Int J Cardiovasc Sci. 2023;36:e20220033

ORIGINAL ARTICLE

Clinical Aspects Of Hypertensive Patients With COVID-19 Hospitalized In A Campaign Hospital In Northeast Brazil

Luan George Xavier,[1] Renato Sampaio Mello Neto,[1] Marcos Henrique de Oliveira Morais,[1] Pedro Jorge Cronemberger,[1] Maria do Carmo Carvalho Martins,[1] Marta Rosal[1]

Universidade Federal do Piauí,[1] Teresina, PI – Brazil

Abstract

Background: In view of the absence of effective therapy for COVID-19, many studies have been conducted seeking to identify determining factors for the development of severe forms, aiming to direct efforts to avoid the worst outcomes in patients susceptible to severe conditions. One of the main comorbidities associated with complicated forms of the disease is systemic arterial hypertension (SAH).

Objective: To assess aspects of the clinical, demographic, laboratory, and radiological characteristics of hypertensive patients with COVID-19 to contribute to the knowledge of the relationship between the presence of this comorbidity and the severity of the disease.

Methods: A total of 380 patients with a diagnosis of acute SARS-CoV-2 infection hospitalized between June and August 2020 were included. Patients were divided into two groups according to the presence or absence of a previous diagnosis of hypertension. For comparison between groups, a significant difference was established if $p < 0.05$.

Results: Of the total of 380 patients, 202 (53.16%) had a clinical diagnosis of SAH. Hypertensive patients were significantly older ($p < 0.01$) and had more comorbidities ($p < 0.01$) than the non-hypertensive group. In laboratory tests, hypertensive patients had higher levels of blood glucose ($p = 0.014$), creatinine ($p = 0.002$), and urea ($p = 0.003$), while values for alanine aminotransferase (ALT) ($p < 0.01$), aspartate aminotransferase (AST) ($p = 0.006$), and sodium ($p = 0.024$) were lower. There was no difference between groups in radiographic parameters.

Conclusions: This study showed that, although the hypertensive group had some laboratory alterations that elicited severe disease, these patients did not have worse outcomes.

Keywords: Covid-19/complications; Coronavirus/complications; Hypertension; Heart Failure; Severe Acute Respiratory Syndrome; Pandemics; Aged; Comorbidities; Public Health/research; Epidemiology.

Introduction

Since the first cases of coronavirus disease 2019 (COVID-19) in December 2019, in the city of Wuhan, China, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was responsible for the death of more than 3.6 million people, as of June 2021. It has a lethality rate of around 2.15% worldwide, with 171 million people infected, according to data from the World Health Organization.[1,2]

In view of the absence of proven effective therapy for the disease, numerous studies have been developed seeking to identify the determining factors for the development of more severe forms of COVID-19, in order to direct efforts to avoid the worst outcomes in patients with possible profiles of development of severe conditions.[3] Several comorbidities have been associated with the most complicated forms of COVID-19,[4] including systemic arterial hypertension (SAH), a disease that has a prevalence of around 26% in the world's adult population[5] and a prevalence of 24.5% in Brazilian capital cities.[6] Furthermore, several studies have pointed to SAH as the most frequent comorbidity in patients diagnosed with COVID-19 worldwide.

Mailing Address: Luan George Xavier
Universidade Federal do Piauí. Rua Jornalista Helder Feitosa, 1131. Postal code: 64049-550. Teresina, PI – Brazil
E-mail: luanxavier@ufpi.edu.br

DOI: https://doi.org/10.36660/ijcs.20220033

Manuscript received September 26, 2021; revised manuscript May 3, 2022; accepted June 11, 2022.

In this sense, a study carried out in Wuhan, China, with 244 adult patients with a confirmed diagnosis of COVID-19 and some previously diagnosed cardiovascular disease, including SAH, coronary disease, or heart failure, showed that the most common cardiovascular disease was SAH, in 82.79% of the patients.[7] Another study mentions hypertension as the most frequent comorbidity as well, reaching 19.4% of the sample of 201 patients aged between 21 and 83 years old admitted to a hospital in Wuhan, China, with a confirmed diagnosis of COVID-19.[8] In another study in Wuhan, China, hypertension was also the most frequent comorbidity, present in 30% of 191 hospitalized patients above the age of 18 years.[9]

The hypothesis was also proposed that SAH could increase susceptibility to infection by SARS-CoV-2, which was supported by the discovery of the mechanism of cell invasion of the virus based on changes in the angiotensin-converting enzyme (ACE). Considering that inhibitors of this enzyme and angiotensin AT1 receptor blockers are among the classes of drugs most used in the treatment of SAH, the possibility was considered that the increase in ACE synthesis due to an upregulation mechanism induced by the continuous use of these drugs[10,11] could facilitate the entry of the pathogen into host cells.[12-14] However, the action of ACE leads to the formation of angiotensin 1-7 from angiotensin II, which antagonizes the inflammatory action of the latter.[15] Thus, the presence of the enzyme decreases the amount of a substance that favors inflammation in the lungs, while increasing the amount of another, which acts mainly by protecting the lungs, heart, and kidneys from deleterious effects. This protective capacity against lung injury has been demonstrated in experimental studies.[16] Thus, this hypothesis has been questioned, since the use of AT1 receptor blockers and ACE inhibitors does not seem to favor viral infection or increase the risk of unfavorable outcomes.[17,18]

Although results from meta-analysis studies have shown a direct association between SAH and the severity of COVID-19, the mechanisms involved remain unknown.[19,20] The fact that many patients infected with COVID-19 are hypertensive does not necessarily imply a causal relationship between the two diseases, as hypertension is very prevalent in the elderly, and older people seem to be at greater risk of being infected and developing worse outcomes, even if they do not have SAH.

In view of the above, it is possible that the greater susceptibility of hypertensive individuals to develop more severe forms of COVID-19 is related to the presence of other risk conditions associated with SAH, such as advanced age and immunological factors.[4] Clinical, laboratory, and radiological characteristics of hypertensive patients with COVID-19 can contribute to the knowledge of the relationship between the presence of this comorbidity and the severity of the disease caused by SARS-CoV-2, as well as to the understanding of the natural history of the disease. This study, therefore, aims to describe the clinical profile of hypertensive patients with COVID-19.

Methods

Study design

The present study was part of the research project entitled "Research and innovation project in public health management: strategies for coping with the COVID-19 pandemic" and consisted of a descriptive, cross-sectional, observational study, with retrospective data collection, carried out in a field hospital of the Piauí state network, located in Teresina, the state capital. Clinical, laboratory, and radiological data were collected within the first 72 hours after hospital admission. The study included a total of 380 patients with a diagnosis of acute SARS-CoV-2 infection admitted to the aforementioned hospital between June 2, 2020 and August 18, 2020. The hospital had 103 beds exclusively for the purpose of caring for adult patients (≥ 18 years old) diagnosed with low and medium severity COVID-19. The absence of information about a history of hypertension was used as an exclusion criterion. Patients with more severe evolution were transferred to intensive care units of tertiary hospitals in the city of Teresina.

Data source

Data were obtained from survey forms completed during clinical interviews, as well as from electronic medical records and the results of laboratory and imaging test of patients admitted to the field hospital. All information was obtained without showing the names of the patients, compiled in a database, checked, and reviewed by three different researchers to ensure data validity.

The parameters analyzed were related to clinical, social, and demographic characteristics, which consisted of the following: age, sex, length of hospital stay, clinical symptoms (fever, cough, dyspnea, fatigue, malaise,

anorexia, sputum production, sore throat, headache, chest pain, diarrhea, nausea and vomiting, abdominal pain, hyposmia, and hypogeusia), comorbidities (diabetes mellitus, SAH, heart diseases, chronic obstructive pulmonary disease, and asthma), smoking, and body mass index.

Laboratory test results were collected within 72 hours of hospital admission and included the following tests: complete blood count, electrolytes, C-reactive protein, ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine, lactate dehydrogenase, lactic acid, D-dimer, prothrombin activity time, and activated partial thromboplastin time (APTT).

Imaging findings were obtained using chest computed tomography (CT) within the first two days after admission.

Study definitions

Confirmed cases of COVID-19 were defined as acute respiratory illness associated with a flu-like illness, associated with a positive result in the real-time reverse transcriptase polymerase chain reaction (RT-PCR) of nasal and oropharyngeal swab specimens or in the rapid serological test.

Patients with flu-like symptoms were classified on admission into disease stages (1, 2A, 2B, and 3) according to the institutional protocol for managing COVID-19. In phases 1 and 2A, patients had the following characteristics: oxygen saturation ≥ 93% in room air, respiratory rate < 24 breaths/min, age over 60 years, or presence of some comorbidity (hypertension, diabetes, asthma, chronic obstructive pulmonary disease, and obesity). Patients in phase 2B had at least one of the following criteria: dyspnea, respiratory rate ≥ 24 breaths/min, or oxygen saturation ≥ 93% in nasal catheter with up to 3 L/min of oxygen. Finally, patients in phase 3 had dyspnea associated with at least one of the following criteria: need for oxygen therapy > 3 L/min to maintain oxygen saturation ≥ 93%, use of accessory muscles, or presence of organ dysfunction (SOFA score > 2). Patients admitted in phases 2B and 3 were classified as severe.

Comorbidities were defined based on the patient's self-reported past medical history. Obesity was defined based on a body mass index greater than or equal to 30 kg/m².

Statistical analysis

After applying the normality test, the quantitative variables of the hypertensive and non-hypertensive groups were expressed as mean and standard deviation, and comparisons between groups were performed using Student's t test and Mann-Whitney U test for variables with or without normal distribution, respectively. Qualitative variables were presented as absolute frequency and percentages, and associations were tested using Pearson's chi-square test. The independent variable was defined as the presence or absence of a diagnosis of SAH. The study data were processed using Statistical Package for the Social Sciences (IBM®) software, version 27.0.

Results

Three hundred and eighty (380) patients hospitalized with a diagnosis of COVID-19 participated in this study, of which 53.16% had a confirmed clinical diagnosis of SAH. Hypertensive patients were significantly older (p = 0.000) than non-hypertensive patients (68.71; 56.91 to 79.49 years versus 55.15; 43.24 to 71.04 years) (Table 1).

According to the results shown in Table 1, hypertensive patients with COVID-19 admitted to the field hospital had a significantly higher number of comorbidities (p = 0.000) than non-hypertensive patients, and the presence of comorbidities was 2.36 times more frequent among patients with diabetes (111 versus 47 patients; p = 0.000; r = 0.4989). Diabetes mellitus was the most frequent comorbidity, and it was more present among hypertensive patients (p < 0.0001), as shown in Table 2.

As for cardiovascular parameters, with the exception of systolic blood pressure, which was significantly higher in hypertensive patients (p = 0.000), there was no difference between groups (Table 1). Regarding the symptoms presented by the patients (Table 3), only the frequency of fever was statistically different between the groups, with a higher frequency in non-hypertensive patients (p = 0.004).

Regarding the results of laboratory tests (Table 4), hypertensive patients had significantly higher values for glycemia (p = 0.014), creatinine (p = 0.002), and urea (p = 0.003), while ALT (p = 0.000), AST (p = 0.006), and sodium (p = 0.024) were significantly lower.

As for the hematological parameters listed in Table 5, hypertensive patients had significantly lower mean

counts of lymphocytes (p = 0.009) and platelets (0.003), in addition to significantly higher APTT (p = 0.006). The p-value for monocyte count was borderline, tending to a lower value among hypertensive patients.

Discussion

The results of this study indicate that hypertensive patients with COVID-19 admitted to the field hospital had a higher risk clinical profile for developing more severe forms of the disease caused by SARS-CoV-2, characterized by elderly patients with a higher frequency and number of comorbidities, in addition to an association with diabetes mellitus and higher values of glycemia, creatinine, and urea.

The predominance of elderly patients with COVID-19 among hypertensive patients can be partly explained by

Table 1 – Sociodemographic and clinical characteristics in hypertensive and non-hypertensive patients with COVID-19. Teresina, PI, Brazil, 2020

Parameter	Hypertensive (n = 202) mean (SD)	Non-hypertensive (n = 178) mean (SD)	*p-value*
Age (years)	68.15 (13.96)	56.46 (18.53)	**0.000**
Total length of stay (days)	7.55 (6.81)	7.09 (7.643)	0.476
Body mass index (kg/m²)	29.37 (6.17)	28.31 (5.215)	0.142
Comorbidities	2.11 (0.95)	0.71 (0.85)	**0.000**
Heart rate (bpm)	84.86 (16.23)	85.82 (16.69)	0.700
Respiratory rate (RR/min)	20.09 (2.47)	20.81 (3.57)	0.234
Systolic blood pressure (mmHg)	135.7 (22.44)	128 (16.14)	**0.000**
Diastolic blood pressure (mmHg)	80.78 (11.59)	79.38 (9.78)	0.422
Oxygen saturation (%)	95.38 (3.30)	95.27 (5.31)	0.912

Significance level set at p < 0.05; Mann-Whitney test for comparisons between hypertensive and non-hypertensive groups. SD: standard deviation.

Table 2 – Association between sociodemographic and clinical characteristics in hypertensive and non-hypertensive patients with COVID-19. Teresina, PI, Brazil, 2020

Parameter	Hypertensive (n = 202) n (%)	Non-hypertensive (n = 178) n (%)	χ^2 *p-value*
Male	111(55.0)	112 (62.9)	0.115
Severe illness	117 (65.7)	96 (61.1)	0.757
Deaths	32 (16.0)	24 (13.6)	0.891
Obesity	65 (38.7)	46 (31.7)	0.199
Diabetes	89 (44.1)	33 (18.5)	**0.001**
Alcoholism	45 (49.5)	38 (58.5)	0.266
Cardiopathies	12 (5.9)	5 (2.8)	0.141
Smoking	45 (49.5)	29 (44.6)	0.551
CT frosted glass ≥ 50%	16 (39.0)	15 (45.5)	0.577

Significance level set at p < 0.05; Pearson chi-square (x^2). CT: chest computed tomography.

Table 3 – COVID-19 symptoms in hypertensive and non-hypertensive patients. Teresina, PI, Brazil, 2020

Parameter	Hypertensive (n = 202) n (%)	Non-hypertensive (n = 178) n (%)	χ^2 *p-value*
Fever	121 (60.2)	131 (74.0)	0.004
Cough	153 (76.1)	139 (78.5)	0.577
Fatigue	41 (20.4)	31 (17.5)	0.476
Dyspnea	160 (79.6)	137 (77.4)	0.603
Myalgia	100 (49.8)	97 (54.8)	0.327
Anorexia	42 (20.9)	44 (24.9)	0.359
Sore throat	37 (18.4)	40 (22.6)	0.313
Headache	57 (28.4)	66 (37.5)	0.059
Chest pain	36 (17.9)	40 (22.7)	0.245
Anosmia	34 (16.9)	33 (18.8)	0.642
Ageusia	44 (21.9)	36 (20.5)	0.734
Diarrhea	62 (30.8)	49 (27.8)	0.523
Nausea/vomiting	24 (11.90)	17 (9.70)	0.478

Significance level set at $p < 0.05$; Pearson chi-square (χ^2).

Table 4 – Laboratory characteristics in hypertensive and non-hypertensive COVID-19 patients. Teresina, PI, Brazil, 2020

Parameter	Groups		*p-value*
	Hypertensive (n = 202) Mean (SD)	Non-hypertensive (n = 178) Mean (SD)	
Glycemia (mg/dL)	204 (100.5)	175.90 (95.57)	**0.014** [m]
ALT (U/L)	49.59 (41.84)	75.16 (81.23)	**0.000** [m]
AST (U/L)	54.06 (48.59)	63.42 (43.61)	**0.006** [m]
Creatinine (mg/dL)	1.11(1.04)	0.87 (0.65)	**0.002** [m]
Urea (mg/dL)	61.70 (45.61)	48.66 (30.19)	**0.003** [m]
D-dimer (ng/mL)	3452.00 (5041.00)	2861.00 (4747.00)	0.285 [m]
LDH (UI/L)	380.70 (161.10)	378.30 (146.10)	0.788 [m]
Lactate (mg/dL)	4.46 (1.62)	4.43 (1.69)	0.690 [m]
Ferritin (ng/dL)	1127.00 (947.30)	1334.00 (1625.00)	0.587 [m]
CRP (mg/dL)	6.38 (2.93)	5.82 (3.00)	0.092 [m]
Sodium (mmol/L)	137.40 (5.24)	138.50 (4.36)	0.024 [m]
Potassium (mmol/L)	4.79 (0.77)	4.70(0.63)	0.202 [m]
Magnesium (mmol/L)	2.02 (0.30)	2.06(0.27)	0.673 [t]

Significance level set at $p < 0.05$; m: Mann-Whitney; t: two-tailed unpaired t-test for magnesium, variable with normal distribution. ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; LDH: lactic dehydrogenase; SD: standard deviation.

Table 5 – Hematological parameters in hypertensive and non-hypertensive COVID-19 patients. Teresina, PI, Brazil, 2020

Parameter	Comparison between groups		*p-value*
	Hypertensive (n = 202) Mean (SD)	Non-hypertensive (n = 178) Mean (SD)	
Erythrocytes (106 cells/ mm³)	4.58 (0.70)	4.60 (0.68)	0.448
Hemoglobin (g/dL)	13.33 (1.96)	13.49 (1.75)	0.192
Hematocrit (%)	40.19 (5.80)	40.88 (5.23)	0.112
Leukocytes (number/mm³)	9900.00 (5198.00)	9742.00 (4337.00)	0.788
Segmented neutrophils (number/mm³)	7903.00 (4457.00)	7634.00 (3794.00)	0.857
Rod neutrophils (no./mm³)	22.98 (44.59)	258.40 (386.70)	0.408
Eosinophils (number/mm³)	62.17 (94.12)	55.07 (67.15)	0.805
Basophils (number/mm³)	22.98 (44.59)	25.42 (50.53)	0.955
Lymphocytes (number/mm³)	1078.00 (739.70)	1203.00 (732.20)	**0.009**
Monocytes (number/mm³)	507.20 (341.00)	559.20 (346.00)	0.066
Platelets (number/mm³)	229.910.00 (88.845.00)	261.879.00 (104.406.00)	**0.003**
PAT (seconds)	14.89 (3.73)	14.41 (1.54)	0.227
APTT (seconds)	38.26 (9.37)	31.07 (4.12)	0.006

Significance level set at $p < 0.05$; Mann-Whitney test. APTT: activated partial thromboplastin time; PAT: prothrombin activity time; SD: standard deviation.

the fact that hypertension is a non-communicable disease whose prevalence increases with advancing age, reaching around 60% of individuals over 65 years (95% CI: 59.3 to 62.5), and 49.5% (95% CI: 47.6 to 51.4) of Brazilians aged between 55 and 64 years living in state capitals.[6]

Specifically regarding COVID-19, several studies have shown a higher risk of infection with the new coronavirus as well as worse disease outcomes in the elderly, especially before the appearance of the P.1 variant in Manaus, Amazonas, Brazil in the beginning of 2021.[21,22]

Accordingly, it should be noted that the distribution of cases of the disease and deaths by age group shows that, although it has a higher incidence in the adult population, it is more lethal in the elderly population, in Brazil and worldwide, as demonstrated in a report of the WHO-China Joint Mission, which concluded that patients over 60 years of age and those with comorbidities had a higher risk of developing severe disease and death.[23,24]

Furthermore, when considering the complications associated with hypertension that are more frequent in the elderly, the even greater risk associated with SARS-CoV-2 infection in this age group is evident. It should be noted that a report with 44,672 confirmed cases of COVID-19 by the Chinese Center for Disease Control and Prevention showed that the general fatality rate in hospitalized patients with COVID-19 was 6.0% among hypertensive patients, 10.5% among patients with cardiovascular diseases, and 7.3% among patients with diabetes, despite the mortality rate of 2.3% in the general sample.[21]

It should also be noted that aging brings changes in the immune response, which can make the elderly more susceptible to the development of more severe forms of COVID-19. With aging, the immune system undergoes changes in its cell lineages, deregulated cytokine secretion, and other functional alterations.[25] Immunosenescence contributes not only to greater susceptibility to infectious diseases, but also to chronic diseases, such as hypertension, which is very prevalent in the elderly population.[22]

The lymphoid lineage is the subpopulation most affected by aging. Although type B lymphocytes do not reduce in number, T lymphocytes, dependent on the thymus for full maturation, end up reducing in number and capacity for activity, due to the involution of the thymus, which is progressively replaced by adipose tissue.[26]

Another aspect to be emphasized is that unsuccessful aging is often accompanied by the development of several non-communicable diseases, especially cardiovascular and metabolic diseases, among which diabetes mellitus stands out. This synergism is rooted in the phenomenon of immunosenescence.[25]

The combination between SAH and diabetes may also help explain the greater severity of COVID-19 cases in hypertensive patients. In this study, almost half of the hospitalized hypertensive patients diagnosed with COVID-19 had diabetes, with a ratio of 2.7 hypertensive patients for each non-hypertensive patient. In a study that included 1,099 patients with a confirmed diagnosis of COVID-19, in a subgroup of 173 patients with severe disease who had comorbidities, 23.7% had SAH, 16.2% had diabetes mellitus, and 5.8% had coronary diseases.[27] In another study of 140 patients who were hospitalized with COVID-19, 30% had hypertension, and 12% had diabetes mellitus.[28]

However, in this study, although it is cross-sectional and did not follow up the patients for the outcome of death, while the patients were hospitalized, there were no significant differences between the groups in the number of patients who developed severe disease, died, or had greater than or equal to 50% of the lungs compromised according to CT evaluation.

Regarding the main symptoms in both groups, only fever had a significant difference between the groups. Non-hypertensive patients had more fever, which can be explained by the decrease in lymphocyte counts in the hypertensive group. Platelets and APTT were also lower in the hypertensive group. These changes suggest more pronounced immune dysregulation in this group.[29] In addition, creatinine and urea levels were also higher in hypertensive patients. This represents a severity criterion[30] and may occur due to complications of hypertensive nephropathy, which is among the most frequent in hypertensive patients.[31]

ALT and AST were lower in the hypertensive group. In a similar study, AST showed no difference between the hypertensive and non-hypertensive groups, but ALT was higher in the hypertensive group.[29] However, the groups in the cited study had the same mean age, while our hypertensive group was older than the non-hypertensive group. In this case, it can be hypothesized that these heterogeneous results may be due to the aforementioned immunosenescence process.

It is important to highlight some limitations of this study, with emphasis on the following: cross-sectional research design, which limits the establishment of causal inference from the results obtained; sample size and representativeness; inability to control analyses for potential confounders; and descriptive nature of the analyses. Despite this, the results of the present study contribute with information about the clinical profile of hypertensive patients with COVID-19.

Conclusion

The group of hypertensive patients with COVID-19 admitted to the field hospital had a high proportion of elderly people with obesity and diabetes, in addition to higher levels of glycemia, creatinine, and urea, a higher risk clinical profile for developing more severe forms of the disease caused by SARS-CoV-2. However, the patients did not have worse outcomes than the non-hypertensive group.

Author Contributions

Conception and design of the research: Xavier LG, Martins MCC, Rosal M; acquisition of data and writing of the manuscript: Xavier LG, Mello Neto RS, Cronemberger P, Morais MHO; analysis and interpretation of the data: Xavier LG, Mello Neto RS, Cronemberger P, Morais MHO, Martins MCC; statistical analysis: Xavier LG, Mello Neto RS; critical revision of the manuscript for intellectual content: Martins MCC, Rosal M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This research was conducted in accordance with the provisions of the 1975 Declaration of Helsinki. The study was approved by the Research Ethics Committee of the University Hospital of the Federal University of Piauí (opinion number 4,083,222). All participants confirmed their participation in the study by signing an informed consent form.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33. DOI: 10.1056/NEJMoa2001017.

2. World Health Organization (WHO). Coronavirus disease (COVID-19) pandemic. [Cited in 2021 August 19]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAiAkJKCBhAyEiwAKQBCkiyD7xX8OSaz60UmCQzLiarpfMxcUeospGtC53gaCiSWVeLWkOqoaBoCzSwQAvD_BwE.

3. Kaur G, Lungarella G, Rahman I. SARS-CoV-2 COVID-19 susceptibility and lung inflammatory storm by smoking and vaping. J Inflamm (Lond). 2020;17:21;2020. doi: 10.1186/s12950-020-00250-8.

4. Schiffrin EL, Flack JM, Ito S, Muntner P, Webb RC. Hypertension and COVID-19. Am J Hypertens. 2020;33(5):373-4. doi: 10.1093/ajh/hpaa057.

5. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton P, He J. Global burden of hyperten-sion: analysis of worldwide data. Lancet. 2005;365(9455):217-23. DOI: 10.1016/S0140-6736(05)17741-1.

6. Brasil. Ministério da Saúde. Vigitel Brasil 2019: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. Surveillance of risk and protective factors for chronic diseases by telephone. Estimativa de 26 capitais dos Estados da Republica Federativa Brasileira. Brasilia; 2020. 137p.

7. Peng Y, Meng K, He M, Zhu R, Guan H, Ke Z, et al. Clinical Characteristics and Prognosis of 244 Cardiovascular Patients Suffering From Coronavirus Disease in Wuhan, China. J Am Heart Assoc. 2020 Oct 20;9(19):e016796. doi: 10.1161/JAHA.120.016796.

8. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43. doi: 10.1001/jamainternmed.2020.0994.

9. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506. DOI: 10.1016/S0140-6736(20)30183-5.

10. Furuhashi M, Moniwa N, Mita T, Fuseya T, Ishimura S, Ohno K, et al. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. Am J Hypertens. 2015;28(1):15-21. DOI: 10.1093/ajh/hpu086.

11. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111(20):2605–10. DOI: 10.1161/CIRCULATIONAHA.104.510461.

12. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? [published correction appears in Lancet Respir Med. 2020 Jun;8(6):e54]. Lancet Respir Med. 2020;8(4):e21. doi: 10.1016/S2213-2600(20)30116-88888.

13. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-80.e8. DOI: 10.1016/j.cell.2020.02.052.

14. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol. 2020;94(7):e00127-20. DOI: 10.1128/JVI.00127-20.

15. Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. Int J Pept. 2012:256294. DOI: 10.1155/2012/256294.

16. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yet al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005;436(7047):112-6. DOI: 10.1038/nature03712.

17. Phadke M, Saunik S. Rapid response: use of angiotensin receptor blockers such as Telmisartan, Losartsan in nCoV Wuhan Corona Virus infections — novel mode of treatment. Response to the emerging novel coronavirus outbreak. Br Med J. 2020;368:m406.

18. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020;17(5):259-60. doi:10.1038/s41569-020-0360-5.

19. Ou M, Zhu J, Ji P, Li H, Zhong Z, Li B, et al. Risk factors of severe cases with COVID-19: a metaanalysis. Epidemiol Infect. 2020;148:e175. doi. org/10.1017/ S095026882000179X.

20. Zhang J, Wu J, Sun X, Xue H, Shao J, Cai W, et al. Association of hypertension with the severity and fatality of SARS-CoV-2 infection: A metaanalysis. Epidemiol Infect. 2020;148:e106:1-7. https:/ doi.org/10.1017/S095026882000117X.

21. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42. DOI: 10.1001/jama.2020.2648.

22. Krabbe KS, Pedersen M, Brunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol. 2004;39(5):687-99. DOI: 10.1016/j.exger.2004.01.009.

23. Shahid Z, Kalayanamitra R, McClafferty B, Kepko D, Ramgobin D, Patel R, et al. COVID-19 and older adults: what we know. J Am Geriatr Soc. 2020; 68(5):926-9. DOI: 10.1111/jgs.16472.

24. Barbosa IR, Galvão MH, Souza T, Gomes S, Medeiros A, Lima K. Incidência e mortalidade por COVID-19 na população idosa brasileira e sua relação com indicadores contextuais: um estudo ecológico. Rev Bras Geriatr Gerontol. 2020;23(1):e200171. http://dx.doi.org/10.1590/1981-22562020023.200171.

25. Tonet AC, Nobrega OT. Imunossenescência: a relação entre leucócitos, citocinas e doenças crônicas. Rev Bras Geriatr Gerontol. 2008;11(2):259-73.

26. Rink L, Cakman I, Kirchner H. Altered cytokine production in elderly. Mech Ageing Dev. 1998;102:199-209. DOI: 10.1016/s0047-6374(97)00153-x.

27. Guan W, Ni Z, Hu Y. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. DOI: 10.1056/NEJMoa2002032.

28. Zhang JJ, Dong X, Cao YY. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-41. DOI: 10.1111/all.14238.

29. Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, et al. Effects of ARBs and ACEIs on vírus infection, inflammatory status and clinical outcomes in COVID-19 patients with hypertension: a single center retrospective study. Hypertension. 2020;76(1):51–8. https://doi.org/10.1161/HYPERTENSIONAHA.1120.15143.

30. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020 Jun 25;58(7):1021-8. doi: 10.1515/cclm-2020-0369.

31. Barroso WKS, Rodrigues CIS, Bortolotto LA, Mota-Gomes MA, Brandão AA, Feitosa ADM, Machado CA, et al. Diretrizes Brasileiras de Hipertensão Arterial – 2020. Arq Bras Cardiol. 2021;116(3):516-658. DOI: 10.36660/abc.20201238.