

SUPPLEMENTAL MATERIAL

The Pathogenesis and Long-Term Consequences of COVID-19 Cardiac Injury: State-of-the-Art Review

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Supplemental Table 1.

1.1. Reports on surviving patients with COVID-19-related myocarditis/myocardial injury

Publication	Patient	Presenting complaints	Examination/Investigation	Management	Complication(s)
Kim et al.(1)	21 years, female	Fever, productive cough, diarrhea, shortness of breath	Troponin I = 1.26 ng/mL (<0.3 ng/mL) NT-proBNP = 1929 pg/mL (<125 pg/mL) ECG: multiple PVCs, intraventricular conduction delay Echo: severely reduced LVEF Cardiac CT: hypertrophic myocardium due to edema with subendocardial perfusion defect on lateral LV CMR: diffused high SI in LV on T2, myocardial wall thickening and transmural LGE	N/A	N/A
Paul et al.(2)	35 years, male	Chest pain and fatigue, afebrile	Troponin I = 2885 ng/L ECG: repolarization changes in the precordial ECG leads Echo: normal LVEF without pericardial effusion CMR: subepicardial LGE in the inferior and lateral walls	Ramipril 5 mg Bisoprolol 5 mg	None 3 weeks later asymptomatic and troponin levels back to normal.
Zeng et al.(3)	63 years, male	Productive cough, fever, shortness of breath and chest tightness on exertion	Troponin I = 11.37 g/L NT-proBNP = 22,600 pg/mL IL-6 = 272.4 pg/mL (raised) ECG: sinus tachycardia, no ST segment elevation Echo: LVEF = 32%, diffuse myocardial dyskinesia and enlarged LV	Respiratory support Lopinavir-ritonavir Interferon alpha 1b Methylprednisolone IVIg Piperacillin-Tazobactam Continuous renal replacement therapy ECMO	LVEF improved to 68% LV wall thickness returned to normal Impaired right cardiac function Septic shock DIC Death on 33 rd day of admission
Irabien-Ortiz et al.(4)	59 years, female	Fever, angina chest pain	Hypoperfusion ECG: concave diffuse ST elevation and PR depression Troponin T = 220-1100 ng/dL (elevated) NT-proBNP = 4421 ng/L	CPR Emergent pericardiocentesis High dose vasopressors ECMO via femoral artery IVIg	Normal biventricular function regained in a few days Continued dyspnea

			Echo: moderate concentric hypertrophy, reduced intraventricular volumes, preserved LVEF, pericardial effusion	Prednisolone Lopinavir/ritonavir	
Doyen et al. (2020)(5)	69 years, male	Fever, cough, dyspnea, respiratory distress syndrome and severe hypoxia	Troponin I = 9002 ng/L (<40) ECG: new diffuse inverted T waves Echo: mild LVH with preserved LVEF and normal wall motion Coronary angiography: no occlusion CMR: subepicardial LGE of the apex and inferolateral wall	Mechanical ventilation hydrocortisone	Discharged from ICU after 3 weeks
Inciardi et al. (2020)(6)	53 years, female	Dry cough, severe fatigue, afebrile	ECG: diffuse ST elevation Elevated troponin T and elevated NT-proBNP Coronary angiography: no occlusion CMR: increased wall thickness with diffuse biventricular hypokinesis, especially in the apical segments, and severe left ventricular dysfunction (left ventricular ejection fraction of 35%). Short tau inversion recovery and T2-mapping sequences showed marked biventricular myocardial interstitial edema, and there was also diffuse LGE of the entire biventricular wall.	Dobutamine Lopinavir/Ritonavir Steroids chloroquine	N/A
Trogen et al. (2020) (7)	17 years, male	Fever, neck pain, abdominal pain, diarrhea and vomiting	BP 79/66 mmHg, HR 150 Troponin I 6.17 ng/mL BNP = 2124 pg/mL ECG: sinus tachycardia with inverted T waves in the inferior leads Echo: reduced LVEF, no pericardial effusion CMR: LVEF 40%, mid-wall LGE in inferior LV-RV junction corresponding to an area of increased SI in T2 and area of hypokinesia.	Enoxaparin (for prophylaxis against VTE risks in COVID-19 patients) Ibuprofen Acetaminophen Oxygen (nasal cannula 4L)	Normalization of BP on day 1 O ₂ desaturation on day 2 Discharged on day 5 Follow-up 1 week post discharge: LVEF 59% Residual myocardial dysfunction (low GLS, diminished signals of the mitral valve annulus), persistent T wave inversion in lead III.

Sardari et al.(8)	31 years, male	Dyspnea on exertion, low-grade fever	BP 110/80, HR 70, RR 18 Troponin T < 0.03 ng/mL Echo: mild LV dysfunction CMR: LVEF 50%, Subepicardial LGE in the mid inferior wall and edema/inflammation in the mid inferoseptal and inferior wall	Bisoprolol Lisinopril	Myocarditis presented 3 weeks after discharge (COVID-19)
Kesici et al.(9)	2 years, male	Nausea, vomiting, and poor oral intake	Low BP, hepatomegaly CXR: pleural effusion, cardiomegaly Echo: severely reduced EF EMB: dilated cardiomyopathy, secondary to viral myocarditis	Inotropes ECMO Extrapulmonary CPR	Fatal fulminant myocarditis (suspected)
Besler et al.(10)	20 years, male	Fever, chest pain	BP 146/63 HR 111 Troponin I = 7.621 ng/mL (<0.045 ng/mL) CK-MB = 21.92 mcg/L NT-proBNP = 1525 ng/L (<125 ng/L) CMR: subepicardial LGE of the posterolateral wall in the mid ventricle, also high SI in the same area in T2 short tau inversion recovery	Hydroxychloroquine, azithromycin, ceftriaxone, tigecycline, favipiravir, colchicine	Full recovery and discharged on day 7
Chiu et al.(11)	10 years, male	Fever, fatigue, diarrhea, cough, rash and conjunctivitis	BP 75/44 NT-proBNP = 9477 pg/mL Echo: severely reduced LVEF	Fluid resuscitation Dopamine	Patient still critically ill at referral to another institution
Oleszak et al.(12)	52 years, male	Cough, dyspnea, single episode of hemoptysis	BP 161/109 HR 118, RR 20 ECG: sinus tachycardia, LV hypertrophy, bi-atrial enlargement, QTc 449 Troponin T 0.017 ng/mL NT-proBNP = 1220 pg/mL Echo: LVEF 10-15% with global dilatation	Hydroxychloroquine Azithromycin Intravenous furosemide High flow O ₂ via nasal cannula (15 L/min)	LVEF improved to 20-25% NT-proBNP = 802 pg/mL Hemodynamically stable
Lara et al.(13)	12 years, female	Fatigue, fever, abdominal pain, vomiting	BP 60/30 HR 40 RR 24 ECG: complete heart block with atrial rate of 150 bpm	CRP (2 mins) – return of spontaneous circulation Epinephrine infusion Milrinone IVIG	Steadily improved Extubated day 4 Normal cardiac function on day 10 Discharge

			Troponin I >50 mg/mL BNP 2652 pg/mL Echo: LVEF 27%		
Coyle et al. (2020) (14)	57 years, male	Severe hypoxia	ECG: sinus tachycardia Raised troponin I Raised NT-proBNP Echo: LVEF 35-40%, moderate diffuse hypokinesia CMR: LGE of the midwall of the basal inferolateral segments, high SI of both atria and ventricles in T2	Hydroxychloroquine Azithromycin Ceftriaxone Endotracheal intubation Mechanical ventilation with neuromuscular blockade Methylprednisolone (for myocarditis) Colchicine Milrinone infusion and norepinephrine for cardiogenic shock 14-day course of aldose reductase inhibitor	Extubation on day 10 Discharged on day 19
Rehman et al. (2020)(15)	39 years, male	Chest pain worsened with exertion	ECG: ST elevation in lead I, aVL, ST depression in aVR, mild J point elevation and T waves inversion in leads II, III, and aVF Troponin: 6.24 ng/mL Coronary angiography: no occlusion Echo: no wall motion abnormality and LVEF 55-60%, no pericardial effusion NT-proBNP 379 pg/mL	Acetaminophen	Chest pain improved after cardiac catheterization Discharged with acetaminophen alone
Yokoo et al. (2020)(16)	81 years, male	Fever, dyspnea	ECG: sinus rhythm Troponin T 33 pg/mL (<5 pg/mL) Echo: LVEF 35% CMR: mid-wall LGE in the LV base septum wall, diffuse hypokinesia	Antibiotics Steroids Anticoagulation	Discharged 3 weeks after admission with 5 days of anticoagulants
Bernal-Torres et al. (2020) (17)	38 years, female	Palpitations, general malaise	BP 98/54 HR 137	O ₂ therapy Methylprednisolone IVIG	Discharged on day 16 with heart failure management

			ECG: diffuse and concave ST elevation with PR segment depression Troponin I 1190 ng/L (<14 ng/L) BNP 13000 pg/mL (<100 pg/mL) Echo: LVEF 30% mild pericardial effusion CMR: inferobasal LGE with increased SI in T2 transmural	Hydroxychloroquine Azithromycin Lopinavir/ritonavir Norepinephrine, dobutamine, levosimendan Furosemide	
Bonnet et al.(18)	27 years, male	Respiratory distress	Troponin I 100 ng/L NT-proBNP 9,300 pg/mL Echo: LVEF 20% Coronary CT angiography: no occlusion	Diuretics Noninvasive ventilation	Discharged on day 9 With treatment for heart failure management
Auer et al.(19)	42 years, female	Dyspnea	BP 109/62 HR 75 ECG: T wave inversion in leads III, aVF Troponin I 28.1 ng/L (<16 ng/L) NT-proBNP 636.8 pg/mL (<125 pg/mL) Autopsy: lymphocytic infiltrates of the myocardium with anti-CD3 antibodies present	O ₂ therapy	Fatal ventricular fibrillation
Volis et al.(20)	21 years, male	Fever	BP 130/70 HR 110 Hepatosplenomegaly Troponin I 965 ng/L (<34 ng/L) ECG: ST depression and T wave inversion in lead III, PR depression in leads II and III	Symptomatic relief only	Normalization of troponin, Echo showed no wall motion abnormalities and normal LVEF (65%)
Dahl et al.(21)	37 years, male	Fever, headache, unilateral painful neck swelling	BP 119/76 HR 119 RR 22 ECG: sinus tachycardia, flattened T waves Troponin T 1,959 ng/L (<15) NT-proBNP 11,169 ng/L (<85) Echo: reduced LVEF (to 40%) CMR: diffuse myocardial edema CT angiogram: no coronary occlusion	O ₂ therapy 3L/min Fluid resuscitation Low-dose norepinephrine Furosemide Continuous positive airway pressure	Discharged on day 11 1 week after discharge readmitted with Bell's palsy (thought to be due to Lyme's disease – later r/o with serology) Later improved but still lower exercise tolerance.

Hu et al.(22)	37 years, male	Chest pain, dyspnea, diarrhea	BP 80/50 CXR: cardiothoracic ratio 0.7 ECG: ST elevation in III, aVF Troponin T 10,000 ng/L BNP 21025 ng/L CT coronary angiogram: no occlusion Echo: LVEF 27%	Methylprednisolone IVIG Norepinephrine Diuretics (toracemide and furosemide) Milrinone	At 1 week: Echo: LVEF 66% CXR: Cardiothoracic ratio 0.49 Troponin T 220.5 ng/L BNP 1587 ng/L At 3 weeks, all cardiac enzyme/biomarkers were in the normal range
Sala et al. (2020) (23)	43 years, female	Chest pain, dyspnea	BP 120/80 HR 79 ECG: ST segment elevation in V1-V2 and aVR, reciprocal ST depression in V4-V6 with diffused U waves. Troponin T: 135 ng/L NT-proBNP 512 pg/mL Echo: LVEF 43%, inferolateral wall hypokinesis CT coronary angiogram: no occlusion CMR (day 7): LVEF 64% Mild hypokinesia at basal and mid left ventricular segments, no LGE EMB: diffused T lymphocytic infiltrates > 7/mm ² , large interstitial edema, limited foci of necrosis	Lopinavir/ritonavir Hydroxychloroquine	Patient discharged with no symptoms on day 13
Papageorgiou et al. (2020)(24)	43 years, male	Fever and cough	BP 85/70 HR 130 ECG: sinus tachycardia, diffuse ST elevation Tropinin T: 590 ng/L NT-proBNP: 6100 ng/L Echo: LVEF 15% EMB: no lymphocytic infiltrates	Aspirin, ticagrelor, fondaparinux Levosimendan Norepinephrine Milrinone MCS (impella) ECMO	Day 7: LVEF normalized
Spano et al. (2020)(25)	49 years, male	Dyspnea, NYHA 3, general weakness, intermittent epigastric pain and nocturia	Elevated troponin and NT-proBNP ECG: dynamic T wave changes Echo: Diffuse hypokinesia with severely depressed left and right ventricular function	-	-

			CT coronary angiogram: no occlusion CMR: diffuse thickening of the myocardium and pericardium due to edema. Diffuse LGE. Impaired global myocardial strain.		
Ashok et al. (2020)(26)	53 years, male	Fever and abdominal pain	HR 30-40 ECG: atrioventricular block (Mobitz type II), then complete AV heart block Echo: mild LV impairment	Isoprenaline Dual chamber pacemaker (DDD-R) implantation IV antibiotics	Discharged on day 10 Follow-up at 6 weeks: pacemaker checks satisfactory, pacing-dependent with > 95% ventricular pacing Heart block as a potential side effect from COVID-19 myocarditis (?)
Gnecchi et al.(27)	16 years, male	Chest pain radiating to left arm, fever	ECG: inferolateral ST elevation Echo: hypokinesia of the inferior and inferolateral segments of the LV, LVEF 52% Troponin I 16,862 ng/L CMR: subepicardial increased SI in T2 Short-T1 Inversion Recovery as well as LGE in the same area	Ibuprofen Hydroxychloroquine Antivirals	Asymptomatic and well by day 12
Richard et al. (28)	28 years, female	Lethargy, hematemesis	BP 70/38 HR 144 ECG: sinus tachycardia, nonspecific ST changes in the lateral leads with possible septal infarct Echo: LVEF 26-30% CT coronary angiogram: no occlusion CMR: myocardial necrosis, fibrosis and hyperemia	Intubation IV dobutamine and heparin LVAD (Impella) – in lieu of norepinephrine Methylprednisolone	On day 3: LVEF > 55% Impella removed and dobutamine weaned off
Craver et al.(29)	17 years, male	Severe headache, dizziness, nausea and vomiting, collapse	Autopsy findings: Diffuse inflammatory infiltrates composed of <i>lymphocytes</i> , macrophages with prominent eosinophils. Primarily in the interstitium of both the right and left ventricles.	Patient failed to respond to ALS	Fatal
Khalid et al.(30)	76 years, female	Fever, cough, dyspnea	BP 110/53 HR 124	Intubation Norepinephrine	Recovery of LVEF to 50%

			Troponin: 503 ng/L (<14) NT-proBNP: 35,000 pg/mL (<450 pg/mL) ECG: normal sinus rhythm Echo: LVEF 25-30%	Tocilizumab IVIg	
Khatri et al.(31)	50 years, male	Fevers, non-productive cough, dyspnea, near-syncope	ECG: ST segment changes Hs-troponin: 544 ng/L Coronary angiogram: no occlusion Echo: severe LV dysfunction, pericardial effusion	IV dobutamine, vasopressin and norepinephrine Enteral hydroxychloroquine Remdesivir IVIg IV methylprednisolone	Patient passed away on day 4 due to multi-organ failure
Dalen et al. (2020) (32)	55 years, female	Fatigue, near syncope, chest discomfort	BP 102/72 HR 100 ECG: sinus tachycardia, insignificant ST elevation in inferior leads and T wave inversion in the precordial leads. Troponin T: 108 ng/L NT-proBNP: 1025 ng/L Echo: reduced LVEF, pericardial effusion CMR: epicardial LGE in the anterolateral wall.	Norepinephrine Pericardiocentesis for cardiac tamponade	Discharged on day 17 Day 39: showed full recovery
Faridan et al. (2021)(33)	78 years, female	Weakness, fever	BP 92/52 HR 110 ECG: occasional premature ventricular contractions with no features of ischemia Troponin I raised	Remdesivir Dexamethasone	N/A
Hussain et al. (2020) (34)	51 years, male	Dry cough, fatigue, dyspnea	BP 141/89 HR 97 ECG: diffuse ST elevation Echo: marked decrease in ventricular systolic function and LVEF 20% Coronary angiogram: non-obstructive Troponin 0.29 ng/mL NT-proBNP 1,287 pg/mL	Indomethacin CPAP IV methylprednisolone Colchicine Dobutamine Fluid resuscitation Antivirals	LVEF after treatment 23% Conditions deteriorating at the time of report.

Sheikh et al. (2021)(35)	28 years, male	Cough, worsening dyspnea and chest pain	BP 107/72 HR 103 ECG: accelerated junctional rhythm with retrograde conduction Echo: LVEF 30%	Metoprolol, Lisinopril Low-dose aspirin	Discharged on day 16 (complicated with new onset cranial/central diabetes insipidus)
Beaudry et al. (2021)(36)	15 years, female	Epigastric pain, loss of appetite, nasal congestion, rhinorrhea	BP 81/52 ECG: sinus tachycardia Echo: severely diminished LVEF Pro-BNP 8328 pg/mL Troponin 2.48 ng/mL Autopsy: diffuse lymphoplasmacytic inflammatory infiltrate, inflammation of the venules, lymphatics and small arterioles.	IVIg BiPAP and then intubation Norepinephrine Vasopressin Bolus epinephrine	Patient sustained 3 PEA, the last of which she did not achieve return of spontaneous circulation
Garot et al.(37)	18 years, male	Cough, fever, fatigue and myalgia.	ECG: sinus tachycardia, inverted T waves in V2-V4 Echo: LVEF 30%, increased LV wall thickness, diffuse hypokinesia NT-proBNP: 11,719 pg/mL Troponin: 11,716 IU/mL CMR: Short T1 inversion recovery (STIR) showed marked extensive hypersignal of the LV basal posterolateral wall (edema), subepicardial nodular LGE of the LV basal posterolateral wall. Lake-Louise positive	Acetaminophen Hydroxychloroquine Nasal oxygen Norepinephrine	CMR on day 14 showed: LVEF 54% clear decrease of focal myocardial edema, stable LGE lesions in the subepicardium of the posterolateral wall. Patient had complete clinical recovery with normal respiratory function and hemodynamics Discharged on day 15.
Milla-Godoy et al. (38)	45 years, female	Diarrhea, nausea, vomiting	BP 113/85 HR 116 ECG: sinus tachycardia, diffuse ST elevation in I, II, aVL, V3-V6 Troponin T: 0.43 ng/mL (<0.02) NT-proBNP: 4,585 pg/mL (<450) Echo: LVEF 10% with global hypokinesia	Intubation Norepinephrine Phenylephrine, dopamine IVIg Methylprednisolone	Patient became asystolic and passed away after 15 mins of resuscitation (including 4 doses of IV epinephrine and 1 IV bicarbonate)
Lozano-Gomez et al.(39)	53 years, male	Fever, dyspnea	BP 94/59 HR 133 ECG: sinus tachycardia, diffuse ST segment elevation	Dobutamine Intubation Norepinephrine	Patient developed new-onset AF, LVEF declined to <10% and raised cardiac

			Echo: LVEF 35%, slightly dilated LV	Amiodarone and electrical cardioversion	enzymes. Patient was anuric despite aggressive furosemide.
Naneishivili et al.(40)	44 years, female	Fever, lethargy, myalgia, syncope	BP 85/40 ECG: no features of ischemia Echo: LVEF 37%, pericardial effusion Troponin I 639 ng/L	Methylprednisolone Milrinone norepinephrine	Normalization of LVEF by day 3. Patient discharged on day 41.
Cuomo et al. (2020)(41)	49 years, female	Fever, chest pain, cough	ECG: right bundle branch block Troponin: 820 ng/L BNP: 950 pg/mL Echo: LVEF 45% CMR: widespread increase in T2 SI and moderate pericardial effusion at the posterior lateral wall of the LV.	Sotalol Acetylsalicylic acid	LVEF improved to 55% on day 7, patient discharged on day 12
Chitturi et al.(42)	65 years, female	Fever, dry cough, exertional dyspnea	Troponin 1.682 ng/mL (<0.04) BNP 401 pg/mL (<100) ECG: new onset T wave inversion in leads V1 and V2 Echo: LVEF 25%, RV systolic function with paradoxical septal motion	Remdesivir Rapid sequence intubation Tocilizumab Norepinephrine Vasopressin Dobutamine Sodium bicarbonate	LVEF eventually improved to 64% within 24 hrs of treatment Patient then discharged from ICU to a long-term acute care facility for a ventilator wean
Tseng et al.(43)	5 years, male	Fatigue, vomiting	Troponin I 1658 ng/L (<7) BNP 2298 pg/mL (<101) Echo: severely reduced LVEF	IVIg Amiodarone Electrical cardioversion ECMO	Decannulate from ECMO on day 5 Extubated on day 6 and discharged.
Ciuca et al.(44)	6 years, male	Persistent fever	Echo: LVEF 48%, mild pericardial effusion	Non-invasive ventilator support Inotropic therapy Dexamethasone, hydroxychloroquine Low-molecular weight heparin	Normalization of the LVEF within 72 hrs of ventilatory and inotropic support.

Gay et al.(45)	56 years, male	Dyspnea and lethargy	Troponin I 1.3 ng/mL ECG: rapid AF and low voltage Echo: concentric left ventricular hypertrophy and LVEF 20%, small pericardial effusion.	ECMO Methylprednisolone Tocilizumab	Patient's LVEF improved to 65% on day 7 Recovering in the general medical ward
Ozturan et al. (46)	25 years, male	Chest pain, dyspnea, fever, fatigue	HR 140 BP 130/90 eCG: sinus tachycardia with ST elevation and PR depression in leads I, aVL, V5 and V6. ST depression and PR elevation in aVR. Troponin: 21.471 ng/mL (normal 0-60 ng/mL) Echo: diffuse left ventricular hypokinesia with LVEF 35% Blood and sputum cultures were negative	Ampicillin-sulbactam Clarithromycin Oseltamivir acetylsalicylic acid metoprolol	Echo on day 8 showed LVEF = 55%
Caraffa et al. (47)	40 years, female	Atypical chest pain, fever	Normal ECG Normal troponin Severe LV dysfunction	ECMO Apical venting surgery Methylprednisolone Azathioprine	LVEF 48% on day 13 post-operative
Gauchotte et al. (48)	69 years, male	Fever, abdominal pain, fatigue	Echo: LVEF 30% Troponin: 8066 pg/mL Creatinine kinase – MB: 2103 UI/L PCI: no significant lesion/obstruction	ECMO	Refractory shock and multi-organ failure Deceased 6 days after admission
Cairns et al. (49)	58 years, female	Fever, diarrhea, vomiting	BP 85/45 HR 91 Pericardial effusion	Pericardiocentesis Vasopressor support IV Tazocin	Discharged on day 12
Gioia et al. (50)	57 years, Female	Trouble breathing	BP 98/58 ECG: diffused ST segment elevation Troponin: 64.0 ng/mL PCI: non-occlusive Echo: normal LVEF	Pericardiocentesis Transcutaneous pacing Vasopressor	Patient passed away
Ford et al. (51)	53 years, Male	Malaise, fever, cough	HR 140 BP 97/55 ECG: wide-complex, irregular tachycardia, left bundle branch block Troponin: high	Metoprolol Losartan Spironolactone	Patient have left middle cerebral artery stroke 3 days after discharged stable

			BNP: 588 pg/mL Echo: LVEF 15% CMR: global hypokinesia, increased T2 signal, hyperemia, edema		
Tiary et al. (52)	30 years, Male	Fatigue, shortness of breath, abdominal flank pain, tiredness, light-headedness	BNP 557 pg/mL Troponin: 7.52 ng/mL ECG: sinus rhythm	Pericardiocentesis Remdesivir Convalescent plasma Dexamethasone Empirical antibiotics	Discharged on day 27
Meel et al. (53)	31 years, male	Shortness of breath Chest discomfort	BP: 122/76 HR 76 ECG: normal Troponin: 319 ng/L NT-proBNP: 143 ng/L Echo: normal LVEF CMR: midwall and epicardial LGE	Colchicine prednisolone	Discharged at.1 week
Trpkov et al. (54)	62 years, female	Altered consciousness, hypoxemia, shock	BP 55/32 HR 120 ECG: sinus tachycardia with diffuse anterolateral ST-elevation Troponin: 4986 ng/L NT-proBNP: 51,439 ng/L CMR: sub-epicardial LGE Echo: LVEF 24%	Anakinra IV	Patient recovered and finally discharged
Fischer et al. (55)	15 years, Male	Chest pain, mild fever	BP 100/60 HR 75 ECG: diffused ST elevation without reciprocal changes Troponin: 6.1 mcg/L NT-proBNP 65 ng/L ECG: LVEF 50%	Beta blockers Angiotensin-converting enzyme inhibitors	Discharged from the hospital day 9 with LVEF 55%
Kohli et al. (56)	15 years, Female	Headache, vomiting, fatigue, fever	BP: 70/40 HR: 150 Echo: LVEF 20%	Milrinone Epinephrine IVIG	Patient recovered

			Troponin: high NT-proBNP: high	IV methylprednisolone Anakinra amiodarone	
Sassone et al. (57)	38 years, Male	Sudden-onset oppressive chest pain	ECG: mild ST segment elevation in the inferior leads PCI: no obstruction Echo: preserved LVEF with inferolateral wall hypokinesis Troponin: 4038 ng/L CMR: subepicardial LGE	N/A	Discharged on day 20
Bemtgen et al. (58)	18 years, Male	Hyperpyrexia, chills, tachycardia	ECG: sinus tachycardia Echo: LVEF 25% Troponin: 341 ng/L (<14 ng/L) EMB: significant infiltration of immune cells especially CD68+ macrophages and CD3+ t cells around small vessels (lymphohistiocytic myocarditis)	Dexamethasone, IVIg Anakinra V-A ECMO Impella	LVEF full recovery Discharged 32 days after admission.
Tseng et al. (59)	5 years, Male	Fatigue, vomiting	ECG: monomorphic ventricular tachycardia Troponin: 1658 ng/L (normal range 3-7 ng/L) BNP: 2298 pg/mL (<101 pg/mL) Echo: bilaterally reduced LVEF	Synchronized cardioversion Lidocaine VA-ECMO IVIg Methylprednisolone Remdesivir Milrinone Enalapril	Full recovery
Belli et al. (60)	53 years, Male	Typical symptoms of COVID-19	ECG: normal sinus rhythm Troponin: 236 ng/L NT-proBNP: 18,732 ng/L Echo: LVEF 30%, apical ballooning and extensive akinesia Angiography: 30% stenosis of the left anterior descending	N/A	Takotsubo cardiomyopathy diagnosed.
Nedeljkovic et al.(61)	32 years, Male	Asymptomatic COVID- 19 at first then	ECG: premature ventricular complexes	Ibuprofen, bisoprolol, coenzyme Q-10	3 months follow-up showed preserved left and

		Dyspnoea and dizziness during exercise after self-isolation	CMR: late gadolinium enhancement in the mid-lateral left ventricular wall, pericarditis present		right ventricular function (61% & 65% respectively). However, there was persistent LGE in the LV lateral wall.
Singh et al.(62)	25 years, Male	Substernal chest pain with radiation to both arms.	ECG: 1mm ST elevation in II, III and aVF without reciprocal changes. Troponin: 14,122 ng/L Echo: normal Coronary angiography: normal CMR: subepicardial enhancement of the basal to mid inferolateral wall and the apical lateral wall. T2 signal in the lateral wall, indicating edema, mild hypokinesia.	Lifestyle advice	6-week follow-up showed resolution of the T2 signal and decreased LGE
Ishikura et al. (63)	35 years, Male	Fever and general weakness	ECG: sinus tachycardia Troponin: 31,516 pg/mL (<30 pg/mL) NT-proBNP: 3905 pg/mL (<18.4 pg/mL) Echo: LVEF 7.4% Coronary angiography: normal EMB: diffuse lymphocytic infiltrate, SARS-CoV-2 positive in the myocardium via RT-PCR	IABP Veno-arterial ECMO IVIG Steroids Continuous renal replacement therapy Antiviral agents	2 weeks after admission patient recovered and was weaned of ECMO & IABP
Gaudriot et al. (64)	38 years, Male	Chest pain, vomiting	ECG: sinus tachycardia with incomplete right bundle branch block Troponin: 1600 pg/mL (<14 pg/mL) NT-proBNP: 10,500 pg/mL (<300 pg/mL) Echo: biventricular infiltrative myocardial hypertrophy, associated with a circumferential non-compressive pericardial effusion and restrictive mitral valve inflow profile, worsening oedema and increasing wall thickness CMR: T2 signal with increased myocardial thickening, subepicardial LGE	Veno-arterial ECMO IABP Heart transplantation	Explanted heart shows pericarditis and myocarditis with large myocardial necrosis, suppurated lesions, lymphocytic infiltration (no SARS-CoV-2 RNA detected)
Meyer et al. (65)	81 years, Male	Worsening dyspnea, fever	ECG: normal sinus rhythm, ST-T changes secondary to left ventricular hypertrophy.	Amoxicillin-clavulanic acid Ceftriaxone	6-month follow-up showed reduced LVEF 39% on echo

			Troponin: 11.9 ng/L BNP: 46 ng/L (<100 ng/L) Echo: LVEF 59% (1 month post admission for COVID-19)	Prednisolone For myocarditis → bisoprolol, ramipril.	due to mild hypokinesia and severe inferior wall hypokinesia CMR showed infero-basal LV wall edema, subepicardial and mid-wall LGE in the basal inferior, basal inferolateral and anterior LV walls. ECG showed inverted T waves on lateral leads
Mentor et al. (66)	47 years, Female	Flu-like symptoms, unconsciousness and apnea	ECG: ST depression across all leads (except aVR) Coronary angiogram: Normal Echo: reduced LVEF 30% Troponin: 272 ng/L BNP > 70,000 ng/L	Adrenaline/noradrenaline Prophylactic antibiotics 2 x CPR	RIP 48 hours after admission Autopsy of the heart: mild diffuse necrotizing myocarditis with positive SARS-CoV-2 in the heart tissue by RT-PCR
Gaine et al.(67)	58 years, Male	Palpitations, progressive dyspnea	ECG: atrial fibrillation, no ST-T abnormalities Troponin: 25 ng/L (<14 ng/L) NT-proBNP: 3428 pg/mL (<400 pg/mL) Echo: LVEF 20%, mitral regurgitation Coronary angiography: no obstructive disease CMR: biventricular dysfunction, edema and reduced myocardial T1 signal.	Intravenous diuretics Rate-control antiarrhythmics ACE inhibitor Mineralocorticoid antagonist	Patient remained afebrile throughout admission and discharged
Ghafoor et al. (68)	54 years, Female	Dyspnea, nausea, and vomiting	ECG: 1 mm ST elevation in leads II, III and aVF Right and left heart catheterization: normal epicardial coronary arteries but reduced ventricular ejection fraction (10%) Echo: global hypokinesia and reduced ejection fraction	CPR Inotropic agents Vasopressor Veno-arterial ECMO	Patient family went for palliative care
Ziaie et al. (69)	39 years, Female	Chest pain, orthopnea, cough	<i>Initial admission due to COVID-19 pneumonia found:</i> NT-proBNP: 23,000 ng/L	Heparin Beta blocker	Eosinophilic syndrome with myocarditis post-COVID-19

			<p>Echo: LVEF 48% with apical LV clot</p> <p><i>1 month after discharged</i></p> <p>LVEF = 35% with right ventricular enlargement and dysfunction and restrictive diastolic pattern and mild pericardial effusion.</p> <p>CMR showed myocardial edema and hyperemia. Hypereosinophilic syndrome was confirmed.</p>	<p>Angiotensin converting enzyme inhibitor</p> <p>Spironolactone</p> <p>Warfarin</p>	
Martinez et al.(70)	64 years, Male	Severe chest pain 3 weeks after the first positive test for SARS-CoV-2	<p>ECG: sinus tachycardia, no ST-T changes</p> <p>Troponin: 548.3 pg/mL (<34.2 pg/mL)</p> <p>Echo: LVEF 56% no wall motion abnormalities</p>	<p>Beta blockers</p> <p>Prednisolone</p>	Query multisystem inflammatory syndrome since also found reactive hepatitis and subacute thyroiditis after SARS-CoV-2. Discharged on Day 3, now recovered and asymptomatic.
Boylan et al.(71)	61 years, Male	Cardiac injury detected during routine monitoring 5 weeks after tested positive for SARS-CoV-2	<p>ECG: sinus rhythm</p> <p>Troponin: 6142 ng/L</p> <p>NT-proBNP: 2180 pg/mL</p> <p>Echo: normal LVEF</p> <p>Coronary angiography: normal</p>	<p>Methylprednisolone</p> <p>Intubation for hypoxemia</p>	<p>3 months post ICU discharge</p> <p>CMR: LGE found in mid-wall and subepicardial aspect of the basal segments of the septum.</p>
Roest et al. (72)	50 years, Male	Acute symptoms of cardiac decompensation	<p>NT-proBNP 212 pm/L</p> <p>Troponin: 55 ng/L</p> <p>Echo: biventricular failure and congestion</p> <p>EMB: subendocardial fibrosis</p> <p>CMR: extensive subepicardial and midwall LGE</p>	Implantable cardioverter-defibrillator	Partial recovery of LVEF to 46% 2 months after discharge
Das (73)	16 years, Female	Dyspnea and fatigue	<p>ECG: sinus tachycardia with chamber hypertrophies</p> <p>Troponin <0.01 ng/mL (<0.03 ng/mL)</p> <p>BNP 53 pg/mL (<100 pg/mL)</p> <p>Echo: normal function</p> <p>CMR: patchy myocardial edema without any fibrosis or scarring.</p>	<p>Symptomatic therapy</p> <p>Lifestyle advice</p>	Discharged home after 1 day hospitalization during which her Holter did not record any arrhythmias.

Ghugre et al. (74)	62 years, Male	Mild reduction in exercise tolerance 2 weeks after tested positive for SARS-CoV-2 infection	ECG: normal sinus rhythm, no ST-T changes Troponin: 12 ng/L (<15 ng/L) CMR: normal biventricular function, midwall and subepicardial LGE in the basal inferolateral wall.	N/A	Patient continued to have cardiac symptoms at the time of reporting
Perez-Acosta et al. (75)	61 years, Male	Progressive dyspnea	ECG: sinus rhythm with generalized concave ST elevation. Troponin: reported high Echo: mild to moderate pericardial effusion with adequate LVEF	Mechanical ventilation analgesia	N/A
Taouihar et al.(76)	51 years	Epigastric pain	ECG: sinus tachycardia, ST elevation in V1, V2 with pathological Q waves, poor R wave progression and T wave inversion in II, III and aVF. Echo: akinesia of the tip of the anteroseptal and inferior wall of LV and severe hypokinesia of the inferior wall, LVEF = 40% Troponin 20.000 ng/L (1000x normal) Coronary angiography: non-occlusive coronary arteries CMR: focal hypertrophy of the anteroseptal and inferior segment of the LV and anteroinferior RV. T2 signal in the aforesaid areas.	Clopidogrel Aspirin ACE inhibitor Bisoprolol Dexamethasone Enoxaparin Vitamin C, zinc, azithromycin	Troponin declined after treatment and patient discharged on day 7
Berg et al. (77)	66 years, Male	Dyspnea and fatigue, patient received orthotropic heart transplant in 2013	ECG: diffused T wave inversions Echo: LVEF 37% EMB: subendothelial fibrosis and Quilty lesion but no evievidence of acute cellular rejection or antibody mediated rejection.	Methylprednisolone	Day 3 echo showed LVEF of 66% and grossly normal right ventricular function.

AF = Atrial Fibrillation, ALS = Advanced Life Support, BiPAP = Bi-level Positive Airway Pressure, BP = Blood Pressure, CMR = Cardiovascular Magnetic Resonance, CPAP = Continuous Positive Airway Pressure, CPR = Cardiopulmonary Resuscitation, CT = Computerized Tomography, DIC = Disseminated Intravascular Coagulation, ECG = Electrocardiogram, Echo = Echocardiogram, ECMO = Extracorporeal Membrane Oxygenation, EMB = Endomyocardial Biopsy, GLS = Global Longitudinal Strain, HR = Heart Rate, IVIG = Intravenous Immunoglobulin , LGE = Late Gadolinium Enhancement, LV = Left Ventricular, LVAD = Left Ventricular Assist Device, LVEF = Left Ventricular Ejection Fraction, LVH = Left Ventricular Hypertrophy, NT-proBNP = N-terminal pro-B-type Natriuretic Peptide, RR = Respiratory Rate, RT-PCR = Real Time-Polymerase Chain Reaction

1.2. Reports on case series of patients with COVID-19-related myocarditis/myocardial injury

Publication	Patients	Cardiac MRI	EMB	Autopsy	Complications
Kogan et al. (58)	5 patients, 2 females	N/A	N/A	Anti-CD3 antibody positive Increased TLR-4 expression Lymphocytic myocarditis satisfying the Dallas criteria	None was suspected to have myocarditis at the time of death Microvascular thrombosis was found in all cases.
Ng et al.(59)	16 patients, 7 females. Median age 68 years. 15 patients had mild or moderate COVID-19 (WHO severity classification)	3 patients had non-ischemic LGE with elevated global T2 mapping values fulfilling Lake-Louise criteria (CMR performed at a median length of 56 days post-recovery)	N/A	N/A	A proportion of patients who recovered from COVID-19 showed subclinical ongoing or healed myocarditis.
Bajaj et al. (60)	9 patients (7 males, 2 females) Median age 36	All had CMR at a mean of 11 days following admission LGE seen in 6/9, increased T1 signal in 7/7, increased T2 signal in 6/9	N/A	N/A	Multisystem inflammatory syndrome in adults (MIS-A) causing cardiogenic shock
Maurus et al. (81)	18 patients	6/18 had myocarditis satisfying the Lake-Louise criteria	N/A	N/A	N/A 18 patients were selected based on SARS-CoV-2 +ve and raised troponin.
Daniels et al. (82)	1597 athletes	37/1597 were diagnosed with myocarditis based on MRI	N/A	N/A	Follow-up in 27 of myocarditis patients revealed total resolution of T2 in all and late gadolinium enhancement in 11.
Starekova et al. (83)	145 patients (108 male, 37 female) recovering from COVID-19	2/145 diagnosed with myocarditis based on CMR Both patients had nonischemic LGE and T2 weighted signal abnormalities	N/A	N/A	Prevalence of myocarditis is low (1.4%) among student athletes recovering from COVID-19

Dal Ferro et al. (84)	40 deceased patients with severe SARS-CoV-2	N/A	N/A	1/40 patient was found to have histological evidence of myocarditis but no SARS-CoV-2 RNA found via RT-PCR	Myocardial damage found and correlate with the severity of COVID-19 and pre-existing comorbidities.
Garg et al. (85)	2 COVID-19 patients with large LV thrombi and multisystem thrombotic events	N/A	N/A	N/A	Both patients had large mural thrombi and multisystem thrombotic events, the authors attributed this to cytokine storm secondary to COVID-19
Galea et al. (86)	27 COVID-19 patients with suspected cardiac involvement enrolled to study correlations between CMR findings and cardiac biomarkers.	20 patients with abnormal CMR <ul style="list-style-type: none"> - 11 with increased T1 signals - 14 with myocardial T2 - 12 with LGE - 9 patients met the CMR criteria for myocarditis - 11 patients had MI - 2 had pericarditis 	N/A	N/A	Abnormal T2 was the most commonly observed CMR finding in COVID-19 patients with cardiac complications. This shows edematous changes in the active phase of the disease.
Malek et al.(87)	26 consecutive athletes (21 females, 5 males) with mild or asymptomatic COVID-19. CMR was performed a median of 32 days after diagnosis.	CMR abnormalities were found in 5 (19%) including 4 who had signs of myocardial edema and 1 with non-ischemic LGE with pericardial effusion.	N/A	N/A	Acute myocarditis was not observed among participants but a minority (19%) showed some CMR abnormal findings.

Kotecha et al. (88)	148 recovered COVID-19 patients who had raised troponin levels during their initial illness.	CMR performed on a median of 68 days after COVID-19 diagnosis. LGE was found in 80/148 among these 39 had myocarditis-like scars, 32 had ischemic scars and 9 had dual pathology.	N/A	N/A	Myocarditis-like injury can be observed in recovered COVID-19 patients with raised cardiac enzymes. These patients often had minimal functional consequences of myocarditis despite a proportion showing signs of ongoing inflammation.
Joy et al. (89)	74 recovered COVID-19 patients vs 75 matched seronegative subjects.	CMR: LGE and T1, T2 abnormalities were found in 13, 6 and 9 individuals respectively, equally distributed between case and control cohorts.	N/A	N/A	Cardiovascular abnormalities are no more common in seropositive versus seronegative subjects who are otherwise healthy.
Peterson et al. (90)	67 patients who were admitted due to myocarditis pre and during the pandemic.	N/A	N/A	N/A	45% of the patients admitted with myocarditis during the pandemic tested positive for SARS-CoV-2. Pre-pandemic incidence of myocarditis is 1.5/month while the pandemic incidence of myocarditis is 3.7/month.

Abbreviations

AF = Atrial Fibrillation, ALS = Advanced Life Support, BiPAP = Bi-level Positive Airway Pressure, BP = Blood Pressure, CMR = Cardiovascular Magnetic Resonance, CPAP = Continuous Positive Airway Pressure, CPR = Cardiopulmonary Resuscitation, CT = Computerized Tomography, DIC = Disseminated Intravascular Coagulation, ECG = Electrocardiogram, Echo = Echocardiogram, ECMO = Extracorporeal Membrane Oxygenation, EMB = Endomyocardial Biopsy, GLS = Global Longitudinal Strain, HR = Heart Rate, IVIG = Intravenous Immunoglobulin, LGE = Late Gadolinium Enhancement, LV = Left Ventricular, LVAD = Left Ventricular Assist Device, LVEF = Left Ventricular Ejection Fraction, LVH = Left Ventricular Hypertrophy, NT-proBNP = N-terminal pro-B-type Natriuretic Peptide, RR = Respiratory Rate, RT-PCR = Real Time-Polymerase Chain Reaction

Supplementary table 2

Empirical treatments for SARS-CoV-2-related myocarditis

Treatments		
Inotropes and vasodilators	Indication(s)	References
Dobutamine, norepinephrine, epinephrine, isoprenaline, milrinone, levosimendan, vasopressin	<ul style="list-style-type: none"> - Hypotension - Reduced LVEF - Cardiogenic shock <p>NB: Almost all patients have deranged cardiobiomarkers (troponin, BNP, NT-proBNP) and/or abnormal ECG changes</p>	(9, 13, 14, 21, 22, 24, 26, 28, 30–32, 34, 36, 38–40, 42, 49, 50, 56, 91, 92)
Mechanical circulatory support		
Percutaneous heart pump (Impella®)	<ul style="list-style-type: none"> - Cardiogenic shock <p>NB: Impella reported successful as a sole mechanical circulatory support when poorest LVEF > 26-30%</p>	(24, 28)
Extracorporeal membrane oxygenation (ECMO)	<ul style="list-style-type: none"> - Cardiogenic shock with severely reduced LVEF 	(4, 9, 24, 43, 45, 47, 48, 93)
Non-steroidal anti-inflammatory agents		
Ibuprofen	<ul style="list-style-type: none"> - Symptomatic relief of chest pain and other associated pain 	(7, 27)

Indomethacin	- Acute myopericarditis	(34)
Colchicine	- Acute myopericarditis - Recurrent myopericarditis	(10, 14, 34, 53)
Immunomodulatory drugs		
Corticosteroids (e.g. dexamethasone, methylprednisolone, prednisolone, hydrocortisone)	- patients with hypoxia requiring supplemental oxygen/unable to tolerate supplemental oxygen - Initial treatment for acute myopericarditis - Clinical symptoms of systemic inflammation/cytokine storm	(4, 5, 14, 22, 28, 31, 33, 34, 38, 40, 44, 45, 52, 53, 56, 91–93)
Intravenous immunoglobulin (IVIG)	- Severe myocarditis with symptoms in keeping with systemic inflammation/cytokine storm - In some cases, IVIG is used when corticosteroid therapy is contraindicated i.e. severe immunosuppression.	(4, 13, 22, 30, 31, 36, 38, 43, 56, 92, 93)
Tocilizumab	- Severe hypoxia requiring ventilatory support - Possible role in the management of myocarditis	(30, 42, 45)
Anakinra	- Fulminant myocarditis - Recurrent/persistent ventricular dysfunction in the context of myocarditis	(54, 56)
Diuretics		
Furosemide, spironolactone	- Oedema, fluid overload	(12, 21, 39, 51, 92)

Other treatments		
Pericardiocentesis	- Cardiac tamponade secondary to myopericarditis	(4, 32, 49, 50, 52)
Antivirals (remdesivir, ritonavir/lopinavir)	- As per local protocol for COVID-19 management	(4, 23, 30, 41, 51, 91–93)
Hydroxychloroquine Chloroquine	- Early empirical treatment for COVID-19	(10, 12, 14, 23, 27, 31, 37, 44, 91, 92)

Abbreviations

ECG = Electrocardiogram, ECMO = Extracorporeal Membrane Oxygenation, IVIG = Intravenous Immunoglobulin, LV = Left Ventricular, LVEF = Left Ventricular Ejection Fraction, NT-proBNP = N-terminal pro-B-type Natriuretic Peptide,

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