

Findings on the Relationship between Cardiovascular Disease and Coronavirus Disease 2019: A Systematic Review

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Abstract

Coronavirus disease 2019 (COVID-19) presents as the main cause of death, respiratory and heart failures, especially in the elderly, immunosuppressed, and those with cardiovascular comorbidities. Therefore, a better understanding of these findings is needed. A systematic review was carried out looking for articles published on the MEDLINE/PubMed using the following descriptors: ("cardiovascular disease") OR ("acute myocardial infarction") OR ("coronary artery disease") OR ("acute coronary syndrome") OR ("atherosclerosis") OR ("cardiac insufficiency") OR ("pericarditis") OR ("myocarditis") AND ("COVID-19") OR ("SARS-CoV-2") and considering inclusion and exclusion criteria. Of the total number of patients included in the 10 studies selected for this review, 40% of patients infected with SARS-CoV-2 had hypertension or other cardiovascular comorbidities, while 27% presented cardiovascular complications, mainly acute cardiac injury, arrhythmia, and heart failure. The hypotheses of involvement of an intense inflammatory response, decreased immunity and greater expression of ACE2 in the heart, associated with more severe heart conditions, were discussed in this study. The increase in cardiac and inflammatory markers was associated with worse clinical outcomes and risk of death, confirming the need to evaluate them since admission to the hospital. The articles analyzed presented as a limitation the small number of patients inserted, to the detriment of the pandemic state. We warned about the need for better clinical management of patients with cardiovascular comorbidities aiming at reducing the number of fatal cases due to infection.

Keywords: Cardiovascular disease; Novel coronavirus; SARS-CoV-2

Introduction

In 2019 the first cases of a new betacoronavirus were reported, caused by the agent called SARS-CoV-2 [1]. The outbreak of Coronavirus Disease 2019 (COVID-19) started in China, more precisely in Wuhan, Hubei province, and took proportions on a global scale leading the World Health Organization (WHO), on March 11, 2020, to declare a pandemic state [2,3]. The spread of the disease has as its main characteristic the person-to-person transmission which allows its epidemiological picture to evolve daily, having as updated data on January 05, 2022, the global number of cases exceeding 290,000,000, and the number of deaths exceeding 5,500,000 [4,5]. After gene sequencing, it was verified that SARS-CoV2 shares about 79.6% of the SARS-CoV genome and, the pathogenesis mechanism of both are similar. Angiotensin-converting enzyme 2 (ACE2) is used as a receptor [6], a protein that has expression in several human organs such as intestine, kidneys, lung and, heart, making them targets susceptible to infection. In the myocardium, besides the ACE2 being strongly expressed in pericytes, the enzyme showed a higher expression in patients with heart failure, contributing to an increase in the probability of adverse prognosis in this group in the case of SARS-CoV-2 contagion [7].

The SARS-CoV-2 infection has taken different forms: asymptomatic; mild to moderate; severe; critical and lead to death [8]. It is observed that, initially, the appearance of non-specific symptoms such as fever, cough, myalgia, or fatigue is more common. Studies show that the most present comorbidities in hospitalized patients are diabetes, hypertension, and cardiovascular diseases, the latter two being more frequent in ICU (intensive care units). Moreover, heart failure and acute heart injury are the most reported complications in deceased patients [9-11]. In this review, we discuss the association between cardiovascular diseases and COVID-19 considering risk factors and main complications found in infected patients.

Methodology

The study is a systematic review of the literature in search of an

updated answer to a central and guiding question: what relationships have been found so far between cardiovascular diseases and COVID-19? The descriptors were organized using the Boolean operators "AND" and "OR" according to the sequence: (("cardiovascular disease") OR ("acute myocardial infarction")) OR ("coronary artery disease") OR ("acute coronary syndrome") OR ("atherosclerosis") OR ("cardiac insufficiency") OR ("pericarditis") OR ("myocarditis")) AND ("COVID-19") OR ("SARS-CoV-2"). The following filters were applied as inclusion criteria: full text, case reports, classical article, clinical study, clinical trial, comparative study, controlled clinical trial, journal article or multicenter study, articles published between January 2019 and May 8, 2020, research with humans, in English, MEDLINE. The exclusion criteria were: duplicate articles, reviews, Meta-analyzes, and those that presented a main theme or methodologies that did not contribute to the study proposal. So, the descriptors together with the Boolean operators were entered on the MEDLINE platform *via* PubMed, inclusion criteria were selected in the search for eligible articles and, exclusion criteria were observed by reading abstracts and full text.

Results and Discussion

10 articles were selected using the filters on the PubMed platform and by consensus between two researchers after reading the abstracts or full texts (Figure 1). Table 1 shows a brief description of the selected

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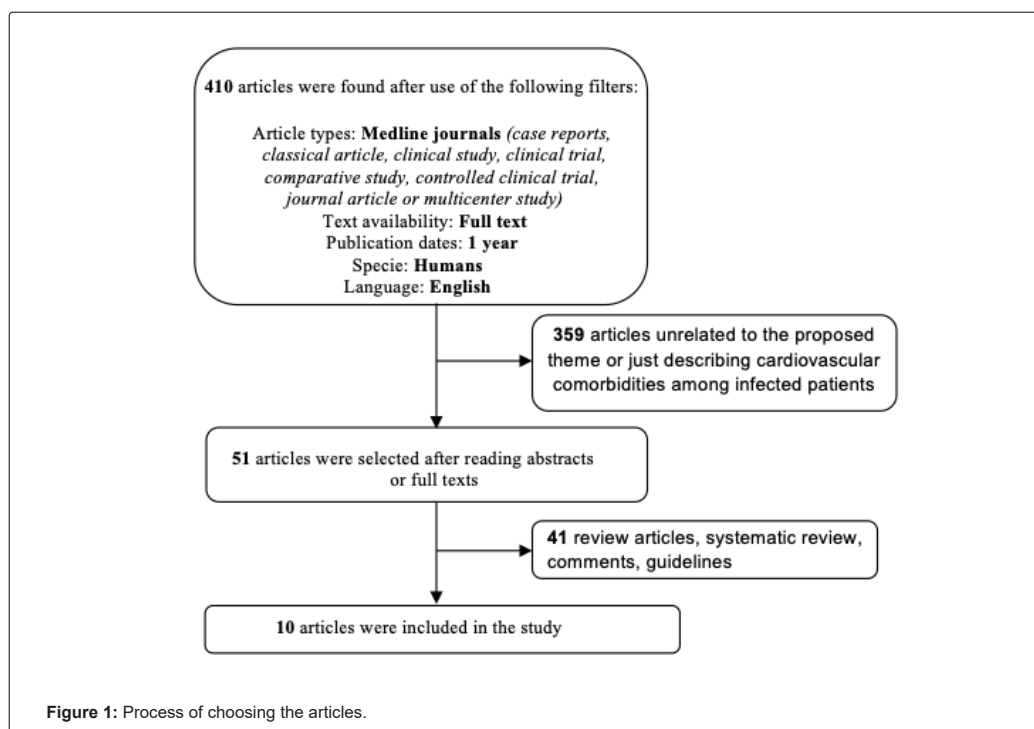
articles. A limitation that we can observe in these studies is the small number of patients inserted in the face of a pandemic. Probably, the rapid spread of the virus found the medical scientific community with insufficient tools to deal with the problem more widely. The urgent interest in understanding COVID-19 in several aspects such as comorbidities, complications, transmission, treatment, among others, has accelerated publications, including many preliminary studies. This can be monitored daily by increasing the number of publications available per day on digital platforms since the beginning of the

pandemic. Considering the 848 patients of the 10 articles included in this review, it was observed that approximately 40% of the cases presented cardiovascular comorbidities, while cardiac complications were reported in about 27% of the patients, being distributed in 17% of Acute Heart Injury and 10% of Heart Failure. In study 7, a retrospective and single-center case series of the 138 COVID-19 patients reported that 16.7% patients had arrhythmia. We also observed that the male gender was more prevalent, representing 62% of the patients.

S.No	Our numbering authors, year of publication, journal	Country	Article title	Patients included/Sex	Average ages	Main findings and conclusion related to cardiovascular diseases
1	Chen et al., 2020 [9], The Journal of Clinical Investigation	China	Clinical and immunological features of severe and moderate coronavirus disease 2019.	21/17 male	61 years (severe cases) 52 years (moderate cases)	Hypertension was comorbidity found in 36.4% of severe cases and 10% of moderate cases. 100% of severe cases (mortality of 36.4%) had acute respiratory distress syndrome and 83.3% respiratory failure. Secondary infection (27.3%), acute cardiac injury (9.1%), hypoxic encephalopathy (18.2%), acute kidney injury (18.2%), shock (9.1%), and acute liver injury (9.1%) were the least frequent findings in these cases.
2	Chen et al., 2020 [10] BMJ	China	Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study.	274/171 male	68 years (deceased patients) 51 years (recovered patients)	Hypertension and cardiovascular disease were found in 48% and 14% of severe cases and 24% and 4% of moderate cases, respectively. The most frequent complications in patients who died were: acute respiratory distress syndrome (113; 100%), type I respiratory failure (18/35; 51%), sepsis (113; 100%), acute cardiac injury (72/94 ; 77%), heart failure (41/83; 49%), alkalosis (14/35; 40%), hyperkalaemia (42; 37%), acute kidney injury (28; 25%) and hypoxic encephalopathy (23; 20%). Cardiac complications were more found in patients with cardiovascular comorbidities.
3	Huang et al., 2020 [12] Lancet	China	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.	41/30 male	49 years	Hypertension and cardiovascular disease were comorbidities found in 15% and 23% of patients in the ICU and 14% and 11% of the cases without ICU care, respectively. The main complications presented by the patients were: acute respiratory distress syndrome (29%), acute cardiac injury (12%; among this 31% of patients in the ICU and 4% of the cases without ICU care), and secondary infection (10%).
4	Su et al., 2020 [13] Emerging Microbes & Infections	China	The different clinical characteristics of corona virus disease cases between children and their families in China—the character of children with COVID-19.	9 children/ 3 male and 14 adults/ 8 male	Children: 4.5 years Adults: 42.9 years	6 children and 4 adults had no symptoms e no child needed intensive care. An increase in CK-MB occurred in 66.7% of children and only in 14.3% of adults.
5	Barton et al., 2020 [14] American Journal of Clinical Pathology	USA	COVID-19 autopsies, oklahoma, usa.	2 male	59.5 years	One of the findings in the cardiovascular system of a 77-year-old man (with obesity and history of hypertension) was an acute ischemic injury (coronary artery atherosclerosis) but without myocarditis. 42-year-old Man also was found coronary artery disease, mild and aorta intimal fatty streaking but without acute ischemic injury. Died with COVID-19, not from COVID- 19.
6	Borba et al., 2020 [15] JAMA Network Open	Brazil	Effect of high vs. low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial.	81/61 male	51.1 years	37% of patients who received low doses of chloroquine and 53.6% of those who received high doses were hypertensive. Heart disease was found in 17.9% of patients who received high doses of chloroquine and none in the other group. The QTc interval corrected by the Fridericia method (QTcF) greater than 500 milliseconds was mostly found in the group that received high doses of chloroquine and 1 patient per group had myocarditis.
7	Gao et al., 2020 [16] Respiratory Research	China	Prognostic value of NT-proBNP in patients with severe COVID-19.	54/24 male	60.4 years	Plasma NT-proBNP was positively correlated with age, urea, cardiac injury markers, and inflammation markers. NT-proBNP may be an independent risk factor for in-hospital death in critically ill patients with COVID-19. But also a history of hypertension (HP), myoglobin (MYO), creatine kinase-MB (CK-MB), and high-sensitivity troponin-I (HS-Tnl) were correlated with the risk of in hospital death.

8	Zhou et al., 2020 [11] Lancet	China	Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.	191/119 male	56 years	Hypertension and coronary heart disease were found in 48% and 24% of non-survivors and 23% and 1% of survivors, respectively. Cardiac failure and acute cardiac injury occurred in 52% and 59% of non-survivors and 12% and 1% of survivors, respectively. 70% of those who died had septic shock and this did not occur in any survivors.
9	Wang et al., 2020 [17] Critical care	China	Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China.	107 / 57 male	51 years	Hypertension and cardiovascular disease were found in 52.6% and 36.8% of non-survivors and 18.2% and 6.8% of survivors, respectively. The acute cardiac injury occurred in 42.1% of patients who did not survive and in 4.5% of those who survived. Age and male gender were independent risk factors for death
10	Korean Society of Infectious Diseases and Korea Centers for Disease Control and Prevention. 2020 [18] Journal of Korean Medical Science	Korea	Analysis on 54 Mortality Cases of Coronavirus Disease 2019 in the Republic of Korea from January 19 to March 10, 2020.	54/33 male	75.5 years	Cardiovascular disease was the most common comorbidity found among patients, 58% of those over the age of 70, and 50% of the others. There was no significant difference in symptom duration between patients with comorbidities and those who did not. The highest number of fatal cases was in patients over 70 year: age.

Table 1: Description of selected articles.



Cardiovascular comorbidities and worse prognosis in COVID-19

The findings from studies 1, 2, 3, 6, 7, 8, and 9 in Table 1 shows clinical outcomes (transfer to the ICU, respiratory and cardiac complications, for example, and death) in patients with COVID-19 and history of hypertension or another cardiovascular disease. Considering the studies that presented data, which enabled a joint assessment (comorbidities and cardiovascular complications compared between groups of patients with the better and worse clinical outcome), it can be noted that heart failure, acute cardiac injury, and elevation of the QTcF interval on the electrocardiogram of patients tend to be directly proportional to the presence of cardiovascular comorbidities (Figure 2) [9-12,15,17,19]. These findings reinforce the inclusion of patients with such comorbidities in the risk group for SARS-CoV2 infection.

In study 7 (Table 1), the group of patients who presented NT-proBNP > 88.64 pg/mL had a higher percentage of cardiovascular comorbidities and elevations in other markers of cardiac injury (myoglobin, CKMB, and Hs-TnI). Mortality in this group was 60%, while in the group of patients with NT-proBNP < 88.64 pg/mL there was no death. Although NT-proBNP was related to cardiac injury, it was also an independent factor for the risk of in-hospital death, as well as other markers of cardiac injury and hypertension. A more recent study also revealed higher levels of NT-proBNP in patients with cardiovascular comorbidity infected with COVID-19 [20]. It is known that high concentrations of cTnI, NT-proBNP and other cardiac biomarkers such as CK-MB and MYO are associated with a higher mortality rate in patients with COVID-19. Among the complications that lead to death, acute myocarditis, acute myocardial infarction and rapid-onset heart failure have higher mortality among those infected with COVID-19 [21].

In study 10 (Table 1), it is observed that among the fatal cases analyzed, the percentage of cardiovascular comorbidities (hypertension and other heart diseases such as myocardial infarction) was 8% more in the group of people over 70 years of age and the increase in mortality was mainly related to males in this age group. However, the main symptoms, biochemical tests, and complications that led patients to death were not detailed.

The ACE2 is an aminopeptidase bound to the cell membrane that is involved in cardiac function and the development of hypertension. This enzyme also functions as a receptor for entry into the cell for both SARS-CoV and SARS-CoV-2 [2]. The expression of ACE2 in human cardiac tissues was evaluated and it was noted that those obtained from patients with muscle heart disease showed greater expression of the enzyme, indicating in this group of patients a greater vulnerability to SARS-CoV-2 infection, which may develop lesions, more severe cardiac conditions, and contribute to a worse prognosis [7]. However, it is still unclear in the literature whether hypertensive patients with COVID-19 and treatment with an ACE inhibitor or angiotensin receptor blocker can contribute to an increase in ACE2 and consequently lead to an increased risk of infection in the myocardium by SARS-CoV-2 [2]. Despite that, it has been recommended that these patients should continue treatment unless a change in therapy is made on medical advice [22].

New studies show that ACE inhibitors (ACE) and angiotensin receptor blockers (ARB) increase the number of ACE2 receptors on the myocardial surface. However, lower rates of severe COVID-19 and lower levels of interleukin-6 (IL-6) in addition to a decreased viral load were observed in patients using ACE inhibitors and ARBs [23]. In addition, the study by Rossi et al., states that patients with hypertension who use ACE inhibitors and ARBs were not associated with mortality from COVID-19. This underpins the recommendations of not discontinuing or replacing treatment because of COVID-19 [24].

Another point to be considered is that hypertensive patients have high levels of plasminogen, which increases the ability of many viruses to bind to ACE2. The envelope proteins in SARS-CoV-2 are cleaved by furin-like intracellular proteases and this increases the ability of viruses to enter host cells. A type of non-furin cleavage can be exerted by plasmin, generated through plasminogen cleavage. However, despite the participation of plasmin in the entry of various viruses into cells, further *in vivo* studies are needed to prove this participation concerning SARS-CoV-2 [25].

Cardiac markers and prognosis

The studies from 1 to 4, 6 to 9 of Table 1 presented laboratory findings, among which some markers stand out, such as hypersensitive cardiac troponin I (hs-cTnI); Creatine Kinase MB (CK-MB); Creatine Kinase (CK); B-type Natriuretic Peptide (NT-proBNP); Lactate Dehydrogenase (LDH); High Sensitivity Reactive C Protein (hsCRP) and Myoglobin (MYO). It is observed that these markers were higher in the group of patients who presented more severe cases or who died as a result of infection, than in groups of moderate or recovered cases, thus showing the correlation of the high level of these markers with poor prognosis. It is also observed that cardiac markers had higher levels in elderly patients [16].

It is worth noting that advanced age is associated with the risk of death of patients infected by SARS-CoV-2, and in this age group, among the main comorbidities are hypertension and coronary heart disease [11]. Age-related dysfunctions also reverberate in the T-cell function, making it difficult to recognize new antigens and making the elderly more susceptible to infections. Additionally, an increase in the expression of pro-inflammatory cytokines is also observed in this group [26]. Both contribute negatively to the control of the replication of the coronavirus, besides prolonging the inflammatory response that demonstrates to be one of the main causes of the severity of COVID-19, that is, the cytokine storm is part of the pathological process of infection [9,11].

More recent studies agree with the findings described above, as increasing age continues to be observed as a major risk factor for severity in COVID-19. Although severe manifestations of COVID-19 have been reported in all age groups, about 90% of severely ill COVID-19 patients are over 30 years of age. In addition, high rates of comorbidity and mortality are consistently observed in older populations throughout the pandemic [27]. Elderly people have a disproportionate number of severe cases and deaths, with patients aged 75-84 having a 220-fold increased risk of mortality compared to young people aged 18-29. This is linked to the fact that older patients tend to have a dysregulated immune response, in addition to a higher frequency of comorbidities, facilitating viral spread and disease severity [28].

The studies 2 and 7 (Table 1) demonstrate that the levels of inflammatory markers such as hsCRP and Procalcitonin (PCT) are higher in critically ill or deceased patients compared to the group of recovered patients, as well as markers of cardiac injury-hs-cTnI, NT-proBNP, MYO, and CK-MB are also there. These findings indicate a possible association between inflammation and cardiac injury in COVID-19. Linked to this, as patients with cardiac comorbidities present a greater expression of ACE2 [7], this may favor the mechanism of direct injury to the cardiac tissue, caused by the toxicity induced by the virus [29].

Direct myocardial injury *via* SARS-CoV-2 and ACE2 interaction remains a possibility [30]. Direct endothelial infection was documented in autopsies of hearts. Furthermore, viral particles have been identified in endothelial cells of these hearts by electron microscopy, although the appearance and location of these particles within the cells do not appear to be typical of coronavirus-infected cells [31]. The tropism of the virus by the ACE2 enzyme can potentially mediate direct cardiac injury, however, further investigations are needed [32].

In studies 7 and 9 (Table 1), the cardiac markers hs-cTnI, CK-MB, MYO, LDH, and NT-proBNP were associated with mortality. Already in study 8 (Table 1) an association was also found between changes in hs-cTnI levels and the risk of death, with a rapid increase in its concentration after the 16th day of the disease being observed in deceased patients, as well as being present in more than half of them. The trials with hs-cTnI are effective in the diagnosis of Acute Coronary Syndrome (ACS), and its use allows a more precise report in the indication of myocardial injury. However, despite the alteration of the levels of this enzyme to predict suspicion of ACS, it was observed in patients with COVID-19 without heart symptoms, even though its elevation is more common after the onset of symptoms [33]. This raises the possibility of secondary

cardiac injury related to an increase in oxygen demand caused by sepsis in subclinical coronary artery disease. Sepsis would lead to ischemia resulting in type 2 acute myocardial infarction [34]. This sequence of events may contribute to the elucidation of the findings of study 3 (Table 1), which included 113 patients who died as a result of the COVID-19, among which 100% had sepsis and 49% had heart failure. The same study points to higher levels of hs-cTnI, NT-proBNP, and LDH in deceased patients compared to survivors. In study 9 (Table 1), the values of these markers, including the CKMB, were also higher at the admission of non-survivors.

Interestingly, study 4 (Table 1) found changes in the concentration of CK-MB in 66.7% of children and 14.3% of adults. None of the children required intensive treatment or presented serious complications, although the increase in CKMB indicates cardiac injury. This finding can be explained by the fact that the ACE2 enzyme is less expressed in children, which can lead to a milder course of the disease. Myocardium seems to be a target of infection also in children [35,36].

New updates point to an association of SARS-CoV-2 with cases of multisystem inflammatory syndrome in children (MIS-C). Early reports during the early phase of the COVID-19 pandemic indicated that children were relatively spared from severe manifestations, with the low incidence of 2 to 6% having severe COVID-19. However, numerous reports of severe systemic hyperinflammation linked to COVID-19 cases led the WHO, in conjunction with other societies, to identify the cases as a new condition called multisystem inflammatory syndrome in children (MIS-C). Currently, it is known that cardiac involvement is highly present in patients with MIS-C, and that this syndrome is directly linked to cases of COVID-19 infection [37]. Inflammatory markers such as IL-6 and cardiac markers such as NT-proBNP and troponin are present at high levels in patients with MIS-C [38]. Cardiovascular manifestations include ventricular dysfunction, coronary artery dilation and arrhythmias [37]. Most of these patients recover successfully and show good rates of improvement in myocardial dysfunction, but the underlying mechanism of myocardial dysfunction in MIS-C is still not fully understood [38].

In study 7 (Table 1) the NT-proBNP was an independent factor of risk of death in severe cases of infection, although it correlates with the other markers of acute myocardial injury and inflammatory markers. The elevation of cardiac markers seems to represent an adverse prognosis for the SARS-CoV2 patient, evidencing the need for their laboratory request since the patient's admission, aiming at the most appropriate clinical management.

Cardiac complications in COVID-19

After an average incubation period of approximately 4 to 5 days, the symptoms begin to appear, and COVID-19 tends to last for two weeks with worsening in the second week due to the inflammatory response that follows the virus's replication period. In this short time, the most severe complications of the disease can happen [39]. Acute cardiac injury and heart failure were the main cardiovascular complications found in patients infected with SARS-CoV-2 among studies selected for this review (Figure 2). In addition to the involvement of ACE2, which possibly can contribute to increasing the risk of cardiac complications in COVID-19, especially in the presence of cardiovascular comorbidities, as previously described, other hypotheses have been discussed, such as those mentioned by Adão and Guzik [40]. The highlight was given to inflammatory cytokines and hypoxia generated by the impairment of the respiratory system in COVID-19.

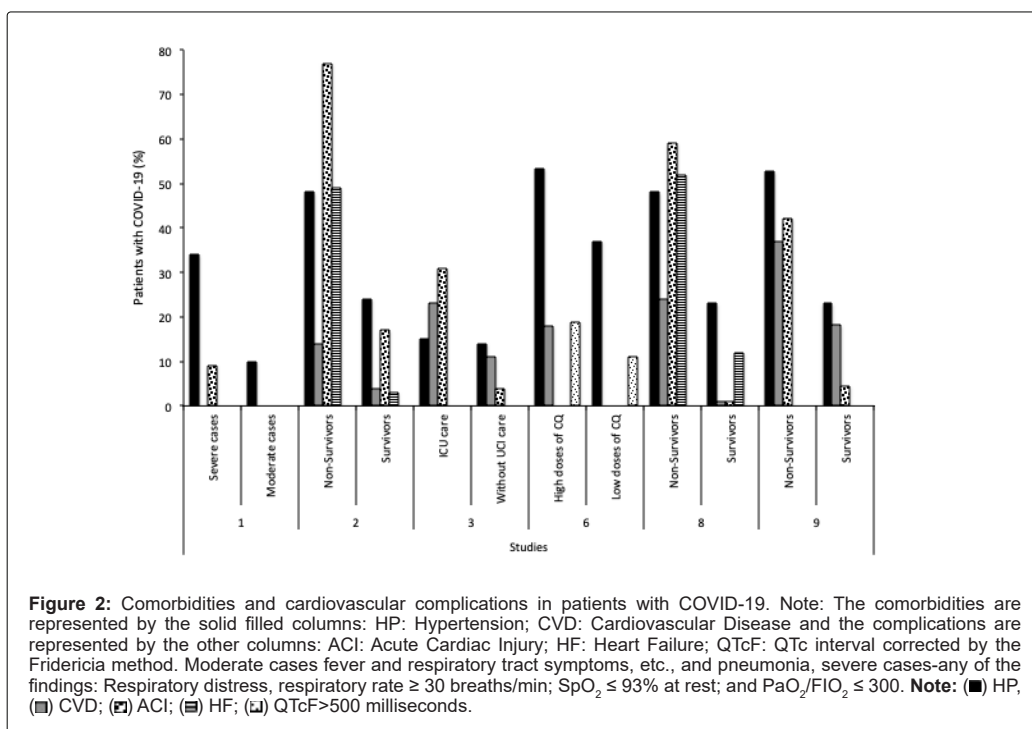
The rapid replication of the virus can cause massive death of epithelial and endothelial cells, and vascular leakage, triggering the

exuberant production of pro-inflammatory cytokines and chemokines [41]. In studies 1, 2, 7 and 8 (Table 1), higher levels of inflammatory markers were found (IL-6, IL-10, and TNF- α ; IL-6, IL-18, IL-10, IL-2, and TNF- α receptors; PCR; ferritin, and IL-6, respectively) in the group of patients with more severe cases of the disease. TNF- α , IL-1, IL-6, IL-8, IL-12, IL-18, and interferon-gamma (IFN γ) are pro-inflammatory cytokines, which act as mediators of the immune system. Anti-inflammatory cytokines, such as interleukins 4, 5, 10, 11, and 13, are also produced and the regulation of this balance is complex. The pro-inflammatory cytokines effectively initiate the inflammatory process against infectious agents. TNF- α , IL-1, IL-6 are responsible for raising protein levels in the acute inflammatory phase, which includes C-reactive protein (CRP) during infection [42,43].

When a set of cytokines is considered, the predictive value for cardiac complications increases, since it is known that cytokines work together leading to a complex inflammatory response [44]. IL-6 participates in the activation of T lymphocytes and the cytotoxicity of these cells leads to an intense inflammatory response that can damage the heart muscle [45]. The T-lymphocytes present a cardiotropism by an interaction between the heart-produced hepatocyte growth factor (HGF) and c-Met, the HGF receptor on naïve T-cells [46]. Also, clinical trials showed that both TNF- α and IL-1 are associated with impaired systolic and diastolic function and, also leading to adverse cardiac remodeling and decreased contractility of the heart muscle due to a reduction in oxygen consumption of the respiratory chain [47-50]. The 77-year-old man (with obesity and a history of hypertension) in study 5 (Table 1) had an acute ischemic injury (coronary artery atherosclerosis), but no evidence of myocarditis was found. So, in patients in whom heart failure is caused by inflammatory mechanisms, there is an expectation that well-targeted anti-inflammatory therapies can be used to obtain a better clinical outcome for patients [51].

One of the therapeutic options being analyzed for COVID-19 are chloroquine (CQ) and hydroxychloroquine (HCQ), antimalarial drugs and also used in treating some chronic rheumatic conditions due to immunomodulatory properties, for example, the inhibition of the production of proinflammatory cytokines such as IL-1, IL-6 and TNF- α [52-54]. Although CQ has antiviral properties tested *in vitro*, it has not always been confirmed during the treatment of patients with viral infections and the mechanisms of action of this drug may vary according to the pathogen. Among these mechanisms stand out the alkalization of endosomes affecting the proper maturation of the viral protein and the recognition of the viral antigen by dendritic cells. This recognition occurs through a pathway that involves the Toll-like receptor that requires endosomal acidification. And finally, QC showed an anti-SARS-CoV-1 effect *in vitro*, decreasing the glycosylation of ACE2 [54,55].

In study 6 (Figure 2), which included patients in severe COVID-19, was observed that the group of patients who received higher doses of QC had a higher percentage of acute cardiac injury, but it should be considered that this group also presented a higher percentage of cardiovascular comorbidities and a higher mean age. Added to this, the group that received high doses of QC (i.e., 600 mg twice daily for 10 days) presented more instance of QTc interval greater than 500 milliseconds compared with the low-dosage group (i.e., 450 mg twice daily on day 1 and once daily for 4 days). Therefore, suggesting that the QC should be administered with caution, especially in severe cases of the infection. At doses beyond the safety margin, chloroquine can show pro-arrhythmic activity mainly because of its ability to inhibit the cardiac potassium current from the internal rectifier and, consequently, induce lethal ventricular arrhythmias [56].



Recent randomized evidence regarding the use of hydroxychloroquine for post-exposure prophylaxis and among hospitalized patients reveals no significant benefits. In 2020, in the United States, more than 890,000 chloroquine and hydroxychloroquine prescriptions were made for the prevention, post-exposure prophylaxis and treatment of COVID-19. In 2021 there were more than 560 thousand prescriptions. This was due to the fact that biological mechanisms support the inhibition of the virus that causes COVID-19. Some case series without comparison groups and observational groups reported possible benefits of use. However, randomized trials published in high quality peer-reviewed journals have shown disappointing results regarding the positive effects of administering these drugs in patients with COVID-19 [57].

A randomized, double-blind, placebo-controlled trial that included 821 subjects tested hydroxychloroquine for post-exposure prophylaxis. The study concluded that after moderate or highrisk exposure to COVID-19, HQ did not prevent COVID-19-compatible disease or confirmed infection when the drug was used as prophylaxis within 4 days of exposure. This study also reported that collateral effects were more common in those taking the drug than those taking placebo [58]. Another randomized clinical trial also tested the prophylactic effects of HQ. It included 2,314 individuals, of which 1,116 were randomly assigned to receive HQ and 1,198 to receive usual care. The study presented a similar conclusion: Post-exposure therapy of healthy people to a PCR positive patient with HQ did not predict symptomatic SARS-CoV-2 or COVID-19 infection [59].

Regarding the care of hospitalized patients, a randomized study of 4,716 patients concluded that those who received HQ had no lower incidence of death than those who received usual care. This study also showed that those in the HQ group had a higher frequency of invasive mechanical ventilation or death. It also showed that there was no difference in the incidence of new cardiac arrhythmias among patients who received hydroxychloroquine [59]. On March 28, 2020, the US Food and Drug Administration (FDA) issued an emergency use authorization for HQ on COVID-19. Since then, no significant benefit has been seen in the randomized evidence, either for post-exposure

prophylaxis or for patients hospitalized with COVID-19. Current evidence points to the lack of efficacy and possible harm of HQ in the treatment and prevention of COVID-19 [57].

Conclusion

The presence of cardiovascular comorbidity points to an increased risk of complications in COVID-19, such as heart failure and acute cardiac injury. Besides, higher levels of inflammatory and cardiac markers were associated with a worse prognosis of infected patients. These findings seem to support the hypothesis that the probable higher expression of ACE2 in the heart of patients with such comorbidities allows greater entry of the virus into the cell, an intense inflammatory response that leads to decreased oxygen consumption and less contractibility. However, it is important to note that the studies discussed in this systematic review, included a small number of infected patients, considering a pandemic. These studies reinforce the need for attention to the group of cardiac patients, both for better clinical management and for new studies due to the poor prognosis that the infection promotes to these patients.

Acknowledgment

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