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COVID-19 AND SYSTEMIC ARTERIAL HYPERTENSION: RISK FACTOR FOR MORBIMORTALITY-SYSTEMATIC REVIEW

COVID-19 E HIPERTENSÃO ARTERIAL SISTÊMICA: FATOR DE RISCO PARA MORBIMORTALIDADE-REVISÃO SISTEMÁTICA

COVID-19 E HIPERTENSIÓN ARTERIAL SISTÉMICA: FACTOR DE RIESGO DE MORBIMORTALIDAD-REVISIÓN SISTEMÁTICA

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ABSTRACT
Objective: To investigate the relationship between systemic arterial hypertension and morbidity and mortality in individuals infected with SARS-CoV-2. **Materials and Methods:** This is a systematic review, carried out in the databases of MEDLINE/PubMed®, SciELO/Lilacs, Virtual Health Library (VHL), EBSCO and Google Scholar. The descriptors in the English language were used: “COVID-19”; "SARS-CoV-2"; "Systemic arterial hypertension"; “Complications”; "Risk factor". The search resulted in 1,005 articles. Among these, duplicate articles were excluded, as well as studies that showed methodological inconsistencies. At the end, 12 articles were selected. **Results:** Studies have shown the high prevalence of SARS-CoV-2 infection in patients with systemic arterial hypertension. Such patients showed an inflammatory response secondary to exacerbated infection, forming part of the high-risk group of the disease. Considering the complications in this specific subgroup, a change in lifestyle and strict adherence to drug therapy are necessary. **Conclusions:** Systemic arterial hypertension is associated with a worse prognosis and higher mortality of patients hospitalized by COVID-19.

KEYWORDS: Coronavirus. COVID-19. Systemic arterial hypertension. Risk factors. Complications.

RESUMO
Objetivos: Investigar a relação entre hipertensão arterial sistêmica e morbimortalidade de indivíduos infectados por SARS-CoV-2. **Materiais e Métodos**: Trata-se de uma revisão sistemática, realizada nas bases de dados do MEDLINE/PubMed®, SciELO/Lilacs, Biblioteca Virtual em Saúde (BVS), EBSCO e Google Acadêmico. Foram utilizados os descritores na língua inglesa: *“COVID-19”; “SARS-CoV-2”; “Systemic arterial hypertension”; “Complications”; “Risk factor*”. A busca resultou em 1.005 artigos. Entre esses, artigos duplicados foram excluídos, assim como estudos que mostraram inconsistências metodológicas. Ao final, selecionou-se 12 artigos. **Resultados**: Estudos evidenciaram a elevada prevalência da infecção por SARS-CoV-2 em pacientes portadores de hipertensão arterial sistêmica (HAS). Tais pacientes mostraram resposta inflamatória secundária exacerbada à infecção, compondo parte do grupo de alto risco da doença. Considerando as complicações neste subgrupo específico, uma mudança no estilo de vida e rigorosa adesão a terapêutica medicamentosa se fazem necessárias. **Conclusão**: A HAS se associa ao pior prognóstico e maior mortalidade de pacientes internados pela COVID-19.

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DESCRITORES: Coronavírus. COVID-19. Hipertensão arterial sistêmica. Fatores de risco. Complicações.

ABSTRACTO
Objetivos: Investigar la relación entre la hipertensión arterial sistémica y la morbilidad y mortalidad de individuos infectados con SARS-CoV-2. **Materiales y métodos:** Se trata de una revisión sistemática realizada en las bases de datos MEDLINE/PubMed®, SciELO / Lilacs, Virtual Health Library (BVS), EBSCO y Academic Google. Se utilizaron los descriptores en inglés: “COVID-19”; "SARS-CoV-2"; “Hipertensión arterial sistémica”; "Complicaciones"; "Factor de riesgo". La búsqueda resultó en 1.005 artículos. Entre estos, se excluyeron los artículos duplicados, así como los estudios que mostraban inconsistencias metodológicas. Al final, se seleccionaron 12 artículos. **Resultados:** Los estudios han demostrado la alta prevalencia de infección por SARS-CoV-2 en pacientes con hipertensión arterial sistémica (HSA). Dichos pacientes mostraron una respuesta inflamatoria secundaria exacerbada a la infección, formando parte del grupo de alto riesgo para la enfermedad. Teniendo en cuenta las complicaciones en este subgrupo específico, es necesario un cambio en el estilo de vida y una estricta adherencia a la terapia con medicamentos. **Conclusión:** la HSA se asocia a peor pronóstico y mayor mortalidad de los pacientes hospitalizados por COVID-19.

DESCRIPTORES: Coronavirus. COVID-19. Hipertensión arterial sistémica. Factores de riesgo. Complicaciones.

INTRODUCTION

Systemic arterial hypertension (SAH) is a multifactorial entity, characterized by a sustained increase in blood pressure levels 140 and/or 90 mmHg. It is often associated with functional alterations, metabolic and/or structural disturbances of target organs. In Brazil, SAH affects 32.5% of the adult population, contributing to half of deaths from cardiovascular disease (CVD).[1]

Physiologically, SAH tends to cause a reduction in respiratory capacity, as the tension developed in the left ventricular wall during ejection is abnormally high, which leads to left ventricular hypertrophy (LVH). This confers a reduction in the volume and compliance of the ventricle, culminating in an increase in the end-diastolic pressure. Thus, ventricular filling becomes more difficult, which causes rapid atrial contraction, resulting in transient distension of the pulmonary veins and increased pulmonary capillary pressure.[2]

According to Rodrigues[11], the functional receptor of SARS-CoV-2 is the Angiotensin-Converting enzyme 2 (ACE2), present in cardiac and pulmonary tissue in high concentrations.[3]

Considering that many patients with SAH use angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), which in turn increase the regulation of ACE inhibitors2, researchers speculate that the use of these drugs could facilitate the infection by COVID-19. Thus, the aim of the study is to investigate the relationship between systemic arterial hypertension and morbidity and mortality in individuals infected with SARS-CoV-2 virus.

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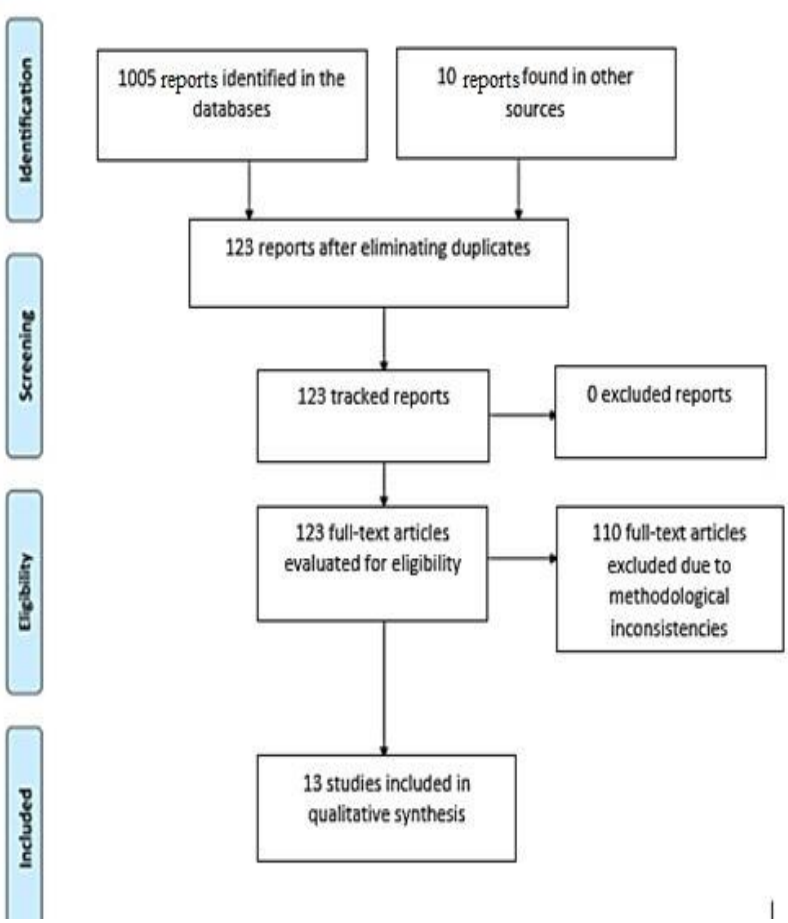
MATERIALS AND METHODS

This is a systematic literature review whose research was conducted by searching the MEDLINE/PubMed®, SciELO/Lilacs, Virtual Health Library (BVS), EBSCO and Academic Google databases. The descriptors in English were used: “COVID-19”; "SARS-CoV-2"; “Systemic arterial hypertension”; “Complications”; “Risk factor”.

The search resulted in 1,005 articles. Of these, 123 duplicate articles were excluded. Of the remaining total, only another 123 full articles were eligible, and of these 110 had methodological inconsistencies. In the end, 12 articles were selected (Figure 1).

The acronym PICO was used to define the search strategy, where: P- Patients with systemic arterial hypertension infected with SARS-CoV-2; Intervention- Use of ACEI's or ABr's; Comparison - Patients who do not use antihypertensive drugs and as an outcome- the reported morbidity and mortality. Thus, the question was raised: Are hypertensive patients who use angiotensin-converting enzyme inhibitors at greater risk of being infected by the SARS-CoV-2 virus?

Figure 1. PRISMA Flowchart



Source: Author’s (2021).

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RESULTS

The selected studies are described in table 1.

Table 1. Summary of selected studies

Authors'/year	Title	Periodical	Theme
Malachias MVB, Plavnik FL, Machado CA, et al. (2016)[1]	7ª Diretriz Brasileira de Hipertensão Arterial	Arq. Bras. Cardiol.	The chapter provides conceptual, epidemiological and primary prevention information about Arterial Hypertension.
Barros GM, Mazullo Filho JBR, Mendes Júnior AC. (2020)[2]	Considerações sobre a relação entre a hipertensão e o prognóstico da COVID-19.	Journal of Health & Biological Sciences.	The article brings the association between systemic arterial hypertension and the severity of COVID-19, showing the physiological effects of SAH, and that the association between the diseases was in the treatment with angiotensin converting enzyme inhibitors and angiotensin receptor blockers.
Britto Rodrigues CM, Barboza da Costa N, Vieira VR, *et al.* (2020)[3]	COVID-19: sistema renal e cardíaco.	Ulakes Journal of Medicine.	The text addresses that patients with cardiovascular and renal comorbidities are more likely to suffer clinical damage from the inflammatory response caused by SARS-CoV-2 infection, with greater severity and mortality rate due to Covid-19.
Chen N, Zhou M, Dong X, Qu J, *et al.* (2020)[4]	Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.	The Lancet.	The article provides epidemiological information about COVID-19, providing a comparison with SARS and MERS, and how they behaved in patients with comorbidities.
Pinotti F, Wikramaratna PS, Obolski	Potential impact of individual	medRxiv.	The text brings the relationship of cross-reactivity to SARS-CoV-2 with previous exposure to

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U, *et al.* (2020)[5]	exposure histories to endemic human coronaviruses on age-dependence in severity of COVID-19.		coronaviruses, as a driver for both protection against infection and the severity of COVID-19 disease.
Moraes de Oliveira GM & Pinto FJ. (2020)[6]	A Matter Close to the Heart.	International Journal of Cardiovascular Sciences.	The authors provided information regarding the prevalence of chronic conditions in patients with COVID-19, and how they increase the disease fatality rate.
Amit K, Baum, SJ, Gluckman Ty J, *et al.* (2020)[7]	Continuity of care and outpatient management for patients with and at high risk for cardiovascular disease during the COVID-19 pandemic: A scientific statement from the American Society for Preventive Cardiology.	American Journal of Preventive. Cardiology.	The article in question pointed out the fact that outpatient care was interrupted by the COVID-19 pandemic, causing many patients to delay or postpone their necessary care, including preventive care. The authors recommend measures that encourage the reception of such more vulnerable patients.
Pinto BGG, Oliveira AER, Singh Y, *et al.* (2020)[8]	ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19.	The Journal of Infectious Diseases.	The text focuses on angiotensin-2 converting enzyme (ACE2) and its analysis in patients with severe COVID-19 and comorbidities. The authors also observed potential regulators of ACE2 in the human lung, such as genes related to histone modifications.
Brandão SCS, Madruga Godoi ETA, Ramos J de OX, *et al.*	Papel do Endotélio na COVID-19 grave.	Arq. Bras. Cardiol.	The authors of the article emphasized that the endothelial function is directly related to the progression of the clinical stages of COVID-19, as chronic endothelial dysfunction, which occurs in

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(2020)[9]			comorbidities, favors the evolution to the severe form. They also reinforce the importance of focusing on therapeutic targets.
Santos da Silva IB, Bittar CS, Rizk SI, *et al.* (2020)[10]	O Coração e a COVID-19: O que o Cardiologista Precisa Saber.	Arq. Bras. Cardiol.	The article analyzes how the cardiovascular complications evidenced in patients with COVID-19 cause mechanisms that involve both direct damage by the virus and complications secondary to the inflammatory and thrombotic response triggered by the disease.
Rodrigues CIS. (2020)[11]	Posicionamento do Departamento de Hipertensão da Sociedade Brasileira de Nefrologia: Bloqueadores do sistema renina-angiotensina durante o curso de infecção pela Covid-19.	Brazilian Journal of Nephrology.	The article deals with the position of the Hypertension Department of the Brazilian Society of Nephrology (SBN) in relation to the use or suspension/replacement of renin-angiotensin-aldosterone system blockers prophylactically in patients who use these drugs, due to the possibility of theoretically worsening the prognosis of hypertensive individuals with COVID-19.
Ferreira Maria MJ, Irigoyen C, Consolim-Colombo F, Saraiva JFK, De Angelis K. (2020)[12]	Vida Fisicamente Ativa como Medida de Enfrentamento ao COVID-19.	Arq. Bras. Cardiol.	With the COVID-19 pandemic and the recommendations of social isolation, the authors of this article encourage the maintenance of a physically active routine as a preventive measure for health, which is an essential approach to combat COVID-19 and the possible consequences of social confinement.

Source: Author's (2021).

DISCUSSION

In Wuhan (China), the presence of comorbidities such as type 2 diabetes mellitus and systemic arterial hypertension was observed in 68.3% of patients with COVID-19 who progressed to death.[4] Thus, the severe forms of the infection seem to affect the elderly population more than the young.[5]

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Oliveira & Pinto (2020) added that about a quarter to half of patients with COVID-19 have chronic diseases, namely cardiovascular and cerebrovascular, which increases the risk of worsening the disease. A meta-analysis of six studies carried out in China of patients with COVID-19 assessed the prevalence of CVD and reported the following proportions in patients: SAH 17.1%; heart and cerebrovascular diseases 16.4% and DM 9.7%.[6]

Patients who died from COVID-19 often had comorbidities such as SAH, DM and chronic obstructive pulmonary disease (COPD). The Spike protein of this virus is an ACE2 ligand, a transmembrane enzyme expressed in different types of cells, such as intestinal and alveolar epithelium, vascular endothelium, and cardiac myocytes.[7] ACE2 was identified as a factor that facilitates SARS-CoV-2 to couple and enter host cells, and its expression is increased in cases of myocardial infarction and DM.[8]

Considering that the endothelium plays a fundamental role in the response to infection, studies suggest that SARS-CoV-2 has a direct effect of endothelial aggression. Endothelial cells release chemokines, which attract white blood cells to the infected site and produce cytokines, which activate the inflammatory response. Thus, patients with chronic endothelial dysfunction present important alterations, which result in greater adhesion and leukocyte extravasation, inducing a state of hypercoagulability and reduced fibrinolytic action. Thus, chronic endothelial dysfunction contributes to the development of the severe form of COVID-19, as it has an overactive and unregulated immune site.[9]

Studies describe that the virus can affect the cardiac system, especially in individuals with cardiovascular risk factors. Such damage may present as diverse manifestations such as myocardial injury, heart failure, arrhythmias, myocarditis and shock. These lesions, in turn, are probably multifactorial and result from an imbalance involving a high metabolic demand and reduced cardiac reserve. In addition, there is systemic inflammation and thrombogenesis in those affected, with an increase in inflammatory cytokines resulting from the infectious condition. On the other hand, inflammation may also occur due to direct cardiac injury by the virus, culminating in more serious complications and even death.[10]

Reports from the February 11, 2020, China Infectious Disease Information System and the Chinese Centers for Disease Control and Prevention also revealed that the majority of deaths and complications from COVID-19 occurred in patients aged 60 and over, who suffer underlying diseases such as SAH, CVD and DM. In another retrospective cohort study of 201 patients with pneumonia secondary to COVID-19, 84 of them developed Acute Respiratory Distress Syndrome and, of these, 23 had SAH.[2]

A survey in Wuhan showed that the fatality rate of the virus is approximately 2%, but when patients had concomitant cardiovascular disease, this rate increased to 10.2%. Brazilian data also maintained this trend by showing that 90% of deaths occurred in the elderly, and 84% of this total also had at least one chronic comorbidity, with 51% of them of cardiovascular origin10. SAH was the most

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prevalent comorbidity in patients affected by the disease, related to a worse prognosis and higher mortality, representing 15 to 30% of those affected.[3]

Given the fact that many patients with SAH, DM or CVD make use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), which in turn increase the regulation of ACE2, studies speculated that the use of these drugs could facilitate COVID-19 infection. However, there are also contradictory data suggesting that ACEI/ARB may be beneficial in individuals with Acute Respiratory Distress Syndrome, probably because they cause anti-inflammatory and antioxidant effects.[6]

On the other hand, another study presented controversial results on the association of drugs such as ACE inhibitors and ARBs for the treatment of SAH and the prognosis of COVID-19. A reduction in ventilatory capacity was revealed in individuals with SAH, which can worsen the health of an individual affected by SARS-CoV-2. Furthermore, the association of the disease with other respiratory morbidities seems to demonstrate the affinity of SAH and the respiratory system.[2]

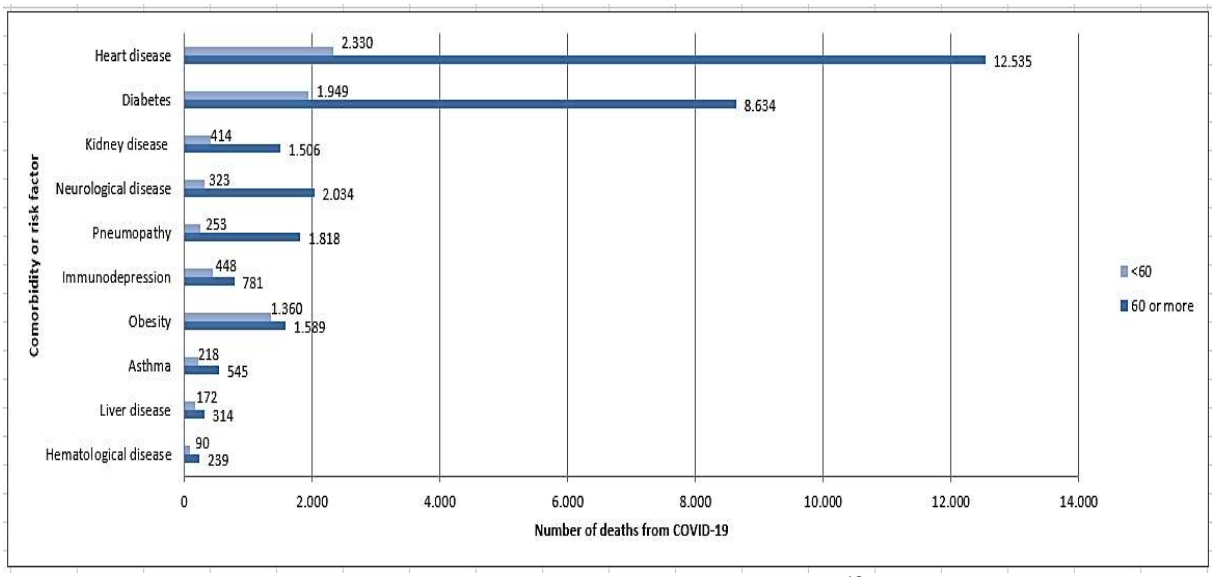
Both the Department of Hypertension of the Brazilian Society of Nephrology, as well as other Societies of National and International Specialties, recommend the maintenance of blockers of the renin-angiotensin-aldosterone system (SRAA), particularly ACE inhibitors or ARB. Individual treatment should be taken into account that results in greater benefit to the patient.[11]

Considering the facts related to the complications of COVID-19 in hypertensive patients, it is essential that these individuals perform regular physical exercise, combined with pharmacological treatment, adapting to the current condition of social distance. The fact of remaining physically active should be emphasized even more in elderly individuals, who have a greater number of comorbidities and greater cardiovascular risk and are therefore more vulnerable to COVID-19.[12]

Figure 2 illustrates the comorbidities and risk factors of death due to Severe Acute Respiratory Syndrome (SARS) in COVID-19 in elderly individuals.

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Figure 2. Comorbidities and risk factors for death due to Severe Acute Respiratory Syndrome at COVID-19



Source: Brazil. Ministério da Saúde (2021)[13].

As limitations of the study, we can mention the small number of eligible articles and the lack of studies in the literature on the effects of inhibitors of the renin-angiotensin-aldosterone system in patients with COVID-19, mentioned by[15].

CONCLUSIONS

The study showed an association between SARS-CoV-2 infection and a worse outcome in patients with comorbidities. It was concluded that SAH, as well as other comorbidities, are related to a worse prognosis and higher mortality of patients hospitalized by COVID-19. In addition, the use of antihypertensive drugs presented controversial results in relation to the benefits or harms of their use during infection, and individualized treatment of the patient is recommended.

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