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Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Vicious Circle

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Abstract

Over the last two decades we have witnessed major epidemics of severe acute respiratory infections that pose a serious threat to global health, with high morbidity and mortality rates. The more widespread and faster human mobility by modern transports, allowing quick international connections, has contributed to the fast spread of epidemics, leading, as in the case of Coronavirus Disease 2019 (COVID-19), to a pandemic state in a short time. The first literature data show a high COVID-19 infectivity, with a marked respiratory tropism, and a mortality rate ranging between 2 and 8% in different countries, in relation to people affected different mean age and comorbidity. In fact, in COVID-19 patients a close association between mortality, age and comorbidity has been demonstrated. Pre-existing cardiovascular diseases are widely represented in these patients and are associated with a poorer prognosis. Moreover, this virus has also shown a specific tropism towards the cardiovascular system, showing itself responsible for a series of severe acute and chronic diseases. Because of the frequent association with cardiovascular diseases, it is important to keep in mind the principal pharmacological interactions between cardiovascular drugs and those commonly used for the treatment of COVID-19 patients. Finally, given the complexity of these patients and their comorbidities, it seems essential to propose the establishment of a multi-specialist COVID-Team.

Keywords

COVID-19; Myocardial injury; Cardiovascular complications; Cardiovascular therapy; Pandemic.

Introduction

Over the past two decades, epidemics of acute respiratory coronavirus infections have represented a serious threat to global health, with significant morbidity and mortality rates. Six species of coronavirus are known to cause human disease: four viruses (229E, OC43, NL63 and HKU1) are prevalent and typically cause common cold symptoms in immuno-

competent individuals [1,2]. The other two strains, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) are of zoonotic origin and have been linked to sometimes fatal diseases [3,4]. Given the ubiquitous distribution and high prevalence of coronaviruses, the frequent recombination of their genomes, as well as the increased human-animal interface, new coronaviruses are likely to emerge periodically in humans due to frequent cross-infection and occasional relapse events [1,6,7]. In December 2019, some cases of pneumonia caused by a new coronavirus, called Coronavirus Disease 2019 (COVID-19) or Wuhan coronavirus, based on the name of the city where the first viral outbreak occurred, have started to be reported [2,5,8]. The COVID-19 causes a subclinical or mild degree disease in 85% of cases, but compared to common influenza viruses it promotes more frequent respiratory complications such as severe interstitial pneumonia, evident in 10-15% of cases. About 5% of infected patients require hospitalization in intensive care and the mortality rate is estimated at 2-3%. Compared to previous coronavirus outbreaks, the contagiousness is higher, but the mortality rate is much lower compared to the severe acute respiratory syndrome (SARS-CoV) of 2002 and the Middle East respiratory syndrome (MERS-CoV) of 2012, which showed a mortality rate of 10% and 37%, respectively [9-11]. Since January 2020, COVID-19 has gradually spread to Europe and then America and the World Health Organization (WHO) has declared a pandemic status. In Europe the number of cases and the mortality rate is progressively and rapidly exceeding the data recorded in China [12-14]. In Italy, the main country involved in Europe, the mortality rate was higher than in other countries, with values that in mid-March reached about 8% of infected patients. The main reason for this high prevalence is that Italy is the second oldest nation in the world. In fact, likewise to other pathological conditions common in elderly patients, mortality rate of COVID-19 is directly related to patients' age, frailty and comorbidities [15,16] (Figure 1 and 2).

Figure 1: Age-related mortality rate in COVID-19 patients.

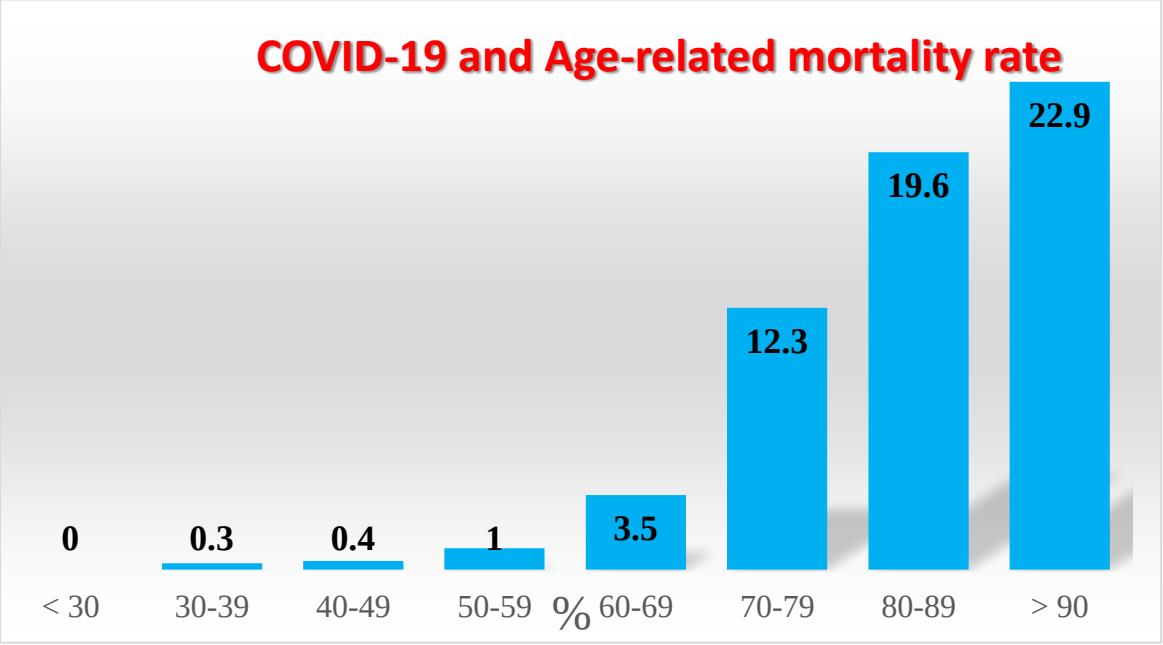

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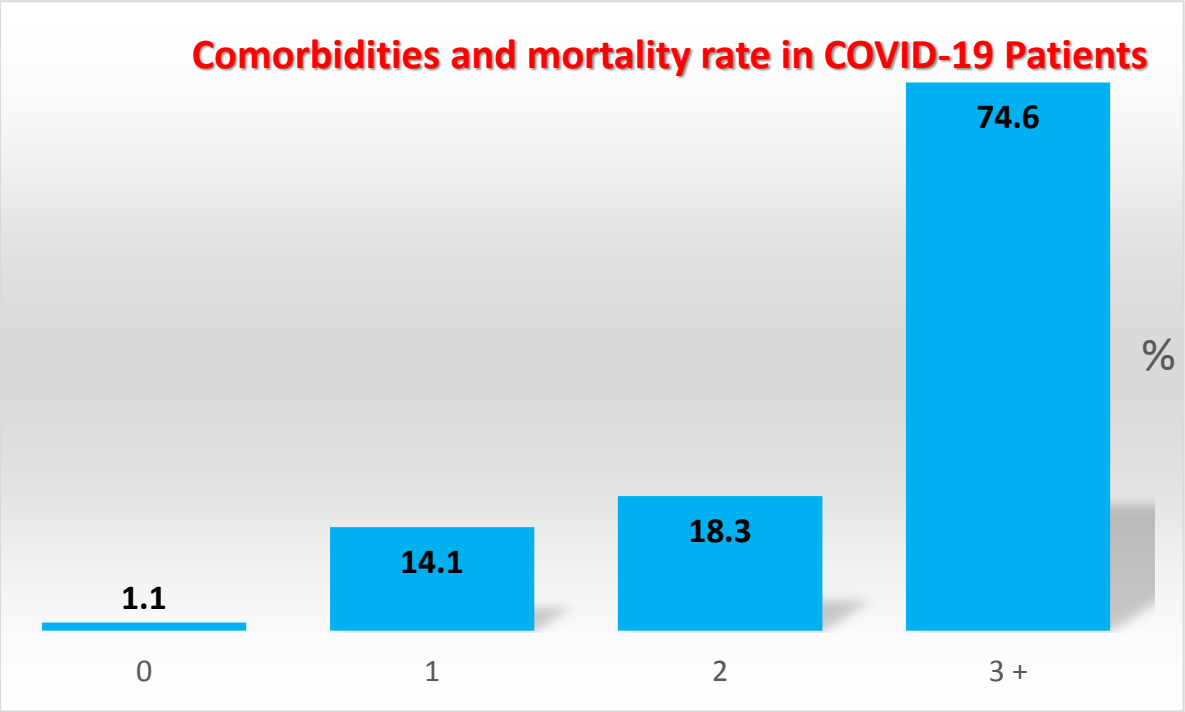
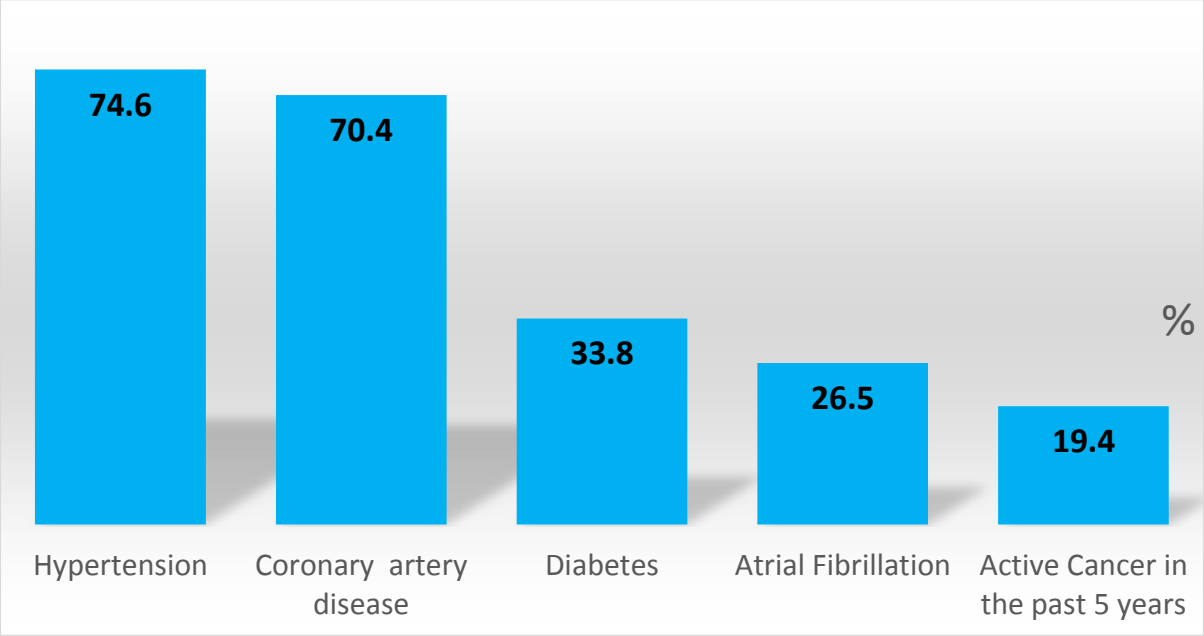
Figure 2: Role of comorbidities in influencing COVID-19 patient's outcome.



The COVID-19 infection is not only of pneumological and internistic interest, but must also see cardiologists in the front row. Indeed the cardiac implications of COVID-19 are far from marginal and provide an opportunity for draw the cardiologist's attention to the relevant interactions between respiratory virus infections and cardiovascular risk. The correlation between influenza virus infection and myocardial infarction has long been known, as well as the incidence of myocarditis, often undiagnosed, and the association with the onset of left ventricular dysfunction [17,18] Similarly, it is worth remembering the protective role of flu vaccination against acute coronary syndrome and heart failure. Despite this evidence, little attention has unfortunately been paid so far to the cardiovascular burden of influenza pandemics and other respiratory viruses [19]. In patients with pneumonia from COVID-19 a first report of 99 patients admitted to Jinyntan Hospital in Wuhan, China in January 2020, showed that 40% of the cases had a pre-existing cardiovascular or cerebrovascular disease [20]. Subsequent reports of COVID-19 patients with pneumonia showed a significantly higher prevalence of comorbid dities such as diabetes, cardiovascular and cerebrovascular disease (Fig. 3) highlighting that 15-25% of patients needed treatment in intensive care [21,22].

In addition, a higher incidence of cardiovascular disease was noted among these patients, with 16.7% developing arrhythmic complications and 7% acute myocardial injury [21,22]. A subsequent larger report of 1099 patients with COVID-19 infection confirmed these data [23], underlining that the presence of concomitant diseases, such as hypertension, diabetes, ischemic heart disease and cerebrovascular disease, was more common in the subgroup of patients with a more severe form of the disease (38.7% vs 21.0%).

Figure 3: Prevalence of cardiovascular comorbidities in COVID-19 patients.



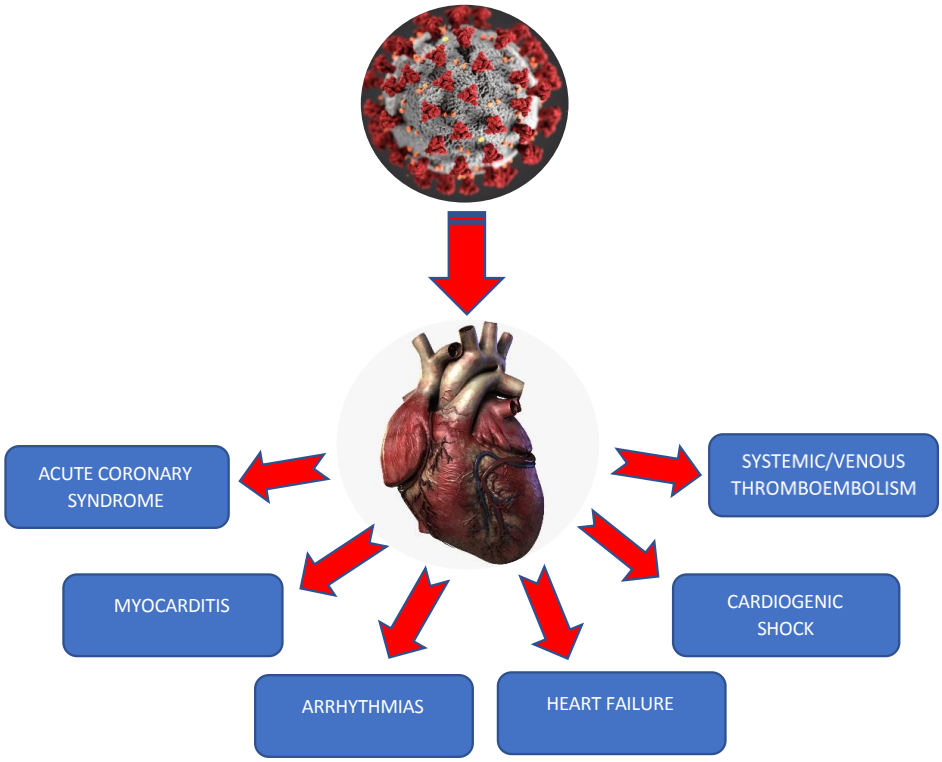
In addition, the presence of comorbidity has been shown to be associated with significantly different mortality rates: in fact, data provided by the Chinese Center for Disease Control and Prevention for 72314 cases showed that, compared to an overall mortality of 2.3%, this was 10.5% in patients with pre-existing cardiovascular disease and 7.3% in those with diabetes. Similar results, unfortunately on larger samples, are being highlighted in Europe and chiefly in Italy, the most affected country [22,24]

Cardiovascular complications in COVID-19 patients

Beyond the acquired association between pre-existing cardiovascular diseases and the severity of respiratory infections with negative outcome for patients, attention should be focused on cardiovascular complications directly associated with COVID-19 [Figure: 4].

Very often in COVID-19 patients, especially in severe forms evolving into ARDS, cardiac injury appears with increased troponin values [25,26], not necessarily associated with an acute coronary syndrome, since it can also be related to non-ischemic forms such as myocarditis [26,27]. A meta-analysis of 4 studies, involving 341 COVID-19 patients, showed that cardiac troponin I values were significantly higher in patients with more severe expression of the disease [26], acquiring a negative prognostic significance even more evident when associated with electrocardiographic and echocardiographic alterations. Cohort studies of hospitalized patients in China estimate that cardiac injury occurs in 7-17% of patients hospitalized with the disease [5,21,28] and is significantly more common in patients admitted to intensive care (22,2% vs. 2,0%, $p < 0,001$) and among those who died (59% vs. 1%, $p < 0,0001$) [28,29].The association between viral pathologies and acute coronary syndromes has been known in the literature for years now [28].

Figure 4: Cardiovascular diseases promoted by COVID-19.



The instabilization of a pre-existing coronary plaque, mediated by the systemic inflammatory process with consequent rupture of the fibrous cap, exposure of thrombogenic material and thrombotic occlusion of the vessel, represents the most probable pathogenetic hypothesis. The inflammatory state contributes to this sequence of events through several determinants, such as the release of inflammatory cytokines, sympathetic hyperactivation, increased free radicals and wall stress, tachycardia, hypoxia and finally a state of increased thrombophilia [30]. In this regard, a recent study has shown that patients with acute respiratory infections are at higher risk of developing an acute myocardial infarction both after influenza (HR = 6.1) and after not influenza viral diseases, including the other species of coronavirus previously mentioned (HR 2.8) [31]. Initial literature data from COVID-19 patients with STEMI suggest that this clinical scenario is highly likely [32]. The role of myocarditis in COVID-19 patients should not be underestimated. Previous studies on other coronavirus species (MERS-CoV) have demonstrated a high prevalence of acute myocarditis using cardiac MRI [33]. In a recent study of 150 patients with COVID-19, myocarditis was shown to be the direct cause of death in 7% of cases, representing a contributing cause in 33% of cases [34]. Several reports described cases of fulminant myocarditis with histological evidence of high inflammatory mononuclear infiltration into myocardial tissue [35-37].

Pericardial involvement has not yet been reported, but further studies are needed. Virus induced cardiac injury can promote a scenario of heart failure in these patients. In fact, a recent study showed a 23.0% incidence of heart failure in COVID-19 patients [28], which was frankly higher in patients with a worse prognosis (51.9% vs. 11.7%). It is unclear whether heart failure is more commonly due to exacerbation of a pre-existing left ventricular dysfunction than a new cardiomyopathy due to myocarditis or stress cardiomyopathy [38]. Right heart failure and subsequent pulmonary hypertension should always be considered, particularly in the context of severe parenchymal lung disease and ARDS. In fact, it is essential to determine whether or not a concomitant cardiogenic component is present when considering the appropriateness of using mechanical respiratory and circulatory support with extracorporeal membrane oxygenation (ECMO) or other techniques, as this may result in changes in device selection, although the limited literature data demonstrate the poor efficacy of these devices in such patients, given that about 83% of COVID-19 patients, although treated with ECMO, fail to survive [39]. Cardiac arrhythmias are another common cardiovascular manifestation described in COVID-19 patients, related to hypoxia, neuro-hormonal stress, cytokine release and metabolic disorders. In patients hospitalized with COVID-19, cardiac arrhythmia was observed in 16.7% and was more common in intensive care patients (44.4% vs. 6.9%) [21]. A new onset of malignant tachyarrhythmias associated with an elevation of troponin values should raise suspicion for underlying myocarditis [40]. In these patients, moreover, we should not forget that changes in inflammatory parameters expose them to a presumably increased risk of systemic and venous thromboembolism (VTE). Although at present there are no extensive scientific data on this subject, an alteration of coagulation parameters has been noted in hospitalized patients with severe COVID-19 disease [41,42]. In a retrospective multicenter cohort study from China, high levels of D-dimer (> 1g/L) were strongly associated with hospital death (OR 18.4; p=0.003) (28).In another study comparing COVID-19 survivors with non survivors, the latter showed significantly higher levels of D-dimer and fibrin degradation products (FDP) and 71.4% of these met the clinical criteria for disseminated intravascular coagulation (DIC) during their disease [42]. In addition to DIC, severely ill patients with prolonged immobilization are at high risk of VTE. The optimal thromboprophylactic regimen for patients with COVID-19 related disease is not known. Therefore, current strategies approved by the guidelines should be observed [43]. Pharmacological interactions between some antiviral treatments and direct oral anticoagulants mean that low molecular weight heparins or unfractionated heparin are likely to be preferred in these patients.

Drug interactions in COVID-19 patients

Given the use, in part experimental, of the drugs used in COVID-19 patients, it is advisable to have a unique tool in which to quickly see the main known interactions [Table 1], whose specifications may or not be confirmed in the coming months, in the light of data that will emerge during this period [44-53]. ACE-I (Angiotensin Converting Enzyme Inhibitors) and ARBs (Angiotensin Receptors Blockers) deserve a separate evaluation. The angiotensin

conversion enzyme receptors 2 (ACE2) are the entry point into human cells for the COVID-19 virus [17,54,55]. In some experimental studies with animal models, both angiotensin conversion enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to upregulate the expression of ACE2 in the heart [56,57], leading to speculation about a potential increased risk of severe COVID-19 infection in patients treated with these drugs. It is important to note that these data have never been demonstrated in humans [58]. On the contrary, other studies seem to show, in patients with viral pneumonia, a pulmonary protective action of both ACEi and ARBs [59-61], leading to speculation about a protective action also in COVID-19 patients. Therefore, in the absence of clear, non-speculative data, the International Cardiological Scientific Societies have all agreed that ACEI or ARBs therapy should be continued, even in COVID-19 patients [62,63].

Table 1: Drugs used in COVID-19 patients: potential cardiovascular interactions and adverse effects

Drug	**Mechanism of action**	**CV drugs interaction**	**Mode of interaction**	**CV adverse effects**
Antiviral Drugs				
Lopinavir/ Ritonavir	Ritonavir inhibits CYP3A increasing levels of lopinavir which is a protease inhibitor	Antiarrhythimics Anticoagulants Antiplatelets statins	CYP3A4 inhibition: Apixaban should be administered at 50% of dose while Rivaroxaban should be avoided; Dabigatran and warfin can be administered with D1caution. Do not use clopidogrel (reduced effect) and ticagrelor (Increased effect). Prasugrel can be used. Atorvastatin should be used to maximum dose 20mg/day Lovastatin and Simvastatin should be avoided - OATTP1B1 and BCRP inhibition: Rosuvastatin can be used to aximum dose 10mg/day. - P-glycoprotein inhibition: Digoxin levels should be monitored	QTc prolongation, Impaired cardiac conduction, high degree AV block, torsade de pointes
Remdesivir	inhibitor of RNA dependent RNA polymerases	Unknown	Unknown	Hypotension?
Ribavir in	Inhibits replication of DNA and RNA viruses	Warfarin	Unknown	Hypotension/Hypertension Arrhythmias Acute coronary syndrome
Drug	**Mechanism of action**	**CV drugs interaction**	**Mode of interaction**	**CV adverse effects**

Other commonly used drugs				
Bevacizumab	Inhibits VEGF (increased in COVID-19 patients) reducing vascular permeability and pulmonary edema.	Unknown	Unknown	Direct myocardial toxicity; Serve hypertension Thromboembolic events
Chloroquine/ Hyroxychloroquine	Modifies cellular pH inhibiting virus adhesion to cells	Antiarrhythmics QT-prolonging agents	CYP 2D6 inhibition: Dose reduction for beta blockers may be required. P-glycoprotein inhibition: Digoxin levels should be monitored	Direct myocardial toxicity Altered cardiac conduction:AV block, bundle branch block, torsade de pointes, ven tricular tachycardia/fibrillation
Eculizumab	Inhibits complement activation	Unknown	Unknown	Hypertension, tachycardia, peripheral edema
Fingolimod	Immunosuppressive action with lymphocyte sequestration in lymph nodes	Antiarrhythmics lvabradine	Sphingosine-1-phosphate receptor inhibition (on atrial myocytes):class IA and lll antiarrhythmics should be avoided	Hypertension, first and second-degree AV block, bradycardia, QTc prolongation Contraindication: Sick sinus syndrome, high degree AV block, QTc ≥ 500 ms acute coronary/cerebrovascolar syndromes,
Interferon	Immunomodulation	Unknown	Unknown	Direcr myocardial toxicity, hypotention, arrhythmia, cardiomyopathy, acute coronary syndrome
Pirfenidone	Promotes a reduction in the production of inflamation medicators such as TNF-α and interleukin IL-1β	Unknown	Unknown	Unknown
Tocilizumab	Inibits IL-6 receptor	Unknown	Unknown	Hypertension, Hypercholesterolemia

Conclusions

In recent years, the development and increased speed and spread of international travel have promoted a new situation for the transmission of infectious diseases worldwide, making global pandemics easier, as in the case of COVID-19. Although this virus, like previous coronaviruses, has a more pronounced tropism for the respiratory system, the associated extrapulmonary manifestations and their long-term consequences are often disregarded. Certainly, pre-existing cardiovascular diseases significantly affect the outcome of these patients, but it is always necessary to keep in mind the heart diseases that may result directly from COVID-19 as well as the pharmacological interactions and adverse effects. Therefore, it is more appropriate than ever to promote interdisciplinary management of COVID-19 patients, especially in patients with pre-existing cardiovascular diseases with a multi-specialist COVID-Team.

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