Chapter

# Cardiovascular System and SARS-CoV-2: Etiology, Physiopathology and Clinical Presentation: A Systematic Review

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## Abstract

During SARS-CoV-1 and Middle East Respiratory Distress Syndrome (MERS) outbreaks it was observed a particularly elevated incidence of cardiovascular disease among patients. With COVID-19, this correlation becomes evident again. However, the cardiovascular impacts by COVID-19 pandemic are not yet well established although publications about its potential deleterious effects are constant. Thus, aimed to carry a systematic review of the literature with meta-analysis, the following question was used as a guide: what practical contributions does the scientific literature produced in the period of 2019-2020 has to offer about the impact of the COVID-19 on cardiovascular system? A systematic review of the literature using the Virtual Health Library (VHL) and PubMed with the following descriptors: #1 "*cardiovascular disease*" [MeSH] AND #2 "*COVID-19*" [keyword], as well as their equivalents in the Portuguese and Spanish language, during the period from December 2019 to March 2020 was performed. One hundred articles were found in Pubmed and twenty-seven were selected. In VHL there are 59 articles and four were selected totaling thirty-one papers. The findings were then divided into three subcategories: Etiology, Physiopathology and Risk factors of SARS-CoV-2 in Cardiovascular System; Clinical presentation, laboratory markers and imagenological aspects of SARS-CoV-2 in cardiovascular system; and Anti-Hypertensive Drugs, Cardiovascular System and SARS-CoV-2. When it comes to the cardiovascular system, these issues are aggravated and urge as a joint commitment from researchers, medical and governmental organizations to carry out more robust studies with bold methodologies aimed at mapping prognostic factors and assertive therapeutic approaches in the management of cardiovascular complications of COVID- 19.

**Keywords:** cardiovascular disease, coronavirus infections, clinical medicine, systematic review

## 1. Introduction

According to the WHO, there has been a recent increase in the burden of cardiovascular disease (CVD), especially in low and middle-income countries [1].

It is estimated that 17.7 million people died from CVD in 2015, representing 31% of all deaths globally [2]. In 2020, CVDs are the number 1 cause of death globally, taking an estimated of 17.9 million lives each year [3, 4].

COVID-19 again brought the need to discussion an extremely relevant topic that was of concern during the SARS-CoV-1 (SARS - 2002) and Middle East Respiratory Distress Syndrome (MERS - 2013) epidemics, the increase incidence of cardiovascular disease among patients [5]. Studies show that patients with comorbidities, such as hypertension, heart failure, diabetes [6] and elderly people [7] are, among other factors, risk factor for severe illness by SARS-CoV-2. Also, COVID-19 is caused by the binding of the viral surface spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor following activation of the spike protein by transmembrane protease serine 2 (TMPRSS2) [8]. Thus, the cardiovascular impacts by COVID-19 pandemic are not yet well established although publications about its potential deleterious effects are constant.

Aimed to carry a systematic review of the literature with meta-analysis, the following question was used as a guide: what practical contributions does the scientific literature produced in the period of 2019-2020 has to offer about the impact of the COVID-19 on cardiovascular system? This review highlights that in a pandemic period, cardiovascular pathologies are risk factors from a worsening result. The pandemic prevention and control measures can also be used as a way to prevent cardiovascular diseases on the population, since fewer people exposed to the virus means less cardiovascular risk.

## 2. Methods

### 2.1 Literature review

A qualitative systematic review with meta-analysis of the literature using the Virtual Health Library (VHL), which hosts recognized databases – LILACS (Literatura Latino-americana e do Caribe em Ciências da Saúde), MEDLINE, SciELO (Scientific Electronic Library Online), and PubMed was performed. Initially, the following descriptors were used: #1 "cardiovascular disease" [MeSH] AND #2 "COVID-19" [keyword], as well as their equivalents in the Portuguese and Spanish language.

### 2.2 Eligibility criteria

The period reported in the literature ranged from December 2019 to March 2020 since the pandemic started in this period. Compilation of the data was performed in April 2020. Manuscript selection occurred primarily through the analysis of titles and abstracts. Article analysis followed the eligibility criteria: (1) At least a combination of the terms described in the search strategy were present in the title or words that refer to the theme; (2) Articles written in English, Portuguese or Spanish; (3) Articles addressing cardiovascular impact of COVID-19 pandemic; (4) Papers repeated in more than one database were computed only once; (5) Original papers with the full text available through in a virtual library created by the Brazilian Ministry of Health where content is restricted to authorized users - the CAPES (Coordination of Personal Improvement of Higher Level) Periodicals Portal. Thesis, dissertations, and monographs were excluded. Some articles were excluded because they generally approached other viruses/pandemics or the sample was children.

| Author (Year) | Journal | Sample (Study type) | Main Findings |
|---|---|---|---|
| Guo et al. [9] | JAMA Cardiol | 187 patients with confirmed COVID-19 at the Seventh Hospital of Wuhan City, China (cross sectional retrospective observational study). | During hospitalization, 66 (35.3%) patients had underlying CVD including hypertension, coronary heart disease, and cardiomyopathy, and 52 (27.8%) exhibited myocardial injury as indicated by elevated TnT levels. Patients with elevated TnT levels had more frequent malignant arrhythmias, and the use of glucocorticoid therapy (37 [71.2%] vs. 69 [51.1%]) and mechanical ventilation (41 [59.6%] vs. 14 [10.4%]) were higher compared with patients with normal TnT levels. |
| Clerkin et al. [8] | Circulation | (Integrative Review) | COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which invades cells through the angiotensin converting enzyme 2 (ACE2) receptor. Among those with COVID-19, there is a higher prevalence of cardiovascular disease and more than 7% of patients suffer myocardial injury from the infection (22% of the critically ill). |
| Bansal [10] | Diabetes Metab Syndr | (Narrative Review) | Acute cardiac injury, defined as significant elevation of cardiac troponins, is the most commonly reported cardiac abnormality in COVID-19. |
| Cheng et al. [11] | Curr Cardiol Rep | (Integrative Review) | Emerging epidemiological evidence suggest cardiovascular risk factors are associated with increased disease severity and mortality in COVID-19 patients. Patients with a more severe form of COVID-19 are also more likely to develop cardiac complications such as myocardial injury and arrhythmia. |
| Li et al. [12] | Infection Dis Poverty | 31 normal human tissues (Experimental study) | ACE2 expression levels were the highest in the small intestine, testis, kidneys, heart, thyroid, and adipose tissue, and were the lowest in the blood, spleen, bone marrow, brain, blood vessels, and muscle. ACE2 showed medium expression levels in the lungs, colon, liver, bladder, and adrenal gland |
| Han et al. [13] | J Cardiovasc Magn Reson | (Integrative Review) | First, continued urgent and semi-urgent care for the patients who have no known active COVID-19 should be provided in a safe manner for both patients and staff. Second, when necessary, CMR on patients with confirmed or suspected active COVID-19 should focus on the specific clinical question with an emphasis on myocardial function and tissue characterization while optimizing patient and staff safety. |
| Slawiński and Lewicka [14] | Kardiol Pol | (Integrative Review) | Among comorbidities in patients with COVID-19, cardiovascular disease is most commonly found. And in the most common symptoms of COVID-19 dyspnea is responsible by18.6%-59%. |
| Berre et al. [15] | Diagn Interv Imaging. | 71-year-old man with COVID-19 pneumonia (Case Report) | A case report about concomitant acute aortic thrombosis and pulmonary embolism complicating COVID-19 pneumonia |
| Vignera et al. [16] | Int J Mol Sci. | (Short Communication) | Data on the experimental animal have shown that 17B-estradiol increases the expression and activity of ACE2 in both adipose tissue and kidney. Spontaneously hypertensive male mice have a higher myocardial ACE2 expression than females and its levels decrease after orchiectomy |
| Zhu et al. [17] | Curr Cardiol Rep | (Integrative Review) | The literature reports association between history of cardiac disease and worsened outcome during COVID infection. Development of new onset myocardial injury during COVID-19 also increases mortality. |

| Author (Year) | Journal | Sample (Study type) | Main Findings |
|---|---|---|---|
| Celina and Oliva [18] | Diagn Interv Imaging. | 60-year-old man with COVID-19 pneumonia (Case Report) | A case report about acute pulmonary embolism complicating COVID-19 pneumonia |
| Gonzallez-Jamarillo, Low and Franco [19] | Eur J Epidemiol. | (Short Communication) | SARS-CoV-2 infection produces enzymatic shedding that inactivates ACE2 and prevents conversion of Ang-II. This effect could in part explain the cardiovascular and respiratory manifestations of COVID-19. |
| Gao et al. [20] | Respir Res | 102 patients with severe COVID-19 (cross sectional observational study) | N terminal pro B type natriuretic peptide (NT-proBNP) might be an independent risk factor for in-hospital death in patients with severe COVID-19. |
| Rico-Mesa, White and Anderson [21] | Curr Cardiol Rep | (Integrative Review) | Worse outcomes appear to be more prevalent in patients with hypertension and diabetes mellitus (DM), possibly due to overexpression of angiotensin-converting enzyme 2 (ACE2) receptor in airway alveolar epithelial cells. |
| Wang and Xu [22] | Cells | 17,520 testicular cells (Experimental Study) | ACE2 is predominantly enriched in spermatogonia and Leydig and Sertoli cells. Gene Set Enrichment Analysis (GSEA) indicates that Gene Ontology (GO) categories associated with viral reproduction and transmission are highly enriched in ACE2-positive spermatogonia, while male gamete generation related terms are downregulated. |
| Rizzo et al. [23] | Basic Res Cardiol | (Short Communication) | We might be able to target Notch also to fight heart and lung disease caused directly by SARS-CoV-2 infection and by the cytokine storm in response to the virus. |
| Laccarino et al. [5] | High Blood Press Cardiovasc Prev | (Short Communication) | In vitro studies are available to support the eventual role of ACE inhibitors and ARBs in both the promotion and antagonism of the disease. The available literature, indeed, presents contrasting results. |
| Schiffrin et al. [24] | Am J Hypertens | (Short Communication) | There is as yet no evidence that hypertension is related to outcomes of COVID-19, or that ACE inhibitor or ARB use is harmful, or for that matter beneficial, during the COVID-19 pandemic. |
| Tan and Aboulhousn [25] | Int J Cardiol | (Integrative Review) | COVID-19 results in mild symptoms in the majority of infected patients, but can cause severe lung injury, cardiac injury, and death. |
| Gupta and Misra [26] | Diabetes Metab Syndr | (Integrative Review) | Patients with COVID-19 infection have elevated natriuretic peptides, significance of which is uncertain and Cardiac troponin I levels are significantly increased in patients with severe SARS- CoV-2 infection. |
| Gackowski et al. [27] | Kardiol Pol | (Integrative Review) | Transesophageal echocardiography is considered an aerosol-generating procedure and should be performed only as a lifesaving procedure. Personnel should use appropriate personal protection equipment in the immediate vicinity of the patients in accordance with the relevant guidelines. |
| Guo et al. [28] | J Am Heart Associat | (Integrative Review) | ACE2 plays a protective role in both cardiovascular diseases and acute lung injury. For uninfected patients, we tend to believe it is unnecessary to discontinue ACEIs/ARBs given the lack of evidence to support the hypothesis that ACEIs/ARBs might lead to an increased risk of SARS-CoV-2 infection. For infected patients, although higher ACE2 expression might be associated with higher viral loads, ACEIs/ARBs should not be discontinued assertively because they can block the RAS and protect patients from the potential heart injuries in COVID-19 and might also reduce the severity of lung damage caused by the infection. |

| Author (Year) | Journal | Sample (Study type) | Main Findings |
|---|---|---|---|
| Sommerstein et al. [29] | J Am Heart Associât | (Integrative Review) | Cardiovascular diseases and/or their therapy, by affecting ACE2 levels, may play a pivotal role with regard to infectivity and outcome of COVID-19. Whether treatment or disease induced upregulation of ACE2 influences the course of COVID-19 urgently needs to be determined. |
| Meng et al. [7] | Emerg Microbes Infect. | 51 patients with hypertension and COVID-19 (cross sectional retrospective study) | Patients receiving ACEI or ARB therapy had a lower rate of severe diseases and a trend toward a lower level of IL-6 in peripheral blood. In addition, ACEI or ARB therapy increased CD3 and CD8 T cell counts in peripheral blood and decreased the peak viral load compared to other antihypertensive drugs. |
| Vanduganathan et al. [30] | N Engl J Med | (Integrative Review) | Insufficient data are available to determine whether these observations readily translate to humans, and no studies have evaluated the effects of RAAS inhibitors in Covid-19 |
| Chen et al. [31] | Cardiovasc Res | Human heart tissues were obtained from abandon donors in Center of Cardiovascular Treatment in China (Experimental Study) | The pericytes injury due to virus infection may result in capillary endothelial cells dysfunction, inducing microvascular dysfunction. And patients with basic heart failure disease showed increased ACE2 expression at both mRNA and protein levels, meaning that if infected by the virus these patients may have higher risk of heart attack and critically ill condition. |
| Fang et al. [6] | Lancet Respir Med | (Short Communication) | patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection |
| Chen et al. [32] | Herz | (Short Communication) | The condition of some patients with severe SARS-CoV-2 infection patients might deteriorate rapidly with acute respiratory distress syndrome and septic shock, which is eventually followed by multiple organ failure and fulminant myocarditis |
| Hulot et al. [33] | Arch Cardiovasc Dis | (Short Communication) | COVID-19 can be caused palpitations and chest tightness, myocardial damage with an increase in high-sensitivity cardiac troponin I. |
| South et al. [34] | Am J Physiol Heart Circ Physiol | (Short Communication) | In lieu of the fact that many older patients with hypertension or other CVDs are routinely treated with RAAS blockers and statins, new clinical concerns have developed regarding whether these patients are at greater risk for SARS-CoV-2 infection, whether RAAS and statin therapy should be discontinued, and the potential consequences of RAAS blockade to COVID-19-related pathologies such as acute and chronic respiratory disease. |
| Abassi et al. [35] | Am J Physiol Heart Circ Physiol | (Short Communication) | In patients infected with SARS-CoV-2, ACE2 may transform to a Trojan horse. Its binding with ACE2 neutralizes the advantageous cardiac effects of this enzyme, especially in patients with heart failure. |

*CVD – Cardiovascular Disease; TnT – Troponin T; ACE2 - angiotensin converting enzyme 2; CMR – Magnetic Ressonance; NT-proBNP - N terminal pro B type natriuretic peptide; Ang-II- Angiotensin II; ARB - angiotensin-receptor blockers; RAAS - renin-angiotensin-aldosterone system; CD – Cluster of Differentiation.*

**Table 1.**
*Main Findings.*

To ensure trustworthiness of the findings, data collection was performed, individually, by two researchers with divergences being solved by a third senior researcher.

Each sample article was thoroughly read and the information was inserted in a spreadsheet (**Table 1**), including the author, publishing year and main study findings. According to the PRISMA protocol (http://www.prisma- statement.org/).

### 2.3 Ethical issues

Since this is a systematic review, Resolution 510/16 of the Brazilian National Health Council (CNS) ensures the dispensation of submission to a Human Beings Research Ethics Committee.

## 3. Result

According to the research strategy, 101 articles were found in Pubmed and 27 were selected. In VHL, 59 articles were found and four were selected. After the eligibility criteria was applied (**Figure 1**), the results were input in **Table 1**.

The findings were then divided into three subcategories: Etiology, Physiopathology and Risk factors of SARS-CoV-2 in Cardiovascular System;

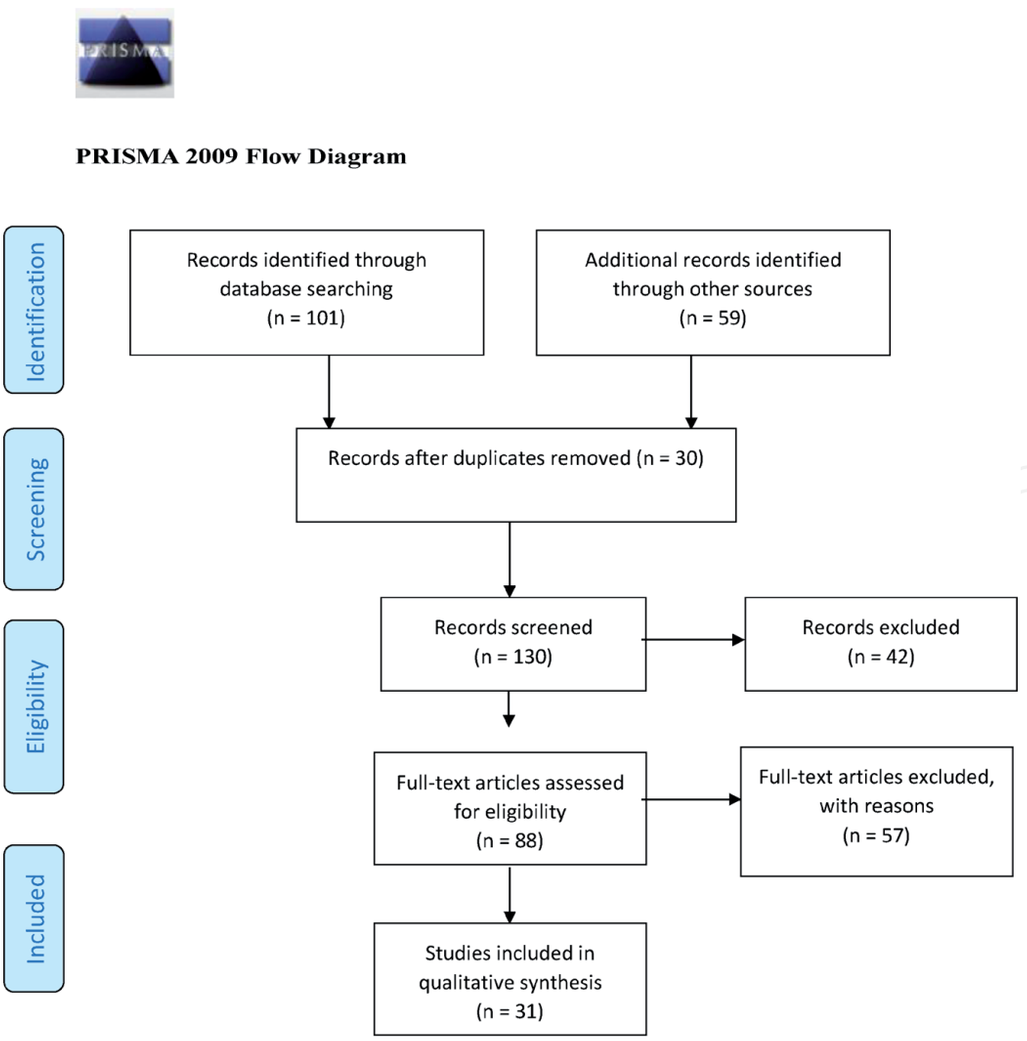


**Figure 1.**
*PRISMA flow diagram.*

Clinical presentation, laboratory markers and imagenological aspects of SARS-CoV-2 in cardiovascular system; and Anti-Hypertensive Drugs, Cardiovascular System and SARS-CoV-2.

## 4. Discussion

### 4.1 Etiology, physiopathology and risk factors of SARS-CoV-2 in cardiovascular system

SARS-CoV-2 is caused by a novel enveloped beta coronavirus that belongs to the Coronaviridae family, a group of positive strand RNA viruses causing human respiratory infections. Named after the crown shaped outer coat seen on the electron-microscopy, it was first discovered in the 1960s, receiving great attention during the 2003 SARS coronavirus (SARS-CoV) outbreak [11]. Seven species of these beta-coronaviruses are known to cause human infections, with four mainly causing mild flulike symptoms and the remaining three resulting in potentially fatal illnesses (SARS, MERS and the ongoing COVID-19) [10].

The transmission of COVID-19 occurs mainly through droplets route. However, there are theories that this can occur by fecal-oral route or/and by airborne. The average incubation time is less than six days (5.1 days), less than three percent of patients (2,5%) develop disease before the third day (2.2 days) after acquiring the virus while the rest (97,5%) develop symptoms 11.5 days after the onset of infection [27].

Although respiratory tract is the primary target for SARS-CoV-2, cardiovascular system (CVS) may get involved in several different ways [10] as destabilized coronary plaque [9], hypoxemia, systemic inflammation and enhanced myocardial oxygen demand, a direct cardiovascular injury, likely develops, initiated by binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) (**Figures 2** and **3**). This receptor is widely expressed in lungs, kidney [5] - renal tubules [26], brain, gut [34], gastrointestinal epithelium, Leydig cells in testis [22, 26], but also in the heart, where it is localized to macrophages, vascular endothelium, smooth muscle and myocytes [33].

Experimental study shows that the immune activity levels (innate immune response - NK cells and acquired immune response - B cells, CD8+ T cells and interferon response) in countless human tissues with large number of ACE2 receptors are statistical significant ($P < 0.05$, $0.27 \leq r \leq 0.78$). In the research, the following tissues obtained higher levels of CD8+ T cell - brain, blood vessels, skin and digestive system (pancreas, colon, stomach and esophagus) [3]. On the other hand, high levels of beta 17ß-estradiol have been shown to be important for increasing the number of ACE2 receptors in kidney and adipose tissues in laboratory studies. Interestingly, spontaneously hypertensive male mice, after orchiectomy, have higher levels of ACE2 than females [16].

In fact, the virus shares the ACE2 as the host cellular receptor for virus spike (S) protein according to structural analysis [31, 35] following activation by transmembrane protease serine 2 (TMPRSS2) [34]. The virus produces enzymatic shedding that inactivates ACE2 and prevents conversion of Ang-II [19]. Besides that, virus infection causes damage to pericytes and endothelial dysfunction, especially due to damage to capillary endothelial cells. The increased expression of ACE2 proteins and mRNAs in patients infected by the virus and with basic heart failure disease may have higher risk of critically ill condition and/or heart attack [31] (**Figure 2**).

Laboratory studies have suggested that other intracellular signaling pathways such as Notch could also explain the cytokine storm that ultimately induces heart

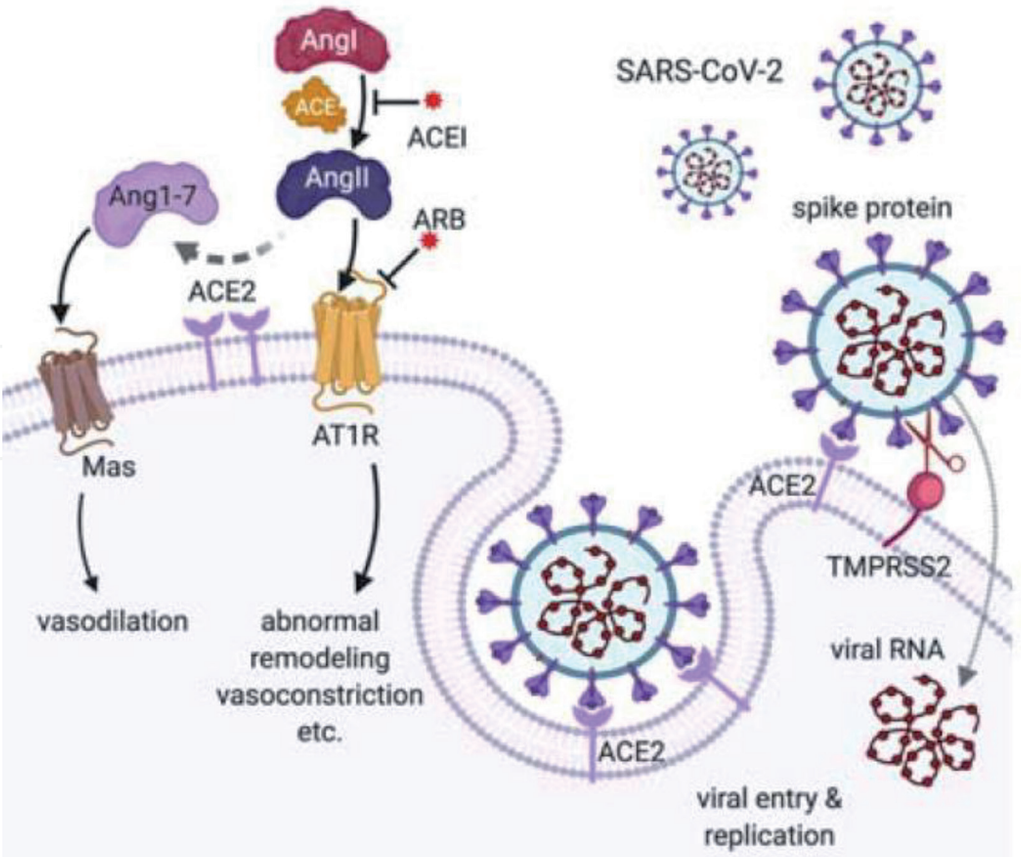


**Figure 2.**
*The role of ACE2 in COVID-19. The spike protein of SARS-CoV-2 binds ACE2 on a cellular membrane, which triggers 1) endocytosis of the virus and subsequent sequestration of ACE2 or 2) cleavage of the viral spike protein via an enzyme TMPRSS2 leading to the entry of viral contents into the cytoplasm [adapted]. Source: Cheng et al. [11].*

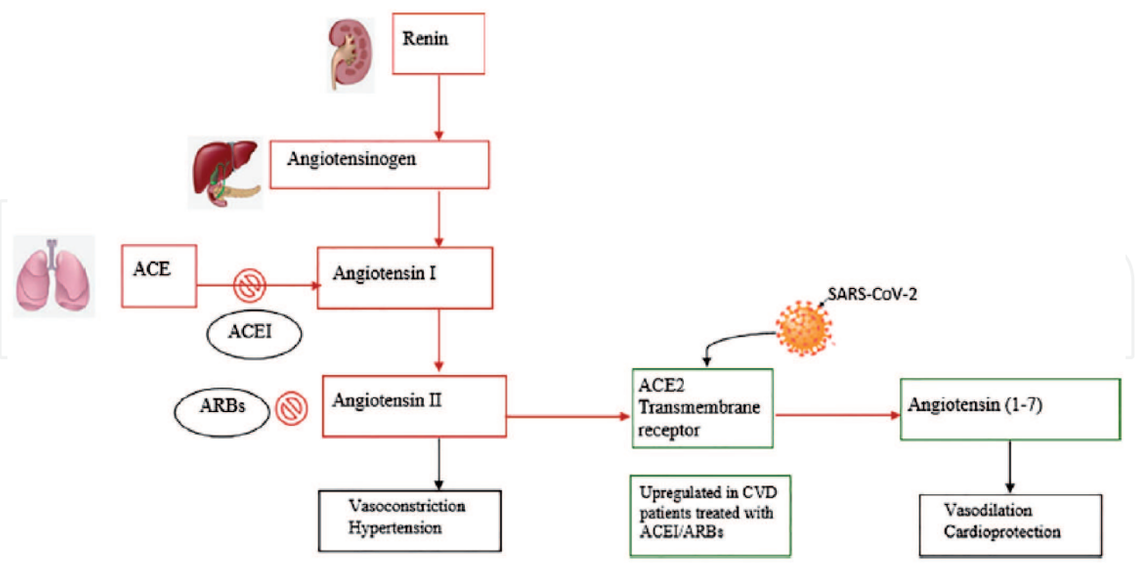


**Figure 3.**
*Renin–angiotensin system inhibition (RAS) by Angiotensin converting enzyme/Ang-II receptor blockers (ACEI/ARBs) and SARS-CoV-2 binding to ACE2 receptors [adapted]. Source: Gonzallez-Jamarilo et al. [19].*

and lung disease caused by SARS-CoV-2 direct damage to tissues [23]. Besides that, other theory is that the "cytokine storm" - term for increasing various interleukins and chemokines as TNF-α, IFN-γ, GCSF, MCP-1, MIP-1-α, IL-10, IL-6 and IL-2 contributes to cardiac injury. These situations are analogous to cardiotoxicity in the setting of CAR- T cell (chimeric antigen receptor - T cell) therapy. In this paper, left

ventricular systolic dysfunction, cardiac injury and cardiovascular events (troponin elevation) post-CAR-T have been demonstrated [17].

Therefore, the exact mechanism of cardiac involvement in COVID-19 remains under investigation but it seems the SARS-CoV-2 can (a) cause cardiac injury indirectly due to a probable overwhelming immune inflammatory response and cytokine storm; (b) cause invasion of cardiomyocytes and direct damage via this process; (c) cause Severe hypoxia from acute respiratory damage caused by the virus may result in oxidative stress and myocardial injury from increased myocardial oxygen demand in the presence of severe hypoxia due to acute lung injury (ARDS) [25].

Cardiovascular disease patients are at particularly high risk for mortality from SARS-CoV-2 due to their frailty and susceptibility for a myocardial involvement [36], perhaps due to the virus's affinity for ACE2 (**Figure 3**) mainly due to the interaction with the renin-angiotensin-aldosterone system (RAAS).

RAAS has an important role in regulating blood pressure and electrolyte balance. This system compromises two pathways: ACE2/Ang (1–7)/Mas receptor and ACE/Ang II/AT1R. In physiological situations, these two metabolic pathways function harmoniously, maintaining the normal function [7] (**Figure 3**). Hence, RAAS is widely implicated in Diabetes mellitus (DM), hypertension, heart failure [21] and Coronary heart disease [29].

Patients with COVID-19 are often diagnosed with coronary artery disease (2.5–8%), diabetes (7.3%–18.8%), hypertension (15%–30.4%) and other cardiovascular disease (4%–14.6%). In addition, of the patients who had been admitted to the intensive care unit (ICU), those with cardiovascular diseases compared to those who had not had a worse prognosis [9, 14, 24].

Another fact to be considered is that COVID-19 is more aggressive in elderly patients. The literature tells us that the elderly and male have more ACE2 receptors than the general population [29]. About that, Li et al. [3] refer that, when studying the expression of ACE2 receptors in various tissues of the body and its correlation with immunogenicity, in the thyroid, lungs, adrenal gland, liver, and kidneys, ACE2 expression levels showed significant positive correlations with CD8+ T cell enrichment levels solely in males.

Finally, patients with chronic kidney and those who have received renal transplant - and have a higher cardiovascular risk - are at increased risk of COVID-19 infection and severity. Moreover, there are frequent renal function abnormalities and increased incidence of acute kidney injury in patients with COVID- 19 [26].

### 4.2 Clinical presentation, laboratory markers and imagenological aspects of SARS-CoV-2 in cardiovascular system

There appears to be two clinical stages to the disease. The first stage is the replicative stage, when SARS-CoV-2 is replicating over the course of several days and the patient presents with relatively mild symptoms [25] such as fever, cough, and myalgia or fatigue; less common symptoms were sputum production, headache, hemoptysis, and diarrhea [32]. The adaptive immunity stage is the second stage. The body produces antibodies against the virus and, as there is viral clearance, the antibody titers will return to baseline values and an infection solves. This creates an "Immune memory". However, a minority of patients becomes critically ill and have high mortality rates [25]. It is important to remember that some symptoms in patients with COVID-19 pneumonia suggest cardiovascular diseases. Fatigue, dyspnea, cough is typical in COVID-19, but these symptoms may also result from exacerbation of chronic heart failure [14].

Chinese study shows large number of patients (81%) with mild symptoms of COVID-19 between (no pneumonia and mild pneumonia). These patients with more aggressive symptoms, 14% has more severe clinical conditions (lung infiltrates >50% within 24 to 48 hours, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, blood oxygen saturation ≤ 93%, respiratory rate ≥ 30/min and dyspnea) and 5% critical medical conditions (septic shock, respiratory failure and/or multiple organ dysfunction or failure) [37]. Others publishing and anecdotal reports indicate manifestations of arrhythmia [28], cardiac arrest, acute heart failure [23] and theoretically fulminant myocarditis [17, 32].

COVID-19 virus enters cells through the angiotensin converting enzyme II (ACE2) receptor, resulting in down-regulation of ACE2 receptor function. This leads to an increase of angiotensin II activity, activation of the renin-angiotensin-aldosterone system (RAAS) following a decrease in ACE2, an increase in vasoactive, proliferative, and profibrotic Ang-II leads to cardiopulmonary damage through hemodynamic changes such as pulmonary hypertension and interstitial edema followed by respiratory failure in the most severe cases (**Figure 3**) [19].

In laboratory markers, definitive diagnosis of SARS-CoV-2 Infection is based primarily on nucleic acid amplification tests, such as real-time reverse transcriptase–polymerase chain reaction (rRT-PCR) [27].

The laboratory alterations found in COVID-19 include in descending level elevated concentrations of serum creatine kinase (7%–13.7%), total bilirubin (10.5–18%), transaminases (21–28%), D-dimer concentration (36%–46.4%), lactate dehydrogenase (41–76%), C-reactive protein (60.7–93%), thrombocytopenia (17%–36.2%) and lymphopenia (35%–82.1%). It is important to note that the first three have been rarely reported [14].

Interesting to note that elevated D-dimer values are common in COVID-19 patients, even in the absence of thrombophlebitis and acute pulmonary embolism and it seems to correlate with acute pulmonary embolism [18], arterial thrombosis, acute respiratory distress syndrome and death [15]; elevated cardiac troponin I (cTnI) levels [32] and N terminal pro B type natriuretic peptide (NT-proBNP), with the cut-off value of 88.64 pg./mL [20] are correlate with cardiovascular injury, hospitalization and death. Including, plasma TnT levels in patients with COVID-19 correlated significantly with both plasma high-sensitivity C-reactive protein levels, NT-proBNP elevation and malignant arrhythmias [20].

According to Clerkin et al. [9] the rise in elevated high sensitivity cTnI tracks with other inflammatory biomarkers (D-dimer, ferritin, interleukin-6 (IL-6), lactate dehydrogenase and elevated creatinine kinase, raising the possibility that it may reflect on cytokine storm or secondary hemophagocytic lymphohistiocytosis more than isolated myocardial injury.

Transthoracic echocardiography is routinely recommended in patients with complicated COVID-19 due to the high prevalence of heart failure or/and myocarditis. This measure is useful to differentiate dyspnea of pulmonary origin from dyspnea of cardiac origin and monitor the sequelae of ARDS. Another useful use of echocardiography in the medical practice of ICU is monitoring treatments such as extracorporeal membrane oxygenation and fluid management in shock. Ultrasound evaluation of the lung may be a sensitive marker of fluid accumulation in the interstitial space and it useful for show the most common changes present in lungs how consolidation, B-line artifacts (the earliest signs in the disease course) and pleural line abnormalities like >1 mm, loss of continuity and irregularity [27].

Cardiovascular Magnetic Resonance (CMR) is useful in mapping of the extent of myocardial injuries, impact on ventricular function and differentiating a etiologies

(ischemic from non-ischemic). It stills helps in differentiating the between myocarditis and other acute myocardial injury that can elevate myocardial enzymes (eg. Troponin) and alter electrocardiographic (ECG) patterns [13].

### 4.3 Anti-hypertensive drugs, cardiovascular system and SARS-CoV-2

Even at the beginning of the pandemic, a publication suggested that due to hyper expression of ACE2 receptors in DM and hypertension, patients with said condition would be more likely to develop severe manifestations of COVID-19 [6] which was not confirmed with subsequent studies [21, 24, 30, 34]. At the same time, there was a theory that anti-hypertensive drugs could cause more severe cases of COVID-19, however it has been refuted. Meng et al. [27] showed that ACE inhibitors (ACEi) or angiotensin receptor-1 blockers (ARB) therapy increased CD3 and CD8 T cell counts in peripheral blood and decreased the peak viral load compared to other antihypertensive drugs and Rico-Mesa et al. [24] suggest that the effects of these drugs were positive, including ACE2 receptor blockade, disabling viral entry into the heart and lungs, and an overall decrease in inflammation secondary to ACEI/ARB.

Moreover, Societies of Hypertension affirms that in hypertensive patients with COVID-19 or at risk of COVID-19 infection, ACEi and ARBs treatment should be maintained according to the recommendations contained in the 2018 ESC/ESH guidelines [5], because blood pressure control remains an important consideration in order to reduce disease burden, even if it has no effect on susceptibility to the SARS-CoV-2 viral infection [24].

## 5. Final considerations

Cardiovascular diseases (CVD) are one of the most important causes of morbidity and mortality in the world being a great challenge for clinicians and researchers in the context of COVID-19. The pathophysiological explanation suggests an intimate correlation between SARS-CoV-2 protein S and ACE2 receptors, which the virus takes advantage of to increase its ability to penetrate host cells. The aggression of the cardiovascular system can be divided into three hypotheses - direct damage of the cardiomyocyte by the virus; hypoxemia due to lung injury or coronary events; or exacerbated immune response. When it comes to patients with COVID-19, the coexistence of previous cardiovascular diseases or risk factors such as hypertension, diabetes, coronary heart disease and heart failure, in addition to biochemical markers such as high troponin and pro-BNP seem to increase mortality.

Thus, when it comes to the cardiovascular system, these issues are aggravated and urge as a joint commitment from researchers, medical and governmental organizations to carry out more robust studies with bold methodologies aimed at mapping prognostic factors and assertive therapeutic approaches in the management of cardiovascular complications of COVID- 19.

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## Conflict of interests

The authors declare that they have no competing interests.



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