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REVIEW ARTICLE

# Cardiovascular system involvement in SARS-CoV-2 infection

## Afectación del sistema cardiovascular en la infección por SARS-CoV-2

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## ABSTRACT

**Introduction:** COVID-19 is an emerging disease with global incidence, which exhibits a greater number of complications in patients with comorbidities, mainly in those with a history of cardiovascular disease.
**Objective:** to describe the implications of COVID-19 in the cardiovascular system.
**Method:** a review of the medical literature was conducted in MEDLINE, SciELO, JAMA and Elsevier databases, recovering 35 articles, which were taken as the basis for the present review. The combination of terms using search formulas was used to retrieve articles.
**Development:** COVID-19 can be variable in correspondence with the presentation form and accompanying symptoms, as well as the immune response of the recipient. SARS-CoV-2 binds to cells through the viral spike structural protein that binds to the angiotensin-converting enzyme 2 receptor from viral receptors; therefore, hypertensive patients or those with other cardiovascular conditions have a higher risk of developing severe forms of COVID-19. Among the cardiovascular diseases associated with infection by a coronavirus, myocarditis, arrhythmias, acute myocardial infarction and heart failure stand out.
**Conclusions:** the main cardiovascular implications in patients with COVID-19 are arrhythmia, thromboembolic disease, myocarditis, heart failure of acute onset and myocardial infarction, which condition a more serious picture of the disease. The inflammatory response, hemodynamic changes secondary to the viral process, as well as hypoxemia, constitute mechanisms of negative impact on cardiovascular health, leading to the development of acute heart failure.

**Keywords:** coronavirus; COVID-19; SARS-CoV-2; hypertension; arrhythmias; cardiomyopathies

## RESUMEN

**Introducción:** la COVID-19 es una enfermedad emergente con incidencia global, que exhibe mayor número de complicaciones en pacientes con comorbilidades, principalmente en aquellos con antecedentes de enfermedades cardiovasculares.
**Objetivo:** describir las implicaciones de la COVID-19 en el sistema cardiovascular.
**Método:** se realizó una revisión de la literatura en las bases de datos MEDLINE, SciELO, JAMA y Elsevier, recuperándose 35 artículos, los cuales se tomaron de base para la presente revisión. Se empleó la combinación de términos mediante fórmulas de búsqueda para recuperar los artículos.
**Desarrollo:** la COVID-19 puede ser variable en correspondencia con la forma de presentación y síntomas acompañantes, así como la respuesta inmunitaria del receptor. El SARS-CoV-2 se une a las células a través de la proteína estructural viral de espiga que se une al receptor de la enzima convertidora de angiotensina 2 a partir de receptores virales; por ello, los pacientes hipertensos o con otras afecciones cardiovasculares tienen un mayor riesgo de desarrollar formas severas de COVID-19. Dentro de las

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afectaciones cardiovasculares asociados a la infección por un coronavirus destacan la miocarditis, arritmias, infarto agudo de miocardio e insuficiencia cardíaca.
**Conclusiones:** Las principales implicaciones cardiovasculares en los pacientes con COVID-19 son arritmia, enfermedad tromboembólica, miocarditis, insuficiencia cardiaca de inicio agudo e infarto de miocardio, las cuales condicionan un cuadro más grave de la enfermedad. La respuesta inflamatoria, los cambios hemodinámicos secundarios al proceso viral, así como la hipoxemia, constituyen mecanismos de repercusión negativa sobre la salud cardiovascular, llevando al desarrollo de lesión cardiaca aguda.

**Palabras clave:** coronavirus; COVID-19; SARS-CoV-2; hipertensión; arritmias; miocardiopatías

## INTRODUCTION

The first quarter of 2020 has been influenced by the spread of a pandemic caused by SARS-CoV 2 virus (Severe acute respiratory syndrome coronavirus 2), which causes damage to the lungs, triggering a pneumonia that leads to Acute Respiratory Distress Syndrome (ARDS) which can lead to a fatal outcome for the patient[1].

Coronaviruses are a large family of viruses that can cause disease in both animals and humans. In humans, several coronaviruses are known to cause respiratory infections that can range from the common cold to more serious illnesses such as Middle Eastern Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV)[1].

It is round or oval in shape and often polymorphic, with a diameter of 60-140 nm. The spike protein, which is found on the surface of the virus and forms a rod-shaped structure, is the main structure used for typing the nucleocapsid protein, encapsulates the viral genome and can be used as a diagnostic antigen[1,2].

Cases of pneumonia caused by a new coronavirus (SARS-CoV-2) were first documented in Wuhan, China. About half of these patients suffered from high blood pressure (BP) and other cardiovascular diseases, diabetes mellitus (DM) and advanced ages. Because of its rapid spread and territorial scope, on January 30, 2020, the WHO declared a state of international health emergency for this outbreak and on March 11, 2020, COVID-19 was considered a pandemic[2,3].

COVID-19 may be variable in association with the form of presentation and accompanying symptoms, as well as the immune response of the recipient. It is estimated that the infection has an incubation period of 2-14 days and has a potential for asymptomatic transmission[1,4].

In the case of mild conditions there is usually a set of non-specific symptoms including general malaise, fever, dry cough, nasal congestion, odynophagia, varying degrees of dyspnea, headache, myalgia, diarrhea and, less frequently, productive sputum and hemoptysis. In the most severe conditions, pneumonia, sepsis, shock and death occur. Other patients from special populations (children, elderly, immunosuppressed, pregnant women) may be atypical in terms of clinical presentation[1,4]. Other manifestations related to COVID-19 are conjunctivitis and olfactory and taste disorders (anosmia, hyposmia, ageusia or dysgeusia)[1].

The available evidence indicates that the subgroups at greatest risk are older male adults with underlying diseases, primarily diabetes mellitus, chronic lung disease, high blood pressure and other cardiovascular diseases[4].

COVID-19 has spread widely throughout the world and on May 13th, 2020, 184 countries had reported positive cases of COVID-19, with 4 223 047 confirmed cases and 291 519 deaths for a lethality of 6,9 % [5,6].

In the region of the Americas, 1 845 638 confirmed cases have been reported, 43,7 % of the total number of reported cases in the world, with 110 714 deaths up to May 13th, 2020, for a lethality rate of 6 %. The United States of America is the country with the highest number of reported cases, exceeding 923 000 confirmed cases and 52 234 deaths [5].

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In Cuba, up to May 13, 2020, 1 830 confirmed cases of the disease had been reported for 79 deaths, and 1 046 patients had been admitted to clinical-epidemiological surveillance and another 6 727 people were being monitored at home, by Primary Health Care[5].

Before this global health problem, the WHO and the Pan American Health Organization (PAHO) have recommended the dissemination of updated information to the population and health systems to stop the progression of this disease[4].

Due to the high level of contagion, mortality and affectation in patients with cardiovascular diseases, the situation of world and national alarm reported, the constant increase of cases, the present research has as objective to describe the implications of COVID-19 in the cardiovascular system.

## METHOD

A narrative bibliographic review was carried out by means of journal articles retrieved from MEDLINE, SciELO, JAMA and Elsevier. Filters were used for the selection of articles in English and Spanish languages, and recently published literature on the cardiovascular implications and management of patients with this disease was considered as selection criteria. A total of 30 references were selected.

Search strategies were applied by means of search formulas using the combination of terms and Boolean Operators. The terms: "coronavirus", "COVID-19", "SARS-CoV-2", "tormenta de citoquinas", "hipertensión", "arritmias", "miocardiopatías", "enfermedades cardiovasculares", as well as their English translations "coronavirus", "COVID-19", "SARS-CoV-2", "cytokine storm", "hypertension", "arrhythmias", "cardiomyopathies", "cardiovascular diseases".

## DEVELOPMENT

The present century has been characterized by the presence of a number of emerging and re-emerging diseases of which COVID-19 is a part. Given the recent onset of the virus, up to the moment, the information about it is scarcely; specifically concerning the mechanism of pathogenesis of SARS-CoV-2 and its direct affectationon thecardiovascular system[1].

### Relationship of SARS-Cov-2 with the Renin-angiotensin-aldosterone system

SARS-CoV-2 causes COVID-19 and there are other types of coronavirus that share characteristics. They bind to cells through the viral structural spike protein (S) which binds to the angiotensin-converting enzyme receptor-2 (ACER2) from viral receptors. This receptor is also widely expressed in cardiomyocytes, cardiac fibroblasts and coronary endothelial cells as it is a regulator of cardiac function[7,8].

ACER2 is an ectoenzyme that promotes the conversion of angiotensin I to angiotensin II, and is found predominantly in the lungs and vascular endothelium, although it is present in almost all tissues of the body[8,9].

Based on the above and on the fact that ACER2 expression is higher in patients being treated with angiotensin converting enzyme inhibitors (ACEi) and/or angiotensin receptor antagonists (ARAs) and that this increased expression provides more potential receptors for SARS-CoV-2; it has been hypothesized that patients with hypertension or other cardiovascular conditions requiring treatment with ACEi/ARAs are at increased risk of developing severe forms of COVID-19[8,10,11].

Scientific societies have made pronouncements on the behavior of continuing or not continuing ACEi and ARA in these patients. The European Society of Cardiology (ESCARDIO) and the American College of Cardiology (ACC), establish that these drugs have previously been shown in clinical trials to decrease mortality and other strong outcomes in cardiovascular disease. So far there is no strong evidence to indicate the need to discontinue these drugs in patients with VOC-19[9,11]. The authors consider that the

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use of this drug should not be suspended, except in situations where it is necessary, due to that the therapeutic protection it provides to the cardiovascular system would be lost.

**Systemic inflammatory response syndrome**

Among the theories related to heart injury is the cytokine storm and its effect on organ failure, triggered by an unbalanced response by the T-helper cells type 1 and 2, macrophage activation syndrome and induction of uncontrolled inflammation[9].

Cytokine storm, or also cytokine release syndrome, results from the release of large amounts of pro-inflammatory cytokines (interleukin [IL]-1b, IL-6, IL-10, IL-12; interferon [IFN]-alpha, IFN-gamma, TNF-alpha or TGF-beta) and chemokines (CCL2, CCL3, CCL5, CXCL8 or CXCL10) by immunosuppressive cells such as macrophages activated by SARS-CoV-2 infection leading to macrophage activation syndrome (MAS)[12,13].

SAM, also known as secondary hemophagocytic lymphohistiocytosis (sHLH), produces overproduction of IL-1ß, which is effected by stimulation of TLR by ferritin and HMGB1, and by the autocrine effect per se of IL-1ß on IL-1R at the macrophage level. This stimulation leads to a cytokine storm and the release of CD-163 from the macrophage cell membrane. The overproduced cytokines stimulate increased ferritin production by the liver and liver dysfunction, while IL-1ß leads to the overproduction of IFN by natural killer (NK) cells, which leads to hemophagocytosis causing fever, exaggerated cytokine release, cytopenias and hyperferritinemia and in approximately half of the patients it causes lung involvement, including Acute Respiratory Distress Syndrome (ARDS)[12,13,14].

This sequence of events leads to an uncontrolled systemic hyper inflammatory status and hypoxemia, due to pulmonary dysfunction, causes secondary damage to myocardial cells and corresponding acute cardiac failure[12].

This cytokine storm, together with thrombogenicity related coagulation disorders, has clear cardiovascular implications that, obviously, impact on the prognosis of COVID-19 patients[15].

Within this massive immune response, lymphocytes, macrophages and neutrophils exert their powerful pro-inflammatory functions and cause further damage to the vascular endothelium and alveolar epithelial cells, resulting in microvascular thrombosis which in the later stages of ARDS can spread locally in the lung and to the microvasculature of other organs such as the heart, brain and kidney[14,15].

**Cardiovascular implications**

Meta-analyses and systematic reviews of cardiovascular effects of COVID-19 infection are not yet available; however, a history of cardiovascular disease has been reported as a risk factor[16].

Studies have shown that older adults with comorbidities are more likely to become infected with SARS-CoV-2, especially those with hypertension, coronary heart disease, or thromboembolic disease. This same group of patients with previous cardiovascular disease is more likely to develop severe symptoms; therefore, they are at greater risk of dying from COVID-19[11,16].

Patients with coronary disease (CD) or with potential risk factors for its development, are at high risk of acute coronary syndrome in the context of acute infectious processes. This may be due to two main factors: increased myocardial oxygen demand secondary to the infectious process, which conditions ischemia or ST-elevation myocardial infarction (STEMI), and the effect of circulating cytokines associated with the inflammatory process, which may induce non-stabilization or rupture of pre-existing atherosclerotic plaque. Similarly, patients with heart failure are prone to hemodynamic decompensation induced by hemodynamic stress secondary to the infectious process[16,17].

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Patients with acute coronary syndrome who are infected with SARS-CoV-2 often have a poor prognosis because in these patients the functional reserve of the heart can be reduced due to ischemia and myocardial necrosis, inflammation, shock, severe hypoxemia and hypoxic pulmonary hypertension; a higher frequency of heart failure is observed, leading to a sudden deterioration of the condition of these patients[17].

In the study carried out by Huang et al.[16], 12 % of the heart was reported to be acutely affected, given the presence of new electrocardiographic or echocardiographic alterations, and in all these cases an elevation of cardiac troponins (Tn) was evident. In addition, 23 % of patients with a history of cardiovascular disease required intensive care.

Another study[17] states that 50 % of confirmed patients who died within 14 days had cardiovascular disease. Shi et al.[18] reported the importance of cardiac damage in mortality rate from COVID-19 in 416 patients hospitalized with COVID-19, 57 of them died. In these patients, 10,6 % suffered from coronary disease, 4,1 % presented heart failure and 5,3 % cerebrovascular disease.

Cardiovascular affectations associated with coronavirus infection have been reported in previous epidemics not related to SARS-CoV-2, including myocarditis, heart failure, acute myocardial infarction and arrhythmias[19].

**Myocarditis in COVID-19**

Myocarditis can be caused by a wide variety of viruses. With the advent of virological and molecular techniques it has been shown that adenoviruses, especially retroviruses and parvoviruses are among the most frequently identified infectious microorganisms in myocarditis. However, patients with COVID-19 may develop cardiovascular manifestations[19,20].

Severe Acute Respiratory Syndrome CoV-2 appears to affect the myocardium and cause myocarditis. Sporadic autopsy cases suggest myocardial infiltration by interstitial mononuclear inflammatory cells. In parallel, cases of severe myocarditis with reduced systolic function have been reported after COVID-19. Studies of cardiac biomarkers suggest a high prevalence of cardiac damage in hospitalized patients[8,20].

Studies conducted in Wuhan[12,17] reported evidence of 28 % acute myocardial injury (defined as elevated troponins T [TnT] greater than the upper 99$^{th}$ percentile limit) in patients with high TnT levels were greater, and male dominated with comorbidities such as hypertension, coronary disease, cardiomyopathy and chronic renal disease.

In addition, they also had elevated counts of leukocytes, D-dimer, C-reactive protein, procalcitonin and pro-brain N-terminal natriuretic peptides[15,17]. This suggested that patients with a high level of TnT show a higher incidence of complications such as ARDS and acute coagulopathy.

In this regard, Chang et al.[22] reported that the presence of dimer D and elevated TnT was associated with higher mortality rates; while patients without elevated TnT, even in the presence of CVD, suggest a lower risk of mortality during SARS-CoV-2 infection.

It is considered that myocardial injury is probably associated with myocarditis secondary to infection and/or myocardial ischemia; constituting an important aggravating and negative prognostic factor during COVID-19.

**Shock**

The prognosis of patients with COVID-19 and shock has not been systematically reported. In a study of 150 patients from two hospitals in Wuhan, shock was the cause of death in 40 % of the cases, and could be due to fulminant myocarditis[22].

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### Acute coronary syndromes

It has been postulated that the inflammatory systemic response and associated hemodynamic changes are the likely triggers of rupture or erosion of atheroma plaques in patients with underlying coronary disease or without it, increasing the incidence of acute coronary syndrome. Some of these cases may present with overlapping symptoms. Chest pain and typical electrocardiographic changes have been reported in patients with epicardium coronary arteries without significant lesions that were positive for COVID-19[14,22,23].

It is unknown whether non-ST elevation myocardial infarction (NSTEMI) generated by supply/demand imbalance in CVD patients has contributed to cardiovascular manifestations in patients with COVID-19. According to Bonow et al.[24] these acute coronary events could result from increased myocardial demands triggered by infection, resulting in injury or myocardial infarction. Case reports of patients who are positive for NSCLC-19 with STEMI have not been published, although in previous influenza studies, their presence was associated with the development of STEMI[23,25].

A different management strategy has been proposed for this type of patient, prioritizing isolation to avoid contagion. In patients with stable STEMI and less than 12 hours after the onset of pain, we recommend first choice infusion of thrombolytic agents in an isolated room, trying to defer coronary angiography until the patient recovers from the infection. In patients who are unstable due to their respiratory pathology, conservative treatment is suggested in an isolation area[24,25].

On the other hand, in STEMI (stable), coronary angiography should not be performed immediately, and initial conservative treatment with isolated patients is recommended, and the angiographic study should be deferred until recovery[24].

In the initial phase of containment (absence of community transmission), intervention of patients with SSTEMI and low clinical probability for COVID-19 will be based on the recommendations of current pre-pandemic institutional protocols; unless a SSTEMI is confirmed or there is another indication, other than cardiac condition, there is no evidence to indicate antiaggregation or anticoagulation in patients with SARS-CoV2 infection and acute myocardial damage[24].

In consideration of the authors, and due to the high probability of patients with COVID-19 and acute myocardial infarction, the treatment of acute coronary syndrome should be individualized as expressed in Cuban protocols.

### Acute heart failure

Acute viral myocarditis caused by SARS-CoV-2 may trigger acute heart failure; however, other causes may be associated with it. The complexity of the mechanisms involved in the physiopathology of COVID-19, in its more advanced stages, explains the ventricular dysfunction, independently of the direct involvement of the myocardium by the virus[13].

The hypoxia produced by the respiratory distress decreases the oxygen supply to the myocardium, which, in turn, has high demands of this gas by the sympathetic stimulation secondary to the infection[13]. On the other hand, the systemic inflammatory response syndrome favors the increase of cytokines that have a known myocardial depressor effect resulting in acute heart failure.

### Arrhythmias

During this pandemic, institutional follow-up studies have described arrhythmias as one of the major complications during the hospitalization of patients with COVID-19[23,26].

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In a report from an inpatient cohort study, arrhythmias occurred in 16,7 % of patients, although the report does not specify the type of arrhythmias. In this context of hypoxia, inflammation and neurohormonal disorder due to viral infection, the appearance of arrhythmias is to be expected, in patients with or without cardiovascular disease[24,26].

In the study by Wang et al.[26] of 138 patients with confirmed diagnosis of COVID-19, 46 patients presented some type of arrhythmia, although the percentage of atrial fibrillation or ventricular arrhythmias was not specified. The arrhythmic potential is not only due to coronavirus infection, it is also related to the treatments needed for the management of circulatory shock.

The management of the patient with COVID-19 must be comprehensive and must take care of the drug interactions that may arise from antiviral treatment. Therefore, the authors recommend adequate use and management of antiviral drugs that can cause arrhythmias and other cardiovascular conditions to avoid increased mortality rates.

**Thromboembolic disease**

Patients infected with COVID-19 are at increased risk of developing venous thromboembolism. In a study by Tang et al.[27], with data from 183 patients, they reported having found the International Society of Thrombosis and Hemostasis criteria for disseminated vascular coagulation (DVC) in 71,4 % of non-survivors and 0,6 % of survivors. The finding was only confirmed at the laboratory level, as no bleeding was mentioned to indicate that DIC was present.

Patients with viral infection are at risk of developing sepsis associated with organ dysfunction. Sepsis is well established as one of the causes of DIC, since when monocytes and endothelial cells are activated they begin to release cytokines after injury; with expression of tissue factor and vonWilllebrand factor. Free circulation of thrombin, not controlled by natural anticoagulants, can activate platelets and stimulate fibrinolysis[1,11,25].

According to the study in the late stages of new coronavirus pneumonia, levels of fibrin markers (D-dimer and FDP) were moderately or significantly elevated in all deaths, suggesting an activation of coagulation and a secondary condition of hyperfribinolysis in these patients. Low-weight or unfractionated heparins are recommended for treatment instead of oral anticoagulants, given the pharmacological interaction of the latter[12,28].

**Congenital heart disease**

Although there are no publications on patients with congenital cardiopathies affected by COVID-19 and it cannot be assured that they are at greater risk of contagion, there is a consensus that those with complex congenital cardiopathies should be considered as patients at high risk of complications and mortality, due to their known decrease in functional reserve; therefore, prevention is vital, and in the presence of symptoms or suspicion of infection, diagnostic tests should be prioritized to guarantee the most appropriate therapeutic strategies[13].

**Heart transplantation**

This is a very vulnerable group, both those on the waiting list and those already transplanted. Only two cases of COVID-19 were reported in transplanted patients in China, one mild and one severe, both of whom continued their immunosuppressive therapy, in addition to receiving high doses of steroids, intravenous immunoglobulin and antibiotics; they managed to overcome the infection without suffering rejection[29,30].

The Spanish Society of Cardiology recommends maintaining immunosuppression in mild cases, or suspension for 48 hours. In moderate-severe cases, consider suspension of mycophenolate/azathioprine

and reducing levels of anti-calcineurin, and may increase doses of corticotherapy or even administer immunoglobulin[31].

**Management of the patient with cardiovascular disease and COVID-19**

The general principles of management for patients who suffer from COVID-19 who develop cardiovascular complications or who have pre-existing cardiovascular disease are the same as for any other patient without COVID-19 according to established protocols. However, some important points should be considered[32]:

Hospital systems must ensure readiness to treat a large volume of patients with COVID-19, many of whom would need care in the ICU and/or acute cardiac care. Appropriate protocols should be developed and tested for rapid diagnosis, classification, isolation and management of patients with COVID-19 with cardiovascular complications[28,29].

Special emphasis should be placed on avoiding unjustified diagnostic tests (e.g. cardiac troponin, echocardiography, etc.) in these patients. This is necessary to minimize unjustified diagnostic/therapeutic procedures, which would exhaust health care resources[32].

The American College of Cardiology has published a warning that discourages the random measurement of cardiac biomarkers such as troponins and natriuretic peptides. It urges all physicians to reserve these trials for circumstances where they would make a significant contribution to the management of patients with COVID-19, using the clinical method as the basis for medical diagnosis[33].

A strong emphasis has been placed on not discontinuing clinically indicated ACEi/ARSi therapy in patients with cardiovascular conditions, should the patient develop COVID-19, because it could lead patients to deteriorate more quickly[34].

Several antiretroviral drugs have significant interactions with cardiac drugs, which should be considered and appropriate dose modification performed. Drugs such as chloroquine, hydroxychloroquine and azithromycin are used as therapeutic options, based on preliminary evidence. These drugs are known to prolong the QT interval and due caution should be exercised when prescribing these agents. It is suggested that a daily electrocardiogram be guaranteed to monitor the QT interval, especially in patients with liver or kidney dysfunction and in those receiving another drug with the potential to prolong the QT interval[33,35].

Cuba approaches the management of these patients in a comprehensive way from prevention. Since the presence of COVID-19 was confirmed on the island, a protocol of action of national scope has been implemented to contribute to its prevention, control and management of cases, as well as to the protection of health workers and the population, taking as a reference the best existing scientific evidence.

However, given the novelty of this disease, the management of these patients is under continuous review and is subjected to modification according to clinical, epidemiological and therapeutic reports. The management of patients, whether confirmed, suspected or at risk of the disease, begins in primary health care, an element that distinguishes the cuban health system from that of other nations.

## CONCLUSIOS

The main cardiovascular implications in patients with COVID-19 are arrhythmia, thromboembolic disease, myocarditis, acute onset heart failure and myocardial infarction, all of which condition a more severe picture of the disease. Inflammatory response, secondary hemodynamic changes to the viral process, as well as hypoxemia, are mechanisms of negative impact on cardiovascular health, leading to the development of acute heart damage.

## CONFLICT OF INTERESTS

The autors declare that does not exist an interest conflicts

## AUTHORSHIP CONTRIBUTION

JJGT conceived and designed the research. CHP and YAV managed the information search and downloaded the bibliography. All the authors participated in the writing and review of the article; as well as its concluding version.

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