

Review Article:

## COVID-19, Hypertension, and Cardiovascular Disease: A Narrative Review


*COVID-19, hipertensión y enfermedad cardiovascular: una revisión narrativa*


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Abstract

SARS-CoV-2 has caused an emerging pandemic, which has dominated the public health landscape. To the characteristic clinical picture of COVID-19, cardiovascular manifestations are added in certain cases, such as acute cardiac injury, heart failure (HF), shock, arrhythmias, among others. The aim of this review is to explore the link between COVID-19, hypertension, and cardiovascular disease. A bibliographic search was carried out using the databases PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Full-text Database (CQVIP). In general terms, it has been described that SARS-CoV-2 manages to penetrate cells by means of angiotensin-converting enzyme 2, a significant participant in the renin-angiotensin-aldosterone system and modulation of the cardiovascular system. Indeed, the use of drugs that inhibit angiotensin converting enzyme and antagonists of angiotensin II receptors could cause an increase in ACE2 and facilitate the entry of the virus. For this reason, it is essential to identify the people with the highest risk in order to establish adequate treatment.

**Keywords:** COVID-19, SARS-CoV-2, Cardiovascular Diseases, Hypertension.

## Resumen

El SARS-CoV-2 ha provocado una pandemia emergente, que ha dominado el panorama de la salud pública. El cuadro clínico característico de la COVID-19 se ve agravado en ciertos casos por manifestaciones cardiovasculares, como daño cardíaco agudo, insuficiencia cardíaca (IC), shock, arritmias, entre otras y el objetivo de esta revisión es explorar el vínculo entre la COVID-19, hipertensión y enfermedades cardiovasculares. Se realizó una búsqueda bibliográfica utilizando las bases de datos PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Full-text Database (CQVIP). En términos generales, se ha descrito que el SARS-CoV-2 logra penetrar en las células por medio de la enzima convertidora de angiotensina 2, participante importante en el sistema renina angiotensina aldosterona y en la modulación del sistema cardiovascular. De hecho, el uso de fármacos que inhiban la enzima convertidora de angiotensina y antagonistas de los receptores de angiotensina II podría provocar un aumento de la ECA2 y facilitar la entrada del virus. Por ello, es fundamental identificar a las personas con mayor riesgo para instaurar un tratamiento adecuado.

Palabras clave: COVID-19, SARS-CoV-2, Enfermedades Cardiovasculares, Hipertensión.

## Introduction

When evaluating the correlation between comorbidities and their role in the exacerbation of coronavirus disease 2019 (COVID-19) leading to fatal outcomes, hypertension, obesity, and diabetes mellitus were identified as the most prevalent comorbidities in patients. COVID-19 patients. In fact, cancer, chronic kidney disease, diabetes mellitus, and hypertension were reported to be independently associated with mortality in COVID-19 patients.<sup>1</sup>

2 The COVID-19 disease outbreak has placed a significant health burden on infected patients, especially those with underlying comorbidities. Events such as acute cardiac injury (17%), heart failure (23%), shock (20%) and arrhythmias (16.7%) have been described to occur in patients with COVID-19 and with a higher prevalence in patients requiring admission to the intensive care unit (ICU)<sup>2</sup>. These phenomena have been attributed to the imbalance caused in cardiac metabolism, due to the increase in metabolic demand and a

reduction in cardiac reserve during infection, favoring the decompensation of patients with pre-established chronic cardiovascular diseases.<sup>3-4</sup>

ACE2 is considered a carboxypeptidase that cleaves an angiotensin I residue from the kidney to generate angiotensin 1-9, and an angiotensin II residue, producing angiotensin 1-7<sup>5</sup>. Indeed, the presence of ACE2 in tissues related to the modulation of cardiovascular function reinforces the link between COVID-19 and CVD<sup>6</sup>.

Because of the tropism of SARS-CoV-2 for angiotensin converting enzyme-2 (ACE2) receptors, viral replication in endothelial cells is likely to lead to infiltration of inflammatory cells, apoptosis, and alteration of the natural antithrombotic state<sup>7</sup>. Furthermore, infection by viral pathogens can elicit complex systemic inflammatory responses as part of innate immunity by procoagulant pathways involving polyphosphates, extracellular neutrophil traps, and intermolecular interactions in glycoctolix. What produces as a result the increase in the secretion of pro-inflammatory cytokines, the activation of the coagulation cascade and the generation of thrombin, in a phenomenon called immunothrombosis.<sup>8-9</sup> Indeed, COVID-19 has seriously threatened high-risk populations with non-communicable diseases, leading to high numbers of hospitalizations and mortality.

Predictors of mortality in COVID-19 patients The particularly infectious capacity of the virus, SARS-CoV-2, together with mortality rates ranging from 1% to more than 5%, has raised global concern.<sup>10</sup> A study that estimated the association of chronic comorbidities in severe and non-severe cases of COVID-19 reported that chronic comorbidities: hypertension, diabetes mellitus, vascular brain, cardio vascular and respiratory diseases can contribute to a severe outcome in patients with COVID-19. In addition, old age and two or more comorbidities have a significant impact on the severity of the disease. (eleven). In fact, hypertension has been reported to have a hazard ratio of 1.70 for death and 1.82 for acute respiratory distress syndrome in COVID-19 patients.<sup>12</sup>

In general terms, the biochemical markers frequently used to assess COVID-19 patients They are: kidney profile, acid-base status, glucose, D-dimer, fibrinogen, ultrasensitive troponin, ferritin, C-reactive protein, lactic acid, procalcitonin, among

others. The neutrophil / lymphocyte ratio is also very important as a predictor of mortality.<sup>13-14.</sup>

In a study carried out in China, in patients with COVID-19, elevated values of prothrombin time (5%), activated partial thromboplastin time (6%) and elevated levels of D-dimer (36%) were found. While thrombocytopenia occurred in 12% of cases. Similarly, biomarkers of inflammation were found to be elevated, including C-reactive protein (CRP), interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), and procalcitonin (fifteen). Indeed, both excessive activation of the coagulation cascade and platelets can explain elevated D-dimer levels and thrombocytopenia. It should be noted that viral infections can provoke an exacerbated systemic inflammatory response and cause an imbalance between the procoagulant and anticoagulant homeostatic mechanisms. Includes endothelial dysfunction, elevation of von Willebrand factor, activation of Toll-like receptors and the tissue factor pathway.<sup>14</sup>

In a retrospective multicenter study, carried out in China, the following were evidenced as predictors of a fatal outcome in COVID-19 cases: age, the presence of comorbidities, secondary infection, and elevated inflammatory indicators in the blood. The results obtained from this study indicated that the mortality of COVID-19 could correspond to a “cytokine storm syndrome”. Indeed, it was pointed out that individuals with cardiovascular diseases have a significantly higher risk of mortality when infected with SARS-CoV-2.<sup>16.</sup>

It has been described in a study carried out in the United States and 93 countries that of the total number of cases of patients with COVID-19, 40.80% had comorbidities, while among fatal cases, 74.37% had comorbidities. Hypertension was the most prevalent comorbidity in severe and fatal cases compared to the total number of cases<sup>17.</sup> In addition, a prospective cohort study detailed that female sex (odds ratio [OR] 1.75, 95% CI 1.39-2.20,  $p < 0.001$ ) and hypertension (OR 1.35, 95 % 1.08-1.68,  $p = 0.007$ ) are associated with an increased risk of developing viral symptoms<sup>18.</sup>

Robust estimates of the magnitude of the risk of COVID-19 hospitalization, ICU admission, and death associated with comorbidities have been detailed. A report carried out in Mexico details that chronic kidney disease increased the risk of death (OR 2.31), followed by diabetes (OR 1.69), immunosuppression (OR 1.62), obesity (OR 1.42), hypertension

(OR 1.24) and chronic obstructive pulmonary disease (OR 1.20). While the comorbidities that most increased the risk of admission to the ICU and intubation were immunosuppression, diabetes, and obesity<sup>19.</sup>

Indeed, hypertension, diabetes, and cardiovascular disease are considered risk factors for severe COVID-19<sup>20.</sup> In fact, the risk of dying from COVID-19 has been reported to be significantly associated with cerebrovascular diseases [combined relative risk (RR) 2.7 (95% CI: 1.7-4.1)] and cardiovascular [RR 3.2 (CI 2.3-4.5)], hypertension [RR 2.6 (CI 2.0-3.4)] and kidney disease [RR 2.5 (CI 1.8-3.4)]. Fatal outcomes have been associated with host-specific factors and comorbidities such as age, hypertension, immunodeficiencies, chronic lung disease, or metabolic disorders.<sup>21</sup>

In Brazil, in the serological survey of patients with COVID-19 between May and June 2021, EPICOID-19, the prevalence of at least one chronic disease in 43% of individuals was reported. The prevalence of antibodies against SARS-CoV-2 was similar between carriers and non-carriers of chronic diseases (2.4% and 2.3%). Regarding to the symptoms, the prevalence of cough, dyspnea, palpitations, and myalgia was significantly higher among those with chronic diseases, but the proportion of symptomatic patients was similar between the groups.<sup>22</sup>

Similar to the problem in Brazil, Mexico has high prevalence rates of non-communicable diseases (NCDs). The hospitalization and death of patients with COVID-19 in these countries has been associated with chronic comorbidities. It is detailed in a cross-sectional study, carried out in Mexico, from 212,802 confirmed cases of COVID-19 that 47.40% of patients diagnosed with COVID-19 presented comorbidity and hypertension stood out as the most frequent (20,12 %)<sup>19-22.</sup>

COVID-19 and cardiovascular disease In general terms, the mechanisms that link COVID-19 with cardiovascular disease (CVD) are not yet conclusive. In particular, the relationship of COVID-19 with angiotensin converting enzyme 2 (ACE2) has raised special interest, as it acts as a receptor to **3** mediate penetration of the virus into the cells **—** of the human host<sup>23.</sup> ACE2 behaves as a type I membrane surface protein and represents a central component of the renin-angiotensin-aldosterone system (RAAS). Additionally, it is highly expressed in pulmonary, cardiac, renal alveolar cells,

vascular endothelial cells, gastrointestinal tract, testicles, placenta, and central nervous system<sup>24</sup>. In fact, the COVID-19 and its relationship with hypertension and cardiovascular disease Table 1<sup>25-4</sup>.

In fact, it has been detailed among patients with a diagnosis of COVID-19 confirmed by RT-PCR, an elevated risk of mortality in individuals with arterial hypertension (OR: 5; 95% CI: 1.748-14.301;  $p < 0.05$ ); and cardiovascular disease

(OR: 7.972; 95% CI: 2.290-27.753;  $p < 0.05$ )<sup>14</sup>. Likewise, it has been reported that the levels of myocardial injury biomarkers are significantly higher in patients requiring admission to intensive care units (ICU). This suggests that a large part of patients with severe symptoms present complications that involve acute myocardial injury.<sup>26</sup>

In addition, the association of arterial hypertension with an alteration of both the innate and adaptive immune responses has been described and this alteration is considered to be responsible for the worse prognosis of these individuals. Likewise, inherently hypertensive individuals appear to have lower ACE2 expression. Therefore, the action of SARS-CoV-2 on residual ACE2 could generate a greater activity of Ang II, facilitating the development of complications.<sup>27</sup>

Parallel to the respiratory clinical picture, there are possible complications related to the cardiovascular sphere, especially in individuals with pre-existing comorbidities. It should be noted that the underlying pathophysiology has not been fully elucidated, the relationship between SARS-CoV-2 and ACE2 could cover a central point in this scenario; linking COVID-19 with cardiovascular disease<sup>28</sup>.

Hypertension has been reported to have a 3.05 hazard ratio for in-hospital mortality in COVID-19 patients<sup>2</sup>. In addition, there is increasing concern that this association with hypertension is confused by treatment with specific antihypertensive drugs: angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs).<sup>2-12</sup>

The link with ACEIs and ARBs is due to the known association between angiotensin converting enzyme 2 (ACE2) and SARS-CoV-2. ACE2 is a co-receptor for SARS-CoV-2 entry<sup>29-30</sup>.

Furthermore, there is concern that the use of ACE inhibitors and angiotensin receptor blockers (ARBs) increases the expression of ECA2 and increases the susceptibility of the patient to the entry and spread of the viral host cell. Increased expression of ACE2 has been reported in cardiac cells after treatment with ARB; however, there is limited evidence showing

**Table 1. Relationship of COVID-19 with hypertension and cardiovascular disease**

- Hypertension and cardiovascular disease are more frequent in individuals with a worse evolution due to COVID-19.
- Individuals over 60 years of age and those with cardiovascular disease should avoid exposure to SARS-CoV-2, not self-medicate and consult promptly when symptoms appear.
- Because of the mechanism of entry of SARS-CoV-2 into the recipient's cells through ACE2, the use of ACEIs and ARBs has been questioned.
- The presumption of a potential benefit of ACEI and ARB has also been evidenced in counteracting the inflammatory imbalance caused by the virus.
- No consistent evidence has yet been described to suggest modifying the use of ACE inhibitors or ARBs.

**ARA: angiotensin 2 receptor blockers; ACEI: angiotensin converting enzyme inhibitors.**

changes in serum or pulmonary ACE2 levels. ACE2 works primarily to counteract the effect of ACE. As ACE generates angiotensin II from angiotensin I, ACE2 generates angiotensin from angiotensin II which, after binding to the receptor more broadly, shifts the balance from vasoconstriction with angiotensin II to vasodilation with receptor activation, evident in the affected vascular bed.<sup>31</sup> Furthermore, it has been suggested that SARS-CoV exacerbates lung injury by reducing ACE2, an effect that is reversed with ARB treatment.<sup>32</sup>

It should be noted that ACE2 is not only an enzyme, but also a functional receptor on cell surfaces for both SARS-CoV and SARS-CoV-2. In addition, it is involved in cardiac function and the development of arterial hypertension (HT) and diabetes mellitus (DM). In this sense, the greater severity of COVID-19 observed in patients with this history could be explained by the greater expression of ACE2 in these individuals.<sup>33</sup>

Adding to the problem is that some individuals with a diagnosis of hypertension request changes in their medications. In addition, there is a growing uncertainty among physicians about the management of these patients. Changes in antihypertensive medication do require frequent dose adjustment and management of adverse effects.<sup>3,4</sup> On the other hand, general confinements, testing, tracing, isolation, vaccination, and hygiene measures have proven crucial during the pandemic.<sup>35</sup>

### conclusion

The underlying pathophysiology has not been fully elucidated, the relationship between SARS-CoV-2 and ACE2 could occupy a central point in this scenario; linking COVID-19 with cardiovascular disease. A comprehensive synthesis of the evidence on the associations between comorbidities and behavioral factors with hospitalization, admission to the intensive care unit (ICU), and death from COVID-19 is required to derive recommendations on prevention and management and management. vaccination. Comorbidities increase the severity of COVID-19 infection. Given the high prevalence rates of chronic non-communicable diseases globally, it is necessary to strengthen special prevention measures in the short, medium, and long term.

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