MYOCARDITIS ASSOCIATED WITH COVID-19 DISEASE: A SYSTEMATIC REVIEW OF PUBLISHED CASE REPORTS AND CASE SERIES

MIOCARDITIS ASOCIADA A LA ENFERMEDAD COVID-19: UNA REVISIÓN SISTEMÁTICA DE REPORTES Y SERIES DE CASOS PUBLICADOS

TESIS PARA OPTAR POR EL TÍTULO PROFESIONAL DE
MÉDICO CIRUJANO

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DEDICATORIA

Dedicado a mis padres, Dr. César Rojas y Dra. Nancy Barahona

Papá, gracias por enseñarme que, ante la adversidad, aún hay esperanza de salir victoriosos, y por darme fuerzas en este maravilloso camino de la medicina.
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DECLARACIONES Y CONFLICTO DE INTERÉS

- Los autores declaran no tener conflictos de interés.

- Los autores declaran que este trabajo de investigación fue aprobado por el Comité Editorial de la Revista The International Journal of Clinical Practice con fecha de 24 de mayo del 2021.

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UNIVERSIDAD PERUANA CAYETANO HEREDIA | Facultad de MEDICINA

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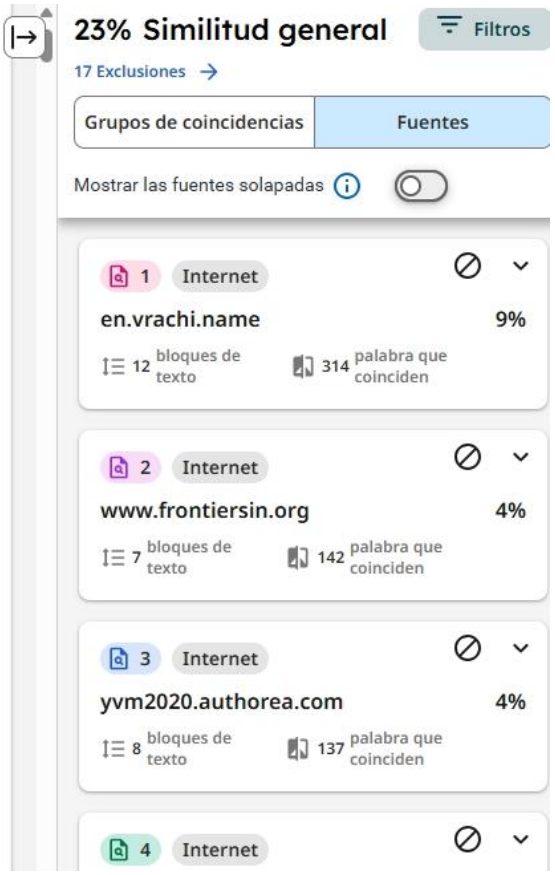

TABLA DE CONTENIDOS

RESUMEN

Antecedentes: La Covid-19, causada por el SARS-CoV-2, es altamente contagiosa y, aunque compromete sobre todo al pulmón, cada vez se reconoce más su impacto cardiaco, en particular la miocarditis. **Objetivo:** Sintetizar las características clínicas, los hallazgos diagnósticos, el manejo y los desenlaces de la miocarditis asociada a Covid-19 mediante una revisión sistemática. **Métodos y materiales:** Se buscaron en MEDLINE/PubMed y Embase todos los informes y series de casos, sin restricción de idioma, que describieran miocarditis aguda confirmada en pacientes con infección por SARS-CoV-2 verificada por laboratorio. **Resultados:** Se analizaron 41 estudios con 42 pacientes. La mediana de edad fue 43,4 años; el 71,4 % eran varones. El síntoma inicial más frecuente fue fiebre (57 %). La comorbilidad predominante fue hipertensión. Troponina y péptido natriurético cerebral estuvieron elevados en 90 % y 87 % de los casos, respectivamente. El electrocardiograma mostró alteraciones inespecíficas de los segmentos ST y ondas T. El ecocardiograma evidenció dilatación y disfunción sistólica del ventrículo izquierdo, mientras que la resonancia magnética cardíaca reveló edema y lesión miocárdica. Histológicamente predominó el infiltrado linfocitario difuso. Los tratamientos más usados fueron antivirales y corticosteroides; 38 % requirió vasopresores. De los 42 pacientes, 28 (67 %) se recuperaron y ocho fallecieron. **Conclusiones:** La miocarditis por Covid-19 se asocia a elevadas morbilidad y mortalidad y puede deteriorar al paciente de forma súbita. Reconocer sus manifestaciones, interpretar adecuadamente los hallazgos de imagen y biomarcadores y aplicar un tratamiento oportuno resultan esenciales para el personal sanitario.

Palabras claves: Covid-19; Miocarditis; SARS-CoV-2.

ABSTRACT

Background: COVID-19, caused by SARS-CoV-2, is highly contagious, and although it primarily affects the lung, its cardiac impact, particularly myocarditis, is increasingly recognized. **Objective:** To synthesize the clinical features, diagnostic findings, management, and outcomes of COVID-19-associated myocarditis through a systematic review. **Methods and materials:** MEDLINE/PubMed and Embase were searched for all case reports and series, without language restriction, describing confirmed acute myocarditis in patients with laboratory-verified SARS-CoV-2 infection. **Results:** 41 studies with 42 patients were analyzed. The median age was 43.4 years; 71.4% were men. The most common presenting symptom was fever (57%). The predominant comorbidity was hypertension. Troponin and brain natriuretic peptide were elevated in 90% and 87% of cases, respectively. The electrocardiogram showed nonspecific ST-segment and T-wave abnormalities. The echocardiogram showed left ventricular dilatation and systolic dysfunction, while cardiac magnetic resonance imaging revealed edema and myocardial injury. Histologically, diffuse lymphocytic infiltrate predominated. The most commonly used treatments were antivirals and corticosteroids; 38% required vasopressors. Of the 42 patients, 28 (67%) recovered and eight died. **Conclusions:** COVID-19 myocarditis is associated with high morbidity and mortality and can cause sudden patient deterioration. Recognizing its manifestations, properly interpreting imaging and biomarker findings, and applying timely treatment are essential for healthcare professionals.

Keywords: Covid-19; Myocarditis; SARS-CoV-2

I. 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.

II. OBJECTIVES

This review article aims to compile and illustrate clinical characteristics, diagnostic findings, management, and acute myocarditis outcomes manifesting in Covid-19 patients.

III. MATERIALS AND 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.

IV. RESULTS

Se In this review, 42 patients reported to be diagnosed with acute myocarditis were included from 41 published studies. (9-49). 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 patients.

V. 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.

VI. CONCLUSIONS

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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VIII. TABLES AND FIGURES

Table 1: Patient demographic and clinical characteristic features

Author	Country	Study design	Covid-19 status (diagnostic technique)	Sample size	Age (y)/sex (men or women)	Past medical history	Presenting symptoms	Physical examination findings on admission
Cizgici et al	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	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-141/89 mm Hg, HR-97 b/m, Spo2%-91%, Auscultation-bilateral wheezing and Ronchi
Coyle et al	USA	Case report	Positive (n/m)	1	57/M	Hypertension	Fevers, cough, diarrhea, myalgia, decreased appetite, dyspnea	N/A
Auer et al	Austria	Case report	Positive (n/m)	1	42/F	Bariatric surgery for morbid obesity 6 y ago and occasional hypertension	Shortness of breath	BP-109/62 mm Hg, HR-75 b/m, Spo2%-82%
Dabbagh et al	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-118/82 mm Hg, HR-122 b/m, RR-24 breaths/min

Nicol et al	France	Case report	Positive (serology)	1	40/M	Obesity	Fever, odynophagia, and left neck pain	Temperature-39.9°C, BP-110/60 mm Hg, HR-123 b/m, tonsillitis with cervical adenopathy
Hu et al	China	Case report	Positive (RT-PCR)	1	37/M	None reported	Chest pain, dyspnea, and diarrhea	BP-80/50 mm Hg
Oberweis et al	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-94/40 mm Hg
Inciardi et al	Italy	Case report	Positive (RT-PCR)	1	53/F	None	Severe fatigue, cough and fever week before	Temperature-36.6°C, BP-90/50 mm Hg, HR-100 b/m, Spo2%-98%
Irabien-Ortiz et al	Spain	Case report	Positive (RT-PCR)	1	59/F	Hypertension, lymph node tuberculosis diagnosed by presence of erythema nodosum, and migraine	Fevers, squeezing chest pain	Temperature-39.3°C, BP-75/53 mm Hg, Spo2%-96% (with nasal cannula at 2 L/min)
Sala et al	Italy	Case report	Positive (RT-PCR)	1	43/F	None	Chest pain and dyspnea	Temperature-37.7°C, BP-120/80 mm Hg, HR-79 b/m, Spo2%-89%, decreased breath sounds at lung bases with Ronchi
Rehman et al	USA	Case report	Positive (RT-PCR)	1	39/M	None	Midsternal chest pain	N/A
Kim et al	Republic of Korea	Case report	Positive (RT-PCR)	1	21/F	None	Fevers, productive cough, shortness of breath, diarrhea	N/A
Zeng et al	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	USA	Case report	Positive (RT-PCR)	1	40/M	None	Fever, dry cough, dyspnea on exertion	Temperature-39.4°C
Yuan et al	China	Case report	Positive (RT-PCR) detected in stool	1	33/M	Hypertension	Chest pain, fever, myalgias	Temperature-37.3°C, BP-115/79 mm Hg, HR-121 b/m, RR-18 breaths/minutes
Pavon et al	Switzerland	Case report	Positive (RT-PCR)	1	64/M	Pulmonary sarcoidosis and epilepsy	Chest pain and dyspnea	Temperature-39.3°C

Juusela et al	USA	Case series	Positive (RT-PCR)	2	1. 45/F, pregnant (39 weeks) 2. 26/F, pregnant (33 weeks)	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-183/114 mm Hg, HR-120 b/m, Spo2%-96% 2nd patient: Temperature-99.6°F, BP-110/70 mm Hg, HR-130 b/m, Spo2%-95%
Beşler et al	Turkey	Case report	Positive (RT-PCR)	1	20/M	None	Febrile sensation and chest pain	Temperature-39°C, BP-146/63 mm Hg, HR-111 b/m, Spo2%-97%
Sardari et al	Iran	Case report	Positive (RT-PCR)	1	31/M	None	Dyspnea on exertion and low-grade fever	Temperature-37.8°C, BP-110/70 mm Hg, HR-70 b/m, Spo2%-98%
Trogen et al	USA	Case report	Positive (RT-PC)	1	69/M	Obesity, asthma, spondylolysis	Fever, neck pain, diarrhea and vomiting	Temperature-103°F, BP-79/66 mm Hg, HR-150 b/m, Spo2%-91%
Tavazzi et al	Italy	Case report	Positive (RT-PCR)	1	69/M	N/A	Cough, dyspnea and weakness	N/A
Luetkens et al	Germany	Case report	Positive (RT-PCR)	1	79/M	None	Dyspnea, fatigue, syncope	Temperature-35.6°C, BP-101/64 mm Hg, HR-75 b/m, Spo2%-94%
Kesici et al	Turkey	Case report	Positive (RT-PCR)	1	2/M	None	Nausea, vomiting and, decreased appetite	N/A
Hua et al	UK	Case report	Positive (RT-PCR)	1	47/F	None	Shortness of breath, chest pain, dry cough, fevers	N/A
Yokoo et al	Brazil	Case report	Positive (RT-PCR)	1	81/M	Hypertension and ischemic stroke	Fever, dyspnea	N/A

Khatri et al	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	Italy	Case report	Positive (RT-PCR)	1	35/F	None	Worsening fatigue, dyspnea on minimal exertion, and orthopnea	Temperature-36.6°C, BP-110/70 mm Hg, HR-120 b/m, RR-26 breaths/minutes
Gnecchi et al	France	Case report	Positive (RT-PCR)	1	16/M	None	Intense chest pain	Temperature-38.5°C
Fischer et al	France	Case report	Positive (RT-PCR)	1	15/M	None	Persistent chest pain with mild fever	Temperature-36.9°C, BP-100/60 mm Hg, HR-75 b/m, Spo2%-98%
Dalen et al	Norway	Case report	Positive (n/m)	1	55/F	None	Fatigue with near-syncope	Temperature-37.2°C, BP-102/72 mm Hg, HR-100 b/m, RR-17 breaths/minutes
Doyen et al	France	Case report	Positive (RT-PCR)	1	69/M	Hypertension	Fever, cough, and dyspnea	Temperature-39°C, Spo2: 91%
Spano et al	Switzerland	Case report	Positive (serology)	1	49/M	None	Dyspnea, fatigue, intermittent epigastric pain and, nocturia	N/A
Khalid et al	USA	Case report	Positive (n/m)	1	76/F	Hypertension, hyperlipidemia, and hypothyroidism	Fever, nonproductive cough and dyspnea	Temperature-102.3°F, BP-110/53 mm Hg, HR-124 b/m, RR-31 breaths/min, Spo2%-79%
Giacomet et al	Italy	Case report	Positive (RT-PCR)	1	2 months/F	None	Fever, nonbloody diarrhea and vomiting	Temperature-37.4°C, BP-88/50 mm Hg, HR between 170 and 230 b/m, RR-40 breaths/minutes, Spo2%-96%
Warchoł et al	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	USA	Case report	Positive (RT-PCR) at autopsy	1	17/M	None	Full cardiac arrest	N/A
Chiu et al	USA	Case report	Positive (RT-PCR)	1	10/M	None	Fever, weakness, diarrhea, cough, rash, and, conjunctivitis	Temperature-40.2°C, BP-95/61, HR-168 b/m, RR-24 breaths/minutes, Spo2%-96%
Singhavi et al	India	Case report	Positive (RT-PCR)	1	20/M	None	Fever	Temperature-101°F, BP-90/60 mm Hg, HR-120 b/m, RR-30 breaths/minute, Spo2%-92%
Garot et al	France	Case report	Positive (RT-PCR)	1	18/M	None	Cough, fever, fatigue, and muscle pain	BP-120/70 mm Hg, HR-110 b/m, RR-22 breaths/minutes, Spo2%-94%
El-Assaad et al	USA	Case report	Positive (RT-PCR)	1	10/M	Pityriasis lichenoides chronica	Fever, cough, diarrhea, vomiting, myalgias, nonpruritic rash	BP-84/40 mm Hg, HR-130 b/m, RR-24 breaths/min, Spo2%-98% (on 2-l nasal cannula)

Abreviations: 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	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	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	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 LVEF of 35%-40%, no pericardial effusion
Auer et al	Body mass index (BMI)-42 kg/m²	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	Chest X-ray-enlarged cardiac silhouette	C-reactive protein-15.9 mg/dL, ferritin-593 ng/mL, D-dimer-6.52 µg/mL, interleukin-6 (IL-6)-8 pg/mL	Troponin I < 18 ng/L, pro-BNP-54 pg/mL	Shallow voltage in limb leads, non-specific ST alteration	A decrease in LVEF to 40%, massive peripheral pleural effusion, early right ventricular diastolic collapse, dilated but collapsing inferior vena cava
Nicol et al	Leukocytosis with neutrophilia, Chest CT-moderate bilateral pleural effusion	C-reactive protein-604 mg/L, fibrinogen-12.5 g/L, procalcitonin-14 µg/L, IL-6-75.6 µg/L, D-dimer-5700 ng/L	Troponin I-485 ng/L and BNP-2960 ng/L	Sinus tachycardia	A decrease in LVEF at 45%, with subtle hypertrophy and akinesia of posterolateral LV wall and small pericardial effusion
Hu et al	Chest X-ray-significant	N/A	Troponin T > 10 000 ng/L,	ST elevation in leads III	Enlarged heart, decreased

	enlargement of the heart, pulmonary infection, pleural effusion		CK-MB-112.9 ng/L, pro-BNP-21025 ng/L	and aVF	systolic function, LVEF of 27%, trace 2 mm pericardial effusion
Oberweis et al	Leukopenia, lymphopenia, thrombocytopenia	C-reactive protein-73 mg/L, D-dimers->4.40 µg/mL, 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, impaired LV function and trace mitral insufficiency, small pericardial effusion
Inciardi et al	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	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 h severe biventricular failure and diffuse myocardial edema
Sala et al	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%) along with inferolateral left ventricular wall hypokinesis
Rehman et al	Chest CT- normal	C reactive protein-3.3 mg/dL, D-dimer-0.96 mcg/mL, erythrocyte sedimentation rate (ESR)-44 mm/h	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	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	Chest X-ray-typical	Interleukin-6 (peak)-272.40	Troponin I (peak)-11.37	Sinus tachycardia without	Enlarged LV, diffuse

	ground-glass changes indicative of viral pneumonia	pg/mL	g/L, myoglobin (peak) >600 ng/mL, NT-proBNP (peak)-22 500 pg/mL	ST elevation and left axis deviation	myocardial dyskinesia, LVEF reduced to 32%, pulmonary hypertension, and normal RV function
Radbel et al	Chest X-ray-bilateral chest infiltrates	Elevated C reactive protein	Troponin (peak)-0.39 ng/mL	ST depressions in V4-V6 (day 5)	Mild global hypokinesis
Yuan et al	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	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 LVEF of 47% (72 h after CMR)
Juusela et al	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 LVEF of 40% with global hypokinesia; Patient 2: Moderately reduced LVEF of 40%-45% with global hypokinesia
Beşler et al	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	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	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	LVEF mildly depressed without obvious intracardiac clots or pericardial effusion
Tavazzi et al	Lymphopenia	C-reactive protein-52.7 mg/L	Troponin I-4331 ng/L	N/A	Dilated left ventricle, severe and diffuse LV hypokinesia with LV ejection fraction of 34%
Luetkens et al	Chest CT- pulmonary ground-glass peripheral infiltrates in the left upper lobe and discreet pleural	C-reactive protein (peak)-64.23 mg/L	Troponin T-63.5 ng/L, NT-proBNP-1178.0 pg/mL	Normal	N/A

	and pericardial effusion				
Kesici et al	Bilateral interstitial infiltration, cardiomegaly, and pleural effusion on Chest X-ray	N/A	N/A	N/A	Severe cardiac failure
Hua et al	N/A	N/A	Troponin T (peak)-253 ng/L	Sinus tachycardia, concave inferolateral ST elevation	LVEF was normal with pericardial effusion of size 11 mm and absence of cardiac tamponade
Yokoo et al	Chest CT-small round ground-glass opacities, with multifocal distribution on both lungs	N/A	Troponin T-33 pg/mL	Normal	Reduction in the ejection fraction to 35%
Khatri et al	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 66 ng/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, and moderate-to-large pericardial effusion anterior to the RV
De Vita et al	Elevated transaminase and lactate dehydrogenase. Chest CT scan: interstitial and alveolar thickening in right middle and both inferior lobes, bilateral pleural and pericardial effusion, cardiomegaly, subsegmental pulmonary embolism	D-dimer-3328 µg/L, C-reactive protein-9.7 mg/L	Troponin-T-37 ng/L, NT-proBNP-6608 ng/L	Diffuse ST changes with inverted T-waves in leads V3-V6	Dilated LV with severe reduction in ejection fraction to 20%, impaired LV diastolic function with marked hypokinesis, moderate mitral regurgitation, slight RV dilation and dysfunction, with pericardial effusion
Gnecchi et al	WBC-neutrophilia with lymphopenia	C-reactive protein-32.5 mg/dL	Troponin I-9449 ng/L	Inferolateral ST-segment elevation	Hypokinesia of inferior and inferolateral segments of the LV, preserved LVEF of 52%, no pericardial effusion
Fischer et al	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 LVEF at 50%
Dalen et al	WBC-increased	C-reactive protein-11 mg/dL	Troponin T-108 ng/L, NT-proBNP-1025 ng/L	Sinus tachycardia, insignificant ST-elevation in inferior leads with T-wave inversion in	Left ventricular concentric hypertrophy

				precordial leads	
Doyen et al	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 LVEF and normal wall motion
Spano et al	CT chest: left heart congestion	Elevated C-reactive protein	Elevated troponin level	Dynamic T-wave inversion	Diffuse hypokinesia with severely decreased left- and right-ventricular function
Khalid et al	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	N/A	Elevated C-reactive protein and D-dimer, also elevated IL-6-236 ng/L	Troponin T-103 ng/L, NT-proBNP-12 507 ng/L	Sinus tachycardia	Hypokinesia of the inferior left ventricular wall and the inferior interventricular septum, with mildly reduced ejection fraction to 57%-58%
Warchot et al	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	N/A	N/A	N/A	N/A	N/A
Chiu et al	Leukocytosis with neutrophilia and lymphopenia	ESR-57 mm/h, C-reactive protein 280 mg/L, procalcitonin-28 ng/mL, D-dimer-2727 ng/mL	Troponin-84 ng/L, NT-proBNP-9477 pg/mL	Sinus tachycardia with low voltages	N/A
Singhavi et al	Hemoglobin-1.9 gm%, leukocytosis with thrombopenia	C-reactive protein-26 mg/L, ESR-75 mm/h	Troponin I-9565.2 ng/L, BNP-8000 pg/mL	Mild ST depression and T wave inversion	Global hypokinesia, with a preserved wall thickness and reduced LVEF to 30%
Garot et al	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 LV with increased wall thickness and marked diffuse hypokinesis, LVEF 30%

El-Assaad et al	Leukocytosis with neutrophilia and lymphopenia	C-reactive protein-22 mg/dL, ferritin-1138 ng/mL, D-dimer-3.1 μg/mL	Troponin-84 ng/mL, BNP-2000 pg/mL	Sinus tachycardia	Severe LV systolic dysfunction with LVEF of 32%

Abbreviations: CAD, coronary artery disease; CK-MB, creatine kinase-MB; CT- computed tomography; ESR, erythrocyte sedimentation rate; LV, left ventricle; LVEF, left ventricular ejection fraction; N/A, not available; NT-proBNP, N-terminal pro–B-type natriuretic peptide; RV, right ventricle; ST, ST-segment changes; WBC, white blood cell.

Table 3: Cardiac magnetic resonance imaging (CMRI) and histopathological findings

Author	Cardiac magnetic resonance imaging (CMRI)	Lake Louise Criteria used to diagnose miocarditis	Endomyocardial biopsy (EMB)/autopsy
Coyle et al	Diffuse edema of both atria and both ventricles along with small foci of late gadolinium enhancement	–	N/M
Auer et al	N/M	–	Lymphocytic infiltration in the myocardium and positive staining with anti-CD3 antibody defining T cells (Autopsy findings)
Nicol et al	Normal left ventricular size with mild systolic dysfunction (ejection fraction: 45%) with global hypokinesia. Focal lateral sub-epicardial enhancement on late gadolinium enhancement	Yes	Multiple foci of lymphocytes in a diffuse inflammatory and oedematous background with myocyte necrosis, infiltrated by inflammatory cells; numerous CD138+ plasmocytes, CD3+ CD8+ T cells, and CD163+ macrophages
Oberweis et al	Biventricular systolic dysfunction with small pericardial effusion, mild sub-epicardial gadolinium enhancement of the lateral wall, and signs of diffuse edema	Yes	N/M
Inciardi et al	Generalized hypokinesia of both ventricles, particularly in the apical region, and severe LV dysfunction. Short tau inversion recovery and T2-mapping sequences showed biventricular myocardial interstitial edema	Yes	N/M
Sala et al	Mild hypokinesia at basal and mid-LV segments, diffuse myocardial edema. Late gadolinium enhancement showed no detectable scar or necrosis	Yes	Diffuse T-lymphocytic inflammatory infiltrates with immense interstitial edema and foci of necrosis
Kim et al	T2 STIR showed diffuse elevated signal intensity in LV myocardium and thickening of myocardial wall (suggestive of edema)	–	N/M
Yuan et al	Elevated T2 signal in LV apical segment indicating myocardial edema. Mild LV systolic dysfunction with standard early and late gadolinium enhancement	Yes	N/M
Pavon et al	LV systolic dysfunction (EF 42%) with mild hypokinesia of lateral wall, myocardial edema and sub-epicardial late gadolinium enhancement in	–	N/M

	anterior interventricular septum and inferolateral walls		
Beşler et al	Sub-epicardial elevated signal in mid-posterolateral LV on STIR and gadolinium enhancement in sub-epicardial region of posterolateral wall	Yes	N/M
Sardari et al	Mildly reduced EF 50%. Edema/inflammation in inferoseptal and inferior wall on T2-weighted. Sub-epicardial fibrosis on gadolinium	–	N/M
Trogen et al	Normal size of both ventricles with slightly decreased systolic function. Segment of mid-wall late gadolinium enhancement in inferior junction of both ventricles correlated to increased T2 signal and hypokinesia	–	N/M
Tavazzi et al	N/M	–	Low-grade myocardial inflammation with viral particles in interstitial cells. CD68-positive vacuolated macrophages seen on immunolight microscopy
Luetkens et al	Diffuse interstitial myocardial edema with increased T2 signal intensity ratio. T2 mapping showed diffuse myocardial inflammation (day 10)	Yes	N/M
Kesici et al	N/M	–	SARS-CoV-2 RT-PCR positivity in cardiac tissue
Yokoo et al	Pronounced diffuse hypokinesia and global systolic dysfunction with late enhancement in ischemic pattern in LV base septum	–	N/M
De Vita et al	Enlarged LV with normal thickness; diffuse hypokinesia of LV walls, EF 17%. Enlarged RV with diffuse hypokinesia and reduced contractility. LV apical thrombus	–	N/M
Gnecchi et al	T2 mapping showed edema of inferior, inferolateral walls and lateral wall	–	N/M
Fischer et al	Moderate LV dysfunction (EF 48%), late gadolinium enhancement with interstitial edema and myocardial damage	Yes	N/M
Dalen et al	T1 mapping: relaxation times of 1260–1270 ms in anterolateral wall and 1090 ms in septum. Late gadolinium enhancement in anterolateral wall	–	N/M
Doyen et al	Sub-epicardial late	–	N/M

	gadolinium enhancement of apex and inferolateral wall suggestive of myocarditis		
Spano et al	T2 weighted imaging and T2 mapping revealed diffuse thickening of myocardium and pericardium due to edema	–	N/M
Warchot et al	Left atrial enlargement and global LV hypokinesia, EF 20%. Inferior/inferolateral wall with patchy nonischemic fibrosis on late gadolinium enhancement	–	N/M
Craver et al	N/M	–	Mixed interstitial inflammatory infiltrate with focal rarefaction and eosinophilic infiltrate and slackening of myocytes (autopsy)
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 sub-epicardial 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	Inotropic / Vasopressor	Mechanical support	Complications	Outcomes
Czigci et al	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	Remdesivir, hydroxychloroquine and azithromycin, and Indomethacin 7th day	Methylprednisolone and colchicine	—	Mechanical ventilation	ARDS on 2nd day	N/R
Coyle et al	Hydroxychloroquine, azithromycin, ceftriaxone, and tocilizumab	IV methylprednisolone 500 mg daily × 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	—	—	—	Mechanical ventilation	—	Died on day 9 due to ventricular fibrillation
Dabbagh et al	Hydroxychloroquine	Glucocorticoids and colchicine	—	Intubated	—	Discharged
Nicol et al	Angiotensin-converting enzyme inhibitors and beta-blockers	—	—	—	—	Recovered
Hu et al	IV immunoglobulin, torsemide and furosemide, piperacillin-sulbactam, pantoprazole	IV methylprednisolone 200 mg daily × 4 days	Norepinephrine and milrinone	—	Cardiogenic shock day 1	Recovered
Oberweis et al	Enoxaparin, IV immunoglobulins (2 g/kg)	—	Dobutamine, milrinone	—	—	Discharged on day 10
Inciardi et al	Hydroxychloroquine (200 mg bid), lopinavir/ritonavir (250 q12 h), kanrenone 50 mg, furosemide 25–50 mg, bisoprolol 2.5 mg	IV methylprednisolone 1 mg/kg × 3 days	Dobutamine	—	Cardiogenic shock day 1	Recovered
Irabien-Ortiz et al	Immunoglobulins 80 mg/day, interferon-β 0.25 mg q48 h, ritonavir/lopinavir	IV methylprednisolone 500 mg daily (taper × 14 days)	Norepinephrine	ECMO	Cardiogenic shock day 1	N/R
Sala et al	Lopinavir/ritonavir 500 mg, hydroxychloroquine 200 mg	—	—	—	—	Recovered

Rehman et al	Acetaminophen	—	—	—	—	Discharged
Kim et al	N/R	N/R	N/R	N/R	N/R	N/R
Zeng et al	High-flow O_2, lopinavir-ritonavir, interferon-α1b, immunoglobulin, piperacillin-tazobactam, continuous RRT	IV methylprednisolone	Vasopressors from day 26	ECMO on day 11	Cardiogenic shock day 11; septic shock day 26; ARDS day 1	Passed away on day 33
Radbel et al	Hydroxychloroquine, azithromycin, tocilizumab	—	Norepinephrine day 4	Mechanical ventilation on day 3	Septic shock day 4; cardiogenic shock day 5; ARDS day 3	Died on day 7
Yuan et al	N/R	N/R	N/R	N/R	N/R	Discharged
Pavon et al	Piperacillin-tazobactam	—	Catecholamine	Intubated	—	Discharged
Juusela et al	Pt 1: Hydroxychloroquine, tocilizumab Pt 2: Metoprolol, ceftriaxone IV, azithromycin IV	Pt 1: IV methylprednisolone	—	Pt 1: Intubated	—	Cesarean in both patients
Beşler et al	Hydroxychloroquine, azithromycin, favipiravir, tigecycline, ceftriaxone	Colchicine	—	—	—	Discharged
Sardari et al	Bisoprolol plus ACE-inhibitor lisinopril	—	—	—	—	Discharged
Trogen et al	Hydroxychloroquine, piperacillin-tazobactam, enoxaparin	—	—	—	Septic shock	Discharged
Tavazzi et al	—	—	Adrenaline 0.07 μg/kg/min; noradrenaline 0.1 μg/kg/min	ECMO + IABP	Cardiogenic shock day 1; septic shock	Died
Luetkens et al	N/R	N/R	N/R	N/R	N/R	N/R
Kesici et al	N/R	N/R	N/R	ECMO	Cardiogenic shock	N/R
Hua et al	—	—	Vasopressors	—	Cardiogenic shock day 1	Recovered
Yokoo et al	Antibiotics, steroids	—	—	—	—	Discharged
Khatri et al	Hydroxychloroquine (400 mg bid day 1, then 200 mg bid × 4 days), IV azithromycin, IV vancomycin, IV cefepime, methylene blue	IV methylprednisolone 200 mg/day (day 3)	Dobutamine, vasopressin, norepinephrine	—	Cardiogenic and distributive shock; multi-organ	Died on day 4

	infusion				failure	
De Vita et al	Ethacrynic acid 25 mg, enoxaparin 8000 + 6000 IU sc, spironolactone 25 mg, bisoprolol 2.5 mg, ramipril	—	—	—	—	Recovered
Gnecchi et al	Hydroxychloroquine and ibuprofen	—	—	—	—	Recovered
Fischer et al	Bisoprolol 2.5 mg daily and ramipril 2.5 mg daily	—	—	—	—	Discharged on day 5
Dalen et al	IV fluids	—	Norepinephrine and dobutamine	—	Cardiogenic shock	Recovered
Doyen et al	Aspirin, fondaparinux	IV hydrocortisone for 9 days	—	Mechanical ventilation	Acute respiratory distress syndrome	Discharged from ICU after 3 weeks
Spano et al	N/R	N/R	N/R	N/R	N/R	N/R
Khalid et al	Tocilizumab (two doses 480 & 240 mg), IV immunoglobulin (25 g × 5 days), ceftriaxone, cefdinir, cefepime	—	Norepinephrine	Intubated	Cardiogenic shock, ARDS	Recovered
Giacomet et al	Cefotaxime plus ampicillin, IV immunoglobulins	—	—	—	—	Recovered
Warchol et al	Azithromycin, oseltamivir, magnesium, amiodarone	—	—	—	—	N/R
Craver et al	—	—	—	—	—	Died
Chiu et al	Ibuprofen	—	Dobutamine	—	—	—
Singhavi et al	Pack cell volume transfusion to correct anemia, IV noradrenaline, LMWH, IV vitamin K, low-dose diuretics	Methylprednisolone pulse therapy	Norepinephrine	—	Cardiogenic shock	Discharged on day 10
Garot et al	Paracetamol, hydroxychloroquine (400 mg daily), 2 L/min nasal O_2, cefotaxime, rovamycin	—	Noradrenaline	Intubated	—	Discharged on day 15
El-Assaad et al	IV immune globulin 1 g/kg, anakinra 100 mg tid, unfractionated heparin, remdesivir 100 mg daily	Methylprednisolone 2 mg/kg bid	Epinephrine and norepinephrine infusions	Bi-level positive airway pressure	—	Recovered

Table 5: Management, complications, and outcomes in Covid-19 patients diagnosed with acute myocarditis

Parameter	Patients with reported data on a particular parameter	Total patients: 42 n (%)
Mean age	42	43.4 y
Women	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)
Ischemic stroke		2 (4.9)
Other (asthma, allergic cough, smoking, lymph node tuberculosis, pulmonary sarcoidosis, epilepsy, etc.)		9 (22)
Inflammation 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)

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

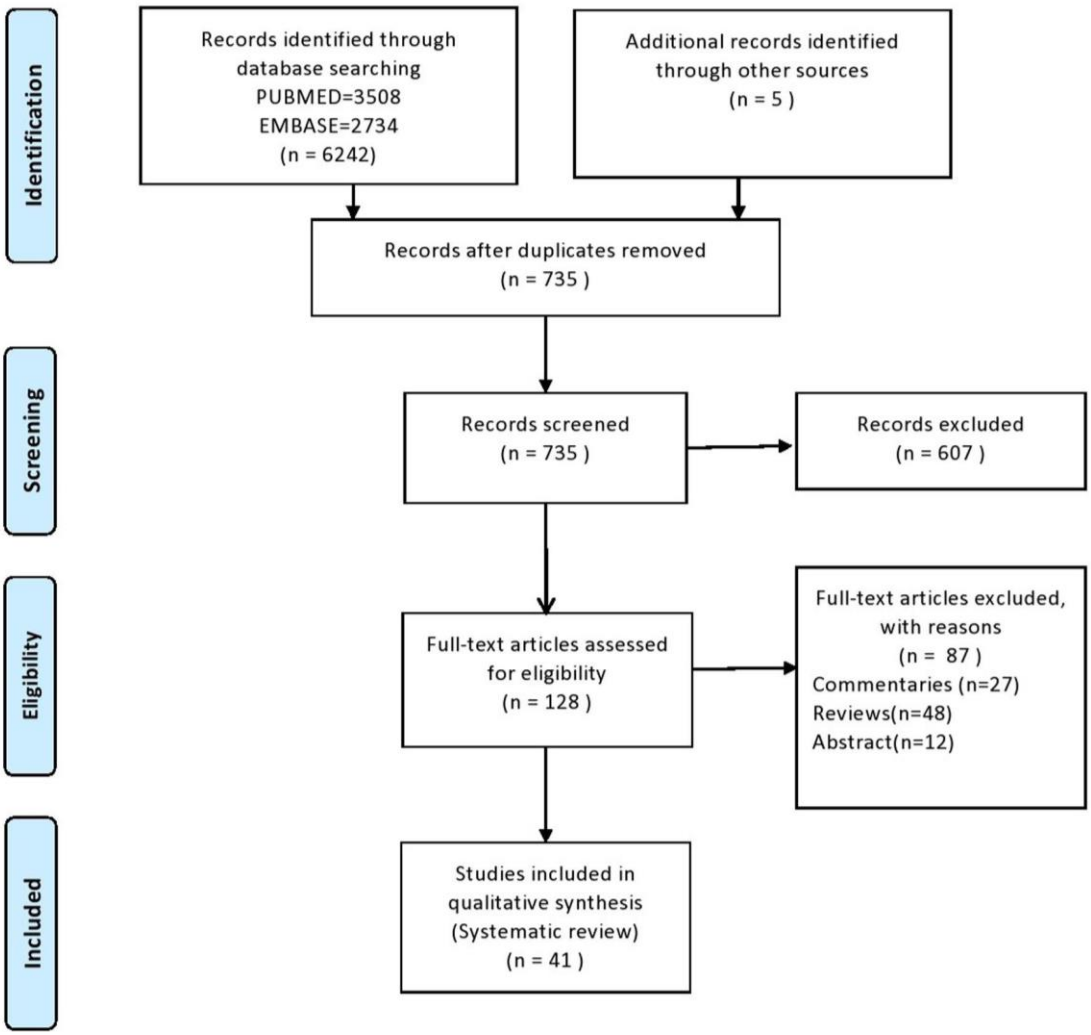
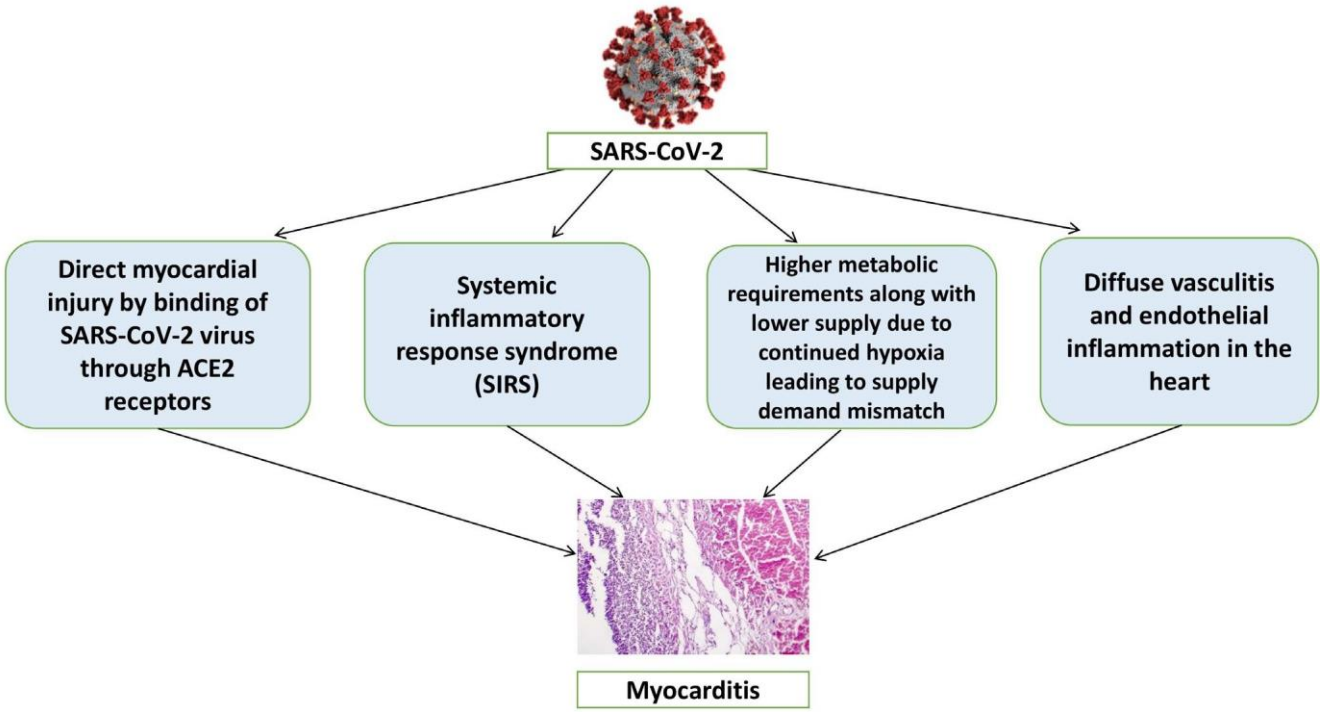


Figure 2: Illustrating several proposed pathophysiological mechanism of myocarditis in Covid-19 patients



Anexo 1. Aprobación de la publicación en la Revista International Journal of Clinical Practice

UNIVERSIDAD PERUANA CAYETANO HEREDIA

Gianpier Alonzo Rojas Barahona <gianpier.rojas@upch.pe>

In Production: Your article accepted in International Journal of Clinical Practice

1 mensaje

cs-author@wiley.com <cs-author@wiley.com> 9 de junio de 2021, 2:19
Para: gianpier.rojas@upch.pe

Dear Gianpier Rojas,

Article ID: IJCP14470
Article DOI: 10.1111/ijcp.14470
Internal Article ID: 17133290
Article: Myocarditis associated with Covid-19 disease: a systematic review of published Case reports and Case series
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