Title: Myocarditis associated with Covid-19 disease: a systematic review of published Case reports and Case series

Abstract

Background:

Covid-19 is an extremely contagious illness caused by the severe acute respiratory syndrome (SARS-CoV-2) virus. Although this disease primarily involves pulmonary tissue, rapidly advancing research has established cardiac involvement in Covid-19 patients.

Objective:

This systematic review article aimed to compile and illustrate clinical characteristics, diagnostic findings, management, and outcomes manifesting in myocarditis linked with Covid-19.

Methods:

A literature search was accomplished for published eligible articles with MEDLINE/PubMed and Embase databases. All eligible case reports and case series were included from around the world without any language restrictions. For this review, inclusion criteria were laboratory-confirmed SARS-CoV-2 infection cases reporting a diagnosis of acute myocarditis.

Results:

Data from 41 studies describing myocarditis in 42 Covid-19 patients was obtained. The median age of these patients was 43.4 years, with 71.4% of them being male. Fever was the

most prevalent presenting symptoms seen in 57% of patients. Hypertension was the most pervasive comorbidity accompanying these patients. Cardiac biomarkers troponin and Brain natriuretic peptide (BNP) were raised in almost 90% and 87% of patients, respectively. Electrocardiogram findings were Non-specific and included ST-segment and T-wave changes. Echocardiogram commonly showed left ventricular systolic dysfunction with increased heart size. Cardiac magnetic resonance (CMR) imaging exhibited myocardial edema and injury. The most prevalent histopathological feature appreciated was diffuse lymphocytic inflammatory infiltrates. Antivirals and corticosteroids were the most frequently used medications. About 38% of patients also needed vasopressor assistance. Out of 42 patients, 67% recovered, and eight died.

Conclusion:

Due to the risk of a sudden worsening of patients conditions and myocarditis association with considerable mortality and morbidity, a knowledge of this cardiac complication of Covid-19 disease is crucial for healthcare professionals.

Keywords: Covid-19; Myocarditis; Heart; SARS-CoV-2; Cardiac magnetic Resonance Imaging; Corticosteroid

Abbreviations: Covid-19, coronavirus disease 2019; SARS-CoV, severe acute respiratory syndrome coronavirus; ECG, Electrocardiogram; CMR, Cardiac magnetic resonance imaging; EMB, Endomyocardial biopsy; RT-PCR, Reverse transcription polymerase chain reaction

Review criteria

- A literature search was accomplished for published eligible articles with MEDLINE/PubMed and Embase databases.
- The scanning was focused on unique keywords and accomplished for articles published from December 2019 till January 5, 2021.
- The study selection and data extraction embodied in the methodology section. section.

Message for the clinic

- Hypertension seems to be the most pervasive comorbidity accompanying Covid-19 associated myocarditis.
- Electrocardiogram findings in these patients are non-specific and included ST-segment and T-wave changes. Left ventricular systolic dysfunction seems to be a common finding on the echocardiogram.
- Due to the risk of a sudden worsening of patients conditions in these group, knowledge of this cardiac complication of Covid-19 disease is crucial for healthcare professionals

INTRODUCTION

In December 2019, a new infectious pathogen known as a severe acute respiratory syndrome (SARS-CoV-2) came into sight in China. It was linked with an unexplained cause of pneumonia. The disease was later coined as coronavirus disease 2019 (Covid-19).[1] Subsequently, this disease has quickly disseminated across the globe. On March 11, the World Health Organisation (WHO) announced this disease as a pandemic, owing to its asymptomatic transmission, elevated infectivity, and high mortality risk among the elderly and the immunocompromised.

The clinical manifestation of COVID−19 differs considerably, fluctuating from minimum symptoms to critical respiratory failure, septic shock, subsequently to multiorgan failure. Although this disease primarily involves pulmonary tissue, quickly advancing research has established cardiac involvement in Covid-19 illness. In a cohort study from China, Shi et al. reported cardiac injury in 19.7% of patients out of 416 hospitalized for Covid-19.[2] A recent meta-analysis of 16 studies and 2224 patients reported cardiac injury incidence in 24.4% of hospitalized patients.[3] The portion of this cardiac injury seen in Covid-19 patients believed to be myocarditis.

Acute myocarditis is stated as inflammation of the myocardium with recent-onset established by clinical features or histopathological criteria. It may be caused by infection, medication toxicity, or excessive immune activation.[4] Viral infection remains a common etiology behind myocarditis in the developed world, but in developing countries bacterial infection, rheumatic fever and *Trypanosoma cruzi* are still the prevalent causes of myocarditis.[5] Parvovirus B19, adenoviruses, and enterovirus are the conventional viral causes of myocardial inflammation.[6] However, growing research on Covid-19 disease has described the incidence of acute myocarditis in the form of case reports and case series with a deficit of any large-scale study.

Since myocarditis often leads to severe heart failure, cardiogenic shock, and refractory arrhythmias, and is associated with considerable mortality and morbidity, a knowledge of myocarditis as a complication of Covid-19 disease is crucial for healthcare professionals. This review article aims to compile and illustrate clinical characteristics, diagnostic findings, management, and acute myocarditis outcomes manifesting in Covid-19 patients.

METHODS

This systematic review is concluded and reported in conjunction with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[7]

Search strategy:

A literature search was accomplished for eligible articles published from December 2019 till January 5, 2021 with MEDLINE/PubMed and Embase databases. Subsequent search strategy was used , (([coronavirus] or [Covid-19] or [SARS-CoV-2] and [myocarditis] or [myopericarditis] or [cardiomyopathy] or [myocardial inflammation] or [myocardial injury] or [Myocardium])). The eligibility for the case report was determined in accordance with the title and the abstract. For additional qualifying reports, reference lists of included studies and related literature were manually checked. PRISMA flow diagram is illustrated in figure 1.

Eligibility Criteria:

All eligible case reports and case series were included from around the world without any language restrictions. For this review, inclusion criteria were laboratory-confirmed SARS-CoV-2 infection cases reporting a diagnosis of acute myocarditis. Articles like review articles, hypothesis articles, and commentaries were discarded.

Study selection and quality assessment:

The title and abstract of studies from formerly investigated databases were evaluated by three authors (S.P., N.K., N.K.A). These authors ascertained studies based on predetermined eligibility criteria. Quality appraisal for included case reports and case series was done with help of a tool established by Murad et al.[8] With aid of this tool, three authors (R.S., U.T.B., Q.W.) analyzed all studies taking into consideration four aspects which are selection, ascertainment, causality, and reporting. Studies were graded as good, fair, and poor quality.

Data extraction:

From these selected studies, three authors (S.S.R., G.A.R., M.S..) retrieved data manually. For every report, subsequent details were extracted, author, country of origin, study design, sample size, mean age, past history, presenting symptoms, physical examination at admission, laboratory findings, electrocardiogram findings(ECG), echocardiogram findings, cardiac magnetic resonance imaging (CMR) findings, endomyocardial Biopsy (EMB) findings, in-hospital treatment, complication, and outcomes.

RESULTS

In this review, 42 patients reported to be diagnosed with acute myocarditis were included from 41 published studies.[9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49] The median age of included patients was 43.4 years (which ranged from the infant of 2 months old to 81 years old patient), with 28.6% of them being female. Most of the reported cases were from Europe(22 patients,52.4%), followed by the Americas (14 patients, 33.3%) and Asia (6 patients, 14.3%). Table 1 compiles the patient demographic and clinical characteristic features of each case.

Fever was the most prevalent presenting symptoms seen in 57% of patients, followed by dyspnea(52.4%), cough(40.5%), Chest pain(28.6%), vomiting, and diarrhea(28.6%). Other atypical symptoms observed were neck pain, [14,29] rash,[46,49,] and conjunctivitis.[46] More than half of the patients(53.7%) did not have any remarkable past history. In the patients having any comorbidities, hypertension(26.2%) and obesity(9.7%) were the most common. Peculiar

past history witnessed was lymph node tuberculosis,[18] Pulmonary sarcoidoses,[25] spondylolysis,[29] and Pityriasis lichenoides chronica.[49]

Diagnostic findings:

The most prominent etiology behind acute myocarditis is viral infections. Several cases of acute myocarditis associated with Covid-19 have been described around the globe and are diagnosed in multiple ways. Taking into consideration serology, leukocytosis with neutrophilia and lymphopenia was found in many patients. Cardiac biomarkers troponin and N-terminal (NT)-prohormone BNP (NT-proBNP) were elevated in almost 90% and 87% of patients, respectively. Similarly, the level of inflammation-related markers such as C-reactive protein, D-dimer, IL-6, procalcitonin was significantly increased, indicating an inflammatory process in the body. Table 2 summarizes laboratory findings, serology, Electrocardiogram(ECG), and Echocardiogram findings.

***Electrocardiogram(ECG) findings*:** ECG was normal in 4 patients.[28,31,34,42] In other patients, electrocardiogram findings were variable and ranged from sinus tachycardia(12 patients), ST-segment elevation(14 patients), T-wave inversion(12 patients) and ST-depression in 7 patients. In a few cases, arrhythmia was also reported, which included Atrial fibrillation,[8] multiple premature ventricular complexes,[21] and Supraventricular tachycardia.[26]

***Echocardiogram findings*:** Echocardiogram was done in 35 patients, of which 74% of patients exhibited decreased left ventricular ejection fraction(LVEF). Mean LVEF in these patients equaled 37%. Other features observed were Left Ventricular(LV) hypokinesia (37.2% patients), LV dilation (8.5% patients), and pericardial effusion (26% patients). In some cases, the pericardial effusion of upto 11 mm was also identified.[12,28] Other features

described were mitral regurgitation,[16,36] increased left ventricular wall thickness,[17,48] and right ventricular (RV) enlargement.[35,36]

Cardiac magnetic resonance (CMR) findings: CMR is the non-invasive gold standard technique for diagnosing myocarditis. It was reported in 21 patients out of 42 cases we studied. Common findings appreciated were T2-weighted images demonstrating myocardial edema and subepicardial late gadolinium enhancement indicative of myocardial injury leading to necrosis and fibrosis.

Histopathological findings: Endomyocardial Biopsy (EMB) and autopsy findings were reported in four and two patients respectively. Diffuse lymphocytic inflammatory infiltrates with interstitial edema and foci of necrosis were commonly observed findings. In one case, viral particles were seen in the interstitial cell, and another case reported SARS-CoV-2 RT–PCR positivity in the cardiac tissue.[30,32] Table 3 summarizes fundamental Cardiac magnetic resonance (CMR) findings and important histopathological hallmarks observed in acute myocarditis patients.

Management and outcomes:

Medication used for management were aimed against SARS-CoV-2, control of myocarditis, and treatment of heart failure associated with it. The most frequent drugs targeted against SARS-CoV-2 were Hydroxychloroquine(32.5% patients), Azithromycin(19%), and Antibiotics(32.5%). Common medications given for myocardial inflammation were corticosteroid(32.5%), IV immunoglobulin(19%) and colchicine (11%). About 38% of patients needed vasopressor assistance and 22% required inotropic (mostly dobutamine and milrinone) support. Tocilizumab and interferon-beta were also used in some patients. Taking

into consideration mechanical support, five patients required each intubation and mechanical ventilation while four patients were supported by extracorporeal membrane oxygenation (ECMO). Table 4 compiles management, complications, and outcomes in Covid-19 patients diagnosed with acute myocarditis.

Out of 42, around 67% (28 patients) recovered or were discharged. Six patients died due to various complications. The fate of 8 patients (19%) remained unprecedented. Table 5 summarizes composite characteristic features across all cases.

DISCUSSION

The impact of the SARS-CoV-2 pandemic is catastrophic, as it has healthcare, financial and social influences on millions around the world. Asymptomatic transmission, high infectivity, and droplet infection render management of this virus a horrible task. Although this disease primarily involves pulmonary tissue, quickly advancing research has established cardiac involvement in Covid-19 disease.[2,3] The portion of this cardiac injury seen in Covid-19 patients believed to be myocarditis. Since these patients exhibit common symptoms such as fever, shortness of breath, and chest pain symptoms as observed in other Covid-19 patients without myocarditis, diagnosing this complication becomes daunting for the physician. Besides these common symptoms, other symptoms identified in this review were vomiting, diarrhea, and myalgia.

Hypertension seems to be the most prevalent risk factor for myocardial injury in Covid-19 disease. It was reported in 58% of individuals with cardiac injury in a recent meta-analysis by Zou et al.[3] In most of the studies, Cardiac biomarkers troponin and N-terminal (NT)-prohormone BNP (NT-proBNP) were elevated, which is consistent with findings observed in myocarditis due to any other cause. Guo et al. reported an increased cardiac markers level in

critically ill patients with severe Covid-19 disease, possibly suggestive of the increased extent of myocardial injury.[50] However, the lack of elevated cardiac biomarkers does not preclude myocarditis as observed in some of the studies we reviewed.

On, electrocardiogram ST-Segment abnormalities were observed in 53% of patients we reviewed; other than that, T-wave inversion was another common anomaly observed on ECG. These non-specific and highly variable ECG findings are homogenous with non-specific ECG findings in myocarditis reported previously in the literature.[51] ECG may provide a cost-effective, fast, and non-invasive technique to diagnose myocarditis at initial stages. The bulk of patients in this review exhibited reduced left ventricular ejection fraction and pleural effusion on echocardiogram. Echocardiography is an essential part of myocarditis diagnostics that helps assess LV function and eliminate other causes of heart failure.[52,53] Despite the fact that non-specific findings are seen on echocardiograms in myocarditis, a comprehensive review of the results may help to indicate a diagnosis, initial management, and to evaluate prognosis.

Cardiac magnetic resonance imaging (CMR) is an essential myocarditis diagnostic test in particular in cases where endomyocardial biopsy is not or cannot be obtained. In this systematic review, Cardiac magnetic resonance imaging exhibited myocardial edema and injury, and these findings are consistent with CMR findings reported previously in the literature.[54] In eight cases, myocarditis was diagnosed on the basis of Lake Louise Criteria, which defines Cardiac magnetic resonance (CMR) based guidelines for the diagnosis of myocarditis.[14,16,17,24,27,31,38,48,55] Diagnosing myocarditis with help of Lake Louise Criteria has 91% specificity and a sensitivity of 67%. CMR can be used as a primary diagnostic technique for screening Covid-19 associated myocarditis if there are no contraindications.[55]

Endomyocardial biopsy [EMB] remains the gold standard invasive technique in diagnosing myocarditis; however, due to the increased risk of infection, it is not done in Covid-19 patients. It was reported in a few studies in our systematic review. Diffuse lymphocytic inflammatory infiltrates with edema and foci of necrosis was a common finding appreciated in these biopsies. In one case, viral particles were seen in the interstitial cell, and another case reported SARS-CoV-2 RT–PCR positivity in the cardiac tissue suggestive of direct viral injury to the myocardium.[30,32] There is not a standard test or examination for myocarditis diagnosis; if it is suspected, the diagnosis would require a spectrum of various techniques.

Despite the fact that pathophysiology behind the myocardial injury in Covid-19 patient remains elusive, there are several proposed mechanism which includes;

1) Binding of SARS-CoV-2 virus through ACE2 receptors present on cardiac myocytes leading to direct myocardial injury

2) Systemic inflammatory response syndrome (SIRS) due to excess cytokine release arbitrated through pathologic T cells and monocytes.[57]

3) Higher metabolic requirements related to systemic infection and lower supply due to continued hypoxia cause injury to the myocardial system.[58]

4) Diffuse vasculitis and endothelial inflammation in the heart, primarily due to direct endothelial cell infection by virus or due to host immunologic response.[59]

SARS-CoV-2 invades the human cell via protein receptor angiotensin-converting enzyme 2 (ACE2). While this virus predominantly targets the respiratory tract, ACE2 expression has been detected by many human tissues, including the heart, gastrointestinal tract, kidney, and blood vessels.[60] This Binding of the SARS-CoV-2 virus through ACE2 receptors present in

heart tissue may be responsible for direct viral injury leading to myocarditis. In a study done during the SARS outbreak, SARS virus RNA was ascertained in the autopsy of heart specimens in 35% of the patients who died due to SARS.[61] A recent study by Nicin et al. found expression of ACE2 in cardiomyocytes, pericytes, fibroblasts, endothelial cells, and leukocytes. They also observed that an already diseased heart has increased expression of ACE2 receptor contrasted to healthy individuals.[62] In one of the cases we included, Tavazzi et al. reported viral particles in the interstitial cells of heart tissue on Endomyocardial Biopsy; similarly, another study by Kesici et al. detected SARS-CoV-2 RT–PCR positivity in the cardiac tissue.[30,32] These all evidence suggest that the SARS-CoV-2 virus may be directly involved in injury to heart myocytes.

Hyperactive immune responses in Covid-19 Patients may lead to the initiation of the cytokine storm. This excess release of cytokines may lead to myocardial injury. In a cohort performed on 138 patients, 10 patients developed an acute cardiac injury of which ICU admission was required in 8 patients. These patients requiring ICU admission had a higher level of D-dimer levels in contrast to the non-ICU patients suggesting the role of cytokine in cardiac injury.[63] Another cohort study by Shi et al. on 416 patients reported cardiac injury in 19.7% of patients. In contrast to patients without cardiac injury, these patients had a higher level of C-reactive protein, procalcitonin, suggestive of the inflammatory process responsible for myocardial injury.[2]

There is insufficient validation of the efficacy of existing management and treatment interventions for Covid-19 patients. Earlier, there was a dispute over the use of corticosteroids in COVID-19 disease. However, a recent meta-analysis of observational studies and randomized control trial RCTs has demonstrated the favorable outcome of short-term mortality and the decline of mechanical ventilation needs in Covid-19 patients on

corticosteroids.[64] In our systematic review, out of 12 patients with myocarditis on a corticosteroid, only two patients died; others all recovered. The European Medical Agency (EMA) has endorsed dexamethasone use for Covid-19 disease in adults and children from 12 years of age and weighing at minimum of 40 kg, and requiring oxygen supplementation.[65] This decision was backed by the result of the RECOVERY trial reporting decrease in 28 days mortality in Covid-19 patients who were receiving either invasive mechanical ventilation or solitary oxygen therapy at randomization and were treated with dexamethasone.[66] The United States Food and Drug Administration (US FDA) has recently approved Remedsivir for use in adults and children above the age of 12 years hospitalized with Covid-19 disease.[67] Although its use was not reported in any of the studies we reviewed, numerous RCTs have proved the beneficial effect of remedsivir, and hence it may use as a therapeutic option in Covid-19 patients even when presenting with Myocarditis as a complication.[68,69] Additional RCTs conducted on the use of few immunomodulatory drugs such as inhaled interferon-beta, baricitinib, tocilizumab, and sarilumab has reported clinical benefit.[70-72] As discussed earlier the role of the cytokine storm and hyperactivated immune system in causing the pathological effect of Covid-19, these immunomodulatory medications can be effective in these patients. An aggregate treatment with antiviral, corticosteroids with immunomodulatory therapy, and supportive care can be used until any large clinical trials on Covid-19 associated myocarditis prove efficacious.

In this systematic review, one of the limitations that must be taken into account is that since research related to Covid-19 and myocarditis is rapidly evolving, these reports are small-scale studies based on early restricted understanding, rather than large-size clinical trials, hence these data may not be decisive and relevant for the entire population. Further large-scale

studies addressing Covid-19 associated myocarditis and its clinical characteristics, diagnosis, and management are necessitated.

CONCLUSION:

This systematic review summarizes clinical features, diagnostic findings, management, and acute myocarditis outcomes associated with Covid-19. We confined 42 Covid-19 infected cases diagnosed with acute myocarditis. Since these patients exhibited common symptoms such as fever, shortness of breath, and chest pain symptoms as observed in other Covid-19 patients without myocarditis, diagnosing myocarditis in these patients becomes daunting for the physician. An elevated level of troponin and N-terminal prohormone of brain natriuretic peptide (NT-BNP), together with ECG anomalies, can trigger suspicion. Cardiac magnetic resonance (CMR) can aid in the diagnosis of myocarditis. Owing to the risk of a sudden worsening of the condition of patients, and due to myocarditis association with considerable mortality and morbidity, a knowledge of myocarditis as a complication of Covid-19 illness is crucial for healthcare professionals. Although research linking to Covid-19 disease and its compilation is expanding, there are many domains that still need to be investigated. Further large-scale studies, especially addressing the definitive diagnosis and management of myocarditis in Covid-19 patients, are warranted.

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Tables

Table 1: Patient demographic and clinical characteristic features

Author	Country	Study design	Covid-19 status (diagnostic technique)	Sample size	Age(years)/Sex (male or female)	Past medical history	Presenting symptoms	Physical examination findings on admission
Cizgici et al.[9]	Turkey	Case report	Positive(n/m)	1	78/M	Hypertension	Chest pain and shortness of breath	BP(systolic/diastolic)-115/79 mm Hg, HR-150 b/m
Hussain et al.[10]	USA	Case report	Positive(RT-PCR)	1	51/M	Hypertension	Dry cough, fatigue,dyspnea, and Covid-19 fever	Temperature-39.6 °C, RR-26 breaths/min, BP(systolic/diastolic)-141/89 mm Hg, HR-97 beats/min, Spo2-91%, Auscultation-bilateral wheezing and Ronchi
Coyle et al.[11]	USA	Case report	Positive(n/m)	1	57/M	Hypertension	Fevers, cough, diarrhea, myalgia, decreased appetite, dyspnoea	N/A
Auer et al.[12]	Austria	Case report	Positive(n/m)	1	42/F	Bariatric surgery for morbid obesity 6 years ago and occasional hypertension	Shortness of breath	BP(systolic/diastolic)-109/62 mm Hg , HR-75 b/m, Spo2-82%
Dabbagh et al.[13]	USA	Case report	Positive(RT-PCR)	1	67/M	Non-ischemic cardiomyopathy with LVEF of 40%	Cough, mild shortness of breath, and left shoulder pain	Temperature- 36.8°C, BP(systolic/diastolic)-118/82 mm Hg, HR-122 b/m, and RR-24 breaths/min
Nicol et al.[14]	France	Case report	Positive(serology)	1	40/M	obesity	Fever, odynophagia, and left neck pain	Temperature-39.9°C, BP(systolic/diastolic)-110/60 mm Hg, HR-123 b/m, and tonsillitis with cervical adenopathy

Hu et al.[15]	China	Case report	Positive(RT-PCR)	1	37/M	None reported	Chest pain, dyspnea, and diarrhea	BP(systolic/diastolic)- 80/50 mm Hg
Oberweis et al.[16]	Luxembourg	Case report	Positive(RT-PCR)	1	8/M	None	Fever, coughing, weight loss, and severe fatigue	Temperature-39.6°C), HR-138 b/m, BP(systolic/Diastolic)- 94/40 mm Hg
Inciardi et al.[17]	Italy	Case report	Positive(RT-PCR)	1	53/F	None	Severe fatigue, cough and fever week before	Temperature-36.6 °C, BP(systolic/diastolic)- 90/50 mm Hg, HR-100 b/m, Spo2-98%
Irabien-Ortiz et al.[18]	Spain	Case report	Positive(RT-PCR)	1	59/F	Hypertension, lymph node tuberculosdiagnosed by presence of erythema nodosum, and migraine	Fevers, squeezing chest pain	Temperature- 39.3°C, BP(systolic/diastolic)- 75/53 mm Hg, Spo2- 96%(with nasal cannula at 2 L/min)
Sala et al.[19]	Italy	Case report	Positive(RT-PCR)	1	43/F	None	Chest pain and dyspnea	Temperature- 37.7°C, BP(systolic/diastolic)- 120/80 mm Hg, HR- 79 b/m, Spo2-89% and decreased breath sounds at lung bases with Ronchi
Rehman et al.[20]	USA	Case report	Positive(RT-PCR)	1	39/M	None	Midsternal chest pain	N/A
Kim et al.[21]	Republic of Korea	Case report	Positive(RT-PCR)	1	21/F	None	Fevers, productive cough, shortness of breath, diarrhea	N/A
Zeng et al.[22]	China	Case report	Positive(RT-PCR)	1	63/M	Allergic cough, smoking	Productive cough, fever, shortness of breath, exertional chest tightness	Temperature-39.3°C , Spo2-91%

Radbel et al.[23]	USA	Case report	Positive(RT-PCR)	1	40/M	None	Fever, dry cough, dyspnea on exertion	Temperature-39.4°C
Yuan et al.[24]	China	Case report	Positive(RT-PCR) detected in stool	1	33/M	Hypertension	Chest pain, fever, myalgias	Temperature-37.3 °C, BP(systolic/diastolic)-115/79 mmHg, HR-121 b/m, RR- 18 breaths/minutes
Pavon et al.[25]	Switzerland.	Case report	Positive(RT-PCR)	1	64/M	Pulmonary sarcoidosis and epilepsy	Chest pain and dyspnea.	Temperature- 39.3°C
Juusela et al.[26]	USA	Case series	Positive(RT-PCR)	2	1. F, pregnant(39 weeks) 2. F ,Pregnant (33week)	1st patient.Obesity, gestational diabetic 2nd .Obesity, polycystic ovary syndrome	1st patient: Contractions and vomiting 2nd patient: Shortness of breath, dyspnea,	1st patient: Temperature-99.6°F, BP(systolic/diastolic)-183/114 mm Hg, HR-120 b/m and Spo2-96% 2nd patient: Temperature- 99.6 °F, BP(systolic/diastolic)-110/70 mm Hg, HR- 130 b/m and Spo2-95%
Beşler et al.[27]	Turkey	Case report	Positive(RT-PCR)	1	20/M	None	Febrile sensation and chest pain	Temperature- 39 °C, BP(systolic/diastolic)-146/63 mm Hg, HR- 111 b/m, Spo2-97%
Sardari et al.[28]	Iran	Case report	Positive(RT-PCR)	1	31/M	None	Dyspnea on exertion and low-grade fever	Temperature- 37.8 °C, BP(systolic/diastolic)-110/70 mm Hg , HR-70 b/m, Spo2- 98%
Trogen et al.[29]	USA	Case report	Positive(RT-PC)	1	69/M	Obesity, asthma, spondylolysis	Fever,neck pain, diarrhea and vomiting	Temperature- 103 °F, BP(systolic/diastolic)-79/66 mm Hg, HR- 150 b/m , Spo2- 91%
Tavazzi et al.[30]	Italy	Case report	Positive(RT-PCR)	1	69/M	N/A	Cough,Dyspnea and Weakness	N/A
Luetkens et al.[31]	Germany	Case report	Positive(RT-PCR)	1	79/M	None	Dyspnea,fatigue,syncope	Temperature- 35.6 °C, BP(systolic/diastolic)-101/64 mm Hg , HR- 75 b/m , Spo2- 94%

Kesici et al.[32]	Turkey	Case report	Positive(RT-PCR)	1	2/M	None	Nausea, vomiting and, decreased appetite	N/A
Hua et al.[33]	UK	Case report	Positive(RT-PCR)	1	47/F	None	Shortness of breath, chest pain, dry cough, fevers	N/A
Yokoo et al.[34]	Brazil	Case report	Positive(RT-PCR)	1	81/M	Hypertension and ischemic stroke	Fever , dyspnea	N/A
Khatri et al.[35]	USA	Case report	Positive(RT-PCR)	1	50/M	Hypertension and ischemic stroke	Fevers, chills, non-productive cough, dyspnea	N/A
De Vita et al.[36]	Italy	Case report	Positive(RT-PCR)	1	35/F	None	Worsening fatigue, dyspnea on minimal exertion, and orthopnea	Temperature-36.6°C, BP(systolic/diastolic)-110/70 mm Hg, HR-120 b/m, and RR-26 breaths/minutes
Gnecchi et al.[37]	France	Case report	Positive(RT-PCR)	1	16/M	None	Intense chest pain	Temperature-38·5°C
Fischer et al.[38]	France	Case report	Positive(RT-PCR)	1	15/M	None	Persistent chest pain with mild fever	Temperature-36.9°C, BP(systolic/ diastolic)100/60 mm Hg, HR-75 b/m, Spo2-98%
Dalen et al.[39]	Norway	Case report	Positive(n/m)	1	55/F	None	Fatigue with near-syncope	Temperature -37.2°C, BP(systolic/diastolic)-102/72 mm Hg, HR-100 b/m, RR-17 breaths/minutes
Doyen et al.[40]	France	Case report	Positive(RT-PCR)	1	69/M	Hypertension	Fever, cough, and dyspnea	Temperature-39°C, Spo2: 91%
Spano et al.[41]	Switzerland	Case report	Positive(serology)	1	49/M	None	Dyspnea, fatigue, intermittent epigastric pain and, nocturia	N/A

Khalid et al.[42]	USA	Case report	Positive(n/m)	1	76/F	Hypertension, hyperlipidemia, and hypothyroidism	Fever, nonproductive cough and dyspnea	Temperature-102.3°F, BP(systolic/diastolic)-110/53 mm Hg, HR-124 b/m, RR-31 breaths/min, Spo2-79%
Giacomet et al.[43]	Italy	Case report	Positive(RT-PCR)	1	2 months/F	None	Fever, nonbloody diarrhea and, vomiting.	Temperature-37.4°C, BP(systolic/diastolic)-88/50mm Hg, HR between-170 and 230 b/m, RR-40 breaths/minutes, Spo2-96%
Warchoł et al.[44]	Poland	Case report	Positive(RT-PCR)	1	74/M	Atrial fibrillation, arterial hypertension, type 2 diabetes, and hypothyroidism	New-onset ventricular tachycardia	N/A
Craver et al.[45]	USA	Case report	Positive(RT-PCR) at autopsy	1	17/M	None	Full cardiac arrest	N/A
Chiu et al.[46]	USA	Case report	Positive(RT-PCR)	1	10/M	None	Fever, weakness, diarrhea, cough, rash, and, conjunctivitis	Temperature- 40.2 °C, BP(systolic/diastolic)-95/61, HR-168 b/m, RR-24 breaths/minutes, Spo2- 96%
Singhvi et al.[47]	India	Case report	Positive(RT-PCR)	1	20/M	None	Fever	Temperature- 101 °F, BP (systolic/diastolic)-90/60 mmHg, HR-120 b/m, RR-30 breaths/minute, Spo2-92%
Garot et al.[48]	France	Case report	Positive(RT-PCR)	1	18/M	None	Cough, fever, fatigue, and muscle pain	BP(systolic/diastolic)-120/70 mm Hg, HR- 110 b/m, RR-22 breaths/minutes, Spo2-94%

El-Asaad et al.[49]	USA	Case report	Positive(RT-PCR)	1	10/M	Pityriasislic henoides chronica	Fever,cough, diarrhea, vomiting, myalgias, nonpruritic rash	BP(Systolic/diastolic)-84/40 mm Hg), HR-130 b/m, RR-24 breaths/min, Spo2-98% (on 2-l nasal cannula)

Abbreviations- Covid-19: Coronavirus disease 2019; RT-PCR: Reverse transcription polymerase chain reaction; BP: Blood pressure; HR: Heart rate; RR:Respiratory rate; Spo2: Oxyegn saturation; b/m: Beats per minute; N/A: Not available

Table 2: Laboratory analysis , Electrocardiogram (ECG), and Echocardiogram findings

Author	Lab findings and imaging	Inflammation related markers	Cardiac biomarkers	Electrocardiogram (ECG)	Echocardiogram
Cizgici et al.[9]	Leukocytosis with Lymphopenia. CT chest-small pericardial effusion and ground-glass opacification with consolidation	C reactive protein-94.6 mg/L	Troponin-998.1 ng/L	Atrial fibrillation besides heart rate of 150 bpm, concave ST elevation except for aVR lead	N/A
Hussain et al.[10]	Blood PH-7.44	N/A	Troponin-18 ng/mL and CK-MB-14.7 ng/mL	Diffuse ST elevation	Enlarged heart, marked decrease in ventricular systolic function with an ejection fraction of 20%
Coyle et al.[11]	Lymphopenia	C reactive protein-20.7 mg/L	Troponin I(peak) -7.33 on day 3, pro-BNP(peak) -1300 on day 5	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
Auer et al.[12]	Body mass index(BMI)-42 kg/ m^2	C-reactive protein-54.3 mg/L, elevated lactate dehydrogenase	Troponin I level-28.1 ng/L, NT-proBNP-636.8 pg/mL	T-wave inversion in leads III and aVF and repolarization anomalies in left precordial leads	Normal systolic left ventricular function
Dabbagh et al.[13]	chest X-ray-enlarged cardiac silhouette	C-reactive protein-15.9 mg/dl, ferritin-593 ng/ml, D-dimer- 6.52	Troponin I < 18 ng/L, pro-BNP-54 pg/mL	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

		µg/ml and interleukin-6(IL-6)- 8 pg/ml			collapse, dilated but collapsing inferior vena cava
Nicol et al.[14]	Leukocytosis with neutrophilia, Chest CT-moderate bilateral pleural effusion	C−reactive protein-604 mg/L, fibrinogen-12.5 g/L, procalcitonin-14 µg/L,Interleukin−6-75.6 µg/L and D−dimer-5700 ng/L	Troponin I-485 ng/L and BNP-2960 ng/L	sinus tachycardia	A decrease in left ventricular ejection fraction at 45%, and both subtle hypertrophy and akinesia of posterolateral left ventricular wall with small pericardial effusion
Hu et al.[15]	Chest X-ray-significant enlargement of the heart. Chest CT-pulmonary infection, enlarged heart, and pleural effusion	N/A	Troponin T > 10,000 ng/L, CK-MB- 112.9 ng/L, pro-BNP-21,025 ng/L	ST elevation in leads III and aVF	Enlarged heart, with decreased ventricular systolic function, LVEF of 27%, with trace 2 mm pericardial effusion
Oberweis et al.[16]	Leukopenia,lymphopenia,thrombocytopenia	C-reactive protein-73 mg/L,D-dimers ->4.40 µg/mL) and interleukin-6 (IL-6)-377.8 pg/mL	Troponin T levels-0.044 ng/mL, NT-proBNP-5112 pg/mL	Discrete ST elevation in V3 consistent with pericarditis	Normal cardiac anatomy with impaired left ventricular function and trace mitral insufficiency as well as a small pericardial effusion
Inciardi et al.[17]	Lymphocytosis	C reactive protein- 25 mg/dl , D-dimer- 500 U/F	Troponin T(peak)- 0.89 ng/mL , CK-MB(peak)- 39.9 ng/mL , BNP(peak)-8465 pg/mL	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

Irabien-Ortiz et al.[18]	Mild leukocytosis. Chest X-ray- mild signs of vascular redistribution, with no infiltrations	C reactive protein- 10 mg/L	Troponin T(peak)- 1100 ng/dL , NT-proBNP - 4421 ng/L	Diffuse ST-elevation and PR-segment depression	Concentric hypertrophy, diminished LV volumes, preserved LVEF, moderate pericardial effusion, absence of tamponade. After 2 hours severe biventricular failure and diffuse myocardial edema
Sala et al.[19]	Chest X-ray- subtle bilateral opacities indicative of interstitial inflammatory lung disease	N/A	Troponin T-135 ng/L, NT-proBNP- 512 pg/mL	Mild ST-segment elevation in leads V1–V2 and aVR, reciprocal ST depression in V4–V6 and QTc 452 ms with diffuse U-waves	Mild left ventricular systolic dysfunction (LVEF 43%) alongwith inferolateral left ventricular wall hypokinesis
Rehman et al.[20]	Chest CT- Normal	C reactive protein- 3.3 mg/dL, d-dimer- 0.96 mcg/mL, erythrocyte sedimentation rate (ESR)- 44 mm/hr,	Troponin(peak)-6.24 ng/mL, NT-proBNP-379 pg/mL	ST elevations in lead I and aVL of about 1-2 mm, ST depression in aVR, T-wave inversion in leads II, III and aVF and slight J-point elevation	Normal ejection fraction at 55%–60% without any wall motion anomalies
Kim et al.[21]	Cardiac CT-normal coronary arteries, hypertrophied myocardium due to edema associated with a subendocardial perfusion defect on the lateral left ventricle	N/A	Troponin I- 1.26 ng/mL, BNP-1929 pg/mL	Non-specific IV conduction delay, multiple premature ventricular complexes with T wave inversions in II, III, aVF, V3-V6	Severe LV systolic dysfunction
Zeng et al.[22]	Chest X-ray-Typical ground-glass changes indicative of viral pneumonia	Interleukin-6(peak)-272.40 pg/mL	Troponin I (peak)- 11.37 g/L , myoglobin (peak)>600 ng/mL , NT-pr(peak)- 22,500 pg/mL	Sinus tachycardia without ST elevation and left axis deviation	Enlarged LV, diffuse myocardial dyskinesia, LVEF reduced to 32%, pulmonary hypertension, and normal RV function
Radbel	Chest x-ray-	Elevated C	Troponin (peak)-	ST depressions	Mild global hypokinesis

et al.[23]	bilateral chest infiltrates	reactive protein	0.39 ng/ml	in V4-V6 (day 5)	
Yuan et al.[24]	Chest CT- nodular calcification in upper lobe of the left lung near the mediastinum, and thickening of the right pleura	N/A	N/A	N/A	N/A
Pavon et al.[25]	Leukocytosis, Chest x-ray- bilateral reticulation and ill-defined opacities, indicative of interstitial edema	C-reactive protein-466 mg/L, D-Dimers-1210 ng/mL	Troponin(peak)-1843 ng/L	Unremarkable	Moderately reduced left ventricular ejection fraction of 47%(72 hours after CMR)
Juusela et al.[26]	Patient 1: Chest X-ray- small peripheral bilateral opacities patient 2: Chest X-ray - bilateral infiltrates	Patient 2: C-reactive protein-7.68 mg/dL	1st patient:Troponin (peak)-0.930 ng/mL , BNP(peak)- 323 pg/mL 2nd patient: Troponin-0.046 ng/mL, BNP<10 pg/mL	1.Nonspecific T-wave abnormalities 2.Supraventricular tachycardia	patient 1: Moderately reduced left ventricular ejection fraction of 40% with global hypokinesia patient 2nd: Moderately reduced left ventricular ejection fraction of 40-45% with global hypokinesia
Beşler et al.[27]	Lymphopenia, Chest CT-subpleural consolidation with foci of ground-glass opacification in the left upper lobe	C-reactive protein-0.0812 g/L	Troponin-0.572 ng/mL, NT-proBNP-127 ng/L	N/A	N/A
Sardari et al.[28]	Blood cell count (CBC)-normal	C-reactive protein- 3.3 mg/L	Troponin- 2.97 ng/ml	Normal	Mild left ventricular dysfunction
Trogen et al.[29]	Mild lymphopenia	C-reactive protein-167 mg/L, D-dimer-218 ng/mL	Troponin-2.97 ng/ml, BNP-2124 pg/mL	Sinus tachycardia and T-wave inversion particularly in the inferior leads	Left ventricular ejection fraction mildly depressed without obvious intracardiac clots or pericardial effusion
Tavazzi et al.[30]	Lymphopenia	C−reactive protein-	Troponin I-4331 ng/L	N/A	Dilated left ventricle, severe and diffuse LV hypokinesia

		52.7 mg/L			with LV ejection fraction of 34%
Luetkens et al.[31]	Chest CT-pulmonary ground-glass peripheral infiltrates in the left upper lobe and discreet pleural and pericardial effusion	C-reactive protein(peak) - 64.23 mg/L	Troponin T-63.5 ng/L , NT-proBNP- 1178.0 pg/ml	Normal	N/A
Kesici et al.[32]	Bilateral interstitial infiltration, cardiomegaly, and pleural effusion on Chest X-ray	N/A	N/A	N/A	severe cardiac failure
Hua et al.[33]	N/A	N/A	Troponin T (peak)-253 ng/L	Sinus tachycardia, concave inferolateral ST elevation	Left ventricular ejection fraction was normal with pericardial effusion of size 11 mm and absence of cardiac tamponade
Yokoo et al.[34]	Chest CT-small round ground-glass opacities, with multifocal distribution on both lungs	N/A	Troponin T-33pg/mL	Normal	Reduction in the ejection fraction to 35%
Khatri et al.[35]	WBC-Leukocytosis with lymphopenia, elevated transaminases, acute kidney injury (AKI) elevated lactate dehydrogenase	D-dimer-1068 ng/mL, procalcitonin-8.16 ng/mL, C-reactive protein-11.85 mg/dL, Ferritin 66ng/mL	Troponin- 544 ng/L, CK-MB-54.3 ng/mL	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

De Vita et al.[36]	Elevated transaminase and lactate dehydrogenase. Chest CT scan-interstitial and alveolar thickening in the right middle and both inferior lobes of lung , bilateral pleural and pericardial effusion, cardiomegaly, and subsegmental pulmonary embolism	D−dimer-3328 µg/L,C−reactive protein-9.7 mg/L	Troponin−T - 37 ng/L, NT−pro−BNP- 6608 ng/L	Diffuse ST changes with inverted T−waves in leads V3−V6	Dilated left ventricle (LV) with a severe reduction in ejection fraction to 20%, impairment of LV diastolic function with diffuse marked hypokinesis of LV walls . moderate mitral regurgitation, slight right ventricular dilation and dysfunction, along with pericardial effusion
Gnecchi et al.[37]	WBC-Neutrophilia with lymphopenia	C-reactive protein-32·5 mg/dl	Troponin I-9449 ng/L	Inferolateral ST-segment elevation	Hypokinesia of the inferior and inferolateral segments of the left ventricle, with a preserved ejection fraction of 52% without pericardial effusion
Fischer et al.[38]	WBC count-Normal	C-reactive protein level-41 mg/L, Normal D-dimer level	Cardiac troponin-6.1 µg/ L , NT-proBNP-65 ng/L	Diffuse ST elevation	Mild diffuse hypokinesia with left ventricular ejection fraction at 50%
Dalen et al.[39]	WBC-increased	C-reactive protein-11mg/dl	Troponin T-108 ng/L, NT-proBNP-1025 ng/L	Sinus tachycardia, insignificant ST-elevation in inferior leads with a T-wave inversion in precordial leads	Left ventricular concentric hypertrophy
Doyen et al.[40]	Leukocytosis with neutrophilia and lymphocytopenia. Chest CT-bilateral crazy paving pattern, ground-glass opacities and condensation	N/A	Troponin I-9002 ng/L BNP-22.600 pg/ mL	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
Spano	CT chest-left heart	Elevated	Elevated	Dynamic T-	Diffuse hypokinesia with

et al.[41]	congestion	C-reactive protein	troponin level	wave inversion	severely decreased left- and right-ventricular function
Khalid et al.[42]	WBC- increased with neutrophilia, Chest X-ray-diffuse bilateral pulmonary edema vs infiltrates	C-reactive protein 23.10 mg/L,interleukin-6 (IL-6) 781.46 mg/L, elevated lactate dehydrogenase and ferritin	Troponin 503 ng/l , proBNP-35,000 pg/mL	Normal sinus rhythm with a short PR interval	Severe left ventricular systolic dysfunction with segmental wall motion anomalies
Giacomet et al.[43]	N/A	elevated C-reactive protein and D-dimer and also elevated IL-6-236ng/L	Troponin T-103ng/L and NT-proBNP-12,507ng/L	Sinus tachycardia	Hypokinesia of the inferior left ventricular wall and the inferior interventricular septum, with mildly reduced ejection fraction to 57–58%
Warchoł et al.[44]	N/A	C-reactive protein levels-94 mg/l ,D-dimers-1.39 mg/l, elevated transaminases and lactate dehydrogenase	Troponin T-ranged from 72 ng/l to 102 ng/l, NT-proBNP-2451 ng/l	N/A	N/A
Craver et al.[45]	N/A	N/A	N/A	N/A	N/A
Chiu et al.[46]	Leukocytosis with neutrophilia and lymphopenia	ESR-57 mm/h, a c-reactive protein of 280 mg/L, procalcitonin-28 ng/mL, d-dimer-2727	Troponin-84 ng/L ,NT-proBNP-9,477 pg/mL	Sinus tachycardia with low voltages	N/A

		ng/mL,			
Singhvi et al.[47]	Hemoglobin-1.9 gm%, leukocytosis with thrombopenia	C-reactive protein-26 mg/L, ESR-75 mm/hr	Troponin I - 9,565.2 ng/L and BNP- 8,000 pg/ ml	Mild ST depression and T wave inversion	Global hypokinesia, with a preserved wall thickness and reduced left ventricular ejection fraction (LVEF) to 30%
Garot et al.[48]	N/A	C-reactive protein-351 mg/l	Troponin-11,716 IU/ml, NT-proBNP-11,719 pg/ml	Sinus tachycardia with inverted T waves from V2 to V4	Mildly enlarged left ventricle (LV) with increased LV wall thickness and marked diffuse hypokinesis with an ejection fraction of 30%
El-Asaad et al.[49]	Leukocytosis with neutrophilia and lymphopenia	C-reactive protein-22 mg/dl, ferritin-1,138 ng/ml, and D-dimer-3.1 µg/ml	Troponin- 84 ng/ ml, BNP-2,000 pg/ml	sinus tachycardia	Severe left ventricular systolic dysfunction with LVEF of 32%

Abbreviations- WBC: White blood cell; CT- Computed tomography; ESR: Erythrocyte sedimentation rate; CK-MB: Creatine kinase-MB; NT-proBNP: N-terminal pro–B-type natriuretic peptide; ST: ST-segment changes; LV: Left ventricle; RV: Right ventricle; LVEF: Left ventricular ejection fraction; CAD: Coronary artery disease; N/A: Not available

Table 3: Cardiac magnetic resonance (CMR) and histopathological findings

Author	**Cardiac magnetic resonance imaging(CMR)**	**Lake Louise Criteria used to diagnose myocarditis**	**Endomyocardial Biopsy (EMB) /Autopsy**
Coyle et al.[11]	Diffuse edema of both atria and both ventricles along with small foci of late gadolinium enhancement	-	N/M
Auer et al.[12]	N/M	-	Lymphocytic infiltration in the myocardium and positive staining with anti-CD3 antibody defining T cells (Autopsy findings)

Nicol et al.[14]	Normal left ventricular size with mild systolic dysfunction (left ventricular ejection fraction: 45%) with global hypokinesia. Focal lateral subepicardial enhancement on Late gadolinium enhancement	Yes	Multiple foci of lymphocytes in a diffuse inflammatory and oedematous background with myocyte necrosis, infiltrated by inflammatory cells these inflammatory cell were numerous CD138+ plasmocytes, CD3+ CD8+ T cells, and numerous CD163+ macrophages.
Oberweis et al.[16]	Biventricular systolic dysfunction with small pericardial effusion, mild subepicardial Gadolinium enhancement of the lateral wall, and signs of diffuse edema	Yes	N/M
Inciardi et al.[17]	Generalized hypokinesia of both ventricles, particularly in the apical region, and severe LV dysfunction. Short tau inversion recovery and T2-mapping sequences exhibited distinguished biventricular myocardial interstitial edema	Yes	N/M
Sala et al.[19]	Mild hypokinesia at basal and mid-left ventricular segments, diffuse myocardial edema, Late gadolinium enhancement sequences revealed the absence of detectable myocardial scar/necrotic foci (on day 7)	-	Diffuse T-lymphocytic inflammatory infiltrates with immense interstitial edema and finite centers of necrosis
Kim et al.[21]	T2 short inversion recovery showed diffuse elevated signal intensity in the left ventricle myocardium along with thickening of myocardial wall, suggestive of myocardial wall edema	-	N/M
Yuan et al.[24]	Elevated T2 weighted image signal in left ventricle apical segment, which symbolized the likelihood of myocardial edema. Mild left ventricular systolic dysfunction along with standard early and late gadolinium enhancement	Yes	N/M
Pavon et al.[25]	Left-ventricular (LV) systolic dysfunction (LV ejection fraction of 42%) with mild hypokinesia of the lateral wall. showed myocardial edema and sub-epicardial late gadolinium enhancement on T2-mapping sequences particularly in the anterior interventricular septum and in the inferior and inferolateral walls	-	N/M

Beşler et al.[26]	Subepicardial elevated signal intensity in the mid posterolateral wall of the left ventricle on short tau inversion recovery (STIR) sequence, highly suggestive of myocardial wall edema. Late gadolinium enhancement in the subepicardial region of the posterolateral wall at the level of the mid ventricle	Yes	N/M
Sardari et al.[28]	Mildly reduced ejection fraction of 50%. The edema/inflammation in at the level of mid inferoseptal and the inferior wall on T2-weighted sequence. Subepicardial fibrosis in the mid inferior wall revealed on late gadolinium enhancement	-	N/M
Trogen et al.[29]	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/M
Tavazzi et al.[30]	N/M	-	Low−grade myocardial inflammation with viral particles in the interstitial cells. vacuolated, CD68−positive macrophages were observed with immune−light microscopy
Luetkens et al.[31]	Diffuse interstitial myocardial edema with an increased T2 signal intensity ratio. T2 mapping showed diffuse myocardial inflammation(on day 10)	Yes	N/M
Kesici et al.[32]	N/M	-	SARS-CoV-2 RT–PCR positivity in the cardiac tissue
Yokoo et al.[34]	Pronounced diffuse hypokinesia and global systolic dysfunction along with the presence of late enhancement areas with an ischemic pattern on the left ventricle base septum wall	-	N/M
De Vita et al.[36]	Enlarged left ventricle with normal thickness; diffuse hypokinesis of LV walls with reduced ejection fraction to 17%, enlarged right ventricle enlarged with diffuse hypokinesis and reduced contractile function(Ejection frction-19%) and LV apical thrombus	-	N/M
Gnecchi et al.[37]	T2 mapping showed edema of inferior, inferolateral walls and lateral wall	-	N/M

Fischer et al.[38]	Moderate left ventricular dysfunction with LVEF of 48%, late gadolinium enhancement sequences revealed interstitial edema and myocardial damage	Yes	N/M
Dalen et al.[39]	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/M
Doyen et al.[40]	Subepicardial late gadolinium enhancement of the apex plus inferolateral wall suggestive of myocarditis	-	N/M
Spano et al.[41]	T2 weighted imaging and T2 mapping revealed diffuse thickening of the myocardium and pericardium attributable to edema	-	N/M
Warchoł et al.[44]	Left atrial enlargement and global left ventricular hypokinesia with reduced left ventricular ejection fraction of 20%. Inferior and inferolateral wall large, patchy, and linear nonischemic pattern of fibrosis with late gadolinium enhancement	-	N/M
Craver et al.[45]	N/M	-	Mixed interstitial inflammatory infiltrate with focal zones of rarefaction and eosinophilic infiltrate with the slackening of myocytes (Autopsy findings)
Garot et al.[48]	Increased left ventricular (LV) wall thickness, raised LV volumes with marked diffuse hypokinesis with reduced left ventricular ejection fraction to 33%. Prominent extensive hyper signal of the LV basal posterolateral wall symbolic of myocardial edema. Nodular subepicardial enhancement of the Left ventricular basal posterolateral wall on late gadolinium enhancement	Yes	N/M

Abbreviations- LV: Left ventricle; LVEF: Left ventricular ejection fraction; N/M: Not mentioned

Table 4: Management, complications, and outcomes in Covid-19 patients diagnosed

with acute myocarditis

Author	In-hospital medications	Corticosteroids/colchicine	Ionotropic/ Vasopressor	Mechanical support	Complications	Outcomes
Cizgici et al.[9]	Furosemide, angiotensin-converting enzyme (ACE) inhibitor and, beta-blocker along with Covid-19 specific therapy.	-	-	-	ARDS	Transferred back to Covid-19 center
Hussain et al.[10]	Remdesivir, hydroxychloroquine and azithromycin, and Indomethacin 7th day,	methylprednisolone and colchicine	-	Mechanical ventilation	ARDS on 2nd day	N/R
Coyle et al.[11]	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
Auer et al.[12]	-	-	-	Mechanical ventilation	-	Died on day 9 due to ventricular fibrillation
Dabbagh et al.[13]	Hydroxychloroquine	Glucocorticoids, and colchicine	-	Intubated	-	Discharged
Nicol et al.[14]	Angiotensin−converting enzyme inhibitors and beta−blockers	-	-	-	-	Recovered
Hu et al.[15]	IV Immunoglobulin, torsemide and furosemide, piperacillin-sulbactam, pantoprazole	IV methylprednisolone 200 mg daily for 4 days	Norepinephrine and milrinone	-	Cardiogenic shock day 1	Recovered
Oberweis et al.[16]	Enoxaparin, IV immunoglobulins (2 g/kg)	-	Dobutamine,	-	-	Discharged on

			Milrinone			day 10
Inciardi et al.[17]	Hydroxychloroquine (200 mg two times a day), lopinavir/ritonavir (250 every 12 hours), kanrenone (50 mg), furosemide(25-50 mg), and bisoprolo(2.5 mg)l	IV methylprednisolone 1 mg/kg for 3 days	Dobutamine	-	The cardiogenic shock on day 1	Recovered
Irabien-Ortiz et al.[18]	Immunoglobulins (80 mg/day) , interferon-B (0.25 mg every 48 hours) and ritonavir/lopinavir	IV methylprednisolone 500 mg daily at decreasing doses for 14 days	Norepinephrine	ECMO	The cardiogenic shock on day 1	N/R
Sala et al.[19]	Lopinavir/ritonavir 500 mg, hydroxychloroquine 200 mg	-	-	-	-	Recovered
Rehman et al.[20]	Acetaminophen	-	-	-	-	Discharged
Kim et al.[21]	N/R	N/R	N/R	N/R	N/R	N/R
Zeng et al.[22]	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	The cardiogenic shock on day 11, Septic shock on day 26, ARDS day 1	Passed away on day 33
Radbel et al.[23]	Hydroxychloroquine, azithromycin, tocilizumab	-	Norepinephrine day 4	Mechanical ventilation on day 3	Septic day shock on day 4, cardiogenic shock on day 5, ARDS on day 3	Died on day 7
Yuan et al.[24]	N/R	N/R	N/R	N/R	N/R	Discharged
Pavon et al.[25]	Piperacillin-tazobactam	-	Catecholamine	Intubated	-	Discharged
Juusela et al.[26]	Patient 1: Hydroxychloroquine, tocilizumab Patient 2: Metoprolol, ceftriaxone IV,	Patient 1: IV methylprednisolone	-	Patient 1: Intubated	-	Cesarian in both patients

	and azithromycin IV.					
Beşler et al.[27]	Hydroxychloroquine, azithromycin, favipiravir Tigecycline and ceftriaxone	Colchicine	-	-	-	Discharged
Sardari et al.[28]	Bisoprolol along with angiotensin-converting enzyme (ACE) inhibitor lisinopril	-	-	-	-	Discharged
Trogen et al.[29]	Hydroxychloroquine, piperacillin/tazobactam, enoxaparin	-			septic shock, Dischrged	
Tavazzi et al.[30]	-	-	Adrenaline (0.07 µg/kg/min), and noradrenaline (0.1 µg/kg/min)	ECMO and IABP	The cardiogenic shock on day 1 and septic shock	Died
Luetkens et al.[31]	N/R	N/R	N/R	N/R	N/R	N/R
Kesici et al.[32]	N/R	N/R	N/R	ECMO	Cardiogenic shock	N/R
Hua et al.[33]	-	-	Vasopressors	-	Cardiogenic shock day 1	Recovered
Yokoo et al.[34]	Antibiotics, steroids	-	-	-	-	Discharged
Khatri et al.[35]	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
De Vita et al.[36]	Ethacrynic acid 25 mg, enoxaparin 8000 plus 6000 IU sc, spironolactone 25 mg, bisoprolol 2.5 mg, and ramipril	-	-	-	-	Recovered
Gnecchi et al.[37]	Hydroxychloroquine and ibuprofen	-	-	-	-	Recovered
Fischer et al.[38]	Bisoprolol 2.5 mg daily and ramipril 2.5 mg daily	-	-	-	-	Discharged on day 5
Dalen et	IV fluids	-	Norepine		Cardiogeni	Recover

al.[39]			phrine and dobutamine		c shock	ed
Doyen et al.[40]	Aspirin, fondaparinux	IV hydrocortisone for 9 days	-	Mechanical ventilation	Acute respiratory distress syndrome	Discharged from ICU after 3 weeks
Spano et al.[41]	N/R	N/R	N/R	N/R	N/R	N/R
Khalid et al.[42]	Tocilizumab (two-dose of 480 mg and 240 mg), intravenous immunoglobulin (25 g for 5 days), ceftriaxone, cefdinir, and cefepime	-	Norepinephrine	Intubated	Cardiogenic shock, ARDS	Recovered
Giacomet et al.[43]	Cefotaxime plus ampicillin, IV immunoglobulins	-	-	-	-	Recovered
Warchoł et al.[44]	Azithromycin, oseltamivir, magnesium, and amiodarone	-	-	-	-	N/R
Craver et al.[45]	-	-	-	-	-	Died
Chiu et al.[46]	Ibuprofen	-	Dobutamine	-	-	-
Singhvi et al.[47]	Pack cell volume transfusion to correct anemia, IV noradrenaline, low molecular weight heparin, IV vitamin K, and a low dose of diuretics	Methylprednisolone pulse therapy.	Norepinephrine	-	Cardiogenic shock	Discharged on day 10
Garot et al.[48]	Paracetamol, hydroxychloroquine (400 mg daily), 2 l/min nasal oxygen, cefotaxime and rovamycine	-	Noradrenaline	Intubated	-	Discharged on day 15
El-Asaad et al.[49]	Intravenous immune globulin at 1 g/kg, anakinra, 100 mg 3 times daily, unfractionated heparin and remdesivir 100 mg daily	Methylprednisolone, 2 mg/kg twice daily	Epinephrine and norepinephrine infusions	Bilevel positive airway pressure	-	Recovered

Abbreviations- IV: Intravenous; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; ARDS: Acute respiratory distress syndrome; N/R: Not reported

Table 5: Composite characteristic features across all cases

Parameter	Cases with reported data on a particular parameter	Total Patients: 42 n(%)

Mean age	42	43.4 years
Female	42	28.60%
Presenting symptoms	42	
Fever		24(57.1)
Dyspnea		22(52.4)
Cough		17(40.5)
Chest pain		12(28.6)
Weakness		11(26.2)
Vomiting and diarrhea		12(28.6)
Myalgia		5(12)
Past History	41	
None		22(53.7)
Hypertension		11(26.2)
Obesity		4(9.7)
Diabetes mellitus		2(4.9)
Hypothyroidism		2(4.9)
Ischaemic stroke		2(4.9)
Other(asthma, allergic cough, smoking, lymph node tuberculosis, Pulmonary sarcoidosis, and epilepsy, etc.		9(22)
Inflammaton related markers	31	
Elevated CRP level	30	26(86.6)
Elevated D-dimer level	14	13(93)
Cardiac biomarker		
Elevated Troponin	39	35(90)
Elevated NT-pro-BNP	23	20(87)
Electrocardiogram(ECG)	36	
Normal		4(11.1)
Sinus tachycardia		12(33.3)
Arrhythmia		3(8.3)
ST-segment elevation		14(38.9)
ST-segment depression		7(19.4)
T-wave inversion		12(33.3)
Echocardiogram	35	
Decreased LVEF(<50%)		26(74.3)

Mean LVEF(%)		37.05%
LV hypokinesia		13(37.2)
LV dilatation		3(8.5)
Pericardial effusion		9(25.8)
Cardiac Magnetic resonance(CMR) imaging		21(50)
Endomyocardial biopsy or autopsy		5(11.9)
Hospital treatment	37	37
Hydroxychloroquine		12(32.5)
Azithromycin		7(19)
Lopinavir/ritonavir		4(11)
Antibiotics(other than azithromycin)		12(32.5)
Tocilizumab		4(11)
Corticosteroids		12(32.5)
Colchicine		4(11)
IV immunoglobulin		7(19)
Beta-blocker		12(32.5)
Vasopressor		14(38)
Inotropes		8(21.7)
Mechanical support	38	
Intubation		5(13.1)
Mechanical ventilation		5(13.1)
ECMO		4(10.5)
Complications	38	
Cardiogenic shock		13(34.2)
Septic shock		4(10.5)
Outcome	42	
Recovered or discharged		28(66.6)
Death		6(14.3)
Not reported		8(19)

Abbreviations- NT-proBNP: N-terminal pro–B-type natriuretic peptide; ECMO: extracorporeal membrane oxygenation

Figure Legends

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram