

# **CARDIOVASCULAR COMPLICATIONS IN ADULTS AFTER SARS-COV-2 INFECTION: A COMPARATIVE SYSTEMATIC REVIEW**

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#### **ABSTRACT**

**Objective:** To identify cardiovascular complications triggered by SARS-CoV-2 infection in patients with and without pre-existing cardiovascular disease and to present the associated pathophysiological mechanisms. **Methods:** Systematic literature review with meta-analysis. Searches were performed in the PubMed, Web of Science, Lilacs, and Scopus (Elsevier) databases. The following DeCS terms were used: "SARS-CoV-2," "COVID-19," "cardiovascular diseases," "post-COVID syndrome," and "cardiovascular abnormalities." A total of 10 studies were included. **Results:** Echocardiographic abnormalities were found to occur with similar probability among all patients. Heart rate turbulence and variability remained abnormal even six months after the acute phase, indicating cardiac autonomic dysfunction and risk for further morbid cardiac complications. Alterations in left and right ventricular diastolic function and a higher risk of venous thromboembolic events were observed in patients with COVID-19. Endothelial dysfunction was prevalent, especially in those with heart failure and acute myocardial injury. Autonomic dysfunction may result from diffuse endotheliitis and vascular injury. Ischemic myocardial injury arises from cytokine storm, catecholamine surge, plaque rupture or erosion, hypoxic damage, coronary artery spasm, and thrombosis. Heart failure is hypothesized to occur due to immune system hyperactivation and downregulation of ACE2. **Conclusion:** SARS-CoV-2 infection affects the cardiovascular system, leading to myocardial injury, endothelial dysfunction, impaired myocardial oxygen supply and demand, and global dysfunction of both left and right ventricles.

**Keywords:** SARS-CoV-2; COVID-19; Cardiovascular Diseases; Post-COVID Syndrome; Cardiovascular Abnormalities.

#### **RESUMO**

**Objetivo:** Identificar as complicações cardiovasculares desencadeadas pela infecção do Sars-CoV-2, em pacientes com e sem Doenças Cardiovasculares e apresentar os mecanismos fisiopatológicos. **Métodos:** Revisão sistemática da literatura com metanálise. As buscas foram realizadas nas bases de dados: PubMed; Web of Science; Lilacs e Scopus (Elsevier). Foi utilizado os DeCS: "sars-cov-2", "covid-19", "doenças cardiovasculares", "síndrome pós-covid", "anormalidade cardiovasculares". Seleção final de 10 estudos. **Resultados:** É observado que anormalidades ecocardiográficas possuem a mesma probabilidade de ocorrer em todos os pacientes, a turbulência da frequência cardíaca e a variabilidade da frequência cardíaca foi anormal mesmo 6 meses após a fase aguda da doença, indicando disfunção autonômica cardíaca e risco para o desenvolvimento de outras complicações cardíacas morbidas. Alterações na função diastólica do ventrículo esquerdo e direito e o risco de desenvolvimento de eventos tromboembólicos venosos em pacientes críticos é maior na presença de COVID-19. Há uma prevalência de disfunção endotelial, principalmente em pacientes com insuficiência cardíaca e lesão miocárdica aguda. Um dos mecanismos responsáveis pela disfunção autonômica é a endotelite difusa e a lesão vascular. A lesão miocárdica isquêmica resulta da tempestade de citocinas, picos de catecolaminas, ruptura ou erosão da placa e lesão hipóxica, espasmo da artéria coronária e trombose, postula-se que a insuficiência cardíaca ocorre devido à hiperativação do sistema imunológico e à regulação negativa da ECA2. **Conclusão:** A infecção pelo vírus SARS-CoV-2 afeta o sistema CV levando a lesão miocárdica, disfunção endotelial, disfunção na oferta e demanda de oxigênio do miocárdio e disfunção global do ventrículo esquerdo e direito.

**Palavras-chave:** Sars-cov-2; Covid-19; Doenças Cardiovasculares; Síndrome pós-Covid; Anormalidade Cardiovasculares.

#### **RESUMÉN**

**Objetivo:** Identificar las complicaciones cardiovasculares desencadenadas por la infección del SARS-CoV-2 en pacientes con y sin enfermedades cardiovasculares previas y presentar los mecanismos fisiopatológicos asociados. **Métodos:** Revisión sistemática de la literatura con metanálisis. Las búsquedas se realizaron en las bases de datos PubMed, Web of Science, Lilacs y Scopus (Elsevier). Se utilizaron los DeCS: "SARS-CoV-2", "COVID-19", "enfermedades cardiovasculares", "síndrome pos-COVID" y "anormalidades cardiovasculares". Se seleccionaron 10 estudios. **Resultados:** Se observó que las anormalidades ecocardiográficas presentaron una probabilidad similar de ocurrir en todos los pacientes. La turbulencia y la variabilidad de la frecuencia cardíaca permanecieron alteradas incluso seis meses después de la fase aguda, lo que indica disfunción autonómica cardíaca y riesgo de complicaciones cardíacas morbidas adicionales. Se identificaron alteraciones en la función diastólica de los ventrículos izquierdo y derecho, y un mayor riesgo de eventos tromboembólicos venosos en pacientes con COVID-19. La disfunción endotelial fue prevalente, especialmente en casos con insuficiencia cardíaca y lesión miocárdica aguda. La disfunción autonómica puede deberse a endotelitis difusa y lesión vascular. La lesión miocárdica isquémica resulta de la tormenta de citocinas, el aumento de catecolaminas, la ruptura o erosión de la placa, la hipoxia, el espasmo coronario y la trombosis. Se postula que la insuficiencia cardíaca ocurre por la hiperactivación del sistema inmunológico y la regulación negativa de la ECA2. **Conclusión:** La infección por el virus SARS-CoV-2 afecta el sistema cardiovascular, provocando lesión miocárdica, disfunción endotelial, alteraciones en la oferta y demanda de oxígeno del miocardio y disfunción global de los ventrículos izquierdo y derecho.

**Palabras clave:** SARS-CoV-2; COVID-19; Enfermedades Cardiovasculares; Síndrome Pos-COVID; Anormalidades Cardiovasculares.

## INTRODUCTION

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus, which produces a wide range of symptoms, varying from a common cold to severe respiratory complications and systemic effects; there may even be asymptomatic cases<sup>1</sup>.

The SARS-CoV-2 virus belongs to the Coronaviridae family; the best-known members of this group are the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). During 2002 and 2003, SARS-CoV was responsible for an outbreak of severe respiratory disease in China, and MERS-CoV, in 2012, for an outbreak of severe respiratory diseases centered in the Middle East<sup>2</sup>.

On January 31, 2020, the World Health Organization (WHO) received an alert from the city of Wuhan, China, regarding severe pneumonia caused by a virus that, until then, had no known history of infecting humans. This virus, now known as SARS-CoV-2, quickly spread throughout the country and to other continents, and was classified on January 30, 2020, as a Public Health Emergency of International Concern (PHEIC) and subsequently, on March 11 of the same year, as a pandemic, which did not end until three years later, on May 5, 2023<sup>3</sup>.

The coronavirus pandemic, as it became known, had recorded, as of May 26, 2024, approximately 775 million confirmed cases of the disease and 7 million deaths worldwide<sup>4</sup>. According to the Coronavirus Dashboard, in

Brazil, as of July 8, 2024, there were 38,832,913 confirmed cases and 712,537 reported deaths<sup>5</sup>.

The SARS-CoV-2 virus is an enveloped virus containing an RNA genome; there are 4 groups and 7 strains that infect humans. According to Sharma, studies reveal that the SARS-CoV-2 genome is 96.2% similar to the genome of SARS RaTG13, which very commonly infects bats—compared to SARS-CoV and MERS-CoV, which share 79% and 51.8% similarity, respectively. Thus, it is suggested that bats are the origin of SARS-CoV-2<sup>6</sup>.

According to Rodrigues<sup>7</sup>, the SARS-CoV-2 virus enters the cell via the angiotensinogen-converting enzyme (ACE2), which is found in the alveolar epithelium, as well as in renal, cardiac, and gastrointestinal cells and blood vessels, and plays a key role in the renin-angiotensin-aldosterone system by regulating blood pressure and fluid volume within the vessels. Because its cellular receptor is an enzyme present in so many organs of the body and due to the body's own defense against the pathogen, the pathophysiology of COVID-19 is complex and is not restricted to a single system.

In this regard, in the lungs, the first organ affected because they serve as the entry point—the virus induces inflammatory and immune reactions, primarily in the interstitial tissue of the lungs and the alveoli, leading to exudate accumulation, and lesions in the alveolar and vascular epithelium trigger an inflammatory cascade and consequent acute respiratory distress, while the destruction of type II

pneumocytes leads to atelectasis due to a lack of surfactant <sup>7</sup>.

The virus has been detected in renal tissue, causing acute kidney injury, proteinuria, and edema. In the liver, the cytopathic effect of the virus and the immune response lead to sepsis and liver injury; in the enterocytes of the small intestine, it causes intestinal dysbiosis, reducing immunity. In turn, in the central and peripheral nervous systems, it induces headache, anosmia, and hyposmia, and may lead to intracerebral and subarachnoid hemorrhages. Furthermore, it can trigger cytokine production, leading to disseminated intravascular coagulation (DIC), thrombus formation, and vascular occlusion <sup>8</sup>.

Because the virus uses the ACE2 enzyme, which is directly linked to the cardiovascular system, as its cellular entry point, significant manifestations occur exclusively within this system. These cardiovascular manifestations can be misdiagnosed and complicate the diagnosis of COVID-19, potentially increasing the severity of the disease and thereby exacerbating cardiac complications; even patients without underlying heart disease may develop such complications during the course of the infection <sup>9</sup>.

Despite these clear associations between COVID-19 and the cardiovascular (CV) system, the impacts on the system and the CV complications resulting from SARS-CoV-2 infection remain an actively studied field, with findings constantly updated in light of new evidence, as does the relationship between the infection and complications in individuals with

and without a history of cardiovascular disease (CVD). Thus, the present study aims to identify the cardiovascular complications triggered by SARS-CoV-2 infection in adult patients with and without prior CVD and to present the pathophysiological mechanisms underlying these complications.

## METHOD

A systematic literature review was conducted, following these steps: 1) definition of the guiding research question; 2) selection of the sample, including the definition of inclusion and exclusion criteria; 3) definition of data and extraction from the studies; 4) analysis of the studies; 5) analysis of the results; 6) presentation and discussion of the results.

The guiding question was formulated using the PICO strategy, Population, Interest, Context. The study population consists of adults infected with the SARS-CoV-2 virus; the focus is on the development of cardiovascular complications triggered by the disease, whether as a new condition or the progression of a preexisting one; and the context is the COVID-19 pandemic. Thus, the research question formulated was: “What is the relationship between SARS-CoV-2 infection and cardiovascular complications in adults resulting from COVID-19?”

Searches were conducted from April to June 2024 in the following databases: PubMed; Web of Science; Latin American and Caribbean Health Sciences Literature (LILACS) via the Virtual Health Library (VHL); and Scopus

(Elsevier), through the Portal for the Coordination of the Improvement of Higher Education Personnel (CAPES). Remote access was provided through the Federated Academic Community (CAFe) and an account at the Federal University of Maranhão (UFMA).

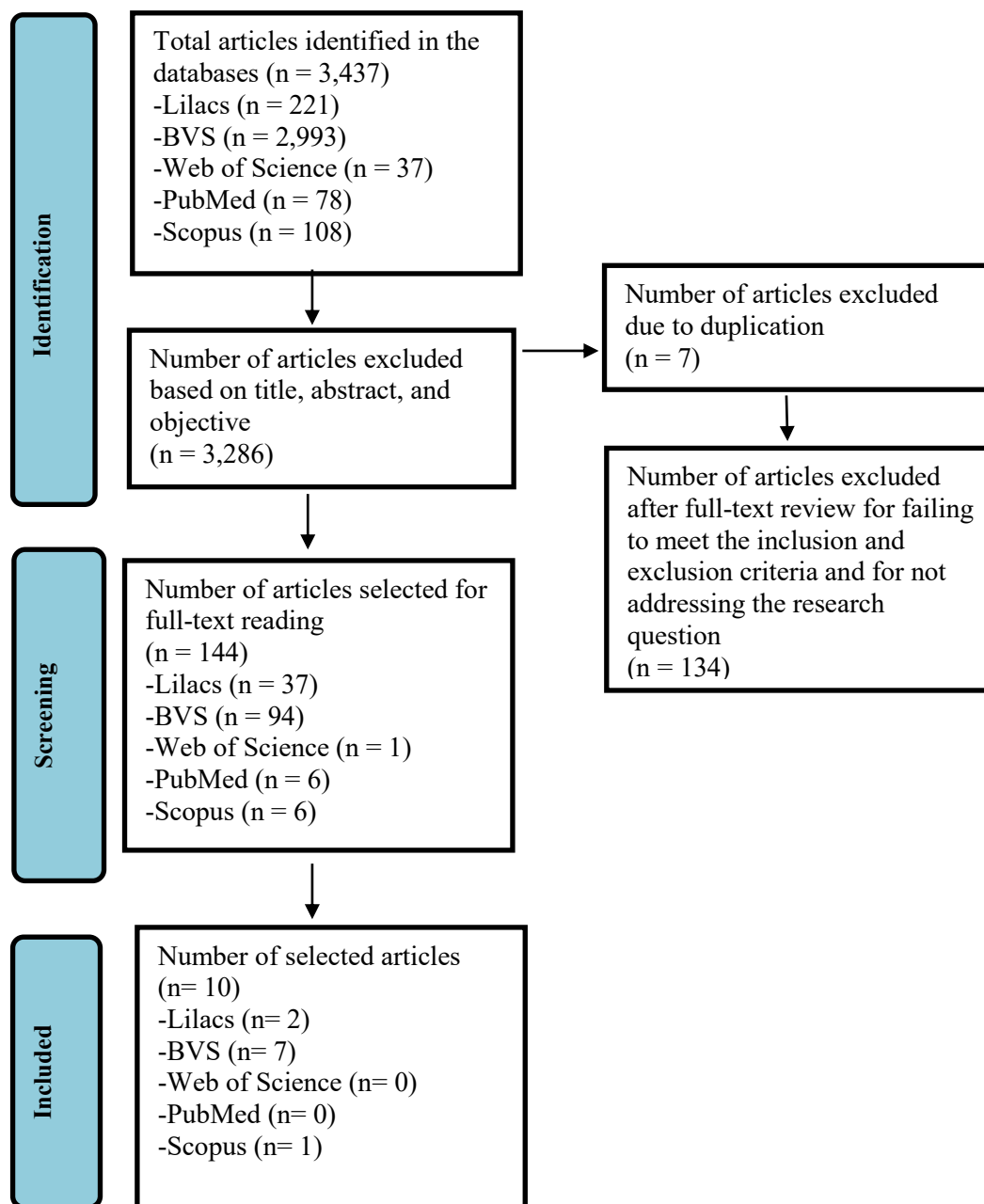
The following Health Sciences Descriptors (DeCS) were used: “sars-cov-2,” “covid-19,” “cardiovascular diseases,” “post-COVID syndrome,” “cardiovascular abnormalities,” and, in English, the subject headings: “heart disease risk factors,” “cardiovascular diseases,” “cardiovascular abnormalities,” “Post-Acute COVID-19 Syndrome.” The descriptors were combined using the Boolean operators OR and AND, as well as square brackets [ ].

Full-text articles published from 2020 to 2024 in English, Portuguese, and Spanish were

included, while studies that did not address the research question and literature review studies were excluded. To select the articles, the titles and abstracts were reviewed, the inclusion criteria were applied, the full texts were read to confirm the relevance of the article to the study, and duplicates were removed.

After conducting the search using the search terms, 3,437 articles were identified. 3,286 articles were excluded based on their title, abstract, and objectives, and 7 were excluded due to duplication. A total of 144 studies were selected for full-text review; of these, 134 articles were excluded for failing to meet the inclusion criteria and for not addressing the guiding question, resulting in a final selection of 10 studies used for this review. The steps described are illustrated in the PRISMA Flowchart (Figure 1).

**Figure 1** - Stages of the article selection process according to the PRISMA Flowchart. Imperatriz, MA, Brazil, 2024.



Source: Adapted from Mendes, C. *et al.* Prisma Flowchart (2020)

## RESULTS

A total of 10 studies were included, of which 2 were identified in LILACS (20%), 7 in BVS (70%), and 1 in Scopus (10%). All studies found were published in English. Regarding study type, 2 were multicenter observational studies (20%), 3 were prospective cohort studies

(30%), 2 were retrospective (20%), 2 were multicenter retrospective observational studies (20%), and 1 was a cross-sectional study (10%). Regarding levels of evidence, 3 studies were classified as level 3 (30%) and 7 studies were classified as level 4 (70%), based on the categorization by the U.S. Agency for Healthcare Research and Quality (AHRQ).

Table 1 presents the characteristics of 6 studies, including authors, year, country, journal, study type, study objective, sample, and level of evidence. It also identifies the results found in the studies, the specific cardiovascular complication reported, and its incidence, in relation to patients without a history of cardiovascular disease (CVD). Table 2 presents the same characteristics, results, and incidence of the cardiovascular complications listed in Table 1, but in relation to patients with a history of CVD.

The first two studies in Table 2 are already described in Table 1 but are also included in Table 2 because they addressed cardiovascular complications triggered by the infection in both groups of patients with and without a history of CVD. Table 3, on the other hand, presents the pathophysiology of cardiovascular complications and COVID-19, which are addressed in the results, discussion, and conclusion sections of the 8 studies that also address this pathophysiological topic among the 10 analyzed in the study as a whole.

**Table 1** - Characterization of cardiovascular complications developing after SARS-CoV-2 infection in adult patients without prior CVD. Systematic review, Brazil, 2024.

| Order | Author/Year/County                               | Title                                                                                                                                                                       | Journal/<br>Study Type / Level of Evidence                                                      | Sample/Objective                                                                                                                                                                                    | Results                                                                                                                                                                                                                                                                                                                                                                                              | Incidence of CVD                                                                                                                                                                                                                                                                                                                                                                                    |
|-------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1     | Barberato et al., 2021. <sup>10</sup><br>Brazil. | Echocardiographic Findings in Patients with COVID-19 with and without Pre-existing Cardiovascular Disease                                                                   | Brazilian Archives of Cardiology/<br><br>Prospective, multicenter observational study/<br><br>4 | 223 patients/<br><br>To describe the prevalence of the main abnormal echocardiographic findings in hospitalized patients with COVID-19 with and without prior cardiovascular disease (CVD).         | Right ventricular (RV) systolic dysfunction is common in patients with and without prior cardiovascular disease (CVD).<br><br>Echocardiographic abnormalities are equally likely to occur in patients with or without a history of cardiovascular disease (CVD).                                                                                                                                     | -48% had echocardiographic abnormalities;<br>- Left ventricular (LV) hypertrophy: 7%;<br>- Left ventricular systolic dysfunction (13%, regional contractility abnormalities 8%);<br>-Grade II or III left ventricular (LV) diastolic dysfunction: 11%;<br>- Right ventricular systolic dysfunction: 17%;<br>-Pulmonary hypertension: 24%;<br>-48% of them had regional contractility abnormalities. |
| 2     | Barberato et al., 2021. <sup>11</sup><br>Brazil. | Transthoracic Echocardiographic Findings in Patients Hospitalized with COVID-19: Results from the Brazilian Echocardiography Registry during the COVID-19 Pandemic (ECOVID) | Brazilian Archives of Cardiology/<br><br>Prospective, multicenter observational study/<br><br>4 | 310 patients<br><br>To determine the prevalence of the main abnormal echocardiographic findings in hospitalized patients with COVID-19, comparing patients with and without a history of prior CVD. | Patients without a history of CVD have fewer left ventricular (LV) abnormalities.<br><br>Right ventricular (RV) dysfunction occurs in patients with and without a history of CVD.<br><br>Patients without a history of CVD have more LV hypertrophy and pulmonary hypertension, RV systolic dysfunction, and LV systolic dysfunction.<br><br>Patients without a history of CVD rarely exhibit severe | -1 in every 13 patients had severe echocardiographic abnormalities;<br>- Left ventricular hypertrophy: 25%; left ventricular systolic dysfunction: 13%;<br>-Regional contractility abnormalities: 6%;<br>-Grade II or III LV diastolic dysfunction: 9%;<br>-Pulmonary hypertension: 22%;<br>-Right ventricular systolic dysfunction 13%.                                                            |

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|   |                                                       |                                                                                                                                |                                                                                               |                                                                                                                                                                                                                           | <p>echocardiographic abnormalities.</p> <p>Patients with myocardial injury have worse RV function compared to patients without injury.</p> <p>Patients without CVD exhibit more right ventricular systolic dysfunction than left ventricular systolic dysfunction.</p>                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 3 | <p>Taş et al., 2023.<sup>12</sup></p> <p>Turquia.</p> | <p>Effects of COVID-19 on the autonomic cardiovascular system: heart rate variability and turbulence in recovered patients</p> | <p>Journal of the Texas Heart Institute/</p> <p>Cohort study</p> <p>Prospective/</p> <p>3</p> | <p>146 patients, 51 patients analyzed, and 95 control patients/</p> <p>To evaluate heart rate turbulence and heart rate variability as markers of autonomic dysfunction in patients who have recovered from COVID-19.</p> | <p>Heart Rate Turbulence (HRT) and Heart Rate Variability (HRV) remained abnormal even 6 months after the acute phase of the disease, indicating cardiac autonomic dysfunction and an increased risk for the development of other morbid cardiac complications, respectively.</p> <p>Sinus tachycardia and reduced HRV are common in the acute and post-acute phases of the disease.</p> <p>Some symptoms, such as palpitations, chest pain, fatigue, and dyspnea, persist in the post-COVID period.</p> <p>Changes in left ventricular (LV) and right ventricular (RV) diastolic function were common during the acute phase of the disease.</p> | <p>The study did not report the incidence of the aggravating factors among the patients studied.</p> <p>The following symptoms were reported during the 6-month follow-up:</p> <ul style="list-style-type: none"> <li>- Palpitations: 60.8%;</li> <li>-Chest pain: 43.1%;</li> <li>-Fatigue: 47.1%;</li> <li>-Shortness of breath: 27.5%.</li> </ul> <p>Abnormalities observed:</p> <ul style="list-style-type: none"> <li>-Abnormal HRV and RR;</li> <li>-Cardiac autonomic dysfunction;</li> <li>-Risk of developing fatal and morbid cardiac complications;</li> <li>-Sinus tachycardia;</li> <li>-Reduced HRV;</li> <li>-Palpitations;</li> <li>-Chest pain;</li> <li>-Altered diastolic function of the left ventricle (LV) and right ventricle (RV).</li> </ul> |

|   |                                                   |                                                                                                                                             |                                                       |                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                    |
|---|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4 | Erdem et al., 2023. <sup>13</sup><br>Turquia.     | Pulmonary artery pressures and right ventricular dimensions in post-COVID-19 patients without previous significant cardiovascular pathology | Heart & Lung/<br>Retrospective cohort study/<br>4     | 91 patients/<br>To investigate pulmonary artery pressure and cardiac dimensions in post-COVID-19 patients with no history of significant cardiac disease. | Right ventricular dimensions—basal diameter, mean diameter, and longitudinal dimensions—are larger in more severely ill patients and in patients with severe pulmonary involvement. Mild and moderate patients with pulmonary involvement may develop right ventricular dysfunction. Diastolic and systolic pulmonary arterial pressure and right ventricular dimensions remain elevated even 3 months after recovery from COVID-19. During hospitalization, the most common cardiac manifestation is right ventricular dilation/dysfunction, and it can be used to identify patients at high risk for an unfavorable outcome. Myocardial injury occurs in 20%–30% of patients hospitalized with COVID-19. | -The most common presenting symptom was exertional dyspnea (52.7%), followed by palpitations (48.3%), chest pain (31.8%), and dyspnea at rest (15.3%). Pulmonary hypertension was observed in 15 patients (16.4%). -14% presented with right ventricular dilation. |
| 5 | Stavileci et al., 2022. <sup>14</sup><br>Turquia. | De novo development of fragmented QRS during a six-                                                                                         | Journal of Electrocardiology/<br>Retrospective study/ | 256 patients/<br>To examine the QRS wave on the electrocardiogram of patients who have                                                                    | The presence of fQRS, which is an indicator of myocardial fibrosis and enlargement of the heart chambers. The fQRS is most                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | The prevalence of post-COVID-19 tachycardia syndrome at the six-month mark was 9.67%.                                                                                                                                                                              |

|   |                                                            |                                                                                                     |                                                                         |                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|   |                                                            | month follow-up period in patients with COVID-19 and its cardiac effects                            | 4                                                                       | recovered from COVID-19;                                                                                                                         | frequently located in the inferior leads on the ECG.<br>There is a correlation between fQRS and IgG levels, indicating the severity of the disease.<br>Diastolic dysfunction, lower left ventricular ejection fraction (LVEF), and enlarged cardiac chambers were significant in the fQRS group.                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 6 | Shanmuganathan et al., 2023. <sup>15</sup><br>Reino Unido. | Acute changes in myocardial tissue characteristics during hospitalization in patients with COVID-19 | Frontiers in Cardiovascular Medicine/<br>Prospective cohort study/<br>3 | 42 patients/<br>To investigate cardiac findings during the acute and recovery phases of COVID-19 in patients without a history of heart disease. | T1 and T2 are weighting sequences in magnetic resonance imaging that have different characteristics. They are ideal for assessing the anatomy and morphology of soft tissues and fat, and for evaluating fluids and pathologies, such as tumors, inflammation, and trauma, respectively.<br>Abnormally elevated T1 and T2SI were present in 26% and 50% of patients with acute COVID-19, respectively. Those with abnormally elevated T1 had a significantly higher left ventricular ejection fraction (LVEF) compared to patients with normal T1.<br>All patients showed normal myocardial T1 and T2SI at the 6-month follow-up. No new abnormalities were | Abnormally elevated T1 and T2SI (measures of acute myocardial edema) were present in 26% and 50% of patients with acute COVID-19, respectively.<br><br>Those with abnormally elevated T1 values had a significantly higher LVEF (left ventricular ejection fraction) compared to patients with normal T1 values.<br><br>Pathological LRE (late gadolinium enhancement on MRI: capable of identifying tissue abnormalities, particularly myocardial fibrosis) was observed in 2 out of 8 (25%) patients with elevated cardiac troponin (CTnI) levels and 1 out of 15 (6.5%) patients with normal CTnI levels, leading to further cardiological referrals and coronary revascularization in one patient. |

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|  |  |  |  |  | <p>observed on chest X-ray at follow-up.</p> <p>The mechanism underlying elevated T1 and T2 signals in acute COVID-19 may, in part, be attributed to the presence of intracellular edema.</p> <p>Acute COVID-19 appears to induce acute myocardial edema in some patients, which resolves during convalescence without a significant impact on biventricular structure and function in the acute and short-term phases.</p> |  |
|--|--|--|--|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

Source: Prepared by the authors.

**Table 2** - Characterization of cardiovascular complications developing after SARS-CoV-2 infection in adult patients with a history of CVD. Systematic review, Brazil, 2024.

| Order | Author/Year/Country                                  | Title                                                                                                     | Journal/<br>Study Type                                                                            | Sample/objective                                                                                                                                                              | Results                                                                                                                                                                                                                                                                                     | Incidence of CVD                                                                                                                                                                                                                    |
|-------|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1     | Barberato et al., 2021. <sup>10</sup><br><br>Brazil. | Echocardiographic Findings in Patients with COVID-19 with and without Pre-existing Cardiovascular Disease | Brazilian Archives of Cardiology/<br><br>, prospective, multicenter observational study/<br><br>4 | 223 patients/<br><br>To describe the prevalence of the main abnormal echocardiographic findings in hospitalized patients with COVID-19, with and without prior cardiovascular | Right ventricular (RV) systolic dysfunction is common in patients with and without a history of cardiovascular disease (CVD).<br><br>Patients with a history of cardiovascular disease (CVD) are more likely to present with systolic and diastolic dysfunction of the left ventricle (LV). | -LV hypertrophy 52%;<br>-LV systolic dysfunction: 34%, regional contractility abnormalities 24%,<br>-Grade II or III LV diastolic dysfunction 26%;<br>- Right ventricular systolic dysfunction 22%;<br>-Pulmonary hypertension 38%. |



|   |                                                                    |                                                                                                                                                                             |                                                                                                 |                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|   |                                                                    |                                                                                                                                                                             |                                                                                                 | disease (CVD).                                                                                                                                                                                                                                     | Echocardiographic abnormalities are equally likely to occur in patients with or without a history of CVD, but in patients with a history of CVD, left ventricular (LV) systolic dysfunction is the most common finding.                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 2 | Barberato et al., 2021. <sup>11</sup><br><br>Brazil                | Transthoracic Echocardiographic Findings in Patients Hospitalized with COVID-19: Results from the Brazilian Echocardiography Registry during the COVID-19 Pandemic (ECOVID) | Brazilian Archives of Cardiology/<br><br>Prospective, multicenter observational study/<br><br>4 | 310 patients<br><br>To determine the prevalence of the main abnormal echocardiographic findings in hospitalized patients with COVID-19, comparing patients with and without a history of prior CVD.                                                | Right ventricular dysfunction occurs in patients with and without a history of CVD. Patients with myocardial injury have worse RV function compared to patients without injury. LV hypertrophy, systolic dysfunction, and diastolic dysfunction are more common in patients with a history of CVD. | -LV hypertrophy: 45%;<br>-LV systolic dysfunction: 36%;<br>Regional contractility abnormalities: 29%;<br>-Grade II or III left ventricular diastolic dysfunction: 29%;<br>-Pulmonary hypertension 36%;<br>-Right ventricular systolic dysfunction 25%.                                                                                                                                                                                                                                                                                                                                                                      |
| 3 | Juan Esteban Gomez-Mesa et al., 2023. <sup>16</sup><br><br>Caribe. | Latin American Registry of Cardiovascular Diseases and COVID-19: Final Results                                                                                              | Global Heart/<br><br>Observational, multicenter, prospective registry/<br><br>4                 | 3,260 patients from 44 institutions located in 14 regions of the Caribbean, Central, and South America./<br><br>To describe laboratory findings, clinical presentation at admission, and clinical outcomes at discharge and 30 days post-discharge | The risk of developing venous thromboembolic events in critically ill patients is higher in the presence of COVID-19 and is related to hemostatic abnormalities, immobility, systemic inflammation, mechanical ventilation, and central catheters.                                                 | The most common clinical signs and symptoms at admission were dyspnea (72.5%), cough (68.6%), and fever (64.4%).<br>Of the 1,626 patients who underwent an electrocardiogram, the following findings were observed: right bundle branch block (6.5%), atrial fibrillation (5.4%), left bundle branch block (3.1%) and ventricular extrasystoles (1.7%).<br>3,019 patients underwent X-rays: cardiomegaly in 16.8%.<br>634 patients underwent an echocardiogram: globally reduced systolic function (15.7%), right ventricular dysfunction (16.3%), pericardial effusion (10.9%), and inferior vena cava dilatation (15.6%). |

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| 4 | Reyes et al., 2023. <sup>17</sup><br><br>Colômbia | Major Adverse Cardiovascular Events (MACE) in Patients with Severe COVID-19 Registered in the WHO ISARIC Clinical Characterization Protocol: A Prospective, Multinational, Observational Study | Journal of Critical Care/<br><br>Prospective, multinational, observational study/<br><br>4 | 49,479 patients/<br><br>To determine the cumulative incidence of MACE ( <i>cardiac arrhythmia, heart failure, myocardial injury, stroke</i> ) in patients hospitalized due to severe COVID-19 | MACE is a clinical outcome that includes: cardiac arrhythmia, heart failure, myocardial injury, and stroke; The most common clinical diagnoses were cardiac arrhythmias, cardiac arrest, and heart failure; Patients who developed MACE had a higher median heart rate and lower diastolic blood pressure.<br><br>Age and prior cardiovascular disease are associated with myocardial injury.<br><br>Patients who developed MACE were older, between 60 and 79 years of age, and more frequently male.<br><br>Compared to patients without MACE, those with MACE more frequently had comorbidities such as hypertension and diabetes mellitus.<br><br>The need for vasopressors or ventilatory support in the first few days increases cardiovascular risk and the likelihood of developing MACE.<br><br>The development of MACE in patients dramatically increased the risk of death at 28 and 90 days by approximately | The cumulative incidence of MACE (major adverse cardiovascular events) during hospitalization was 17.8%.                                                                                               |

|   |                                                     |                                                                                                                                        |                                                      |                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                              |
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|   |                                                     |                                                                                                                                        |                                                      |                                                                                                                                                                | 40%.<br>Patients with COVID-19 may develop MACE following the acute episode and should be monitored for early diagnosis and potential secondary prevention.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                              |
| 5 | Araújo, et al., 2023. <sup>18</sup><br><br>Brazil   | Endothelial function, arterial stiffness, and heart rate variability in patients with cardiovascular disease hospitalized for COVID-19 | Heart & Lung/<br><br>Cross-sectional study/<br><br>4 | 27 patients/<br><br>To assess endothelial function, arterial stiffness, and HRV (heart rate variability) in adult patients with CVD hospitalized for COVID-19. | Patients in the group with endothelial dysfunction had a higher percentage of adverse cardiac events, primarily acute myocardial infarction and atrial fibrillation with high ventricular response.<br><br>Patients exhibited impaired endothelial function three months after COVID-19, and half of the survivors showed reduced flow-mediated dilation.<br><br>COVID-19 can cause endothelial injury and changes in the vascular wall (i.e., damage to the tunica media), resulting in arterial stiffness.<br><br>Many patients with preserved endothelial function exhibited arterial stiffness, and heart rate variability was correlated with endothelial dysfunction. | -The prevalence (51.8%) of endothelial dysfunction.<br>-There was a high prevalence of endothelial dysfunction, particularly in patients with chronic heart failure (71.4%). |
| 6 | Puttegowd, et al., 2021. <sup>19</sup><br><br>Índia | Patterns of cardiovascular disease in patients with COVID-19 admitted to a tertiary cardiac care center                                | Heart Journal/<br><br>Retrospective study/<br><br>3  | 511 patients/<br><br>To analyze the pattern of CVD in patients with COVID-19 admitted to a tertiary cardiac care center                                        | Pre-existing CVD was present in 258 patients (50.5%), with ischemic heart disease being the most common.<br><br>ST-segment elevation myocardial infarction (STEMI) was observed in 161 patients (31.5%). It was more common than non-ST-segment elevation acute coronary syndrome                                                                                                                                                                                                                                                                                                                                                                                           | Acute myocardial injury was observed in 60.8%.                                                                                                                               |

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|  |  |  |  |  | <p>(NSTEMI).</p> <p>Mild, moderate, and severe left ventricular systolic dysfunction was observed in 27, 15, and 10 patients, respectively.</p> <p>Serum troponin T was elevated in 311 patients (60.9%), suggesting myocardial injury.</p> |  |
|--|--|--|--|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

Source: Prepared by the authors.

**Table 3** - Pathophysiological mechanisms of cardiovascular complications developing in adult patients following SARS-CoV-2 infection and the pathophysiology of COVID-19. Systematic review, Brazil, 2024.

| Order | Title                                                                                                                                                                      | Author/Year/Country                              | Pathophysiology of Cardiovascular Complications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1     | Echocardiographic Findings in Patients with COVID-19 with and without Pre-existing Cardiovascular Disease                                                                  | Barberato et al., 2021. <sup>10</sup><br>Brazil. | Pulmonary hypertension and right ventricular systolic dysfunction may be associated with phenomena affecting the lungs, such as hypoxia, inflammation, acute respiratory distress syndrome, pulmonary microvascular thrombosis, pulmonary thromboembolism, and even the use of mechanical ventilation.                                                                                                                                                                                                                                                                                                                                                                        |
| 2     | Transthoracic Echocardiographic Findings in Patients Hospitalized with COVID-19: Results from the Brazilian Echocardiography Registry during the COVID-19 Pandemic (ECOVID | Barberato et al., 2021. <sup>11</sup><br>Brazil. | The development of right ventricular (RV) abnormalities in COVID-19 may result from various phenomena affecting the lungs, such as hypoxia, inflammation, acute respiratory distress syndrome, pulmonary microvascular thrombosis, pulmonary thromboembolism, and mechanical ventilation, among others.                                                                                                                                                                                                                                                                                                                                                                       |
| 3     | Effects of COVID-19 on the autonomic cardiovascular system: heart rate variability and turbulence in recovered patients                                                    | TAŞ et al., 2023. <sup>12</sup><br>Turquia.      | <p>When the cardiovascular system is involved in COVID-19, disturbances in regulatory mechanisms can cause autonomic dysfunction, resulting in sympathetic hyperactivation or vagal impairment. Thus, sympathetic tone also becomes dominant in the ventricular myocardium and decreases myocardial compliance.</p> <p>It is believed that COVID-19 involves the right ventricle both directly and indirectly and has different effects on the lungs during the acute and chronic phases. Changes in the size and function of the right ventricle have also been associated with increased sympathetic tone and volume changes due to the systemic inflammatory response.</p> |



|   |                                                                                                                                              |                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---|----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|   |                                                                                                                                              |                                                      | <p>One of the mechanisms responsible for autonomic dysfunction is diffuse endotheliitis and vascular injury. Another explanation for cardiac involvement is that the hyperinflammation syndrome and coagulopathy can cause dysautonomia at the micro- and macro-levels. Furthermore, COVID-19 itself can cause myocardial damage and necrosis, and necrotic and non-contractile segments cause geometric changes during heartbeats, stimulating sympathetic afferent nerve endings.</p> <p>A reduced HRV has been associated with high levels of pro-inflammatory cytokines and worse outcomes in patients with coronary artery disease, heart failure, diabetes, hypertension, obesity, and autoimmune diseases. Regardless of the underlying disease, however, reduced HRV is primarily associated with sympathetic hyperactivity or parasympathetic hypoactivity.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 4 | Pulmonary artery pressures and right ventricular dimensions in post-COVID-19 patients without previous significant cardiovascular pathology. | Erdem et al., 2023. <sup>13</sup><br><br>Turquia.    | <p>Hypoxic pulmonary vasoconstriction, mechanical ventilation with high airway pressure, and thrombotic events contribute to endothelial and alveolar injury and consequent fibrosis, which in turn lead to pulmonary hypertension (PH) and altered pulmonary hemodynamics, leading to an increase in pulmonary arterial pressure (PAP) and right ventricular involvement.</p> <p>COVID-19 pneumonia affects both the left and right ventricles of the heart, and the most common cardiac manifestation in the acute phase of the disease is right ventricular dilation/dysfunction.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 5 | De novo development of fragmented QRS during a six-month follow-up period in patients with COVID-19 and its cardiac effects                  | Stavileci et al. 2022. <sup>14</sup><br><br>Turquia. | <p>fQRS is an electrocardiographic sign of myocardial scar tissue, which explains the non-homogeneous delay in ventricular conduction in damaged and/or ischemic myocardium. fQRS has been associated with the severity of coronary artery disease, mortality, the development of heart failure, and arrhythmias. The development of fQRS in patients with COVID-19 has been considered an indicator of myocardial fibrosis and enlargement of the cardiac chambers.</p> <p>Patients with post-acute COVID-19 syndrome present a wide variety of symptoms, such as fatigue, chest pain, decreased exercise tolerance, rapid heartbeat, and palpitations, among others. The persistence of these symptoms for 4 to 12 weeks or longer is defined as post-acute COVID-19 syndrome, and in this syndrome, tachycardia may occur as postural orthostatic tachycardia syndrome or in d inappropriate sinus tachycardia.</p> <p>The pathophysiological mechanism of postural orthostatic tachycardia syndrome remains unclear. However, there is evidence that autoantibodies activate adrenergic and muscarinic receptors, leading to a hyperadrenergic state—similar to the loss of taste and smell—peripheral denervation, and deconditioning, leading to blood pooling in the lower extremities and reflex tachycardia.</p> <p>There are mechanisms that contribute to post-COVID-19 tachycardia syndrome, such as persistent lung injury or exacerbation of underlying lung disease, which causes desaturation and reflex tachycardia; persistent or intermittent fever, which can increase heart rate; pain; anxiety and depression; neuroinflammation; and hypovolemia.</p> |
| 6 | Latin American Registry of Cardiovascular Diseases and                                                                                       | Juan Esteban Gomez-Mesa et al., 2023. <sup>16</sup>  | -                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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|    | COVID-19: Final Results                                                                                                                                                                        | Caribe.                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 7  | Major Adverse Cardiovascular Events (MACE) in Patients with Severe COVID-19 Registered in the WHO ISARIC Clinical Characterization Protocol: A Prospective, Multinational, Observational Study | Reyes et al., 2023. <sup>17</sup><br><br>Colômbia   | -                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 8  | Endothelial function, arterial stiffness, and heart rate variability in patients with cardiovascular disease hospitalized for COVID-19.                                                        | Araújo et al., 2023. <sup>18</sup><br><br>Brazil    | <p>The severity of inflammation is directly related to arterial stiffness. Increased intravascular pulsatile pressure damages the vascular wall and causes arterial stiffness, promoting atherosclerosis and increasing the inflammatory component and the stiffening effect. However, it is not fully understood whether patients with COVID-19 are predisposed to early atherosclerosis.</p> <p>Suppressed sympathetic activity and predominant parasympathetic activity induced a compensatory anti-inflammatory response in patients with COVID-19. Post-COVID-19 cardiovascular dysautonomia is characterized by an imbalance in sympathetic or parasympathetic activity and may be attributed to virus-related damage, a cytokine storm, or immune-mediated dysregulation of the autonomic nervous system (symptoms of which include deconditioning, hypovolemia, a hyperadrenergic state, or immune-mediated viral damage).</p>                                                                                     |
| 9  | Patterns of cardiovascular disease in COVID-19 patients admitted to a tertiary cardiac care center.                                                                                            | Puttegowda et al., 2021. <sup>19</sup><br><br>Índia | <p>Elevated troponin T levels are associated with higher levels of biomarkers such as C-reactive protein (CRP) and procalcitonin, as well as higher white blood cell counts, indicating that myocardial injury correlates with the severity of inflammation.</p> <p>Ischemic myocardial injury results from a cytokine storm and a surge in catecholamines, predisposing to plaque rupture or erosion (type 1 myocardial infarction). It may also be due to hypoxic injury, mismatch between supply and demand, coronary artery spasm, and thrombosis (type 2 myocardial infarction).</p> <p>It is postulated that heart failure occurs in COVID-19 due to hyperactivation of the immune system and downregulation of ACE2, leading to increased levels of angiotensin II.</p> <p>Arrhythmias in COVID-19 infection may be due to acute cardiac injury from various causes, such as ischemia, direct myocardial damage, systemic inflammatory response syndrome, or the effects of medications used to treat COVID-19.</p> |
| 10 | Acute changes in myocardial tissue characteristics during                                                                                                                                      | Shanmuganathan et al., 2023.                        | Such a change in water content (as indicated by changes in T1 and T2) may occur in one or both of the intracellular or extravascular compartments (including the coronary arteries) and may be attributed to                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

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|  | hospitalization in patients with COVID-19 | <sup>15</sup><br>Reino Unido. | physiological changes during stress.<br>The presence of a higher left ventricular ejection fraction (LVEF) in patients with abnormally elevated myocardial T1 values raises the possibility that COVID-19 leads to a hyperdynamic state resulting in increased myocardial blood volume (plasma and red blood cells), which may have been detected as elevated myocardial T1. |
|--|-------------------------------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Source: Prepared by the authors.

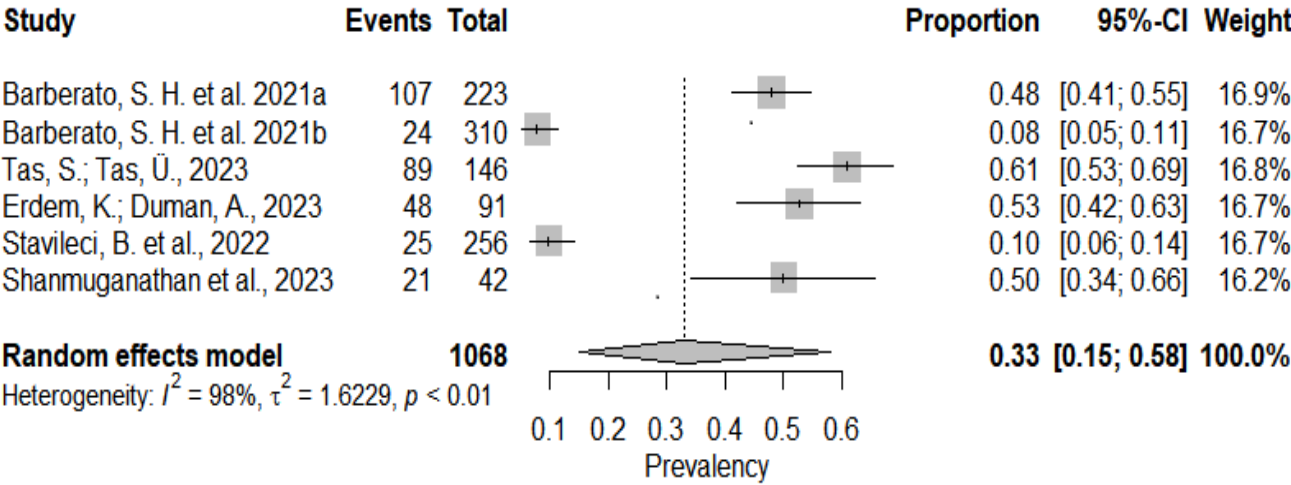
A study was conducted on the prevalence and a meta-analysis of cardiovascular complications in adults with and without a history of CVD, as reported in the analyzed studies. Figure 1 presents the meta-analysis of the prevalence of cardiovascular complications following SARS-CoV-2 infection in adults without a history of CVD, based on 6 studies totaling 1,068 participants. The combined results, using a random-effects model, indicate an estimated prevalence of cardiovascular complications of 33%, with a 95% CI of 15% to 58% (the 95% CI provides a range of values within which the prevalence would be expected to fall if a larger sample size were obtained in each study), suggesting considerable heterogeneity among the studies ( $I^2 = 98\%$ ,  $p < 0.01$ ), with individual estimates ranging from 8% to 61%.

Figure 2 presents the meta-analysis of the prevalence of cardiovascular complications following SARS-CoV-2 infection in adults with a history of CVD, based on 6 studies involving a total of 53,810 participants. The estimated pooled prevalence, using a random-effects

model, was 52%, with a 95% CI of 34% to 70%, indicating a high prevalence of cardiovascular complications and a wide confidence interval. Furthermore, the analysis revealed extremely high heterogeneity among the studies ( $I^2 = 100\%$ ,  $p = 0$ ), suggesting a wide variation in the reported results. Individual prevalence estimates varied significantly, ranging from 18% to 73%, which may be attributed to differences in the study populations, clinical contexts, and methodologies used in the studies.

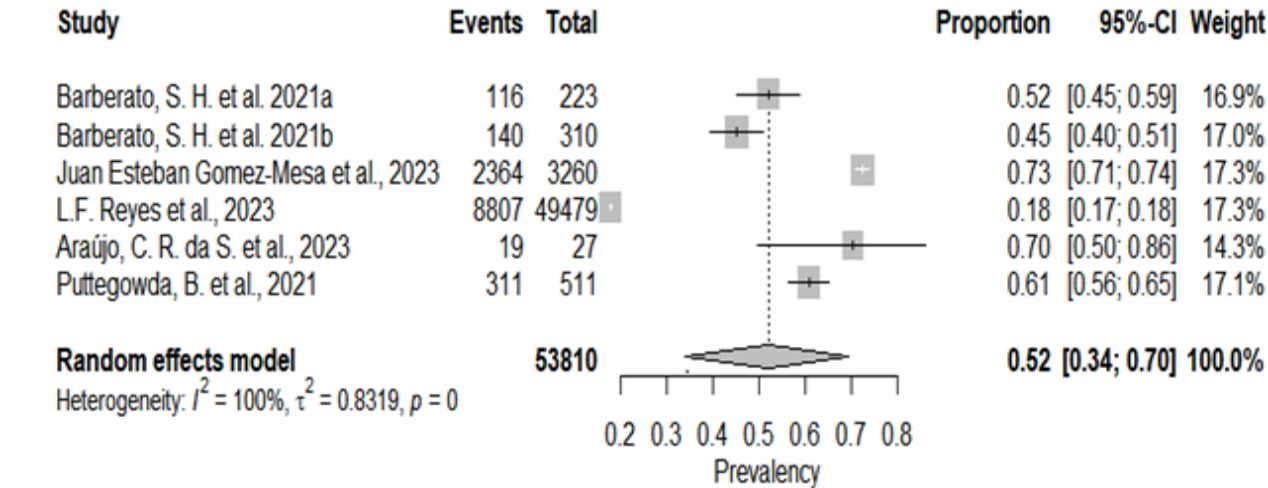
This high heterogeneity reflects significant variations in the reported prevalences and can be attributed to methodological or population-based differences among the analyzed studies. The high heterogeneity observed underscores the need for caution in interpreting the results and suggests that future studies should explore the causes of these variations to improve our understanding of the factors influencing cardiovascular complications in patients with COVID-19.

**Figure 1** - Meta-analysis of the prevalence of cardiovascular complications following SARS-CoV-2 infection in adults without prior cardiovascular disease. Systematic review, Brazil, 2024.



Source: Prepared by the authors.

**Figure 2** - Meta-analysis on the prevalence of cardiovascular complications following SARS-CoV-2 infection in adults with pre-existing cardiovascular disease. Systematic review, Brazil, 2024.



Source: Prepared by the authors.

## DISCUSSION

The SARS-CoV-2 virus infects host cells, causing COVID-19, when the viral membrane S protein binds to Angiotensin-Converting Enzyme 2 (ACE2) and is cleaved by Transmembrane Serine Protease 2 (TMPRSS2),

which allows the viral genome to enter the cell and replicate; thus, for the cell to become infected, expression of the ACE2 receptor on the cell membrane is necessary, as well as TMPRSS2, ADAM17, and CTSL—two other

auxiliary proteases expressed in the cardiovascular system<sup>21,21</sup>.

The ECA2 receptor is present in nearly all vascular cells, endothelial cells, fibroblasts, and pericytes, and ECA2 itself plays an active role in the renin-angiotensin-aldosterone system, which is essential for homeostasis, blood pressure regulation, and immune system function. Thus, at the cellular and tissue levels, SARS-CoV-2 infection leads to a cytokine storm, cellular oxidative stress, and consequent inflammation and endothelial dysfunction<sup>21,21</sup>.

Among the selected articles, there is a consensus that SARS-CoV-2 infection and COVID-19 lead to cardiovascular manifestations and/or complications, including: heart rate irregularities, r sinus tachycardia, reduced heart rate variability, palpitations, chest pain, myocardial injury, enlarged right ventricular (RV) dimensions, elevated diastolic and systolic pulmonary artery pressures, myocardial fibrosis, right bundle branch block, atrial fibrillation, left bundle branch block, right ventricular dysfunction, inferior vena cava dilatation, pericardial effusion, cardiac arrhythmia, heart failure, endothelial dysfunction or vascular wall abnormalities, acute myocardial infarction, atrial-ventricular fibrillation, mild left ventricular (LV) systolic dysfunction, and acute myocardial edema.

The clinical manifestations that were most common in the analyzed studies, and which trigger other cardiovascular complications, to be discussed in greater detail here, are: myocardial injury, endothelial dysfunction, acute

myocardial infarction (AMI), stroke, heart failure, right ventricular (RV) dysfunction, and left ventricular (LV) systolic dysfunction.

Myocardial injury is characterized by elevated troponin levels above the 99th percentile, and is usually accompanied by abnormalities on the electrocardiogram and echocardiogram, such as wall abnormalities and left ventricular diastolic dysfunction, right ventricular dysfunction, and the development of scarring resembling myocarditis, and occurs in 20% to 30% of patients with COVID-1<sup>22,23</sup>. Myocardial injury and the resulting increase in troponin also serve as predictors of mortality. When comparing patients with and without myocardial injury, those who develop this complication exhibit more cardiovascular abnormalities than patients without myocardial injury, such as changes in the electrocardiogram and echocardiogram, hyperinflammation, and anatomical and functional abnormalities of the ventricles<sup>22</sup>.

Myocardial injury generally occurs during the acute phase of the disease, either due to direct viral damage to the myocardium via entry through the ACE2 receptor, or due to the immune response and resulting cytokine storm, or through an indirect mechanism resulting from respiratory failure and the induction of hypoxia in myocardial tissue<sup>24</sup>. Myocardial injury was observed in 60.8% of cases, and non-ischemic myocardial injury in the form of possible myocarditis was observed in 10.1% of cases<sup>19</sup>. fQRS is an electrocardiographic sign of the presence of myocardial scar tissue in response to

myocardial injury; it indicates delayed ventricular conduction and the development of heart failure and arrhythmias, and was present in 36.9% of cases<sup>14,17</sup>. Vascular injury, hyperinflation, myocardial injury, and necrosis alter the heartbeat and lead to autonomic dysfunction and sympathetic hyperactivity or parasympathetic hypoactivity, as observed by heart rate variability. Changes in cardiac autonomy and in the sympathetic and parasympathetic activities of the nervous system lead to a condition of atrioventricular fibrillation<sup>12</sup>.

Endothelial dysfunction, in turn, can be explained largely by the direct consequences of viral invasion and by the immune response to the infection. Changes in nitric oxide availability trigger immune reactions that disrupt vascular homeostasis, causing damage to the tunica media and an increase in the expression of prothrombotic factors, thereby exacerbating the body's pro-inflammatory state. Direct infection of the endothelial cell itself causes its dysfunction and accelerates the state of coagulopathy and thrombosis, creating a risk of stroke and ischemic heart attacks<sup>18,21</sup>. Endothelial dysfunction is prevalent in 51.8% of cases, and patients with this complication have a higher incidence of chronic heart failure (71.4%) and hypertension (78.6%) compared to patients with preserved endothelial function<sup>19,18</sup>.

A relationship can be observed between endothelial dysfunction and other cardiovascular complications identified in the studies: acute myocardial infarction (AMI) and stroke. AMI is

the ischemia and death of myocardial tissue that can occur due to obstruction of the coronary arteries (type 1 AMI) or due to an imbalance between oxygen demand and supply, while stroke is a neurological deficit caused by a vascular event, such as a cerebral infarction, and occurs in a small number of cases, approximately 0.6%<sup>17,23</sup>. Endothelial dysfunction and systemic inflammation lead to thrombus formation and the clinical presentation of type 1 AMI, and this same inflammatory state increases the myocardium's oxygen demand, which, exacerbated by respiratory problems and secondary hypoxia, can lead to a type 2 AMI<sup>25</sup>. Furthermore, ST-segment elevation myocardial infarction (STEMI) was observed in 31.5% of cases, 12.1% more prevalent than non-ST-segment elevation myocardial infarction (19.4% of cases)<sup>19</sup>.

Heart failure (HF), in turn, is a syndrome resulting from cardiac abnormalities, whether functional or structural in nature<sup>17</sup>. It generally occurs as a consequence of acute myocarditis or as a response to the cardiac muscle's oxygen demand and hyperinflammation. Dysfunction of ACE2 and elevated angiotensin II levels are also factors that explain its pathophysiology, occurring in 44.4% of cases among patients with pre-existing CVD<sup>23,19</sup>. Heart failure is a predictor of patient mortality, which is 1.6 times higher compared to those without heart failure, and SARS-CoV-2 infection may be a risk factor for its development at other stages of life<sup>19,12</sup>.

Left ventricular (LV) systolic dysfunction is defined as a reduction of less than

50% in the left ventricular ejection fraction (LVEF) and can range from mild (with an LVEF between 40 and 50%), moderate (between 30 and 39%), to severe (with an LVEF less than 30%)<sup>11</sup>. Left ventricular diastolic function is also assessed using parameters other than LVEF, and the most accurate measure of left ventricular diastolic function is the E/Em ratio, which is the ratio of the peak early mitral inflow velocity (E) to the early diastolic mitral annular velocity (Em)<sup>12</sup>.

Changes in right ventricular (RV) dimensions are assessed by the Myocardial Performance Index (MPI), a representative marker of overall function that has prognostic value for many cardiac conditions. Right ventricular (RV) structural and functional abnormalities are associated with increased sympathetic tone and decreased HRV (heart rate variability). One hypothesis for these abnormalities and cardiac structural changes may be pneumonia<sup>13</sup>. The most common manifestation in the acute phase of COVID-19 is right ventricular dilation/dysfunction, and these changes are used as an independent predictor of 60-day mortality and a high-risk factor for an unfavorable outcome<sup>12,13</sup>.

There are some differences between the cardiovascular complications that occur in patients with and without a history of prior CVD. Left ventricular (LV) systolic and diastolic dysfunction, as well as LV dilation and hypertrophy, are reported in 4%, 39.4%, 7.6%, and 27.2% of cases, respectively, in patients without a history of CVD<sup>10</sup>. Complications such

as right ventricular (RV) systolic dysfunction are more common in patients without a history of CVD compared to those with a history of CVD and are the most frequent complication; and only 52% of patients without a history of CVD had a normal echocardiogram; LV hypertrophy and pulmonary hypertension are more common in patients without CVD, followed by right ventricular systolic dysfunction and left ventricular systolic dysfunction<sup>10</sup>.

It is worthwhile to analyze studies that highlight the persistence or emergence of new cardiovascular complications even after the acute phase of COVID-19 and in patients with no history of cardiovascular disease (CVD). Cardiac involvement was observed in 78% of patients who recovered from COVID-19, and the persistence of at least one symptom months after the acute phase, with the most commonly reported being palpitations (60.8%), chest pain (43.1%), fatigue (47.1%), and dyspnea (27.5%). The mean systolic blood pressure and mean diastolic blood pressure in post-COVID patients are 128.9 and 79.3, respectively—values very similar to those observed in patients during the acute phase, which were 130.4 and 80.5, respectively. The rate of abnormal initial heart rate variability is higher in post-COVID-19 patients, and endothelial function remains impaired three months after SARS-CoV-2 infection<sup>12,18</sup>. HRV and HRT abnormalities persisted in the post-COVID group, indicating the persistence of cardiac autonomic dysfunction after clinical resolution; therefore, medical

follow-up is necessary even after clinical resolution<sup>12</sup>.

Thus, it can be observed that COVID-19 can lead to long-term cardiovascular complications even in patients with no history of CVD and even months after the acute infection, potentially serving as a risk factor for the development of cardiovascular diseases, such as heart failure and hypertension<sup>18,12</sup>.

## CONCLUSION

This study shows that SARS-CoV-2 infection affects the cardiovascular system both directly and indirectly, with pathophysiological manifestations at the cellular, tissue, and systemic levels. Myocardial injury, endothelial dysfunction, and disturbances in oxygen supply and demand affect the myocardium and exacerbate other immunological and pathological reactions in the cardiac, respiratory, and immune systems, among others. Heart failure, right ventricular dysfunction, systolic dysfunction of the left and right ventricles, atrial fibrillation, and stroke are some of the most common cardiovascular complications triggered by SARS-CoV-2 infection.

The absence of a prior history of cardiovascular disease (CVD) does not guarantee that SARS-CoV-2 infection will not lead to cardiovascular complications, and there is no significant difference compared to patients with a prior history of CVD. SARS-CoV-2 infection may even lead to future complications in patients without a history of CVD or exacerbate pre-

existing cardiomyopathies.

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