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ORIGINAL ARTICLE

Covid-19 and Heart Involvement: A Systematic Review of Literature

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Abstract

Background: Recent reports in the literature have indicated that infection by coronavirus disease 2019 (COVID-19) causes cardiac complications, such as heart failure, arrhythmia, myocardial infarction, and even fulminant myocarditis. These complications have been identified as the cause of death in some patients infected with SARS-CoV-2.

Objectives: To analyze echocardiographic and electrocardiographic changes, treatments used, and clinical outcomes in patients with myocarditis and COVID-19.

Methods: The items described for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed. This review included articles in English, Portuguese, and Spanish that reported cardiac involvement, injury, or myocardial inflammation in patients who acquired COVID-19 (SARS-CoV-2).

Results: Five databases were consulted to find 1,726 articles. After applying the eligibility criteria, a total of 22 studies were considered qualified. ST-segment (section of the electrocardiogram corresponding the end of the S wave to the beginning of the T wave) elevation and tachyarrhythmia were the most common changes found in the electrocardiographic analysis of patients affected with COVID-19. Concerning echocardiography, there was a high frequency of decreased ejection fraction and occurrence of pericardial effusion.

Conclusion: This systematic review provides a potential tool for the analysis of cardiac changes and implications caused in patients affected by SARS-CoV-2 infection, with emphasis on the presence of tachyarrhythmia on electrocardiogram (ECG) and decreased ejection fraction on echocardiogram.

Keywords: COVID-19; Myocarditis; Systematic Review.

Introduction

At the end of December 2019, Chinese health authorities reported a sudden increase in cases of pneumonia that were epidemiologically linked to a market for seafood and wet animals located in Wuhan, Hubei Province, China. The causative agent of viral origin was isolated and identified as a new coronavirus strain, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2]

Coronavirus disease 2019 (COVID-19) has mainly respiratory manifestations, with clinical symptoms of cough, fever, progressive shortness of breath, and complications resulting from pneumonia and acute respiratory distress syndrome. As cases increased, cardiovascular manifestations and complications were reported.[3-5]

The infection occurs in humans through contact with respiratory secretions. The entry of SARS-CoV-2 into the human body is through angiotensin-converting enzyme 2 (ACE2). ACE2 is highly expressed in cell membranes of lungs, heart, intestine, blood vessels, and others, and it becomes a mediating receptor of SARS-CoV-2 entry into the cell membrane. The virus has a more compact structure with greater binding stability and a high affinity for ACE2. ACE2 is also responsible for acting in the modulation of the renin-angiotensin-aldosterone

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system, which is important for regulating blood pressure and other functions related to the cardiovascular and renal systems.[6,7]

COVID-19 can cause myocarditis, which leads to serious damage to the cardiovascular health of patients with coronary artery disease. The main mechanisms involved in the pathogenesis are the hyperinflammatory state mediated by pro-inflammatory cytokines such as the interleukins IL-2, IL-10, IL-6, IL-8 and tumor necrosis factor (TNF-α); endothelial dysfunction resulting from the interaction between ACE2 and SARS-CoV-2; processes of macro- and microthrombotic arterial occlusion induced by stress in the autonomic nervous system; and endothelial, coronary, and smooth muscle cell dysfunction associated with macrophages and platelet activation, precipitating instability and rupture of the atheromatous plaque that leads to thrombus formation. These factors together lead to myocardial injury, hypoxia, and cardiotoxicity, which cause myocarditis and aggravation in patients with preexisting coronary artery disease.[6-9]

Viral infection is described as one of the most common infectious causes of myocarditis onset, particularly influenza and parvovirus B19. However, cardiac involvement as a complication of SARS-CoV-2 infection is still poorly understood. It appears that it affects the cardiovascular system because of an elevation of cardiac biomarkers such as troponin T and type B natriuretic peptide.[10,11]

Cardiac dysfunction does not present as a common sequela in patients affected by SARS-CoV-2; however, a significant number of patients were observed with myocardial injury. COVID-19 infection can cause cardiac complications, such as heart failure, arrhythmia, myocardial infarction, and even fulminant myocarditis. The literature also reports the occurrence of acute myopericarditis and pericardial effusion in patients with COVID-19, even in the absence of severe pulmonary disease. Myocarditis has already been identified as the cause of death in some patients infected with SARS-CoV-2. The highest frequency of cardiac involvement is in the focal myocardium, with risk of arrhythmia, progression to fulminant heart failure, and cardiogenic shock.[3,12-14]

The objective of this systematic review is to map the clinical changes in electrocardiogram (ECG) and echocardiogram of patients with COVID-19 confirmed by reverse-transcriptase chain reaction (RT-PCR), who developed myocarditis, as well as the clinical outcomes and treatments employed in each case.

Methods

Protocol and Registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), which consists of a checklist with 27 items and a four-step flowchart to assist the construction of systematic reviews and meta-analyses.[15]

Eligibility Criteria

Inclusion Criteria

Only case reports and case series that recorded cardiac involvement, injury, or myocardial inflammation in patients who acquired COVID-19 confirmed by RT-PCR were chosen for this study. The articles were in English, Portuguese, and Spanish, and only studies that presented information on clinical manifestations, with or without changes in the ECG and echocardiogram were included. Alterations considered abnormal in the ECG were based on the Recommendations for the Standardization and Interpretation of the Electrocardiogram Guidelines from the American Heart Association/American College of Cardiology/Heart Rhythm Society, consisting of atrial or ventricular arrhythmias, conduction disorders, or other electrophysiological information indicated in the exam as suggestive of pathology. Abnormalities in echocardiogram followed recommendations from the American Society of Echocardiography and included reduced ejection fraction, motility disorders, wall or ventricle thickening, presence of blood clots, or other morphological and non-morphological changes that imply abnormal heart functioning.[16-22]

Exclusion Criteria

In this study, articles that were not case reports, series of cases, or observational studies were excluded. Articles from literature reviews, encyclopedias, editorials, book chapters, conference summaries, correspondence, reviews, news, and small communications were also excluded. Studies that did not present data regarding age, sex, ECG, echocardiogram, RT-PCR result, and myocarditis related to SARS-CoV-2 infection were excluded.

Information Sources and Search Strategies

The literature review used databases in which all studies reporting infection-induced myocarditis due to COVID-19 were described. The following descriptors were used: "coronavirus", "COVID-19", "myocarditis", "myopericarditis", "case report", and "coronavirus infections".

The articles used are indexed in the Medical Literature Analysis and Retrieval System Online (Medline) databases, consulted in PubMed, Scientific Electronic Library Online (SciELO), Cochrane CENTRAL, LILACS, and Science Direct.

Study Selection

The screening of the articles included in this work was performed based on the analysis of whether the title and abstract met the eligibility criteria, which were elected by fulfilling the inclusion criteria and not meeting any of the exclusion criteria. Articles that met the inclusion criteria were read in full, while the articles that met any of the exclusion criteria were excluded from the selection of this review.

Data Collection Process and Data Items

Among the articles included, the authors' names, year, place of publication, and methodology were removed. For case reports, information on age, sex, and possible complaints presented by the patient during the admission period were removed. Diagnostic strategies, laboratory tests performed, treatment, outcomes, and complications were extracted.

Synthesis of Results and Summary of Measures

For the analysis of the results obtained, the data were tabulated and duly described regarding their absolute frequency and relative frequency.

Risk of Bias of the Included Studies

To reduce the risk of bias, all studies included in this work underwent peer review.

Results

Study Selection

Five databases were consulted to find 1,726 articles, and, of these, 266 duplicated articles were excluded from more than one database, resulting in 1,075 articles. In addition, 363 articles were not included in the analysis because of the non-association between COVID-19 and myocarditis. Thus, out of a total of 1,726 articles, 22 were selected, according to the eligibility criteria for the study, which represents 0.01% of all the articles found (Figure 1).

Study Characteristics

Of the 22 articles selected, 21 were case report studies[23-44] and 1 was a case series study.[27] Therefore, the number of participants in the studies ranged from 1 to 2 patients. Of the articles, 17 were published in 2020[23,25,26,28,29,31-34,36-44] and 5 in 2021.[24,27,29,30,35] All articles were peer-reviewed. Ten studies were conducted in the United States of America.[27-30,32,33,37-40] Six studies were conducted in Europe: three in France,[25,34,42] two in Spain,[36,41] and one in Italy.[31] In the Asian continent, three studies were conducted: two in Iran[24,26] and one in the United Arab Emirates.[23] In the African continent, one study was conducted in Morocco.[35] In South America, two studies were conducted: one in Brazil,[43] and one in Colombia.[44]

Risk of Bias within the Studies

Descriptive studies, such as case reports and case series are subject to bias, due to their format, methods, and level of evidence.

Results of Individual Studies

Twenty-two case reports were selected for the systematic review. Al-Assaf et al.[23] described an atypical presentation of COVID-19 as subclinical myocarditis with persistent high-degree atrioventricular block treated with pacemaker implant, in a 58-year-old man in the United Arab Emirates. Nikoo et al.[24] presented a case of systolic dysfunction and complete heart block as complications of fulminant myocarditis in a case of recovered COVID-19 in a 38-year-old woman from Iran. Fischer et al.[25] described a case report of isolated myocarditis due to COVID-19 infection in a pediatric patient in France. The study from Iran by Malekrah et al.[26] reported a rare cardiac complication caused by novel coronavirus disease in a 76-year-old man. The article by Purdy et al.[27] registered a case series of myocarditis in COVID-19 presenting with cardiogenic shock, in the United States of America, in two patients age 53 and 30 years old. The article by Tiwary et al.[28] reported a rare

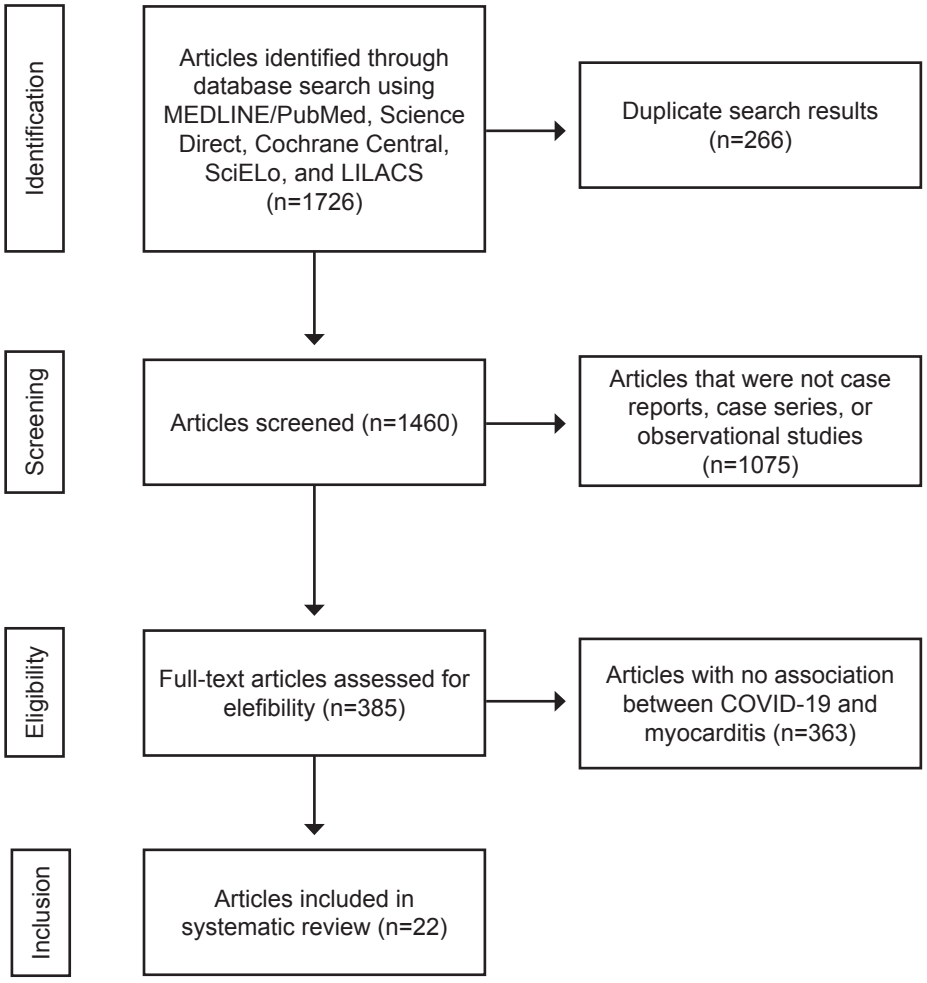

Figure 1 – Diagram of the research selection flow adapted from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

case of COVID-19 myocarditis with cardiac tamponade in a young adult with diabetes and renal failure, in the United States of America. In the study by Albdelazeem et al.,[29] persistent cardiac magnetic resonance imaging (CMRI) features of myocarditis detected months after COVID-19 infection were described in a 41-year-old woman from the United States of America. Mathew et al.[30] reported subacute thyroiditis and heart failure in a patient presenting with COVID-19 in the United States of America. Veronese et al.[31] described fulminant myocarditis triggered by OC43 subtype coronavirus in an Italian patient. The study from the United States of America by Venkata et al.[32] registered a case of acute right ventricular dysfunction in a critically ill 67-year-old patient with COVID-19. Dabbagh et al.[33] registered a cardiac tamponade secondary to COVID-19 in a 67-year-old man from the United States of America. Mangiamelli et al.[34] described the feasibility of prone position coronary angiography in a patient with COVID-19 pneumonia and refractory hypoxemia from France and its consequences for the heart. Faraj et al.[35] described a case report of acute pericarditis revealing COVID-19 infection in a 36-year-old man in Morocco. In the Spanish study by Cardenes et al.,[36] acute coronary syndrome (ACS) and shock in the context of acute COVID-19 infection were presented in a 74-year-old man. Bascuñana et al.[37] described thrombotic microangiopathy in a 40-year-old male kidney transplant patient with COVID-19 in the United States of America. Minhas et al.[38] reported a 58-year-old woman with Takotsubo syndrome in the setting of COVID-19 from the United States of America. The case report of a 71-year-old woman with complete heart block and COVID-19

infection in the United States of America was described by Haddadin et al.[39] Loghin et al.,[40] in an article from the United States of America, described a pseudo-acute myocardial infarction in a young COVID-19 patient. The Spanish study by Rey et al.[41] registered COVID-19 infection and simultaneous thrombosis of two coronary arteries in a 59-year-old man. Nicol et al.[42] described delayed acute myocarditis and COVID-19–related multisystem inflammatory syndrome in a 40-year-old male patient from France. The Brazilian study by Yokoo et al.[43] described COVID-19 myocarditis in an 81-year-old man. Finally, Bernal-Torres et al.[44] reported COVID-19 fulminant myocarditis in a 38-year-old female Colombian patient with recent history of travel to Spain.

Table 1 exhibits the identification of the articles included in the study.

Synthesis of Results

Patient Profiles

In the respective studies, the age group ranged from 15 to 81 years, with the mean age of 51 years. In addition, the male sex (63.6%) was the most prevalent.

Clinical Manifestations

Most patients had fever at hospital admission, accounting for 54.5% of the articles that reported myocarditis in COVID-19.[25-27,31,34,36-38,40-43] Subsequently, symptoms such as dyspnea (54.5%),[26 27,30-33,35-37,39,40,43] cough (45.4%),[26,27,29,32-34,38-41] and chest pain (22.7%),[24,25,28,29,35] respectively, affected patients (Table 2).

Table 1 – Identification of the articles included in the study

Authors	Country	Type of study	Publication year
Al-Assaf et al.[23]	United Arab Emirates	Case Report	2020
Nikoo et al.[24]	Iran	Case Report	2021
Fischer et al.[25]	France	Case Report	2020
Malekrah et al.[26]	Iran	Case Report	2020
Purdy et al [27]	United States of America	Case Series	2021
Tiwary et al.[28]	United States of America	Case Report	2020
Abdelazeem et al.[29]	United States of America	Case Report	2021
Mathews et al [30]	United States of America	Case Report	2021
Veronese et al.[31]	Italy	Case Report	2020
Venkata et al.[32]	United States of America	Case Report	2020
Dabbagh et al.[33]	United States of America	Case Report	2020
Mangiameli et al.[34]	France	Case Report	2020
Faraj et al.[35]	Morocco	Case Report	2021
Cárdenes et al.[36]	Spain	Case Report	2020
Bascuñana et al.[37]	United States of America	Case Report	2020
Minhas et al.[38]	United States of America	Case Report	2020
Haddadin et al.[39]	United States of America	Case Report	2020
Loghin et al.[40]	United States of America	Case Report	2020
Rey et al.[41]	Spain	Case Report	2020
Nicol et al.[42]	France	Case Report	2020
Yokoo et al.[43]	Brazil	Case Report	2020
Bernal-Torres et al.[44]	Colombia	Case Report	2020

Comorbidities

Regarding the comorbidities associated with the clinical status of the patients, the most prevalent were systemic arterial hypertension (27.3%)[23,28,36,38,41,43] and type 2 diabetes mellitus (22.7%).[32,36,38,39,41] However, it is worth noting that 31.8% of the patients did not present comorbidities,[23,26,27,34,35,40,44] as shown in Table 2.

ECG changes

The ECG showed that most patients presented elevation of the ST segment (31.8%).[25,34,36,38,40,41,44] In addition, six studies (27.3%) reported normality in their patients,[24,30,32,35,37,42] as shown in Table 3.

Changes in Echocardiogram

When observing the results of the echocardiograms presented in the studies, the presence of hypokinesis (31.8%),[24,25,27,31,34,36,44] left ventricular ejection fraction below 50% (45.5%),[24,27,30,31,33,34,38,42-44] and pericardial effusion (27.3%) were significant.[27,28,33,35,42,44]

Cardiac Magnetic Resonance Imaging

CMRI was performed in 40.9% of the studies.[23-25,29,31,40,42-44] The presence of myocarditis (88.8%),[23,25,29,31,40,42-44] edema (66.6%),[23,25,31,40,44] myocardial inflammation (66.6%),[23,24,29,42,43] and late gadolinium enhancement (LGE) (55.5%)[25,31,42-44] were the most frequent characteristics among the studies that reported CMRI.

Hemodynamic Aspects

The increased levels of troponin I or troponin T (63.6%)[24,25,28-34,36-38,42-44] were the most recurrent hemodynamic alterations in patients who developed cardiac involvement due to COVID-19. There were frequent reports of oxygen saturation (SaO_2) below 95% (40.9%),[24,26,31,34,35,37,38,41,43] increased D-dimer (31.8%),[27,29,32,36,37,41,42] evolution of patients to cardiogenic shock (22.7%),[27,31,36,38,44] and occurrence of metabolic acidosis (18.1%).[27,31,37,44]

Management

It is possible to observe that the treatment varied, from more conservative to more invasive treatments. For the most part, treatment was based on the use of drugs (72.4%), such as antibiotics,[27-29,35,37,38,41-44] antimalarials,[26,27,33,36-38,41,44] antihypertensive,[25,27,34,42,44] antiarrhythmic,[24,25,27,29,34,42,44] antiretroviral,[26,28,29] corticosteroids,[24,27-31,33,37,43,44] and others. Others were managed with procedures, associated or not with medical therapy, such as pacemaker implantation (18.1%)[23,24, 26,39] and orotracheal intubation (13.6%).[32,33,40]

Clinical Outcome

Hospital discharge was prevalent in 59.1% of cases.[23-25,27-29,33,35,37,42-44] However, in 27.3% of the studies, the patients died, and these clinical outcomes were the most representative.[32,34,36,38,39,41] Table 3 summarizes the data.

Risk of Bias across the Studies

Due to the nature of the descriptive studies, the results presented are liable to investigator bias, selection procedure bias, and selection bias.

Discussion

SARS-CoV-2 is a beta coronavirus that presents the composition of a positive enveloped RNA simple tape structure. It belongs to the subfamily Coronavirinae. The virus invades the human cell by binding with ACE2, a protein present in the cell membrane that is present in the cardiovascular epithelium. With its entry into the cellular environment, it migrates to the inside of the core for replication and apoptosis.[10,45]

The pathophysiology of severe COVID-19 has not yet been fully elucidated. However, the presence of a pro-inflammatory peak, known as a cytokine storm has been observed.[43] The damage caused by COVID-19 to the cardiovascular system is multifactorial, and it can result in a disorder between the high metabolic demand of cardiac tissue and low cardiac reserve, thrombogenesis, inflammation on a systemic level, and injury to cardiac tissue by the invasion of the virus to the myocardium. Generally, the most severe cases of acute cardiac injury occur in patients with preexisting comorbidities, such as diabetes mellitus, systemic arterial hypertension, chronic kidney disease, and cardiovascular disease, which are linked to a worse clinical prognosis.[46,47] These characteristics were observed in this study where we noticed that, in 31.8% (n = 7) of the studies in which the patients died,[32,34,36,38-41] 71.4% (n = 5) had registered comorbidities.[32,36,38,39,41]

Myocarditis presents various clinical manifestations, from mild symptoms, such as chest pain, palpitations, and fatigue, to cardiogenic shock or sudden cardiac death

Table 2 – Clinical characteristics of the patients included in the study

Authors	Age	Sex	Symptoms/ Clinical manifestations	Comorbidities
Al-Assaf et al.[23]	58-year-old	Male	Asymptomatic	SAH
Nikoo et al.[24]	38-year-old	Female	Malaise, chest pain, nausea, vomiting	Not informed
Fischer et al.[25]	15-year-old	Male	Chest pain, fever	Not informed
Malekrah et al.[26]	71-year-old	Male	Weakness, fever, cough, dyspnea	Not informed
Purdy et al.[27]	53-year-old	Male	Fever, cough, weak breath, tachycardia, tachypnea	Not informed
	30-year-old	Female	Fatigue, weak breathing, tachycardia, tachypnea, hypotension	Obesity
Tiwary et al.[28]	30-year-old	Male	Abdominal pain, chest pain, fatigue, vertigo	DM1, obesity, SAH, glaucoma, diabetic nephropathy, and CKD
Abdelazeem et al.[29]	41-year-old	Female	Chest pain, cough	Not informed
Mathews et al.[30]	67-year-old	Male	Diarrhea and dyspnea	DM1, history of acute myocardial infarction, coronary artery disease, and CKD
Veronese et al.[31]	51-year-old	Female	Dyspnea, palpitations, fever	Thalassemia minor
Venkata et al.[32]	67-year-old	Male	Malaise, anorexia, dry cough, dyspnea, severe respiratory distress	Chronic obstructive pulmonary disease, CKD, DM2; history of hepatocellular carcinoma, rectal adenocarcinoma, and non-small cell lung cancer
Dabbagh et al.[33]	67-year-old	Female	Cough, pain in the left shoulder, severe dyspnea, and orthopnea	Non-ischemic heart disease with LVEF of 15% in 2018, but improved to 40% after treatment
Mangiameli et al.[34]	57-year-old	Female	Fever, cough and severe fatigue	Not informed
Faraj et al.[35]	36-year-old	Male	Chest pain and dyspnea	Not informed
Cárdenes et al.[36]	74-year-old	Male	General malaise, fever, dyspnea, and severe hypoxemia	SAH, DM2, and history of hemorrhagic stroke
Bascuñana et al.[37]	40-year-old	Male	Fever, dyspnea, diarrhea, and abdominal pain	CKD
Minhas et al.[38]	58-year-old	Female	Productive cough, fatigue, fever, and diarrhea	DM2, SAH, and dyslipidemia
Haddadin et al.[39]	71-year-old	Female	Nonproductive cough, dyspnea at minimal efforts, orthopnea, and loss of smell and taste	Parkinson's disease, bipolar disorder, and DM2
Loghin et al.[40]	29-year-old	Male	Nonproductive cough, fever, myalgia, sore throat, malaise, and dyspnea	No comorbidities
Rey et al.[41]	59-year-old	Male	Nonproductive cough, low fever, asthenia, and headache	SAH, DM2, and history of hemorrhagic stroke
Nicol et al.[42]	40-year-old	Male	Fever, fatigue, anosmia, and myalgia	Obesity
Yokoo et al.[43]	81-year-old	Male	Fever and dyspnea	SAH
Bernal-Torres et al .[44]	38-year-old	Female	Palpitations	No comorbidities

CKD: chronic kidney disease; DM1: type 1 diabetes mellitus; DM2: type 2 diabetes mellitus; SAH: systemic arterial hypertension.

Table 3 – Clinical Outcome

Authors	ECG changes	Echocardiogram changes	RT-PCR	CMRI Description	Hemodynamic Aspects	Treatment	Clinical Outcome
Al-Assaf et al. [23]	Bradycardia, sinus rhythm, and 2:1 atrioventricular block	Slightly dilated aorta	Positive	Edema of the interventricular septum and myocarditis	No changes were recorded.	Definitive cardiac pacemaker	Hospital discharge
Nikoo et al. [24]	Sinus rhythm	Diffuse hypokinesis with reduced LVEF of 20% to 25%	Positive	Diffuse myocardial inflammation of the left ventricular myocardium	Hypotension; SaO_2 92%; hypercoagulability; increased troponin I, prothrombin time, and INR; and hydroelectrolytic disorders	Amiodarone; dexamethasone; temporary cardiac pacemaker	Hospital discharge
Fischer et al. [25]	Diffuse elevation of the ST segment without reciprocal changes	Mild diffuse hypokinesis with preserved LVEF (50%)	Positive	Moderate left ventricle dysfunction, involvement of posterolateral wall of the left ventricle related to acute myocardial edema, LGE, and myocarditis	The hemodynamics of the patient remained stable. Increased high-sensivity troponin I was related.	Bisoprolol; ramipril	Hospital discharge
Malekrah et al. [26]	Intermittent block of the left branch; episodes of atrial fibrillation with bradycardia	Normal	Positive	Not performed	SaO_2 85% and normal blood pressure	Hydroxychloroquine; combination of lopinavir and ritonavir; permanent cardiac pacemaker	Persistence of left branch block
Purdy et al. [27]	Sinus taquicardia with J-spot elevation in inferolateral leads	Reduced LVEF (25%) with diffuse hypokinesis and moderately dilated right ventricle with reduced right ventricular function	Positive	Not performed	Low cardiac output and cardiac index with progression to cardiogenic shock; SaO_2 95%	Methylprednisolone; hydroxychloroquine + empirical antibiotic; aspirin, atorvastatin, isosorbide, dinitrate, hydralazine, carvedilol, and eplerenone	Hospital discharge
	Sinus tachycardia	Reduced LVEF (45%), hypokinesis, and moderate pericardial effusion	Positive	Not performed	Lactic acidosis, elevated NT-proBNP and D-dimer, and diagnosis with cardiogenic shock, which was treated	Hydroxychloroquine, vitamin C, zinc, and atorvastatin	Hospital discharge

Tiwary et al.[28]	Left bundle branch block	Pericardial effusion, early right ventricular ventricle prolapse, and ventricular wall thickening	Positive	Not performed	Increased troponin I, progressive hypotension, and progressive increase of fraction of inspired oxygen	Norepinephrine and vasopressin, remdesivir, convalescent plasma, dexamethasone and cefepima + doxycycline	Hospital discharge
Abdelazeem et al. [29]	Atrial fibrillation	Left ventricular hypertrophy and infiltrative cardiomyopathy	Positive	Extensive myocarditis involving sub-epicardial and mid-wall of the left ventricular and interventricular septum	Increased troponin I, increased BNP, and increased D-dimer	Diltiazem, steroids, antibiotics, remdesivir, and convalescent plasma	Hospital discharge
Mathews et al. [30]	Sinus rhythm	Reduced LVEF (24%)	Positive	Not performed	Increased troponin, increased NT-proBNP, and increased erythrocyte sedimentation rate	Metimazole + prednisone	Not informed
Veronese et al. [31]	Ventricular tachycardia	Hypocontratile left ventricle, reduced LVEF (30%), and wall thickening	Positive	Biventricular functional recovery, diffuse edema recovery, LGE involving LV basal-lateral and basal-inferior walls, and myocarditis	Cardiogenic shock with severe metabolic acidosis, increased troponin I, hypotension, signs of peripheral hypoperfusion, and SaO_2 93%	Mechanical circulatory support with intra-aortic balloon counterpulsation + veno-arterial extracorporeal membrane oxygenator + methylprednisolone pulse therapy	Not informed
Venkata et al. [32]	Sinus rhythm	Preserved LVEF, severely dilated right ventricle, and severe tricuspid regurgitation	Positive	Not performed	Elevated high-sensitivity troponin I and D-dimer	Ventilatory support in prone position, norepinephrine, and vasopressin	Death
Dabbagh et al . [33]	Low voltage in member derivations	Slightly reduced LVEF and pericardial effusion	Positive	Not performed	Normal troponin I and midly elevated BNP	Intubation, cardiac catheterization, hydroxychloroquine, colchicin, and glucocorticoids	Hospital discharge
Mangiameli et al. [34]	ST-segment elevation in anteroseptal leads and ST-segment depression with T-wave inversion in DIII and aVF	Anteroapical wall hypokinesis and reduced LVEF (20%)	Positive	Not performed	Normal blood pressure, SaO_2 81%, elevated high-sensitivity troponin T	Emergency coronary angiography, nitroglycerin, and verapamil	Death

Faraj et al. [35]	Sinus rhythm	Pericardial effusion	Positive	Not performed	Normal blood pressure, SaO_2 85% to 88%, elevated platelet counts, and elevated ferritin	Colchicin, vitamin C, vitamin D, zinc, and azithromycin	Hospital discharge
Cárdenes et al. [36]	Isolated elevation in D3 and ST unevenness in V2-V4	Left ventricular dysfunction with inferolateral hypokinesis	Positive	Not performed	Increased troponin T, D-dimer, BNP, and lactate dehydrogenase; septic shock and cardiogenic shock associated; hypercoagubility; and DIC	Norepinephrine, emergency cardiac catheterization, percutaneous coronary intervention, and placement of 2 drug-eluting stents; hydroxychloroquine and tocilizumab	Death
Bascuñana et al. [37]	Sinus rhythm	No changes	Positive	Not performed	Normal blood pressure, SaO_2 93%, lymphopenia, thrombocytopenia, high serum C-reactive protein and D-dimer levels, high-sensitivity cardiac troponin I level, metabolic acidosis, anemia, and elevated lactate dehydrogenase	Oxygen therapy, volume replacement, hydroxychloroquine, azithromycin, and methylprednisolone	Hospital discharge
Minhas et al. [38]	Sinus tachycardia and ST segment elevation in I and aVL leads	Reduced LVEF (20%)	Positive	Not performed	High blood presure, SaO_2 82%, increased troponin I level, and evolution to cardiogenic shock	Dual antiplatelet therapy, heparin, hydroxychloroquine, and azithromycin	Death
Haddadin et al. [39]	Complete heart block with junctional ventricular escape rhythm	Thickened mitral valve leaflets and dilated left atrium	Positive	Not performed	High blood pressure, SaO_2 97%, leukocytosis, anemia, hyponatremia, elevated C-reactive protein, and elevated fibrinogen	Introduction of dual camera cardiac pacemaker	Death

Loghin et al. [40]	Sinus taquicardia and ST elevation in leads II, III, aVF, and V6	No changes	Positive	Myocardial edema and myocarditis	Hemodynamic stability	Orotracheal intubation	Hospital discharge
Rey et al. [41]	ST-segment elevation in the lower leads and v4 to V6, Q wave, and first degree atrioventricular block	No changes	Positive	Not performed	Thrombocytosis, atherosclerotic plaque rupture, high blood pressure, SaO_2 92%, elevated C-reactive protein, elevated D-dimer, and DIC	Tirofiban, aspirin, plasugrel, enoxaparin, hydroxychloroquine, ceftriaxone, and azithromycin	Death
Nicol et al. [42]	Sinus tachycardia	Reduced LVEF (45%), low cardiac output, and small pericardial effusion	Positive	Systolic dysfunction with global hypokinesia, myocardial inflammation, pericardial effusion, myocarditis, and LGE	High blood pressure; elevated BNP, C-reactive protein, fibrinogen, procalcitonin, D-dimer, and cardiac troponin (high-sensitivity troponin I)	Angiotensin-converting enzyme inhibitors, beta blockers, and antibiotic	Hospital discharge
Yokoo et al. [43]	Showed no signs of ischemia	Reduced LVEF (35%)	Positive	Ischemic pattern on the left ventricle base septum wall, diffuse hypokinesia, global systolic function involvement, myocarditis, and LGE areas with an ischemic pattern on the left ventricle base septum wall	SaO_2 91% and high troponin T	Antibiotics, steroids, and hemodynamic monitoring	Hospital discharge
Bernal-Torres et al.[44]	Diffuse elevation of the ST segment, with depression of the PR segment and Spodick sign	Reduced LVEF (30%), global hypokinesis, and mild pericardial effusion	Positive	Transmural extent of myocardial edema to both ventricles, myocarditis, and left ventricular LGE	Elevated jugular venous pressure, hypontesion, cardiogenic shock, SaO_2 95%, metabolic acidosis, and increased troponin I and BNP	Oxygen therapy, methylprednisolone, human immunoglobulin, hydroxychloroquine, azithromycin, norepinephrine, dobutamine, levosimendan, and furosemide	Hospital discharge

BNP: type B natriuretic peptide; DIC: disseminated intravascular coagulation; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; RT-PCR: reverse-transcriptase chain reaction; PR Segment: the period of the electrocardiogram from the beginning of the P wave to the beginning of the Q wave; SaO2: oxygen saturation; ECG: electrocardiogram; CMRI: cardiac magnetic resonance imaging.

due to association with ventricular arrhythmias.[4,12-14,47] In myocarditis, there is focal or global myocardial inflammation, necrosis, and even ventricular dysfunction. The suspicion of focal myocarditis is raised in the presence of chest pain after a syndrome that is similar to influenza, thus presenting clinical evidence that points to an ACS for ECG or laboratory tests, or even with the presentation of cardiac wall movement abnormalities, but without evidence of an obstructive coronary artery disease for coronary angiography.[2,5,11,46,48-52]

The mechanisms and manifestations of cardiac arrhythmia are variable and include supraventricular tachycardia, polymorphic ventricular tachycardia, and torsade. However, the etiology of these abnormalities is still unclear. They may come from the disease itself through the inflammatory cascade, myocarditis, and hypoxia, or from the therapies based on chloroquine, hydroxychloroquine, moxifloxacin, and azithromycin.[47-49] In our study, the use of these medications was reported in 54.5% of the studies in which there was cardiac involvement after diagnosis of COVID-19.[26-29,33,35-37,41-44]

Acute respiratory infection caused by SARS-CoV-2 may be linked to an increased risk for classic myocardial infarction, as it is already known that inflammatory responses in the endothelium, such as that occurring in COVID-19, can increase the occurrence of plaque rupture.[48]

Transthoracic echocardiography is more likely to detect changes in contractility of the ventricular segment, perfused by the coronary artery, which is involved in patients with ACS. Therefore, echocardiography may be an aid tool for differential diagnosis between myocarditis and ACS resulting from COVID-19 infection.[45,46,53,54]

For myocarditis, we usually find diffuse hypokinesis with a reduction of ventricular ejection fraction, with possible presentation of a slightly associated pericardial effusion; however, segmental dyskinesia may also occur with even a hypodynamic state. Myocarditis may also clinically present with preserved ventricular function, with no change to segmental ventricular contractility in echocardiography.[14,45]

The most frequent alterations and characteristics found in echocardiography of patients with cardiac impairment are reduced left ventricular ejection fraction, pericardial effusion, global hypokinesis, left ventricular hypertrophy, diastolic dysfunction, pulmonary hypertension, and reduced overall longitudinal deformation. In the most severe cases, the following manifestations were observed: hyperdynamic phase, in which there is an increase in parameters for cardiac output and the left ventricular ejection fraction, with a consequent decrease in peripheral vascular resistance; acute cardiomyopathy generated by stress, which presents abnormalities for segmental contraction and ballooning of the apical region of the left ventricle (known as Takotsubo cardiomyopathy); acute pulmonary hypertension and right ventricular hypertrophy; and systolic and/or diastolic global dysfunction resulting from long-term anoxia, severe hypoxia, or systemic inflammation.[46,53-56] Regarding our study, we noticed that the most frequent manifestations on echocardiogram were similar to those already described in the literature, with significant presence of hypokinesis (31.9%),[24,25,27,31,34,36,44] reduced left ventricular ejection fraction (45.5%),[24,27,30,31,33,34,38,42-44] pericardial effusion (27.3%),[27,28,33,35,42,44] ventricular dysfunction (9.0%),[27,36] and ventricular hypertrophy (13.6%).[28,29,31]

Therefore, transthoracic echocardiography has been shown to be a means of early clinical evaluation of patients with SARS-CoV-2, since this method allows the visualization of hemodynamic evidence, capable of guiding the appropriate management. For patients with the most severe form of COVID-19, it is recommended to perform and evaluate daily echocardiography, as well as guidance for treatment that presents inotropic and/or circulatory support. In this study, echocardiographic analysis proved to be of fundamental importance for the determination of the therapeutic strategies aimed at intervening favorably in the cardiac picture of the patient affected by the disease. We have observed the use of pacemakers (18.1%),[23,24,26,39] beta-blockers and other antiarrhythmics (31.8%),[24,25,27,29,34,42,44] ACE inhibitors (9.0%),[25,42] diuretics (18.1%),[27-29,44] in patients depending on the specific clinical need of each case, thus contributing to and corroborating previous analyses.[23,46]

The causative factors of the alterations observed in ECG induced by COVID-19 are not yet fully described. However, studies indicate that the virus can have a direct action on cardiomyocytes through an infiltration process with a consequent breakdown of the action potential of cells and structures, such as communicating junctions, causing several changes in the electrical conduction process.[57-59] Some of these abnormalities are still considered nonspecific but are highlighted in studies before the high frequency of ST-segment abnormalities; others that are more nonspecific, with variable appearance include: sinus tachycardia, atrioventricular block, occasional branch block, atrial

fibrillation, bradycardia, premature atrial contractions, intraventricular block, and right branch block.[55-60] In our study, the elevation of the ST segment (31.9%) was the most characteristic change,[25,34,36,38,40,41,44] followed by atrioventricular or branch block (22.7%)[23,26,28,39,41] and sinus tachycardia (18.1%).[27,38,40,42] Notably, many cases showed sinus rhythm (27.3%).[24,30,32,35,37,42]

CMRI is an extremely useful imaging exam for analyzing myocardial structure and function, in addition to providing information about the composition of cardiac tissue less invasively than myocardial biopsy.[61] As for its use in cardiac impairment caused by COVID-19 evaluation, studies by Petersen et al.,[61] Ojha et al.,[62] and Shafiabadi Hassani et al.[63] described findings, such as myocarditis according to the Lake Louise criteria,[64] LGE (an imaging finding indicating tissue inflammation and early fibrosis),[65] edema, areas of nonischemic necrosis, pericardial effusion, and myocardial inflammatory activity causing damage to heart tissue.[61-63] Our study was similar to those described; CMRI was performed in 40.9% of studies,[23-25,29,31,40,42-44] reporting myocarditis (88.8% of those who performed CMRI)[23,25,29,31,40,42-44] edema (66.6% of those who performed CMRI)[23,25,31,40,44] description of myocardial inflammation (66.6% of those who underwent CMRI)[23,24,29,42,43] and LGE (55.5% of those who underwent CMRI).[25,31,42-44] Thus, this corroborates the usefulness of this test in assessing the degree of cardiovascular impairment in patients infected with SARS-CoV-2.[61-63]

COVID-19 can affect several organs and systems of the human body and cause hemodynamic impact.[66] The main characteristics described in the studies conducted by Sastry, Cuomo, and Muthusamy[67] and by Jasiński and Stefaniak[68] include the occurrence of thromboembolic events, hypercoagulability, microangiopathies, respiratory failure, septic shock, cardiogenic shock, hypoxia, metabolic acidosis, renal injury, and myocardial stress. From this perspective, the results of our research corroborate with previous studies, since these characteristics were also recorded in the description of increased levels of cardiac troponins (63.6%),[24,25,28-34,36-38,42-44] indicating possible damage to myocardial function;[69] SaO_2 below 95% (40.9 %);[24,26,31,34,35,37,38,41,43] increased D-dimer (31.8%),[27,29,32,36,37,41,42] which is an important biochemical marker whose increased serum levels indicate increased predisposition to thromboembolism;[70] evolution of patients to cardiogenic shock (22.7%);[27,31,36,38,44] and occurrence of metabolic acidosis (18.1%).[27,31,37,44] This combination of factors has been reported to be directly involved in the pathogenesis of myocardial damage in the form of myocarditis and in infarction with and without atheroma plaque formation.[6,8,9,61]

Moreover, cytokines also play an important role in this aspect, with a different activity, since they are related to changes in the expression of calcium and potassium channels resulting from disturbances in the duration of the action potential.[58]

Most patients with SARS-CoV-2 show nonspecific characteristics for the manifestation of myocarditis, with a presentation of sinus tachycardia, including ST-segment elevation, nonspecific intraventricular conduction delay, and T-wave abnormalities, with inversion in the previous leads, and the occasional appearance of atrioventricular block, corroborating the results of our study. One of the possible factors indicated in previous studies as related to ECG alterations would be due to the effect of antivirals used.[49,52,57-59]

Thakore et al.[57] observed the relevance of QT interval (period of the ECG from the beginning of the Q wave to the end of the T wave) analysis among patients infected with COVID-19. In this retrospective study, it was observed that an increase of 10 ms in corrected QT interval was related to a 16% increase in the patient's chance of having a higher severity index and, therefore, a higher risk of fatal evolution, given that, among patients who died during hospitalizations, a significant portion had a longer corrected QT interval on baseline ECG. In other studies, ECG findings were also frequently found to be associated with echocardiogram demonstrating ejection fraction lower than 50%, hypokinesis, and slight wall thickening.[57,71-73]

Conclusion

We conclude that the current systematic review provides a potential tool for the analysis of cardiac changes and implications of SARS-CoV-2 infection, with an emphasis on the main ECG and echocardiographic findings, but also with coverage of clinical characteristics, treatment, and outcomes. ST-segment and tachyarrhythmias are the most frequent changes in the ECG, while diffuse hypokinesis, reduced ejection fraction, and pericardial effusion are more present on the echocardiogram.

The results obtained in this article corroborate previous studies' conclusions on the subject. Further epidemiological and clinical research is needed to better understand these conditions, as well as to establish therapies to provide a better prognosis.

Author Contributions

Conception and design of the research: Moraes FCA and Souza DSM; acquisition of data, analysis and interpretation of the data, statistical analysis and writing of the manuscript: Moraes FCA, Santos RRE, Moraes JC, Mota ACC, Pessoa FR, Sarges DC, Moraes DA; critical revision of the manuscript for intellectual content: Souza DSM.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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