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Risk Factors That Increases Covid-19 Severity

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ABSTRACT

Introduction: The relation between some risk factors and its impact on COVID 19 progression was described; as well as the effectiveness of certain vaccines.
Material and methods: Recent articles from different digital platforms were consulted for this manuscript.
Results: Several studies have shown that some of the main risk factors for COVID 19 were age, hypertension and obesity.
Conclusion: From the studies reviewed in this article, it is concluded that hypertension is one of the aggravating factors in COVID 19 disease due to ACE receptors; vitamin D and the use of different vaccines were also discussed.

KEYWORDS: COVID-19; coronavirus SARS-CoV-2; arterial hypertension; medication; vaccine; obesity, diabetes, age, risk factors.

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INTRODUCTION

The main objective of this research is to determine which risk factors may influence on the progression of COVID-19, as well as to determine if there is any difference between the effectiveness of certain vaccines in patients with Covid-19 disease. [1]

The outbreak and spread of SARS-CoV-2, the virus responsible for COVID-19, has taken the world by surprise since December 2019. Several risk factors that accelerate the progression of the clinical picture have been linked, so recognizing these factors can help detect the high-risk population and determine the best prevention strategies. Old age, chronic diseases, respiratory and cardiovascular diseases have been intensively studied and a significant association with the severity of COVID-19 was determined. Patients with obesity and diabetes are also at high risk.[2]

To date, the most common comorbidities associated with COVID-19 are hypertension (56.6%), obesity (41.7%) and diabetes (33.8%), however, there are others such as cancer (6%), cardiovascular disease (11.1%) and congestive heart failure (6.9%).[3] According to data from the 2016 National Health and Nutrition Survey (ENSANUT), in Mexico 72. 5% of the adult population over 20 years is overweight and obese; 25.5% have hypertension, of which 40% were unaware that they had this disease and only 58.7% of adults with previous Diagnosis were in adequate control (<140/90 mmHg). In addition, the previous diagnosis of this disease is usually higher in women than men (70.5 vs. 48.6%). In humans, the coronavirus causes a common cold, which can lead to lower respiratory tract infections.[4] SARS-2 has been identified as having similarities to severe acute respiratory syndrome (SARS) and Near East respiratory syndrome (MERS). So far it is known that the routes of transmission are through droplets when sneezing or coughing, and are ingested or inhaled by people close to the infected person. Another route of transmission is by touching contaminated surfaces and some studies even state that the contagion can be oral-fecal. The incubation period is 2 to 14 days, with a maximum of 28 days. The most common symptoms of this disease are fever in 98% of patients; dry cough in 76%; dyspnea, myalgia or fatigue in 44%; headache in 8%; and diarrhea in 3%.[5]

MATERIALS AND METHODS

For the following research, an extensive search for articles was carried out in various digital platforms such as The New England Journal of Medicine (NEJM), National Center of Biotechnology Information (CBI), ELSEVIER, PubMed, among others. The summary of COVID19 cases were obtained from official epidemiological sites such as INEGI, SINAVE, among others.

RESULTS

In the research work we can identify the results obtained in the various studies according to mortality depending on the group of people. A study conducted by The Journal of the American Medical Association and Centers for Disease Control and Prevention conducted in China and Japan identify an epidemiology of mortality in adults.[3] In these studies we can determine that advanced age is a common prevalence factor for presenting a more severe form of COVID-19 disease. In addition to age, underlying medical conditions have been proposed as risk factors and hypertension was found to be the most prevalent. [3]

Studies like Zhou in China and Graselli in Italy, have shown a higher prevalence in hypertensive individuals and in older adults. [1] A JAMA study in Italy states that there is more prevalence in persons with hypertension. Other comorbidities such as obesity that is accompanied by hypertension has been recognized as a risk factor with the theory that it could worsen the clinical course of COVID-19 by decreasing expiratory reserve volume, impeding diaphragm excursion and restricting ventilation. [6]

Patients with higher body mass index were 2 times more likely to require intensive care according to a study in New York .[6] Diabetes has also been observed to be accompanied by hypertension and studies reported that these comorbidities accelerate atherosclerosis, leading to cardiovascular complications and may increase the prevalence of morbidity and mortality if they contract COVID-19. [3] However, studies support that hypertensive patients with other related comorbidities such as diabetes and obesity are clearly at risk for developing a more severe form of the disease and a high mortality rate, although there is no evidence as to why this is so prevalent; however, other studies suggest that hypertension may not be an independent risk factor and may be related to other factors such as age.[7]

Some theories describe that hypertension could be an independent risk factor because it is known that the SARS-Cov-2 virus infects through the respiratory route by means of an S-peak protein, whose surface unit is coupled to angiotensin 2 as a receptor. [6] Having this in mind, the virus is required to have an angiotensin-converting enzyme 2 interaction. Thus an editorial published by Fang et al. The Lancet states that ACE2 is increased in patients treated with angiotensin-converting enzyme inhibitors and/or blocking angiotensin receptor antagonists and that this increased expression provides more potential receptors for SARS-COV-2. [8] And although discontinuation of treatment with these drugs was proposed, studies have shown that the association of hypertensive treatment with disease is related to disease severity but not to lower mortality, studies are still needed to be able to reach a universal conclusion, therefore, discontinuation of such drugs would imply the severity of the underlying disease. [3,6,9.]

COVID-19 is a current issue since it has become a pandemic, it is important to analyze the most vulnerable group of people in this situation which are people with comorbidities and older adults that throughout our research work were analyzed and the prevalence of having a more severe forms of COVID-19 and death. We can affirm that age is a risk factor for COVID-19, as for hypertension we still cannot confirm that it is an independent risk factor since morbidity and mortality is directly related to other comorbidities such as diabetes and obesity, and above all with the age of the patients since hypertension is more prevalent in older adults. It is necessary to take measures on this population, but definitely until it is proven that treatment does not directly affect hypertensive patients to suffer from COVID 19 disease in more severe forms, ACEI AND ARB should continue to be administered. [1,4,8,9.]

There is no specific treatment for COVID 19 but it is necessary to take more measures to avoid contagion in the most vulnerable persons who, according to statistics, have shown more severe forms of COVID 19 and a higher mortality rate. As well as treating the disease from the beginning, treating symptomatically, until there is no vaccine there will be contagion. The population most affected by the pandemic is those with comorbidities and those of advanced age, so it is important to focus on the most vulnerable groups.[4,10.]

In terms of vaccination campaigns, it is important that all citizens receive some of the vaccines to continue to reduce infection and mortality rates. It is important that further research be conducted to determine the appropriate vaccination schedule in order to provide earlier boosters for these special populations and, if the pandemic ends, to include them in the vaccination schedule. [1,10.]

DISCUSSION

COVID-19 belongs to the Coronaviridae family and is characterized by the presence of petal-shaped spicules or peplomeres, which protrude from the surface of the envelope and give it the appearance of a "sun crown". The peplomeres play an important role in inducing cellular immune and neutralization responses.[11]

Initially, when the pathophysiology was completely unknown, many hypotheses were put forward, including the use of modulators of the renin-angiotensin-aldosterone system (RAAS) pathway that inhibit the production and/or activity of angiotensin II, which enhances a positive regulation of angiotensin-converting enzyme 2 (ACE2) receptors and thus increases the risk of COVID-19 disease due to increased viral entry through an increase in the number of ACE2 receptors. Another hypothesis talks about the "bradykinin storm" which is responsible for some of the manifestations attributed to the cytokine storm. [11]

As is already known SARS-Cov-2 is the causative virus of Covid-19, and its mechanism by which it infects man is via the respiratory route through an S-peak protein, whose S1 surface unit is coupled to angiotensin-converting enzyme 2 as a receptor. Therefore, for infection to occur, the virus is

required to have a membrane-bound ACE 2 interaction with the respiratory epithelium.[9] In January 2020, Wan et al published a paper reporting the association between angiotensin-converting enzyme (ACE) and the pathophysiology of SARS-CoV-2. [8]

ACE 2 is part of the RAAS and its neurohormonal pathways; it has two forms: a circulating soluble form and a full form that is predominant in type II pneumocytes, the heart and blood vessels, which explains the predilection of the virus for the lung and cardiovascular system. This full form has a structural transmembrane domain that binds to the S-peak protein of SARS-CoV-2.

According to an editorial published by Fang et al. in The Lancet, based on the information given above, states that ACE 2 expression is increased in hypertensive patients treated with angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) and that this increased expression provides more potential receptors for SARS-CoV-2, these authors present a hypothesis in which hypertensive patients or other patients suffering from cardiovascular disease requiring treatment with ACEI/ARB II are at increased risk of developing severe forms of COVID-19. [8]

As the pandemic has progressed, there has been a plethora of research that has helped to identify risk factors that may aggravate the course of the disease; age has emerged as one of the main factors that may progress to a severe state of the disease. The Journal of the American Medical Association (JAMA) has recently published data on 1,625 patients who died in Italy from COVID-19, where only 14 deaths occurred under the age of 50 years; 95% of the deaths occurred in those over 60 years of age and the mortality rate increased with increasing age respectively.[6]

In addition to age, it has been suggested that a variety of underlying medical conditions are associated with the severity and mortality of COVID-19 disease. In general, the comorbidities presented by the patient are the main risk factors; such a fact is reflected in clinical practice when taking the clinical history, where hypertension was determined to be the most present in patients with Covid-19 (Table 1). [5]

CONCLUSION

Table 1. Characteristics of Coronavirus Disease

Table 1. Clinical Characteristics of the Study Patients. According to the Disease Severity and the Presence or Absence of the Primary Composite End Point.

Characteristic	All Patients (N=1099)	Disease Severity		Presence of Primary Composite End Point	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Coexisting disorder ---no (%)					
Any	261 (23.7)	194 (21.0)	67 (38.7)	39(58.2)	222 (21.5)
Chronic obstructive pulmonary disease	12 (1.1)	6 (0.6)	6 (3.5)	7 (10.4)	5 (0.5)
Diabetes	81 (7.4)	53 (5.7)	28 (16.2)	18 (26.9)	63 (6.1)
Hypertension	165(15.0)	124(13.4)	41(23.7)	24 (35.8)	141 (13.7)
Coronary heart disease	27 (2.5)	17 (1.8)	10 (5.8)	6 (9.0)	21 (2.0)
Cerebrovascular disease	15 (1.4)	11 (1.2)	4 (2.3)	4 (6.0)	11 (1.1)
Hepatitis B Infection	23 (2.1)	22 (2.4)	1 (0.6)	1 (1.5)	22 (2.1)
Cancer	10 ((0.9)	7 (0.8)	3 (1.7)	1 (1.5)	9 (0.9)
Chronic renal disease	8 (0.7)	5 (0.5)	3 (1.7)	2 (3.0)	6 (0.6)
Immunodeficiency	2 (0.2)	2 (0.2)	0	0	2 (0.2)

Again, JAMA republished data from 1,591 patients admitted to intensive care in Lombardy, Italy. The most frequent comorbidities were arterial hypertension (49%) and Cardiovascular disease (21%); while cancer (8%) and chronic obstructive pulmonary disease (4%) were the least frequent.[7]

In addition, epidemiological findings on the association between hypertension and COVID-19 have been found. Several examples reflect the above, such as the following: in the study by Zhou in China, 58 of 191 Chinese patients with COVID-19 had hypertension (30.4%, mean age 56 years); in

another study by Grasselli in Italy, 509 of 1043 Italian patients (48.8%, mean age 63 years) had hypertension. Both studies reported a high prevalence of hypertension, in addition to the fact that these patients were older, so that the mortality of older patients was higher than that of younger patients.[3]

Another study compared mild and severe cases in patients with Covid-19 to assess whether hypertension is a risk factor that aggravates the disease; it was found that of 487 patients with COVID-19 in Zhejiang Province, China, the prevalence of hypertension was higher in the 49 severe cases than in the 438 mild cases.[5,12.]

That analysis also revealed that male sex, age ≥ 50 years, and hypertension were independent factors for COVID-19 severity at admission. In another study involving 548 hospitalized patients in Wuhan, China, the prevalence of hypertension was significantly higher in patients with severe COVID-19 than in non-severe cases (38.7% vs. 22.2%). Male sex, age ≥65 years, high white blood cell count, LDH, cardiac injury, hyperglycemia were observed.[12]

For this reason, health professionals initially suggested immediate discontinuation of hypertensive treatment with ACE inhibitors or angiotensin receptor blockers (ARBs) as it was believed that they may somewhat increase the risk of more severe forms of Covid-19, in addition, these concerns were fueled by the fact that hypertension may be associated with an increased risk of death among Covid-19 patients. The downregulation of cell surface ACE2 by these pathways appears to reduce the likelihood of further virus invasion. However, it may also attenuate RAS inhibition by ACE2 in infected organs. ACE2 depletion was reported to worsen acute lung inflammation induced by acid aspiration, sepsis, or endotoxin in mice.[3] In addition, one research group reported that SARS spike protein binds to lung ACE2, exacerbating acid-induced pneumonia accompanied by an increase in angiotensin II concentration. Given the evidence that angiotensin II is a key mediator of tissue inflammation, these findings suggest that downregulation of ACE2 in response to SARS-CoV binding, and probably SARS-CoV2, may serve as a mechanism to counteract the virus. [3,6,8.]

Infection produces the systemic inflammatory response syndrome that is controlled by the cytokine storm resulting from the release of proinflammatory cytokines and chemokines by immune effector cells. Elevated levels of cytokines and chemokines have been detected which are IL1-β, IL7, IL8, IL9, IL10, FGF2, GMCSF, IFNγ, MCP1, PDGFB, TNFα among others. [13] This cytokine storm triggers a violent inflammatory immune response that contributes to ARDS, multiple organ failure and ultimately death in severe cases. [11]

Interestingly, Ziegler et al. recently reported that ACE2 is positively regulated by stimulation by interferon, an antiviral cytokine, in SARS-CoV-2 target cells, such as those in the lung, nose, and small intestine.

Given the aforementioned roles of ACE2 in the respiratory system, positive regulation of ACE2 appears to be involved in the series of interferon-induced tissue protective responses. However, SARS-CoV-2 may take advantage of this innate immune mechanism to potentiate infection, and the process would eventually lead to a decrease of ACE2 in cell surface.

Considering the presence of cytokine storm in the pathophysiology, it may also affect the cardiovascular level, causing atheroma plaque instability and promoting cardiovascular inflammation and myocardial depression, which may be implicated in myocarditis and stress-induced cardiomyopathy in patients with COVID-19. Because severe respiratory viral infection induces hypoxemia and abnormal hemodynamic changes, increased blood pressure variability may also trigger cardiovascular events in COVID-19 patients with atherosclerotic risk factors. [3,6,8.]

Whether SARS-CoV-2 infects cardiomyocytes is unknown at this time, but autopsy studies have reported detection of SARS-CoV-2 RNA in the heart. In one endomyocardial biopsy in a case of COVID-19 with cardiogenic shock revealed viral particles in interstitial macrophages, but not in cardiomyocytes. Recent reports have analyzed the effect of ACE inhibitors and ARBs on clinical outcomes in patients with COVID-19 and hypertension. A single-site, retrospective cohort study from Wuhan compared clinical outcomes between 126 COVID-19 patients with preexisting hypertension (43 of whom were taking ACE inhibitors or ARBs; 83 of whom were not taking these agents) and 125 age- and sex-matched COVID-19 control patients without hypertension. In that study, ACE inhibitors or ARBs were found not to increase the risk of morbidity or mortality in patients with SARS-CoV-2 infection. In addition, the study showed a non-significant trend toward marginally lower rates of critical illness and death in patients taking ACE inhibitors or ARBs compared with those taking other antihypertensive agents. This study concluded that ACE inhibitors or ARBs do not increase the risk of COVID-19 requiring hospital admission, including fatal cases and those admitted to the ICU, and that these agents should not be discontinued to prevent the development of severe COVID-19.[3]

In addition, a clinical study from New York revealed that none of the major classes of antihypertensive drugs, including ACE inhibitors and ARAs, were associated with a positive SARS-CoV-2 test or severity of illness.[8]

In nine studies involving 3936 patients with hypertension and COVID-19, ACE inhibitors or ARA treatment were not associated with disease severity, but were associated with lower COVID-19 mortality compared with other antihypertensive drugs. Although well-designed randomized controlled trials are needed in the future, these results suggest that treatment with ACE inhibitors or ARAs is not associated with disease severity.[8]

Vitamin D has also had an association between COVID-19 infection and its deficiency. Voltage-dependent calcium channels (VGCCs) are located on the surface of excitable

cells, and their activation causes influx of calcium ions, allowing downstream physiological effects, such as synaptic transmission and muscle activation and relaxation. Virus entry by sars-cov occurs through the interaction of VGCC and viral surface proteins. This is why depleting calcium can cause decreased viral entry.[1]

Therefore, vitamin D has an integral role in many aspects of viral pathogenesis and could play a role in the fight against SARS-CoV-2 virus, this is mainly due to the protective effect due to maintaining epithelial integrity, stimulating the production of antimicrobial peptides, reducing the inflammatory response, and modifying the ACE/ACE2 ratio by increasing ACE2 expression.[1]

SARS-CoV-2 has continued to spread dramatically with limited treatment options. There are clinical trials in which the results are not yet known. Various drugs have been used such as: Oseltamivir, which is a neuraminidase inhibitor whose efficacy is not yet clear and is recommended only in co-infection with influenza; Hydroxychloroquine is an immunomodulatory drug, effective in reducing viral replication in COVID-19, but when administered, laboratory tests should be requested to avoid anemia, thrombocytopenia or leukopenia, and electrography to avoid QT interval prolongation or bradycardia; Lopinavir/ Ritonavir, a protease inhibitor, has been proposed that could show greater suppression of viral load; Remdesivir, a nucleotide analog antiviral with activity against SARS-CoV-2, could inhibit virus infection efficiently in a human cell line, however in a clinical trial published on May 16, 2020 in Lancet, no clinical improvement, mortality or time to viral clearance was found in patients with COVID-19. Patients treated with Remdesivir within the first 10 days of symptom onset were associated with a 5-day reduction in median time to clinical improvement; and Tocilizumab, which inhibits high levels of Interleukin 6 (IL-6) protein that drive some inflammatory diseases. It is being evaluated in a clinical trial for patients with COVID-19. [1]

A large percentage of the population has the asymptomatic form of the disease, some others the mild form and a small percentage the more severe form; however, treatment and follow-up of the disease needs to be adequately established, especially for the percentage of the population with more severe forms of the disease. There is still much to be known about the disease and even more at this time due to the recent variants that have been presented as Alpha, Beta, Gamma, Delta and Omicron; being the most severe delta and omicron.[1]

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