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COVID-19 Infection and Myocarditis: A State-of-the-Art Systematic Review

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Abstract

Background: COVID-19 was initially considered to be a respiratory illness, but current findings suggest that SARS-CoV-2 is increasingly expressed in cardiac myocytes as well. COVID-19 may lead to cardiovascular injuries, resulting in myocarditis, with inflammation of the heart muscle. **Objective:** This systematic review collates current evidence about demographics, symptomatology, diagnostic, and clinical outcomes of COVID-19 infected patients with myocarditis. **Methods:** In accordance with PRISMA 2020 guidelines, a systematic search was conducted using PubMed, Cochrane Central, Web of Science and Google Scholar until August, 2021. A combination of the following keywords was used: SARS-CoV-2, COVID-19, myocarditis. Cohorts and case reports that comprised of patients with confirmed myocarditis due to COVID-19 infection, aged >18 years were included. The findings were tabulated and subsequently synthesized. **Results:** In total, 54 case reports and 5 cohorts were identified comprising 215 patients. Hypertension (51.7%), diabetes mellitus type 2 (46.4%), cardiac comorbidities (14.6%) were the 3 most reported comorbidities. Majority of the patients presented with cough (61.9%), fever (60.4%), shortness of breath (53.2%), and chest pain (43.9%). Inflammatory markers were raised in 97.8% patients, whereas cardiac markers were elevated in 94.8% of the included patients. On noting radiographic findings, cardiomegaly (32.5%) was the most common finding. Electrocardiography testing obtained ST segment elevation among 44.8% patients and T wave inversion in 7.3% of the sample. Cardiovascular magnetic resonance imaging yielded 83.3% patients with myocardial edema, with late gadolinium enhancement in 63.9% patients. In hospital management consisted of azithromycin (25.5%), methylprednisolone/steroids (8.5%), and other standard care treatments for COVID-19. The most common in-hospital complication included acute respiratory distress syndrome (66.4%) and cardiogenic shock (14%). On last follow up, 64.7% of the patients survived, whereas 31.8% patients did not survive, and 3.5% were in the critical care unit. **Conclusion:** It is essential to demarcate COVID-19 infection and myocarditis presentations due to the heightened risk of death among patients contracting both myocardial inflammation and ARDS. With a multitude of diagnostic and treatment options available for COVID-19 and myocarditis, patients that are under high risk of suspicion for COVID-19 induced myocarditis must be appropriately diagnosed and treated to curb co-infections.

Keywords

myocarditis, COVID–19, SARS-CoV-2, symptomatology, biomarkers, adverse events, cytokine storm, systematic review

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Introduction

Coronavirus disease 2019 (COVID-19) has led to fright among populations worldwide since it was first reported.[1] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially only considered to be a respiratory illness, but it is now recognized as a complex multi systems disease.[2,3] Current literature suggests that the increased expression of angiotensin-converting enzyme 2 (ACE2) receptors of SARS-CoV-2 in cardiac myocytes accounts for the relatively high cardiovascular involvement in COVID-19.[4] Comorbidities such as pre-existing cardiovascular diseases, hypertension and diabetes mellitus have led to worse prognosis among patients infected with

COVID-19.[5] However, infected patients may experience added-on cardiovascular injuries, even in the absence of pre-existing cardiac disease.[6] Myocarditis is an inflammation of the heart muscle with symptoms such as chest pain, shortness of breath, and palpitations.[7] A study identified 42 COVID-19 patients with myocarditis, where fever was the most common presenting sign in 57% patients, and hypertension was the most pervasive comorbidity.[8]

SARS-CoV-2 is posited to gain entry into human cells by binding the spike protein to the membrane protein angiotensin-converting enzyme 2 (ACE2).[9,10] As depicted in Figure 1, SARS-CoV-2 gains entry into the bloodstream, making its way to the heart and cardiac muscle. In the cardiomyocytes, the binding to ACE2 upregulates the receptor eventually leading to apoptosis, releasing viral and cardiac antigens. These antigens, when fixed to the antigen presenting cells (APCs), lead to the release of interleukins (IL1, IL6, IL12, TNF alpha), which when presented to CD4+ T helper cells, CD8+ T cells, and B cells, lead to autoreactive virus specific antibodies. The entire mechanism is posited to lead to myocarditis, with elevated inflammatory biomarkers, cardiac biomarkers, EKG changes, and symptoms such as shortness of breath and chest pain (Figure 1).

While our systematic review does not delve into the myocardial effects of COVID-19 vaccines, a report in the New England Journal of Medicine identified 2 cases of histologically confirmed, fulminant myocarditis within 2 weeks of COVID-19 vaccination.[11] As of September 1 2021, the Centers for Disease Control and Prevention writes that the risk of myocarditis is far higher after COVID-19 infection as opposed to the mRNA virus.[12] Based on a study that identified 1.5 million inpatient records with COVID-19, myocarditis was uncommon among patients with or without COVID-19, however, there was a relatively higher risk in the 50 to 75 and over age groups.[12] The under 16 age group could be more prone due to the related multisystem inflammatory syndromes.[12] The paper also noted an 18-fold higher chance of developing myocarditis due to COVID-19.[12]

The objective of this systematic review is to collate evidence about demographics, symptomatology, diagnostic techniques, and clinical outcomes of COVID-19 infected patients with myocarditis.

Methods

This systematic review was conducted and reported in conformity with the Cochrane and PRISMA (Preferred Reporting Items for Systematic review and Meta-Analyses) 2020 guidelines (Figure 2). A comprehensive literature search was done using the search engines PubMed, Google Scholar, Cochrane CENTRAL, and Web of Science database from their inception up until August 31, 2021. The search terms included "SARS-CoV-2" and/or "COVID 19" and/or "myocarditis." Reference lists of included studies were also manually screened to identify any relevant studies that may have been missed during the search (umbrella review).

Articles retrieved from the systematic search were exported to EndNote Reference Library software (Clarivate), where duplicates were removed. 2 authors (V.J. and S.Y.) carried out an independent search and screened the titles and abstracts of the identified articles for inclusion. Afterward, full-text articles were reviewed to validate if they satisfied the inclusion criteria. Any discrepancies were resolved by discussion till consensus was achieved. Articles were included if they met all the prespecified eligibility criteria: (1) Patients with confirmed myocarditis in association with COVID-19; (2) Age groups > 18 years; (3) Cohorts, case series and case reports.

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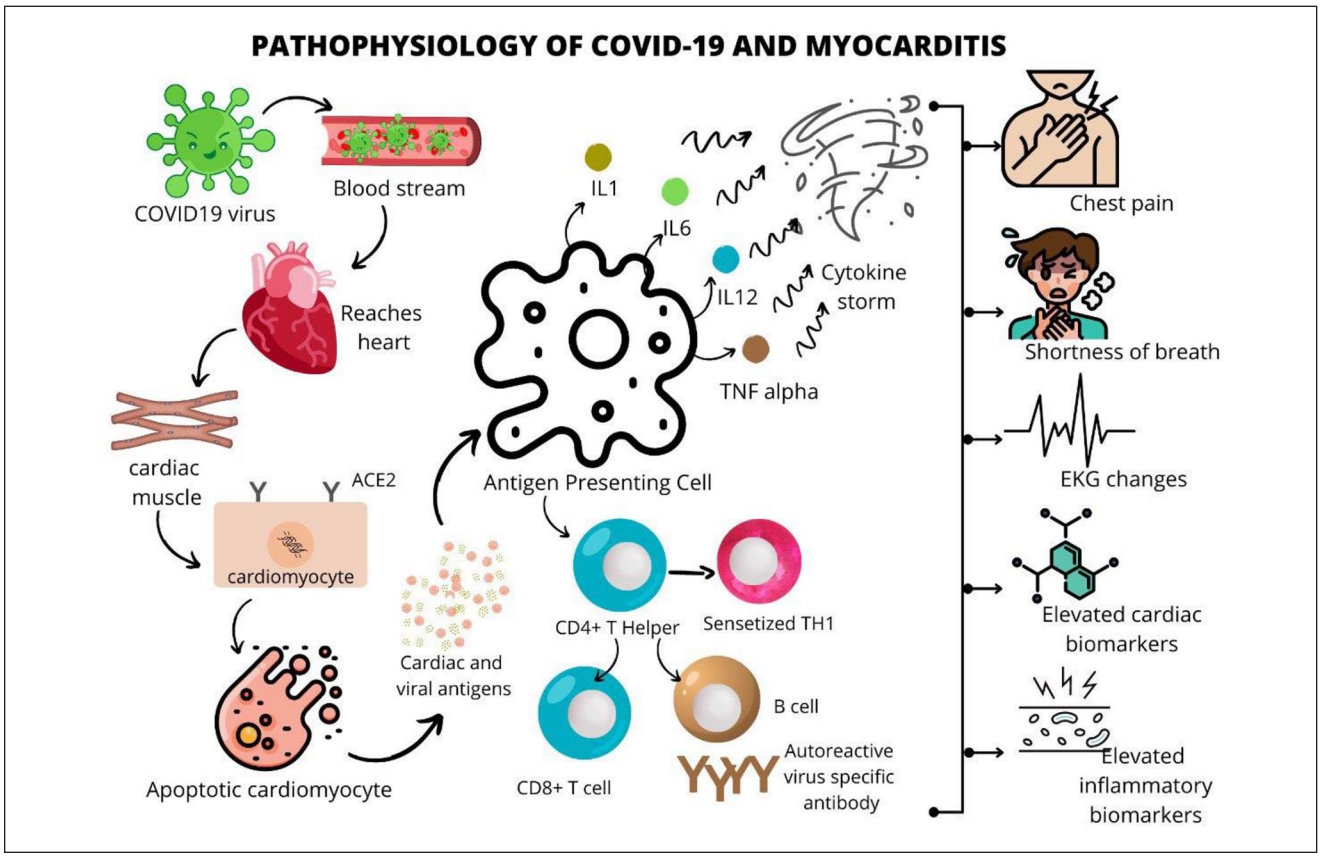

Figure 1. A schematic representation of the pathophysiology leading to COVID-19 induced myocarditis.

Studies with post-mortem findings consistent with acute myocarditis were also included. All other studies were excluded.

Data extracted from articles included publication related characteristics (i.e. author/s, study design, number of patients, year of publication, and country) and patient related characteristics. In specific, demographics (age in years, gender, comorbidities), and clinical characteristics along with laboratory findings (particularly, inflammatory markers and cardiac enzymes) were documented (Tables 1-3). Additionally, features of imaging modalities including Chest X-ray/CT scan, ECG, ECHO, CMR, and endomyocardial biopsy were noted. Management pertaining to both COVID-19 and myocarditis, complications, and final clinical outcomes were also recorded. All data was extracted onto a predesigned Excel spreadsheet.

Results

In total, 54 case reports and 5 cohorts were identified comprising 215 adult patients. Among the 59 studies, the following comorbidities were noted among 178 patients. Hypertension (n = 92, 51.7%), diabetes mellitus type 2 (n = 47, 46.4%), cardiac comorbidities (n = 26, 14.6%), hyperlipidemia (n = 6, 3.4%), obesity (n = 5, 2.8%), ischemic stroke (n = 2, 1.1%), asthma (n = 2, 1.1%), hypothyroidism (n = 2, 1.1%), smoking (n = 2, 1.1%), cancer (n = 2, 1.1%), sarcoidosis (n = 1, 0.6%), epilepsy (n = 1, 0.6%), multiple sclerosis (n = 1, 0.6%), tuberculosis (n = 1, 0.6%), migraine (n = 1, 0.6%), spondylitis (n = 1, 0.6%), renal transplant (n = 1, 0.6%), and sleep apnea (n = 1, 0.6%) (Table 1).

Presenting symptoms on admission were acquired from 139 of 215 patients. They include cough (n = 86, 61.9%), fever (n = 84, 60.4%), shortness of breath (n = 74, 53.2%), chest pain (n = 61, 43.9%), diarrhea (n = 43, 30.9%), fatigue (n = 37, 26.6%), myalgia (n = 34, 24.5%), dyspnea (n = 17, 12.2%), hypoxia (n = 7, 5%), syncope (n = 6, 4.3%), tachycardia (n = 6 4.3%), hypotension (n = 4, 2.9%), tachypnea (n = 4, 2.9%), malaise (n = 4, 2.9%), vomiting (n = 4, 2.9%), ARDS (n = 1, 0.7%) (Table 1).

Of 215, inflammatory markers were reported among 185 patients. The inflammatory markers were elevated among 181 (97.8%) patients, and were normal in the remaining 4 (2.2%) patients. The cardiac markers were documented in 212 patients, of which 201 (94.8%) had elevated levels, whereas, 11 (5.2%) patients had normal cardiac markers. The mean value of CRP was 91.6 mg/L (Normal: Less than

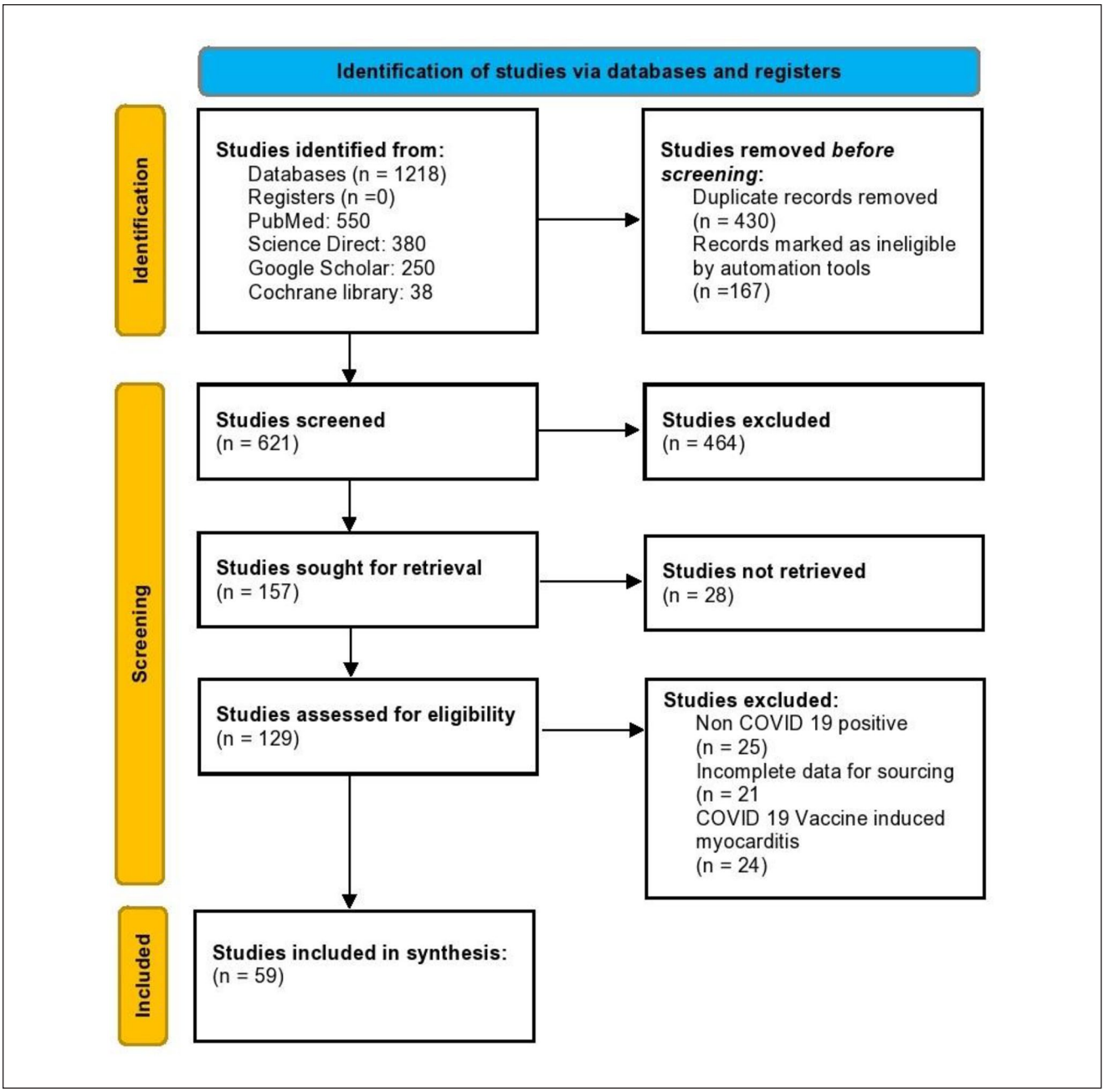

Figure 2. PRISMA flowchart.

10 mg/L. High: Equal to or greater than 10 mg/L).[71] The mean D-dimer value was 2419.2 ng/ml (reference concentration of D-dimer is < 500 ng/mL).[72] Mean ferritin laboratory values of 908.9 ng/ml (the normal range for ferritin in blood serum is: 20 to 250 ng/mL for adult males. 10 to 120 ng/mL for adult females)[72]; and Interleukin 6 of 271.2 pg/mL (normal values: 5-15 pg/ml) were reported.[73] Troponin values were reported as 44.85 ng/ml (normal range for troponin I is between 0 and 0.04 ng/mL but for high-sensitivity cardiac troponin (hs-cTn) normal values are below14ng/L).[74]

Radiographic imaging studies particularly, CT and Chest X-ray were indicated in COVID-19 patients (Table 2). Radiographic findings were obtained from 120 individuals with COVID-19 myocarditis. Variable features were noticed, of which cardiomegaly (32.5%) was the most prominent. Precisely, 120 patient radiographic findings were noted, of which cardiomegaly (n = 39, 32.5%) was the most common occurrence. This was followed by pulmonary venous congestion (n = 27, 22.5%), ground glass opacity (n = 23, 19.2%), consolidation (n = 9, 7.5%), pericardial

Table 1. Demographics, Comorbidities, and Presenting Symptoms Among all Patients.

Authors	Study design	Country	Sample size	Age (y)	Gender	Comorbidities	Presenting symptoms
Cizgic et al[13]	Case report	Turkey	1	78	M	HTN	Chest pain, shortness of breath
Yokoo et al[14]	Case report	Brazil	1	81	M	HTN, Ischemic Stroke	Fever, shortness of breath
Pietsch et al[15]	Case report	Germany	1	59	F	None	ARDS and dyspnea
Pavon et al[16]	Case report	Switzerland	1	64	M	Isolated pulmonary sarcoidosis and epilepsy	Fever, chest pain, shortness of breath, cough
Khatri et al[17]	Case report	USA	1	50	M	HTN, Ischemic stroke	Fever with chills, malaise, shortness of breath, cough, syncope
Hussain et al[18]	Case report	USA	1	51	M	HTN	Cough, shortness of breath, fatigue, fever
Dalen et al[19]	Case report	Norway	1	55	F	None	Fatigue, myalgia, syncope, chest pain
Zeng et al[20]	Case report	China	1	63	M	None	Fever, cough, shortness of breath, chest pain
Doyen et al[21]	Case report	France	1	69	M	HTN	Fever, cough, shortness of breath, vomiting, diarrhea
Faircloth et al[22]	Case report	USA	1	60	M	Multiple sclerosis	Fever, tachycardia, hypotension, shortness of breath, tachypnea, hypoxia
Coyle et al[23]	Case report	USA	1	57	M	HTN	Fever, myalgia, cough, shortness of breath, decrease appetite, nausea, diarrhea
Luetkens et al[24]	Case report	Germany	1	79	M	Asthma	Fatigue, syncope, shortness of breath, wheeze
Jain et al[25]	Case report	India	1	60	M	HTN, DM II	Cough, shortness of breath, hypoxia (75% SpO2)
Mustafa et al[26]	Case report	USA	1	56	M	None	Fatigue, myalgia, chest pain, cough, shortness of breath
Mansoor et al[27]	Case report	USA	1	72	F	HTN	Myalgia, fever, tachycardia, cough, cold, tachypnea, hypoxia (60% Sp02)
Al-assaf et al[28]	Case report	UAE	1	58	M	HTN	Asymptomatic
Khalid et al[29]	Case report	USA	1	76	F	HTN, hyperlipidemia, hypothyroidism	Fever, dyspnea, cough, tachycardia, tachypnea, hypoxia (79%SpO2)
Inciardi et al[30]	Case report	Italy	1	53	F	None	Fatigue, fever, hypotension, cough
Fried et al[31]	Case report	USA	1	64	F	HTN, hyperlipidemia	Asymptomatic
Wehit et al[32]	Case report	Argentina	1	68	M	HTN, obesity, DM II	Fever, fatigue
Butler et al.[33]	Case report	USA	1	50	M	HTN, DM II	Tachycardia, shortness of breath, hypoxia, confusion
Lagana et al.[34]	Cohort	Italy	12	76(Mean)	5M,7F	75%—Systemic HTN, 66.7% Cardiac,	Fever, cough, shortness of breath
Kallel et al[35]	Case report	USA	1	56	M	Diabetes, obesity	Fever, myalgia, chest pain, cough, hypoxia
Ghurge et al.[36]	Case report	Canada	1	62	M	HTN, dyslipidemia	Fever, fatigue, cough, shortness of breath, tachypnea, lethargy
Fath et al[37]	Case report	USA	1	61	M	HTN, obesity, hyperlipidemia	Fatigue, myalgia, hypotension, tachypnea, hypoxia (spO2 85%), shortness of breath
Dabbagh et al[38]	Case report	USA	1	67	M	Non-ischemic cardiomyopathy with LVEF of 40%	Cough, shortness of breath, left shoulder pain
Irabien-Ortiz et al[39]	Case report	Spain	1	59	F	HTN, lymph node tuberculosis diagnosed by presence of erythema nodosum, and migraine	Fever, squeezing chest pain
Albert et al[40]	Case report	USA	1	49	M	None	Fever, dyspnea
Escher et al[41]	Case report	Germany	1	39	M	None	Fever, dyspnea
Ford et al[42]	Case report	USA	1	53	M	Dyslipidemia	Malaise, fever, chest pain
Gauchott et al[43]	Case report	France	1	69	M	DM II, HTN, IHD	Fever, fatigue, abdominal pain
Hua et al[44]	Case report	UK	1	47	F	None	Fever, dry cough, chest pain, shortness of breath
Jacobs et al[45]	Case report	Belgium	1	48	M	HTN	Diarrhea, cough, dyspnea
Labani et al[46]	Case report	French	1	71	F	Breast Cancer	Flu-like symptoms, chest pain
Spano et al[47]	Case report	Switzerland	1	49	M	None	Dyspnea, fatigue, intermittent epigastric pain, nocturia
Tavazzi et al[48]	Case report	Italy	1	69	M	None	Cough, dyspnea, weakness
Trogen et al[49]	Case report	USA	1	69	M	Obesity, asthma, spondylolysis	Fever, neck pain, diarrhea, vomiting
Varga et al[50]	Case report	N/A	1	71	M	Renal transplant, CAD, HTN	Dyspnea, fever, tachycardia, confusion
Warchoł et al.[51]	Case report	Poland	1	74	M	Atrial fibrillation, arterial HTN	New-onset ventricular tachycardia

(continued)

Table 1. (continued)

Authors	Study design	Country	Sample size	Age (y)	Gender	Comorbidities	Presenting symptoms
Sardari et al[52]	Case report	Iran	1	31	M	None	Dyspnea, fever,
Dahl et al[53]	Case report	Norway	1	37	M	None	Fever, headache, unilateral left painful neck swelling
Hu et al.[54]	Case Report	China	1	37	M	None	Chest pain, dyspnea, diarrhea
Volis et al[55]	Case report	Israel	1	21	M	Smoking	Chest pain, cough, dyspnea, fever
Besler et al.[56]	Case report	Turkey	1	20	M	None	Chest pain, fever
Gaine et al[57]	Case report	Ireland	1	58	M	Smoking	Palpitations, dyspnea
Sheikh et al[58]	Case report	USA	1	28	M	None	Chest pain, cough, dyspnea
Salamanca et al[59]	Case report	Spain	1	44	M	None	Dyspnea, syncope
Naneishvili et al[60]	Case report	UK	1	44	M	None	Syncope, fever, lethargy
Kim et al[61]	Case report	Korea	1	21	F	None	Fever, dyspnea, cough
Nikoo et al[62]	Case report	Iran	1	38	F	None	Chest pain, nausea, vomiting, malaise
Sala et al[63]	Case report	Italy	1	43	F	Unremarkable	Dyspnea, fever, chest pain.
Yuan et al[64]	Case report	China	1	33	M	N/R	Fever, chest pain
Warchol et al.[51]	Case report	Poland	1	74	M	Atrial fibrillation, atrial HTN, type II DM, hypothyroidism	No symptoms
Asif and Ali[65]	Case series	USA	2	64,71	P1:M, P2: F	P1: HTN, Hyperlipidemia, P2: Multiple Myeloma	P1: dyspnea, hypotension. P2: Fever, cough, dyspnea
Khalid et al[66]	Case series	USA	2	48, 34	P1: M, P2: F	P1: Obesity, Diabetes, Obstructive sleep apnea. P2: None	P1: Fever, chills, myalgias, diarrhea, nonproductive cough and shortness of breath. P2: Fever, chills, body ache
Ng et al.[67]	Cohort	China	16	68	9M,7F	None	All have chest pain, cough, shortness of breath
Jirak et al[68]	Cohort	Europe	76	66.8	53M,23F	Arterial hypertension—56.6% CAD—13.2% PVD—5.3% DM II- 26.3%	N/A
Xu yan et al.[69]	Cohort	China	27	69	10M, 17F	CHD-11%	Fever (82.4%), chest pain (7,6%), cough (68.1%), shortness of breath (40.3%), diarrhea (31.1%)
Kunal et al.[70]	Cohort	India	28	60.9 ± 15.1	14M,14F	Diabetes = 71.4%, HTN = 64.3%,	Myalgia, fever, fatigue, chest pain, cold, cough, shortness of breath, confusion, headache, diarrhea

effusion (n = 3, 2.5%), pleural effusion (n = 1, 0.83%), and no abnormal finding (n = 5, 4.2%) were noted in the cohort of included patient (Table 2).

Electrocardiography (ECG) findings were obtained for 96 patients, which were normal in 2 (2%) patients while other patients had varied ECG findings comprising of ST segment elevation among 43 (44.8%) patients, T wave inversion in 7 (7.3%) patients, ST depression in 5 (5.2%) patients, sinus tachycardia in 11 (11.5%) patients, atrial fibrillation in 3 (3.1%) patients, sinus bradycardia in 1 (1%) patient, ventricular tachycardia in 2 (2%) patients, and finally LBBB was reported in 1 (1%) patient as well (Table 2). Echocardiography was conducted in 175 patients, where 9 (51.4%) patients showed normal ejection fractions while 55 (31.4%) patients demonstrated reduced ejection fraction with a mean EF% of 35. Pericardial effusion was demonstrated in 12 (6.9%) patients, left ventricular hypertrophy in 7 (4%) patients, cardiomegaly in 7 (4%) patients, myocardial dyskinesia in 19 (10.9%) patients, and LV thrombus in 1 (0.6%) patient (Table 2).

Cardiovascular magnetic resonance (CMR) imaging is a non-invasive, gold standard test for diagnosing myocarditis. Our synthesis identifies that 42 of 215 patients underwent CMR and 36 of them were diagnosed with Myocarditis by the Lake Louis Criteria. The most common findings were increased signal intensity in T2 weighted imaging that is, myocardial edema (30/36; 83.3%) suggestive of myocardial inflammation and/or ischemia. Late Gadolinium enhancement was observed in 23/36 (63.9%) patients in both ischemic and non ischemic patterns. Hypokinesis and decreased systolic function were present in 8/36 (22.2%) and 6/36 (16.7%) patients respectively. Myocardial fibrosis was found in 1/36 (2.8%) patients. In total, 6 (14.3%) of 42 patients were found to have normal CMR findings (Table 2).

On noting the biopsy and histopathological examination findings, and considering the invasive in nature, these findings were reported in 9 (4.2%) patients out of 215 (Table 2). The most common findings were multifocal or diffuse lymphocytic infiltrates in the myocardium and endothelium along with myocardial edema and necrosis. Other findings included positive myocardial anti-SARS COV nucleocapsid protein antibodies, cardiac hypertrophy, and multiple sites of ischemia and thrombosis with a left atrial and left pulmonary artery thrombus in one patient.[37] Only 1 (11.1%) patient had normal findings on biopsy.

The in-hospital management acquired from 165 patients comprised of azithromycin (n = 42, 25.5%), hydroxychloroquine (n = 41, 24.9%), methylprednisolone/steroid (n = 14, 8.5%), norepinephrine (n = 10, 6%), dobutamine (n = 7, 4.3%), tocilizumab (n = 6, 3.6%), and remdesivir (n = 1, 0.6%) (Table 3). Standard care of treatment for COVID-19 was used for majority of the patients.

Complications during in-hospital stay reported in 128 patients included ARDS (n = 85, 66.4%), cardiogenic shock (n = 18, 14%), pleuritic chest pain (n = 6, 4.7%), multiorgan failure (n = 4, 3.1%), septic shock (n = 3, 2.3%), distributive shock (n = 2, 1.6%), sepsis (n = 2, 1.6%), bells palsy (n = 1, 0.8%) (Table 3). Of 85 patients, 55 (64.7%) survived, whereas 27 (31.8%) died. Three patients (3.5%) were in critical care unit on the last follow-up (Table 3).

Discussion

This systematic review aimed to describe the symptomatology, prognosis, and clinical findings of patients with probable and confirmed COVID-19-related myocarditis. Frequent clinical findings of COVID-19 infection constitute fever, cough, shortness of breath, and fatigue.[75] The World Health Organization has cited fever and cough as striking features of COVID-19.[76] Fever, dyspnea, and/or chest pain are typical manifestations of myocarditis that tend to overlap with COVID-19 symptomatology, thus making the diagnosis challenging.[77,78] Laboratory investigations such as rising levels of cardiac biomarkers and electrocardiogram findings may assist in diagnosing COVID-19 induced myocarditis.

Our systematic review finds hypertension was the most common comorbidity with prevalence among 51.7% patients. This was followed by diabetes mellitus type 2 (46.4%) and cardiac comorbidities (14.6%). Our synthesis also finds that the most common presenting symptoms on admission comprised of 61.9% patients with cough, 60.4% with fever, and 53.2% with shortness of breath. The inflammatory markers were elevated among 97.8% patients, and the cardiac markers were increased in 94.8% of patients. The mean CRP levels were 91.6 mg/L, mean D-dimer values were 2419.2 ng/ml, and mean ferritin was 908.9 ng/ml. Mean Interleukin 6 values were 271.2 pg/mL and troponin values were identified as 44.85 ng/ml. The most distinct radiographic findings were cardiomegaly noted in 32.5% patients, followed by pulmonary venous congestion (22.5%), and ground glass opacity (19.2%). On noting ECG findings, ST segment elevation was reported in 44.8% patients, sinus tachycardia in 11.5%, and T wave inversion in 7.3% patients. Echocardiography noted normal ejection fractions in 51.4% patients, but 31.4% had reduced ejection fraction with a mean percentage of 35%. CMR imaging identified increased signal intensity in T2 weighted imaging, with myocardial edema in 83.3% patients, suggesting myocardial ischemia/inflammation. Late gadolinium enhancement was observed in 63.9% patients. The biopsy and histopathological examination findings found multifocal or diffuse lymphocytic infiltrates in the myocardium and endothelium along with myocardial edema and necrosis. In-hospital management comprised of 22.5% patients treated with azithromycin, 24.9% with hydroxychloroquine, 8.5% with methylprednisolone/steroid and 6% with norepinephrine. Standard of care and treatment was used for the

Table 2. Biomarkers, Radiographic, Electrocardiography, Echocardiography, and Biopsy Findings.

Authors	Inflammatory markers	Cardiac markers	Radiographic findings	Electrocardiography	Echocardiography	CMR	Myocardial biopsy
Cizgic et al[13]	C reactive protein 94.6 mg/L	Troponin-998.1 ng/L	CT chest-small pericardial effusion and ground-glass opacification with consolidation	Atrial fibrillation besides heart rate of 150 bpm, concave ST elevation except for aVR lead	N/A	N/A	N/A
Yokoo et al[14]	N/A	Troponin T-33 pg/ml	Chest CT-small round ground-glass opacities, with multifocal distribution on both lungs	N/A	Reduction in the ejection fraction to 35%	Late enhancement areas with an ischemic pattern on the left ventricle base septum wall, with diffuse hypokinesis, and global systolic function	N/A
Pietsch et al[15]	NA	Troponin-83.6 ng/L CK-MB-7.14 ng/ml	NA	NA	Severe diastolic dysfunction III with an increased wall thickness (inter-ventricular septum, 14 mm), and pericardial effusion	NA	EMB: Intra-myocardial inflammation with absence of signs of necrosis. Increased no. of CD45R0+ T memory cells (96.15 cells/mm2), CD3+ cells (20.54 cells/mm2), CD11a+ cells (24.36 cells/mm2), CD11b+ cells (91.56 cells/mm2), and CD54+ cells (area fraction 1.91%), histology: hypertrophied myocytes (diameter 31 μm)
Pavon et al[16]	C-reactive protein-466 mg/L, D-dimer-1210 ng/mL	Troponin (peak)- 1843 ng/L	Chest x-ray bilateral reticulation and ill-defined opacities, indicative of interstitial edema	N/A	Moderately reduced left ventricular ejection fraction of 47%(72h after CMR)	Reduced left-ventricular (LV) systolic function (42%), mild hypokinesia of the lateral wall. T2-mapping sequences showed myocardial edema (segmental T2 = 55-57 ms)	N/A
Khatri et al[17]	D-dimer-1068 ng/mL, procalcitonin-8.16 ng/mL, C-reactive protein110.85 mg/dL, Ferritin 66 ng/mL	Troponin- 544 ng/L, CK-MB54.3 ng/mL	N/A	Sinus tachycardia along with ST elevation in leads II, III, aVF, and ST depression in I, aVL	Severe global left ventricular systolic dysfunction, right ventricular (RV) enlargement causing its systolic dysfunction, and moderate-to-large pericardial effusion anterior to the Right ventricle	N/A	N/A
Hussain et al[18]		Troponin-18 ng/mL and CKMB-14.7 ng/mL	N/A	Diffuse ST elevation	Enlarged heart, marked decrease in ventricular systolic function with an ejection fraction of 20%	N/A	N/A
Dalen et al[19]	C-reactive protein 11 mg/dl	Troponin T-108 ng/L, NTproBNP-1025 ng/L	N/A	Sinus tachycardia, insignificant ST elevation in inferior leads with a T-wave inversion in precordial leads	Left ventricular concentric hypertrophy	T1-mapping exhibited relaxation times of 1260-1270 ms in the anterolateral wall contrasted with 1090 ms in the septum. Late gadolinium enhancement in the anterolateral wall.	N/A
Zeng et al[20]	Interleukin-6(peak)- 272.40 pg/mL	Troponin I (peak)- 11.37 g/L, myoglobin (peak) > 390.97 ng/mL, NTpr(peak)- 22 500 pg/mL	Chest X-ray-Typical ground glass changes indicative of viral pneumonia	Sinus tachycardia without ST elevation and left axis deviation	Enlarged LV, diffuse myocardial dyskinesia, LVEF reduced to 32%, pulmonary hypertension, and normal RV function	N/A	N/A
Doyen et al[21]	N/A	Troponin I-9002 ng/L	Chest CT-bilateral crazy paving pattern, ground glass opacities and condensation	Diffuse T-wave inversion with the sign of left ventricular hypertrophy	Mild left ventricle hypertrophy, with normal left ventricular ejection fraction and nomal wall motion	Sub-epicardial late gadolinium enhancement of the apex and inferolateral wall	N/A
Faircloth et al[22]	C-reactive protein- 20.02 mg/dl, Ferritin-757 ng/ml ESR—78 mm/h	Troponin-25 000 ng/L	NA	NA	NA	NA	NA
Coyle et al[23]	NA	Troponin I(peak) -7.33 on day 3,	N/A	Sinus tachycardia, with normal ST/T wave	Diffuse hypokinesis with relative apical sparing, with a left ventricular ejection fraction of 35–40%, no pericardial effusion	Diffuse edema of both atria and both ventricles along with small foci of late gadolinium enhancement	N/A
Luetkens et al[24]	C-reactive protein (peak)—64.23 mg/L	Troponin T63.5 ng/L, NTproBNP—1178.0 pg/ml	Chest CT pulmonary ground glass peripheral infiltrates in the left upper lobe and discreet pleural and pericardial effusion	Normal	N/R	Diffuse interstitial myocardial edema with an increased T2 signal intensity ratio. T2 mapping showed diffuse myocardial inflammation(on day 10)	N/R
Jain et al[25]	Elevated inflammatory markers	Elevated troponin	Chest X-ray showed bilateral diffuse opacities	Age indeterminate inferior infarct versus left anterior fascicular block	EF <30% along with akinesis of the mid to apical myocardial segments	N/A	N/A
Mustafa et al[26]	C-reative protein—160 mg/L	Troponin I: 8.6 ng/ml	Chest x-ray was suggestive of increased interstitial prominence	Normal sinus rhythm with ST elevations in the antero-lateral distribution	N/A	N/A	N/A
Mansoor et al[27]	C-reactive protein: 27 mg/dl Ferritin: 928 ng/dl ESR: 82 mm/h WBC: 24000/μl, D-dimer: 3455 ng/ml	NT-proBNP: 4639 pg/ml, troponin T (hsTt): 118 ng/L	N/A	Sinus tachycardia, PR elevation in aVR and PR depression in leads II and aVF on admission	Mildly decreased left ventricular function but no significant segmental wall motion abnormalities, mild mitral regurgitation, mildly enlarged right ventricle with normal right ventricular function, no tricuspid regurgitation, and no pericardial effusion.	N/A	N/A
Al-assaf et al[28]	Normal ranges of inflammatory markers and cardiac biomarkers.	N/A	Normal	Sinus bradycardia, no ST-T changes	Unremarkable study showing only a mildly dilated ascending aorta	T1 mapping showing a high value of 1062. T2 mapping showing an abnormal value of 57	N/A

(continued)

Table 2. (continued)

Authors	Inflammatory markers	Cardiac markers	Radiographic findings	Electrocardiography	Echocardiography	CMR	Myocardial biopsy
Khalid et al[29]	C-reactive protein 23.10 mg/L, Interleukin-6 (IL-6) 781.46 mg/L, elevated lactate dehydrogen 334 U/L and ferritin 457 ng/ml	Troponin 503 ng/l, proBNP35,000 pg/mL	Chest X-ray-diffuse bilateral pulmonary edema vs infiltrates	Normal sinus rhythm with a short PR interval	Severe left ventricular systolic dysfunction with segmental wall motion anomalies	N/R	N/R
Inciardi et al[30]	C reactive protein- 1.3 mg/dl mg/dl, D dimer- 500 U/F	Troponin T(peak)- 0.89 ng/mL, CKMB(peak)- 39.9 ng/mL, BNP(peak)—8465 pg/mL	N/A	Minimal diffuse ST elevation, low voltage in limb leads, ST depression, and T wave inversion in V1 and aV	Increased left ventricular wall thickness with diffuse hypokinesis, and LVEF of 40%. Large circumferential pericardial effusion of size 11 mm with the absence of tamponade	Diffuse biventricular apical hypokinesis, severe LV dysfunction (LVEF of 35%), Short tau inversion recovery and T2-mapping sequences showed marked biventricular myocardial interstitial edema.	N/A
Fried et al[31]	C reactive protein: 0.0054 mg/dl, ferritin: 967 ng/ml ESR: 166 ng/ml	Troponin- 7900 ng/L,	N/A	Sinus tachycardia, ST segment elevation in leads I, II, aVL, V2-V6, and PR elevation and ST depression in aVR. Low voltage QRS complexes in the limbs leads.	EF: 30% (reduced) Severe concentric left ventricular hypertrophy, and a dilated, severely hypokinetic right ventricle. Pericardial effusion	N/A	N/A
Wehit et al[32]	LDH-198 Ul/l, ferritin- 723 ng/mL, Dimer D- 300 ng/mL	Troponin T- 16 pg/mL, BnP 370 pg/mL	Chest radiography revealed right basal opacities	N/A	Deterioration in both global and segmental longitudinal strain	N/A	N/A
Butler et al[33]	N/A	Troponin: 67 ng/L, NT-proBNP: 4529 pg/ml	N/R	N/R	N/R	N/A	N/A
Lagana et al[34]	N/A	Troponin:39.9 pg/ml, NT-proBNP: 1557.6 pg/ml	N/R	Ischemic alteration (66.66%)	Diffuse left ventricular hypokinesis 66.66%, 25%QTc prolongation	N/A	N/A
Kallel et al[35]	C-reactive protein: 315 mg/l, WBC count: 17940/UL, Creatinine: 45 mg/l, D-dimer: 1.04 mg/l	Troponin I: 677 ng/L, CPK-MB: 19 Ul/l	CT chest showed typical findings of COVID-19 with ground-glass opacification	Diffuse ST elevation and simple monomorphic supraventricular extrasystoles	Normal systolic function	N/A	N/A
Ghurge et al[36]	NA	NA	NA	NA	NA	Normal left ventricular (LV) and right ventricle (RV) size and function, LV ejection fraction was 62%, area of mid myocardial/subepicardial late enhancement in the basal inferolateral wall in a non-ischemic pattern most consistent with a myocarditis type pattern, abnormal hyperintense MRI relaxation associated with the presence of edema, abnormal T2 hyperintense relaxation associated with the presence of edema.	N/A
Fath et al[37]	Creatinine-1.16 mg/dL INR-1.5 CRP- 306.8 mg/L LDH- 707U/L IL-6- 23 pg/mL D-dimer-32563 ng/mL Ferritin-2831.22 ng/mL CK-86U/L	Elevated Troponin I 7.454 ng/ml	NA	Diffuse, mainly anterolateral, ST elevation	Reduced ejection fraction	NA	Multiple microscopic sites of myocardial ischemia together with thrombi in the left atrium and pulmonary vasculature and, scattered microscopic cardiomyocyte necrosis. Autopsy also revealed an adherent organizing left atrial thrombus (1.5 cm) and marked thromboembolism of the left pulmonary artery
Dabbagh et al[38]	C-reactive protein-15.9 mg/dl, ferritin-593 ng/ml, D-dimer- 6.52 μg/ml and interleukin 6(IL-6)- 8 pg/ml	Troponin I < 18 ng/L, pro-BNP-54 pg/mL	Chest X-ray enlarged cardiac silhouette	Shallow voltage in limb leads, non-specific ST alteration	A decrease in left ventricular ejection fraction to 40%, massive peripheral pleural effusion, an indication of early right ventricular diastolic collapse, dilated but collapsing inferior vena cava	N/A	N/A
Irabien-Ortiz et al[39]	C reactive protein- 10 mg/L	Troponin T(peak)- 1100 ng/dL, NTproBNP - 4421 ng/L	Chest X-ray- mild signs of vascular redistribution, with no infiltrations	Diffuse ST elevation and PR-segment depression	Concentric hypertrophy, diminished LV volumes, preserved LVEF, moderate pericardial effusion, absence of tamponade. After 2 h severe biventricular failure and diffuse myocardial edema	N/A	N/A
Albert et al[40]	N/A	Elevated troponin, NT-proBNP	No pathological features	Sinus tachycardia, no ST-T changes	Globally depressed LVEFof 20% with LVEDD of 5.8 cm, increased wall thickness	N/A	Inflammatory infiltrates with visualization of viral particles
Escher et al[41]	N/A	Troponin-3264 pg/mL, BNP-12232(pg/mL)-	N/A	N/A	LVEF = 22%	N/A	Active myocarditis with CD3+ 106 cell/mm2
Ford et al[42]	N/A	BNP 588 pg/mL, TnT normal	Left lower lobe consolidation	Wide-complex, irregular tachycardia with a LBBB morphology, as well as a long QT interval	Mild LV dilation with hypokinesis (EF 15%). New transthoracic echo revealed LV thrombus and worsening LV dilation	LV dilation with global hypokinesis, increased T2 signal, hyperemia, and edema	N/A

(continued)

Table 2. (continued)

Authors	Inflammatory markers	Cardiac markers	Radiographic findings	Electrocardiography	Echocardiography	CMR	Myocardial biopsy
Gauchotte et al[43]	N/A	Troponin I 8066 pg/mL and CK–MB 2103 UI/L)	Normal	Normal	Severe and diffuse LV hypokinesia, LVEF = 30%	N/A	Post mortem: Multifocal inflammatory infiltration, in both ventricles and septum, composed in its majority of macrophages and lymphocytes. The myocardium was edematous, containing dystrophic cardiomyocytes, without necrosis. Strong presence of anti-SARS-CoV nucleocapsid protein antibody in the myocardium
Hua et al[44]	N/A	Troponin T (peak)-253 ng/L	N/A	Sinus tachycardia, concave inferolateral ST elevation	Left ventricular ejection fraction was normal with pericardial effusion of size 11 mm and absence of cardiac tamponade	N/A	N/A
Jacobs et al[45]	Ferritin- 32 401 μg/L, interleukin 6 level- 281 pg/mL	NTproBNP, 9,223 pg/mL, TnI 14 932 ng/L	Multiple patchy ground-glass opacifications in all lung fields	QRS widening and a positive Deflection at the end of the T wave	Hyperdynamic ventricular function (inotropes). IVS 12mm, PW 11mm, LV EDD 48mm	NA	Post Mortem: Hypertrophic Cardiac tissue with patchy muscular, sometimes perivascular, and slightly diffuse interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes. Positive immunohistochemical staining with E06 in morphologically degenerating and necrotic cardiomyocytes adjacent to the infiltrate of lymphocytes
Labani et al[46]	C-reactive protein 9 mg/L	TnT: 60 ng/L, BNP: 474 ng/L	Mild bilateral peripheral lower pulmonary lobe ground-glass opacities	Diffuse inverted T waves and elongated QT	Infero-septal and infero-apical LV wall hypokinesia, LVEF 56% and a moderate pericardial effusion	LV wall motion, normal LVEF 61% and persistence of a mild pericardial effusion. STIR and T2 map showed suggestive of myocardial edema in the basal inferior LV wall. LGE: multiple areas of inferior subepicardial and mid-wall	N/A
Spano et al[47]	Elevated C-reactive protein	Elevated troponin and NT-proBNP levels	CT chest-left heart congestion	Dynamic T- wave inversion	Diffuse hypokinesia with severely decreased left- and right-ventricular function	T2 weighted imaging and T2 mapping revealed diffuse thickening of the myocardium and pericardium attributable to edema	N/A
Tavazzi et al[48]	C reactive - protein 52.7 mg/L	Troponin I- 4332 ng/L	N/A	N/A	Dilated left ventricle, severe and diffuse LV hypokinesia with LV ejection fraction of 34%	N/A	N/A
Trogen et al[49]	C-reactive protein- 167 mg/L, D-dimer 1218 ng/mL, ferritin 1274.6 ng/mL	Troponin I: 2.97 ng/ml, BNP- 2124 pg/mL	N/R	Sinus tachycardia and T-wave inversion particularly in the inferior leads	Left ventricular ejection fraction mildly depressed without obvious intracardiac clots or pericardial effusion	The normal size of both ventricles along with slightly decreased systolic function. A segment of a mid-wall late gadolinium enhancement at the level of the inferior junction of both ventricles correlative to an area of increased T2 signal, along with an area of hypokinesia	N/R
Varga et al[50]	C-reactive protein: 232 mg/l D-dimers: 2.42 mg/l	Troponin T: 51 ng/l, NTproBNP: 10 456 ng/l	Bilateral infiltration and ground glass opacities with consolidations in the right lung	N/A	Preserved left ventricular ejection fraction, but a severely enlarged left atrium (59ml/m2) indicating longstanding diastolic dysfunction	N/R	Postmortem: accumulation of inflammatory cells associated with endothelium, as well as apoptotic bodies, in the heart
Warchoł et al[51]	C-reactive protein levels-94 mg/l,D dimers: 1.39 mg/l, lactate dehydrogenase: 369 U/l	Troponin T ranged from 72 ng/l to 102 ng/l, NT-proBNP: 2451 ng/l	N/R	N/R	N/R	Left atrial enlargement and global left ventricular hypokinesia with reduced left ventricular ejection fraction of 20%. Inferior and inferolateral wall large, patchy, and linear non-ischemic pattern of fibrosis with late gadolinium enhancement	N/R
Sardari et al[52]	CRP = 105 mg/L, ESR = 70 mm/h	Troponin T = <0.03 ng/ml	Bilateral ground glass and consolidative opacities	N/R	Left ventricular dysfunction	Normal LV size, EF of 50	No
Dahl et al[53]	CRP-230 mg/L, procalcitonin-2.1 μg/L	TnT- 90 ng/L, NT-proBNP - 160 ng/L	bibasal consolidations	sinus tachycardia with moderately flattened T-waves	deterioration of the left ventricular function,EF-40%	diffuse myocardial edema suggestive of significant acute myocardial injury.	N/R
Hu H et al[54]	N/A	Troponin T-10 000 ng/L,CKMB 112.9 ng/L, BNP—21 025 ng/L	CXR-cardiomegaly, CT-pulmonary infection, enlarged heart	III, AVF ST-segment elevation	enlarged heart and a marked decrease in ventricular systolic function, LVEF-27%,trace 2mm pericardial effusion	N/R	N/R
Volis et al[55]	CRP-3.87 mg/dl	Troponin-I-965 ng/L	chest CT-unremarkable	minimal ST-depressions and T-wave inversions in lead III	Normal left ventricular ejection fraction-65%, normal function, no wall-motion abnormalities.	N/R	N/R

(continued)

Table 2. (continued)

Authors	Inflammatory markers	Cardiac markers	Radiographic findings	Electrocardiography	Echocardiography	CMR	Myocardial biopsy
Besler et al[56]	CRP-0.0812 g/L	Troponin I-7.621 ng/mL,CKMB-21.92 μg/L,NT-proBNP-1525 ng/L	CXR-focal consolidation on the upper zone of left lung, CHEST CT-subpleural consolidation with ground-glass opacification in the left upper lobe	N/R	N/R	Myocardial wall edema, subepicardial late gadolinium enhancement of the posterolateral wall in the mid ventricle-suggestive of myocarditis,ef-64%	N/R
Gaine et al[57]	CRP-7 mg/L	Troponin T -25 ng/L, NTproBNP-3428 pg/mL	CXR-cardiomegaly, increased interstitial lung markings	atrial fibrillation	severely impaired LVEF of 20% and mitral regurgitation	Biventricular oedema suggestive of generalized severe myocarditis	N/R
Sheikh et al[58]	CRP-32.5 mg/dL,ESR-88 mm/h	Troponin-0.43 ng/mL, BNP-19600 pg/mL	CXR-patchy bibasilar opacities	Accelerated junctional rhythm, non specific T wave changes	Left ventricular dysfunction-ejection fraction 30%	N/R	N/R
Salamanca et al[59]	N/R	troponin T-745 ng/l, CKMB-30 U/l, NTproBNP-24,167 pg/ml	CXR-bilateral pneumonia	Third-degree atrioventricular block	severely dysfunctional left ventricle,ejection fraction [LVEF] ~ 15%	Diffuse edema, negative Late gadolinium enhancement	No significant inflammatory infiltrates
Naneishvili et al[60]	CRP-47 mg/L, D-dimer 579 ng/mL	Troponin I-639 ng/L, CK-1403 U/L	CXR-bilateral patchy air space shadowing consistent with SARS-CoV-2 pneumonia,CHEST CT-1 cm rim of pericardial fluid and minimal bi-basal lung inflammatory changes.	Atrial fibrillation converted to sinus rhythym by DC cardioversion	Moderate concentric biventricular hypertrophy, diffused left ventricular hypokinesia with moderate to severe left-ventricular systolic dysfunction EF-37% and pericardial effusion with no signs of tamponade	N/R	N/R
Kim et al[61]	N/R	Troponin I-1.26 ng/mL,NT-proBNP-1929 pg/mL	CXR-multifocal consolidation on both lung fields and cardiomegaly, CHEST CT-multifocal consolidation and ground-glass opacification in both lungs in the lower lobe.	Multiple premature ventricular complexes	Severe left ventricular systolic dysfunction	Myocardial edema, Extensive transmural late gadolinium enhancement	N/R
Nikoo et al[62]	CRP-23 mg/L,ESR-4 mm/h	Troponin I 10.32 Mic gr/L),CKMB-83 IU/L	N/R	Sustained ventricular tachycardia	Biventricular dilation and global hypokinesia with left ventricular ejection fraction-20–25%.	CMR after discharge-normal ventricles size, EF of 52%, diffuse myocardial inflammation of the LV myocardium	N/R
Sala et al[63]	CRP: 18 mg/l	Troponin T: 135 ng/L, NT pro BNP: 512 pg/ml	B/L opacity in lungs	Mild ST-segment elevation(V1-V2 and aVR), ST- depression (V4-V6), and diffuse U waves	LVEF = 43%, inferolateral wall hypokinesis and no pericardial effusion	Hypokinesia of left ventricle mid and basal segment, diffuse myocardial oedema	T lymphocytes inflammatory infiltrates and necrosis
Yuan et al[64]	N/R	N/R	No ground glass appearance in Lungs.	Ventricular Tachycardia	N/R	Increased left ventricular apical region	N/R
Warchol et al[65]	CRP: 94 mg/l, D-dimer: 1.39 mg/l	Trop I: 102 ng/L, NTpro BNP: 2451 ng/l	N/R		55%	Left atrial enlargement, global left ventricular hypkinesia, myocardial edema with ejection fraction of 20%	N/R
Asif and Ali[65]	P1: N/R, P2: N/R	P1: 0.17ng/ml. P2: 1.6 ng/ml	P1: B/L Diffuse opacity, P2: B/L Diffuse lung opacity	P1: ST- elevation in lead I, aVL and V1-V4 T wave change, P2: ST- elevation in lead V2-V6 and Q waves in lead V4-V6	P1: 70%, P2: 65%	P1: No regional wall abnormalities, P2: No regional wall abnormalities	N/R
Khalid et al[66]	P1: CRP: 8.5 mg/L, D-dimer: 0.73ug/mL, ESR: 29mm/h, Ferritin: 559 ng/mL. P2: Normal	P1: Troponin-I(116 ng/mL), P2: Troponin-I(2.7 ng/mL), NT pro- BNP(2917) pg/ml	P1: N/R, P2: N/R	P1: Sinus Rhythm,inferioposterior infarct without ST-elevation. P2: Sinus tachycardia, low amplitude QRS, and poor R- wave progression	P1: EF = 45% . P2: EF = 25%	P1: N/R, P2: N/R	N/R
Ng et al[67]	Elevated CRP: 4, WBC: 4	Elevated Troponin: 7 patients	N/R	14 patients have ECG changes for Myocardial injury	N/R	14 patients have abnormal CMR finding (High T1 and /or T2, +/- no ischemic LGE)	N/R
Jirak et al[68]	C-reactive protein: 27.5 ± 12.2 mg/dl, CK levels: 518 U/L, D-dimer: 6720 ng/ml, Procalcitonin: 1.59 ng/ml WBC count: 14820/μl	Troponin: 354 ng/L CK-MB: 22 U/L NT-proBNP: 811 pg/ml	35 Patient shownCardiomegaly (46%), 26 Patient shown Pulmonary venous congestion (34.2%)	N/R	24 patient shown LVEF, Pericardial effusion in 3 patients.	N/R	N/R
Yan et al[69]	CK levels: 80 U/L, Creatinine: 0.72-0.92 mg/dl, Ferritin: 975ng/ml[Male] 748 ng/ml [Female], ESR: 35 mm/h, Procalcitonin: 5850/μl, D-dimer: 1.43ng/ML	Troponin: 6.9 ng/L, CK-MB: 1.2 ng/ml, NT-proBNP: 221 pg/ml	N/R	N/R	N/R	N/R	N/R
Kunal et al[70]	D-dimer = 84.2% (elevated)	Troponin T = 0.66 ± 1.28 ug/L, CK-MB(U/L) = 55.7 ± 30.1	N/R	ST- T change = 32.1%, Max QTc = 457.37 ± 32.7	N/R	N/R	N/R

Table 3. In-Hospital Management, Complications, and Outcomes of Patients.

Authors	In-hospital management	Complications	Outcomes
Cizgic et al[13]	Furosemide, angiotensin converting enzyme (ACE) inhibitor and, beta-blocker along with Covid-19 specific therapy	ARDS	Transfer red back to Covid19 center
Yokoo et al[14]	Antibiotics, steroids	—	Discharged
Pietsch et al[15]	N/A	N/R	N/R
Pavon et al[16]	Piperacillin-tazobactam, catecholamine, Intubated	N/R	Discharged
Khatri et al[17]	Hydroxychloroquine (400 mg twice on the first day, succeeded by 200 mg twice a day for 4 days), IV azithromycin, IV vancomycin, IV cefepime, and methylene blue infusion, IV methylprednisolone (200 mg/d) on 3 day, dobutamine, vasopressin, and norepinephrine	Cardiogenic and distributive shock, with multi-organ failure	Died on day 4
Hussain et al[18]	Remdesivir, hydroxychloroquine and azithromycin, and Indomethacin 7th day, methylprednisolone and colchicine, mechanical ventilation	ARDS on 2nd day	N/R
Dalen et al[19]	IV fluids, norepinephrine, and dobutamine	Cardiogenic shock	Recovered
Zeng et al[20]	High-flow oxygen, lopinavir-ritonavir, interferon α-1b, immunoglobulin, piperacillin-tazobactam, and continuous renal replacement therapy, IV methylprednisolone, vasopressors used from day 26, ECMO on day 11	Cardiogenic shock on day 11, Septic shock on day 26, ARDS day 1	Passed away on day 33
Doyen et al[21]	Aspirin, fondaparinux, IV hydrocortisone for 9 days, Mechanical ventilation	ARDS	Discharged from ICU after 3 weeks
Faircloth et al[22]	Norepinephrine, vasopressin, dobutamine, and methylprednisolone	—	Discharged
Coyle et al[23]	Hydroxychloroquine, azithromycin, ceftriaxone, and tocilizumab, IV methylprednisolone 500 mg daily x 4 days, followed by decreasing dose and, colchicine, milrinone day 4, norepinephrine day 4, mechanical ventilation on day 3	ARDS on day 3, Cardiogenic shock on day 4	Discharged on day 19
Luetkens et al[24]	N/R	N/R	N/R
Jain et al[25]	Vasoactive drugs, vancomycin and cefepime, IVIG, pulse dose steroids, and mechanical ventilation.	Cardiogenic shock and multi-organ failure	Discharged on day 46
	Renal replacement therapy for acute kidney injury and N-acetylcysteine for acute liver injury,	NA	NA
Mustafa et al[26]	Aspirin, unfractionated heparin and nitroglycerin infusion for acute coronary syndrome. Azithromycin and hydroxychloroquine	N/R	Improvement in symptoms over the next few days
Mansoor et al[27]	Vancomycin, meropenem, chloroquine, and azithromycin, norepinephrine, phenylephrine, vasopressin, diuretics, and subcutaneous heparin	Multi-organ system failure and pulseless electrical activity.	Mortality on day 6 in ICU
Al-assaf et al[28]	Enoxaparin, amlodipine, and scheduled a permanent pacemaker implant.	—	Discharged in stable condition.
Khalid et al[29]	Tocilizumab (2-dose of 480 mg and 240 mg), intravenous immunoglobulin (25 g for 5 days), ceftriaxone, cefdinir, and cefepime, norepinephrine, Intubated	Cardiogenic shock, ARDS	Recovered
Inciardi et al[30]	Hydroxychloroquine (200 mg 2 times a day), lopinavir/ritonavir (250 every 12 h), kanrenone (50 mg), furosemide(25-50 mg), and bisoprolo(2.5 mg)l, IV methylprednisolone 1 mg/kg for 3 days, dobutamine	Cardiogenic shock on day 1	Recovered
Fried et al[31]	Intraaortic baloon pump was inserted and dobutamine infusion	Cardiogwnic shock	Discharge
Wehit et al[32]	Ampicillin/sulbactam, liponavir/ritonavir and hydroxychloroquine, orotracheal intubation and mechanical ventilation	On day 15, bacteraemic sepsis and multi-organ failure	Patient was still in the intensive care unit
Butler et al[33]	Rehabilitation	N/R	N/R
Lagana et al[34]	Methyl prednisolone (100%), Ace Inhibitor (75%)	Cardiogenic shock (33.33%)	3(25%)
Kallel et al[35]	Oxygen therapy with a high concentration mask (10 litters/minute) for acute respiratory failure on admission. Dobutamine (5 γ/kg/min) and noradrenaline (3 mg/h). One dose of 80mg of Tocilizumab), corticosteroid, and azithromycin; (500mg the first day then 25 mg/day for 4 days).	N/R	Discharged 7 days later in-patient management
Fath et al[37]	Aspirin and ticagrelor, along with the heparin infusion and inotropic support with norepinephrine, vasopressin, and dobutamine for acute coronary syndrome.	Cardiac arrest	Died
Dabbagh et al[38]	Hydroxychloroquine, glucocorticoids, and colchicine; Intubated.	—	Discharged
Irabien-Ortiz et[39]	Immunoglobulins (80 mg/day), interferon-B (0.25 mg every 48 h) and ritonavir/lopinavir, IV methylprednisolone 500 mg daily at decreasing doses for 14 days, and norepinephrine, ECMO	Cardiogenic shock on day 1	N/R
Albert et al[40]	Tocilizumab, Methyprednizone, IV immunoglobulin, Inotropes, ECMO.	—	Discharged
Escher et al[41]	Cyclophosphamide and steroids.		Recovered
Ford et al[42]	Amiodarone load, ceftriaxone/azithromycin, tissue plasminogen activator, warfarin.	—	Recovered and discharged
Gauchotte et al[43]	Vasopressors, Inotropic support, ECMO, intubation.	N/R	Deceased at 6th day of hospitalization
Hua et al[44]	Vasopressors	Cardiogenic shock day 1	Recovered
Jacobs et al[45]	Hydroxychloroquine, azithromycin, noradrenaline, adrenaline, and dobutamine	Refractory shock	Died
Labani et al[46]	N/R	—	Recovered and discharged
Spano et al[47]	N/R	N/R	N/R
Tavazzi et al[48]	Adrenaline (0.07 μg/kg/mi n), and noradren aline (0.1 μg/kg/mi n), ECMO and IABP	Cardiogenic shock on day 1 and septic shock	Died

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Table 3. (continued)

Authors	In-hospital management	Complications	Outcomes
Trogen et al[49]	Hydroxychloroquine, piperacillin/tazobactam, enoxaparin	Septic shock	Discharged
Varga et al[50]	N/R	N/R	Died
Warchoł et al[51]	Azithromycin, oseltamivir, magnesium, and amiodarone	N/R	N/R
Sardari et al[52]	Bisoprolol and lisinopril	Plueritic chest pain	N/R
Dahl et al[53]	Cefotaxime, clindamycin,3 L/min- oxygen, Furosemide, norepinephrine, Continuous positive airway pressure	respiratory distress,right side bell's palsy	Discharged on day 11
Hu et al[54]	methylprednisolone,immunoglobulin,norepinephrine,toracemide,furosemidemilrinone,piperacillin,sulbactam, pantoprazole	cardiogenic shock and pulmonary infection	Discharge
Volis et al[55]	N/R	Pleuritic chest pain, dyspnea	Discharge
Besler et al[56]	Hydroxychloroquine, azithromycin, ceftriaxone, tigecycline, favipiravir, colchicine	chest pain	Discharged on day 7
Gaine et al[57]	Diuretics, rate-control agents, anticoagulants, ACE inhibitor, mineralocorticoid antagonist	Heart failure	discharge
Sheikh et al[58]	Metoprolol, lisinopril, low-dose aspirin, hydrochlorthiazide, desmopressin	Diabetes insipidus	Discharge
Salamanca et al[59]	Dobutamine, norepinephrine, methylprednisolone, tocilizumab, hydroxychloroquine, azithromycin, lopinavir-ritonavir, temporary pacemaker, extracorporeal membrane oxygenation, intra-aortic balloon pump	Cardiogenic shock	Discharge
Naneishvili et al[60]	Methylprednisolone, dobutamine, amiodarone, milrinone, norepinephrine, antibiotics	cardiogenic shock	Discharge
Kim et al[61]	N/R	N/R	N/R
Nikoo et al[62]	Amiodarone, dexamethasone, standard heart failure therapies (details n/r),therapeutic anticoagulation, temporary pacemaker	Cardiogenic shock	Discharge
Long ma et al[3]	NA	NA	NA
Sala et al[63]	Lopinavir, Hydroxychloroquine	Chest Pain, dyspnoea	Discharge
Yuan et al[64]	N/R	Chest Pain	Discharge
Warchol et al	Azithromycin, oseltamivir	Hemodynamically unstable	N/R
Asif and Ali[65]	P1: Aspirin, clopidogrel and heparin, azythromycin, hydroxychloroquine, tocilizumab, merooenum, norepinephrine. P2: Azythromycin, tocilizumab, nor epinephrine, midazolam	P1: ARDS, P2: ARDS	P1: Died, P2: ICI
Khalid et al[66]	P1: Aspirin, clopidogrel and diuretics P2: Methylprednisone, colchicine	P1: N/R. P2: Refractory shock	P1: Discharge, P2: Discharge
Ng et al[67]	N/R	N/R	N/R
Jirak et al[68]	Catecholamine, extracorporeal membrane oxygen therapy, Antibiotics.	ARDS,	N/R
Yan et al[69]	N/R	N/R	N/R
Kunal S et al[70]	Hydroxychloroquine, Azithromycin	N/R	57.% Died

majority of patients. complications during in-hospital stay included 66.4% patients acquiring ARDS and 14% with cardiogenic shock, in addition to others. Overall, 64.7% patients survived. A summary of the findings obtained is depicted in Figure 3.

Pirzada et al[79] elucidated the features of myocarditis found during the initial waves of the COVID-19 pandemic. The authors write that while the exact pathophysiology of severe COVID-19 was still elusive, a consistent observation of the pro-inflammatory surge, namely the cytokine storm was made.[79] Observations of elevated interleukins (IL-2R, IL-6, IL-10, TNF- α) were presented in a single-center cohort.[80] Viral myocarditis may be considered a direct response of autoimmunity, inflammation, or both.[81] Based on a cohort of 416 patients at the Renmin Hospital of Wuhan University conducted from January 20, 2020 until February 10, 2020, 82 (19.7%) patients had cardiac injury.[82] The cardiac involvement in the cohort of patients had a hazard ratio of 4.26, which is notably high.[82] Mortality in the myocardial injury group versus the general group was significantly higher (51.2% vs 4.5%, $P < .001$).[82] The symptoms of myocarditis among COVID-19 patients range from mild symptoms such as chest pain, fatigue, and palpitations to life-threatening symptoms such as sudden cardiac death associated with ventricular arrythmia or cardiogenic shock. Classically, myocarditis has a viral prodrome including myalgias, fever, and gastrointestinal/respiratory symptoms, with ranges of 10% to 80%.[79]

Sawalha et al[83] identified COVID-19 related myocarditis focusing on management and outcomes until June 30, 2020, including a total of 14 cases. The authors found a male predominance (58%), with a median age of 50.4 years.[83] One thirds of all cases were younger than 40 years, and a majority of patients did not have comorbidities (50%), but among those that did have pre-existing conditions, hypertension was the most prevalent (33%).[83] Among the 14 patients, dyspnea/shortness of breath were the most common presenting features (75%), in addition to fever (75%).[83] On noting the hemodynamic status, 64% patients were in shock, of which 71% of the patients had cardiogenic shock, whereas 29% had a mixed septic and cardiogenic shock.[83] Around 42% of the patients had acute respiratory distress syndrome or developed it during the in-hospital period.[83] ECG findings were variable with ST-segment depression, ST-segment elevation, and T wave inversion occurring at 25% each.[83] Troponin was elevated in 91% of the cases, whereas pro-BNP and CK-MB were less frequently checked.[83] Among the 14 patients, echocardiography was performed in 83% of the case and 60% had a reduced ejection fraction.[83] Cardiac tamponade was reported in 20% of all echocardiograms, where diffuse hypokinesis was prevalent among 30% patients.[83] None of the patients had obstructive coronary disease. Around 50% patients required vasopressor support, with 25% of them warranting inotropic support.[83] Mechanical ventilation was utilized for 17% of the patients, of which ECMO was the most commonly used modality.[83] Many treatment modalities were used to manage myocarditis of which glucocorticoids (58%) were mostly used, followed by immunoglobulin therapy (25%) and colchicine (17%). Therapies to mitigate cytokine storm were interferon and tocilizumab (17% each).[83] Sawalha et al[83] found that 81% survived to discharge whereas 19% did not survive; the patients who did not survive were noted to have both myocarditis and ARDS.

Castiello et al[84] identified 38 case reports of COVID-19 patients with myocarditis based on the WHO/IFSC or ESC criteria. Around 45% of the cases had fever or a mild temperature increase; 21.1% had gastrointestinal symptoms, and 10.5% had a presenting or previous syncope.[84] Troponin levels varied substantially whereas BNP was raised in 57.9% patients. ECG findings were normal in 10.5% patients with variations among the rest.[84] Of 34 patients, only 18.4% patients had no functional or structural abnormality.[84] On noting CMR findings, myocardial inflammation and diffuse edema were captured in 50% patients.[84] EMB was performed only in 21.2% patients, where only 1 case reported the presence of SARS-CoV-2 in the cardiomyocytes.[84] Histological data obtained from autopsies were available for 10.5% patients, of which inflammatory infiltrates, accumulated inflammatory cells in the endothelium and signs of ferroptosis were noted.[84] The medical treatment was variable ranging from hydroxychloroquine (26.3%), tocilizumab (10.5%), lopinavir/ritonavir (7.9%), antibiotics (36.8%), steroids (34.2%), heart failure medications (36.8%), and anticoagulants (21.1%). Of 33 cases with reported outcomes, 84.8% patients survived, whereas 15.2% did not survive.[84]

Rathore et al[8] present recent data, until January 5, 2021, of 42 patients with myocarditis and COVID-19, with 71.4% being males, and with a median age of 43.4 years. Hypertension was the most common finding in these patients, where cardiac biomarkers BNP and troponin were raised in 87% and 90% of the patients respectively.[8] ECG findings were nonspecific with T-wave and ST-segment changes noted. Echocardiogram commonly showed ventricular systolic dysfunction with cardiomegaly.[8] The commonest histopathological feature was diffuse lymphocytic inflammatory infiltrates.[8] Moreover, corticosteroids and antivirals were most frequently used. Around 40% of the patients required vasopressor support.[8] Of 41 patients, 67% survived, whereas 33% died.[8] Due to the sudden risk of worsening patient conditions and associations with myocarditis, knowledge of this cardiac complication due to COVID-19 is critical for healthcare workers across all settings. Kamarullah et al[85] also conducted a search until January 2021 where 18 patients were included. The findings were suggestive of the beneficial effects of corticosteroids in treating myocarditis associated with COVID-19; the most commonly applied

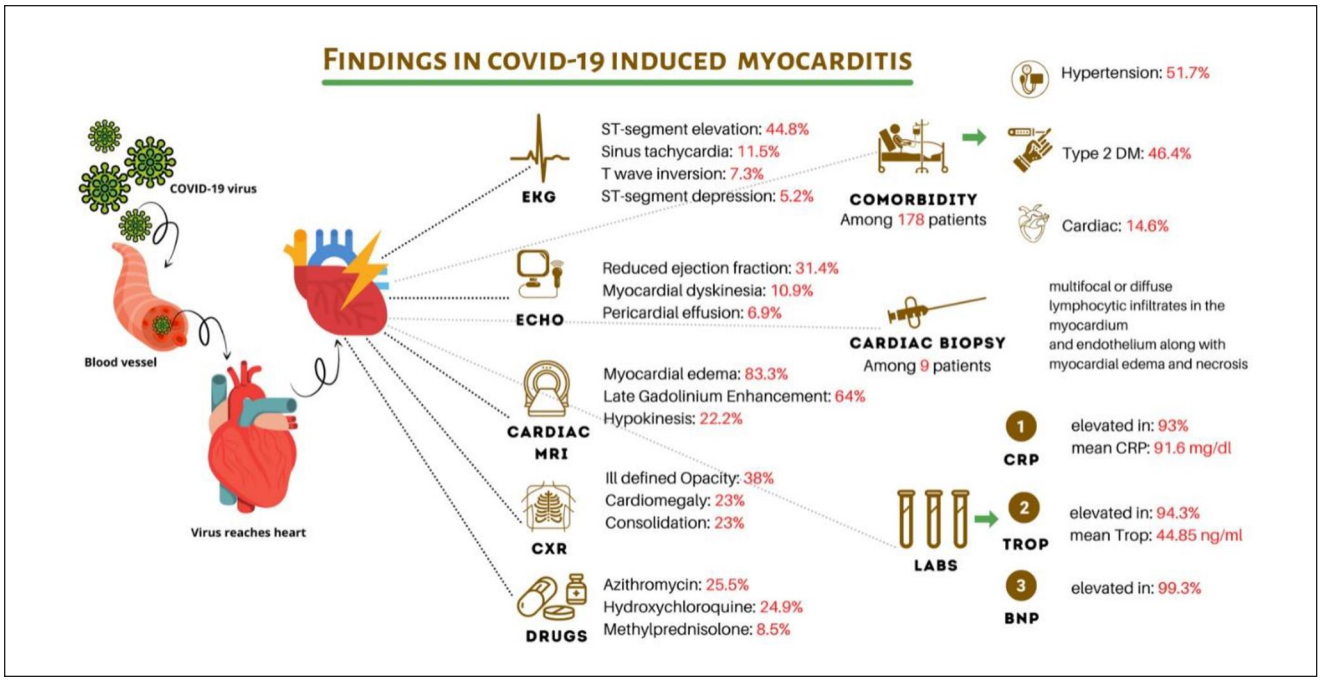

Figure 3. A summary of COVID-19 infection induced myocarditis.

steroids were hydrocortisone (5.5%), methylprednisolone (89%), and prednisolone (5.5%), with the intravenous route being the most common and duration of treatment ranging from 1 to 14 days.[85,86]

Strengths and Limitations

This systematic review synthesizes the most recent evidence of COVID-19 infection and myocarditis, until August 31, 2021. Published literature obtained during the systematic search presents data collected until January 2021, enabling our collated findings, obtained until August 2021, to be a critical piece of information for healthcare workers worldwide. We present key findings about demographics, COVID-19 and myocarditis symptomatology, essential diagnostic techniques of use to clinicians, and clinical outcomes of interest of COVID-19 infection and myocarditis. The findings further strengthen the benefits of evidence-based healthcare where we gather evidence from reliable published literature to inform healthcare decisions, and reduce variations in healthcare delivery during the COVID-19 pandemic.

This systematic review has certain limitations. First, COVID-19 and myocarditis symptomatology may be overlapping, suggesting difficult clinical demarcations. Second, COVID-19 infections compounded with myocarditis were expected to be underreported as patients who did not previously have comorbidities presented with newly diminished ejection fractions and elevated myocardial markers. Thirdly, our systematic review presents that a low proportion of patents had confirmed myocarditis via MRI/endomyocardial biopsy. A plausible reason was the fear of contracting COVID-19 infection on undergoing MRI/endomyocardial biopsy. Fourthly, ECG and echocardiography were considered to be reliable screening tests, but not diagnostic tests, except for pericardial effusion. Lastly, while biomarkers such as troponin, BNP, and CK-MB were useful in diagnosing myocarditis, they are non-specific because the levels may also rise in other conditions such as demand ischemia and acute heart failure.

Conclusion

This systematic review presents findings about demographics, symptomatology, diagnostic techniques, and clinical outcomes of adult COVID-19 patients with myocarditis. A total of 229 patients were included in this analysis, who were diagnosed with myocarditis. The patients commonly presented with fever, cough, and shortness of breath making the clinical presentations difficult to differentiate. Elevated inflammatory and cardiac marker in addition to ECG and echocardiographic findings were useful indicators of myocardial disease. Gold standard testing such as MRI and endomyocardial biopsy were under-utilized suggesting that a definitive diagnostic approach may be required for those patients who fall under a high risk of suspicion for COVID-19 induced myocarditis. Due to the peaked risk of death among patients contracting both

ARDS and myocardial inflammation, it is essential that healthcare workers are aware that myocarditis may be associated with COVID-19 infections. While the treatment approaches were variable across the cohort of patients included in this systematic review, further large-scale randomized controlled trials may help in establishing the best care of treatment for those with a definitive diagnosis of myocarditis with COVID-19.

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