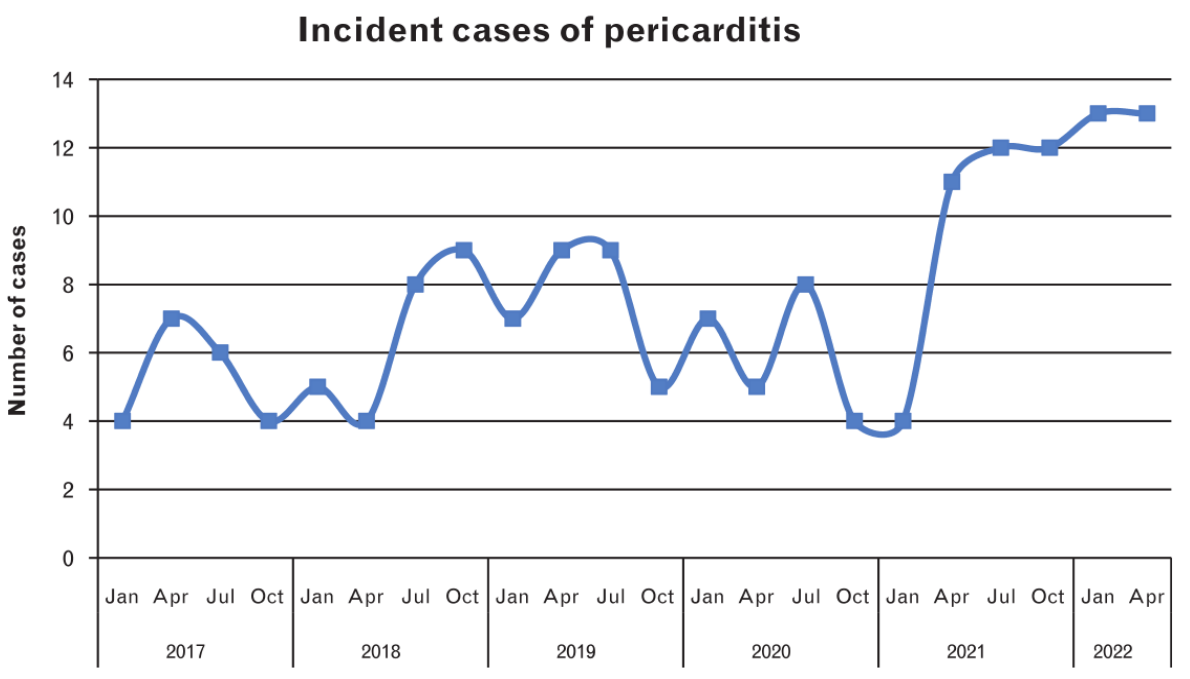
	Total ($n=24$)	Acute pericarditis ($n=11$)	Myopericarditis ($n=13$)	*P*-value
Age (years) (mean ± SD)	39.7 ± 19.8	55.3 ± 17.6	26.5 ± 9.0	<0.01[a]
Male sex (*n*)	19/24 (79%)	8/11 (73%)	11/13 (85%)	0.63[b]
Comorbidities				
No comorbidities	17/24 (71%)	5/11 (45%)	12/13 (92%)	0.02[b]
BMI >25 (kg/m^2)	16/24 (67%)	8/11 (73%)	8/13 (62%)	0.68[b]
Diabetes type II	2/24 (8%)	1/11 (9%)	1/13 (8%)	1[b]
Smoker (active or former)	5/24 (21%)	4/11 (36%)	1/13 (8%)	0.14[b]
Hypertension	6/24 (25%)	4/11 (36%)	2/13 (15%)	0.35[b]
Hypercholesterolemia	3/24 (13%)	2/11 (18%)	1/13 (8%)	0.58[b]
Autoimmune disease	3/24 (13%)	2/11 (18%)	1/13 (8%)	0.58[b]
History of pericarditis	5/24 (21%)	0/11 (0%)	5/13 (38%)	0.04[b]
History of COVID-19 disease	2/24 (8%)	0/11 (0%)	2/13 (15%)	0.48[b]
Others	5/24 (21%)	5/11 (45%)	0/13 (0%)	0.01[b]
Vaccine type				
BNT162b2	16/24 (67%)	8/11 (73%)	8/13 (62%)	0.68[b]
mRNA-1273	7/24 (29%)	2/11 (18%)	5/13 (38%)	0.39[b]
AZD1222	1/24 (4%)	1/11 (9%)	0/13 (0%)	0.46[b]
Ad26.COV2-S	0/24 (0%)	0/11 (0%)	0/13 (0%)	1[b]
Dose given				
First	4/24 (17%)	2/11 (18%)	2/13 (15%)	1[b]
Second	12/24 (50%)	5/11 (45%)	7/13 (54%)	1[b]
Third	8/24 (33%)	4/11 (36%)	4/13 (31%)	1[b]
Time between second and third vaccine (months ± SD)	5.3 ± 0,8	5.4 ± 0,6	5.3 ± 0,9	0.10[a]
Clinical findings [no (%)]				
Timing of pericarditis diagnosis (days ± SD)	7.0 ± 4.9	8.5 ± 4.6	5.7 ± 4.7	0.17[a]
Pericarditic chest pain	20/24 (83%)	10/11 (91%)	10/13 (77%)	0.60[b]
Pericardial rub	3/24 (13%)	2/11 (18%)	1/13 (8%)	0.58[b]
Fever	10/24 (42%)	5/11 (45%)	5/13 (38%)	1[b]
Dyspnea	10/24 (42%)	3/11 (27%)	7/13 (54%)	0.24[b]
Cough	6/24 (25%)	2/11 (18%)	4/13 (31%)	0.65[b]
Others	11/24 (46%)	5/11 (45%)	6/13 (46%)	1[b]
ECG				
ST-segment elevation and PR depression	15/24 (63%)	8/11 (73%)	7/13 (54%)	0.42[b]
T wave inversion	6/24 (25%)	2/11 (18%)	4/13 (31%)	0.65[b]
Others	3/24 (13%)	1/11 (9%)	2/13 (15%)	1[b]
Echo findings				
Pericardial effusion	11/24 (46%)	7/11 (64%)	4/13 (31%)	0.22[b]
Mild	8/11 (73%)	4/7 (57%)	4/4 (100%)	0.24[b]
Moderate	2/11 (18%)	2/7 (29%)	0/4 (0%)	0.49[b]
Large	1/11 (9%)	1/7 (14%)	0/4 (0%)	1[b]
Cardiac tamponade	0/24 (0%)	0/11 (0%)	0/13 (0%)	1[b]
Ejection fraction (<55%)	4/24 (17%)	0/11 (0%)	4/13 (31%)	0.10[b]
Laboratory				
WBC (cells/μl) [median (IQR)]	10 525 (7400–13 000)	10 556.4 (7600–13 000)	10 497.5 (6825–12 995)	0.95[c]
CRP level (mg/l) [median (IQR)]	60.2 (25–99)	74.2 (30–125)	44.5 (14–49)	0.29[c]
Elevated Hs-TNI	16/24 (67%)	3/11 (27%)	13/13 (100%)	<0.01[b]
Medications, no (%)				
One anti-inflammatory drug	4/24 (17%)	2/11 (18%)	2/13 (15%)	1[b]
Two anti-inflammatory drugs	18/24 (75%)	8/11 (73%)	10/13 (77%)	1[b]
More than three anti-inflammatory drugs	2/24 (8%)	1/11 (9%)	1/13 (8%)	1[b]
Colchicine	21/24 (88%)	10/11 (91%)	11/13 (85%)	1[b]
Ibuprofen	20/24 (83%)	9/11 (82%)	11/13 (85%)	1[b]
Aspirin	1/24 (4%)	1/11 (9%)	0/13 (0%)	0.46[b]
Prednisone	5/24 (21%)	2/11 (18%)	3/13 (23%)	1[b]
Anakinra	1/24 (4%)	1/11 (9%)	0/13 (0%)	0.46[b]
Outcomes				
Admitted to hospital	19/24 (79%)	6/11 (55%)	13/13 (100%)	0.01[b]
Hospitalization (days ± SD)	4.2 ± 2.6	5 ± 2.7	2,57 ± 1.4	0.21[a]
Pericarditis recurrence	5/24 (21%)	2/11 (18%)	3/13 (23%)	1[b]
Constrictive pericarditis	0/24 (0%)	0/11 (0%)	0/13 (0%)	1[b]
Death	0/24 (0%)	0/11 (0%)	0/13 (0%)	1[b]
Mean follow-up (months)	8.0 ± 3.2	8.2 ± 3.5	7.9 ± 2.8	0.85[a]

COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IQR, interquartile range; SD, standard deviation; WBC, white blood cell. [a] Student's *t*-test. [b] Fisher's exact test. [c] Mann–Whitney *U* test.

According to the literature,[18] these inflammatory heart diseases appear to be a typical adverse event following mRNA vaccines (96% of our patients) compared with the recombinant adenovirus vector-based vaccine (only one patient in our series).

Although the exact mechanism underlying mRNA vaccine-related pericarditis is poorly understood, it has been proposed that, in the presence of a genetic predisposition, the otherwise less immunogenic modified spike protein-coding mRNA molecule used in the vaccine is detected

Fig. 1



Number of pericarditis admitted every 3 months in our hospital.

as antigen. This leads to activation of an aberrant immune system response resulting in a pro-inflammatory cascade.[15]

For this reason, extreme caution is required in administering the vaccine to chronically immunosuppressed subjects and in those with immune-mediated diseases or a recent history of pericarditis (4, 13 and 21% of our patients, respectively). In our cases, a patient known for previous postviral pericarditis and celiac disease, developed myopericarditis 14 days after the second dose of the vaccine and 37 days after the third one.

Other possible mechanisms could be a molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens[19] (i.e. a cross-reaction between antibodies against SARS-CoV-2 spike glycoproteins and α-myosin has been experimentally demonstrated) or a nonspecific innate inflammatory response.[20]

All patients diagnosed with myopericarditis underwent cardiac MRI within 15 days from clinical presentation and tissue characterization using T1 and/or T2 mapping was suggestive for acute myocarditis in all cases.[21,22] No patient underwent endomyocardial biopsy as all myopericarditis appeared transient and self-limited.[23]

We found pericardial effusion in 11 (46%) patients and was reported as large only in one patient. As in previous reports, pericardial effusion does not seem related to the severity of the pericarditis, unlike what happens in COVID-19 patients in which it appears related to poor prognosis.[24]

No data are available on specific treatment for vaccine-associated pericarditis; however, favorable evolution with prompt resolution of symptoms has been reported in most cases. The most commonly used therapeutic strategy includes anti-inflammatory drugs and guided medical therapy if left ventricular function is reduced. In tachycardic patients, beta-blocker drugs may also improve symptoms by slowing heart rate.[25]

In our case series, four patients were treated with only one anti-inflammatory drug and almost all others were treated with the mainstay therapy for acute pericarditis:[1] the combination therapy with colchicine and NSAIDs.

Overall, short-term clinical outcomes have been favourable, without relevant arrhythmias and with rapid complete recovery. No patient developed cardiac tamponade, only four patients had a recurrence of pericarditis and one (already known for autoimmune disease) received anakinra after failure of therapy with NSAIDs, colchicine and prednisone.

These findings seem to confirm the mild clinical course of this condition and support the effectiveness of evidence-based therapy for acute pericarditis in this setting as well.

Limitations

First, the study was composed of a small sample of a single large center, limiting the generalizability of the results. Second, it is an observational study, thus prospective studies with larger patient cohorts are needed to confirm our findings. Third, temporal association does not

prove causation, although the short time span between vaccination and pericarditis onset strongly supports the possible relationship. Fourth, although all published studies had reported clinical outcomes in the short term, the mid-term to long-term prognosis remains unknown.

Conclusion

We report 24 cases of pericarditis after COVID-19 vaccination. Most cases were in young healthy male individuals, within a few days after the second or third vaccination, typically with mild clinical signs and were commonly self-limited. In conclusion, despite these rare side effects, the benefits of COVID-19 vaccination clearly outweigh the limited risk of pericarditis and myocarditis, and vaccination is strongly recommended to prevent COVID-19 infection, transmission and related complications.

Conflicts of interest

There are no conflicts of interest.

References

1 Adler Y, Charron P, Imazio M, *et al.* 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* 2015; **36**:2921–2964.

2 Imazio M, Cecchi E, Demichelis B. Myopericarditis versus viral or idiopathic acute pericarditis. *Heart* 2008; **94**:498–501.

3 Baden LR, El Sahly HM, Essink B, *et al.*, COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; **384**:403–416.

4 Polack FP, Thomas SJ, Kitchin N, *et al.*, C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; **383**:2603–2615.

5 Sinagra G, Porcari A, Merlo M, *et al.* Miocarditi, pericarditi e vaccino a mRNA contro il COVID-19. Expert opinion della Società Italiana di Cardiologia [Myocarditis and pericarditis following mRNA COVID-19 vaccination: expert opinion of the Italian Society of Cardiology]. *G Ital Cardiol (Rome)* 2021; **22**:894–899.

6 Mei R, Raschi E, Forcesi E, Diemberger I, De Ponti F, Poluzzi E. Myocarditis and pericarditis after immunization: gaining insights through the vaccine adverse event reporting system. *Int J Cardiol* 2018; **273**:183–186.

7 Su JR, McNeil MM, Welsh KJ, *et al.* Myopericarditis after vaccination, Vaccine Adverse Event Reporting System (VAERS), 1990–2018. *Vaccine* 2021; **39**:839–845.

8 Engler RJ, Nelson MR, Collins LC Jr, *et al.* A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. *PLoS One* 2015; **10**: e0118283.

9 Marshall M, Ferguson ID, Lewis P, *et al.* Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. *Pediatrics* 2021; **148**:e2021052478.

10 Snapiri O, Vanziger CR, Chairman N, *et al.* Transient cardiac injury in adolescents receiving the BNT162b2 mRNA COVID-19 vaccine. *Pediatr Infect Dis J* 2021; **40**:e360–e363.

11 Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. *JAMA* 2021; **326**:1210–1212.

12 Yap J, Tham MY, Poh J, *et al.* Pericarditis and myocarditis after COVID-19 mRNA vaccination in a nationwide setting. *Ann Acad Med Singap* 2022; **51**:96–100.

13 Girón-González JA, Moral FJ, Elvira J, *et al.* Consistent production of a higher TH1:TH2 cytokine ratio by stimulated T cells in men compared with women. *Eur J Endocrinol* 2000; **143**:31–36.

14 Grimaud M, Starck J, Levy M, *et al.* Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. *Ann Ann Intensive Care* 2020; **10**:69.

15 Caso F, Costa L, Ruscitti P, *et al.* Could SARS-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? *Autoimmun Rev* 2020; **19**:102524.

16 Imazio M, Gaita F, LeWinter M. Evaluation and treatment of pericarditis: a systematic review. *JAMA* 2015; **314**:1498–1506.

17 Imazio M, Squarotti GB, Andreis A, *et al.* Diagnostic and prognostic role of the electrocardiogram in patients with pericarditis. *Heart* 2022.

18 Li M, Yuan J, Lv G, Brown J, Jiang X, Lu ZK. Myocarditis and pericarditis following COVID-19 vaccination: inequalities in age and vaccine types. *J Pers Med* 2021; **11**:1106.

19 Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. *Clin Immunol* 2020; **217**:108480.

20 Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry an immune cross-reaction. *Cell Mol Immunol* 2018; **15**:586–594.

21 Ferreira VM, Schulz-Menger J, Holmvang G, *et al.* Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol* 2018; **72**:3158–3176.

22 Friedrich MG, Sechtem U, Schulz-Menger J, *et al.*, International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. *J Am Coll Cardiol* 2009; **53**:1475–1487.

23 Sinagra G, Anzini M, Pereira NL, *et al.* Myocarditis in clinical practice. *Mayo Clin Proc* 2016; **91**:1256–1266.

24 Li K, Wu J, Wu F, *et al.* The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. *Invest Radiol* 2020; **55**:327–331.

25 Imazio M, Andreis A, Agosti A, *et al.* Usefulness of beta-blockers to control symptoms in patients with pericarditis. *Am J Cardiol* 2021; **146**:115–119.