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Myocarditis post SARS-CoV-2 vaccination: A systematic review

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Abstract:

Background: Variable clinical criteria taken by medical professionals across the world for myocarditis following COVID-19 vaccination along with wide variation in treatment necessitates understanding and reviewing the same.

O**bjectives and Method**s: A systematic review was conducted to elucidate the clinical findings, laboratory parameters, treatment and outcomes of individuals with Myocarditis after COVID-19 vaccination after registering with PROSPERO. Electronic databases including MEDLINE, EMBASE, PubMed, LitCovid, Scopus, ScienceDirect, Cochrane Library, Google Scholar, Web of Science were searched.

Results: A total of 85 articles encompassing 2184 patients were analysed. It was a predominantly male (73.4%) and young population (Mean age 25.5 $\pm$ 14.2 years) with most having taken an mRNA-based vaccines (99.4%). The mean duration from vaccination to symptom onset was 4.01 $\pm$ 6.99 days. Chest pain (90.1%), dyspnoea (25.7%) and fever (11.9%) were the most common symptoms. Only 2.3% had comorbidities. CRP was elevated in 83.3% and cardiac troponin in 97.6% patients. An abnormal ECG was reported in 979/1313 (74.6%) patients with ST-segment elevation being most common (34.9%). Echocardiographic data was available for 1243 patients (56.9%) of whom 288 (23.2%) had reduced left ventricular ejection fraction. NSAIDS (76.5%), steroids (14.1%) followed by colchicine (7.3%) were used for treatment. Only 6 patients died among 1317 of whom data was available.

Conclusion: Myocarditis following COVID-19 vaccination is often mild, seen more commonly in young healthy males and is followed by rapid recovery with conservative treatment. The emergence of this adverse event calls for harmonizing case definitions and definite treatment guidelines which require wider research.

Keywords- COVID-19, SARS-Cov-2, COVID-19 Vaccines, Myocarditis

Myocarditis post COVID-19 vaccination: A systematic review

Introduction:

Coronavirus disease 2019 (COVID-19) has spread as a pandemic causing global morbidity and mortality. Vaccination against COVID-19 infection is of prime importance during the ongoing pandemic as it can help in prevention of disease, lower the severity and decrease spread of COVID-19; especially following the emergence of novel COVID-19 variants of concern.[1] There are multiple types of COVID-19 vaccines including inactivated virus, virtual vector-based and RNA-based vaccines. Administration of COVID-19 vaccines can lead to Adverse events following vaccination (AEFI). COVID-19 vaccine related AEFI are most often mild[2] with local symptoms, however, at times there can be severe and systemic manifestations. One such AEFI reported recently is the vaccine induced myocarditis which was found to occur in various countries using the mRNA based COVID-19 vaccines. Post vaccination myocarditis has been previously reported as an adverse event[4] following smallpox and anthrax vaccines.[4] With an ever-expanding global coverage with mRNA vaccines, there has been an increase in the number of reported cases of myocarditis following COVID-19 vaccination. Current estimates suggest that the overall prevalence of COVID-19 vaccine associated myocarditis is around 3 per 100,000 patients (0.003%).[5] This led to the United States Food and Drug Administration adding a warning regarding the risk of myocarditis following administration of BNT162b2, and mRNA-1273 vaccines.[6] This systematic review was conducted to elucidate the clinical features, laboratory findings, treatment modalities and outcomes of individuals with myocarditis following COVID-19 vaccination.

Methods:

We aimed to evaluate the demographic profile, clinical signs and symptoms, laboratory findings, treatment modalities and outcomes of individuals with myocarditis following vaccination against COVID-19. Electronic databases including MEDLINE, EMBASE, PubMed, LitCovid, Scopus, ScienceDirect, Cochrane Library, Google Scholar, Web of Science were searched. Additionally, preprint repositories (BioRxiv and MedRxiv) and reference lists of the included studies were taken as additional sources. All publications in the English language from 1st December 2020 up to 10th January 2022 were reviewed. The combination of the following keywords was used as the search strategy for literature search in the various databases: "Age group [individuals with age restriction (12

years)] AND Vaccine (COVID-19 vaccine, novel coronavirus vaccine, SARS-CoV-2 vaccine, 2019-nCoV vaccine, severe acute respiratory syndrome coronavirus 2 vaccine, mRNA vaccine, BNT162b2 vaccine, Ad26.COV2. S vaccine, mRNA-1273 vaccine) AND Condition [Myocarditis, myopericarditis, heart inflammation]". The search strategy had focussed on keywords involving the myocarditis (myocarditis, myopericarditis), as well as the association with COVID-19 vaccine and individuals over 12 years of age. Studies including case reports, case series, case-control and observational (prospective or retrospective) studies, brief communications and letters to the editors which incorporated incidence, clinical, laboratory, imaging, as well as the hospital course of patients with myocarditis post COVID-19 vaccination in individuals above 12 years were included. Studies with no accessible full text versions, reporting cases with only pericarditis without myocarditis, no patient data or incomplete data and those which were not in English language were excluded. The titles and abstracts of the articles were screened based on the above inclusion criteria independently by three authors (PI, MG, DM). In case of any conflict, it was settled by the senior most author (PI). Following this, the entire text of all the articles was screened by two authors (SK and PI). The entire data collected included first author name, year, journal, country, study design, number of cases, study population, age, sex distribution, type of vaccine received, number of doses received, interval between symptoms and first dose, interval between symptoms and second dose, symptomatology, duration of symptoms, comorbidities, organ system involvement, laboratory investigations, cardiac imaging including echocardiography and cardiac magnetic resonance imaging (MRI) findings, complications, treatment details, need for intensive care unit (ICU) admission, oxygen support, mechanical ventilation, vasoactive drugs, renal replacement therapy, extracorporeal membrane oxygenation [ECMO], length of stay and outcome in terms of ICU stay, need for mechanical ventilation, inotropic support and mortality were recorded using Google Sheets (Google, Mountain View, CA, USA). All signs and symptoms pre and any time during the patient's hospitalization were included. All echocardiograms were taken into consideration. Ejection fraction (EF), wall motion abnormalities, valvular dysfunction, pericardial effusion, coronary artery dilation, or aneurysm were recorded. Cardiac dysfunction was defined as an LVEF <55% and was categorized into mild (LVEF: 41-55%), moderate (LVEF: 31-40%) and severe (LVEF: <30%) left ventricular (LV) dysfunction.[7] The diagnosis of vaccine induced myocarditis was based on the Brighton Collaboration case definition[8] which is enumerated in Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist were followed to guide the data extraction process. Study quality was determined based on the quality assessment tool published by the National Institutes of Health.[9] Furthermore, the level of evidence was assessed according to Sackett.[10] The study protocol was registered with PROSPERO (International

Prospective Register of Systematic Reviews) with the following registration number CRD42021287188. Continuous data was summarized as mean ± standard deviation and categorical data summarized as counts with percent. Data analysis was performed using SPSS Statistics version 24 for Mac (IBM Corporation). Important outcomes of the review were determining the clinical presentation and outcomes of myocarditis post vaccination against COVID-19 in individuals above 12 years for which (a) pooled estimate of demographic features, clinical details and organ system involvement, (b) pooled estimate of laboratory investigations, treatment details and (c) pooled estimate of outcome including length of stay, need for ICU stay, mechanical ventilation, inotropic support and mortality were calculated.

Results:

A total of 2011 potentially relevant abstracts were identified from Medline, PubMed, Embase, Scopus, Cochrane Library, WHO global COVID database and Google scholar from Dec 1, 2020 till Jan 10, 2022. Out of these, 1427 were removed as they were duplicates. Out of 584 studies left, 499 were excluded due to various reasons including articles not in English, inclusion criteria not met, only abstract, no data on myocarditis, focus on COVID-19 only, review article and scientific letter with no patient data. Ultimately, 85 articles were included in this review with a total sample size of 2184 patients who had developed myocarditis following COVID-19 vaccination (Figure 2 shows the PRISMA flow diagram). The summary of the included studies is summarized in Table 1.[11-95]

Demographic features and clinical characteristics:

Of the 2184 cases included, a majority of them were males (73.4%) with a mean age of 25.5 ± 14.2 years. Most of the patients (63.1%) belonged to the age group 0-20 years reflecting a high prevalence of vaccine induced myocarditis among young adults. Data regarding the race/ethnicity was available for 1688 (77.3%) individuals with subjects mostly belonging to the Caucasian (67.7%) and Hispanic (17.4%) ethnicity. The mean duration from vaccination to symptom onset was 4.01 ± 6.99 days. Chest pain (90.1%), dyspnoea (25.7%) and fever (11.9%) were the three most common presenting symptoms. Only a fraction (2.3%) of patients diagnosed with vaccine induced myocarditis had comorbidities such as hypertension (46%) and obesity (40%) as summarized in Table 2. Most of the patients with vaccine induced myocarditis were recipient of the mRNA-based vaccines (99.4%) while it was rare in those who had received Janssen Ad26.CoV2. S (0.3%), AZD1222/ChAdOx1 (0.2%) and COVAXIN (0.04%).

Laboratory, ECG and radiological investigations:

The details of various laboratory and radiological investigations have been summarized in Table 3. Inflammatory markers such as CRP was elevated in 325/390 (83.3%) patients. An elevated cardiac troponin T/ troponin I was reported in 1330/1363 (97.6%) patients while elevated Brain natriuretic peptide (BNP) and NT-pro BNP were observed in 24.5% and 65.6% patients each. An abnormal ECG was reported in 979/1313 (74.6%) patients with ST segment elevation in 342 (34.9%), T-wave inversion in 90 (9.2%), non-sustained ventricular tachycardia (NSVT) in 19 (1.9%), ventricular tachycardia (VT) and ventricular fibrillation (VF) in 1 (0.1%) patient each. Complete heart block and atrial fibrillation were reported in 2 (0.2%) patients each. Echocardiographic data was available for 1243 patients (56.9%) of whom 288 (23.2%) had a reduced left ventricular ejection fraction (LVEF<55%) while 955 (76.8%) had normal left ventricular systolic functions. Data regarding the severity of LV dysfunction was available in 119/288 (41.3%) patients with most of them [92 (77.3%)] having mild LV systolic dysfunction (LVEF:41-55%) with severe LV dysfunction (LVEF<30%) in only 15 (12.6%) patients. Right ventricular dysfunction was present in 8 (0.6%) while pericardial effusion was reported in 23 (1.8%). Data regarding CMR was available for 670 patients of whom had 424 (63.3%) evidence of myocardial edema, 541 (80.7%) had late gadolinium enhancement and 28 (4.2%) had pericardial effusion. None of the patients had any evidence of coronary artery aneurysms/obstructive coronary artery disease (CAD) on cardiac imaging. LGE had a predominant sub-epicardial distribution in 169 (86.2%) patients followed by mid-myocardial in 48 (24.5%) patients, subendocardial and transmural in 2 (1%) patients each.

Diagnosis of vaccine induced myocarditis:

A diagnosis of definite myocarditis was established in (523; 39.1%), probable in (797; 59.5%) and possible myocarditis in (19; 1.4%). In the majority of cases, this was based on symptoms, raised cardiac biomarkers and cardiac imaging findings supportive of myocarditis. However, a subset of patients (11;0.5%) underwent histopathological evaluation based on EMB (8;0.37%) or autopsy (3;0.14%) specimens. Histopathological findings included lympho-histiocytic myocarditis in 8 (0.37%) while in three patients (0.14%) there was no evidence of inflammatory infiltrate. Additionally, eosinophilic infiltrate was observed in four patients (0.18%) while none had any evidence of myocyte necrosis.

Treatment and outcomes:

Eighty-three (7.1%) of the patients diagnosed with vaccine induced myocarditis were admitted into the ICU. Shock was reported in 23 (1.9%) patients during the course of hospital stay mandating cardiovascular support in the form of inotropes in 23 (1.9%), intra-aortic balloon pump [IABP] in 1 (0.08%) or extracorporeal membrane oxygenation [ECMO] in 3 (0.2%). NIV support was reported in 3 (0.2%) and mechanical ventilation in 4 (0.3%)

patients. Table 4 summarizes the information regarding the treatment administered and the outcomes. A variety of anti-inflammatory therapies were used for the treatment of vaccine induced myocarditis including NSAIDS (891; 76.5%), steroids (164; 14.1%), colchicine (85; 7.3%), intravenous immunoglobulin (IVIG) (155; 13.3%) and biologics 3 (0.2%) such as Anakinra. Additional therapies included beta-blockers in 72 (6.2%), diuretics in 32 (2.7%), ACE inhibitors/ARBs in 51 (4.4%), ARNI in 3 (0.2%) patients. Concomitant antibiotic therapy was administered in 0.7% patients while 5.7% of the subjects' received anticoagulants. The mean duration of the hospital stay was 4.3±5.8 days. Data regarding the outcomes was available for 1317 subjects of whom 6 6 (0.5%) died during the course of hospital stay while 1311 (99.5%) were discharged from the hospital.

Discussion:

This review describes the demographic profile, clinical features, diagnostics and therapeutics of the patients developing myocarditis post COVID-19 vaccination. Our results indicated that post-COVID-19 vaccine myocarditis was more prevalent among young males with the majority of reported cases being below 20 years of age. The predilection for younger age could be due to stronger immune responses seen in this age group as compared to adults. Studies have reported that the levels of proinflammatory cytokines such as TNF-alpha and IFN-gamma often increase at puberty and decline thereon.[96] Additionally, gender differences could be due to varying effects of sex hormones on the immune system. Testosterone has been shown to lead to a stronger cellular immune response mediated by Th1 cells while estrogen has an inhibitory effect on the pro-inflammatory T cells.[97] These are significant observations as vaccination drives are being launched across the globe to enhance coverage, especially among children and adolescents. Awareness of this possible complication amongst medical professionals and the vaccination beneficiaries is crucial for seeking early medical attention. The apparent predilection for caucasian race noted in our review requires watchful consideration as vaccine coverage improves and data emerges from other parts of the globe. Another striking observation in our review was that myocarditis occurred more frequently following administration of mRNA vaccines (99.4%) especially after the second dose (83.2%). While it may be a reporting bias or possibly be due to the greater global coverage by mRNA vaccines, there is always a chance of pathophysiological links which needs to be explored. mRNA vaccines have a nucleoside-modified mRNA which encodes the viral spike glycoprotein of SARS-CoV-2. This viral spike protein then incites an adaptive immune response to identify and thereby neutralize the future infections with the virus. mRNA molecules can itself be immunogenic and the nucleoside modification tends to lower the innate immunogenicity with less production of inflammatory cytokines.[98] However, in individuals with certain genetic

predispositions, the immune system might detect mRNA as an antigen leading to an inflammatory cascade with production of pro-inflammatory cytokines and development of myocarditis.[99] Other probable mechanisms of hyperimmunity include molecular mimicry by antibodies to SARS-CoV-2 spike proteins which cross-react with myocardial contractile proteins such as α-myosin and the possible role of natural killer (NK) cells.[100] These hypotheses are also supported by the fact that a majority of cases of COVID-19 vaccine induced myocarditis occurred following administration of the second dose of the vaccine. However, further research dwelling into plausible mechanisms of myocardial injury is of paramount importance to understand the clinico-pathophysiology and tailoring the therapeutics.

A possibility of COVID-19 vaccine induced myocarditis should be considered among individuals developing chest pain, dyspnoea or fever within 3-4 days following vaccination. A diagnosis is often established based on clinical presentation and supplemented by elevated levels of cardiac biomarkers and supportive cardiac imaging. EMB, despite being the gold standard, has been sparingly used for the diagnosis of vaccine induced myocarditis due to its invasive nature. for a condition of mild nature with a conservative treatment approach.[101] In our review, EMB was performed in only 0.37% of patients with the majority of them having lympho-histiocytic infiltration in the myocardium. A diagnosis of vaccine induced myocarditis can often be challenging in individuals with recent SARS-CoV-2 infection hence, protocols for testing for recent COVID-19 infection to eliminate its confounding effect should be in place. Cardiac imaging using echocardiography and CMR plays an important role in assessment of cardiac functions and morphology in patients with myocarditis. CMR not only helps in establishing the diagnosis of myocarditis but also excludes confounding abnormalities. The diagnosis of myocarditis on CMR is often established based on the revised Lake Louise criteria.[102] In our review, classical CMR findings of myocarditis viz. LGE and myocardial oedema were reported in 80.7% and 63.3% patients respectively. A majority of patients had a sub-epicardial distribution of LGE, a feature consistent with that of myocarditis. A majority of patients were categorized as definite/probable myocarditis (98.6%) while possible myocarditis was reported in 1.4 % patients.

The treatment of myocarditis following COVID-19 vaccination is highly variable, probably due to absence of defined guidelines as well as regional preferences, varying severity and clinical presentation. Overall, the therapeutic approach for symptomatic patients includes the use of NSAIDS and/or colchicine. Corticosteroids, IVIg and immunomodulators such as TNF-alpha inhibitors are often reserved for severe cases. Findings from our review too suggested that NSAIDS were the most common treatment modality, followed by colchicine and steroids. An important grey zone in the treatment strategy is the determination of need for hospitalization or

intensive care. Most of the cases of vaccine induced myocarditis were mild in nature with only 8.7% of them requiring ICU stay. Findings of our review suggested that clinical outcomes of vaccine-associated myocarditis were mostly very favourable with mortality reported in 1.4% of subjects while the rest of them had rapid spontaneous recovery. It is important to conclude that despite the alarming nature of this rare adverse event, it should not be a deterrent to mass vaccination as most of the patients had favourable outcomes with rapid recovery following therapy with oral anti-inflammatory agents and a short hospital stay. The risk-benefit ratio of vaccination unanimously favours the use of COVID-19 vaccines which prevents severe forms of infection, reduces risk of hospitalization, ICU admissions and death in both young and elderly age groups.[103] Large data registries and clinical cohorts are needed to strengthen diagnostic criteria, risk stratification and therapeutic approaches for vaccine induced myocarditis. Till larger evidence emerges, the vaccine coverage should continue globally albeit the fear of myocarditis. However, prospective research should continue to systematically document this adverse event alongside, especially in the current scenario where boosters have entered the ball game, to strengthen our understanding of the precise nature of this condition.

Limitations

Our systematic review on COVID-19 vaccine induced myocarditis had a few limitations. This study is mainly descriptive including primarily case reports and case series due to which the level of evidence is low. Additionally, due to the inclusion of multiple studies, there is a risk of reporting bias. Vaccine inequity across the world and the availability of certain vaccines in different countries makes it difficult to evaluate and compare regional variations in occurrence and severity of myocarditis.

Conclusion

Myocarditis following COVID-19 vaccination has the potential to spark fear and vaccine hesitancy. There is a need to understand that myocarditis following COVID-19 vaccination is often mild, more commonly diagnosed in young healthy adults after 2nd dose of mRNA vaccine, is acute in onset followed by rapid recovery with conservative treatment. There is a need for prompt recognition of Myocarditis in order to limit the hyperinflammatory response and prevent poor outcomes. The emergence of this adverse event calls for harmonizing case definitions for establishing a correct diagnosis as well as definite treatment guidelines. This would largely be possible through wider research, collaborative efforts and development of data registries and clinical cohorts.

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Table Legends:

Table 1- Summary of the studies reporting Myocarditis after *SARS-CoV-2* vaccination

Table 2- Patient characteristics and laboratory parameters of Myocarditis after *SARS-CoV-2* vaccination

Table 3- Imaging findings in Myocarditis after *SARS-CoV-2* vaccination

Table 4- Treatment and outcome of Myocarditis after *SARS-CoV-2* vaccination

Figure legends:

Figure 1- Brighton Collaboration case definition for the diagnosis of vaccine induced myocarditis

Figure 2- PRISMA diagram of the systematic review

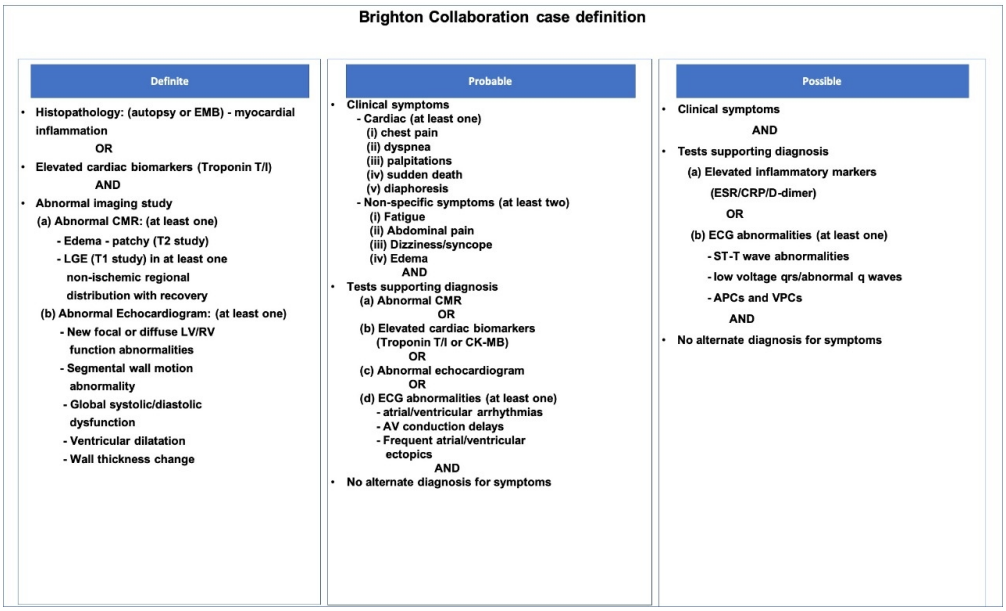

Figure 1- Brighton Collaboration case definition for the diagnosis of vaccine induced myocarditis

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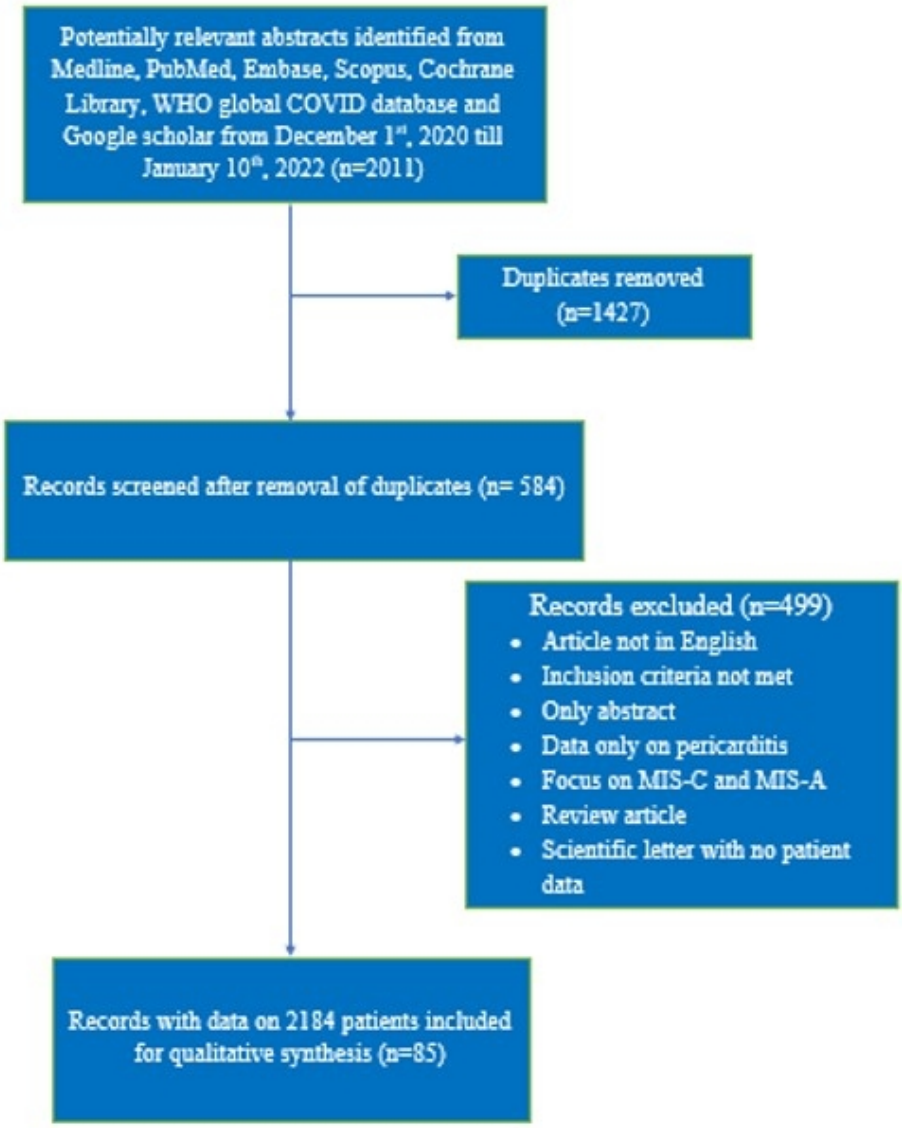

Figure 2- PRISMA diagram of the systematic review

139x167mm (96 x 96 DPI)

Table 1- Summary of the studies reporting myocarditis after vaccination

Sn	First author	Number of cases/ age range	Vaccine/ dose	Symptoms	Laboratory Investigations	ECG/ Echocardiography	Cardiac imaging (LGE) and biopsy	Treatment	Outcome
1	Shaw et al[11]	n=4 / 16-31 years	Pfizer (3/4), Moderna (1/4)/ 1st dose (2/4), 2nd dose (2/4)	Chest pain (4/4)	Raised Trop I (4/4)	ST elevation (¼)/ Normal Echo (4/4)	LGE (4/4), No biopsy done	Treatment not reported	Recovered and did not require hospitalization (4/4)
2	Schauer et al[12]	n=13 /12-17 years	Pfizer (13/13), 2nd (13/13)	Dyspnea (5/13), fever (5/13), headache (5/13), arthralgia (6/13), nausea (1/13), vomiting (1/13), myalgia (7/13)	Raised CRP (3/13), Raised Trop T (13/13)	ST elevation (8/13), nonspecific ST (1/13) / Reduced EF (2/13)	LGE (4/4), No biopsy done	IVIG (3/13), symptomatic therapy (13/13)	Hospitalized and discharged (13/13)
3	Azir et al[13]	n=1/ 17 yrs	Pfizer/ 2nd	Dyspnoea, chest pain	Raised Trop T	ST elevation/ Normal ECHO	LGE +, No biopsy done	Anti-platelet	Hospitalized & discharged
4	Wilson et al[14]	n=1/ 16 yrs	Pfizer/ 2nd	Chest pain	Raised Trop T, Raised BNP	Nonspecific ST- T changes/ Normal ECHO	LGE +, No biopsy done	NSAIDs	Recovered and did not require hospitalization
5	Mansour et al[15]	n=2/ 21-25 yrs	Moderna/ 2nd	Fever (1/2), dyspnoea (1/2), chest pain (2/2), myalgia (1/2), headache (1/2)	Raised CRP (2/2), Raised D- dimer (1/2), Raised Trop I (2/2)	ST elevation (2/2)/ Reduced EF (1/2)	LGE + (2/2), No biopsy done	Managed conservatively	Recovered and did not require hospitalization (2/2)
6	Miqdad et al[16]	n=1/ 18 yrs	Pfizer/ 2nd	Chest pain	Raised CRP, Raised Trop I	ST elevation/ Normal ECHO	Myocardial edema +, LGE +, No biopsy done	NSAIDs, colchicine, antiplatelet, ACEi/ARB	Hospitalized & discharged
7	Gautam et al[17]	n=1/ 66 years	Pfizer/ 2nd	Palpitation, chest pain, nausea, vomiting, myalgia	Raised ESR, Raised Trop I	Nonspecific ST-T changes, ECHO not done	LGE +, No biopsy done	Managed conservatively	Hospitalized & discharged

8	Das et al[18]	n=25/12-17 years	Pfizer (25/25)/ 1st dose (3/25), 2nd dose (22/25)	Dyspnea (3/25), fever (7/25), syncope (1/25), chest pain (25/25), nausea (2/25), vomiting (2/25), myalgia (3/25), headache (2/25), chills (1/25), sweating (1/25), shoulder and neck pain (1/25)	Raised CRP (10/17), Raised Trop T (25/25)	ST elevation (14/25), T wave inversion (3/25), nonspecific ST-T changes (3/25), NSVT (3/25), VPC (1/25), ST depression (1/25), PR depression (1/25), 1st degree AV block with LBBB (1/25)/ Reduced EF (2/25)	Myocardial edema (4/16), LGE + (16/16), No biopsy done	NSAIDs (23/24), Steroids (1/24), antiplatelet (1/24), diuretics (3/24), ACEi/ARB (2/24), IVIg (2/24)	Hospitalized & discharged (22/25), Recovered and did not require hospitalization (3/25)
9	Koizumi et al[19]	n=2/ 22-27 years	Moderna/ 2nd	Chest pain (2/2)	Raised Trop T (2/2), Raised CPK-MB (1/2)	ST elevation (2/2)/ Normal ECHO (2/2)	LGE (1/1), Biopsy - no specific findings (1/2), No inflammatory cell infiltrates (1/2)	NSAIDs (2/2)	Hospitalized & discharged (1/2), Recovered and did not require hospitalization (1/2)
10	Ujueta et al[20]	n=1/ 62 years	Janssen/ 1st	Myalgia	Positive procalcitonin, Raised CRP, Raised Trop I, Raised Pro-BNP, Raised AST, Raised ALT	Sinus tachycardia, T inversion/ Reduced EF, RV dysfunction, pericardial effusion.	MRI not reported, biopsy - lymphohistiocytic myocarditis with sparse eosinophils	Steroids, oxygen, ventilation, inotropes	Hospitalized & died.
11	Nevet et al[21]	n=3/ 20-29 years	Pfizer/ 2nd (3/3)	Fever (3/3), chest pain (3/3)	Raised CRP (1/1), Raised Trop T/I (3/3)	ST elevation (3/3)/Normal ECHO (3/3)	Myocardial edema (3/3), LGE + (3/3), No biopsy done	NSAIDs (3/3), colchicine (3/3)	Hospitalized & discharged (3/3)
12	Cereda et al[22]	n=1/ 21 years	Pfizer/ 2nd	Fever, chest pain	Raised Trop I	ST elevation, NSVT/ LV hypokinesia	Myocardial edema, LGE +, No biopsy done	Beta-blockers, ACEi/ARB, antibiotics	Hospitalized & discharged

13	Nguyen et al[23]	n=1/ 20 years	Moderna/ 1st	Fever, chest pain, myalgia, chills	Thrombocytopenia, Raised Trop T, Raised Pro-BNP	Pre-excitation/ Reduced EF	Myocardial edema, LGE +, Biopsy - myocardial edema and profound mononuclear infiltration	Not reported	Hospitalized & discharged
14	Watkins et al[24]	n=1/ 20 years	Pfizer/ 2nd	Chest pain	Raised Trop T	ST elevation, PR depression/ Small pericardial effusion	MRI done - Myocardial edema & LGE not reported, no biopsy done	NSAIDs, Colchicine, beta blocker	Hospitalized & discharged
15	Choi et al[25]	n=1/ 22 years	Pfizer/ 1st	Chest pain	Not reported	Ventricular fibrillation/ ECHO not reported	MRI not reported, biopsy - diffuse inflammatory infiltration with neutrophils and histiocyte predominance	Not reported	Hospitalized & died
16	Rosner et al[26]	n=7/ 19-39 years	Janssen (1/7), Pfizer (5/7), Moderna (1/7)/ 1st dose (2/7), 2nd dose (5/7)	Dyspnoea (2/7), fever (2/7), chest pain (7/7), myalgia (1/7), headache (1/7), chills (1/7), numbness and tingling (1/7)	Raised ESR (1/6), Raised CRP (5/7), Raised Trop I (7/7)	Sinus tachycardia (2/7), ST elevation (3/7), T inversion (1/7), nonspecific ST-T changes (1/7), PR depression (1/7)/ Reduced EF (4/7)	LGE + (7/7), No biopsy done	NSIADs (3/7), colchicine (3/7), steroids (1/7), Beta blockers (3/7), ACEi/ARB (2/7)	Hospitalized & discharged (7/7)
17	Chelala et al[27]	n=5/ 16-19 years	Pfizer (4/5), Moderna (1/5)/ 2nd dose (5/5)	Chest pain (5/5)	Raised CRP (2/5), Raised Trop I (5/5), Raised BNP (1/1)	Sinus bradycardia (1/5), ST elevation (1/5)/ Reduced EF (1/5), LAD and RCA ectasia (1/5)	Myocardial edema (4/5), LGE + (5/5), No biopsy done	NSIADs (1/5), Colchicine (1/5), antiplatelet (1/5), Beta blocker (3/5)	Hospitalized & discharged (5/5)

18	Verma et al[28]	n=2/ 42-45 years	Pfizer (1/2), Moderna (1/2)/ 1st dose (1/2), 2nd dose (1/2),	Dyspnoea (2/2), fever (1/2), chest pain (1/2), dizziness (1/2)	Raised Trop I (2/2), Raised Pro-BNP (1/1), Raised AST (2/2), Raised ALT (1/2),	Sinus tachycardia (1/2), ST elevation (1/2), ST depression (1/2)/ Reduced EF (2/2), Pericardial effusion (2/2)	LGE + (1/1), Biopsy - Inflammatory infiltrates (2/2)	NSAIDs (1/2), Parenteral anticoagulant (2/2), sterioids (2/2), antiplatelet (1/2), diuretics (2/2), beta blockers (1/2), ACEi/ARB (1/2), antibiotics (2/2), oxygen (1/2), ventilation (1/2), inotropes (2/2)	Hospitalized & discharged (1/2), Hospitalized & died (1/2)
19	Fleming-Nouri et al[29]	n=8/ 16-24 years	Pfizer (8/8)/ 2nd dose (8/8)	Chest pain (8/8)	Raised Trop T (1/1), Raise Trop I (7/7)	ST elevation (7/8)/ Mild LV hypokinesia (1/8)	LGE+ (3/5), No biopsy done	NSAIDs (5/5), steroids (4/5), antiplatelets (3/5), IVIg (4/5)	Hospitalized & discharged (8/8)
20	Shumkova et al[30]	n=1/ 23 years	Pfizer/ 2nd	Dyspnoea, fever, chest pain	Raised CRP, Raised CPK-MB, Raised Trop T, Raised Pro-BNP	Sinus tachycardia, ST elevation/ Reduced EF	LGE+, No biopsy done	NSAIDs, steroids, antibiotic	Hospitalized & discharged
21	Vollman et al[31]	n=1/ 28 years	Pfizer/ 1st	Fever, chest pain, myalgia	Raised CRP, Raised Trop T	ST elevation/ ECHO not done	LGE+, No biopsy done	NSAIDs	Hospitalized & discharged
22	Cimaglia et al[32]	n=1/ 24 years	Pfizer/ 1st	Chest pain	Raised CPK-MB, Raised Trop T	Sinus tachycardia, ST elevation/ Reduced EF	Myocardial edema, LGE+, No biopsy done	NSAIDs	Hospitalized & discharged

23	Patrignani et al[33]	n=1/ 56 years	Pfizer/ 1st	Abdominal pain, sweating	Raised Trop T	Normal ECG/ Normal ECHO	Myocardial edema, LGE+, No biopsy done	NSAIDs	Hospitalized & discharged
24	Habib et al[34]	n=1/ 37 years	Pfizer/ 2nd	Fever, chest pain, myalgia, joint pain, headache, chills	Raised Trop T	ST elevation/ Normal ECHO	LGE+, No biopsy done	Parenteral anticoagulant, antiplatelet, Beta- blocker	Hospitalized & discharged
25	Schmitt et al[35]	n=1/ 19 years	Pfizer/ 2nd	Chest pain, myalgia, headache	Raised CRP, Raised Trop T,	Sinus tachycardia, ST elevation/ Normal ECHO	Myocardial edema, LGE+, No biopsy done	Not reported	Hospitalized & discharged
26	Alania- Torres et al[36]	n=1/ 28 years	Pfizer/ 2nd	Dyspnoea, fever, chest pain, diarrhoea, myalgia, headache	Raised Trop I	Normal ECG/ Reduced EF	MRI not reported, No biopsy done	Colchicine, antiplatelet, diuretic, beta blocker, ARNI	Hospitalized & discharged
27	Kim et al[37]	n=1/ 24 years	Pfizer/ 2nd	Chest pain, myalgia	Raised CRP, Raised Trop I	ST elevation/ Pericardial effusion	Myocardial edema, LGE+, No biopsy done	Not reported	Hospitalized & discharged
28	Matta et al[38]	n=1/ 27 years	Pfizer/ 2nd	Chest pain, myalgia	Thrombocytopenia, Raised CRP, Raised Trop I	Normal ECG/ Normal ECHO	MRI not reported, No biopsy done	NSAIDs	Hospitalized & discharged
29	Tiwari et al[39]	n=1/ 33 years	Covaxin/ 1st	Dyspnoea, Edema	Raised CPK-MB, Raised AST, Raised ALT	Sinus tachycardia/ Normal ECHO	Myocardial edema +, No biopsy done	Steroid, beta blocker	Recovered and did not require hospitalization
30	Mouch et al[40]	n=6/ 16-45 years	Pfizer/ 1st dose (1/6), 2nd dose (5/6),	Chest pain (6/6)	Thrombocytopenia (1/6), Raised CRP (5/6), Raised Trop T (6/6), Raised AST (4/6), Raised ALT (1/6)	Sinus tachycardia (1/6), ST elevation (6/6), T inversion (3/6), PR depression (1/6)/ Reduced EF (2/6), Minimal MR (1/6), Minimal TR (1/6)	Myocardial edema (4/6), LGE+ (6/6), No biopsy done	NSAIDs (6/6), colchicine (6/6)	Hospitalized & discharged (6/6)

31	Tailor et al[41]	n=1/ 44 years	Moderna/ 2nd	Dyspnoea, chest pain	Raised CRP, Raised Trop T, Raised Pro-BNP	ST elevation/ Reduced EF	LGE+, No biopsy done	Colchicine, diuretics, beta blocker, ACEi/ARB	Hospitalized & discharged
32	Dickey et al[42]	-n=6/ 17-37 years	Pfizer (5/6), Modrna (1/6)/ 2nd dose (6/6)	Fever (3/6), chest pain (6/6), myalgia (4/6), headache (1/6), chills (1/6), rhinorrhoea (1/6)	Raised Trop T (6/6)	ST elevation (5/6), nonspecific ST-T changes (1/6), NSVT (1/6), PR depression (2/6)/ Reduced EF (5/6)	LGE+ (6/6), No biopsy done	Not reported	Hospitalized & discharged (6/6)
33	Sokolska et al[43]	n=1/ 21 years	Pfizer/ 1st	Chest pain	Raised CRP, Raised Trop T, Raised Pro-BNP	ST elevation, T inversion/ Normal ECHO	Myocardial edema, LGE+, No biopsy done	NSAIDs	Hospitalized & discharged
34	Nassar et al[44]	n=1/ 70 years	Janssen/ 1st	Dyspnoea	Positive procalcitonin, Raised CRP, Raised Trop I	Sinus tachycardia, T inversion/ Reduced EF	MRI not reported, no biopsy done	Antibiotics, oxygen, ventilation, inotropes	Hospitalized & died
35	Montgomery et al[45]	n=23/20-51 years	Pfizer (7/23), Moderna (16/23)/ 1st dose (3/23), 2nd dose (20/23)	Chest pain (23/23)	Raised Trop (23/23)	ST elevation (19/23), T inversion (19/23), Nonspecific ST-T changes (19/23)/ Reduced EF (4/23)	Myocardial edema (8/8), LGE+ (8/8), No biopsy done	Not reported	Hospitalized & discharged (23/23),
36	Minocha et al[46]	n=1/ 17 years	Pfizer/ 2nd	Fever, chest pain, myalgia	Raised Trop T	ST elevation/ Reduced EF	LGE+, No biopsy done	NSAIDs	Hospitalized & discharged
37	Starekova et al[47]	n=5/ 17-38 years	Pfizer (3/5), Moderna (2/5) / 2nd (5/5)	Dyspnoea (2/5), fever (3/5), chest pain (5/5), nausea (2/5), myalgia (4/5), headache (2/5)	Raised Trop I (5/5)	ST elevation (2/5), T inversion (3/5)/ Reduced EF (3/5)	Myocardial edema (5/5), LGE+ (5/5), No biopsy done	Not reported	Hospitalized & discharged (5/5)
38	Kim et al[48]	n=4/ 23-70 years	Pfizer (2/4), Moderna (2/4), / 2nd (4/4)	Dyspnoea (3/4), fever (3/4), palpitations (1/4), syncope (1/4), chest	Raised ESR (1/3), Raised CRP (2/3), Raised Trop T (2/2),	ST elevation (4/4), PR depression (2/4)/ Reduced EF (2/4)	LGE+ (4/4), No biopsy done	NSAIDs (2/4), colchicine (3/4), steroids (1/4)	Hospitalized & discharged (4/4)

				pain (1/4), myalgia (3/4), headache (1/4), diaphoresis (1/4)	Raised Trop I (2/2), Raised Pro-BNP (2/3)				
39	Witberg et al[49]	n=54/ 21-40 years	Pfizer (54/54)/ 2nd (54/54)	Fever (5/54), dyspnoea (3/54), palpitations (1/54), chest pain (44/54), myalgia (1/54)	Raised CRP (18/28), Raised Trop T (41/41)	ST elevation (18/38), sinus tachycardia (1/38), T inversion (7/38), nonspecific ST-T changes (2/38), AF (1/38), NSVT (2/38),/ Reduced EF (14/48), pericardial effusion (10/48)	LGE+ (9/11), Biopsy - lymphocyte & eosinophil infiltration (1/1)	NSAIDs (12/54), colchicine (17/54), oral NOAC (1/54), steroid (1/54), antiplatelet (2/54), beta blockers (20/54), ACEi/ARB (16/54), ECMO (1/54), inotropes (1/54),	Hospitalized & discharged (53/54), Hospitalized & died (1/54)
40	Muthukumar et al[50]	n=1/ 52 years	Moderna/ 2nd	Chest pain	Raised ESR, Raised CRP, Raised D-dimer, Raised Trop T, Raised AST, Raised ALT	RBBB/ Normal ECHO	LGE+, No biopsy done	Beta blocker, ACEi/ARB	Hospitalized & discharged
41	Istampoulouoglou et al[51]	n=14/ 17-88 years	Pfizer (4/14), Moderna (10/14)/ 1st dose (5/14), 2nd dose (9/14)	Dyspnoea (2/14), fever (2/14), palpitation (2/14), syncope (1/14), chest pain (9/14), abdominal pain (1/14), myalgia (1/14)	Raised Trop I (1/1), Raised Trop T (11/12)	NSVT and SVT (1/10)/ Reduced EF (5/13)	Myocardial edema (9/13), LGE+ (9/14), No biopsy done	NSAIDs (4/14), colchicine (2/14), diuretics (2/14), beta blockers (6/14), ACEi/ARB (7/14), SGLT-2i (1/14), antibiotic (3/14)	Hospitalized & discharged (14/14)

42	Abbate et al[52]	n=2/ 27-34 years	Pfizer (2/2)/ 1st dose (1/2), 2nd dose (1/2)	Fever (1/2), cough (1/2), chest pain (1/2), nausea (2/2), vomiting (2/2)	Raised CRP (2/2), Raised D-dimer (1/2)	Sinus tachycardia (2/2), ST elevation (1/2), nonspecific ST-T changes (1/2)/ Reduced EF (2/2)	Myocardial edema (1/1), LGE+ (1/1), No biopsy done	Steroids (2/2), IVIg (2/2), anakinra (2/2), ECMO (2/2)	Hospitalized & discharged (1/2), Hospitalized & died (1/2)
43	Viskin et al[53]	n=8/ 20-34 years	Moderna (8/8)/ 2nd (8/8)	Chest pain (8/8), myalgia (8/8)	Raised Trop T (8/8)	ST elevation (5/8)/ Reduced EF (3/8)	LGE+ (6/8), No biopsy done	Not reported	Hospitalized & discharged (8/8)
44	Vidula et al[54]	n=2/ 18-19 years	Pfizer (1/2), Moderna (1/2)/ 2nd (2/2)	Dyspnoea (1/2), fever (1/2), chest pain (2/2), myalgia (1/2)	Raised CRP (2/2), Raised Trop T (2/2)	ST elevation (2/2), sinus tachycardia (1/2)/ Reduced EF (2/2)	Myocardial edema (2/2), LGE+ (2/2), No biopsy done	NSAIDs (1/2), colchicine (1/2), beta blockers (2/2), ACEi/ARB (1/2)	Hospitalized & discharged (2/2)
45	Chamling et al[55]	n=3/ 20-68 years	Pfizer (2/3), Astra-Zeneca (1/3)/ 1st dose (2/3), 2nd dose (1/3)	Fever (1/3), chest pain (3/3), headache (1/3)	Raised CRP (1/3), Raised Trop T (3/3)	ST elevation (2/3)/ Normal ECHO (3/3)	LGE+ (3/3), No biopsy done	Parenteral anticoagulant (1/3), antiplatelet (2/3), beta blocker (1/3), ACEi/ARB (1/3)	Hospitalized (3/3). Outcome not reported
46	Albert et al[56]	n=1/ 24 years	Moderna/ 2nd	Fever, chest pain, myalgia, chills	Raised Trop I	Normal ECG/ Normal ECHO	Myocardial edema +, LGE +, No biopsy done	Beta blocker	Hospitalized & discharged
47	Onderko et al[57]	n=3/ 25-36 years	Pfizer (2/3), Moderna (1/3)/ 2nd (3/3)	Chest pain (3/3), myalgia (2/3), chills (1/3)	Raised CRP (2/2), Raised Trop T (3/3)	ST elevation (2/3)/ Normal ECHO	Myocardial edema (3/3), LGE+ (3/3), No biopsy done	NSAIDs (1/3), colchicine (1/3), beta blockers (3/3)	Hospitalized & discharged (3/3)
48	Jain et al[58]	n=63/ 12-20 years	Pfizer (59/63), Moderna (4/63)/ 1st dose (1/63), 2nd dose (62/63)	Dyspnoea (22/63), fever (28/63), chest pain (63/63), nausea (15/63),	Raised CRP (62/63), Raised Trop T (63/63)	ST elevation (44/63), T inversion (44/63), NSVT (3/63), CHB	Myocardial edema (50/56), LGE+ (49/56), No biopsy done	NSAIDs (54/63), colchicine (4/63), steroid	Hospitalized & discharged (63/63)

				myalgia (24/63), headache (16/63)		(1/63)/ Reduced EF (9/63)		(15/63), antiplatelet (6/63), beta blocker (6/63), IVIg (17/63)	
49	Patel et al[59]	n=5/ 19-37 years	Pfizer (4/5), Moderna (1/5)/ 1st dose (1/5), 2nd dose (4/5)	Dyspnoea (4/5), fever (1/5), chest pain (5/5), nausea (3/5), vomiting (1/5), myalgia (3/5), headache (3/5), chills (1/5), diaphoresis (1/5)	RaisedESR (1/4), Raised CRP (3/3), Raised Trop T (5/5)	Sinus tachycardia (1/5), ST elevation (1/5), PR depression (3/5), ST depression (1/5)/ Reduced EF (1/5)	Myocardial edema (3/5), LGE+ (5/5), No biopsy done	NSAIDs (2/5), colchicine (4/5), antiplatelet (1/5), beta blocker (1/5), ACEi/ARB (1/5)	Hospitalized & discharged (5/5)
50	Tano et al[60]	n=8/ 15-18 years	Pfizer (8/8)/ 1st dose (1/8), 2nd dose (7/8)	Fever (1/8), palpitations (1/8), cough (1/8), chest pain (8/8), abdominal pain (1/8), diarrhea (1/8), myalgia (2/8), headache (1/8)	Raised D-dimer (2/6), Raised CPK-MB (3/5), Raised Trop T (8/8)	ST elevation (4/8), PR depression (2/8), ST depression (2/8)/ Normal ECHO (8/8)	Myocardial edema (3/3), LGE+ (3/3), No biopsy done	NSAIDs (5/8), IvIg (1/8)	Hospitalized & discharged (8/8)
51	Deb et al[61]	n=1/ 67 years	Moderna/ 2nd	Dyspnoea, fever, PND, nausea, myalgia, chills	Raised ESR, Raised CRP, Raised Trop T, Raised BNP	Sinus tachycardia, non-specific ST-T changes/ Reduced EF	MRI not reported, no biopsy done	Diuretics, oxygen, HFNC/ NIMV	Hospitalized & discharged
52	Marshallet al[62]	n=7/ 14-19 years	Pfizer (7/7)/ 2nd (7/7)	Dyspnoea (3/7), fever (2/7), palpitation (1/7), chest pain (5/7), nausea (3/7), vomiting (2/7), myalgia (5/7), headache (1/7), chills (1/7), anorexia (1/7), paresthesia (1/7)	Raised ESR (3/7), Raised CRP (4/7), Raised Trop T (4/4), Trop I (3/3), Raised Pro-BNP (3/4), Raised AST (6/7), Raised ALT (1/7)	Sinus bradycardia (1/7), ST elevation (6/7), T wave abnormalities (2/7), AV dissociation with junctional escape rhythm (1/7) /RV dysfunction (1/7), Normal ECHO (7/7)	Myocardial edema (6/7), LGE+ (6/7), No biopsy done	NSAIDs (6/7), Colchicine (1/7), Steroids (4/7), Antiplatelet (2/7), Diuretics (1/7), IVIg (4/7), oxygen (1/7), HFNC/ NIV (1/7)	Hospitalized & discharged (7/7)

53	Ambati et al[63]	n=2/ 16-17 years	Pfizer (2/2)/ 2nd (2/2)	Dyspnoea (1 2), fever (1/2), chest pain (2/2), nausea (1/ 2), vomiting (1/2), myalgia (1/2), headache (1/2)	Raised ESR (1/2), Raised CRP (1/2) Raised D-dimer (1/2) Trop I (2/2)	ST elevation (2/ 2)/ ECHO- not reported	MRI not reported, No biopsy done	NSAIDs (2/2)	Hospitalized & discharged (2/2)
54	Sulemankhil et al[64]	n=1/ 33 years	Janssen/ 1st	Chest pain, myalgia, chills	Raised CRP, Raised Trop T	ST elevation/ Reduced EF	LGE+, No biopsy done	Managed conservatively	Hospitalized & discharged
55	Simone et al[65]	n=15/ 18-40 years	Pfizer (8/15) Moderna (7/15)/ 1st dose (2/15), 2 nd dose (13/15)	Chest pain (15/15)	Raised Trop I (15/15)	ST tachycardia (1/15), ST elevation (10/15), T inversion (1/15) / Reduced EF (5/15)	MRI not reported, no biopsy done	Managed conservatively (15/15)	Hospitalized & discharged (15/15)
56	Ehrlich et al[66]	n=1/ 40 years	Pfizer/ 1st	Dyspnoea, fever, chest pain, headache	Raised CRP, Raised Trop T, Raised CPK-MB	ST elevation, ST depression/ Reduced EF	LGE+, Biopsy - Acute lymphocytic myocarditis	Parenteral anticoagulant, antiplatelet, beta blocker, ACEi/ARB, ARNI,	Hospitalized & discharged
57	Kaul et al[67]	n=2/ 21-28 years	Pfizer (1/2), Moderna (1/2)/ 2nd dose (2/2)	Fever (2/2), chest pain (2/2), myalgia (1/ 2), headache (2/2), chills (1/2)	Raised CRP (2/ 2), Raised D-dimer (1/2), Trop I (2/2)	ST elevation (2/2)/ Reduced EF (1/2)	LGE+ (2/2), No biopsy done	Colchicine (1/2), ACEi/ARB (1/ 2). ARNI (1/2)	Hospitalized & discharged (2/2)
58	Snapiri et al[68]	n=7/ 16-18 years	Pfizer (7/7)/ 1st dose (6/7), 2nd dose (1/7)	Dyspnoea (2/7), fever (1/7) , cough (1/7), chest pain (7/7), nausea (1/7), diarrhea (1/7), headache (1/7),	Raised CRP (6/7), Raised Trop T (7/7), Raised Pro-BNP (3/4)	ST elevation (6/7), RBBB (1/7), ST depression (1/7), PR depression (1/7) / Reduced EF (1/3), Pericardial effusion (2/7)	MRI - not reported, No biopsy done	NSAIDs (5/7), Antiplatelet (1/7),	Hospitalized & discharged (7/7)
59	Issak et al[69]	n=1/ 15 years	Pfizer/ 2nd	Fever, myalgia,	Raised CRP, Raised Trop T/I	ST elevation/ Normal ECHO	Myocardial edema, LGE+, No biopsy done	Not reported	Hospitalized & discharged

60	Park et al[70]	n=2/ 15-16 years	Pfizer (2/2)/ 1st dose (1/2), 2nd dose (1/2)	Fever (1/2), chest pain (2/2), headache (1/2)	Raised ESR (1/2), Positive procalcitonin (1/2) Raised Trop T (2/2), Raised CPK-MB (2/2) Raised Pro-BNP (2/2)	ST elevation (2/2), T-wave inversion (1/2)/ Reduced EF (1/2)	LGE+ (1/2), No biopsy done	Managed conservatively (2/2)	Hospitalized & discharged (2/2)
61	Diaz et al[71]	n=20/ Median- 36 (26.3-48.3) years	Pfizer (9/20), Moderna (11/20)/1st dose (4/20), 2nd dose (16/20)	Chest pain (20/20)	Raised Trop T/I (19/20), Raised AST (6/20), Raised ALT (1/20)	ST elevation (9/20), PR depression (1/20), BBB (1/20) / Reduced EF (5/20)	MRI - not reported, no biopsy done	NSAIDs (15/20), colchicine (9/20), diuretics (8/20), beta blockers (8/20), ACEi/ARB (8/20)	Hospitalized & discharged (20/20)
62	Singh et al[72]	n=1/ 24 years	Pfizer/ 2nd	Fever, chest pain, myalgia, headache, chills	Raised Trop I	ST depression/ Normal ECHO	LGE+, No biopsy done	Treatment not reported	Hospitalized & discharged
63	Chai et al[73]	n=1/ 17 years	Pfizer/ 2nd	Dyspnoea, fever, chest pain, vomiting, diarrhea, myalgia, headache, rash	Thrombocytopenia, Positive procalcitonin, Raised CRP, Raised Trop T and Trop I, Raised D-dimer, Raised CPK-MB,	ECG - normal/ Reduced EF	LGE+, No biopsy done	Antibiotics, IVIg, oxygen, HFNC/NIV, inotropes	Hospitalized & discharged
64	Larson et al[74]	n=8/ 21-40 years	Pfizer (5/8), Moderna (3/8) 1st dose (1/8), 2nd dose (7/8)	Dyspnoea (1/ 8), fever (5/8), cough (1/8), chest pain (8/8), myalgia (2/8), chills (2/8)	Raised CRP (7/8), Raised Trop T (8/8), Raised Pro-BNP	ST elevation (6/8), aVR depression (2/ 8), ST depression (1/8), Peaked T waves (1/8)/ Reduced EF (6/8)	Myocardial edema (6/8), LGE+ (8/8), Biopsy (1/1) - normal	NSAIDs (3/8), colchicine (2/8), steroids (2/8)	Hospitalized & discharged (8/8)

65	Williams et al[75]	n=1/ 34 years	Moderna/ 2nd	Fever, chest pain, myalgia,	Raised Trop T	ST elevation, PR depression/ Reduced EF	Myocardial edema, LGE+, No biopsy done	NSAIDs, colchicine, beta blockers, ACEi/ARB	Hospitalized & discharged
66	McLean et al[76]	n=1/ 16 years	Pfizer/ 2nd	Fever, chest pain, myalgia,	Raised CRP, Raised Trop T, Raised CPK-MB, Raised BNP	ST elevation/ ECHO - not reported	Myocardial edema, No biopsy done	NSAIDs, IVIg	Hospitalized & discharged
67	King et al[77]	n=4/ 20-30 years	Pfizer (1/4), Moderna (3/4)/ 2nd dose (4/4)	Chest pain (4/4),	Raised CRP (3/4), Raised Trop T (4/4)	ST elevation (3/4), T wave inversion (1/4), PR depression (3/4)/ Reduced EF (1/4)	LGE+ (1/1), No biopsy done	Treatment not reported	Hospitalized & discharged
68	Singh et al[78]	n=2/ 52-65 years	ChAdOx1 (2/2)/ 1st dose (1/2), 2nd dose (1/2)	Dyspnoea (2/2), fever (1/2), cough (1/2), chest pain (1/2)	Raised CRP (2/2), Raised Trop I (2/ 2), Raised BNP (1/2), Raised ALT (2/2)	Sinus tachycardia (1/2), ST depression (2/2)/ Pericardial effusion (1/2), Reduced EF (2/2)	MRI - not reported, No biopsy done	Antiplatelet (2/2), diuretics (1/2), beta blocker (1/ 2), ACEi/ARB (1/2), statin (1/2), nitrate (1/2), amlodipine (1/2)	Hospitalized & discharged (2/2)
69	Kim et al7[9]	n=1/ 29 years	Pfizer/ 2nd	Chest pain	Raised Trop I	ECG - normal/ Pericardial effusion, Normal ECHO	MRI - not reported, No biopsy done	NSAIDs, steroids	Recovered and did not require hospitalization
70	D'Angelo et al[80]	n=1/ 30 years	Pfizer/ 2nd	Dyspnoea, chest pain, nausea, sweating	Raised CRP, Raised Trop T, Raised CPK-MB	ST elevation, non-specific ST-T changes/ Pericardial effusion, Normal ECHO	LGE+, No biopsy done	NSAIDs, steroids, beta blockers,	Hospitalized & discharged
71	Sivakumaran et al[81]	n=1/ 20 years	Pfizer/ 2nd	Palpitation, chest pain	Raised Trop T, Raised Pro-BNP	ST elevation/ Reduced EF	Myocardial edema, LGE+, No biopsy done	Colchicine,	Hospitalized & discharged

72	Pareek et al[82]	n=11/ 16-53 years	Pfizer (9/11), Moderna (1/11), Ad26.COV2.S (1/11)/ 1st dose (1/11), 2nd dose (10/11)	Dyspnoea (2/11), fever (7/11), palpitation (2/11), chest pain (10/11), nausea (2/11), abdominal pain (1/11), myalgia (8/11), headache (4/11), chills (2/11)	Raised CRP (6/11), Raised Trop T (9/9), Raised Trop I (2/2), Raised Pro-BNP (3/7)	Sinus tachycardia (2/11), ST elevation (8/11), T inversion (1/11), PR depression (2/ 11), ST depression (1/11) / Reduced EF (1/2), Normal ECHO (1/2)	Myocardial edema (4/9), LGE+ (8/9), No biopsy done	NSAIDs (11/11), colchicine (4/11), steroids (4/11), beta blockers (3/11), ACEi/ARB (2/11), IVIg (4/11)	Hospitalized & discharged (11/11)
73	Walters et al[83]	n=1/ 29 years	Pfizer/ 2nd	Chest pain, nausea	Raised Trop T	Sinus bradycardia, ST elevation/ Normal ECHO	MRI - not reported, No biopsy done	NSAIDs, colchicine, antiplatelet	Hospitalized & discharged
74	Hasnie et al[84]	n=1/ 22 years	Moderna/ 1st	Fever, chest pain, myalgia	Raised Trop T	ST elevation, PR depression/ Reduced EF	LGE+, No biopsy done	NSAIDs, colchicine, antiplatelet, beta blocker	Hospitalized & discharged
75	Khogali et al[85]	n=1/ 29 years	Moderna/ 2nd	Fever, nausea, vomiting, diarrhea, myalgia	Raised D-dimer, Raised Trop T, Raised Pro-BNP	ST elevation, non-specific ST-T waves, short PR interval/ Pericardial effusion, Reduced EF	MRI - not done, No biopsy done	NSAIDs, colchicine, steroid, antiplatelet, inotrope	Hospitalized & discharged
76	Di Tano et al[86]	n=1/ 29 years	Moderna/ 1st	Fever, chest pain	Raised CRP, Raised Trop T	ST elevation/ ECHO - not reported	Myocardial edema, LGE+, No biopsy done	NSAIDs, colchicine	Hospitalized & discharged
77	Maki et al87	n=1/ 20 years	Moderna/ 2nd	Dyspnoea, fever, chest pain	Raised Trop I	Sinus tachycardia, ST elevation/ Pericardial effusion, Reduced EF	LGE+, Biopsy - Lymphocytic infiltration in myocardium	Diuretics, beta blockers, inotrope, ACEi/ARB	Hospitalized & discharged
78	Ammirati et al[88]	n=1/ 56 years	Pfizer/ 2nd	Chest pain	Raised D-dimer, Raised CPK-MB,Raised Trop T	ST elevation, peak T waves/ ECHO - not reported	Myocardial edema, LGE+, No biopsy done	NSAIDs, colchicine	Hospitalized & discharged

79	Rodriguez et al[89]	n=1/ 68 years	AstraZeneca/ 1st	Chest pain, sweating	Thrombocytopenia, Raised CRP, Raised Trop T	Atrial fibrillation/ Reduced EF	MRI - not reported, No biopsy done	Parenteral anticoagulant, inotrope	Hospitalized & discharged
80	Chen et al[90]	n=1/ 16 years	Pfizer/ 1st	Fever, chest pain, myalgia,	Raised Trop T	ST elevation, PR depression/ Reduced EF	Myocardial edema, LGE+, No biopsy done	NSAIDs, beta blocker, ACEi/ARB	Hospitalized & discharged
81	Hudson et al[91]	n=2/ 22-24 years	Pfizer (2/2)/ 2nd (2/2)	Fever (2/2), chest pain (1/2), nausea (1/2), vomiting (1/2), myalgia (1/2), chills (2/2), substernal pain (1/2), diaphoresis (1/2)	Raised CRP (2/2), Raised D-dimer (1/2), Raised Trop T (2/2)	J point elevation (1/2), wide QRS complexes (1/2)/ Reduced EF (1/2)	MRI - nor reported, No biopsy done	NSAIDs (2/2), colchicine (2/2), antiplatelet (2/2)	Hospitalized & discharged (2/2)
82	Visclosky et al[92]	n=1/ 15 years	Pfizer/ 2nd	Fever, chest pain, headache	Raised Trop T	ST elevation/ Reduced EF	MRI - not reported, No biopsy done	NSAIDs	Hospitalized & discharged
83	Dionne et al[93]	n=15/ 29 years	Pfizer/ 1st dose (1/ 15), 2nd dose (14/15)	Fever (10/ 15), chest pain (15/15), palpitation (1/15), nausea (1/15), vomiting (1/15), myalgia (9/15), headache (6/15)	Raised CRP (8/14), Raised Trop T (15/15)	ST elevation (9/15), T inversion (2/15), non-specific ST-T changes (2/15), NSVT (1/15), PAC (1/ 15)/ Reduced EF (3/15)	Myocardial edema (2/15), LGE+ (12/15), No biopsy done	Steroids (7/7), IVIg (7/7),	Hospitalized & discharged (15/15)
84	Oster et al[94]	n= 1626/21 years	Pfizer (490/1626) Moderna (1136/1626) 1st dose (273/1626); 2nd dose (1265/1626); dose NA:(88/1626)	Dyspnea (242/1626), palpitation (65/1626), chest pain (727/1626)	Raised Trop T/I (792/809)	ECG (569/794) Normal echo (598/721) LVEF normal (637/721)	Cardiac MRI (223/312), LGE:223; edema:223, no biopsy done	Rx Received by 676/1626, NSAIDS (589/676), Intravenous.anticoagulant (54/676), steroids (81/676), diuretics (11/676), IVIg (78/676),	Hospitalized (784/813)

								antiarrhythmics (18/676), O2 (12/676), inotrope (12/676)	
85	Truong et al[95]	n=139/ 15.8 years	Pfizer: (131/139); Moderna:(5/139); J&J:(1/139); NR:(2/139); Dose 1: (12/139) Dose 2:(128/139)	Dyspnea (38/139), fever (43/139), palpitation (7/139), chest pain (138/139), vomiting (17/139), diarrhea (3/139), myalgia/fatigue (26/139), joint pain (22/139), rash (5/139)	Raised Trop T/I (139/139), raised BNP (101/139), raised NT pro BNP (8/139)	ECG (97/138), ST elevation (95/138), atrial tachycardia in 1, NSVT (7/138), VPCs: 3; PACs: 1; CHB: 1 Echo done in (139/139), normal echo & EF (113/139),	Cardiac MRI (97/139), LGE: (74/97); edema: (54/97). No biopsy done	Rx by 139, NSAIDS (113/139), Colchicine (11/139), steroids (30/139), IVIg (30/139), Biologics given to 1 (anakinra), 2 patients got inotropes.	Hospitalized and discharged (139/139) Hospital stay 2 days average & 26 were admitted to the ICU. Myocarditis was definite in 49 & probable in 91

BNP- B-type natriuretic peptide, CRP- C reactive protein, NT Pro- BNP- N terminal Pro BNP, IL-6- Interleukin-6, IvIG- Intravenous Immunoglobulin, Trop- Troponin, EF- Ejection fraction, ESR- Erythrocyte sedimentation rate, LDH- Lactate dehydrogenase, ALT- Alanine transaminase, AST- Aspartate transaminase, LGE Late gadolinium enhancement, VPC- Ventricular premature complexes, ACEi- Angiotensin-converting enzyme inhibitor, ARB- angiotensin II receptor blocker, NSAID- Non steroidal anti-inflammatory drugs, PAC- Premature atrial contractions, CHB- Complete heart block, ICU- intensive care unit

Table 2: Patient characteristics

Characteristics	**Number of Patients (N=2184)**	**N (%)**
Age [Mean ± SD]	Data available: n=2170	25.5± 14.2 years
Age Groups 0-20 years: 21-40 years: 41-60 years: 61-80 years: > 80 years:	Data available: n=537	 339 (63.1%) 173 (32.2%) 14 (2.6%) 9 (1.7%) 2 (0.4%)
Gender	Data available: n=2184	Males: 1842 (91.2%) Females: 342 (8.8%%)
Ethnicity Caucasian Hispanic Latin Asian African Afro-American Other	Data available: n=1688	 1143 (67.7 %) 294 (17.4 %) 0 (0 %) 107 (6.3 %) 74 (4.4 %) 15 (0.9 %) 55 (3.2 %)
Clinical features Fever Dyspnoea Cough Chest pain Nausea Vomiting Diarrhoea Abdominal pain Palpitation Orthopnoea Syncope Peripheral Oedema Myalgia Joint pain Headache Chills Numbness Rash	Data available: n=1375	 164 (11.9%) 354 (25.7%) 5 (0.4%) 1239 (90.1%) 43 (3.1%) 32 (2.3%) 8 (0.6%) 4 (0.3%) 84 (6.1%) 1 (0.07%) 4 (0.3%) 1 (0.07%) 138 (10.0%) 7 (0.5%) 79 (5.7%) 19 (1.4%) 3 (0.2%) 5 (0.4%)

Comorbidities Hypertension Diabetes Dyslipidaemia Overweight/Obesity Coronary artery disease Asthma Malignancy Chronic kidney disease Prior myocarditis GERD	n=50/419 (11.9%)	 23 (46%) 6 (12%) 13 (26%) 20 (40%) 6 (12%) 8 (16%) 2 (4%) 2 (4%) 6 (12%) 2 (4%)
Hospital stay	Data available: n=1365	1331 (97.5%)
Duration of hospital stay [Mean ± SD]	Data available: n=487	4.3±5.8 days
Time between vaccination and symptom onset [Mean ± SD]	Data available: n=2183	4.01± 6.99 days
Vaccine type	Data available: n=2182	Pfizer-BioNTech (BNT162b2): 1594 (73%) mRNA-1273 (Moderna): 577 (26.4%) Janssen Ad26.CoV2.S (J&J): 6 (0.3%) AZD1222/ChAdOx1 (Astrazeneca): 4 (0.2%) COVAXIN (Bharat Biotech): 1 (0.04%)
Vaccine dose	Data available: n=2092*	First dose: 351[#] (16.8%) Second dose: 1741 (83.2%)

SD- Standard deviation, GERD- Gastro-oesophageal reflux diseases, COVID-19- coronavirus disease, RTPCR- reverse transcriptase polymerase chain reaction, *Janssen Ad26.CoV2.S (J&J) administered as one dose hence excluded

One patient had myocarditis following both the doses of COVID-19 Vaccine

Table 3

Investigations	Number of Patients (N=2184)	N (%)
Haematology:		
Haemoglobin (g/dl)	Data available: 82	14.395± 2.352
Total leucocyte count (per mm^3)	Data available: 137	10038.23± 4841.86
Absolute lymphocyte count (per mm^3)	Data available: 40	2044.10 ± 814.04
Platelet count (per mm^3)	Data available: 34	219139.29±156160.25
Thrombocytopenia	Data available: 34	5 (17.8%)
Organ functions:		
Serum creatinine (mg/dl)	Data available: 73	1.06 ± 0.50
Cardiac troponin T (ng/ml)	Data available: 389	7.96±22.90
Cardiac troponin I (ng/ml)	Data available: 124	11.51 ± 12.30
Positive Troponin T/I*	Data available: 1363	1330 (97.6%)
Serum CK-MB	Data available: 23	49.29 ± 49.78
Serum BNP (pg/ml)	Data available: 154	1347.49 ± 6991.65
Raised BNP (>100 pg/ml)	Data available: 53	13 (24.5%)
Serum NT-proBNP (pg/ml)	Data available: 40	10914.61 ± 47220.97
Raised NT-proBNP (>300 pg/ml)	Data available: 32	21 (65.6%)
AST (U/L)	Data available: 24	63.22 ± 44.28
ALT (U/L)	Data available: 24	36.52±23.93
Inflammatory markers:		
LDH (U/L)	Data available: 12	382.92 ± 176.15
CRP (mg/dl)	Data available: 411	7.89±11.43
Raised CRP (>3 mg/dl)	Data available: 390	325 (83.3%)
ESR (mm/hr)	Data available: 113	19.78±12.58
Raised ESR (>30 mm/hr)	Data available: 113	11 (9.7%)
D-Dimer (ng/ml)	Data available: 31	1558.33 ± 3938.55
Imaging		
Echocardiogram:	Data available: 1243	
Baseline EF (%)		52.6±9.9
Normal LVEF (≥55%)		955 (76.8%)
Mild LV dysfunction (LVEF: 40-54%)	Data available: 119	92 (77.3%)
Moderate LV dysfunction (LVEF: 30-39%)		12 (10.1%)
Severe LV dysfunction (LVEF: <30%)		15 (12.6%)
Right ventricular dysfunction		8 (0.6%)
Pericardial effusion		23 (1.8%)
Cardiac MRI:		
LGE	Data available: 670	541 (80.7%)
LGE distribution:	Data available: 196	
• Sub-epicardial		169 (86.2%)
• Mid myocardial		48 (24.5%)
• Sub-Endocardial		2 (1%)
• Transmural		2 (1%)
Myocardial oedema	Data available: 670	424 (63.3%)
Pericardial effusion	Data available: 670	28 (4.2%)
T1 values (mean ± SD)	Data available: 74	987.3±351.6 ms
T2 values (mean ± SD)	Data available: 68	58.1±8.7 ms

BNP- B-terminal natriuretic peptide, CRP- C reactive protein, CPK- creatine phosphokinase, NT Pro- BNP- N terminal Pro BNP, IL-6- Interleukin-6, IvIG- Intravenous Immunoglobulin, EF- Ejection fraction, ESR- Erythrocyte sedimentation rate, LDH- Lactate dehydrogenase, ALT- Alanine transaminase, AST- Aspartate transaminase, LVEF-. Left ventricular ejection fraction, LGE- Late Gadolinium Enhancement, CT- computed tomography, GGO- Ground glass opacities

Trop T: Reference normal ≤0.014 ng/mL; Trop I: Reference normal <0.04 ng/mL;

Table 4

Medications and Outcome	Number of Patients	N (%)
Medical treatment NSAIDS Steroids Colchicine Biologics Tocilizumab Anakinra Rituximab IVIG Antibiotics Antiplatelets Anticoagulants • Parenteral • Oral ACE inhibitors/ARBs Beta-blockers ARNI SGLT-2i Diuretics Antiarrhythmic	Data available: 1164	 891 (76.5%) 164 (14.1%) 85 (7.3%) 3 (0.2%) 0 (0%) 3 (0.2%) 0 (0%) 155 (13.3%) 8 (0.7%) 32 (2.7%) 66 (5.7%) 65 (5.6%) 1 (0.08%) 51 (4.4%) 72 (6.2%) 3 (0.2%) 1 (0.08%) 32 (2.7%) 18 (1.5%)
Shock Inotropes IABP ECMO	Data available: 1164 Data available: 1164 Data available: 1164 Data available: 1164	23 (1.9%) 23 (1.9%) 1 (0.08%) 3 (0.2%)
Oxygen support NIV IMV	Data available: 1164 Data available: 1164 Data available: 1164	18 (1.5%) 3 (0.2%) 4 (0.3%)
ICU stay	Data available: 1164	83 (7.1%)
Outcome Died Discharged	Data available: 1317	 6 (0.5%) 1311 (99.5%)

MIS-Multisystem inflammatory syndrome, NSAIDs- Non steroidal anti-inflammatory drugs, ARB- angiotensin receptor blockers, IVIG-Intravenous immunoglobulin, ARNI- Angiotensin Receptor Neprilysin Inhibitor, SGLT-sodium-glucose cotransporter-2 inhibitors, IABP-Intra Aortic balloon pump, ECMO-Extracorporeal membrane oxygenation, NIV- Non-invasive ventilation. IMV-Invasive mechanical ventilation, ICU-Intensive care unit