Systematic Review/Meta-analysis

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Clinical outcome of established diagnostic and treatment modalities of COVID-19-associated myocarditis: a systematic review

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Background: Despite the significant research and development of COVID-19 diagnostic and therapeutic approaches, the virus still poses a concern, particularly to groups that are already vulnerable. Several individuals experienced cardiac problems like myocardial infarction, arrhythmia, heart failure, cardiomyopathy, myocarditis, and pericarditis after they had recovered from the infection. Early diagnosis and timely management of sequelae are part of the therapy. However, there are gaps in the knowledge of the diagnostic and definitive treatment options for COVID-19 myocarditis. This review focuses on myocarditis associated with COVID-19.
Objective: This systemic review provides the most recent overview of myocarditis caused by COVID-19, including clinical manifestations, diagnostic techniques, available treatments, and outcomes.
Methods: The PubMed, Google Scholar, and ScienceDirect servers were used to conduct a systematic search in compliance with the PRISMA guidelines. Boolean search terms included "(COVID-19)" OR "(COVID19)" OR "(COVID-19 VIRUS INFECTION)" AND "(MYOCARDITIS)". The results were tabulated and analyzed.
Results: A total of 32 studies, including 26 case reports and 6 case series, were included in the final analysis, and 38 cases of COVID-19-associated myocarditis were analyzed. Middle-aged men constituted the most affected population (60.52%). Dyspnoea (63.15%), chest pain or discomfort (44.73%), and fever (42.10%) were the prevalent presentations. ST-segment abnormalities were reported in 48.38% of cases on electrocardiography testing. Leucocytic infiltration (60%) was the frequent finding obtained on endomyocardial biopsy. Cardiac magnetic resonance imaging yielded myocardial oedema (63.63%), and late gadolinium enhancement (54.54%) as the most common findings. Reduced ejection fraction (75%) was the frequent result obtained on echocardiography. Corticosteroids (76.31%) and immunomodulators (42.10%) were the well-established in-hospital medications. Veno-arterial extracorporeal membrane oxygenation (35%) was the most common intervention used to support the treatment. The frequent in-hospital complications were cardiogenic shock (30.76%), followed by pneumonia (23.07%). The mortality rate was 7.9%.
Conclusion: Early detection and timely management of myocarditis are essential to reduce the risk of developing further complications. It is crucial to emphasize the need to evaluate COVID-19 as a possible cause of myocarditis in populations that are young and healthy to avoid fatal consequences.

Keywords: cardiac magnetic resonance imaging, COVID-19, echocardiography, endomyocardial biopsy, myocarditis, steroids

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HIGHLIGHTS

- The current study is an overview of COVID-19-associated myocarditis cases reported so far.
- This systematic review analyzes all the aspects of COVID-19-associated myocarditis which include, patient characteristics, clinical presentation, diagnostic methods, treatment modalities, outcomes, complications, and mortality rate.
- This review is restricted to case reports/ case series following ESC criteria.

Background

SARS-CoV-2 is a single-stranded RNA virus transmitted via respiratory secretions, most often presenting with fever, dyspnoea, cough, myalgia, and fatigue. It continues to evolve significantly, contributing to morbidity, and mortality and producing newer variants. The uncontrolled spread of COVID-19 from China to the rest of the world prompted active research

into its complications[1,2]. Following the recovery from the infection, a percentage of patients experienced systemic insults, including renal failure, stroke, pulmonary fibrosis, and myocarditis[3]. The cardiovascular focus of complications includes myocardial infarction, arrhythmia, heart failure, cardiomyopathy, myocarditis, and pericarditis[4]. With that preface, the central point of our discussion in the review revolves around COVID-19 myocarditis, a rare but debilitating complication. The symptoms range from fatigue and shortness of breath to chest discomfort and chest pain. It is known that the virus invades host cells by binding to the angiotensin-converting enzyme 2 (ACE-2) receptor found in the cardiac myocytes. Following the entry of the virus, the inflammatory response is elicited through the cytokine storm mediated by the cytotoxic action of CD8 T lymphocytes and interferon hyperactivation of the immune system. This cytokine storm results in myocardial damage leading to myocarditis. Cardiac biomarkers, particularly troponin, the electrocardiogram, echocardiography, cardiovascular magnetic resonance imaging, and endomyocardial biopsy, all help make a definitive diagnosis. Management of sequelae and steroids are implicated in the treatment. This review emphasizes the significance of diagnostic and therapeutic approaches for the recovery while summarising the reported instances of COVID-19 myocarditis. However, the unsettled determinants in the comprehension of myocarditis and treatment options for isolated COVID-19-associated myocarditis necessitate a finer evaluation[5].

Methods

Search strategy

A comprehensive search was conducted from December 2019 to January 2023 at PubMed, Google Scholar, and ScienceDirect databases. The keywords with Boolean operators were "(COVID-19)" OR "(COVID19)" OR "(COVID-19 VIRUS INFECTION)" AND "(MYOCARDITIS)". The search process was completed separately by two researchers. Duplicates were removed using Revman software. The level of significance of the studies was further screened by appropriately evaluating the title, abstract, and full text of the publications. A total of 32 articles were included and reviewed. The review was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[6]. (Fig. 1). The work has been reported in line with AMSTAR (Assessing the methodological quality of systematic reviews) guidelines.

Eligibility criteria

The studies were included or excluded as per the defined inclusion and exclusion criteria. The inclusion criteria included case reports or series of COVID-19 patients or patients with a history of COVID-19 infection of age older than or equal to 18 years and who suffered myocarditis. The case reports that specified clinical presentation, diagnostic criteria, management, and outcome were included. The studies were excluded if they were published in a language other than English, lacked access to the full text, involved patients with cardiovascular comorbidities, or were case reports that did not meet the ESC (European science society) criteria[7]. Review articles, meta-analyses, letters, comments, opinions, animal studies, and editorials were also excluded.

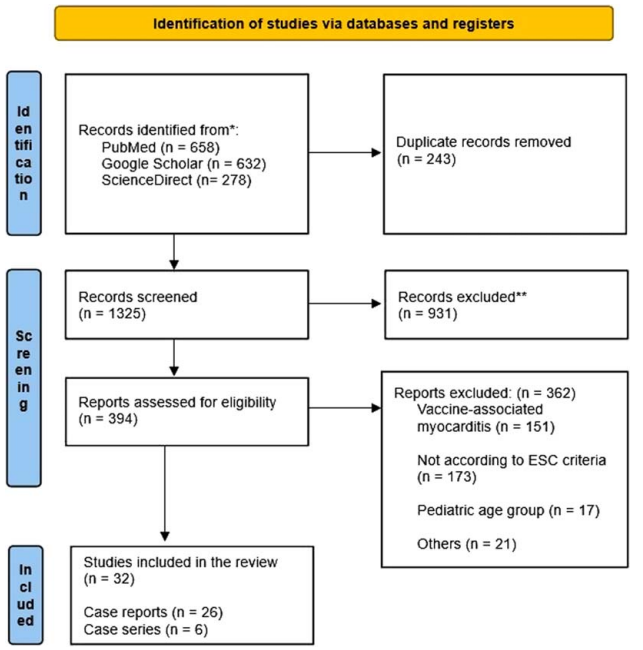

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of included studies.

Study selection

Revman software was used to organize the search results and remove duplicates. Eight authors independently screened 1325 non-duplicated records and the conflicts were resolved after a discussion with D.A. and S.S.M.

Study quality assessment

Joanna Briggs Institute Critical Appraisal tool (JBI) for case reports and case series were implemented to critically appraise the included studies. The Risk of bias was assessed by eight authors independently. The Risk of bias of studies was reported based on the following cut-off: low risk of bias if 70% of answers scored yes, a moderate risk if 50–69% of questions scored yes, and a high risk of bias if yes scores were below 50%. Twenty studies reported a low risk of bias, five studies reported a moderate risk of bias, and a high risk of bias was reported in one study.

Statistical analysis

All data were extracted onto a predesigned excel sheet. The data are represented in percentages, mean and SD for appropriate variables.

Results

A total of 32 studies, including 26 case reports and 6 case series, were included in the final analysis, and 38 cases of COVID-19-associated myocarditis were analyzed. Data from the included studies are presented in the Table 1.

Patient characteristics

Men constituted 23 out of 38 cases (60.52%); the mean age was 41.71 years (SD = 14.56). 25 out of 38 cases (65.78%) presented

Table 1

Table representing patient characteristics, investigations, treatment modalities, and outcomes.

Paper	Sex/age	Myocarditis during COVID-19	Myocarditis post-COVID-19 (time period between COVID-19 infection and myocarditis)	Troponin	ECG	Echocardiography	CMR/MRI	EMB	Treatment and duration (days)	Outcome
Hudowenz *et al.*[8]	M/48	Yes	No	Elevated	NR	RVEF reduced (28%), LVEF reduced (22%)	LGE of LV myocardium with dark foci and intracardiac thrombi	Lymphocytic myocarditis with necrosis and areas of organization	Cyclophosphamide, steroids (60)	Recovery
Bollano *et al.*[9]	M/40	No	Yes (1 month)	NR	NR	NR	Severe left ventricular dysfunction, myocardial oedema	NR	VA-ECMO, triple immunosuppressive therapy, ICD, amiodarone–mexiletine–bisoprolol combination	Recovery
Bernal-Torres *et al.*[10]	F/38	Yes	No	Elevated	Diffuse and concave elevation of the ST-segment, with PR-segment depression, Spodick's sign	Global hypokinesia of the LV, with severely reduced systolic function, an EF of 30%, mild pericardial effusion (2 mm)	Transmural myocardial oedema of both ventricles with inferobasal LGE	NR	Oxygen therapy, methylprednisolone, IVIG, hydroxychloroquine, azithromycin, lopinavir/ritonavir (10)	Recovery
Aboumari *et al.*[11]	M/60	Yes	No	Elevated	Diffuse ST-segment elevation, PR-segment depression	Severe segmental LV systolic dysfunction, EF of 15–20%, hypokinesia of the apex, distal anterior septum, anterior and lateral walls, pericardial effusion	NR	NR	IVIG, methylprednisolone (4)	Recovery
Afriyie *et al.*[12]	M/27	Yes	No	Elevated	Diffuse ST-segment elevation without reciprocal ST changes	EF of 15% with severely depressed RV systolic function	NR	NR	Remdesivir, methylprednisolone, dobutamine, milrinone, norepinephrine, epinephrine, intubation, peripheral VA-ECMO, LVAD, IABP	Death
Richard *et al.*[13]	F/28	Yes	No	Elevated	Sinus tachycardia, non-specific ST changes in the lateral leads	LVEF of 26-30%, mild MR	Myocardial necrosis, fibrosis, hyperaemia, myocarditis	NR	methylprednisolone, intubation, insulin drip, vancomycin, IV potassium, norepinephrine (3)	Recovery
Purdy *et al.*[14]	M/53	Yes	No	Elevated	Sinus tachycardia with J-point elevation in the inferolateral leads	EF of 25% with diffuse hypokinesia and moderately dilated RV with reduced RV function	NR	NR	Milrinone, pulse dose steroids with methylprednisolone, empirical antibiotics, hydroxychloroquine, isosorbide dinitrate, hydralazine, carvedilol, eplerenone (7)	Recovery
Coyle *et al.*[15]	M/57	Yes	No	Elevated	Sinus tachycardia without ST-T-wave changes	Moderate diffuse hypokinesia with relative apical sparing and LVEF of 35% to 40%	Diffuse biventricular and biatrial oedema with a small area of LGE	NR	Methylprednisolone, prednisone, colchicine, tocilizumab (4)	Recovery
Tiwary *et al.*[16]	M/30	Yes	No	Elevated	Wide QRS complex, LBBB	Pericardial effusion, thickened ventricular wall	NR	NR	Remdesivir, convalescent plasma, dexamethasone, cefepime, doxycycline, amiodarone, oxygen therapy (27)	Recovery

Table 1

(*Continued*)

Paper	Sex/age	Myocarditis during COVID-19	Myocarditis post-COVID-19 (time period between COVID-19 infection and myocarditis)	Troponin	ECG	Echocardiography	CMR/MRI	EMB	Treatment and duration (days)	Outcome
Bollano *et al.*[9]	M/35	No	Yes (1 month)	Elevated	NR	NR	Severe biventricular dysfunction and acute myocardial inflammation	Well-formed non-necrotizing granulomas and solitary giant cells	Steroids, CRT-D (1 year)	Recovery
Bollano *et al.*[9]	F/53	No	Yes (Nil)	NR	Limb leads showed first-degree AV block, low QRS amplitude, and T-wave inversions in inferior leads Precordial leads showed first-degree AV block, T-wave inversions in right precordial leads V1–3, and epsilon wave	NR	Mild LV dysfunction, marked RV dysfunction, and RV dilation with extensive LGE of LV	Signs of extensive myocyte destruction, necrosis, abundant giant cells, eosinophils, and loose granuloma formation.	Steroids, tacrolimus, mycophenolate mofetil, ICD	Recovery
Bollano *et al.*[9]	F/47	No	Yes (3 months)	NR	NSVT	NR	Signs of extensive myocardial inflammation	EMB- no signs of inflammation. MRI-guided EMB- signs consistent with granulomatous myocarditis	Steroids, tacrolimus, mycophenolate mofetil, ICD	Recovery
Usui *et al.*[17]	F/44	Yes	No	Elevated	Sinus rhythm with low voltage in limb leads, ST-segment elevation, QT prolongation	Biventricular dysfunction with oedematous wall thickening	Acute myocardial oedema and subsequent fibrosis	Mild interstitial inflammatory infiltrates with endomyocardial fibrous thickening and mild interstitial fibrosis of the myocardium	Remdesivir, methylprednisolone, baricitinib, VA-ECMO (10)	Recovery
Purdy *et al.*[14]	F/30	Yes	No	Elevated	Sinus tachycardia	EF of 45% with moderate diffuse hypokinesia and a moderate pericardial effusion	NR	NR	Hydroxychloroquine, atorvastatin, empirical antibiotics, milrinone, methylprednisolone	Recovery
Aldeghaither *et al.*[18]	M/21	Yes	No	Elevated	NR	Severe biventricular systolic dysfunction, LVEF of 5–10%	NR	Lymphocytic infiltrate	IV methylprednisolone, IV anakinra, IVIG, femoral-femoral VA-ECMO (56)	Recovery
Kallel *et al.*[19]	M/56	Yes	No	Elevated	Sinus rhythm with diffuse ST elevation and simple monomorphic SVE	Normal systolic function with a normal wall-motion, with no pericardial effusion	NR	NR	Oxygen therapy, dobutamine, noradrenaline, tocilizumab, azithromycin, corticosteroids (5)	Recovery
Hedayat *et al.*[20]	M/24	Yes	No	Elevated	Sinus tachycardia with ST-segment elevations less than 1 mm in leads I and aVL, ST-segment depression of 1 mm in leads III and aVF	Normal LV size and systolic function with an EF of 55%	NR	NR	Lopinavir/Ritonavir during admission, Metolazone	Recovery
Hedayat *et al.*[20]	M/28	Yes	No	Elevated	Normal except for slight coning of ST segments in inferior wall leads	Normal LV size with mild systolic dysfunction with an EF of 45% with global hypokinesia	NR	NR	Hydroxychloroquine, metoprolol succinate, enalapril (10)	Recovery

Martínez *et al.*[21]	M/64	No	Yes (1 month)	Elevated	Sinus tachycardia, no ST-T-wave abnormalities	LV cavity size, wall-motion, and thickness were normal, with an EF of 56%	NR	NR	Prednisolone, atenolol (14)	Recovery
Shotwell *et al.*[22]	M/23	No	Yes (3 months)	Elevated	Sinus bradycardia with incomplete RBBB	LVEF of 60% with no valvular or wall-motion abnormalities	NR	NR	Colchicine, Ibuprofen (90)	Recovery
Salamanca *et al.*[23]	M/44	Yes	No	Elevated	Third-degree AV block	Severe global LV systolic dysfunction with LVEF around 15%	Native T1 and T2 SIR and ECV diffusely increased with slightly less involvement of the inferolateral wall.	No necrosis, inflammation, or fibrosis	Temporary cardiac pacemaker, dobutamine, oxygen therapy, norepinephrine, intubation, mechanical ventilation, VA-ECMO, IABP, methylprednisolone, tocilizumab, hydroxychloroquine, azithromycin, lopinavir/ritonavir (6)	Recovery
Sala *et al.*[24]	F/43	Yes	No	Elevated	Low atrial ectopic rhythm, mild ST-segment elevations in leads V1-V2 and aVR, reciprocal ST-segment depressions in V4-V6, QTc of 452 ms with diffuse U-waves	Mild LV systolic dysfunction with LVEF of 43% with inferolateral wall hypokinesia	Diffuse myocardial oedema was observed at basal and middle LV segments. LGE negative	Diffuse T lymphocytic inflammatory infiltrate with large interstitial oedema and limited foci of necrosis	CPAP, lopinavir/ritonavir, hydroxychloroquine	Recovery
Rasras *et al.*[25]	F/47	Yes	No	Elevated	NR	Biventricular DCM, LVEF is 10%, low CI at 1.20 L/min/m3 with a large intra-LV "horseshoe" thrombus, also showing a high heart LV filling pressure with elevated PAP at 51 mmHg, dilated inferior vena cava	NR	NR	Dobutamine, norepinephrine, bisoprolol, ramipril, spironolactone, furosemide, left lower limb embolectomy with FOGARTY probe, low molecular weight heparin, ceftriaxone, ciprofloxacin, methylprednisolone, vitamin supplementation.	Recovery
Lastra *et al.*[26]	M/31	No	Yes (2 weeks)	Elevated	N/A	Mild PAH (45 mmHg), LVEF of 40%, and mild diastolic dysfunction	Inferoseptal hypokinesia, mild global myocardial hyperintensity	NR	Ibuprofen, colchicine, methylprednisolone (1 year)	Recovery
Hasan *et al.*[27]	F/28	Yes	No	Elevated	Sinus tachycardia, regular rhythm	Normal wall-motion at rest, LVEF of 60%, and an average LV global peak longitudinal strain of 19.5%	Hyperintensity signal changes in pericardium and myocardium in T2-weighted and STIR images, increased LGE in the sub-epi-myocardial layer	NR	Prednisolone, beta-blockers, ibuprofen, colchicine (14)	Recovery
Tabatabai *et al.*[28]	M/28	No	Yes (1 month)	Elevated	Sinus tachycardia, RBBB, and ST-segment changes in the anterior leads	Normal LV size (4.7 cm), there was severe global hypokinesia of LV and severely impaired LV systolic function with an EF estimated between 20% and 25%, elevated LVEDP, and the RV systolic function was moderately impaired	NR	NR	Enoxaparin, methylprednisolone, sodium succinate, bisoprolol, ramipril, furosemide, spironolactone, oxygen therapy, ventilatory support (7)	Recovery
Naneishvili *et al.*[29]	F/44	Yes	No	Elevated	AF	Moderate concentric biventricular hypertrophy, diffuse LV hypokinesia with moderate to severe LV systolic dysfunction (estimated EF: 37% by Simpsons)	NR	NR	Methylprednisolone, dobutamine, amiodarone, milrinone (3)	Recovery

Table 1

(*Continued*)

Paper	Sex/age	Myocarditis during COVID-19	Myocarditis post-COVID-19 (time period between COVID-19 infection and myocarditis)	Troponin	ECG	Echocardiography	CMR/MRI	EMB	Treatment and duration (days)	Outcome
Zayour *et al.*[30]	M/56	Yes	No	Elevated	ST-segment elevation of around 1 mm in inferior leads	Good contractility with no visible wall-motion abnormalities but showed a decrease in longitudinal strain, mainly in the posterior segment.	Normal global LV and RV systolic functions with no wall-motion abnormalities but a hyperintense signal at the inferolateral segment with LGE present	NR	Aspirin, colchicine	Recovery
Nikoo *et al.*[31]	F/38	No	Yes (2 months)	Elevated	CHB with NSVT	Biventricular dilation and global hypokinesia with LVEF of 20–25%	Normal ventricle size, evidence of diffuse myocardial inflammation of the LV myocardium with no regional wall-motion abnormality	NR	Amiodarone, temporary cardiac pacemaker, dexamethasone, anticoagulants, heart failure management (6)	Recovery
Albert *et al.*[32]	M/49	Yes	No	Elevated	Sinus tachycardia	Globally depressed LVEF of 20% with LVDD of 5.8 cm, and increased wall thickness of 1.7 cm and 1.4 cm measured in the interventricular septum and posterior walls	NR	Infiltration of mononuclear cells in the endocardium and myocardium, microvasculature showed endothelial swelling, and myocytes showed no degenerative or apoptotic changes	VA-ECMO, LVAD, tocilizumab, methylprednisolone, IVIG, IV inotropes, carvedilol (17)	Recovery
Sasbou *et al.*[33]	M/25	Yes	No	Elevated	ST-segment elevation in lateral and posterior territories with Q wave	Myocardial wall-motion abnormalities with apical akinesia, large apical thrombosis, low LVEF (23%), restrictive mitral profile, and PAH	NR	NR	Mechanical ventilation, hydroxychloroquine, azithromycin, unfractionated heparin, vasoactive drugs (15)	Death
Pourshahid *et al.*[34]	F/22	No	Yes (1 month)	NR	NR	LVEF of 65% and an abnormal mobile density in the left atrium that was not attached to the mitral valve or septum	Mild biventricular cardiomyopathy, small pericardial effusion, small bilateral pleural effusion, and apical RV hypokinesia with patchy areas of LGE	NR	Oxygen therapy, antibiotics, methylprednisolone	Recovery
Shahrami *et al.*[35]	M/78	Yes	No	Elevated	AF	LVEF = 15%, high PAP, mildly enlarged LV, moderate to severe LV dysfunction, mild diastolic	NR	NR	Mechanical ventilation, hydroxychloroquine, dexamethasone, IVIG, IV Ascorbic	Death

						dysfunction (grade 1), mild MR, and normal septal thickness			acid, Melatonin, broad-spectrum antibiotics, vasopressors, amiodarone, Midodrine, ICD (44)	
Rajpal *et al.*[36]	F/60	No	Yes (2 week)	Elevated	Sinus tachycardia, ST-segment elevation in V1, V2, aVR, ST-segment depression in some leads	Moderately increased LV wall thicknesses, mild global LV systolic dysfunction, LVEF 49%, grade II diastolic dysfunction, small pericardial effusion	Diffuse hyperintensity on T2 mapping, inferolateral epicardial LGE	Scattered perivascular and interstitial inflammatory cells consisting of CD3-positive T-lymphocytes, CD20-positive B-lymphocytes, and histiocytes, along with interstitial and myocyte injury	Mechanical ventilation, IV dobutamine, IV furosemide, norepinephrine, vasopressin, epinephrine, phenylephrine, IV amiodarone, VA-ECMO, CRRT, IV methylprednisolone, prednisone taper, haemodialysis, milrinone, metoprolol succinate, isosorbide dinitrate, hydralazine, antibiotics, mexiletine, ICD (40)	Recovery
Doyen *et al.*[37]	M/69	Yes	No	Elevated	Diffuse inverted T waves	Mild LVH. LVEF, and wall-motion tenderness were normal	Subepicardial LGE of the apex and inferolateral wall	NR	Mechanical ventilation, hydrocortisone (21)	Recovery
Almanza-Hurtado *et al.*[38]	F/54	Yes	No	Elevated	Sinus tachycardia and diffuse ST-segment elevation	Evidence of Ischaemic heart disease, normal biventricular function, LVEF = 64%	Non-ischaemic LGE	NR	Supportive treatment	Recovery
Almanza-Hurtado *et al.*[38]	F/32	No	Yes (nil)	Normal	Sinus bradycardia	LVEF = 68% with altered myocardial strain and pericardial effusion	Subepicardial LGE	NR	Colchicine, NSAIDs	Recovery
Meel *et al.*[39]	M/31	No	Yes (3 wk)	Elevated	T-wave inversion in lead III	Preserved RV and LV contractility and no wall-motion abnormalities	Delayed LGE within the mid-wall and epicardial regions	NR	Colchicine, prednisone (14)	Recovery

AF, atrial fibrillation; CHB, complete heart block; CI, cardiac index; CRRT, continuous renal replacement therapy; CRT-D, cardiac resynchronisation therapy; DCM, dilated cardiomyopathy; ECV, extra cellular volume; EF, ejection fraction; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; IV, intravenous; IVIG, intravenous immunoglobulins; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVAD, left ventricular assist disease; LVD, left ventricular dysfunction; LVDD, left ventricular end-diastolic dimension; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; N/A, not applicable; NR, not reported; NSVT, non-sustained ventricular tachycardia; PAH, pulmonary artery hypertension; PAP, pulmonary arterial pressure; RV, right ventricle; RVEF, right ventricular ejection fraction; SIR, signal intensity ratio; STIR, short tau inversion recovery; SVE, supraventricular extrasystole; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

with myocarditis during the course of COVID-19 infection, while 13 cases presented after testing negative for COVID-19 infection (post-COVID). The average time period between COVID-19 infection and the onset of myocarditis is 1–3 months in the 13 cases.

Investigations

Troponin and electrocardiography (ECG)

ECG results were reported in 31 cases (81.57%) and all of them were abnormal. ST-segment abnormalities were reported in 15 cases (48.38%), with 12 patients showing ST-segment elevation and 3 patients showing ST-segment depression. Other ECG findings reported were sinus tachycardia ($n=11$, 35.48%), heart blocks and bundle branch blocks ($n=6$, 19.35%), supraventricular tachycardia ($n=4$, 12.90%), T-wave inversion ($n=3$, 9.67%), QRS complex abnormalities ($n=3$, 9.67%), sinus bradycardia ($n=2$, 6.45%), ventricular tachycardia ($n=2$, 6.45%), and PR-segment depression ($n=2$, 6.45%). Troponin levels were assessed in 34 cases (89.47%) and 33 cases reported elevated values (97.05%), while one case reported normal values[27].

Endomyocardial biopsy (EMB)

EMB results were reported in 10 cases (26.31%). Leucocytic infiltration ($n=6$, 60%), necrosis of cardiac myocytes ($n=3$, 30%), granulomatous inflammation ($n=3$, 30%), giant cells ($n=2$, 20%), and myocyte destruction ($n=2$, 20%) were among the significant results. In addition, interstitial oedema and fibrosis were seen rarely. However, one case showed normal EMB findings[31].

Cardiac magnetic resonance imaging (CMR)

CMR was done in 22 cases (57.89%), and the most frequent finding was myocardial inflammation and oedema, appreciated as myocardial hyperintensity ($n=14$, 63.63%). Late gadolinium enhancement was reported in 12 cases (54.54%). 4 cases (18.18%) had findings suggesting cardiomyopathy or ventricular dysfunction, and 2 patients (9.09%) had a regional wall-motion abnormality in the form of hypokinesia or akinesia. Other findings reported were pericardial effusion ($n=2$, 9.09%), myocardial fibrosis ($n=2$, 9.09%), and chamber dilatation ($n=2$, 9.09%). Pericardial hyperintensity, myocardial necrosis, intracardiac thrombosis, and hyperaemia were reported infrequently.

Echocardiography

Echocardiography was done in 34 cases (89.47%) and was reported as normal in 6 cases (17.65%). Among the reported cases, 21 reported reduced ejection fraction (75%). Other findings were systolic dysfunction ($n=13$, 38.23%), wall-motion abnormalities ($n=11$, 32.35%), and pericardial effusion ($n=6$, 17.65%). Other rare findings reported were ventricular wall thickening ($n=4$, 11.76%), valve regurgitations ($n=3$, 8.82%), enlarged chambers ($n=4$, 11.76%), and ventricular hypertrophy ($n=2$ cases, 5.88%).

Treatment

Pharmacotherapy

Management involved the use of various drugs and interventions. Corticosteroids were administered in 29 cases (76.31%), which included methylprednisolone ($n=17$), dexamethasone ($n=3$), prednisone ($n=3$), prednisolone ($n=2$), and hydrocortisone ($n=1$). Immunomodulators were used in 16 cases (42.10%), which included intravenous immunoglobulin (IVIG) ($n=5$), tacrolimus ($n=2$), mycophenolate mofetil ($n=2$), tocilizumab ($n=4$), baricitinib ($n=1$), cyclophosphamide ($n=1$), and anakinra ($n=1$). Vasopressors and inotropes were administered in 9 cases (23.68%), which included dobutamine ($n=6$), norepinephrine ($n=5$), milrinone ($n=5$), epinephrine ($n=2$), and phenylephrine ($n=1$). Other drugs used were hydroxychloroquine ($n=8$, 21%), NSAIDs ($n=8$, 21%), antibiotics ($n=7$, 18.42%), beta-blockers ($n=7$, 18.42%), antivirals ($n=7$, 18.42%), colchicine ($n=7$, 18.42%), antiarrhythmics ($n=6$, 15.78%), diuretics ($n=4$, 10.52%), antihypertensives ($n=4$, 10.52%), anticoagulants ($n=3$, 7.89%), vitamin supplements and electrolytes ($n=3$, 7.89%), and vasodilators ($n=2$, 5.26%). Insulin, melatonin, and atorvastatin were used rarely.

Interventions

Interventions were performed in 22 cases (57.89%). The most frequently performed intervention was mechanical circulatory support with veno-arterial extracorporeal membrane oxygenation ($n=7$, 35%). Other frequently performed interventions were mechanical ventilation ($n=6$, 30%), oxygen therapy ($n=6$, 30%), implantable cardioverter defibrillator ($n=5$, 22.72%), temporary cardiac pacemaker ($n=2$, 10%), intra-aortic balloon pump ($n=2$, 10%), intubation ($n=2$, 10%), and percutaneous left ventricular assist device ($n=2$, 10%). Other infrequently used interventions included cardiac resynchronization therapy defibrillator, left lower limb embolectomy with the FOGARTY probe, continuous positive airway pressure, continuous renal replacement therapy, and intermittent haemodialysis.

The total duration of the treatment was revealed in 29 cases (76.31%) and is highly variable, ranging from 3 days to 1 year.

Outcome

The current study describes a total of 38 cases of COVID-19 myocarditis, of which 35 cases (92.1%) recovered and the mortality rate was 7.9%. All the 3 reported deaths were in patients who were diagnosed with myocarditis during COVID-19 infection.

Discussion

A majority of the patients analyzed in the review were males with a mean age of 41.71 years. This evidence supports the study conducted by Urban *et al.*[40], conveying that myocarditis is common in middle-aged male patients. However, among the reported cases, both extremes of age were noticed[18–37]. The risk factors for developing COVID-19 myocarditis are similar to those causing severe COVID-19 infection. Hypertension (42.85%) and diabetes mellitus (28.57%) were the most common risk factors. The analysis also showed a significant burden of obesity, an independent risk factor for poor sequelae following

COVID-19 infection[41,42]. Myocarditis can develop during the COVID-19 infection or after a specific period following the infection. 34.21% developed myocarditis after the infection, necessitating continuous surveillance even after the infection.

COVID-19 myocarditis presents with symptoms similar to COVID-19 infection which makes it difficult to identify myocarditis in a COVID-infected patient. The most common presentations were dyspnoea, chest pain, fever, and fatigue. These symptoms are a result of SARS-CoV-2 entry into the cell by binding its spike protein to a membrane protein, ACE-2. ACE-2 is found in epithelial cells of the respiratory tract, type II pneumocytes, and cardiomyocytes. The virus multiplies in cardiomyocytes and causes injury by interrupting the production of stress granules through an accessory protein. Damaged cells release viral antigens that are presented by antigen-presenting cells to naive T lymphocytes. Primed CD8 + T lymphocytes further cause inflammation through cell-mediated cytotoxicity. It also damages endothelial cells in coronary vessels, resulting in extra-pulmonary migration of alveolar macrophages, which causes complement activation and apoptosis. In some cases, a cytokine storm develops with IL-6 as the key mediator. IL-6 attracts inflammatory cells, causing myocardial damage and aggravation of pre-existing myocarditis[43,44]. Platelet activation and high clotting factor concentrations in systemic inflammation increase the risk of thrombus formation in coronary arteries, resulting in myocardial ischaemia[45]. These mechanisms ultimately lead to myocarditis (Fig. 2).

A high level of suspicion early in the course of the disease with the use of appropriate investigations to identify the cause is imperative. The ESC criteria for clinically suspected myocarditis include all the relevant clinical presentations as well as features of ECG, CMR, echocardiography, EMB, etc[46]. Cardiac troponin levels, ECG, echocardiography, CMR, and EMB are analyzed in the current study. Cardiac troponin appears in the blood due to myocardial injury and is a good marker of the same. The normal range is 0–14 pg/ml[47]. 97.05% of cases showed elevated troponin levels. Hence, it may be a prudent measure to estimate troponin levels on the admission of a patient with COVID-19 for the establishment of the baseline, devising the formation of a trend throughout the patient's stay and therefore, assisting in the early detection of myocarditis. However, troponin levels are not relevant to the prognosis and long-term outcomes of acute myocarditis[48]. In patients with elevated troponin, the subsequent investigations are done using ECG and echocardiography to assess the cardiac injury further. An algorithm proposed for diagnosing myocarditis in COVID-19 patients states that ECG and echocardiography should also be done in patients with negative biomarkers but a high clinical suspicion of myocarditis[49]. ST-segment abnormalities and sinus tachycardias were the most common ECG findings among the reported cases. Although an ECG is not diagnostic for myocarditis due to the various non-specific changes, it should raise a suspicion of myocarditis in COVID-19 patients. Echocardiography can be used as a confirmatory diagnostic investigation for myocarditis, and also as a tool to assess disease progression[49]. Decreased EF (systolic dysfunction), dilated chambers, increased wall thickness, and pericardial effusion are specific signs of myocarditis, but the presence of pre-existing cardiac conditions should be taken into consideration. In the current review, 61.76% reported reduced LVEF, and 41.18% of cases reported systolic dysfunction, as the most common echo findings. CMR is considered the best non-invasive method of diagnosis due to its high sensitivity[5]. CMR

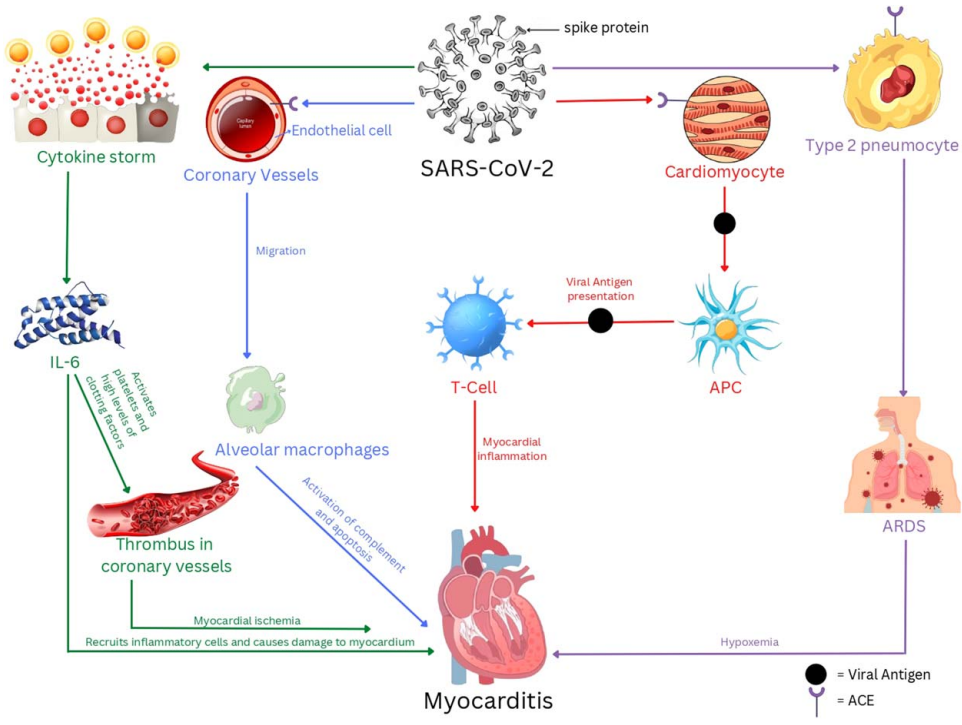

Figure 2. Pathogenesis of COVID-19-associated myocarditis. ACE, Angiotensin-converting enzyme; APC, antigen-presenting cells (macrophages, B lymphocytes, dendritic cells); ARDS, acute respiratory distress syndrome; IL, interleukin.

was done in 57.89% of cases and all showed abnormal findings. Diffuse oedema, which appears as myocardial hyperintensity on CMR, was the most common finding similar to a study by Chimenti *et al*.[5]. Late gadolinium enhancement, indicative of irreversible myocardial injury, was seen in more than 50% of cases. EMB is the gold standard to confirm the presence of myocarditis and is done in those patients with severe disease to initiate appropriate therapy[5,50]. EMB results were reported in 10 cases, with 90% of cases showing abnormal findings.

Early detection and timely management of myocarditis reduce the risk of developing further complications. However, there are no standard guidelines regarding the pharmacological management of myocarditis associated with COVID-19. In patients with fulminant myocarditis, the American Heart Association recommends administering inotropes, vasopressors, and mechanical ventilation. Depending on the severity of the cardiogenic shock, mechanical circulatory support with extracorporeal membrane oxygenation, ventricular assist disease, or intra-aortic balloon pump is also recommended[50]. Several therapies have been employed in COVID-19 myocarditis based on our knowledge of the pathogenesis and previous experience treating viral and fulminant myocarditis. In COVID-19 myocarditis, glucocorticoids have been used because hyperinflammation and cytokine release syndrome are likely to cause damage. However, the use of corticosteroids in COVID-19 has been debated. There are reports that patients treated with corticosteroids had delayed viral clearance, a higher risk of secondary infection, adrenal insufficiency, more ICU admissions, and a higher death rate. On the contrary, the administration of corticosteroids was associated with decreased mortality and improved survival. In the current study, corticosteroids were administered in 23 cases (61.5%), of which 21 cases (91.3%) had recovered[50]. More controlled research is required to assess their safety and efficacy. Strong evidence exists to support the use of IVIG in acute myocarditis as well as in critically ill COVID-19 patients. IVIG is an immunomodulator that has anti-inflammatory and antiviral properties. However, no evidence supports its usage in myocarditis associated with COVID-19. In the current study, 5 cases (13.5%) were treated with IVIG, of which 4 cases (80%) had recovered. Antivirals like lopinavir/ritonavir and remdesivir were also used occasionally. In a recent study, it was discovered that remdesivir decreased the hospitalization rate in cases with mild to moderate COVID-19 but had little to no impact on all-cause mortality or in-hospital mortality in people with moderate to severe COVID-19[51]. Surgical interventions such as mechanical circulatory support and mechanical ventilation are life-saving procedures for critically ill patients with fulminant myocarditis whose clinical condition deteriorates despite medical therapy. In the current study, all the patients who underwent cardiac device implantation had a successful recovery, demonstrating the effectiveness of this therapeutic strategy[9,23,31]. In spite of receiving management, most of the cases developed complications (68.42%) which affected the outcome. Cardiogenic shock (30.8%) and viral pneumonia (23.1%) were the most common in-hospital complications. One of the probable mechanisms by which myocarditis leads to cardiogenic shock is the rapid deterioration of cardiac function. Acute respiratory distress syndrome was consistently reported as a complication of COVID-19 myocarditis in some studies[41]. Physicians should look out for such complications so that they can be detected early and treated. In the current review, the mortality rate was 7.9%, which is lower than the mortality rate reported in other studies[52]. However, the number of cases analyzed is too small to comment on the mortality rate.

Limitations

The dearth of research on COVID-19-related myocarditis significantly impairs the inference of our systematic review and the representativeness of our findings. Several case reports and case series were excluded from the study due to incomplete data and failure to follow the ESC criteria. Moreover, the majority of the recorded cases show extremely dramatic scenarios with a severe course, and consequences that do not really represent the usual clinical picture, although it is appealing for publishing purposes. Histologic analysis was not reported in most of the case reports which increases the risk of biased information. While the data of more comprehensive, well-designed research are not yet available, our analysis yields a current, interim review of the data.

Conclusion

In spite of being extensively studied since the commencement of the pandemic, COVID-19 continues to be a prominent field of research for a multitude of reasons, including complications and chronic manifestations. Cardiac pathologies are fairly common after COVID-19 infection creating major concern among physicians and a high percentage of the infected population. The gaps in knowledge on pathophysiology and definitive treatment options in isolated myocarditis and myocarditis in those with associated other systemic diseases cannot be overlooked and are yet to be addressed. This systemic review provides the latest overview of COVID-19-related myocarditis. It is crucial to emphasize the need to evaluate COVID-19 as a possible cause of myocarditis in populations that are generally young and healthy to avoid fatal consequences.

Ethical approval

NA.

Consent

NA.

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Author contribution

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Conflicts of interest disclosure

None.

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References

[1] Rahman S, Montero MTV, Rowe K, *et al*. Epidemiology, pathogenesis, clinical presentations, diagnosis and treatment of COVID-19: a review of current evidence. Expert Rev Clin Pharmacol 2021;14:601–21.

[2] Hadj Hassine I. Covid-19 vaccines and variants of concern: a review. Rev Med Virol 2022;32:e2313.

[3] Kamal M, Abo Omirah M, Hussein A, *et al*. Assessment and characterisation of post-COVID-19 manifestations. Int J Clin Pract 2021;75: e13746.

[4] Mohammad KO, Lin A, Rodriguez JBC. Cardiac manifestations of post-acute COVID-19 infection. Curr Cardiol Rep 2022;24:1775–83.

[5] Chimenti C, Magnocavallo M, Ballatore F, *et al*. Prevalence and clinical implications of COVID-19 myocarditis. Card Electrophysiol Clin 2022;14:53–62.

[6] Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6:e1000097.

[7] McDonagh TA, Metra M, Adamo M, *et al*. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the european society of cardiology (esc) with the special contribution of the heart failure association (HFA) of the ESC. Europ Heart J 2021;42:3599–726.

[8] Hudowenz O, Klemm P, Lange U, *et al*. Case report of severe PCR-confirmed COVID-19 myocarditis in a European patient manifesting in mid-January 2020. Eur Heart J Case Rep 2020;4:1–6.

[9] Bollano E, Polte CL, Mäyränpää MI, *et al*. Cardiac sarcoidosis and giant cell myocarditis after COVID-19 infection. ESC Heart Fail 2022;9: 4298–303.

[10] Bernal-Torres W, Herrera-Escandón Á, Hurtado-Rivera M, *et al*. COVID-19 fulminant myocarditis: a case report. Eur Heart J Case Rep 2020;4(FI1):1–6.

[11] Li A, Garcia-Bengochea Y, Stechel R, *et al*. Management of COVID-19 myopericarditis with reversal of cardiac dysfunction after blunting of cytokine storm: a case report. Eur Heart J Case Rep 2020;4(FI1):1–6.

[12] Afriyie F, Fohle E, Dekowski SS, *et al*. A case of isolated sars-cov-2 fulminant myopericarditis without respiratory failure. Cureus Jf Med Sci 2021;13:e14003.

[13] Richard I, Robinson B, Dawson A, *et al*. An atypical presentation of fulminant myocarditis secondary to COVID-19 infection. Cureus 2020;12:e9179.

[14] Purdy A, Ido F, Sterner S, *et al*. Myocarditis in COVID-19 presenting with cardiogenic shock: a case series. Eur Heart J Case Rep 2021;5:ytab028.

[15] Coyle J, Igbinomwanhia E, Sanchez-Nadales A, *et al*. A recovered case of COVID-19 myocarditis and ARDS treated with corticosteroids, tocilizumab, and experimental AT-001. JACC Case Rep 2020;2:1331–6.

[16] Tiwary T, Baiswar S, Jinnur P. A rare case of COVID-19 myocarditis with cardiac tamponade in a young diabetic adult with renal failure. Cureus 2020;12:e11632.

[17] Usui E, Nagaoka E, Ikeda H, *et al*. Fulminant myocarditis with COVID-19 infection having normal C-reactive protein and serial magnetic resonance follow-up. ESC Heart Fail 2022;10:1426–30.

[18] Aldeghaither S, Qutob R, Assanangkornchai N, *et al*. Clinical and histopathologic features of myocarditis in multisystem inflammatory syndrome (adult)-associated COVID-19. Crit Care Explor 2022;10:e0630.

[19] Kallel O, Bourouis I, Bougrine R, *et al*. Acute myocarditis related to Covid-19 infection: 2 cases report. Ann Med Surg (Lond) 2021;66: 102431.

[20] Hedayat B, Hosseini K. Chest pain and high troponin level without significant respiratory symptoms in young patients with COVID-19. Caspian J Intern Med 2020;11(Suppl 1):561–5.

[21] Martínez AO, González-Razo VT, Navarro-Sánchez V, *et al*. SARS-CoV-2-related subacute thyroiditis, myocarditis, and hepatitis after full resolution of COVID-19 serum markers. Am J Case Rep 2021;22: e932321-1–5.

[22] Shotwell MK, Alyami B, Sankaramangalam K, *et al*. Longitudinal follow-up of asymptomatic COVID-19 myocarditis with cardiac magnetic resonance imaging. Am J Case Rep [Internet] 2022;23:e935492-1–7.

[23] Salamanca J, Díez-Villanueva P, Martínez P, *et al*. COVID-19 "Fulminant Myocarditis" successfully treated with temporary mechanical circulatory support. JACC Cardiovasc Imaging 2020;13:2457–9.

[24] Sala S, Peretto G, Gramegna M, *et al*. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J 2020;41:1861–2.

[25] Rasras H, Boudihi A, Hbali A, *et al*. Multiple cardiovascular complications of COVID-19 infection in a young patient: a case report. Pan Afr Med J 2021;38:192.

[26] Vera-Lastra O, Lucas-Hernández A, Ruiz-Montiel JE, *et al*. Myopericarditis as a manifestation of long COVID syndrome. Cureus 2021;13:e19449.

[27] Hasan MN, Afzal A, Sami CA, *et al*. A young lady with myopericarditis: an unusual presentation of COVID-19 infection. Cureus J Med Sci 2022;14:e26673.

[28] Tabatabai S, Bazargani N, Osman H, *et al*. Acute myocarditis and heart failure associated with multisystem inflammatory syndrome in adults: a rare sequela of coronavirus 2 infection. Heart Views 2022;23: 169.

[29] Naneishvili T, Khalil A, O'Leary R, *et al*. Fulminant myocarditis as an early presentation of SARS-CoV-2. BMJ Case Rep 2020;13: e237553.

[30] Zayour M, Al Ashkar R, Karaki M, *et al*. Focal myocarditis as the first sign in the presentation of a COVID-19 infection: a case report. Cureus, 14:e26358.

[31] Nikoo MH, Mozaffari R, Hatamnejad MR, *et al*. Systolic dysfunction and complete heart block as complications of fulminant myocarditis in a recovered COVID-19 patient. J Cardiol Cases 2021;24:177–81.

[32] Albert CL, Carmona-Rubio AE, Weiss AJ, *et al*. The enemy within. Circulation 2020;142:1865–70.

[33] Sasbou L, El boussaadani B, Fellat I, *et al*. COVID 19 myocarditis: myth or reality? J Saudi Heart Assoc 2020;32:421–4.

[34] Pourshahid S, Khademolhosseini S, Giri B, *et al*. A case of steroid-responsive severe pneumonia following a recent COVID-19 infection in a patient with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. Cureus J Med Sci 2022;14:e26785.

[35] Shahrami B, Davoudi-Monfared E, Rezaie Z, *et al*. Management of a critically ill patient with COVID-19-related fulminant myocarditis: a case report. Respir Med Case Rep 2022;36:101611.

[36] Rajpal S, Kahwash R, Tong MS, *et al*. Fulminant myocarditis following SARS-CoV-2 infection. J Am College Cardiol 2022;79:2144–52.

[37] Doyen D, Moceri P, Ducreux D, *et al*. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. Lancet 2020;395:1516.

[38] Almanza-Hurtado A, Martínez-Ávila MC, Rodríguez-Yánez T, *et al*. Viral cardiomyopathies associated with SARS-CoV-2 infection. Clin Med Insights Case Rep [Internet] 2022;15:11795476221088140.

[39] Meel R, Ramsamy TD, Narsing R, *et al*. Focal myocarditis in a young male with SARS-CoV-2 infection. Oxf Med Case Rep 2021;2021: omaa142.

[40] Urban S, Fułek M, Błaziak M, *et al*. COVID-19 related myocarditis in adults: a systematic review of case reports. J Clin Med 2022;11:5519.

[41] Jaiswal V, Sarfraz Z, Sarfraz A, *et al*. COVID-19 Infection and Myocarditis: A State-of-the-Art Systematic Review. J Prim Care Community Health 2021;12:21501327211056800.

[42] Lasbleiz A, Gaborit B, Soghomonian A, *et al*. COVID-19 and obesity: role of ectopic visceral and epicardial adipose tissues in myocardial injury. Front Endocrinol (Lausanne) 2021;12:726967.

[43] Chimenti C, Magnocavallo M, Ballatore F, *et al*. Prevalence and clinical implications of COVID-19 myocarditis. Card Electrophysiol Clin 2022;14:53–62.

[44] Siripanthong B, Nazarian S, Muser D, *et al*. Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm 2020;17:1463–71.
[45] Ali M, Shiwani HA, Elfaki MY, *et al*. Covid-19 and myocarditis: a review of literature. The Egypt Heart J 2022;74:23.
[46] Caforio ALP, Pankuweit S, Arbustini E, *et al*. 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. Eur Heart J [Internet] 2013;34:2636–48.
[47] Mehta P. What Is a Cardiac Troponin Test? [Internet]. [cited 2023 Feb 9]. https://www.webmd.com/heart-disease/what-is-cardiac-troponin-test.
[48] Janardhanan R. Myocarditis with very high troponins: risk stratification by cardiac magnetic resonance. J Thorac Dis 2016;8:E1333–6.
[49] Haussner W, DeRosa AP, Haussner D, *et al*. COVID-19 associated myocarditis: A systematic review. Am J Emerg Med 2022;51:150.
[50] Sawalha K, Abozenah M, Kadado AJ, *et al*. Systematic review of COVID-19 related myocarditis: insights on management and outcome. Cardiovasc Revasc Med 2021;23:107–13.
[51] Ansems K, Grundeis F, Dahms K, *et al*. Remdesivir for the treatment of COVID-19. Cochrane Database Syst Rev 2021;8:CD014962.
[52] Bemtgen X, Kaier K, Rilinger J, *et al*. Myocarditis mortality with and without COVID-19: insights from a national registry. Clin Res Cardiol 2022:1–7. doi:10.1007/s00392-022-02141-9. [Epub ahead of print].