



Systematic Review of Cardiovascular Manifestations in COVID-19 and Management Consideration

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Abstract

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BACKGROUND: Coronavirus disease 2019 (COVID-19) is a health problem that is still engulfing the world that contributes to the high mortality rate globally. Death arises from the severity of the disease due to complications in important organs such as the heart.

AIM: The purpose of this study was to systematically review the manifestations of cardiovascular disease in COVID-19 patients and their management in terms of published articles.

METHODS: This research is a systematic review research. The research was conducted using the PRISMA method. Article searches are carried out by online publications through PubMed, Science Direct, and Google Scholar that meet the inclusion and exclusion criteria. The population is articles about the manifestations of cardiovascular disease in COVID-19 patients and their management between 2011 and 2021. Inclusion criteria are studies that examine the manifestations of cardiovascular disease in COVID-19 patients and their management using primary data in the form of cohort research designs in English and full text available. The exclusion criteria were a case study, review study, and used secondary data. The data were analyzed by univariate analysis by calculating the frequency and percentage.

RESULTS: The results show that several manifestations of cardiovascular disease in COVID-19 patients include cardiac injury, heart failure, myocardial infarction, myocarditis, cardiomegaly, and others. Complications of these diseases occur with or without comorbidities, and the risk increases with comorbid cardiovascular disease. The management of COVID-19 patients is basically done with antiviral agents, reducing symptoms and protecting important organs such as the heart.

CONCLUSION: In the treatment of COVID-19 patients with cardiovascular complications, the use of antiviral agents such as lopinavir or ritonavir should be used with caution because: may interact with cardiovascular drugs. Mechanical circulation support is suggested, and the use of extracorporeal membrane oxygenation can also be performed to treat cardiovascular complications in COVID-19 patients.

Introduction

Coronavirus disease-2019 (COVID-19) is a disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), which is now a pandemic that is still a health problem in the world [1]. The incidence of COVID-19 continues to increase. Globally, the incidence of COVID-19 is 221,648,869 cases with a death rate of 4,582,338 cases as of September 8, 2021 [2].

One of the causes of death from COVID-19 is due to cardiovascular disease. The death rate from cardiovascular disease in the United States is 397,042 deaths from January 1, 2020, to June 2, 2020. Deaths from ischemic heart disease increased nationwide following the onset of the pandemic in 2020, compared with changes in the same period in 2019 [3]. COVID-19 is more common in patients with underlying cardiovascular comorbidities [4]. COVID-19 also can attack many important organs and cause multiple organ failure with a cytokine storm. The heart is one of the

most important organs that can cause viral myocarditis and myocardial injury and can even be considered one of the leading causes of death in COVID-19 patients [5].

The most common comorbidities that occur in COVID-19 patients are hypertension, diabetes, cardiovascular disease, and respiratory system disease which are risk factors for the severity of COVID-19 and are also risk factors for cardiovascular disease complications [4], [6]. Several factors that explain cardiovascular complications in patients with COVID-19 infection include systemic inflammation, direct invasion of cardiovascular tissue, and drugs [4].

Cardiovascular complications that can arise from COVID-19 such as myocarditis and myocardial injury [4,7]. Signs and symptoms of cardiovascular complications, such as shortness of breath and chest pain, overlap with those of COVID-19. In addition, cardiovascular complications often occur during the disease. It is important to observe the cardiovascular complications that appear in COVID-19 patients and the

symptoms that arise to be able to make early detection. Early detection is useful to be able to immediately carry out appropriate management of COVID-19 patients to improve patient outcomes [4].

Several studies have conducted studies related to the management of cardiovascular disease in COVID-19 such as glucocorticoids, lopinavir, mechanical ventilation, prone position, and extracorporeal membrane oxygenation (ECMO) [8], [9], [10]. Due to the lack of investigations with endomyocardial biopsy and cardiac magnetic resonance, however, in many published reports, myocarditis is only suspected clinically and is largely indistinguishable from other causes of myocardial injury. These conditions cause the treatment strategies and outcomes of COVID-19-related myocarditis to be reviewed [11]. In addition, several recommendations have been issued for the management of patients with cardiovascular disease during the COVID-19 pandemic that need to be studied [12].

Knowledge of the manifestations of cardiovascular disease in COVID-19 patients and their management can be a solution in early detection of cardiovascular disease risk factors and appropriate treatment so as to minimize death from cardiovascular complications due to COVID-19. Therefore, this study conducted a systematic review of research related to the manifestations of cardiovascular disease in COVID-19 patients and their management. The purpose of the study using a systematic review approach was to determine the manifestations of cardiovascular disease in COVID-19 patients and their management based on the results of publications in health journals.

Research Method

This study uses a systematic review method. The source of this research data comes from literature obtained through the internet in the form of research results from publications in journals. A systematic review manifestation of cardiovascular disease in COVID-19 patients and their management then carried out according to PRISMA guidelines. Searches conducted on PubMed, Science Direct, and Google Scholar were assessed according to inclusion and exclusion criteria. Articles are extracted and tabulated.

Population is a research article about manifestations of cardiovascular disease in COVID-19 patients and their management from 2011 to 2021. The inclusion criteria studied were identifying cardiovascular disease manifestations and their management, using primary data for the study, and in English. Data collection was carried out from August 12, to September 30, 2021. The exclusion criteria were a review study, case study and used secondary data for research. The articles in this review were obtained as

many as 17 articles. Data are presented in tabular form. Univariate analysis was performed by calculating the frequency and percentage.

Results

The results of the screening research article identified 17 studies on the manifestations of cardiovascular disease in COVID-19 patients and their management. An overview of the manifestations of cardiovascular disease in COVID-19 patients and their management is shown in Table 1.

The results of the univariate analysis in Table 1, an overview of the research on the manifestation of heart disease in COVID-19 and its treatment, were obtained as many as 17 studies found in 2011–2021. This article is related to the research design, patient age, number of patients, cardiac manifestations, symptoms, comorbidities related to the risk of cardiovascular disease, and their management. Research that examines the number of samples studied varies between 22 samples which is a case study to 10,541 people in the research cohort.

Table 2 shows that of the 17 studies studied, 6 cardiovascular diseases were the result of manifestations of COVID-19 disease. Some of these cardiovascular diseases are cardiac injury, heart failure, myocardial infarction, myocarditis, cardiomegaly, and others. The most common cardiovascular diseases were cardiac injury (35.29%), and myocardial injury (29.41%). In these studies, the incidence of cardiac injury was 17%–69.2%, and the range of myocardial injury was 12.5%–30.6%.

Patients with COVID-19 infection have various complications, including those related to cardiovascular disease, which are basically caused by comorbidities or a history of previous diseases that are risk factors for cardiovascular disease. Several comorbidities of cardiovascular risk factors identified in COVID-19 patients with cardiovascular disease complications are presented in Table 3.

Based on the underlying comorbidities in COVID-19 patients, not all COVID-19 patients with cardiovascular disease have comorbidities. Comorbidities underlying cardiovascular disease in COVID-19 patients include hypertension, chronic heart failure, chronic cardiac disease, acute respiratory distress syndrome (ARDS), chronic heart failure, coronary heart disease, cardiomyopathy, congestive heart failure, myocardial infarction, heart disease, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) use history. Most studies report comorbid hypertension in the form of 76.47% which is the cause of cardiovascular disease in

Table 1: Screening research paper for cardiovascular manifestations in coronavirus disease 2019 and management consideration

Serial number	Name	Year	Region	Number of samples	Age	Design	Comorbid	Cardiac manifestation	Symptom	Treatment
1	Chen <i>et al.</i>	2020	China	274	51 (media)	Cohort	Hypertension 34% Cardiovascular disease 8% Chronic heart failure < 1%	Acute cardiac injury (44%) Heart failure 24%	Fever, cough Fatigue, anorexia, myalgia, dyspnoea, chest tightness, sputum production, haemoptysis, pharyngalgia, diarrhoea, nausea, vomiting, abdominal pain, headache dizziness	Pharmacology: Antiviral (interferon inhalation) Anti inflammatory (glucocorticoid) Antibiotics Adjuvative therapy: Intravenous immunoglobulin Non pharmacology: Oxygen treatment CRRT ECMO
2	Yang <i>et al.</i>	2020	China	22	59.7 (mean)	Single-centred	Chronic cardiac disease 10% Acute respiratory distress syndrome 67%	Cardiac injury (23%)	Fever, cough, dyspnoea, myalgia, malaise, rhinorrhoea, arthralgia, chest pain, headache, vomiting	Pharmacology: Antiviral (lopinavir) Anti inflammatory (glucocorticoid) Non pharmacology: Mechanical ventilation ECMO
3	Shi <i>et al.</i>	2020	China	416	64 (media)	Cohort	Hypertension 30.5% Coronary hearth disease 10.6% Chronic hearth failure 4.1%	Cardiac injury (58.5%)	Fever, cought, shortness of breath, fatigue, sputum production, muscle ache, diarrhea, chest pain, sore throat, headache,	Pharmacology: Antiviral Anti inflammatory (glucocorticoid) Antibiotic Adjuvative therapy: Intravenous immunoglobulin Non pharmacology: Oxygen inhalation Noninvasive ventilation Invasive mechanical ventilation CRRT
4	Guo <i>et al.</i>	2020	China	187	58.5 (mean)	single-center case	Hypertension 32.6% Cardiomyopathy 4.3% ACEI/ARB use history 10.1%	Myocardial injury (27,8%)	Not described	Pharmacology: Antiviral Anti inflammatory (glucocorticoid) Antibiotic Adjuvative therapy: Immunoglobulin ACEI/ARB NTproBNP Non pharmacology: Mechanical ventilation CRRT
5	Hong <i>et al.</i>	2020	Korea Selatan	98	55.4 (mean)	single-center	Cardiovascular disease 11.2% Hypertension 30.6%	Acute cardiac injury (69.2%)	Fever, cough, sputum Myalgia, dyspnea	Pharmacology: Antibiotic Antiviral (hydroxychloroquine, lopinavir/ritonavir) Anti inflammatory (glucocorticoid)
6	Zhou <i>et al.</i>	2020	Cina	191	56 (mean)	Cohort	Hypertension 30% Coronary heart disease 8%	Acute cardiac injury (17%)	Fever, cought, sputum, mualgia, diarrhoea, nausea	Pharmacology: Antiviral Antibiotics Anti inflammatory (corticosteroids) Adjuvative therapy: Immunoglobulin Non pharmacology: High-flow nasal cannula oxygen therapy Noninvasive mechanical ventilation Invasive mechanical ventilation CRRT
7	Yu <i>et al.</i>	2020	Cina	226	64 (median)	Multicenter	Hypertension 42.5% Myocardial infarction 2.7% Coronary heart disease 9.7%	Cardiac injury (27%)	Not described	Pharmacology: Traditional Chinese herb antiviral Antimicrobial Anti inflammatory (glucocorticoid) Adjuvative therapy: Immunoglobulin Blood transfusion
8	Yang <i>et al.</i>	2020	Cina	92	69.8 (mean)	Multicenter	Hypertension 56.1% Heart disease 10.7%	Myocardial infarction (34.1%)	Fever, dry cough, fatigue, myalgia, dyspnea, normal or decreased leukocyte counts and radiographic evidence of pneumonia	Pharmacology: Antihypertensive (ACE-2 receptor) Anti inflammatory (corticosteroids)
9	Wei <i>et al.</i>	2020	Cina	101	49 (mean)	Cohort	Hypertension 21%	Acute myocardial injury	Fever, chest discomfort, dyspnoea	Pharmacology: ACEi/ARB Vasoactive agents Non pharmacology: Mechanical ventilation
10	Lala <i>et al.</i>	2020	Amerika	2736	66.4 (median)	Cohort	Coronary artery disease 8.4% Hypertension 38.9% Heart failure 10.1%	Myocardial injury (16.6%)	Fever	Pharmacology: ACEi/ARB Statin use
11	Shi <i>et al.</i>	2020	Cina	671	63 (median)	Cohort	Hypertension 29.7% Coronary heart disease 8.9%	Acute myocardial injury (30.6%)	Not described	Pharmacology: Antiviral Antibiotic Anti inflammatory (corticosteroids) Adjuvative therapy: Immunoglobulin Non pharmacology: Oxygen inhalation Non-invasive ventilation Invasive mechanical ventilation ECMO CRRT

(Contd...)

Table 1: (Continued)

Serial number	Name	Year	Region	Number of samples	Age	Design	Comorbid	Cardiac manifestation	Symptom	Treatment
12	Huang et al.	2020	Cina	41	49 (mean)	Cohort	Hypertension 30% Coronary heart disease 8%	Cardiovascular diseases (15%)	Fever, cough, myalgia or fatigue, sputum production, headache, haemoptysis, diarrhoea, dyspnoea	Not described
13	Deng et al.	2020	Cina	112	65 (mean)	Cohort	Hypertension 15% Cardiovascular disease 15%	Myocardial injury (12.5%)	Fever, cough, shortness of breath chest pain/tightness	Pharmacology: Antiviral Antibiotic Anti-inflammatory (corticosteroids) Non pharmacology: CRRT Oxygen support Not described
14	Myhre et al.	2021	Cina	58	54 (mean)	Cohort	Hypertension 63% Coronary artery disease 17% peripheral vascular disease and/or heart failure 3%	Cardiovascular disease (25%)	Not described	Pharmacology: Antiviral Antiplatelet Anticoagulant ACEi/ARB Not described
15	Daniels et al.	2021	Amerika	10541	60.3 (mean)	Cohort	Cardiovascular disease 32% Hypertension 66%	Not described	Not described	Pharmacology: Antiviral Antiplatelet Anticoagulant ACEi/ARB Not described
16	Daniels et al.	2021	Amerika	1597	Not described	Cohort	Not described	Myocarditis (2.3%)	Chest pain, palpitations, dyspnea	Not described
17	Kim et al.	2020	Korea	40	58 (median)	Cohort	Hypertention (61.5%) Coronary artery disease (0.0%) Heart failure (0.0%)	Cardiomegaly (61.5%)	Cough, sputum, dyspnea, sore throat, myalgia, febrile sensation, rhinorrhea, ageusia, nausea, diarrhea	Non pharmacology: Mechanical ventilation EMCO Inotropic CRRT

ARB: Angiotensin receptor blocker, ACEI: Angiotensin-converting enzyme inhibitor, ECMO: Extracorporeal Membrane Oxygenation, CRRT: Continuous Renal Replacement Therapy.

COVID-19 patients. In addition, there were comorbid cardiovascular diseases 23.53%, coronary heart disease in 23.53% of the studies, and chronic heart failure in 17.65% of the studies studied.

Table 2: Research result of cardiac manifestation of coronavirus disease 2019

Cardiac manifestation	Prevalence (%)	Number of cases (%)	Reference
Cardiac injury	17–69.2	6 (35.29)	[9], [13], [14], [15], [16], [17]
Heart failure	24	1 (5.88)	[13]
Myocardial infarction	34.1	1 (5.88)	[17]
Myocardial injury	12.5–30.6	5 (29.41)	[1], [5], [7], [18], [19]
Myocarditis	2.3	1 (5.88)	[20]
Cardiomegaly	61.5	1 (5.88)	[21]
Other	15–25	3 (17.65)	[22], [23], [24]

Based on symptoms from 17 studies related to the manifestation of cardiovascular disease in COVID-19 patients, symptoms that appear include fever, cough, chest pain, dyspnea, anorexia, myalgia, sputum production, hemoptysis, pharyngalgia, diarrhea, nausea, vomiting, abdominal pain, headache, dizziness, malaise, rhinorrhea, arthralgia, shortness of breath, chills, afternoon throat, muscle ache, and hemoptysis. The most common symptom reported in COVID-19 patients with complications of cardiovascular

Table 3: The results based on the comorbid

Comorbid	Prevalence (%)	Number of cases (%)	Reference
Hypertension	15–100	13 (76.47)	[5], [7], [13], [16], [17], [18], [19], [20], [21], [22], [23], [25], [26]
Cardiovascular disease	8–15	4 (23.53)	[5], [9], [13], [20]
Chronic cardiac disease	23	1 (5.88)	[17]
Acute respiratory distress syndrome	67	1 (5.88)	[17]
Coronary heart disease	8–10.6	4 (23.53)	[14], [16], [19], [23]
Chronic heart failure	< 1–10.1	3 (17.65)	[13], [14], [22]
Cardiomyopathy	4.3	1 (5.88)	[18]
Myocardial infarction	2.7	1 (5.88)	[16]
Heart disease	10.7	1 (5.88)	[17]
ACEi/ARB use history	10.1	1 (5.88)	[18]

ARB: Angiotensin receptor blocker, ACEI: Angiotensin-converting enzyme inhibitor.

disease is fever (58.82%), cough (58.82%), dyspnea (52.94%), chest pain (35.29%), and diarrhea (35.29%) (Table 4). The management of COVID-19 patients with complications of cardiovascular disease has been reported by several studies which are presented in Table 5.

Table 4: The results based on symptom

Symptom	Number of cases (%)	Reference
Fever	10 (58.82)	[5], [7], [9], [13], [14], [15], [17], [23], [25], [27]
Chest pain	6 (35.29)	[5], [7], [13], [17], [19], [24]
Dyspnoea	9 (52.94)	[6], [7], [9], [13], [17], [21], [23], [24], [25]
Cough	10 (58.82)	[5], [6], [9], [13], [15], [17], [21], [23], [25]
Fatigue	4 (23.53)	[13], [14], [23]
Anorexia	1 (5.88)	[13]
Myalgia	7 (41.17)	[9], [13], [14], [15], [17], [21], [23]
Sputum production	6 (35.29)	[9], [13], [14], [15], [21], [23]
Haemoptysis	1 (5.88)	[13]
Pharyngalgia	1 (5.88)	[13]
Diarrhoea	6 (35.29)	[13], [14], [15], [21], [23], [25]
Nausea	2 (11.76)	[13], [21]
Vomiting	2 (11.76)	[6], [13]
Abdominal pain	1 (5.88)	[13]
Headache	4 (16.67)	[13], [14], [23]
Dizziness	1 (5.88)	[13]
Malaise	1 (5.88)	[6]
Rhinorrhoea	2 (11.76)	[6], [21]
Arthralgia	1 (5.88)	[6]
Shortness of breath	3 (17.65)	[5], [10], [14]
Chills	1 (5.88)	[25]
Sore throat	2 (11.76)	[14], [21]
Muscle ache	1 (5.88)	[14]
Haemoptysis	1 (5.88)	[23]

Based on the management of COVID-19 patients with complications of cardiovascular disease, the results of a review of 17 articles have been treated with antiviral, antibiotics, anti-inflammatory, antibiotic, and adjunctive therapy for pharmacologic treatments. Non-pharmacological treatments include oxygen treatment, mechanical ventilation, EMCO, and CRRT. Most of the articles reported on the treatment of patients with antiviral agents (lopinavir/ritonavir or hydroxychloroquine) by 52.9%, anti-inflammatory agents (glucocorticoids) (41.17%), antibiotics (47.05%), mechanical ventilation

Table 5: The results based on treatment

Treatment	Number of cases (%)	Reference
Pharmacology		
Antiviral	9 (52.94)	[5], [9], [13], [14], [15], [17], [18], [19], [24]
Anti-inflammatory	7 (41.17)	[9], [13], [15], [17], [18], [19], [28]
Antibiotics	7 (41.17)	[5], [9], [13], [14], [15], [18], [19]
Adjuvative therapy: Immunoglobulin	3 (17.64)	[14], [15], [19]
Shock medication (dobutamin)	1 (5.88)	[25]
ACEI/ARB	4 (23.53)	[7], [17], [18], [24]
IABP	1 (5.88)	[25]
Antiplatelet	1 (5.88)	[24]
Anticoagulant	1 (5.88)	[24]
Nonpharmacology		
Oxygen treatment	4 (23.53)	[5], [13], [14], [15]
CRRT	6 (35.29)	[5], [13], [14], [15], [19], [21]
EMCO	2 (11.76)	[13], [14], [21]
Mechanical ventilation	6 (35.29)	[10], [14], [15], [17], [18], [21]

ARB: Angiotensin receptor blocker, ACEI: Angiotensin-converting enzyme inhibitor, CRRT: Continuous Renal Replacement Therapy, ECMO: Extracorporeal Membrane Oxygenation.

(35.29%), and oxygen treatment (35.29%). Several studies report the use of ACEI/ARB by 23.53%.

Discussion

Many studies of cardiovascular disease manifestations and their management in COVID-19 patients have been carried out, and many findings have been described. The results of a review of 17 articles showed that there were several manifestations of cardiovascular disease in COVID-19 patients. The most common cardiovascular diseases are cardiac injury, myocardial injury, and myocarditis.

Several cardiovascular diseases that appear in COVID-19 patients can be explained because COVID-19 is caused by the SARS-CoV-2. The SARS-CoV-2 virus can affect the cardiovascular system. The virus enters the cell by binding to the viral spike protein (S) to ACE2 on the surface of the host cell. ACE2 is expressed in several organs of the body including lung tissue, adult human heart, and endothelial cells. The presence of ACE2 in the heart makes the heart very vulnerable to direct invasion of SARS-CoV-2. In addition, SARS-CoV-2 may increase angiotensin II (Ang II) activity through downregulation in ACE2 activity, reducing the conversion of Ang II to Ang-(1-7). Increasing the activity of Ang II can stimulate the renin-angiotensin-aldosterone system (RAAS), which can damage blood vessels and the heart [29].

The diagnosis of COVID-19 is carried out holistically and comprehensively through anamnesis, physical examination, and supporting examinations. The diagnosis of COVID-19 can be made by hematological examination, including absolute lymphocytes $<1500/\mu\text{L}$, neutrophil-lymphocyte ratio >3.13 , C-reactive protein >10 mg/L, molecular examination (TCM, real-time polymerase chain reaction [PCR]), or a combination of rapid antibody and antibody tests (PCR conventional/TCM/real-time PCR). Radiological examinations such as a chest X-ray to confirm pneumonia and a computed tomography scan of a chest X-ray without

contrast if in doubt about the results of a chest X-ray examination (Ministry of Health of the Republic of Indonesia, 2019). Decreases in white blood cells, neutrophils, lymphocytes, eosinophils, and platelet counts were observed, while lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase were increased in COVID-19-positive patients compared to COVID-19-negative individuals [22].

SARS-CoV2 can also directly infect the myocardium, causing viral myocarditis. However, most cases of myocardial damage occur due to severe pneumonia or ARDS leading to increased cardiometabolic requirements associated with systemic infection and ongoing hypoxia [30].

Viral infections can affect the heart through direct infection of cardiovascular organs and cells and are usually accompanied by a strong immune response. Based on viral replication, one can begin to understand how viruses can directly affect their hosts. The activation of a potent immune response, both innate and adaptive, can actively inhibit viral infection, but it can also damage infected and adjacent cells, leading to uncontrolled viral replication. Inhibition of the immune response has the potential to decrease immune-mediated cytopathic effects. Myocarditis can result from viral-specific inflammation or generalized increased inflammation that directly or indirectly affects the heart as a result of a viral systemic infection (Knowlton, 2020).

Cardiovascular disease in COVID-19 patients occurs due to the severity of patients with comorbidities. This is related to cytokine release syndrome due to severe COVID-19 infection. Severe COVID-19 infection increases pro-inflammatory cytokines such as interleukin (IL)-10, IL-2, IL-8, IL-6, and tumor necrosis factor- α . Cytokines play a role during viral infection (phase 1) and during ongoing severe inflammation (phase 2), resulting in ARDS and other end-organ damage [30]. Increase of pro-inflammatory cytokines can also be caused by a cytokine storm mediated through pathological T cells and monocytes causing myocarditis [29].

SARS-CoV infection causes immune dysregulation that increases the risk of heart disease. Immune dysregulation and prolonged inflammation are the main drivers of poor clinical outcomes for COVID-19 patients. The category and number of comorbidities must be taken into account when predicting the prognosis in patients with COVID-19 as they determine the greater severity of COVID-19 disease. Appropriate patient triage should be implemented by carefully asking for medical histories to help identify patients who are more at risk of developing severe COVID-19. In addition, better protection should be provided to patients with COVID-19 who have comorbidities once the diagnosis is confirmed [31].

In the previous explanation, it was stated that COVID-19 patients with cardiovascular comorbidities

are more at risk of developing cardiac complications. However, cardiac complications can also occur in COVID-19 patients without comorbidities. In the results of this review, there are 3 articles that report cardiovascular complications in COVID-19 patients without comorbid cardiovascular disease risk. In Chen *et al.* (2020), the current pathology of COVID-19 associated with ARDS showed that pulmonary edema with hyaline membrane formation in the lungs, but no obvious histologic changes in cardiac tissue, was identified from a single case report. This suggests that the underlying mechanisms of cardiac injury require further exploration. In patients with COVID-19. Cardiovascular complications should be detected as early as possible. In addition to asking for a history of disease and comorbidities, symptoms of severity can also be observed. In the results of this review, there are several symptoms that most often appear in patients with cardiovascular complications including fever, cough, chest pain, dyspnea, and diarrhea. Lee *et al.* (2021) describe the presenting features of myocardial injury including chest pain, dyspnea, dysrhythmias, and acute left ventricular dysfunction. Chest pain, shortness of breath, dry cough, fever, and diarrhea are expressed as these symptoms appear as the effect of severe pneumonia with cardiac symptoms. These clinical manifestations are closely related to the inflammatory process in the respiratory tract which indicates a mechanism of cardiovascular disease as a result of the severity of pneumonia [26].

The results of this review report the treatment of COVID-19 patients with cardiovascular complications, namely by giving an antiviral agent such as lopinavir or ritonavir, glucocorticoid, antibiotics, mechanical ventilation, oxygen treatment, and intravenous immunoglobulin interferon inhalation and the use of ACEI/ARB. To date, no specific antiviral treatment for COVID-19 has been shown to be effective, so treatment is a supportive therapy that relieves symptoms and protects important organs. In patients without a second bacterial infection, empiric antimicrobial treatment was ineffective and was more effective with antiviral monotherapy or combination antiviral therapy and inhaled interferon treatment. Glucocorticoid therapy is widely used in COVID-19 patients, but this use is more common in patients with severe pneumonia, and cytokine storms were observed in patients who died than patients who recovered [13].

Antiviral drugs or chloroquine have been shown to improve the improvement of COVID-19 disease with acute myocarditis [32]. Chloroquine and hydroxychloroquine alter endosomal pH and reduce glycosylation of the ACE2 receptor, thereby preventing viral entry. However, they have the potential to prolong the QT interval by blocking hERG K⁺ channels, which can result in sudden cardiac death. Acute kidney injury secondary to COVID-19 infection may accumulate chloroquine/hydroxychloroquine,

resulting in further QT prolongation. Concomitant use of azithromycin with hydroxychloroquine increases the risk of QTc prolongation, especially in patients with high transaminases levels, who may exhibit a severe inflammatory response [4].

Lopinavir and ritonavir are protease inhibitors approved by the FDA for the treatment of HIV-1 infection. Lopinavir–ritonavir may interact with cardiovascular drugs such as antiarrhythmic agents, antiplatelet drugs, and anticoagulants metabolized by cytochrome P-450 3A4. The use of these antiviral drugs in COVID-19 patients with cardiovascular complications must be carried out with caution [30].

ACEI/ARB is declared the standard indications for angiotensin-neprilysin receptor blockers, ACEI, or ARBs in the treatment of heart failure with reduced ejection fraction (and for the latter two drugs in the treatment of hypertension) apply to patients with COVID-19. There is an assumption that the increase in ACE2 levels caused by inhibitors of the RAAS may affect susceptibility to SARS-CoV-2 because ACE2 is the receptor for the virus but there is no evidence that these drugs worsen the clinical course of SARS-CoV-infection. 2 [33].

The use of imaging modalities can help diagnose cardiovascular disease complications in COVID-19 patients [4]. Optimal management of myocardial injury associated with COVID-19 involves supportive care (including the management of heart failure, therapy for arrhythmias, and avoidance of cardiotoxins). Mechanical circulatory support is suggested, and the use of ECMO is also possible [33].

Venoarterial ECMO (VA-ECMO) plays a role in treating cardiovascular complications, including acute cardiac injury, heart failure, and cardiogenic shock (CS). COVID-19-associated fulminant myocarditis and CS were rescued using VA-ECMO as a bridge to recovery. Cardiac injury, myocardial infarction with and without obstructive coronary artery disease, viral myocarditis, and decompensated heart failure leading to CS and risk factors for poor/uncertain benefit (age, sepsis, mixed/primarily vasodilatory shock, prothrombotic state or coagulopathy, severe ARDS, multiorgan failure, or high-risk prognostic score) specifically to use VA-ECMO as a bridge to recovery in COVID-19 infection. VA-ECMO may be considered in highly selected cases of refractory CS and echocardiographic evidence of biventricular failure. The decision to initiate this therapy should take into account the availability of resources, the perceived benefit, and the risk of disease transmission [34].

The treatment for COVID-19 is basically determined by severity. If the degree is mild, non-pharmacological measures include education, while pharmacological measures include the administration of Vitamin C, Vitamin D, antivirals, antibiotics, symptomatic treatment, supportive drugs, and comorbid drugs. Non-pharmacological therapies such as oxygen therapy,

noninvasive ventilation, invasive mechanical ventilation, and ECMO are used for the treatment of COVID-19 with severe symptoms. Dobutamine is used to treat shock. Additional therapies such as immunoglobulins are considered for additional therapy for confirmed COVID-19 patients, according to the patient's clinical condition and availability at the respective health care facilities if standard therapy does not provide an improved response. Giving with careful consideration and through discussion with the hospital's COVID-19 team [35].

Conclusions and suggestions

The results of the analysis of systematic studies found that COVID-19 patients complications of cardiovascular disease include: cardiac injury, heart failure, myocardial infarction, myocarditis, cardiomegaly, and others. Complications arise in COVID-19 patients without comorbidities, and the risk of cardiovascular complications increases in COVID-19 patients with comorbid risks of cardiovascular disease such as hypertension, coronary heart disease, chronic heart failure, and other cardiovascular diseases. The most common symptom reported in COVID-19 patients with complications of cardiovascular disease is fever, cough, chest pain, dyspnea, and diarrhea in which these symptoms occur is related to the severity of the acute respiratory syndrome. These results suggest a mechanism of inflammatory dysregulation as a result of the severity of acute respiratory syndrome due to COVID-19 infection. The management of COVID-19 patients is basically done with antiviral agents, but there is no evidence of effective antiviral drugs so that the management is carried out by reducing symptoms and protecting important organs such as the heart. In the treatment of COVID-19 patients with cardiovascular complications, the use of antiviral agents such as lopinavir or ritonavir should be used with caution because: may interact with cardiovascular drugs such as antiarrhythmic agents, antiplatelet drugs, and anticoagulants metabolized by cytochrome P-450 3A4. ACEI/ARB is declared. The standard indications for angiotensin-neprilysin receptor blockers, ACEIs, or ARBs in the treatment of heart failure with reduced ejection fraction (and for the latter two drugs in the treatment of hypertension) apply to patients with COVID-19. Myocardial injury in complications of COVID-19 can also be treated with supportive care such as management of heart failure, therapy for arrhythmias, and avoidance of cardiotoxins. Mechanical circulation support is suggested and the use of ECMO can also be performed to treat cardiovascular complications such as acute heart injury, heart failure, and CS. COVID-19-associated fulminant myocarditis and CS were rescued using VA-ECMO as a bridge to recovery.

The results of research regarding the appropriate management of complications of cardiovascular disease due to COVID-19 have not been found. This is related to the interaction of several drugs and drug efficacy and the types of complications that affect the treatment outcome. Imaging modality assistance to establish the correct diagnosis and further research on treatment outcomes are needed in further research to prevent and treat cardiovascular disease in COVID-19 patients.

References

1. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, *et al.* Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *J Am Coll Cardiol.* 2020;76(5):533-46. PMID:32517963
2. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Geneva: World Health Organization; 2021.
3. Wadhwa RK, Shen C, Gondi S, Chen S, Kazi DS, Yeh RW, *et al.* Cardiovascular deaths during the COVID-19 pandemic in the United States. *J Am Coll Cardiol.* 2021;77(2):159-69.
4. Lee CC, Ali K, Connell D, Mordi IR, George J, Lang EM, *et al.* COVID-19-associated cardiovascular complications. *Diseases.* 2021;9(3):47. PMID:34209705
5. Deng Q, Hu B, Zhang Y. Since January 2020 Elsevier has Created a COVID-19 Resource Centre with Free Information in English and Mandarin on the Novel Coronavirus COVID-19. The COVID-19 Resource Centre is Hosted on Elsevier Connect, the Company's Public News and Information. Netherlands: Elsevier; 2020.
6. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, *et al.* Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. *Int J Infect Dis.* 2020;94:91-5. <https://doi.org/10.1016/j.ijid.2020.03.017> PMID:32173574
7. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ, *et al.* Presymptomatic transmission of SARS-CoV-2-Singapore. *Morb Mortal Wkly Rep.* 2020;69(14):411-5. <https://doi.org/10.15585/mmwr.mm6914e1> PMID:32271722
8. Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Analysis of 92 deceased patients with COVID-19. *J Med Virol.* 2020;92(11):2511-15. <https://doi.org/10.1002/jmv.25891> PMID:32293741
9. Hong KS, Lee KH, Chung JH, Shin KC, Choi EY, Jin HJ, *et al.* Clinical features and outcomes of 98 patients hospitalized with sars-cov-2 infection in daegu, south korea: A brief descriptive study. *Yonsei Med J.* 2020;61(5):431-7. <https://doi.org/10.3349/ymj.2020.61.5.431> PMID:32390367
10. Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, *et al.* First case of COVID-19 complicated with fulminant myocarditis: A case report and insights. *Infection.* 2020;48(5):773-7. <https://doi.org/10.1007/s15010-020-01424-5> PMID:32277408
11. Peretto G, Villatore A, Rizzo S, Esposito A, De Luca G, Palmisano A, *et al.* The spectrum of COVID-19-associated myocarditis: A patient-tailored multidisciplinary approach. *J Clin*

- Med. 2021;10(9):1974.
PMid:34064463
12. Prabhakaran D, Perel P, Roy A, Singh K, Raspail L, Faria-Neto JR, *et al.* Erratum: Management of cardiovascular disease patients with confirmed or suspected covid-19 in limited resource settings. *Glob Heart.* 2020;15(1):44. <https://doi.org/10.5334/gh.823>
PMid:32923338
 13. Chen T, Wu D, Chen H. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. *BMJ.* 2020;368:m1295. <https://doi.org/10.1136/bmj.m1295>
 14. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, *et al.* Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* 2020;5:802-10. <https://doi.org/10.1001/jamacardio.2020.0950>
PMid:32211816
 15. Zhou F. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: A retrospective cohort study. *J Med Study Res.* 2020;3:1-2.
 16. Yu Y, Xu D, Fu S, Zhang J, Yang X, Xu L, *et al.* Patients with COVID-19 in 19 ICUs in Wuhan, China: A cross-sectional study. *Crit Care.* 2020;24:1-10.
PMid:32410714
 17. Yang H, Sun G, Tang F, Peng M, Gao Y, Peng J, *et al.* Clinical features and outcomes of pregnant women suspected of coronavirus disease 2019. *J Infect.* 2020;81:e40-4. <https://doi.org/10.1016/j.jinf.2020.04.003>
PMid:32294503
 18. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, *et al.* Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(7):811-8. <https://doi.org/10.1001/jamacardio.2020.1017>
PMid:32219356
 19. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, *et al.* Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J.* 2020;41:2070-9. <https://doi.org/10.1093/eurheartj/ehaa408>
 20. Daniels CJ, Rajpal S, Greenshields JT, Rosenthal GL, Chung EH, Terrin M, *et al.* Prevalence of clinical and subclinical myocarditis in competitive athletes with recent SARS-CoV-2 infection: Results from the big ten COVID-19 cardiac registry. *JAMA Cardiol.* 2021;6:1078-87. <https://doi.org/10.3410/f.740190589.793586024>
PMid:34042947
 21. Kim M, Nam JH, Son JW, Kim SO, Son NH, Ahn CM, *et al.* Cardiac manifestations of coronavirus disease 2019 (COVID-19): A multicenter cohort study. *J Korean Med Sci.* 2020;35(40):e366.
PMid:33075857
 22. Myhre PL, Heck SL, Skranes JB, Prebensen C, Jonassen CM, Berge T, *et al.* Cardiac pathology 6 months after hospitalization for COVID-19 and association with the acute disease severity. *Am Heart J.* 2021;242:61-70. <https://doi.org/10.1016/j.ahj.2021.08.001>
PMid:34400140
 23. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
PMid:31986264
 24. Daniels LB, Ren J, Kumar K, Bui QM, Zhang J, Zhang X, *et al.* Relation of prior statin and anti-hypertensive use to severity of disease among patients hospitalized with COVID-19: Findings from the American heart association's COVID-19 cardiovascular disease registry. *PLoS One.* 2021;16(7):1-16. <https://doi.org/10.1371/journal.pone.0254635>
PMid:34264974
 25. Fried JA, Ramasubbu K, Bhatt R, Topkara VK, Clerkin KJ, Horn E, *et al.* The variety of cardiovascular presentations of COVID-19. *Circulation.* 2020;141(23):1930-6.
PMid:32243205
 26. Saus PS, Hanafy D, Barack R. COVID 19 with cardiac injury complication, a case report. *Indones J Cardiol.* 2020;41:49-53. <https://doi.org/10.30701/ijc.1011>
 27. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, *et al.* Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA.* 2020;323(16):755-60. <https://doi.org/10.1001/jama.2020.4326>
PMid:32191259
 28. Liu ZM, Li JP, Wang SP, Chen DY, Zeng W, Chen SC, *et al.* Association of procalcitonin levels with the progression and prognosis of hospitalized patients with COVID-19. *Int J Med Sci.* 2020;17(16):2468-76. <https://doi.org/10.7150/ijms.48396>
PMid:33029089
 29. Arévalos V, Ortega-Paz L, Fernandez-Rodríguez D, Jiménez-Díaz VA, Rius JB, Campo G, *et al.* Long-term effects of coronavirus disease 2019 on the cardiovascular system, CV COVID registry: A structured summary of a study protocol. *PLoS One.* 2021;16(7):1-9. <https://doi.org/10.1371/journal.pone.0255263>
PMid:34324524
 30. Basu-Ray I, Almaddah NK, Adebayo A, Soos MP. Cardiac manifestations of coronavirus (COVID-19). In: *StatPearls.* Treasure Island, FL: StatPearls Publishing; 2022.
 31. Guan W, Liang W, Zhao Y, Liang HR, Chen ZH, Li YM, *et al.* Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. *Eur Respir J.* 2020;55:640.
PMid:32217650
 32. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, *et al.* Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5:819-24. <https://doi.org/10.1001/jamacardio.2020.1096>
PMid:32219357
 33. Caforio AL, Mancini D, Dardas TF. COVID-19: Evaluation and Management of Cardiac Disease in Adults. Available from: <https://www.uptodate.com/contents/covid-19-evaluation-and-management-of-cardiac-disease-in-adults> [Last accessed on 16 Jan 2022]
 34. Chow J, Alhussaini A, Calvillo-Argüelles O, Billia F, Luk A. Cardiovascular collapse in COVID-19 infection: The role of venoarterial extracorporeal membrane oxygenation (VA-ECMO). *CJC Open.* 2020;2(4):273-7. <https://doi.org/10.1016/j.cjco.2020.04.003>
PMid:32363334
 35. Burhan E, Susanto AD, Nasution SA. Protokol Tatalaksana Covid-19. Indonesia: Kementerian Kesehatan Republik Indones; 2021.