Hypertension and COVID-19 outcomes: What do we know so far?

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Abstract: Hypertension seems to be associated with an increased risk for severe COVID-19 infection. Observational studies present hypertension as a prevalent comorbidity among patients requiring hospitalization and with critical disease. From a pathophysiological perspective, SARS-CoV-2 infection, particularly in patients with critical disease, is characterized by hyperinflammation and hypercoagulability, leading to pulmonary and extra-pulmonary complications. Thus, the identification of risk factors and clinical predictors of severe disease is vital for patient risk stratification and assessment. Despite emerging observational data, there is no robust epidemiological data which present hypertension *per se* as an independent risk factor for higher COVID-19 severity and mortality. Moreover, early experimental data showed a possible deleterious impact of ACEi/ARB therapy on COVID-19 clinical evolution, association which was not supported by subsequent clinical trials. Besides the impact of hypertension and anti-hypertensive agents on COVID-19 clinical outcomes, due to the profound SARS-CoV-2-induced endotheliitis, it is imperative to evaluate the association between arterial stiffness and COVID-19, analyzing its role as a potential risk factor for severe disease and the effects of hyperinflammation associated with COVID-19 on the systemic vasculature. Therefore, the impact of prior arterial stiffness on COVID-19 severity and, on the other hand, the development of post-COVID arterial stiffness predisposing worse outcomes and sequelae needs to be elucidated. The impact of severe forms of hypertension such as refractory and resistant hypertension in patients with SARS-CoV-2 infection is uncertain.Thus, the present review mainly aims to aggregate the latest evidence concerning the impact of hypertension on COVID-19 severity, mortality and prognosis.

Keywords: COVID-19, Hypertension, SARS-CoV-2, Vascular Stiffness, Renin-Angiotensin System.

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I. INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, resulting in the COVID-19 pandemic brought challenges to healthcare systems worldwide. Until the end of July 2021, 4,170,155 deaths and 194,608,040 cases were confirmed. In Brazil, specifically, the country surpassed 19,000,000 confirmed cases and 550,000 deaths due to the disease [1-2].

The pathophysiology of COVID-19 is complex and mainly in its severe forms, SARS-CoV-2 infection is characterized by hyper-cytokinaemia due to a cytokine storm triggered by the viral infection resulting in immunological imbalance, systemic inflammation, and a pro-thrombotic state [3-4]. Thus, it is necessary to assess clinical predictors and risk factors that may be associated with critical disease allowing risk stratification and clinical probability analysis among patients diagnosed with COVID-19.

Studies have been demonstrating a considerable prevalence of hypertension (HTN) among patients with the most severe forms of the disease [5-6]. A preliminary study assessing clinical outcomes and basal characteristics of patients hospitalized due to COVID-19 in Wuhan, China showed a considerable prevalence of HTN (15%) amongst patients in need of hospitalization [5]. Furthermore, a retrospective study including 3,988 patients with critical COVID-19 in Lombardy, Italy, revealed that HTN was the most prevalent comorbidity [6]. Therefore, a deeper analysis of the association between HTN and severe COVID-19 assessing the independent impact of this co-morbidity in COVID-19 clinical evolution must be performed. In addition, the elucidation of the impact of anti-hypertensive therapies in COVID severity is also of high importance.

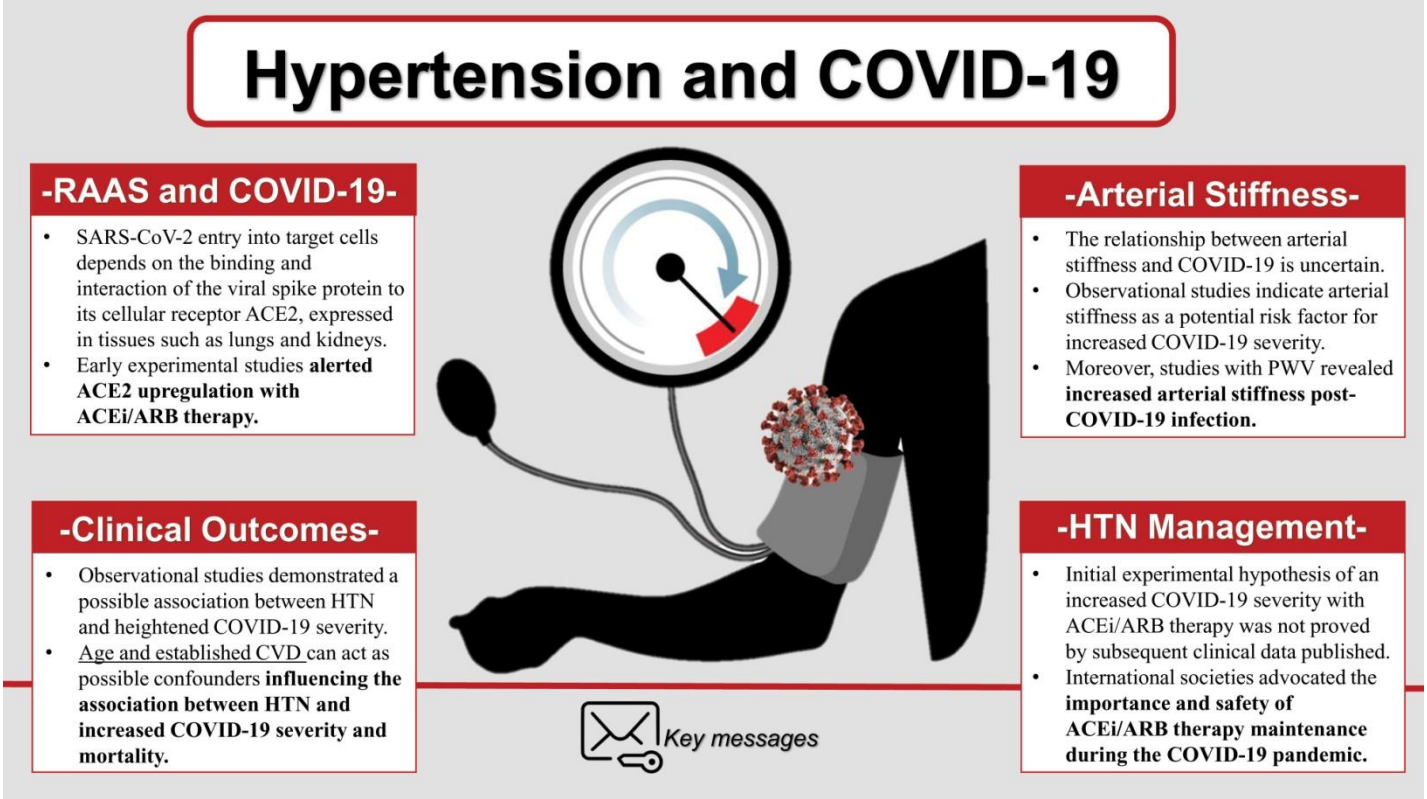

Figure 1: Brief summary of the key points regarding the association between hypertension and COVID-19.

Hence, the present review aims to evaluate the association between HTN and the most severe forms of COVID-19 assessing whether HTN *per se* is an independent risk factor for higher severity, mortality, and a worse COVID-19 prognosis (Figure 1).

II. Discussion

SARS-CoV-2 and RAAS

The renin-angiotensin-aldosterone system (RAAS) plays an important role in HTN genesis, as the increased or inappropriate secretion of renin increases the production of angiotensin II (Ang II) and aldosterone. Ang II is a vasoactive hormone that interacts with angiotensin II type 1 receptor (AT1R) promoting anti-natriuresis, aldosterone secretion, vasoconstriction, vascular remodeling and atherosclerosis, myocardial hypertrophy, inflammation, and fibrosis in several target organs, including lungs [7].

The so-called protective arm of RAAS consists of angiotensin II type 2 receptor (AT2R), angiotensin-converting enzyme type 2 (ACE-2), and angiotensin (1-7) receptors, which causes anti-inflammatory effects and helps to counter balance the inflammatory actions of Ang II via AT1R [8]. ACE-2 seems to play an essential role in SARS-CoV-2 infection pathogenesis, being expressed in many human tissues such as lungs, heart, and endothelium [9]. Therefore, SARS – CoV -2 spike protein may bind to the extracellular domain of pulmonary ACE-2 triggering cellular internalization of these structures with ACE-2 down regulation and subsequent accumulation of Ang II, predisposing severe pulmonary lesion [8]. Conditions associated with chronic endothelial dysfunction, as seen in HTN, represent a potential target for SARS-CoV-2 infection [8]. Chen et al., revealed that pericytes have a high expression of ACE-2, possibly being a target cell for SARS-CoV-2, heightening preexisting chronic endothelial dysfunction present in hypertensive patients [10]. Due to the important interaction between SARS-CoV-2 and RAAS, the impact of anti-hypertensive drugs, particularly RAAS inhibitors, in COVID-19 clinical evolution must be clarified.

COVID-19 and Hypertension: clinical outcomes

Hypertension as a risk factor for severe disease and mortality

Studies performed in several countries presented HTN as one of the most prevalent comorbidities amongst individuals infected by SARS-CoV-2 requiring hospitalization. HTN was associated with a higher prevalence of hospitalization, severe infection, increased disease progression, and worse prognosis [11-14]. In China, preliminary findings in Wuhan described by Guan et al. described HTN as the most prevalent comorbidity among individuals with primary outcomes consisting of ICU admission, mechanical ventilation, or mortality (35.8% vs. 13.7%) [12].

Furthermore, Chen et al., identified HTN (48.0%) as the most prevalent comorbidity among patients hospitalized with COVID-19 who evolved to death [13]. Similarly, in the United States, Richardson and colleagues evaluated the clinical characteristics of 5,700 patients hospitalized with COVID-19 in New York, and HTN had an alarming prevalence of 56.6% [14], raising initial concerns towards HTN as a risk factor for severe COVID-19.

In a meta-analysis published in April 2020 including 2,552 patients with a confirmed diagnosis of COVID-19, HTN doubled the risk of critical infection (OR 2.49 9[IC95% 1.98-3.12]) and was significantly associated with higher in-hospital mortality (OR 2.42 [IC95% 1.51-3.90]) [15]. Moreover, Yang et al. demonstrated that out of 462 patients infected by SARS-CoV-2, 126 presented preexisting HTN. Out of them, 23 (18.3%) had critical COVID-19, 27 (21.4%) severe disease, and 76 (60.3%) mild infection[9]. Moreover, mortality was higher among hypertensive patients than patients without HTN (10.3% vs. 6.4%). Another relevant piece of data presented by the authors which must be highlighted is the analysis of the laboratory profiles of hypertensive patients. Patients with COVID-19 and preexisting HTN, when compared to a control group, had higher levels of urea, ALT, and cardiac troponin. In addition, they presented higher inflammatory markers such as us-PCR, procalcitonin, and IL-6 [9].

Similarly, Huang and collaborators, in a retrospective multicentric study including 310 individuals with COVID-19, demonstrated that hypertensive patients presented higher plasma levels of leucocytes (7.36 vs. 3.25, p=0.002), neutrophils (7.92 vs. 2.52, p=0.003), LDH (316 vs. 302, p=0.038), fibrinogen (4.50 vs. 4.35, p=0.036) and D-dimer (1.09 vs. 0.74, p=0.013) in comparison with non-hypertensive patients, revealing a possible pathophysiological association with increased inflammation and a hypercoagulable state [16]. However, after multivariate logistic regression, HTN was not considered an independent risk factor for severe disease (OR 1.6 [CI95% 0.9-2.6], p=0.092) nor mortality (OR 1.3 [CI95% 0.7-2.3], p=0.458) [16].

Rodilla et al., evaluating clinical data from 12,226 patients with COVID-19 included in Spain's SEMI-COVID-19 registry, identified a higher prevalence of HTN amongst non-survivors (70.6% vs. 45.5%, p=0.0001). The Kaplan-Meier survival analysis demonstrated a noticeable increase in all-cause mortality among hypertensive patients, non-ACEi/ARB and ACEi groups, in comparison with normotensive patients. Curiously, the survival curve of hypertensive patients using ARB was similar to the curve of normotensive patients, evidencing lower lethality than other classes of anti-hypertensives analyzed. Moreover, after age and gender-adjusted multivariate logistic regression, preexisting HTN had an independent prognostic value for all-cause mortality among patients hospitalized with COVID-19. When specifically analyzing classes of anti-hypertensive drugs, previous use of ACEi (OR 1.6 [IC95% 1.35-1.85], p=0.001) or ARB (1.2 [IC95% 1.01-1.38, p=0.035) was not associated with higher mortality when compared to other anti-hypertensive agents (non-ACEi/ARB) (OR 1.3 [IC95% 1.08-1.43]) [17].

In another study, Li et al. revealed that in comparison with non-severe cases, severe cases were associated with a higher prevalence of concomitant comorbidities, including hypertension (38.7% vs. 22.2%, p <0.001). A previous diagnosis of hypertension doubled the risk for a more severe form of disease (OR 2,0 [IC95% 1,3-3,2]). After adjusting for gender, age and smoking, HTN was independently associated with higher disease severity [18]. A systematic literature review including 6,560 patients to evaluate the association between HTN and adverse clinical outcomes among patients with COVID-19 reported that the comorbidity increased the risk for in-hospital mortality (RR 2.21 [IC95% 1.74-2.81]), critical disease (RR 2.04 [IC95% 1.69-2.47]), ARDS (RR 1.64 [IC95% 1.11-2.43]), need of intensive care (RR 2.11 [IC95% 1.34-3.33]), and disease progression (RR 3.01 [IC95% 1.51-5.99]) [19].

A retrospective study assessing risk factors associated with severe COVID-19 in China evidenced that HTN increased 1.5 times the risk for critical disease progression (OR 1.5 [IC95% 1.2-1.8]). It is worth noting that the retrospective analysis data also demonstrated a linear association between age and disease severity since severity risk was progressively higher as age increased. The risk was noticeably higher among older patients (≥ 60 years old) [20]. Therefore, despite clinical data, mainly observational, indicating a higher association between HTN and severe COVID-19, few studies performed multivariate analysis adjusted for confounding biases, especially age, highlighting the presence of robust data in medical literature indicating an increased risk for severe disease as age progresses.

Kim et al., in a study retrospectively analyzing data from 2,491 adult patients hospitalized with COVID-19 in the United States, observed that in-hospital mortality significantly increased with age progression when compared to a population of younger patients (18-39 years old) (50-64: OR 1.53; 65-74: OR 1.65; 75-84: OR 1.84; ≥85: OR 1.43) [21]. At the same time, aging is an important risk factor for HTN development, with populational studies indicating a prevalence higher than 60% amongst older individuals, as well as a linear

association between prevalence and age [22-23]. Furthermore, authors postulate that the progressive deficit of innate and adaptative immunity, called immunosenescence, alongside a chronic pro-inflammatory state induced by aging, contributes to the cytokinetic storm and hyperinflammation observed in severe COVID-19 [3].

The observational, multicentric SARS-RAS study, performed by the Italian Society of Hypertension, evaluated predictors of higher mortality among patients with COVID-19 and did not manage to identify an association between HTN and worse clinical outcomes in these patients [24]. Despite a high prevalence of HTN among non-survivors (72.9% vs. 52.5%, p=0.0001), it is worth noting that patients who did not survive had a considerably higher age average when compared to survivors (79.6±0.8 vs. 64.7±0.4, p=0.0001). After age-adjusted multivariate logistic regression, HTN was not an independent risk factor for mortality among non-survivors. Observational data from Italy corroborate that the association between hypertension and COVID-19 severity, as well as higher mortality, may be influenced by a higher prevalence of advanced age among non-survivors since age presents a linear association with higher mortality and, concurrently, hypertension is a prevalent comorbidity amongst the elderly [24].

Thus, it must be questioned whether there is an actual causal relationship for higher mortality among patients with COVID-19. Advanced age may be a potentially confounding factor in the impact analysis of HTN in SARS-CoV-2 clinical outcomes [22-23,25]. Another important aspect to consider is a significant variation of sample sizes, since data collection was based on hospital admissions – generating self-report of comorbidities and sub notification due to a lack of knowledge and/or comorbidity diagnosis, and short follow-up periods – without an accurate knowledge concerning clinical outcomes and evolution. In addition, it is not clear whether blood pressure *per se* is a risk factor for COVID-19 and there is no certainty whether controlled HTN is associated with a lower risk of adverse clinical outcomes in comparison with patients with uncontrolled blood pressure.

Willamson and collaborators described factors associated with higher COVID-19 mortality utilizing clinical data from 17,278,392 individuals enrolled in an NHS database platform called OpenSAFELY [26]. Curiously, the analysis demonstrated that HTN diagnosis or blood pressure values ≥140/90mmHg were not associated with higher mortality among patients with COVID-19 after age-adjusted multivariate analysis (HR 0.89 [IC95% 0.85-0.93]) [26]. Moreover, Chen et al., in a cross-sectional study with 150 patients hospitalized in China assessed the impact of CVD in COVID-19 severity. After univariate logistic regression, a previous HTN diagnosis (OR 3.6 [CI95% 1.5-9.0], p=0.005) and history of CAD (OR 13.7 [CI95% 3.1-59.5], p<0.001) were predictors of critical disease. However, in multivariate analysis, conversely to history of CAD (OR 16.6 [CI95% 2.3-120.6], p=0.005), HTN (OR 2.6 [CI95% 0.6-11.0], p=0.198) was not an independent risk factor for severe disease [27].

In addition to age and history of CVD, it is imperative to assess HTN alongside other CV risk factors to identify confounding factors and clarify the actual causal relationship with severe disease and worse COVID-19 prognosis. Sun and colleagues in a study including 3,400 patients hospitalized with COVID-19, evaluated the impact of HTN, diabetes mellitus (DM), and both combined in the risk of mortality, ARDS, and critical disease. When compared to individuals without DM2 and HTN, mortality risk was significantly higher in patients with DM2 (OR 5.26 [CI95% 2.39-11.58]) or both comorbidities combined (OR 3.02 [CI95% 1.48-6.15]). In addition to mortality, DM2 was a predictor of ARDS development (OR 4.38 [CI95% 2.41-7.95]) and critical disease (OR 2.21 [CI95% 1.60-3.06]). Notwithstanding, isolated HTN was not an independent risk factor of mortality (OR 0.73 [CI95% 0.33-1.61]) or ARDS (OR 1.19 [CI95% 0.72-1.98]), being only associated with a modest increase in the risk of critical disease (OR 1.22 [1.00-1.51]) [28].

Therefore, there is no clear, robust epidemiological evidence that HTN *per se* is an independent risk factor for the development of severe disease or mortality in patients with COVID-19, emphasizing that the association between HTN and COVID-19 severity is still controversial. Despite a few observational studies correlating HTN and adverse COVID-19 outcomes, it must be highlighted the role of advanced age, previous CVD, and other comorbidities as potential confounding factors when analyzing the association between HTN and severe COVID-19, since hypertension is a prevalent comorbidity amongst older individuals and those with established CVD, risk factors knowingly associated with severe SARS-CoV-2 infection [20-21,27]. Thus, current evidence does not uphold that HTN is an independent risk factor for adverse clinical outcomes and higher COVID-19 mortality. Table 1 summarizes findings of the main studies involving hypertension and COVID-19.

Table 1: Summary of the major studies regarding hypertension and COVID-19.

Author	N	Design	Age (years)	Major findings
Guan et al.[12]	1,099	Observational	47.0 (35-58)	1. HTN prevalence: 1.1 All patients: 15.0% 1.2 Nonsevere: 13.4% 1.3 Severe: 23.7%
Chen et al.[13]	799	Observational	62.0 (44-70)	1.HTN prevalence: 1.1 All patients: 34.0% 1.2 Deaths: 48.0% 1.3 Recovered patients: 24.0%
Huang et al.[16]	310	Observational	62.0 (49-70)	1. Laboratory profile (HTN vs. non-HTN): - WBC (7.36 vs. 3.25, p=0.002); CRP (31.4 vs. 44.4, p=0.011); D-dimer (1.09 vs. 0.74, p=0.013). 2.Outcome of multivariable logistic regression: 2.1 Severity as dependent variable: -HTN (OR 1.562 [CI95% 0.929-2.625], p=0.092) 2.2 Mortality as dependent variable: -HTN (OR 1.262 [CI95% 0.683-2.332], p=0.458)
Iaccarino et al.[24]	1,591	Observational	66.5	1. HTN prevalence: 1.1 Total population: 54.9% 1.2 Non-survivors: 72.9% 1.3 Survivors: 52.5%
Sun et al.[28]	3,400	Observational	61.0 (50-68)	1.HTN prevalence: 1.1 All patients: 52.4% 1.2 Survivors: 52.2% 1.3 Non-survivors: 61.6% 2. Risk factors associated with death in patients with confirmed COVID-19 infection (multivariate analysis): 2.1 HTN alone (OR 0.73 [CI95% 0.33-1.61], p<0.01) 2.2 T2DM alone (OR 5.26 [CI95% 2.39-11.58], p<0.01) 2.3 HTN and T2DM (OR 3.02 [CI95% 1.48-6.15, p<0.01)

The susceptibility and prognosis of patients with severe forms of hypertension, such as resistant (RHTN) and refractory hypertension (RfHTN), is also uncertain. RHTN, defined as uncontrolled BP using three anti-hypertensive drugs and RfHTN, defined as uncontrolled BP using five or more anti-hypertensive drugs, have distinct pathophysiological mechanisms since RHTN is predominantly associated with intravascular volume overload and hyperaldosteronism. In contrast, sympathetic hyperactivity is apparently the pathophysiological determinant of RfHTN. However, both are expressly associated with endothelial dysfunction, vascular remodeling, and adverse CV outcomes [29-30].

Barbaro et al. in a cross-sectional study evaluating the inflammatory profile of 32 individuals with RHTN, 20 with moderate HTN and 20 normotensives, identified that patients with RHTN presented higher serum levels of TNF-alpha and IL-1β when compared to individuals with moderate HTN or normotensive patients [31]. Therefore, due to the pronounced inflammatory profile among patients with severe forms of HTN, such as RHTN, and the well-known hyperinflammation induced by SARS-CoV-2, robust evidence is needed to better understand the impact of severe forms of hypertension in the clinical evolution and severity of COVID-19.

Arterial stiffness and COVID-19: what is the relationship?

Although the association between high blood pressure levels and severe COVID-19 is not yet clear, the impact of arterial stiffness in SARS-CoV-2 clinical outcomes and evolution must also be analyzed. The association between increased arterial stiffness and the severity and duration of chronic inflammation is well established in the medical literature [32-33]. Since SARS-CoV-2 infection causes important impairment and inflammation of vascular endothelium, it must be questioned the impact of viral-induced endothelial dysfunction amongst patients with COVID-19 and no CV risk factors and/or previous CV disease and amongst infected patients with a higher CV risk and established CV disease [32-34].

In another analysis of the same Spanish SEMI-COVID-19 registry, a cohort of 12,710 patients was assessed, and aortic stiffness (pulse pressure (PP)≥60 mmHg) presented an independent prognostic value for all-cause mortality among patients with COVID-19 in need of hospitalization (OR 1.27 [CI95% 1.11-1.45], p=0.0001) [35]. Patients with COVID-19 and aortic stiffness presented a higher age average (72.8 vs. 64.5, p=0.0001) and systolic BP (SBP) values (146 vs. 119, p=0.0001). In terms of mortality, aortic stiffness was a determinant factor, patients with aortic stiffness and SBP ≥140mmHg presented a higher mortality rate in comparison with hypertensive patients without aortic stiffness (25.2% vs. 13.3%). Furthermore, amongst the group of patients with SBP <120mmHg, mortality was noticeably higher in individuals with aortic stiffness when compared to those with PP<60mmHg (36.4% vs. 23.0%). Regardless of SBP, aortic stiffness was associated with higher all-cause mortality than PP <60mmHg. When compared to patients who survived, non-survivors presented higher prevalence of HTN (70.7% vs. 45.5%) and aortic stiffness (43.7% vs. 33.9%). However, it is worth considering a higher prevalence of older age (79.7 vs. 64.1 years old) and other comorbidities such as DM (28.2% vs. 16.6%) and chronic kidney disease (CKD) (12.5% vs. 4.2%) amongst non-survivors. It must be emphasized that HTN and age are important determinants of aortic stiffness, which is an endothelial dysfunction marker associated with hypertension and vascular aging [35]. Therefore, PP may be a useful tool to complement a prognostic analysis of COVID-19 during hospital admission and patient risk stratification analysis [35].

A case-control cross-sectional study assessing young individuals demonstrated that patients with COVID-19 presented higher vascular dysfunction with more severe arterial stiffness than the control group due to the presence of higher values of carotid-femoral pulse wave velocity (PWV) (5.83±0.62 m/s vs. 5.17±0.66 m/s, p<0.01) and lower levels of brachial flow-mediated dilation (FMD) (2.71±1.21% vs. 8.81±2.96%, p<0.01) [36]. In another case-control study including a population of older patients (77 [67-84] years old), carotid-femoral PWV was higher among patients with COVID-19 when compared to the controls (14.3 m/s vs. 11.0 m/s, p=0.07). Additionally, in comparison with survivors, PWV was higher amongst non-survivors [37]. Thus, data from both studies suggest the presence of SARS-CoV-2-induced endothelial dysfunction even amongst younger patients. Interestingly, authors postulate a bidirectional association, where pre-existing arterial stiffness is a risk factor for severe COVID-19 and SARS-CoV-2 induced vascular impairment causes and aggravates post-COVID arterial stiffness [38]. Thus, the direct impact of previous chronic arterial stiffness in COVID-19 severity and, on the other hand, the development of post-COVID arterial stiffness due to viral-induced endothelial injury destabilizing previous atherosclerotic processes needs to be elucidated [35-37].

Therefore, it is not clear whether aortic stiffness *per se* favors worse clinical outcomes in patients with COVID-19 and whether endothelial dysfunction caused by viral infection may decompensate HTN or accentuate the process of previously established arterial stiffness and vascular aging after the course of infection, leading to precocious atherosclerosis and vascular events, demanding more robust analysis to determine the clinical and pathophysiological associations between COVID-19, endothelial dysfunction, and aortic stiffness [35-38].

Does Hypertension management impact COVID-19 severity?

In addition to the analysis of HTN as a risk factor for severe COVID-19 and adverse clinical outcomes, it is essential to evaluate the impact of anti-hypertensive therapies in the clinical evolution of the disease. During the early phase of the pandemic, there was a hypothesis that the use of ACEi/ARB would increase expression and/or tissue activity of ACE2, heightening SARS-CoV-2 infection risk and intensifying inflammatory activity [39]. It is worth noting that the hypothesis was strictly based on previous experimental studies, which demonstrated a modulatory effect of RAAS inhibitors in the upregulation of ACE2 expression [40-42]. However, clinical studies subsequently published did not evidence a deleterious impact of RAAS inhibitors in COVID-19 clinical evolution, ratifying the importance of ACEi/ARB therapy maintenance.

In a multicentric study, Zhang et al. compared adults with HTN and COVID-19 using ACEi orARBs

with those taking anti-hypertensive drugs other than RAAS blockers (N= 940) and COVID-19 patients without HTN (N=2,302). All-cause mortality risk in 28 days was lower in the ACEi/ARB group than in control group when adjusted for age, gender, and comorbidities (0,42 [IC 95%, 0,19-0,92]; p = 0,03) [43]. Reynolds et al., however, did not report an association between anti-hypertensive drug classes, including RAAS inhibitors, and higher risk of COVID-19 infection nor development of severe disease (need of intensive care, mechanical ventilation, or death) [44]. Meng and colleagues investigated hypertensive patients with COVID-19 under RAAS inhibitor therapy and evidenced a lower prevalence of severe disease and lower levels of IL-6 among these patients. In addition, ACEi or ARB treatment increased the level of T CD3 and CD8 cells in peripheral blood and reduced viral load peak when compared to other anti-hypertensive drugs [45].

In the population-based case-control study by Mancia et al., the adjusted odds ratio for COVID-19 associated with the use of anti-hypertensive drugs was 1.03 (95%CI 0.95-1.12) for calcium channel blockers, 0.99 (CI 95% 0.91-1.08) for beta-blockers, 1.03 (95%CI 0.86-1.23) for thiazide diuretics, 1.46 (95%CI 1.23-1.73) for loop diuretics, and 0.90 (95%CI 0.75-1.07) for mineralocortidoid receptor antagonist respectively. The use of ARBs and ACE inhibitors in the study was not significantly associated with higher COVID-19 risk. Furthermore, there was no statistical evidence of an independent association between the use of a combination of anti-hypertensive medications and increased COVID-19 risk [46]. Therefore, the study demonstrated that RAAS blockers did not increase COVID-19 susceptibility; ACEi and ARBs were not independently associated with higher COVID-19 risk in patients with mild to moderate or severe disease; and there was no evidence that patients who received ARBs or ACEi had a better clinical profile than those who received other anti-hypertensive drugs.

The BRACE CORONA clinical trial, the first randomized, controlled multicentric study to evaluate the safety of ACE inhibitors and ARBs in 659 patients hospitalized with mild to moderate COVID-19 recruited in 29 different sites in Brazil, revealed that among patients under chronic treatment with ACEi/ARB and COVID-19, it was observed a similar 30-day mortality rate between patients who maintained and those who suspended ACEi/ARB treatment (2.8% vs. 2.7%), accentuating that there is no clinical benefit in interrupting RAAS inhibitors treatment in hospitalized patients with mild to moderate COVID-19 [47]. Baral and collaborators in a recent systematic review and meta-analysis evaluated the association between RAAS inhibitors and the clinical outcomes of patients with COVID-19. The authors reported a significantly lower risk of mortality (OR 0.57 [IC95% 0.43-0.76], p<0.001) and severe adverse events (OR 0.68 [IC95% 0.53-0.88], p<0.001) among patients with COVID-19 who received ACEi/ARB. Moreover, in a subgroup analysis of hypertensive patients, the use of RAAS inhibitors was associated with a lower risk of mortality (OR 0.51 [CI95% 0.32-0.84], p=0.008) and severe clinical outcomes (OR 0.55 [IC95% 0.36-0.85, p=0.007). Therefore, based on the results of the meta-analysis, the use of RAAS inhibitors was not associated with a higher risk of severe outcomes and mortality among patients with COVID-19, indicating a potential protective effect in hypertensive patients with COVID-19 [48]. Nonetheless, it is important to highlight the small number of randomized clinical trials present in the composition of the meta-analysis, limiting evidence and interpretation of causality.

The initial hypothesis of an increase in infectiousness and morbimortality among patients with CKD, HTN and/or heart failure undergoing chronic RAAS inhibitors treatment was not proven by subsequent clinical studies, prompting international scientific societies to issue recommendations ratifying RAAS therapy maintenance and safety during the pandemic. Therefore, patients with formal indication should not discontinue ACEi/ARB therapy for HTN management during the COVID-19 pandemic. Moreover, there is a need for more robust randomized clinical trials to assess the causal relationship between RAAS inhibitors and a lower incidence of adverse clinical outcomes among patients with COVID-19.

III. Conclusions

Although HTN is a prevalent comorbidity amongst patients with severe COVID-19, there is no robust epidemiological evidence supporting HTN as an independent risk factor for adverse clinical outcomes in COVID-19 infection. Furthermore, older age may be an important confounding factor in the analysis of the impact of HTN in COVID-19 clinical outcomes due to the high prevalence of HTN among older individuals, emphasizing the need for adjusted multivariable analysis. Studies did not reveal an association between anti-hypertensive therapy and increased disease severity. Besides, the initial hypothesis that RAAS inhibitors might cause deleterious effects in COVID-19 clinical evolution was not confirmed in subsequent clinical data published, ensuring the importance and safety of maintaining ACE inhibitors/ARB during the COVD-19 pandemic.

IV. Materials & Methods

The bibliographical research was performed in the PubMed platform using the following descriptors: "COVID-19" "SARS-CoV-2" "Hypertension" "Blood Pressure". Articles with subjects diverging from the theme of this article were excluded. After exclusion, 48 articles were selected and cited directly or by cross-reference in reviews here exposed.

Abbreviations: COVID-19, coronavirus disease 2019; HTN, hypertension; RAAS, renin-angiotensin-aldosterone system; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ACE2, angiotensin converting enzyme 2; PWV, pulse wave velocity, WBC, white blood cell; CRP, C-reactive protein; T2DM, type 2 diabetes.

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