
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Hellenic Journal of Cardiology 61 (2020) 381–395

Contents lists available at ScienceDirect

Hellenic Journal of Cardiology

journal homepage: http://www.journals.elsevier.com/hellenic-journal-of-cardiology/

Review Article

# Involvement of cardiovascular system as the critical point in coronavirus disease 2019 (COVID-19) prognosis and recovery

Charalampos Lazaridis [1, 2, 3], Nikolaos I. Vlachogiannis [1, 3], Constantinos Bakogiannis [2], Ioakim Spyridopoulos [1, 4], Kimon Stamatelopoulos [3, 5], Ioannis Kanakakis [5], Vassilios Vassilikos [2], Konstantinos Stellos [1, 3, *]

[1] Department of Cardiology, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK
[2] Third Cardiology Department, Hippokrateion University Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece
[3] Biosciences Institute, Vascular Biology and Medicine Theme, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[4] Translational and Clinical Research Institute, Vascular Biology and Medicine Theme, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[5] Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

ARTICLE INFO

*Article history:*
Received 19 May 2020
Accepted 28 May 2020
Available online 10 June 2020

*Keywords:*
COVID-19
SARS-CoV-2
Pandemic
Cardiovascular comorbidities
Cardiovascular complications

ABSTRACT

The novel coronavirus disease 2019 (COVID-19) pandemic has already caused more than 300,000 deaths worldwide. Several studies have elucidated the central role of cardiovascular complications in the disease course. Herein, we provide a concise review of current knowledge regarding the involvement of cardiovascular system in the pathogenesis and prognosis of COVID-19. We summarize data from 21 studies involving in total more than 21,000 patients from Asia, Europe, and the USA indicating that severe disease is associated with the presence of myocardial injury, heart failure, and arrhythmias. Additionally, we present the clinical and laboratory differences between recovered and deceased patients highlighting the importance of cardiac manifestations. For the infected patients, underlying cardiovascular comorbidities and particularly existing cardiovascular disease seem to predispose to the development of cardiovascular complications, which are in turn associated with higher mortality rates. We provide mechanistic insights into the underlying mechanisms including direct myocardial damage by the virus and the consequences of the hyperinflammatory syndrome developed later in the disease course. Finally, we summarize current knowledge on therapeutic modalities and recommendations by scientific societies and experts regarding the cardiovascular management of patients with COVID-19.
© 2020 Hellenic Society of Cardiology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## 1. Introduction

In early December 2019, the first cases of a pneumonia-like disease emerged in Wuhan, Hubei Province, China.[1] All cases were linked to a seafood market in the same city[2] and were confirmed to be associated with a novel RNA *Betacoronavirus*, which was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3,4]. On February 11, 2020, the novel disease was named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO), which declared a pandemic on March 11, 2020.[5] COVID-19's high reproduction number has led to worldwide expansion of the disease[6] and has gripped the world in a health and economic crisis.[7,8]

## 2. Etiology – Pathophysiology of SARS-CoV-2 infection

### 2.1. Structure and genome sequence of SARS-CoV-2

SARS-CoV-2 is a round or elliptic *Betacoronavirus* and has a diameter of approximately 60–140 nm[9]. It belongs to the large family of coronaviruses, which are responsible for 5-10% of all respiratory tract infections.[10] Coronaviruses have also been the cause of two previous infectious disease outbreaks; severe acute respiratory syndrome (SARS)[11] and Middle East respiratory syndrome (MERS).[12] Comparative homology analysis has revealed the

* Corresponding author. Faculty of Medical Sciences, Newcastle University and Newcastle Hospitals NHS Foundation Trust, International Center for Life, Central Parkway, Newcastle Upon Tyne, NE1 3BZ, UK. Tel.: +447555609759.
*E-mail address:* konstantinos.stellos@ncl.ac.uk (K. Stellos).
Peer review under responsibility of Hellenic Society of Cardiology.

https://doi.org/10.1016/j.hjc.2020.05.004
1109-9666/© 2020 Hellenic Society of Cardiology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

**Abbreviations**

| | |
|---|---|
| RNA | ribonucleic acid |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| COVID-19 | coronavirus disease 2019 |
| SARS | severe acute respiratory syndrome |
| MERS | Middle East respiratory syndrome |
| SARS-CoV | severe acute respiratory syndrome coronavirus |
| MERS-CoV | Middle East respiratory syndrome coronavirus |
| ACE | angiotensin converting enzyme |
| ACEI | angiotensin converting enzyme inhibitor |
| ARB | angiotensin II receptor blocker |
| RAAS | renin–angiotensin–aldosterone system |
| *O*-GlcNAc | *O*-linked β-*N*-acetylglucosamine |
| IRF5 | interferon regulatory factor–5 |
| RT-PCR | real-time reverse transcription polymerase chain reaction |
| CT | computed tomography |
| IL | interleukin |
| CVD | cardiovascular disease |
| ICU | intensive care unit |

close relation of SARS-CoV-2 with bat coronavirus (RaTG13) demonstrating an overall sequence homology of 96.2%,[13] whereas the association with SARS-CoV (approximately 79% sequence identity) and MERS-CoV (approximately 50% sequence identity) was less significant[4].

### 2.2. Viral cell entry

Angiotensin-converting enzyme 2 (ACE2), a type 1 membrane protein expressed in the intestine, kidneys, heart and type II alveolar cells in the lungs[14] has been recognized as a cell receptor for SARS-CoV[15,16] and can also serve as a cell receptor for the novel SARS-CoV-2.[13,17] The spike glycoprotein (S protein) on the virion surface of SARS-CoV is responsible for receptor recognition and membrane fusion.[18] Similarly, an S protein on the surface of the novel SARS-CoV-2 binds to the peptidase domain of ACE2 at least ten times more tightly than of (SARS)–CoV[19] and subsequently causes membrane fusion, releasing its RNA into the host cell.[19,20] Transmembrane Serine Protease 2 (TMPRSS2) is essential for viral entry being involved in S protein priming and the cleavage of the site.[21] Ou et al. reported that phosphoinositide 5-kinase (PIKfyve), two-pore segment channel 2 (TPC2), and cathepsin L are also critical for viral entry,[22] Once endocytosis is completed, SARS-CoV-2 RNA is translated into viral polyproteins, which are assembled with genome RNA into virions and transported through exocytosis out of the host cell.[23] The SARS-CoV-2 binding to the ACE2 receptors and the subsequent membrane fusion and viral invasion result in the downregulation and the loss of the catalytic effect of ACE2 receptors at the external site of the cell membrane.[24]

## 3. Epidemiology of COVID-19

On January 24, 2020, the first three cases of COVID-19 were reported in Europe, all located in France.[25] At that point, Asia had already recorded 1312 COVID-19 cases and 41 deaths.[26] In Greece, the first confirmed patient with COVID-19 was reported on February 26, 2020.[27] As of May 18, 2020, the WHO has confirmed 4,819,372 cases, 316,961 deaths, and 1,864,269 recovered patients worldwide.[28] The overall fatality rate is currently at 6,6%; however, there are wide variations depending on age, comorbidities, and country.[29] In comparison, SARS-CoV had 8,098 confirmed cases and 774 deaths from November 2002 to July 2003 (mortality 9.6%)[30] and MERS-CoV had 2,494 confirmed cases and 858 deaths from September 2012 to September 2019 (mortality 34.4%).[31]

The high sequence homology of SARS-CoV-2 with bat coronavirus[13] and the vast number of coronaviruses carried by distinct bat species[32,33] have suggested that SARS-CoV-2 has originated from bats.[13] The transmission of SARS-CoV-2 occurs mainly from person to person through respiratory droplets[34–36] and has an incubation period ranging from 2 to 14 days[37] or in extreme cases up to 32 days.[38] Li et al. analyzed the first 425 cases in Wuhan by January 22, 2020 and estimated the mean incubation period of COVID-19 at 5.2 days with the 95$^{th}$ percentile of the distribution at 12.5 days.[36] Airborne transmission[39] and transmission through the oral-fecal route[40] have also been recorded. Of note, Zou et al. reported that the viral load of SARS-CoV-2 in asymptomatic patients was comparable to that in symptomatic patients,[41] suggesting potential transmission by asymptomatic patients in concordance with other studies also reporting transmission from asymptomatic SARS-CoV-2 carriers.[42,43] Despite the ability of SARS-CoV-2 to infect different pet species,[44] the risk of human contamination from pets has not been elucidated so far.[45]

On January 23, 2020, the WHO estimated the basic reproductive number ($R_0$) of COVID-19 at 1.4-2.5.[46] Liu et al suggested that SARS-CoV-2 has a higher $R_0$ in comparison to SARS-CoV, estimating the mean $R_0$ of SARS-CoV-2 at 3.28 by analyzing data from 12 studies.[47] However, as there has not been adequate evidence regarding how asymptomatic carriers contribute to the transmission rate of this novel infectious disease and how each treatment or preventive strategy affects it, the accurate estimation of $R_0$ is difficult.

Gender differences have been reported in the epidemiology of COVID-19, as women have lower infection and mortality rates than men.[29,48] A recent study in patients with heart failure found that circulating levels of ACE2 were higher in men than in women, suggesting increased ACE2 tissue expression, which could contribute to susceptibility to SARS-CoV-2 infection and disease progress.[49] However, further studies are needed to elucidate the gap between sex difference and COVID-19 susceptibility and prognosis.

## 4. Cardiovascular complications in patients with COVID-19

### 4.1. Myocardial injury

Myocardial injury has been a remarkable finding, which contributes to worse prognosis (Figs. 3 and 4) in most patient cohorts with COVID-19 so far[34,48,50–56](Table 1), and being reported in >50% of deceased patients in most included studies. (Table 3) Case reports of probable COVID-19-induced myocarditis claim the direct myocardial injury by SARS-CoV-2.[57–60] According to the fourth universal definition of myocardial infarction by the European Society of Cardiology (ESC), myocardial injury is defined as being present when blood levels of cardiac troponin are increased above the 99th percentile upper reference limit.[61] Most of the published reports have used the same or similar definitions (Appendix).[34,48,52–56] The exact underlying mechanism for the COVID-19-mediated myocardial damage is not clear;[62] however, the following four hypotheses are the main mechanisms considered so far (Fig. 1):

#### 4.1.1. Direct ACE2-mediated myocardial cell invasion

As already described, high ACE2 expression is detected in cardiac tissue,[63] and may therefore facilitate cellular entry of the virus resulting in endothelial dysfunction and myocardial damage

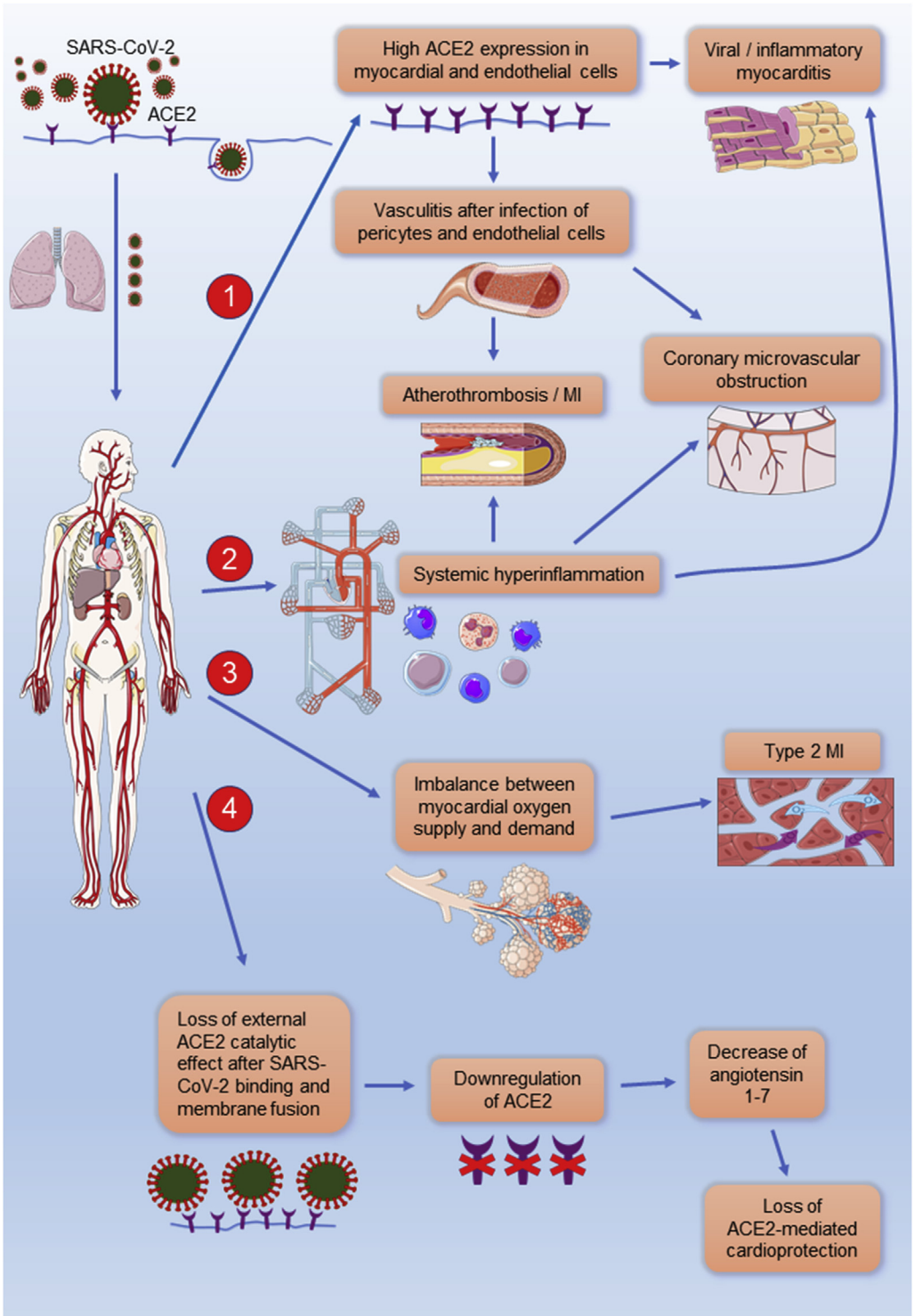


**Figure 1. Clinical manifestations of cardiovascular disease after infection with SARS-CoV-2.** (1) High ACE2 expression is detected in cardiac and vascular tissue and may therefore facilitate cellular entry of SARS-CoV-2 resulting in myocardial and vascular damage. (2) An aberrant T-cell and monocyte activation has been observed in patients with COVID-19 leading to a systemic hyperinflammatory response. Increased circulating proinflammatory cytokines may result in inflammatory cardiomyopathy or atherothrombosis, causing an acute coronary syndrome. Systemic inflammatory response can also activate the microvascular endothelium, provoking the dysfunction of the coronary microvasculature, and consequently resulting in myocardial ischemia and myocardial injury. (3) Decreased myocardial oxygen supply, due to severe COVID-19 respiratory complications and hypoxia, along with increased myocardial oxygen demand, mainly due to high systemic metabolic needs, can provoke myocardial injury and type 2 myocardial infarction. (4) The binding of SARS-CoV-2 to ACE2 is expected to lead to the internalization of ACE2 and loss of the external ACE2 catalytic effect. Therefore, the possible downregulation of ACE2 and the subsequent decrease of angiotensin 1-7 in patients with COVID-19 may also compromise heart function. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com. ACE2: angiotensin-converting enzyme 2, MI: myocardial infarction, and SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

(Table 6) In particular, ACE2 is widely expressed in cardiomyocytes, cardiac pericytes, and coronary endothelial cells.[64] Therefore, SARS-CoV-2 could directly enter cardiomyocytes and provoke myocardial injury. Furthermore, pericytes, which are perivascular mural cells with high ACE2 expression, have been suggested as target host cells by SARS-CoV-2.[64] Considering the essential role of cardiac pericytes in maintaining endothelial cell function in capillary vessels, their infection could lead to coronary microvascular dysfunction and cardiac injury.[64] SARS-CoV-2 has also been shown to infect human blood vessel organoids *in vitro*.[65] Recent pathology reports provided the evidence of direct endothelial cell infection and diffuse endothelial inflammation, which could suggest the induction of "endotheliitis" and endothelial dysfunction, potentially contributing to the destabilization of coronary plaques, atherothrombosis, and vascular disease.[66]

#### 4.1.2. Systemic Hyperinflammation

Viral infections are recognized as one of the most frequent causes of infectious myocarditis, which trigger the activation of the host antiviral immune response, including natural killer cells, macrophages, and virus-specific T lymphocytes.[67] Similarly, an aberrant T-cell and monocyte response has been observed in patients with COVID-19 leading to a systemic hyperinflammatory response characterized by increased proinflammatory cytokine and chemokine production (tumor necrosis factor, IL-2, IL-6, IL-7, and CCL2 among others)[34,48,50,68,69] (Table 5) (Fig. 2). This could lead to consequent myocardial damage as suggested by autopsy reports describing inflammatory mononuclear cell infiltration in cardiac tissues of patients with fulminant myocarditis and high SARS-CoV-2 viral load.[59,70] Systemic inflammation could further stimulate tissue-resident macrophages and leukocyte adhesion molecule expression on the endothelial cells of preexisting atherosclerotic lesions, enhancing their propensity to be disrupted and cause an acute coronary syndrome.[62,71] Elevated circulating cytokines can also activate the microvascular endothelium, provoking dysfunction of the coronary microvasculature, and consequent myocardial ischemia and injury.[72] In line with this concept, blockade of IL-6, which is central in leukocyte transmigration into peripheral tissues, has shown promising results in severe cases of COVID-19.[73,74] Despite the low severity and low mortality of COVID-19 in children[75] there have been reports of severe Kawasaki-like disease (which is a type of vasculitis) cases across Europe.[76] Macrophage activation syndrome-like manifestations, classically associated with rheumatic diseases including Kawasaki disease,[77] have also been reported in patients with COVID-19 supporting the hypothesis that the increase of Kawasaki-like presentations could be a result of COVID-19-induced systemic hyperinflammation and consequent vasculitis.[78]

#### 4.1.3. Imbalance between myocardial oxygen supply and demand

Myocardial injury can be the result of a mismatch between myocardial oxygen supply and demand, being classified as type 2 myocardial infarction.[61] Severe respiratory complications and potential subsequent hypoxia are common findings in patients with COVID-19.[48,53,79–81] In a meta-analysis of 19 studies, including a total of 2,874 patients, the most predominant chest x-ray finding was bilateral pneumonia (72.9%, 95% CI 58.6–87.1%) with ground glass opacity being reported in 68.5% (95% CI 51.8–85.2%) of patients.[82] In addition, ground glass opacity was the most frequent chest CT finding (97.6%) in a Chinese cohort of 83 patients with COVID-19-related pneumonia and was associated with severe outcomes in all (100%) patients.[83] Hypoxia may also contribute to the development of tissue inflammation, which in turn may lead to cardiac damage.[84] Furthermore, hypotension, a frequent clinical sign in sepsis and in cytokine storm syndrome, can also reduce myocardial oxygen supply.[72] On the other hand, systemic infection and fever increase the metabolic needs of peripheral tissues and end organs resulting in a rise of the metabolic demands of the myocardial cells.[85] The decrease in diastolic perfusion time during tachycardia can induce inadequate subendocardial perfusion in patients with coronary artery disease, resulting in cardiac injury.[86] Therefore, the viral infection caused by SARS-CoV-2 may provoke myocardial oxygen supply and demand imbalance, which is translated into myocardial ischemia and injury.

#### 4.1.4. Loss of ACE2-mediated cardioprotection

ACE2 plays an important role in the renin–angiotensin system by catalyzing the conversion of the vasoconstrictor angiotensin II to the vasodilator angiotensin 1-7, which exerts antiarrhythmogenic and antiremodeling protective effects in the cardiovascular system.[87,88] Angiotensin 1-7 has also antiproliferative effects on vascular smooth muscle cells[89] and cardiac fibroblasts.[90] Additionally, ACE2 has a counterregulatory function to ACE1, which hydrolyzes angiotensin I to the octapeptide angiotensin II and inactivates the vasodilator bradykinin.[91] The activation of angiotensin II elicits heterogeneous signaling cascades in the vasculature, which can result in the expression of proinflammatory mediators and endothelial dysfunction.[92] The binding of SARS-CoV-2 to ACE2 is expected to lead to the internalization of ACE2 and loss of the external ACE2 catalytic effect.[24,93] Therefore, the possible downregulation of ACE2 and the subsequent increase of the proatherosclerotic angiotensin II together with the decrease of the cardioprotective angiotensin 1-7 in patients with COVID-19 may ultimately compromise heart function.[94,95] Remarkably, severe COVID-19 has been associated with hypokalemia and higher blood pressure, supporting suggestions of decreased ACE2 function and augmented levels of angiotensin II after SARS-CoV-2 infection.[96]

#### 4.1.5. Heart failure

Current data regarding the incidence of heart failure among patients with COVID-19 are limited (Table 1). Viral infections are the most common cause of myocarditis[97]. Despite the high recovery rates, nearly one out of three biopsy-proven myocarditis patients will later develop dilated cardiomyopathy.[98] Recurrent viral myocarditis and persistent viral replication have also been associated with the deterioration of myocardial function.[99,100] Similarly, fulminant myocarditis, which may be a clinical manifestation of COVID-19,[57,58] can result in left ventricular systolic dysfunction and even cardiogenic shock.[101,102]

Viruses can also contribute to the etiology of heart failure through immune-mediated and inflammatory myocardial damage.[103] Acute systemic inflammation and septic shock can result in an increase of left ventricular end-diastolic volume together with the depression of myocardial function.[104,105] Moreover, an excessive T lymphocyte response in enterovirus-induced myocarditis has been reported to provoke left ventricular dilatation and/or dysfunction.[106] Finally, high levels of circulating cytokines, such as TNF-$\alpha$, IL-1$\beta$, and IL-6 have been shown to cause the deterioration of myocardial cell contraction and relaxation *in vitro*[107,108] and could suggest a potential relation between COVID-19-induced hyperinflammatory syndrome and myocardial dysfunction.

Chen et al. reported heart failure as a complication in 24.4% (n = 43) of a Chinese COVID-19 population (n = 176), using age-related amino-terminal pro-brain natriuretic peptide cutoffs, which yielded 90% sensitivity and 84% specificity for acute heart failure;[56] there was a remarkable difference in the prevalence of

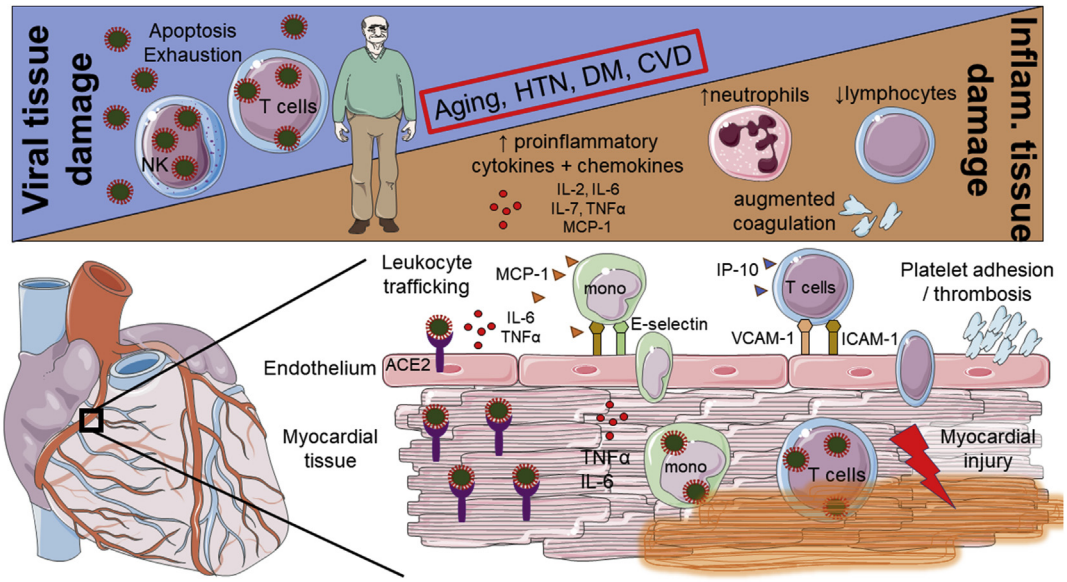


**Figure 2. Mechanistic insights into viral and inflammatory myocardial and vascular tissue damage in COVID-19.** Two phases of COVID-19 have been described: a) an early phase where tissue damage is mainly induced directly by the virus and b) in some severe cases a 2nd phase, where aberrant immune response (hyperinflammation) is the cause of tissue damage (**upper panel**). A large number of proinflammatory cytokines (TNFα, IL-2, IL-6, and IL-7) and chemokines (MCP-1 and IP-10) have been found increased in the circulation of patients with more severe disease. Circulating cytokines can activate endothelial cells and upregulate the expression of leukocyte adhesion molecules such as E-selectin, ICAM-1, and VCAM-1. This could lead to the transmigration of leukocytes into peripheral tissues, such as the myocardium, and cause inflammatory tissue damage (**lower panel**). This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com. ACE2: angiotensin-converting enzyme 2, CVD: cardiovascular disease, DM: diabetes mellitus, HTN: hypertension, ICAM-1: intercellular adhesion molecule 1, IL: interleukin, IP10: interferon γ-induced protein 10, MCP1: monocyte chemoattractant protein-1, mono: monocytes, TNFα: tumor necrosis factor alpha, and VCAM-1: vascular cell adhesion molecule.

heart failure between COVID-19 survivors and nonsurvivors (3.2% vs. 49.4%).[56] Another study including 191 patients reported heart failure as a cardiovascular complication in 23.0% (n = 44) of the population, 63.6% (n = 28) of whom had a fatal outcome[48] (Table 3). Lastly, in a meta-analysis of 43 studies involving 3,600 patients, the prevalence of heart failure as a complication was 17.1% (95%, CI: 1.5–42.2%) among critically ill patients as compared to 1.9% (95% CI: 0.0-26.0%) among non-critically ill patients.[109]

### 4.2. Arrhythmias

Sustained ventricular arrhythmias are significant clinical features of acute myocarditis,[102] which is increasingly being reported as a clinical complication of COVID-19.[57–60] Guo et al. reported sustained ventricular tachycardia or ventricular fibrillation in 5.9% (n = 11) of 187 patients in a designated hospital to treat patients with COVID-19 in China.[55] Arrhythmias could also be precipitated by electrolyte imbalances that have been observed in populations with COVID-19.[56] The interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system (RAAS) has caused increasing concern about sodium and potassium disorders, which may increase vulnerability to various tachyarrhythmias.[96,110] In addition, hypoxia, a common clinical manifestation of severe COVID-19,[48,53,79–81] has been associated with alterations of cardiomyocyte gap-junctions, which could contribute to the development of atrial arrhythmias, particularly atrial fibrillation.[111] A recent retrospective case series study characterizing the first 393 consecutive patients with COVID-19 in two hospitals in New York City found that patients who received mechanical ventilation were more likely to have atrial arrhythmias (18.5% vs. 1.9%).[112]

Arrhythmias can also be induced by novel medical therapies for COVID-19; despite the unclear data about the effectiveness of chloroquine phosphate and hydroxychloroquine sulfate for the treatment of COVID-19,[113] the Food and Drug Administration of the United States of America issued an emergency authorization for their use under determined circumstances in patients with COVID-19.[114] Both agents may increase the risk for Torsades de Pointes or other ventricular arrhythmias through QTc prolongation[115] and could also lead to advanced types of atrioventricular block.[116]

### 4.3. The role of cardiovascular comorbidities and preexisting CVD in the development of CVD complications

Preexisting cardiovascular disease and cardiovascular comorbidities, including arterial hypertension and type 2 diabetes mellitus, are predictors of myocardial injury in hospitalized patients with COVID-19[117] (Tables 1–4). An association between preexisting cardiac disease and higher frequency of cardiovascular complications has been previously shown among patients with pneumonia.[118,119] Recent results indicate multi-organ tropism of SARS-CoV-2, including heart, vascular system, and the circulation, which is speculated to influence the course of the disease as well as aggravate preexisting conditions.[120] The increased myocardial expression of ACE2 in patients with cardiovascular disease and COVID-19[121,122] has been suggested as a possible mechanism of myocardial cell invasion and injury leading to worse outcomes[64] (Fig. 1).

In a cohort of 416 patients with COVID-19, individuals with cardiac injury were more commonly affected by arterial hypertension (59.8% vs 23.4%), diabetes (24.4% vs 12.0%), coronary heart disease (29.3% vs 6.0%), and chronic heart failure (14.6% vs 1.5%) as compared to patients without cardiac injury.[54] Similarly, 52 patients with COVID-19 with elevated troponin T levels had significantly higher rates of comorbidities including arterial hypertension (63.5% vs 20.7%), coronary heart disease (32.7% vs 3.0%), cardiomyopathy (15.4% vs 0%), and diabetes (30.8% vs 8.9%) in comparison to 135 patients with normal troponin T levels.[55] On the other hand, rates of smoking did not differ significantly between those with

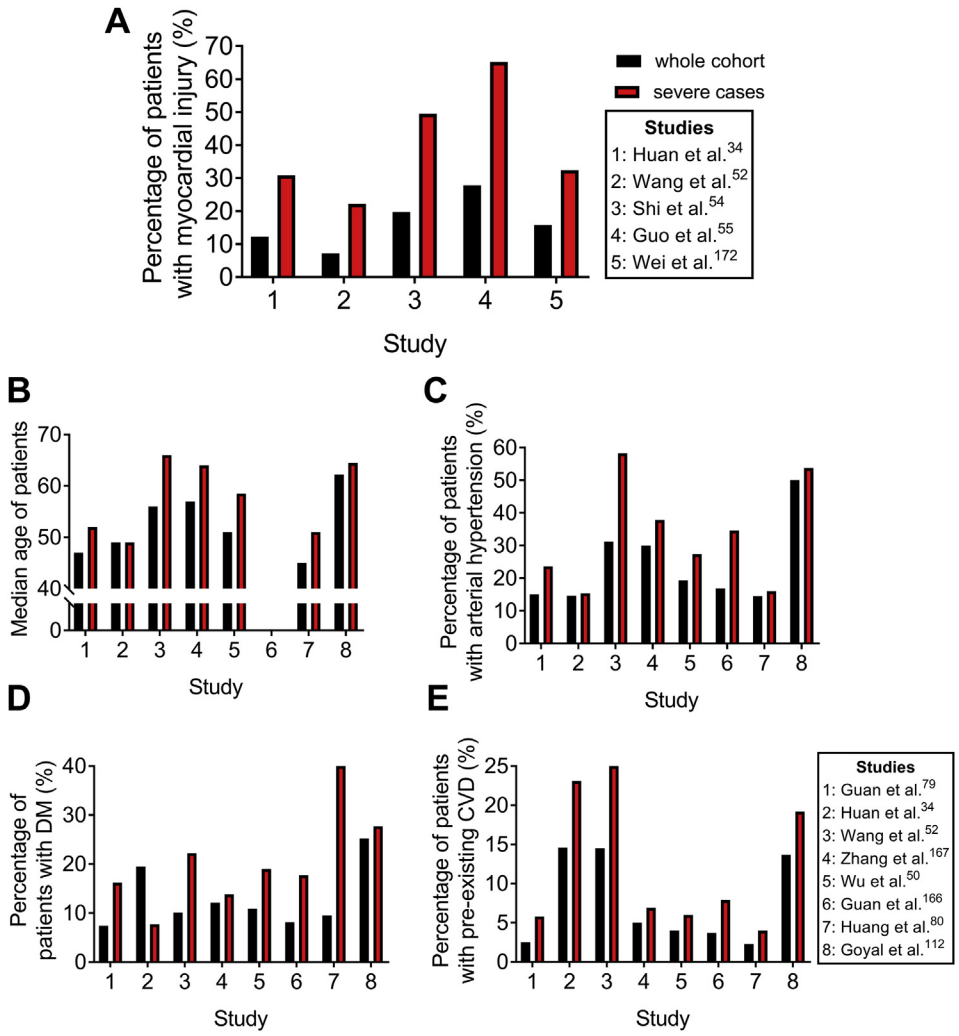


**Figure 3. Comparative analysis of myocardial injury frequency between total and severe patients with COVID-19.** The number of patients included in the whole cohort vs. severe cases in the depicted cohort studies (n whole cohort/severe cases): Huan[34] et al. 41/13, Wang[52] et al. 138/36, Shi[54] et al. 416/97, Guo[55] et al. 187/46, Wei[172] et al. 101/37, Guan[79] et al. 1099/173, Zhang[167] et al. 140/58, Wu[50] et al. 201/84, Guan[166] et al. 1590/254, Huang[80] et al. 221/25, and Goyal[112] et al. 393/130. Bar graphs represent: (**A**) the percentage of patients who developed myocardial injury, (**B**) median age of patients, (**C**) the percentage of patients with arterial hypertension, (**D**) the percentage of patients with DM and (**E**) the percentage of patients with preexisting CVD in the whole cohort (black) and among the severe COVID-19 cases (red) per study. DM: diabetes mellitus and CVD: cardiovascular disease.

normal or elevated troponin T levels (8.1% vs 13.5%).[55] The data about the contribution of smoking to the severity of COVID-19 are conflicting. Although a preliminary meta-analysis of 1,399 Chinese patients with COVID-19 suggested that current smoking is not associated with increased risk of developing severe disease,[123] another systematic review of five studies including a total of 1,549 patients concluded that smoking is most likely associated with worse outcomes,[124] probably due to its detrimental effects in the lungs and cardiovascular system. On the other hand, decreased levels of ACE2 have been observed in smokers,[125,126] while current smoking was reported in less than 17% of patients with severe disease in all 5 original studies included herein (Table 2).

Insufficient glycemic control in patients with diabetes has been strongly associated with the overall risk of serious infections.[127] A recent study revealed the central role of deregulated glucose metabolism in influenza virus-induced cytokine storm through O-GlcNAcylation of IRF-5.[128] Considering that a cytokine storm syndrome has been reported as a potential cause of COVID-19 complications.[129] a similar mechanism may be present in diabetic patients with SARS-CoV-2 infection. Lastly, Liraglutide, a glucagon-like peptide 1 receptor, has been found to increase ACE2 expression in rat models,[130] and could therefore facilitate viral infection in accordance with the aforementioned hypothesis of the potential ACE2 role in COVID-19 cardiovascular complications.

## 5. Current treatment strategies for CVD patients

There are limited data to guide the clinical treatment strategies for COVID-19 and its cardiovascular complications. The best possible approach should be reached with a multidisciplinary team, which includes specialized infectious disease advice, and should be based upon the available information provided by the World Health Organization or reputable societies (Table 7). Numerous clinical trials are currently testing experimental therapies or repurposing of current drugs for the treatment of COVID-19.[131]

The participation of ACE2 in the pathogenesis of COVID-19, acting as a cell receptor for SARS-CoV-2[13] has caused increasing concern about the role of antihypertensive therapy with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in patients with COVID-19.[132] An

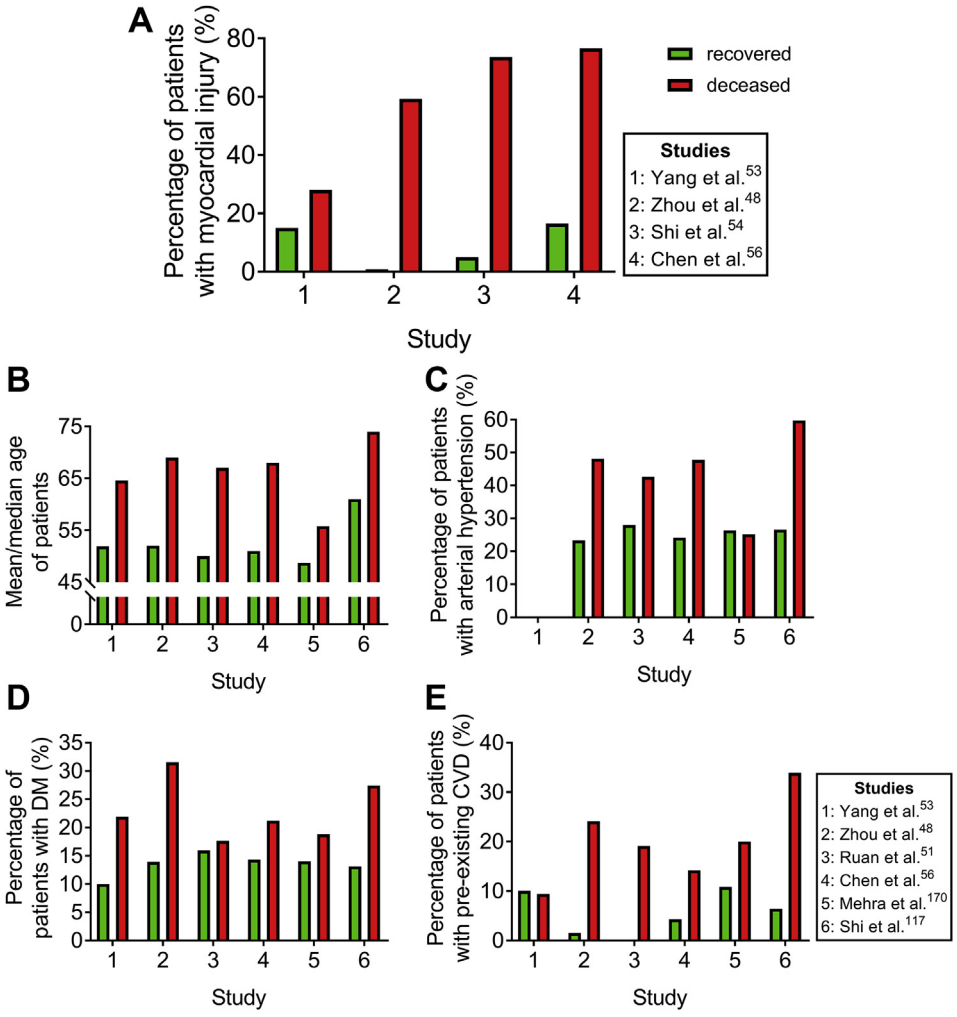


**Figure 4. Comparative analysis of myocardial injury frequency between recovered and deceased patients with COVID-19.** The number of recovered patients vs. deceased patients in the depicted cohort studies (n recovered patients/deceased patients): Yang[53] et al. 20/32, Zhou[48] et al. 37/54, Shi[54] et al. 40/57, Chen[56] et al. 161/113, Ruan[51] et al. 82/68, Mehra[170] et al. 8395/515, and Shi[117] et al. 609/62. Bar graphs represent: (**A**) the percentage of patients who developed myocardial injury, (**B**) the median (Zhou[48], Ruan[51], Chen[56], and Shi[117]) or mean (Yang[53] and Mehra[170]) age of patients, (**C**) the percentage of patients with arterial hypertension, (**D**) the percentage of patients with DM, and (**E**) the percentage of patients with preexisting CVD in recovered (green) and deceased patients with COVID-19 (red) per study. DM: diabetes mellitus and CVD: cardiovascular disease.

observational analysis in a cohort of 12,594 patients who were tested for COVID-19 in New York City indicated that previous treatment with medications acting on the RAAS was not associated with a higher risk of either testing positive for COVID-19 or developing severe COVID-19.[133] Of interest, another retrospective, multicenter study including 1,128 hospitalized hypertensive patients diagnosed with COVID-19 showed that inpatient use of ACEIs or ARBs was associated with lower risk of all-cause mortality compared to ACEI/ARB nonusers (adjusted HR, 0.42; 95% CI, 0.19-0.92).[134] Despite initial concerns that the use of RAAS inhibitors in patients with COVID-19 could increase ACE2 expression, and therefore facilitate viral entry,[135,136] no evident association between RAAS use and more severe COVID-19 course has been observed in large clinical cohorts to date.[49,133,134,137,138] Thus, the European Society of Cardiology and Heart Failure Society of America/American College of Cardiology/American Heart Association guidelines suggest no change in treatment with RAAS antagonists.[139,140]

Chloroquine, an antimalarial agent with known anti-viral effects,[141] has been proven to have beneficial effects against SARS-CoV infection,[142] opening the possibility of its implementation in the prophylaxis and treatment of COVID-19. The available published data have been conflicting so far,[113,143–145] highlighting the necessity of awaiting the results of randomized controlled clinical trials.

Another agent being tested in several clinical trials is Remdesivir[131]. It acts as a chain terminator during RNA replication and was initially developed for the treatment of Ebola virus disease[146]. Activity of Remdesivir against SARS-CoV-2 has been indicated *in vitro*,[147] while clinical data have shown improvement in patients with severe forms of COVID-19.[148]

In addition, severe forms of COVID-19 have been associated with nonspecific widespread immune reactions and cytokine storm syndromes.[129] In line with this, increased levels of inflammatory biomarkers have been associated with high risk of critical COVID-19 cases and death.[34,48,50] Consequently, monoclonal IL-6 receptor inhibitors, such as tocilizumab and siltuximab, IL-1 receptor antagonists (Anakinra), fully human anti-interferon-gamma antibodies (Emapalumab), azithromycin, and corticosteroids are currently being investigated in clinical trials,[131] as they have proven their efficacy against exaggerated immune activation.[149–153] Finally, in view of colchicine's favorable anti-inflammatory profile,[154] including its use in the treatment of pericarditis and post-pericardiotomy syndrome,[155] a prospective, randomized, controlled

**Table 1**
Frequency of cardiovascular comorbidities, preexisting cardiovascular disease, and cardiovascular complications in patients with COVID-19

| | n | Median age, years | CV comorbidities | | | Pre existing CVD | CV complications | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Current smoker | HTN | DM | CVD | Myocardial injury | HF | Arrhythmia |
| Guan[79] | 1099 | 47 | 12.6 | 15.0 | 7.4 | 2.5 | N/A | N/A | N/A |
| Huan[34] | 41 | 49 | 7.3 | 14.6 | 19.5 | 14.6 | 12.2 | N/A | N/A |
| Wang[52] | 138 | 56 | N/A | 31.2 | 10.1 | 14.5 | 7.2 | N/A | 16.7 |
| Zhang[167] | 140 | 57 | 1.4 | 30.0 | 12.1 | 5.0[D] | N/A | N/A | N/A |
| Wu[50] | 201 | 51 | N/A | 19.4 | 10.9 | 4.0 | 4.5 | N/A | N/A |
| Guan[166] | 1590 | 48.9[A] | 7.0[B] | 16.9 | 8.2 | 3.7 | N/A | N/A | N/A |
| Huang[80] | 221 | 45 | 7.7[C] | 14.5 | 9.5 | 2.3 | 1.7 | N/A | N/A |
| Xu[168] | 90 | 50 | N/A | 18.9 | 5.6 | 3.3 | N/A | N/A | N/A |
| Zhou[48] | 191 | 56 | 5.8 | 30.4 | 18.8 | 7.9[D] | 17.3 | 23.0 | N/A |
| Ruan[51] | 150 | N/A | N/A | 34.7 | 16.7 | 8.7 | N/A | N/A | N/A |
| Shi[54] | 416 | 64 | N/A | 30.5 | 14.4 | 10.6[D]<br>4.1[E] | 19.7 | N/A | N/A |
| Guo[55] | 187 | 58.5[A] | 9.6 | 32.6 | 15.0 | 11.2[D] | 27.8 | N/A | 5.9 |
| Chen[56] | 274 | 62 | 4.4 | 33.9 | 17.2 | 8.4 | 43.8 | 24.4 | N/A |
| Mehra[170] | 8910 | 49[A] | 5.5 | 26.3 | 14.3 | 11.3[D]<br>2.1[F]<br>3.4[G] | N/A | N/A | N/A |
| Goyal[112] | 393 | 62.2 | 5.1 | 50.1 | 25.2 | 13.7[D] | N/A | N/A | 7.4 |
| Lechien[171] | 1420[H] | 39.2[A] | 14.3 | 9.2 | 1.7 | 1.8 | N/A | N/A | N/A |
| Wei[172] | 101 | 49 | 7.9 | 20.1 | 13.9 | 5.0[D] | 15.8 | N/A | N/A |
| Richardson[173] | 5700 | 63 | N/A | 56.6 | 33.8 | 11.1[D]<br>6.9[F] | N/A | N/A | N/A |
| Shi[117] | 671 | 63 | N/A | 29.7 | 14.5 | 8.9[D]<br>3.3[E] | N/A | N/A | N/A |

CV: cardiovascular, CVD: cardiovascular disease, DM: diabetes mellitus, HF: heart failure, HTN: hypertension, n: total patients, and N/A: not applicable. [A] Mean age, [B] Former and current smoker, [C] Smoking history, [D] Coronary artery disease, [E] Chronic heart failure, [F] Congestive heart failure, [G] Arrhythmia, and [H] Only patients with mild-to-moderate COVID-19 included.

**Table 2**
Frequency of cardiovascular comorbidities, preexisting cardiovascular disease, and cardiovascular complications in patients with severe COVID-19

| | n | Median age, years | CV comorbidities | | | Pre existing CVD | CV complications | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Current smoker | HTN | DM | CVD | Myocardial injury | HF | Arrhythmia |
| Guan[79] | 173 | 52 | 16.9 | 23.7 | 16.2 | 5.8 | N/A | N/A | N/A |
| Huan[34] | 13 | 49 | 0 | 15.4 | 7.7 | 23.1 | 30.8 | N/A | N/A |
| Wang[52] | 36 | 66 | N/A | 58.3 | 22.2 | 25.0 | 22.2 | N/A | 44.4 |
| Zhang[167] | 58 | 64 | 3.4 | 37.9 | 13.8 | 6.9[A] | N/A | N/A | N/A |
| Wu[50] | 84 | 58.5 | N/A | 27.4 | 19.0 | 6.0 | N/A | N/A | N/A |
| Guan[166] | 254 | N/A | N/A | 34.6 | 17.7 | 7.9 | N/A | N/A | N/A |
| Yang[53] | 52 | 59.7 | 3.8 | N/A | 17.3 | 10.4 | 23.1 | N/A | N/A |
| Huang[80] | 25 | 51 | 8.0[E] | 16.0 | 40.0 | 4.0 | N/A | N/A | N/A |
| Shi[54] | 97 | N/A | N/A | N/A | N/A | N/A | 49.5 | N/A | N/A |
| Guo[55] | 46 | N/A | N/A | N/A | N/A | N/A | 65.2 | N/A | N/A |
| Han[81] | 60[B]<br>15[C] | 59[B,D]<br>57[C,D] | N/A | N/A | N/A | N/A | 76.7[B]<br>80.0[C] | 25.0[B]<br>33.3[C] | N/A |
| Arentz[169] | 21 | 70[D] | N/A | N/A | 33.3 | 42.9 | N/A | 33.3 | N/A |
| Goyal[112] | 130 | 64.5 | 4.6 | 53.8 | 27.7 | 19.2[D] | N/A | N/A | 18.5 |
| Wei[172] | 37 | N/A | N/A | N/A | N/A | N/A | 32.4 | N/A | N/A |

CV: cardiovascular, CVD: cardiovascular disease, DM: diabetes mellitus, HF: heart failure, HTN: hypertension, n: total severe cases, and N/A: not applicable.
[A]Coronary artery disease, [B] Severe COVID-19 [C] Critical COVID-19, [D] Mean age, and [E] Smoking history.

**Table 3**
Frequency of cardiovascular comorbidities, preexisting cardiovascular disease, and cardiovascular complications in patients who died due to COVID-19

| | n | Median age, years | CV comorbidities | | | Pre existing CVD | CV complications | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Current smoker | HTN | DM | CVD | Myocardial injury | HF | Arrhythmia |
| Guan[166] | 50 | N/A | N/A | 56.0 | 26.0 | 16.0 | N/A | N/A | N/A |
| Yang[53] | 32[A] | 64.6[B] | 0 | N/A | 21.9 | 9.4 | 28.1 | N/A | N/A |
| Zhou[48] | 54 | 69 | 9.3 | 48.1 | 31.5 | 24.1[C] | 59.3 | 51.9 | N/A |
| Ruan[51] | 68 | 67 | N/A | 42.6 | 17.6 | 19.1 | N/A | N/A | N/A |
| Shi[54] | 57 | N/A | N/A | N/A | N/A | N/A | 73.7 | N/A | N/A |
| Guo[55] | 43 | N/A | N/A | N/A | N/A | N/A | 72.1 | N/A | N/A |
| Chen[56] | 113 | 68 | 6.2 | 47.8 | 21.2 | 14.2 | 76.6 | 49.4 | N/A |
| Mehra[170] | 515 | 55.8[B] | 8.9 | 25.2 | 18.8 | 20.0[C]<br>5.6[D]<br>6.8[E] | N/A | N/A | N/A |
| Shi[117] | 62 | 74 | N/A | 59.7 | 27.4 | 33.9[C]<br>21.0[F] | 30.6 | 19.4 | N/A |

CV: cardiovascular, CVD: cardiovascular disease, DM: diabetes mellitus, HF: heart failure, HTN: hypertension, n: total deceased patients, N/A: not applicable.
[A] Only critically ill patients with COVID-19 were included in the study, [B] Mean age, [C] Coronary artery disease, [D] Congestive heart failure, [E] Arrhythmia, [F] Chronic heart failure.

**Table 4**
Frequency of cardiovascular comorbidities, preexisting cardiovascular disease and cardiovascular complications in patients with COVID-19 who recovered the disease.

| | n | Median age, years | CV comorbidities | | | Pre existing CVD | CV complications | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Current smoker | HTN | DM | CVD | Myocardial injury | HF | Arrhythmia |
| Yang[53] | 20[A] | 51.9[C] | 10.0 | N/A | 10.0 | 10.0 | 15.0 | N/A | N/A |
| Zhou[48] | 137[B] | 52 | 4.4 | 23.4 | 13.9 | 1.5[D] | 0.8 | 11.7 | N/A |
| Ruan[51] | 82[B] | 50 | N/A | 28.0 | 15.9 | 0 | 6.2[E] | N/A | N/A |
| Shi[54] | 40[B] | N/A | N/A | N/A | N/A | N/A | 5.0 | N/A | N/A |
| Chen[56] | 161 | 51 | 3.1 | 24.2 | 14.3 | 4.3 | 16.5 | 3.2 | N/A |
| Mehra[170] | 8395[B] | 48.7[C] | 5.3 | 26.4 | 14.0 | 10.8[D]<br>1.9[F]<br>3.2[G] | N/A | N/A | N/A |
| Lechien[171] | 264[H] | 34.1[C] | 15.9 | 10.6 | 1.5 | 1.9 | N/A | N/A | N/A |
| Shi[117] | 609 | 61 | N/A | 26.6 | 13.1 | 6.4[D]<br>1.5[I] | N/A | N/A | N/A |

CV: cardiovascular, CVD: cardiovascular disease, DM: diabetes mellitus, HF: heart failure, HTN: hypertension, n: total recovered patients, N/A: not applicable.
[A] Only critically ill patients with COVID-19 were included in the study, [B] Discharged patients, [C] Mean age, [D] Coronary artery disease, [E] Continuous variable representing the median value of cardiac troponin, pg/mL (2.0-28.0), [F] Congestive heart failure, [G] Arrhythmia, [H] Only patients with mild-to-moderate COVID-19 were included in the study, [I] Chronic heart failure.

**Table 5**
Clinical value of cardiovascular and inflammatory biomarkers in patients with COVID-19

| Cardiovascular biomarkers | Clinical relevance |
|---|---|
| Troponin | ↑ in severe COVID-19 as compared to nonsevere COVID-19<br>➢ The median value of high-sensitivity troponin I was increased >2-fold in 36 patients who required ICU as compared to 102 patients who did not require ICU care[52]<br>↑ in deceased patients compared to discharged patients<br>➢ The median value of high-sensitivity cardiac troponin I was increased >7-fold in 54 deceased patients with COVID-19 as compared to 137 discharged patients[48]<br>➢ The median value of high-sensitivity cardiac troponin I was increased >10-fold in 68 deceased patients with COVID-19 as compared to 82 discharged patients[51] |
| NT-proBNP | ↑ in severe COVID-19 as compared to mild COVID-19<br>➢ The median value of NT-proBNP was increased >2-fold in 60 patients with severe COVID-19 as compared to 198 patients with mild COVID-19[81]<br>↑ in deceased patients as compared to discharged patients<br>➢ The median value of NT-proBNP was increased >10-fold in 80 deceased patients with COVID-19 as compared to 93 recovered patients[56]<br>➢ Elevated NT-proBNP (≥285 pg/mL) were reported in 85% (68/80) of the deceased patients with COVID-19 as compared to 18% (17/93) of the recovered patients[56]<br>➢ An NT-proBNP increase of 100 pg/mL was associated with 1.37-fold risk of in-hospital death according to univariate Cox proportional hazards regression analysis of 54 patients with severe COVID-19[174] |
| D-Dimer | ↑ in severe COVID-19 as compared to nonsevere COVID-19<br>➢ Elevated D-Dimers (>0.243 μg/mL) were reported in 61% (23/38) of the severe COVID-19 cases as compared to 28% (12/43) of the nonsevere COVID-19 cases[167]<br>↑ in patients with ARDS as compared to patients without ARDS<br>➢ The median value of D-Dimer was increased >2-fold in 84 patients with COVID-19 who developed ARDS as compared to 117 patients who did not develop ARDS[50]<br>↑ in deceased patients as compared to recovered patients<br>➢ The median value of D-Dimer was increased >8-fold in 54 deceased patients with COVID-19 as compared to 137 discharged patients[48] |
| **Inflammatory biomarkers** | |
| CRP | ↑ in severe COVID-19 as compared to nonsevere COVID-19<br>➢The median value of CRP was increased 1.66-fold in 55 patients with severe COVID-19 as compared to 81 patients with nonsevere COVID-19[167]<br>↑ in deceased patients as compared to discharged patients<br>➢ The median value of CRP was increased >3-fold in 68 deceased patients as compared to 82 discharged patients[51]<br>➢ CRP>100 mg/L was reported in 60% (59/98) of the deceased patients as compared to 14% (21/145) of the recovered patients[56] |
| IL-6 | ↑ in severe COVID-19 compared to nonsevere COVID-19<br>➢ The median value of IL-6 was increased ≈3-fold in 85 patients with refractory COVID-19 as compared to 70 patients with nonrefractory COVID-19[175]<br>↑ in deceased patients as compared to discharged patients<br>➢ The median value of IL-6 was increased ≈2-fold in 68 deceased patients compared to 82 discharged patients[51] |
| Procalcitonin | ↑ in severe COVID-19 as compared to nonsevere COVID-19<br>➢ The median value of procalcitonin was increased ≈2-fold in 50 patients with severe COVID-19 as compared to 68 patients with nonsevere COVID-19[167]<br>↑ in patients who required ICU care as compared to no ICU care<br>➢ Procalcitonin ≥0.1 ng/mL was reported in 50% (6/12) of the patients who required ICU care as compared to 22% (6/27) of the patients who did not require ICU care[34] |
| Neutrophil-to-lymphocyte ratio (NLR) | • 8% higher risk of in-hospital mortality for each unit increase in NLR, as estimated in an analysis of 245 patients with COVID-19[176]<br>• Patients with NLR in the highest tertile had a >15-fold higher risk of death as compared to patients in the lowest tertile after adjustment for potential confounders[176] |

ARDS: acute respiratory distress syndrome, COVID-19: coronavirus disease 2019, CRP: C-reactive protein, ICU: intensive care unit, IL-6: interleukin 6, NLR: neutrophil-to-lymphocyte ratio, and NT-proBNP: N-terminal (NT)- proB-type natriuretic peptide.

**Table 6**
Clinical relevance of cardiovascular and circulatory cells in patients with COVID-19 and potential underlying mechanisms leading to cardiovascular disease.

| Contributing cells | Clinical relevance | Potential underlying mechanisms leading to CVD |
|---|---|---|
| **Cardiovascular cells** | | **Cardiovascular cell-related mechanisms**: |
| Cardiomyocytes[1] | Wide expression of ACE2 | SARS-CoV-2 uses ACE2 as a cell receptor → direct myocardial damage |
| Cardiac pericytes[2] | High ACE2 expression | SARS-CoV-2 uses ACE2 as a cell receptor → pericyte is a potential host cell targeted by SARS-CoV-2 in cardiac tissue capillary → capillary endothelial cells dysfunction → coronary microvascular dysfunction |
| Endothelial cells[3–5] | Evidence of direct SARS-CoV-2 infection of the endothelial cells and diffuse endothelial inflammation | Increased ACE2 expression by endothelial cells and evidence of direct viral infection of vascular organoids *in vitro* → endothelial inflammation ("endotheliitis") and increased leukocyte infiltration in heart tissue → atherosclerotic plaque destabilization → acute coronary syndrome |
| **Blood cells** | | **Leukocyte-related mechanisms:** |
| Lymphocytes[6–10] | ↓ in all cases, especially in severe disease | • ↓ in the number of lymphocytes and NK cells due to functional exhaustion and apoptosis → decreased viral clearance → direct viral infection of cardiomyocytes, cardiac pericytes, and endothelial cells |
| $CD4^+$ T cells[11–14] | ↓ in severe disease<br>✓Autopsy-confirmed CD4+ T infiltration of myocardium | • Apoptosis of plaque infiltrating lymphocytes → plaque destabilization |
| $CD8^+$ T cells[15,16] | ↓ in severe disease | • CD4+ T cells infiltration of myocardium → inflammatory cardiomyopathy |
| NK cells[14,15] | ↓ in all cases | • ↑ in the number of neutrophils → neutrophil plugging → epicardial and/or microvascular obstruction |
| Neutrophils[17–19] | ↑ in severe disease | **Platelet-related mechanism:** |
| Platelets[177,178] | ↓ in severe disease | Platelets become activated → platelets adhere to vascular endothelium promoting further recruitment of leukocytes to vascular wall → vascular inflammation and tissue inflammation → inflammatory cardiomyopathy, atherothrombosis, and vasculitis |

ACE2: angiotensin-converting enzyme 2, COVID-19: coronavirus disease 2019, CV: cardiovascular.
CVD: cardiovascular disease, NK: natural killer, and SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

**Table 7**
Recommendations for the management of CVD patients with COVID-19 as suggested from Societies/Organizations/Experts.

| Society/Organization/ Expert and date issued | Recommendations | Precautions |
|---|---|---|
| American College of Cardiology[179]<br>6 March 2020 | 1. Make plans for quickly identifying and isolating cardiovascular patients with COVID-19 symptoms.<br>2. Advise all cardiovascular patients of the potential increased risk.<br>3. CVD patients should remain current with vaccinations, including the pneumococcal vaccine.<br>4. In geographies with active COVID-19 outbreaks, it may be reasonable to substitute telephonic visits for in-person routine.<br>5. General immunological health remains important for both providers and patients, including eating well, sleeping, and managing stress. | 1. Patients with underlying cardiovascular disease are at higher risk of contracting COVID-19 and have a worse prognosis.<br>2. Classic symptoms and presentation of AMI may be overshadowed in the context of COVID-19, resulting in underdiagnosis.<br>3. For patients with heart failure or volume overload conditions, copious fluid administration for viral infection should be used cautiously.<br>4. It is reasonable to triage patients with COVID-19 according to underlying cardiovascular or other comorbid conditions for prioritized treatment. |
| ESC Council on Hypertension[140]<br>13 March 2020 | Continuation of treatment with the usual antihypertensive therapy. | No evidence about ACEIs and ARBs in humans; however, preclinical evidence suggests that these medications might be rather protective. |
| Chinese Medical Association[180]<br>27 March 2020 | Severe emergent cardiovascular diseases for which hospitalization and conservative medical treatment is recommended:<br>1. STEMI for whom thrombolytic therapy is indicated<br>2. STEMI presenting after exceeding the optimal window of time for revascularization<br>3. High risk NSTE-ACS (GRACE score≥140)<br>4. Uncomplicated Stanford type B aortic dissection<br>5. Acute pulmonary embolism, f) acute exacerbation of heart failure, and g) hypertensive emergency<br>Severe cardiovascular diseases requiring urgent or emergent intervention or surgery:<br>1. Acute STEMI with hemodynamic instability<br>2. Life-threatening NSTEMI<br>3. Stanford type A or complex Type B acute aortic dissection<br>4. Bradyarrhythmia complicated with syncope or unstable hemodynamics<br>5. Pulmonary embolism presenting with hemodynamic instability for whom regular intravenous thrombolytic therapy might lead to excessively bleeding risk | 1. Risk assessment<br>2. Protection for patients and medical staff<br>3. Adapting measures tailored to specific local epidemic situations<br>4. Consider conservative medical treatment as a top priority<br>5. Intervene in a uniquely equipped cardiac catheterization/electrophysiology laboratory specifically engineered with more than standard disinfection procedures<br>6. All suspected and confirmed patients with COVID-19 should be transported with standardized attention to relevant national regulations<br>7. For patients with confirmed or suspected COVID-19 undergoing emergent cardiovascular interventional procedures, preestablished plans for COVID-19 should be initiated<br>8. Patients diagnosed with COVID-19 should be transferred to an ICU with negative-pressure ventilation for continued treatment<br>9. Suspected patients with COVID-19 should be isolated in a single bedroom, and suspected infectious specimens should be handled with care |
| 1) Heart Rhythm Society COVID-19 Task Force<br>2) Electrophysiology | 1. Triage of procedures based on screening and personal protective equipment.<br>2. Postpone or cancel non-urgent, elective procedures. | 1. The proposed HCQ therapy for COVID-19 is relatively short (e.g., 5-10 days), the risk of arrhythmic toxicity is |

**Table 7** (*continued*)

| Society/Organization/ Expert and date issued | Recommendations | Precautions |
|---|---|---|
| Section of the American College of Cardiology<br>3) Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association[181]<br>01 April 2020 | 3. Remote device monitoring.<br>4. Tele-medicine and digital health paradigms.<br>5. It is reasonable to temporarily stop class III antiarrhythmic drugs, with use of a reasonable alternative if there is evidence of QT prolongation.<br>6. ECG monitoring should be considered for patients on multiple QT prolonging medications and avoidance or careful monitoring may be required for congenital LQT patients. | likely quite low. There are specific precautions to be considered for select patients:<br>A Patients with known congenital Long QT Syndrome<br>B Patients with severe renal insufficiency should have the dose reduced (50% for CrCl <10 mL/min)<br>C Patients on QT-prolonging drugs<br>D Electrolyte imbalances must be corrected prior to use<br>None of the above conditions is an absolute contraindication if use of HCQ is warranted.<br>2. Aggressive electrolyte correction can mitigate arrhythmic toxicity. |
| European Association of Cardiovascular Imaging[182]<br>3 April 2020 | 1. Cardiac imaging should be performed if appropriate and only if it is likely to substantially change patient management or be lifesaving<br>2. Use the imaging modality with the best capability to meet the request, but consider also the safety of medical staff regarding exposure<br>3. Elective non-urgent and routine follow-up exams may be postponed or even cancelled | Obligatory preventive measures during TTE and TOE:<br>1. Handwashing<br>2. FFP2/FFP3/N95/N99 masks and gloves<br>3. Protective clothing<br>4. Eye protection<br>5. Head cap<br>6. Full cover or dedicated scanners<br>7. Problem-focused study |

ACE: angiotensin converting enzyme, ARB: angiotensin II receptor blocker, AMI: acute myocardial infarction, CrCl: creatinine clearance, CVD: cardiovascular, ECMO: extracorporeal membrane oxygenation, ESC: European Society of Cardiology, GRACE score: Global Registry of Acute Coronary Events score. HCQ: Hydroxychloroquine, HFOT: high flow oxygen therapy, NSTEMI: Non-ST-elevation myocardial infarction, PPE: personal protective equipment, STEMI: ST-elevation myocardial infarction, TOE: transesophageal echocardiogram, and TTE: transthoracic echocardiogram.

study in Greece (among others) will investigate the effects of colchicine in the prognosis of COVID-19.[156]

## 6. Future perspectives

Epidemiologists have forecasted that 40%–70% of the world's population will be infected by SARS-CoV-2 in the coming year and will present with a wide range of clinical manifestations.[157] Apart from the direct effects of SARS-CoV-2 infection, patients who avoid infection may be affected by self-isolation and social distancing.[158] Hospital attendance and hospital admissions for diseases other than COVID-19 have been significantly decreased since the beginning of the pandemic.[159] There have been reports of significant decrease in the number of patients with acute coronary syndromes as well as large delays in presentation.[160] The reduced healthcare staffing levels along with the increasing ICU demands are causing services to become overwhelmed,[161] while elective procedures and outpatient clinics are being postponed or cancelled.[162] The impact of these factors on the care of cardiovascular patients warrants further investigation.

Cardiologists offering front-line services during the COVID-19 crisis have a pivotal role in the composition of appropriate therapeutic schemes. Because of the scarce ICU resources, critical care triage has become increasingly challenging. Possible delay in the management of urgent cardiac conditions could lead to a remarkable rise in morbidity and mortality. It is crucial for patients with new or worsening symptoms to be encouraged to seek medical assistance. The management of acute coronary syndromes, particularly ST-elevation myocardial infarctions, requires calculated measures,[163] particularly in the era of a pandemic. We believe that further research is needed toward the establishment of comprehensive guidelines, which will provide sufficient preparation and knowledge for such extraordinary conditions.

## 7. Conclusions

COVID-19 poses an outstanding clinical hazard to the general population and the healthcare community. Although most patients develop no or mild symptoms, approximately 20% experience severe or critical COVID-19 symptoms.[164]

For the infected patients, underlying cardiovascular comorbidities and particularly preexisting cardiovascular disease are linked to worse outcomes,[34,48,50,51,79,80,164–167] while the development of cardiovascular complications, including myocardial injury, heart failure, and arrhythmias, are associated with higher mortality rates.[34,48,50–56,79,109,112] Continuous efforts are underway to uncover the pathogenetic mechanisms of COVID-19's cardiovascular complications and develop appropriate and targeted treatment strategies, with the repurposing of available drugs and identification of novel therapeutic targets. However, the acuteness and rapid spread of the COVID-19 pandemic has complicated the elucidation of effective, preventive, and therapeutic schemes.

On the whole, our knowledge of the pathogenesis, diagnosis, clinical course, and treatment of COVID-19 is expeditiously evolving. Nevertheless, in the wake of these unprecedented times, the scientific world has rallied united to progress in the understanding of COVID-19 and develop optimal treatment solutions.

## Conflict of Interest

None.

## Sources of Funding

Dr. K. Stellos is supported by grants from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement No 759248) and the DFG (SFB834 project number 75732319). Dr. C. Lazaridis is supported by a scholarship from the Hellenic Society of Cardiology.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hjc.2020.05.004.

## References

1. Du Toit A. Outbreak of a novel coronavirus. *Nat Rev Microbiol*. 2020;18(3), 123-123.

2. Lu H, Stratton CW, Tang Y. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J Med Virol*. 2020;92(4):401–402.
3. Hui DS, I Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health — The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis*. 2020;91:264–266.
4. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395(10224):565–574.
5. World Health Organization. Coronavirus disease (COVID-19) outbreak. https://www.who.int. Accessed March 22, 2020.
6. Zhao S, Lin Q, Ran J, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. *Int J Infect Dis*. 2020;92:214–217.
7. Lai C-C, Wang C-Y, Wang Y-H, Hsueh S-C, Ko W-C, Hsueh P-R. Global epidemiology of coronavirus disease 2019: disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. *Int J Antimicrob Agents*. 2020;55(4):105946.
8. Johnson HC, Gossner CM, Colzani E, et al. Potential scenarios for the progression of a COVID-19 epidemic in the European Union and the European Economic Area, March 2020. *Euro Surveill*. 2020;25(9).
9. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020;579(7798):265–269.
10. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J Med Virol*. 2020;92(4):418–423.
11. Peiris JSM, Guan Y, Yuen KY. Severe acute respiratory syndrome. *Nat Med*. 2004;10(S12):S88–S97.
12. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia. *N Engl J Med*. 2012;367(19):1814–1820.
13. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579(7798):270–273.
14. Donoghue M, Hsieh F, Baronas E, et al. A Novel Angiotensin-Converting Enzyme–Related Carboxypeptidase (ACE2) Converts Angiotensin I to Angiotensin 1-9. *Circ Res*. 2000;87(5).
15. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426(6965):450–454.
16. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. *Nat Med*. 2005;11(8):875–879.
17. Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. *Nature*. 2020;581(7807):221–224.
18. Gallagher TM, Buchmeier MJ. Coronavirus Spike Proteins in Viral Entry and Pathogenesis. *Virology*. 2001;279(2):371–374.
19. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 2020;367(6483):1260–1263.
20. Hoffmann M, Kleine-Weber H, Krüger N, Müller M, Drosten C, Pöhlmann S. The Novel Coronavirus 2019 (2019-NCoV) Uses the SARS-Coronavirus Receptor ACE2 and the Cellular Protease TMPRSS2 for Entry into Target Cells. *Mol Biol*. 2020;181(2):271–280. e8.
21. Matsuyama S, Nao N, Shirato K, et al. Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. *Proc Natl Acad Sci Unit States Am*. 2020;117(13):7001–7003.
22. Ou X, Liu Y, Lei X, et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat Commun*. 2020;11(1):1620.
23. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *J Adv Res*. 2020;24:91–98.
24. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med*. 2020;76:14–20.
25. Spiteri G, Fielding J, Diercke M, et al. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. *Euro Surveill*. 2020;25(9).
26. Wolrd Health Organization. Novel Coronavirus (2019-nCoV) Situation Report. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200125-sitrep-5-2019-ncov.pdf?sfvrsn=429b143d_8; 2020. Accessed May 17, 2020.
27. Greek National Organization of Public Health. *Daily Report*; 2020. https://eody.gov.gr/wp-content/uploads/2020/03/covid-gr-daily-report-20200325.pdf. Accessed May 17, 2020.
28. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20(5):533–534.
29. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *J Am Med Assoc*. 2020;323(18):1775–1776.
30. World Health Organization. *Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003*; 2020. www.who.int/csr/sars/country/table2003_09_23/en/. Accessed April 14, 2020.
31. World Health organization. *Middle East respiratory syndrome coronavirus (MERS-CoV)*; 2020. https://www.who.int/emergencies/mers-cov/en/. Accessed April 14, 2020.
32. Cui J, Li F, Shi Z-L. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol*. 2019;17(3):181–192.
33. Li W. Bats Are Natural Reservoirs of SARS-Like Coronaviruses. *Science*. 2005;310(5748):676–679.
34. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
35. To KK-W, Tsang OT-Y, Yip CC-Y, et al. Consistent Detection of 2019 Novel Coronavirus in Saliva. *Clin Infect Dis*. 2020. https://doi.org/10.1093/cid/ciaa149.
36. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med*. 2020;382(13):1199–1207.
37. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20–28 January 2020. *Euro Surveill*. 2020;25(5).
38. Qiu C, Deng Z, Xiao Q, et al. Transmission and clinical characteristics of coronavirus disease 2019 in 104 outside-Wuhan patients, China. *J Med Virol*. 2020. https://doi.org/10.1002/jmv.25975.
39. Ong SWX, Tan YK, Chia PY, et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. JAMA. Published online March 4, 2020. Accessed 11.04.2020.
40. Yeo C, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol Hepatol*. 2020;5(4):335–337.
41. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med*. 2020;382(12):1177–1179.
42. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *N Engl J Med*. 2020;382(10):970–971.
43. Pan X, Chen D, Xia Y, et al. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. *Lancet Infect Dis*. 2020;20(4):410–411.
44. Shi J, Wen Z, Zhong G, et al. Susceptibility of Ferrets, Cats, Dogs, and Different Domestic Animals to SARS-Coronavirus-2. *Microbiology*. 2020;368(6494):1016–1020.
45. Leroy EM, Ar Gouilh M, Brugère-Picoux J. The risk of SARS-CoV-2 transmission to pets and other wild and domestic animals strongly mandates a one-health strategy to control the COVID-19 pandemic. *One Health*. 2020;13:100133.
46. World Health Organization. *Statement on the meeting of the International Health Regulations (2005). Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)*; 2020. https://www.who.int/news-room/detail/23-01-2020-statement-on-the-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov. Accessed March 18, 2020.
47. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Trav Med*. 2020;27(2).
48. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–1062.
49. Sama IE, Ravera A, Santema BT, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors. *Eur Heart J*. 2020;41(19):1810–1817.
50. Wu C, Chen X, Cai Y, 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. Published online March 13, 2020. Accessed 18.04.2020
51. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46(5):846–848.
52. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *J Am Med Assoc*. 2020;323(11):1061.
53. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475–481.
54. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;25, e200950.
55. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;27, e201017.
56. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;26:m1091.
57. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J*. 2020;16:ehaa190.
58. Zeng JH, Liu Y-X, Yuan J, et al. First Case of COVID-19 Infection with Fulminant Myocarditis Complication: Case Report and Insights. *Infection*. 2020;10:1–5.
59. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020. https://doi.org/10.1001/jamacardio.2020.1286.
60. Doyen D, Moceri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. *Lancet*. 2020;9:1516.
61. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40(3):237–269.

62. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. *JAMA Cardiol*. 2020. https://doi.org/10.1001/jamacardio.2020.1105.
63. Gembardt F, Sterner-Kock A, Imboden H, et al. Organ-specific distribution of ACE2 mRNA and correlating peptidase activity in rodents. *Peptides*. 2005;26(7):1270–1277.
64. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res*. 2020;1:1097–1100.
65. Monteil V, Kwon H, Prado P, et al. Inhibition of SARS-CoV-2 Infections in Engineered Human Tissues Using Clinical-Grade Soluble Human ACE2. *Cell*. 2020;181(4):905–913.
66. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395(10234):1417–1418.
67. Fung G, Luo H, Qiu Y, Yang D, McManus B. *Myocarditis. Circ Res*. 2016;118(3):496–514.
68. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol*. 2020;20(6):355–362.
69. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. 2020. https://doi.org/10.1093/cid/ciaa248.
70. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8(4):420–422.
71. Hansson GK, Libby P, Tabas I. Inflammation and plaque vulnerability. *J Intern Med*. 2015;278(5):483–493.
72. Libby P. The Heart in COVID19: Primary Target or Secondary Bystander? *JACC Basic Transl Sci*. 2020;10:537–542.
73. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A*. 2020;19:10970–10975.
74. Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. *Nat Rev Rheumatol*. 2020;16(6):335–345.
75. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics*. 2020;145(6), e20200702.
76. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771–1778.
77. Wang W, Gong F, Zhu W, Fu S, Zhang Q. Macrophage activation syndrome in Kawasaki Disease: More common than we thought? *Semin Arthritis Rheum*. 2015;44(4):405–410.
78. Viner RM, Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. *Lancet*. 2020;395(10239):1741–1743.
79. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720.
80. Huang R, Zhu L, Xue L, et al. Clinical Findings of Patients with Coronavirus Disease 2019 in Jiangsu Province, China: A Retrospective, Multi-Center Study. *PLoS Negl Trop Dis*. 2020;14(5), e0008280.
81. Han H, Xie L, Liu R, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. *J Med Virol*. 2020;92(7):819–823.
82. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Trav Med Infect Dis*. 2020;34:101623.
83. Li K, Wu J, Wu F, et al. The Clinical and Chest CT Features Associated with Severe and Critical COVID-19 Pneumonia. *Invest Radiol*. 2020;55(6):327–331.
84. Eltzschig HK, Carmeliet P. Hypoxia and Inflammation. *N Engl J Med*. 2011;364(7):656–665.
85. Musher DM, Abers MS, Corrales-Medina VF. Acute Infection and Myocardial InfarctionLongo DL, ed. *N Engl J Med*. 2019;380(2):171–176.
86. Giuseppe Ferro, Carlo Duilio, Letizia Spinelli, Giovanni Antonio Liucci, Felice Mazza, Ciro Indolfi. Relation Between Diastolic Perfusion Time and Coronary Artery Stenosis During Stress-Induced Myocardial Ischemia. *Circulation*. 1995;92(3):342–347.
87. Patel VB, Zhong J-C, Grant MB, Oudit GY. Role of the ACE2/Angiotensin 1–7 Axis of the Renin–Angiotensin System in Heart Failure. *Circ Res*. 2016;118(8):1313–1326.
88. Jiang F, Yang J, Zhang Y, et al. Angiotensin-converting enzyme 2 and angiotensin 1–7: novel therapeutic targets. *Nat Rev Cardiol*. 2014;11(7):413–426.
89. Freeman EJ, Chisolm GM, Ferrario CM, Tallant EA. Angiotensin-(1-7) inhibits vascular smooth muscle cell growth. *Hypertension*. 1996;28(1):104–108.
90. McCollum LT, Gallagher PE, Ann Tallant E. Angiotensin-(1–7) abrogates mitogen-stimulated proliferation of cardiac fibroblasts. *Peptides*. 2012;34(2):380–388.
91. Sampaio Walkyria O, de Castro Carlos Henrique, Santos Robson AS, Schiffrin Ernesto L, Touyz Rhian M. Angiotensin-(1-7) Counterregulates Angiotensin II Signaling in Human Endothelial Cells. *Hypertension*. 2007;50(6):1093–1098.
92. Touyz RM, Schiffrin EL. Signal Transduction Mechanisms Mediating the Physiological and Pathophysiological Actions of Angiotensin II in Vascular Smooth Muscle Cells. *Pharmacol Rev*. 2000;52(4):639.
93. Alifano M, Alifano P, Forgez P, Iannelli A. Renin-angiotensin system at the heart of COVID-19 pandemic. *Biochimie*. 2020;174:30–33.
94. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. *Am J Physiol Heart Circ Physiol*. 2020;318(5):H1084–H1090.
95. Guo J, Huang Z, Lin L, Lv J. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Viewpoint on the Potential Influence of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on Onset and Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *J Am Heart Assoc*. 2020;9(7):e016219.
96. Chen D, Li X, Song Q, Hu C, Su F, Dai J. pokalemia and Clinical Implications in Patients with Coronavirus Disease 2019 (COVID-19). *medRxiv*. 2020;29. https://www.medrxiv.org/content/10.1101/2020.02.27.20028530v1.
97. Shauer A, Gotsman I, Keren A, et al. Acute Viral Myocarditis: Current Concepts in Diagnosis and Treatment. *Isr Med Assoc J*. 2013;15(3):180–185.
98. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;34(33):2636–2648.
99. Nikolaou M, Lazaros G, Karavidas A, Hatzianastasiou S, Miliopoulos D, Adamopoulos S. Recurrent viral myocarditis: The emerging link toward dilated cardiomyopathy. *Hellenic J Cardiol*. 2018;59(1):60–63.
100. Kühl U, Pauschinger M, Seeberg B, et al. Viral persistence in the myocardium is associated with progressive cardiac dysfunction. *Circulation*. 2005;112(13):1965–1970.
101. Felker GM, Boehmer JP, Hruban RH, et al. Echocardiographic findings in fulminant and acute myocarditis. *J Am Coll Cardiol*. 2000;36(1):227–232.
102. Ammirati E, Cipriani M, Moro C, et al. Clinical Presentation and Outcome in a Contemporary Cohort of Patients With Acute Myocarditis: Multicenter Lombardy Registry. *Circulation*. 2018;138(11):1088–1099.
103. Ponikowski P, Voors AA, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failureThe Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129–2200.
104. Suffredini AF, Fromm RE, Parker MM, et al. The Cardiovascular Response of Normal Humans to the Administration of Endotoxin. *N Engl J Med*. 1989;321(5):280–287.
105. Vieillard-Baron A, Cecconi M. Understanding cardiac failure in sepsis. *Intensive Care Med*. 2014;40(10):1560–1563.
106. Badorff C, Knowlton KU. Dystrophin disruption in enterovirus-induced myocarditis and dilated cardiomyopathy: from bench to bedside. *Med Microbiol Immunol*. 2004;193(2-3):121–126.
107. Kumar A, Thota V, Dee L, Olson J, Uretz E, Parrillo JE. Tumor necrosis factor alpha and interleukin 1beta are responsible for in vitro myocardial cell depression induced by human septic shock serum. *J Exp Med*. 1996;183(3):949–958.
108. Atefi G, Zetoune FS, Herron TJ, et al. Complement dependency of cardiomyocyte release of mediators during sepsis. *Faseb J*. 2011;25(7):2500–2508.
109. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. *J Infect*. 2020;80(6):656–665.
110. Cavusoglu Y, Kaya H, Eraslan S, Yilmaz MB. Hyponatremia is associated with occurrence of atrial fibrillation in outpatients with heart failure and reduced ejection fraction. *Hellenic J Cardiol*. 2019;60(2):117–121.
111. Severino A, Narducci ML, Pedicino D, et al. Reversible atrial gap junction remodeling during hypoxia/reoxygenation and ischemia: a possible arrhythmogenic substrate for atrial fibrillation. *Gen Physiol Biophys*. 2012;31(4):439–448.
112. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med*. 2020;382(24):2372–2374.
113. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;2020:105949.
114. U.S. Food and Drug Administration. *Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease*; 2020. https://www.fda.gov/media/136534/download. Accessed May 2, 2020.
115. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent Guidance for Navigating and Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19). *Mayo Clin Proc*. 2020;95(6):1213–1221.
116. Verny C, de Gennes C, Sébastien P, et al. [Heart conduction disorders in long-term treatment with chloroquine. Two new cases]. *Presse Medicale Paris Fr*. 1992;21(17):800–804.
117. Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J*. 2020;41(22):2070–2079.
118. Dong M, Liu T, Li G. Association between acute infections and risk of acute coronary syndrome: a meta-analysis. *Int J Cardiol*. 2011;147(3):479–482.
119. Corrales-Medina VF, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. *Circulation*. 2012;125(6):773–781.
120. Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. Multiorgan and Renal Tropism of SARS-CoV-2. *N Engl J Med*. 2020. https://doi.org/10.1056/NEJMc2011400.

121. Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: Physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. *Pharmacol Res*. 2017;125:21–38.
122. Nicin L, Abplanalp WT, Mellentin H, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. *Eur Heart J*. 2020;41(19):1804–1806.
123. Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). *Eur J Intern Med*. 2020;75:107–108.
124. Vardavas C, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. *Tob Induc Dis*. 2020;20(18):20.
125. 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. Gallagher T. *J Virol*. 2020;94(7):e00127–e00220.
126. Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X. Nicotine and the renin-angiotensin system. *Am J Physiol Regul Integr Comp Physiol*. 2018;315(5):R895–R906.
127. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic Control and Risk of Infections Among People With Type 1 or Type 2 Diabetes in a Large Primary Care Cohort Study. *Diabetes Care*. 2018;41(10):2127–2135.
128. Wang Q, Fang P, He R, et al. O-GlcNAc transferase promotes influenza A virus–induced cytokine storm by targeting interferon regulatory factor–5. *Sci Adv*. 2020;6(16), eaaz7086.
129. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–1034.
130. Romaní-Pérez M, Outeiriño-Iglesias V, Moya CM, et al. Activation of the GLP-1 Receptor by Liraglutide Increases ACE2 Expression, Reversing Right Ventricle Hypertrophy, and Improving the Production of SP-A and SP-B in the Lungs of Type 1 Diabetes Rats. *Endocrinology*. 2015;156(10):3559–3569.
131. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=&cntry=&state=&city=&dist=; 2020. Accessed April 12, 2020.
132. Tignanelli CJ, Ingraham NE, Sparks MA, et al. Antihypertensive drugs and risk of COVID-19? *Lancet Respir Med*. 2020;8(5):e30–e31.
133. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med*. 2020;382(25):2441–2448.
134. Zhang P, Zhu L, Cai J, et al. Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19. *Circ Res*. 2020;126(12):1671–1681.
135. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? *J Hypertens*. 2020;38(5):781–782.
136. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21.
137. Patel AB, Verma A. COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence? *JAMA*. 2020. https://doi.org/10.1001/jama.2020.4812.
138. Danser AHJ, Epstein M, Batlle D. Renin-Angiotensin System Blockers and the COVID-19 Pandemic: At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers. *Hypertension*. 2020;75(6):1382–1385.
139. *HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19*; 2020. https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp. Accessed May 3, 2020.
140. ESC Council on Hypertension. *Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers*; 2020. https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang. Accessed May 3, 2020.
141. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases. *Lancet Infect Dis*. 2003;3(11):722–727.
142. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2(1):69.
143. Magagnoli J, Narendran S, Pereira F, et al. *Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with Covid-19. Infectious Diseases (except HIV/AIDS)*; 2020. Published online April 23, 2020 . Accessed May 14, 2020.
144. Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020;55(4):105932.
145. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect*. 2020;50(4):384.
146. Mulangu S, Dodd LE, Davey RT, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med*. 2019;381(24):2293–2303.
147. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269–271.
148. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med*. 2020;382(24):2327–2336.
149. Liu Q, Zhou Y, Yang Z. The cytokine storm of severe influenza and development of immunomodulatory therapy. *Cell Mol Immunol*. 2016;13(1):3–10.
150. Guo C, Li B, Ma H, et al. Tocilizumab treatment in severe COVID-19 patients attenuates the inflammatory storm incited by monocyte centric immune interactions revealed by single-cell analysis. *Preprint at bioRxiv https://doi.org/10.1101/2020.04.08.029769 (2020)*. 2020.
151. Zimmermann P, Ziesenitz VC, Curtis N, Ritz N. The Immunomodulatory Effects of Macrolides—A Systematic Review of the Underlying Mechanisms. *Front Immunol*. 2018;9:302.
152. Ascierto PA, Fox B, Urba W, et al. Insights from immuno-oncology: the Society for Immunotherapy of Cancer Statement on access to IL-6-targeting therapies for COVID-19. *J Immunother Cancer*. 2020;8(1), e000878.
153. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing Cytokine Release Syndrome Associated With Novel T Cell-Engaging Therapies. *Canc J*. 2014;20(2):119–122.
154. Marques-da-Silva C, Chaves MM, Castro NG, Coutinho-Silva R, Guimaraes MZP. Colchicine inhibits cationic dye uptake induced by ATP in P2X2 and P2X7 receptor-expressing cells: implications for its therapeutic action. *Br J Pharmacol*. 2011;163(5):912–926.
155. Adler Y, Charron P. The 2015 ESC Guidelines on the diagnosis and management of pericardial diseases. *Eur Heart J*. 2015;36(42):2873–2874.
156. Deftereos SG, Siasos G, Giannopoulos G, et al. The Greek study in the effects of colchicine in COvid-19 complications prevention (GRECCO-19 study): Rationale and study design. *Hellenic J Cardiol*. 2020;S1109-9666(20)30061-0. doi: 10.1016/j.hjc.2020.03.002.
157. Norman Joseph, Bar-Yam Yaneer, Nassim Nicholas Taleb. *Systemic risk of pandemic via novel pathogens – Coronavirus: A note*. New England Complex Systems Institute; 2020. Published online January 26 . Accessed May 14, 2020.
158. Wang C, Pan R, Wan X, et al. Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China. *Int J Environ Res Publ Health*. 2020;17(5):1729.
159. Owens Ben. Reduced attendances and admissions: lessons from the covid crisis (online) *Health Service Journal*; 2020. https://www.hsj.co.uk/coronavirus/reduced-attendances-and-admissions-lessons-from-the-covid-crisis/7027541.article. Accessed May 3, 2020.
160. Tam Chor-Cheung Frankie, Kent-Shek Cheung, Lam Simon, et al. Impact of Coronavirus Disease 2019 (COVID-19) Outbreak on ST-Segment–Elevation Myocardial Infarction Care in Hong Kong, China. *Circ Cardiovasc Qual Outcomes*. 2020;13(4), e006631.
161. Moghadas SM, Shoukat A, Fitzpatrick MC, et al. Projecting hospital utilization during the COVID-19 outbreaks in the United States. *Proc Natl Acad Sci U S A*. 2020;117(16):9122–9126.
162. Iacobucci G. Covid-19: all non-urgent elective surgery is suspended for at least three months in England. BMJ. 020;368:m1106.
163. Koutsoukis A, Kanakakis I. Challenges and unanswered questions in STEMI management. *Hellenic J Cardiol*. 2019;60(4):211–215.
164. 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. https://doi.org/10.1001/jama.2020.2648.
165. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA*. 2020;323(18):1843–1844.
166. Guan W, Liang W, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *Eur Respir J*. 2020;55(5):2000547.
167. Zhang J, Dong X, Cao Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020. https://doi.org/10.1111/all.14238.
168. Xu X, Yu C, Qu J, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. *Eur J Nucl Med Mol Imag*. 2020;47(5):1275–1280.
169. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA*. 2020;323(16):1612–1614.
170. Mehra MR, Desai SS, Kuy S, Henry TD, PatelCardiovascular Disease AN. *Drug Therapy, and Mortality in Covid-19. N Engl J Med*. 2020;18382(25):e102.
171. Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and Epidemiological Characteristics of 1,420 European Patients with mild-to-moderate Coronavirus Disease 2019. *J Intern Med*. 2020. https://doi.org/10.1111/joim.13089.
172. Wei J-F, Huang F-Y, Xiong T-Y, et al. Acute myocardial injury is common in patients with covid-19 and impairs their prognosis. *Heart*. 2020. https://doi.org/10.1136/heartjnl-2020-317007.
173. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *J Am Med Assoc*. 2020;323(20):2052–2059.
174. Gao L, Jiang D, Wen X, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. *Respir Res*. 2020;21(1):83.
175. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis*. 2020. https://doi.org/10.1093/cid/ciaa270.
176. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Infect*. 2020;81(1):e6–e12.
177. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. *Ann Hematol*. 2020;99(6):1205–1208.

178. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin Chim Acta Int J Clin Chem*. 2020;506:145–148.
179. American College of Cardiology A. *COVID-19 Clinical Guidance for the Cardiovascular Care Team*; 2020. https://www.acc.org/latest-in-cardiology/features/~/media/Non-Clinical/Files-PDFs-Excel-MS-Word-etc/2020/02/S20028-ACC-Clinical-Bulletin-Coronavirus.pdf. Accessed May 4, 2020.
180. Han Y, Zeng H, Jiang H, et al. CSC Expert Consensus on Principles of Clinical Management of Patients with Severe Emergent Cardiovascular Diseases during the COVID-19 Epidemic. *Circulation*. 2020;141(20):e810–e816.
181. Lakkireddy DR, Chung MK, Gopinathannair R, et al. Guidance for Cardiac Electrophysiology During the Coronavirus (COVID-19) Pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association. *Heart Rhythm*. 2020. S1547-5271(20)30289-7.
182. Skulstad H, Cosyns B, Popescu BA, et al. COVID-19 pandemic and cardiac imaging: EACVI recommendations on precautions, indications, prioritization, and protection for patients and healthcare personnel. *Eur Heart J Cardiovasc Imaging*. 2020;21(6):592–598.