The role of cardiovascular system in the SARS-CoV-2 infection and aggravation in human

O papel do sistema cardiovascular na infecção e complicações por SARS-CoV-2 em humanos

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ABSTRACT
The coronavirus disease (COVID-19) has several clinical manifestations, highlighting a large number of cases and deaths in patients with specific comorbidities, such as cardiovascular diseases. For this reason, the objective was to analyze the role of the cardiovascular system in SARS-CoV-2 infection and complications in patients with pre-existing cardiovascular alterations. For this, a systematic search was carried out following the PRISMA guidelines in the Latin American and Caribbean Health Sciences Literature databases (Lilacs) and PubMed/Medline, using the association of descriptors: ("Cardiovascular System" OR Cardiovascular Diseases OR "Heart Failure" OR "Hypertension" OR "Cardiac Insufficieny") AND ("COVID 19"). Original studies published from 2020 onwards were included. Results: About 16/18 studies dealt with complications and 2 with a higher rate of infection in patients with preexisting CVD. The cardiovascular comorbidity most associated with the severity of COVID-19 was systemic arterial hypertension. And through a meta-analysis of the included studies, it was concluded that previously hypertensive patients may be up to 2.49 times more likely to have a worse prognosis. Related to a higher infection rate, both studies showed that patients with SAH have a greater amount of angiotensin-converting enzyme 2 (ACE 2), which functions as a receptor for the binding of SAR-CoV-2, presenting a potentially greater risk of infection. The 16 studies on complications associated the manifestations of venous, arterial and microvascular thrombosis with increased prothrombotic signaling and increased release of von Willebrand factor and platelet activation/aggregation, in addition to increased anti-fibrinolytic and immunoactivating activity specific to cardiac fibroblasts in the hearts of patients with

COVID-19. Severe cases were associated with systemic microcirculatory changes with endothelial dysfunction, higher troponin levels, higher values of inflammatory markers, with pro-inflammatory and procoagulant status, atrial fibrillation, and high rates of septic shock. Conclusion: It is inferred that COVID-19 in patients with previous CVD, mainly SAH, have a greater chance of infection due to increased expression of ACE 2 and to present manifestations of thrombosis associated with a pro-coagulant state and inflammatory manifestations associated with a pro-state. -inflammatory triggering a higher rate of hospitalization, resulting in serious complications, requiring intensive treatment, and in some cases death.

Keyword: COVID-19, infectious diseases, cardiovascular diseases, cardiac insufficiency, hypertension.

RESUMO

A doença do coronavírus (COVID-19) possui diversas manifestações clínicas destacando grande número de casos e óbitos em pacientes com comorbidades especificas, como doenças cardiovasculares. Por essa razão, objetivou-se analisar o papel do sistema cardiovascular na infecção e complicações por SARS-CoV-2 em pacientes com alterações cardiovasculares pré-existentes. Para isso procedeu-se uma pesquisa sistemática seguindo as diretrizes PRISMA nas bases de dados Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) e a PubMed/Medline, utilizando a associação de descritores: (“Cardiovascular System” OR Cardiovascular Diseases OR “Heart Failure” OR “Hypertension” OR “Cardiac Insufficieny”) AND (“COVID 19”). Foram incluídos estudos originais, publicados a partir do ano de 2020. Resultados: Cerca de 16/18 estudos tratavam das complicações e 2 da maior taxa de infecção em pacientes com DCV preexistentes. A comorbidade cardiovascular mais associadas a gravidade da COVID-19 foi a hipertensão arterial sistêmica. E através de meta-análise dos estudos incluídos conclui-se que pacientes previamente hipertensos podem ter até 2,49 vezes mais chances de apresentarem um pior prognóstico. Relacionado a maior taxa de infecção ambos os estudos mostraram que pacientes com HAS apresentam uma quantidade maior da enzima conversora de angiotensina 2 (ECA 2), que funciona como receptor para a ligação do SAR-CoV-2, apresentando um risco potencialmente maior de infecção. Os 16 estudos sobre as complicações associavam as manifestações de trombose venosa, arterial e microvascular ao aumento da sinalização pró-trombótica e a um aumento da liberação de fator von Willebrand e ativação/agregação plaquetária, além de aumento da atividade anti fibrinolítica e imunoativante específica de fibroblastos cardíacos em corações de pacientes com COVID-19. Casos graves estavam associados a alterações microcirculatórias sistêmicas com disfunção endotelial, níveis mais altos de troponina, valores mais altos de marcadores inflamatórios, com estado pró-inflamatório e pró-coagulante, fibrilaçãoatrial, e altas taxas de choque séptico. Conclusão: Infere-se que a COVID-19 em pacientes com DCV prévia, principalmente HAS possuem maior chance de infecção devido a expressão aumentada de ECA 2 e apresentar manifestações de trombose associadas a um estado pró-coagulante e a inflamatórias associadas a um estado pró-inflamatório desencadeando maior taxa de internação, repercutindo em complicações graves, necessitando de tratamento intensivo, e em alguns casos a morte.

Palavras-chave: COVID-19, doenças infecciosas, doenças cardiovasculares, insuficiência cardíaca, hipertensão.

1 INTRODUCTION

On December 31, 2019, in the province of Wuhan, the government of China notified the World Health Organization (WHO) of the first cases of pneumonia caused by an unknown etiological agent. On January 7, 2020, the sequencing and identification of a new viral genome from the Coronaviridae family was announced, which was later named Severe Acute Respiratory Syndrome Coronavirus, with the acronym SARS-CoV21. From there, there was a rapid increase and spread in the number of infections, causing the Coronavirus disease (COVID-19), being declared as a pandemic by the WHO on March 11, 2020[2,3]. Due to the impacts on health systems, added to the economic, cultural, social challenges and the enormous damage caused worldwide, the pandemic caused by the new virus has become the greatest challenge ever faced by modern health[4,5].

The clinical picture of COVID-19 presents a heterogeneous spectrum, ranging from asymptomatic patients to mild, moderate or severe cases, requiring intensive care and advanced respiratory support, with the possibility of death. It is estimated that 80% of cases are mild to moderate, evolving with spontaneous cure[6]. Among the main symptoms are: dry cough, fever, dyspnea, anosmia, odynophagia, myalgia, which may be accompanied by headache, and gastrointestinal symptoms such as vomiting, diarrhea and abdominal pain. Although the respiratory system is the most affected, the cardiovascular system is often affected, causing several systemic consequences in the body, with a variable range of severity[7].

Among the most prevalent comorbidities related to severe COVID-19 in Brazil among patients aged ≥ 50 years were cardiovascular diseases (56%), obesity (39%), chronic lung disease (37%) and arthritis (21%)[8]. Data reveal that hospitalizations for COVID-19 in Intensive Care Units (ICU) were related to arterial hypertension in 45% of cases[9].

Another important aspect is the persistence of symptoms after Covid-19, called long Covid, and some of these symptoms are neurological, such as difficulties in concentration and "mental fog". Recent research has linked the immune response triggered by contamination with Sars-CoV-2 to causing damage and inflammation in the blood vessels of the brain and triggering long-term symptoms in the region[10]. Due to the questioning of patients with preexisting CVD being more susceptible to infection and/or complications, and/or a worse prognosis, the present study aimed to analyze the role of the cardiovascular system in SARS-CoV-2 infection and complications in humans.

2 METHODS

This is a systematic, retrospective, qualitative-quantitative, longitudinal bibliographic research, divided into the following stages: a) definition of the problem and elaboration of guiding questions; b) adoption of inclusion and exclusion criteria; c) search and sampling in the literature; d) analysis of selected articles; e) discussion and presentation of results[11]. The steps of search, selection, extraction of data of interest, and analysis of the results were performed according to the rules of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[12].

2.1 GUIDING QUESTIONS

There are three main questions: is it easier for patients with preexisting CVD to be infected? Do concomitant CVDs trigger a worsening of COVID 19 cases? Or is it that the greater ease of infection, associated with a greater worsening of symptoms in patients with CVD, are responsible for the greater number of severe cases of COVID in these patients?

2.2 SEARCH STRATEGY

The PICO[13] strategy was used, as shown in **Table 1**, and from the construction of these elements, the following question was elaborated: does the literature present scientific evidence on the patterns of infection and main complications of COVID-19 in patients with associated cardiovascular diseases.

Table 1. Use of the PICO strategy for the elaboration of the research question.

Acronym	**Definition**	**Description**
P	Pacient	Patients with Covid-19
I	Intervention	Describe the complications and prognosis of patients with COVID-19
C	Comparison	Whether patients with cardiovascular disease are more infected with COVID-19 and have more complications and worse prognosis compared to patients without cardiovascular complications
O	Outvome	Identify which cardiovascular factors favor infection and/or which cardiac complications are secondary to COVID-19.

Source: Authors, 2022.

The electronic databases used for the research were: Latin American and Caribbean Literature on Health Sciences (Lilacs) and PubMed via the National Library of Medicine (NIH). Aiming at a descriptor reliability survey, a survey was carried out through the MeSH (Medical

Subject Headings) platform, selecting the following descriptors ["COVID-19"] AND [“Cardiovascular System” OR “Cardiovascular Diseases” OR “Heart Failure” OR “Hypertension” OR “Cardiac insufficiency”], together with the Boolean operator "AND" according to associations shown in **Table 2**. The reference list of all articles included in this review was analyzed for the inclusion of possible relevant studies.

Table 2. Database, combinations of descriptors and total number of articles

Kay words	**Data base**	**Identification**
COVID-19 AND *Cardiovascular Diseases*	PUBMED	139
	LILACS	66
COVID-19 AND *Cardiovascular System*	PUBMED	43
	LILACS	26
COVID-19 AND C*ardiac insufficiency*	PUBMED	42
	LILACS	1
COVID-19 AND *Heart Failure*	PUBMED	42
	LILACS	15
COVID-19 AND *Hypertension*	PUBMED	60
	LILACS	77
TOTAL		**511**

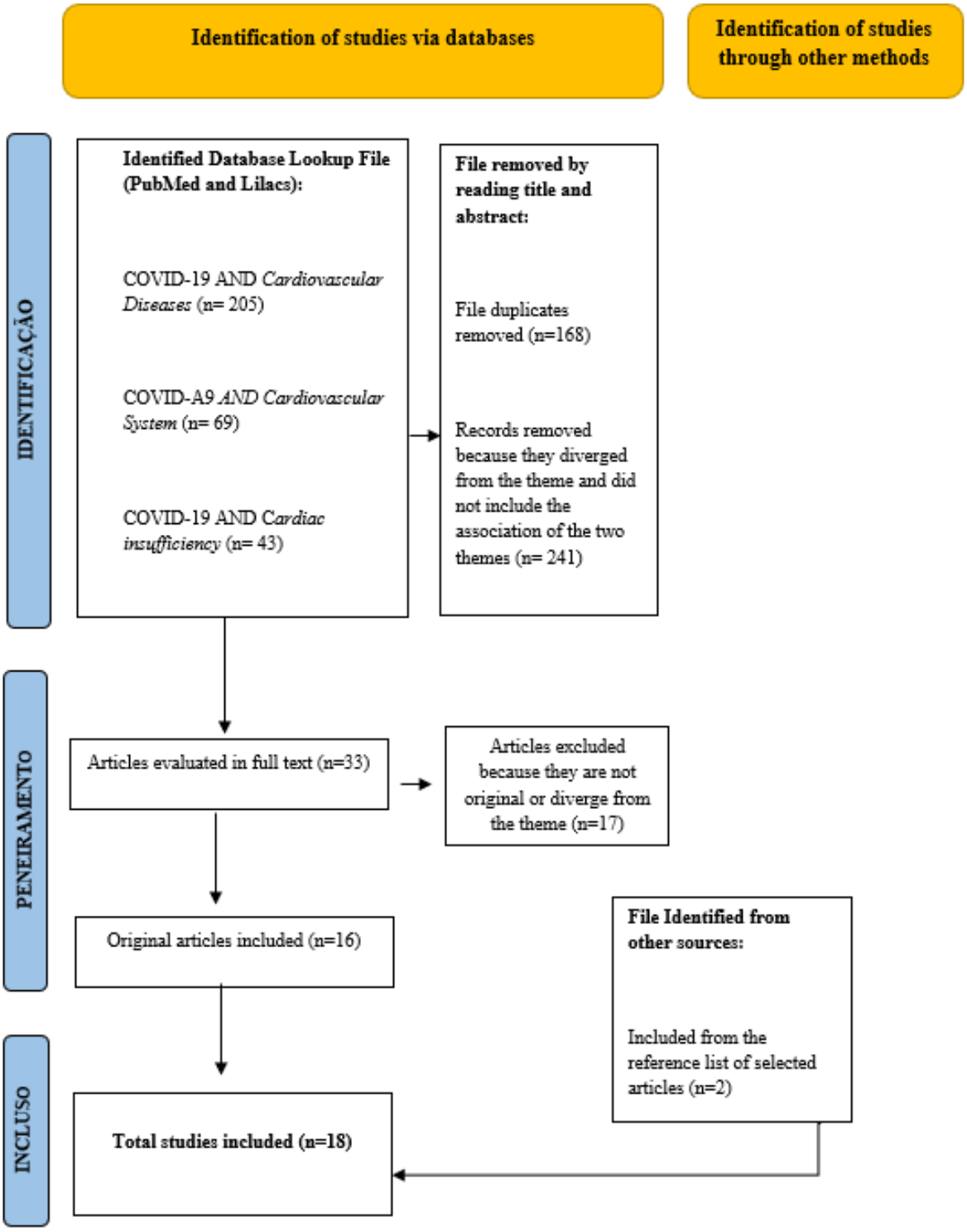
Source: Authors, 2022.

The following inclusion criteria were established: i) original articles of the following types: clinical trials, controlled and random tests; ii) published from the year 2020, iii) without language restriction. The selected period stems from the emergence of the new type of virus in 2019, which causes COVID-19. As exclusion criteria, the following were adopted: i) duplicate articles, integrative review articles, systematic review and meta-analysis, editorials and letters to the editor ii) articles that addressed the topic COVID-19 without a focus on cardiovascular diseases; and iii) articles addressing cardiovascular diseases without a focus on COVID-19.

The selection of articles was made by reading the titles, and soon after, the abstracts, aiming to distinguish which texts would be read in full and thus selected for analysis and interpretation and excluding review and duplicate texts. Before this process, all selected articles were inserted into the Endnote reference manager, to separate duplicate studies and review studies. In this context, 18 articles were included in the final sample, according to the research

flowchart **(Figure. 1**), so that they highlighted the complications that COVID-19 infection can cause in the cardiovascular system.

Figure 1. Flowchart of research conducted on impacts of COVID-19 on cardiovascular disease.



Source: Authors, 2022. Adapted de: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. O comunicado do PRISMA 2020: uma diretriz atualizada para a notificação de revisões sistemáticas. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

After establishing the final sample, the following information was extracted: i) sample characterization; study type and location ii) main CVD and analyzes performed; iii) highligts, as evidenced in **Table 3** and **Table 4**.

Table 3. Description of the main characteristics of the included studies such as sample characteristics, the main CVD and types of analyzes performed.

SAMPLE CHARACTERISTIC	DCV	ANALYSIS
69 deceased with a range of 38 to 97 years[14].	Acute cardiac injuries – myocarditis and cardiac necrosis. HAS	Autopsy. Histology, microscopy and quantitative analysis of histopathology
1138 adult patients hospitalized for CAP or COVID-19[15].	Thrombotic events. Acute myocardial infarction. HAS, FA, DAC and IC.	Statistical analysis of electronic medical records, with demographic, clinical, laboratory and radiological results.
65 male patients with respiratory failure. Positive (with COVID) and negative (without COVID) group[16].	Myocardial Lesion	Three blood samples (at inclusion [T1], after 7 [T2] and 14 days [T3]). Biomarkers of platelet activation, activation of the coagulation cascade, fibrinolysis, endothelial dysfunction and inflammation.
68 adult patients hospitalized positive for COVID-19 in the ICU and outside the ICU. Asymptomatic controls not hospitalized[17].	Coagulopathies. HAS	Endothelial and platelet cell activation markers, including VWF antigen, soluble thrombomodulin, soluble P-selectin and soluble CD40 ligand, clotting factors, endogenous anticoagulants and fibrinolytic enzymes.
187 patients with COVID-19 and positive group with underlying CVD[18].	CVAD, SAH, coronary heart disease and cardiomyopathy, and myocardial injury indicated by high levels of TnT.	Demographic data, laboratory findings, comorbidities, and treatments were collected and analyzed in patients with and without TnT elevation.
140 male patients PCR positive or clinically positive for COVID-19[19].	SAH, coronary artery disease, heart failure	Complete blood count, creatinine, albumin, ferritin, D-dimer, lactate dehydrogenase (LDH), CRP, high-sensitivity cardiac procalcitonin and troponin I (hs-cTnI), and chest CT were performed and repeated to assess treatment response and disease course.
99 positive COVID patients with a history of CVD compared to patients without CVD[20].	Heart failure, atrial fibrillation and CAD.	Demographic, clinical, laboratory, instrumental, treatment, and outcome data were extracted from hospital records.
183 male patients with COVID and CVD[21]	Heart failure, arrhythmias, CAD, SAH.	Medical records. Ultrasensitive TnT by the electrochemiluminescence method AND by the fluorescence immunoassay method.
201 critical and non-critical patients, both positive for COVID 19[22].	SAH and DAC	Myocardial injury through elevation of CKMB and Troponin-I levels. ECG and echocardiographic changes were evaluated.
105 healthy subjects versus critically ill patients with COVID-19 due to hypoxemia[23].	HAS and DAC	StO2 and THC were non-invasively measured on the forearm by near-infrared spectroscopy. A vascular occlusion test, a three-minute induced ischemia for dynamic parameters of StO2: deoxygenation and reoxygenation rate and hyperemic response. ARDS severity was assessed by the ratio of SpO2 to FiO2.
105 positive COVID patients with CVD[24].	AMI, SAH, acute coronary syndrome or heart failure syndrome.	PCR for identification of SARS-CoV-2. Myocardial injury by troponin I tests.

12472 positive COVID patients with FA[25].	FA	Remote monitoring (PaceMate™) was used to assess AF episodes in patients with a pacemaker or defibrillator.
1276 positive COVID patients with SAH and DM26	HAS	City of origin, sex, age group, time between the onset of signs/symptoms and death, signs/symptoms, type of comorbidities and lifestyle.
565 positive COVID patients with HAS[27].	HAS	Electronic medical records. Hypertension data; diabetes mellitus; obesity; malignant neoplasm; C-reactive protein; lymphocytes; urea; use of vasoactive amines on admission and altered level of consciousness on admission).
16 449 positive COVID patients with CVD[28].	CVD, SAH, cardiac risk factor.	Electronic form. Data: symptoms (sore throat, dyspnea, myalgia/arthralgia, fever, cough, nausea/vomiting, headache, diarrhea, runny nose, sputum production, weakness and O2 saturation <95%) and morbidity (COPD, CVD, DM, advanced-stage chronic kidney disease, immunosuppression, high-risk pregnancies, chromosomal disorders or immunologically fragile status, and obesity)
5 087 positive COVID patients with SAH and DM[29].	FA, ICC, HAS, IAM, Doença arterial periférica prévia, AVC prévio/AIT.	Plasma and DNA samples were obtained from two international cohorts of elderly patients with atrial fibrillation. sACE2 protein level. Levels of high-sensitivity cardiac troponin T (hs-cTnT), N-terminal procephalic natriuretic peptide (NT-proBNP), growth differentiation factor 15 (GDF-15), C-reactive protein, interleukin-6, D- dimer, and cystatin-C were determined by immunoassays. Genome-wide association studies were performed by Illumina chips.
62 severe and non-severe positive COVID patients with CVD[30].	DCV, DAC, HAS.	Electronic medical records. Epidemiological data: age, sex, symptoms, coexisting diseases and medication history. Laboratory: blood count, arterial blood gas, blood chemistry, clotting test, liver and kidney function, CRP, cardiac markers and immunological indicators. CT on admission was used for radiological evaluation..
8511 COVID-positive patients with previous CAD and or high risk of CAD[31].	CAD, SAH, AMI, unstable angina, CHF. stroke, FA.	Standardized questionnaire: age, sex, weight, height, waist circumference, educational level, smoking, alcohol consumption, medical history and current drug treatment. Data on the use of antihypertensive agents, hypoglycemic agents, statins, and aspirin.

Source: Authors, 2022. CVD: cardiovascular disease; SAH: systemic arterial hypertension; IRCU: intermediate respiratory units; StO2: tissue/local blood oxygen saturation; THC: local concentration of hemoglobin; TnT: troponin T levels; ICU: intensive care units; VWF: von Willebrand factor; AF: atrial fibrillation; AMI: acute myocardial infarction.

Table 4. Study type and location and main highlights of included research.

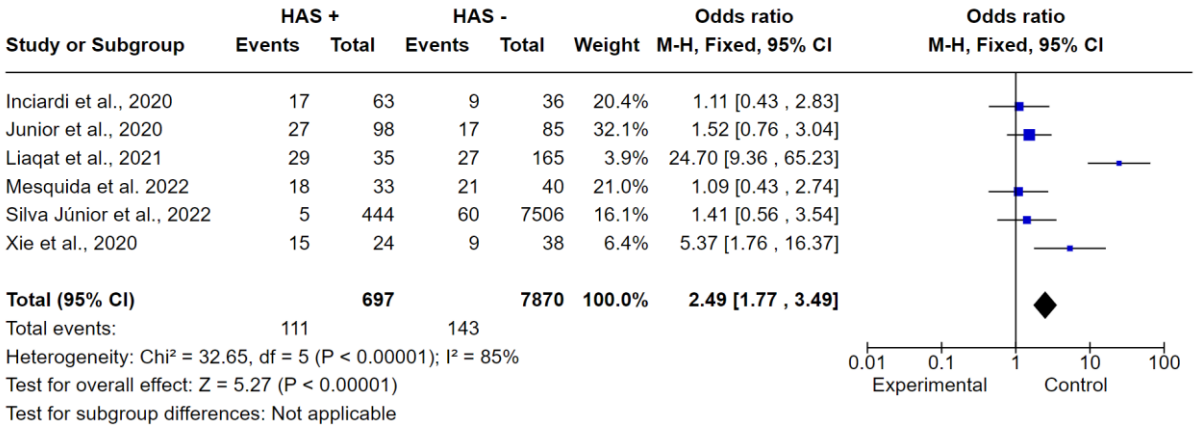
TYPE AND PLACE OF STUDY	HIGHLIGHTS
Prospective Study/ USA[14]	Prothrombotic, anti-fibrinolytic and immunoactivating signaling specific to cardiac fibroblasts in the hearts of patients with COVID-19 who died
Multicenter Observational Study/Italy[15]	COVID-19, when compared to community-acquired pneumonia, has a higher burden of thrombotic events, in addition to presenting a higher risk of in-hospital mortality.
Prospective Study/ Italy [16]	There is increased platelet activation and aggregation in patients with COVID-19. In critical cases there are higher values of inflammatory markers and

	thrombosis. There is a relationship between myocardial injury and a pro-inflammatory and pro-coagulant state.
Single-Center Cross-sectional Study/ USA[17]	COVID-19 is related to a coagulopathy, resulting from an increase in VWF release, platelet activation and hypercoagubulity, which causes prothrombotic manifestations (venous, arterial and microvascular thrombosis).
Retrospective Observational Study/ China[18]	The presence of myocardial injury has a significant relationship with fatal outcomes of COVID-19. Inflammation may be associated with myocardial injury.
Cohort Study / Turkey[19]	Patients with severe CT findings and worse prognosis have higher troponin levels. Myocardial injury characterized by elevated troponin has been noted mainly in patients with underlying CVD.
Demographic and clinical study/Italy[20]	Patients with COVID-19 and concomitant heart disease have a worse prognosis, with higher mortality, thromboembolic events and high rates of septic shock.
Observational, retrospective study of analysis of medical records/ Brazil[21]	Relationship between elevation of troponin with a higher risk of evolution to death or mechanical ventilation in patients infected with COVID-19.
Prospective Study/ Pakistan [22]	Critically ill patients with COVID-19 tend to have elevated troponin levels and electrocardiogram abnormalities, which have a positive correlation with progression to death.
Prospective, Multicenter and Observational Study/ Brazil, Mexico and Spain[23]	Patients with COVID-19, mainly in its severe form, have systemic microcirculatory changes, which suggest endothelial dysfunction.
Observational, retrospective study/ Brazil[24]	High incidence of myocardial injury in patients admitted to an intensive care unit, so that systemic arterial hypertension was configured as a risk factor regardless of the occurrence of this complication.
Multicenter, observational and cohort study /USA[25]	Significant increase in atrial fibrillation episodes during the COVID-19 pandemic when compared to the same period of the previous year.
Retrospective Study cross observational / Brazil[26]	Patients with SAH have a greater amount of the angiotensin-converting enzyme 2, which works as a receptor for the binding of SAR-CoV-2, and thus become more susceptible to the development of more severe cases.
Retrospective Cohort Study /Brazil[27]	As comorbidades mais associadas a gravidade da COVID-19 foram as cardiovasculares, com maior prevalência de hipertensão arterial sistêmica
Census and retrospective study / Brazil[28]	People with a heart risk factor were five times more likely to be referred to the emergency department when compared to people without a heart problem.
Randomized Study / Sweden[29]	Patients with CVD have higher levels of angiotensin-converting enzyme 2 (ACE2), and thus have a potentially higher risk of SARS-CoV-2 binding and more severe COVID-19 infection.
Observational Study / China[30]	More severe cases of COVID-19 were common hypertension and coronary artery disease (CAD), suggesting that CVDs play a critical role in disease severity. High molecular weight (HDL) cholesterol levels in the severe group with CVD were much lower than in the non-severe group.
Longitudinal Data Study/ China[31]	During the COVID-19 pandemic, anxious and hypertensive patients had a short-term increase in home morning systolic blood pressure, leading to an increased risk of cardiovascular events.

Source: Authors, 2022.

Due to the relevance of studies with the theme of systemic arterial hypertension (SAH) among the selected articles, a new selection was made searching for the articles that addressed the theme for risk assessment through meta-analysis. For this, the Odds Ratio (OR) was evaluated by meta-analysis through the Review Manager (RavMan), version 5.4.1, The Cochorane Collaboration 2022, to validate the relevance of the study (**Figure. 2**). In sum, the pooled analysis of six studies that provided data on the risks of patients with SAH having a worse prognosis during infection was performed.

Figure 2. studies



Source: Authors, 2022.

3 RESULTS

The total number of articles found through searches in electronic databases is shown in **Table 2**.

It can be seen that all studies evaluated adults ≥ 18 years. Among them, most patients were over 60 years old. According to sex, 13/18 infected men predominated, 4/18 infected women predominated, and 1/18 did not describe the predominant gender of infected individuals.

In addition, 15/18 studies addressed the correlation of SAH with the worst prognosis of Covid-19, that is, this pathology was highlighted among the cardiovascular changes. For this reason, the 15 studies dealing with SAH were read again in order to extract the following information: i) total number of patients with SAH and who had a good prognosis, ii) total number of patients with SAH and who had a poor prognosis; iii) total number of patients without SAH and who had a good prognosis, and iv) number of patients without SAH and who had a poor prognosis. Such information was contained in only 6/15 articles, for this reason the statistical analysis (risk analysis of worse prognosis during Covid-19 infection in patients with SAH) of these studies that contained the available data was performed. Furthermore, the following were considered as having a good prognosis: a) patients who were not in the ICU; b) were accompanied at home; c) did not require supportive ventilation. The poor prognosis criteria were: a) patients admitted to the ICU; b) who required supportive ventilation; c) who died. Thus, it is concluded that previously hypertensive patients may have up to 2.49 times more ([OR] = 2.49 95% [CI]: 1.77, 3.49) chances of having a worse prognosis, and may even progress to death during SARS-Cov-2 infection (**Figure. 2**).

The studies took place in several countries, from the countries of America, nine studies were addressed and of these we can highlight that six occurred in Brazil, among which one study was integrated and occurred concomitantly in Brazil, Mexico and Spain, and the others in the USA. Furthermore, four analyzes were carried out in European countries (three in Italy and one in Sweden) and five in Asian countries (three in China, one in Turkey and one in Pakistan).

Among the articles covered, 4/18 carried out a prospective study, 6/18 a retrospective study, and among these, one more observational activity can be noted. About 4/18 performed only one observational study and one study performed clinical analysis and another analysis of secondary clinical data. Troponin levels were evaluated in 8/18 studies, 6/18 performed electronic clinical data analysis or correlated existing data with Covid-19, one performed a clinical trial through remote monitoring of patients, and another addressed histopathological characteristics through of patients with comorbidities who died due to Covid-19.

4 DISCUSSION

Early on in the COVID-19 pandemic, a clear relationship was established with a greater number of cases and deaths in patients with some comorbidities. In this context, cardiovascular diseases (CVD) such as systolic arterial hypertension (SAH), cardiomyopathies and coronary artery disease (CAD) stand out, and the real role of the cardiovascular system in infection and complications by SARS-CoV-2 in humans it has several gaps, mainly related to the mechanisms of action and it is still incipient about the possibilities of therapeutic interventions to change this scenario.

Of the 18 studies, 16 dealt with the complications of COVID 19 and 2 discussed aspects related to a higher rate of infection in patients with preexisting CVD. Individuals with a cardiac risk factor were five times more likely to be referred to the emergency department when compared to people without a heart problem [27]. The cardiovascular comorbidity most associated with the severity of COVID-19 was systemic arterial hypertension [23,26,29], followed by coronary artery dysfunction[23].

5 INFECTION

Related to a higher infection rate, both studies showed that patients with SAH have a greater amount of angiotensin-converting enzyme 2 (ACE 2), which functions as a receptor for SARS-CoV-2 binding, presenting a potentially higher risk of infection. and worsening by COVID-19[25,28].

It is clear that patients with preexisting CVD are more susceptible to infection, and a greater number of cases in patients with such comorbidities corroborates this fact. One explanation is based on the fact that the SARS-CoV-2 virus has two glycoprotein subunits (S1 and S2) in its viral envelope. During infection of human cells, the S1 subunit binds to the cell surface of ACE-2, while the S2 subunit fuses with the cell membrane, mainly by endocytosis. The ACE-2 receptor is part of the renin-angiotensin-aldosterone system (RAS), which acts directly in the maintenance of blood pressure, water balance and control of vessel resistance. Renin converts angiotensinogen into angiotensin I (Ang 1), which soon after is converted into angiotensin II (Ang II) by the action of the angiotensin-converting enzyme (ACE)[6,29].

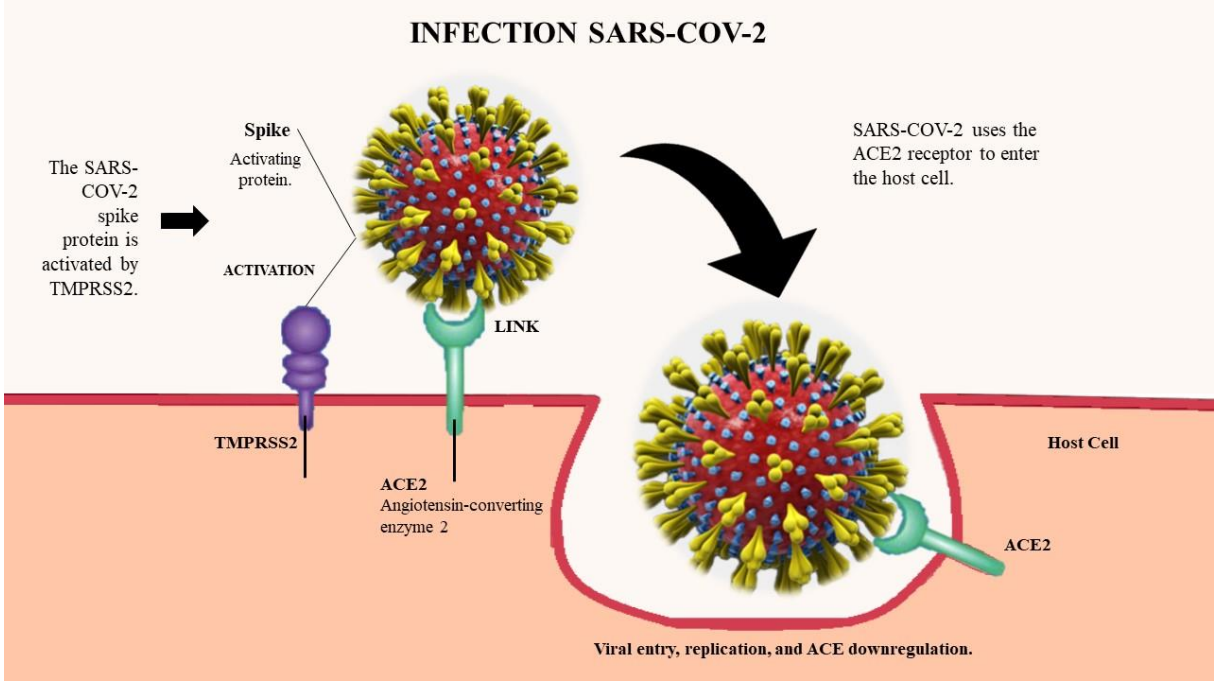
With its formation, Ang II interacts with the type 1 angiotensin receptor (AT1), which promotes vasoconstriction, inflammation, oxidative stress, fibrosis, in addition to aldosterone release, which consequently increases water reabsorption and thus increases blood pressure. arterial. Antagonistic to Ang II, the ACE-2 receptor converts both Ang I and Ang II to Angiotensin (1-7), which produces anti-inflammatory and anti-fibrotic repercussions, resulting in a decrease in blood pressure. Thus, ACE-2 contributes to a compensatory control, especially of blood pressure, in addition to protecting the body[32].

On the other hand, despite the positive effects, ACE-2 acts as an internalizing receptor for SARS-CoV-2, functioning as the main gateway for the virus that causes COVID-19[29]. In patients with advanced age, cardiovascular diseases (mainly hypertension and heart failure), and diabetes mellitus, there is an increase in the amount of ACE-2 receptors, compared to the healthy population, making them more susceptible to infection[33]. Even so, in research carried out by Liaqat, et al. (2021)[22] there is a significant association between the presence of pre-existing clinical comorbidities and the severity of the disease, so that the sum of different comorbidities amplifies the inflammatory response, favoring rapid progression and/or worsening of the clinical condition[26].

In general, the highest rate of infection occurs due to the mechanism of viral internalization in human cells, so that SARS-CoV2 binds to ACE2, which acts as a receptor for the structural spike (S) protein of the virus, and by Through this binding, it enters the host cell. In patients with preexisting cardiovascular diseases (CVD), such as arterial hypertension, cardiomyopathies and coronary artery disease, they tend to have increased serum levels of ACE2, thus facilitating the internalization of the virus in the cell and its consequent infection[34]. ACE2, because it is highly expressed in the lungs and heart, and because it is associated with the SARS-CoV2 transfection mechanism, in patients with cardiovascular risk factors, as well

as those with CVD, are more susceptible to developing the severe form of the disease, in addition to of a worse prognosis, being classified as a risk group[3], as shown in **Figure. 3**.

Figure 3. Mechanism of Sars-Cov-2 recognition and internalization in the human host cell.



Source: Authors, 2022.

6 COMPLICATIONS/WORST PROGNOSIS

Related to complications in patients with CVD, the infection involves several pathophysiological mechanisms, which can be summarized in: endothelial dysfunction, increased oxidative stress, hypoxemia, imbalance between myocardial oxygen supply and demand, immune-mediated myocardial injury and myocardial injury by the virus[24].

In those patients with risk factors and/or the presence of cardiovascular disease, there is a greater propensity to evolve to the more severe forms associated with COVID-19. Initially, the disease manifests as a flu-like syndrome (cough and fever), progresses to pneumonia (dyspnea, hypoxemia and tachypnea), progressing in some cases to respiratory distress syndrome[24].

The 16 studies on complications associated the manifestations of venous, arterial and microvascular thrombosis [16,19], with increased prothrombotic signaling [13–15], and with increased Von Willebrand factor release and activation/aggregation[15,16], in addition to increased anti-fibrinolytic and immunoactivating activity specific to cardiac fibroblasts in the hearts of patients with COVID-19[13]. Patients with COVID-19, mainly in its severe form, have systemic

microcirculatory changes associated with endothelial dysfunction (22) and high rates of septic shock[19].

In critical cases, there are higher values of inflammatory markers, with a relationship between myocardial injury and a pro-inflammatory and pro-coagulant state[15]. Inflammation may be associated with myocardial injury, and the presence of myocardial injury was significantly related to fatal outcomes of myocardial infarction. COVID-19[17]. Additionally, due to the increase in the number of cases of atrial fibrillation, compared to periods before the pandemic, COVID 19 is related to this event[24]. Research has linked severe CT findings and worse prognosis with higher troponin levels, with a higher risk of progression to death or mechanical ventilation[18,20,21]. A short-term increase in morning systolic blood pressure has been reported in anxious and hypertensive patients triggering an increased risk of other cardiovascular events[30].

Among the mechanisms underlying myocardial injury, there is mainly the so-called "cytokine storm" (hypercytonemia), resulting from an intense inflammatory response, with systemic microvascular involvement and endothelial dysfunction in patients with COVID-19, especially in its critical form[23]. These cytokines damage the myocardium, causing troponin elevation (above the 99th percentile) and cardiac dysfunction[21].

In their study, Junior, et al. (2020)21, showed that in patients with severe forms of the disease, higher levels of troponin (TnT) and C-reactive protein were found. Such evidence is corroborated by the study by Ileri, et al. (2021)19 who related higher levels of TnT in patients with severe CT findings, rapid disease progression and need for intensive care unit (ICU) admission. Another important finding is evidence that patients with underlying CVD are more likely to develop high levels of TnT, compared to patients without CVD[18].

Troponin is responsible for muscle contraction, being found in the heart and in lower concentration in the blood. However, when there is an injury to the heart tissue, these levels are altered, becoming higher[18]. According to the retrospective study by Deng, et al. (2020)[35], of the 112 hospitalized patients, 42 showed an increase in cardiac Troponin I, and 32 patients had this value tripled. Added to this, it showed that the highest rate of troponin elevation was in patients with the severe form of the disease[30].

Another study showed that among 187 patients with COVID-19, 57 had myocardial injury, with increased levels of TnT. Even so, it was reported that there was higher mortality in patients with high levels of TnT (59.6%) than in patients with normal levels of TnT (8.9%)[21].

Further on, it is reported by Mesquida, et al. (2021)23 that in critically ill patients with COVID-19, there is a systemic microvascular involvement, supporting an intrinsic relationship

with the degree of endothelial dysfunction (ED). Such dysfunction occurs both by the direct cytopathic effect of the virus and by the action of inflammation mediators resulting from the host's immune response. In its critical form, higher serum values of several inflammation markers, including P-selectin3, were observed[3].

In this context, due to inflammation in the vascular endothelium, there may be instability and rupture of the atherosclerotic plaque, with the formation of thrombi, in patients with coronary artery disease (CAD) and, consequently, the emergence of an ischemic process, not only in the heart, but also in the heart. throughout the cardiovascular system. In addition, it was evidenced that during the SARS-CoV-2 infection process, platelet activation occurs, with the release of clotting factors, secretion of inflammatory enzymes and the formation of platelet aggregates[22].

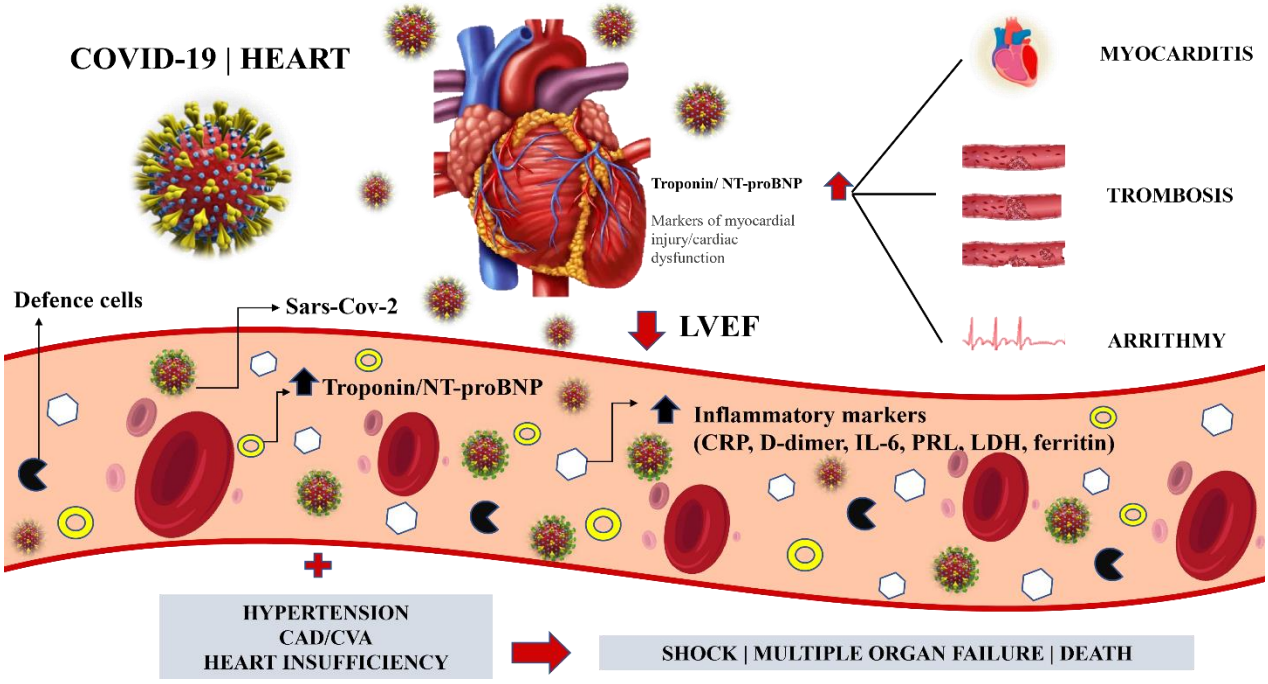
Previously, in another study, it was shown that in patients with CVD who progressed to the severe form of the disease, the level of HDL cholesterol was much lower than in the non-severe group with CVD. It is known that HDL is an atheroprotective cholesterol, acting as a marker for atherosclerosis and being a predictor of cardiovascular events[30]. In this way, dyslipidemia can be configured as a risk factor for severe infection by COVID-19.

In their study, Cangemi, et al. (2022)[15] brought evidence that, compared to community-acquired pneumonia (CAP), COVID-19 is related to a greater number of thrombotic events, with the risk of in-hospital mortality being five times greater. Another fact identified was that patients with COVID-19 had thrombosis in the arterial and venous circulation, with an equivalent incidence rate.

In a study cohort of 69 COVID-19 deaths, an autopsy was performed to identify cardiac histopathological features attributable to SARS-CoV-2 infection. Among the results, there was the discovery of a prothrombotic, antifibrinolytic and immunoactivating signaling of cardiac fibroblasts in microthrombotic positive hearts. Furthermore, it was observed in critically ill patients, elevation of d-dimer and inflammatory markers, such as C-reactive protein (CRP)[14].

The involvement of the cardiovascular system in patients with COVID-19, especially in its severe forms, is not uncommon, covering a wide variety of presentations, such as myocarditis, cardiomyopathies, coagulopathies and myocardial injury, all this described process can be better understood in the image. below (**Figure.4**).

Figure 4. Pathogenesis of Sars-Cov-2 in individuals with cardiovascular disease.



Source: Authors, 2022.

7 FINAL CONSIDERATIONS

The pathophysiology of Covid 19 in patients with associated CVD still needs further investigation, due to the fact that COVID-19 is a new disease with many singularities. However, it was evident that patients with previous CVD had a worse prognosis in the original studies discussed, and that the most debated CVD was SAH. Based on the statistical analysis, we concluded that previously hypertensive patients may be up to 2.49 times more likely to have a worse prognosis and may even progress to death during SARS-Cov-2 infection.

For health professionals, it is important to disclose the factors that trigger the aggravation of cases in patients with CVD. Among them, there are manifestations of venous, arterial and microvascular thrombosis due to increased prothrombotic signaling and an increase in von Willebrand factor release and platelet activation/aggregation, in addition to increased anti-fibrinolytic and immunoactivating activity specific to cardiac fibroblasts. . Systemic microcirculatory changes with endothelial dysfunction, higher troponin levels, higher values of inflammatory markers, with pro-inflammatory and procoagulant status, atrial fibrillation, and high rates of septic shock.

Thus, the surveillance of patients with CVD is of great importance in the face of the COVID-19 scenario, as they are more likely to have a worse prognosis for the disease. Especially patients with SAH, need to optimize measures to avoid contact with the virus, since the greater expression of ACE 2 has a greater chance of internalization of the virus and

developing severe cases. Information about a higher rate of infection and aggravation of cases should be widely disseminated.

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