

Review

Cardiovascular Disease Complicating COVID-19 in the Elderly

Christopher Dayaramani, Joshua De Leon and Allison B. Reiss * 

Department of Medicine and Biomedical Research Institute, NYU Long Island School of Medicine, Mineola, NY 11501, USA; cdayaramani@gmail.com (C.D.); Joshua.DeLeon@NYULangone.org (J.D.L.)

* Correspondence: Allison.Reiss@NYULangone.org

Abstract: SARS-CoV-2, a single-stranded RNA coronavirus, causes an illness known as coronavirus disease 2019 (COVID-19). The highly transmissible virus gains entry into human cells primarily by the binding of its spike protein to the angiotensin-converting enzyme 2 receptor, which is expressed not only in lung tissue but also in cardiac myocytes and the vascular endothelium. Cardiovascular complications are frequent in patients with COVID-19 and may be a result of viral-associated systemic and cardiac inflammation or may arise from a virus-induced hypercoagulable state. This prothrombotic state is marked by endothelial dysfunction and platelet activation in both macrovasculature and microvasculature. In patients with subclinical atherosclerosis, COVID-19 may incite atherosclerotic plaque disruption and coronary thrombosis. Hypertension and obesity are common comorbidities in COVID-19 patients that may significantly raise the risk of mortality. Sedentary behaviors, poor diet, and increased use of tobacco and alcohol, associated with prolonged stay-at-home restrictions, may promote thrombosis, while depressed mood due to social isolation can exacerbate poor self-care. Telehealth interventions via smartphone applications and other technologies that document nutrition and offer exercise programs and social connections can be used to mitigate some of the potential damage to heart health.



Citation: Dayaramani, C.; De Leon, J.; Reiss, A.B. Cardiovascular Disease Complicating COVID-19 in the Elderly. *Medicina* **2021**, *57*, 833. <https://doi.org/10.3390/medicina57080833>

Academic Editor: Manfredi Rizzo

Received: 6 July 2021

Accepted: 12 August 2021

Published: 17 August 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Keywords: COVID-19; atherosclerosis; cardiovascular disease; hypertension; inflammation; cytokines

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide [1,2]. Its incidence increases sharply with age, and the elderly bear a disproportionate burden of CVD morbidity and mortality [3–5]. Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), has also caused significant mortality, specifically amongst the elderly, who are the most likely patient population to be hospitalized and die from the infection [6–8].

Factors that likely contribute to a complicated course and higher death rate in COVID-19 patients with underlying CVD are the hypercoagulable state that can result from COVID-19 infection, as well as polypharmacy (an indicator of comorbidities) [9–12]. Furthermore, the pandemic can disrupt lifestyle, leading to poorer diet and inactivity [13]. Another obstacle for older CVD patients is the avoidance of medical care from fear of contracting COVID-19. Hypertension, diabetes, and obesity, which often accompany CVD, are themselves established risk factors for severe COVID-19 that require careful management [14]. There is also a higher prevalence of cancer within the elderly population [15]. In addition to being immunocompromised from the cancer itself, cancer patients are frequently treated with immunosuppressants and cardiotoxic chemotherapies, making them especially susceptible to both viral illnesses and secondary cardiovascular complications. A particularly high risk of poor outcome is seen in those who have undergone recent bone marrow or stem cell transplantation and those exposed to poly ADP ribose polymerase (PARP) inhibitors [16,17]. The aforementioned conditions are more prevalent in those over age 65 and extremely common in those over age 85. Low vitamin D levels, common in the obese state, may add further risk [18].

Excess production of cytokines and cytokine storms are central to many of the sequelae of COVID-19, including damage to the cardiovascular system via pathways that involve direct cardiotoxicity and through inflammation-induced myocarditis and pericarditis [19,20]. The effects of cytokines, particularly of interleukin (IL)-6, will be discussed in the sections to follow.

Since persons with CVD are susceptible to poor COVID-19 outcomes, targeted treatment and removal of barriers to care are crucial for this population [21]. These may include the use of telemedicine, adjusting antihypertensive regimens, and online activity tracking. In this review, focused on persons over age 65, we explore the interactions between CVD and COVID-19 that lead to increased vulnerability to serious illness and death. We then describe strategies to mitigate these risks.

2. Hypertension, the Immune System, and COVID-19

About 20% of COVID-19 patients are hypertensive, but some older COVID-19 populations have high blood pressure (HBP) rates exceeding 50%, consistent with the prevalence of hypertension in persons of advancing age (Table 1) [22–24]. The status of hypertension as an independent risk factor for morbidity and mortality in COVID-19 is unclear. Data from China indicate a link between HBP and more severe COVID-19 infection [25]. A meta-analysis of 9 studies from China examining COVID-19 comorbidities found a significant correlation between COVID-19 severity and history of hypertension [26,27]. Based on pooled data from another meta-analysis from China, hypertension conferred a 2.5-fold increase in risk of severe COVID-19 illness and a 2.4-fold increase in mortality risk [28]. This relationship between hypertension and COVID-19 was also found, but to a lesser degree, in a community cohort study of persons aged 65 and older in England, where hypertension was found in 59.6% of 502 hospitalized COVID-19 patients and associated with a 1.38-fold greater risk for hospitalization but was not significantly associated with mortality [29]. A cross-sectional study of over 210,000 COVID-19 patients from Mexico found that a number of comorbidities, including hypertension, increased mortality [30]. Of these cases, over 20% were hypertensive, and hypertension increased the risk of death (adjusted odds ratio 1.24). Among older hospitalized COVID-19 patients in Italy, a retrospective study of 87 persons with an average age of 72 years found that over 50% were hypertensive but that hypertension did not predict mortality [31]. A case series of 5700 adults, median age 63 years, hospitalized in the New York City area for COVID-19, found that 56.6% of the patients had HBP, but the report did not address differences in outcome based on comorbidities or medications [18]. A study of 184 COVID-19 patients with a mean age of 64.7 years, admitted to a New York City hospital, found a positive correlation between hypertension and mortality [32]. In the United States, a multicenter cohort study of 2215 patients hospitalized in ICUs for COVID-19 (59.7% with hypertension, mean age 60.5 years) found that HBP did not increase the risk of death [33].

Numerous confounding variables make it difficult to link hypertension directly to COVID-19 severity [38]. Bajgain et al. recently posited that comorbidities such as hypertension may increase disease severity without escalating mortality [34]. Hypertension may increase hospital readmission rates after discharge for COVID-19 patients, with re-hospitalization most often due to respiratory distress or thrombotic episodes [35].

Although a contribution to COVID-19 mortality from hypertension is unconfirmed, increased susceptibility to severe illness may result from a chronic hypertension-induced inflammatory state causing immune dysregulation [39]. Basal levels of proinflammatory cytokines are increased in patients with hypertension, where ILs-6, -8, -18, transforming growth factor (TGF)- β , and tumor necrosis factor (TNF)- α are in disequilibrium with anti-inflammatory cytokines (ILs-4 and -10) [40].

Table 1. Hypertension and COVID-19 studies, with age included.

By First Author	Reference	Age Range	Details
Baradaran et al.	[22]	Mean age 51 years; 95% confidence interval, 49–54 years	Meta-analysis
Richardson et al.	[23]	Median age 63 years; interquartile range, 52–75 years	5700 subjects, New York City area, USA
Ahrenfeldt et al.	[24]	Mean age 68 years; age range 50–104 years	73,274 subjects, European region
Wu et al.	[25]	Median age 51 years; interquartile range, 43–60 years	201 subjects, Wuhan China
Chen et al.	[26]	Unspecified	Systematic review, 1936 subjects
Liu et al.	[27]	Median age 52.4 years; age range 32.5–64.0 years. Severe group older than non-severe group (60.9 years, range 45.0–74.0 years)	Meta-analysis, 10,948 subjects, most from China
Lippi et al.	[28]	COVID-19 severity associated with hypertension observed only in subjects over age 60 years	Systematic review, 2893 subjects, China
Atkins et al.	[29]	Mean age 74.3 years (SD 4.5)	UK Biobank Cohort, 507 COVID-19 positive subjects, hospitalized
Hernández-Galdamez et al.	[30]	45.7 (SD 16.3)	Cross-sectional study, 211,003 subjects, Mexico
De Vito et al.	[31]	Median age 72 years; interquartile range, 62.5–83.5 years	Retrospective, single-center study, 87 subjects, Italy
Mani et al.	[32]	Mean age 64.72 years (SD 14.87)	184 subjects, New York City area, USA
Gupta et al.	[33]	Mean age (all) 60.5 years (SD 14.5). Mean age (died) 66.0 years (SD 13.3)	Multicenter cohort study, 2215 subjects, USA
Bajgain et al.	[34]	Median age 56 years; interquartile range, 48.25–67.4 years	Systematic review, 22,753 subjects
Atalla et al.	[35]	Median age 61 years; interquartile range, 49–74 years	339 patients, Rhode Island, USA
Zheng et al.	[36]	Median age 47.13 years; range, 11–84 years.	Cohort study, 68 patients, China
Pan et al.	[37]	Median age of hypertensive patients 69 years; interquartile range, 62–76 years	Single-center, retrospective study, 996 patients, China

SD: standard deviation.

Hypertension affects CD8+ T-cells, essential components of cell-mediated immunity that protect against acute and persistent viral infections [41]. Hypertension stimulates CD8+ overproduction of cytokines, most notably, interferon (IFN)- γ and TNF- α [42,43]. These cytokines can adversely affect renal epithelium and raise blood pressure by increasing oxidative stress and renal sodium reabsorption [44,45]. Lymphopenia, due to reductions in both CD4+ and CD8+ T-cells, is well-documented in severe COVID-19 and may further disable antiviral defenses [36]. Pan and colleagues found that hypertensive COVID-19 patients have lower CD8+ counts, which may compromise the defense against the damaging flood of cytokines, characteristic of COVID-19 infection [37,38].

Another key potential link between COVID-19 and hypertension is IL-6, a pleiotropic cytokine found at high levels in cytokine storms, which are responsible for stimulating the production of acute-phase proteins [46,47]. Plasma IL-6 levels strongly correlate with

hypertension in humans [48]. In the initial phase of inflammation, IL-6, together with TGF- β , is necessary for the development of Th17 cells, which help induce a state of neutrophilic inflammation [49]. Chronic sustained IL-6 elevation can result in cardiac fibrosis and left ventricular hypertrophy [50–52]. High IL-6 levels are associated with an increased risk of death from COVID-19 infection [53–55]. Whether the IL-6 level rather than blood pressure is the independent variable determining COVID-19 severity risk is unresolved [56].

The possibility that IL-6 worsens COVID-19 outcomes has led to anti-IL-6 therapy trials with tocilizumab and sarilumab, but the results have been mixed [57–60]. A recent meta-analysis showed a significant reduction in all-cause mortality with a combination of tocilizumab and dexamethasone in patients of varying ages, with the median age of approximately late 50s to early 60s [61]. In a randomized study, both tocilizumab and sarilumab were effective in improving the survival of severely ill ICU patients (mean age of about 60 years) with COVID-19 [62]. It is possible that IL-6 either suppresses or increases viral replication and persistence, depending on multiple factors [63–65].

3. Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers (ARB) in COVID-19

The renin–angiotensin system (RAS) plays a key role in blood pressure regulation and sodium balance [66]. In the classical RAS pathway, renin cleaves the proenzyme angiotensinogen to form angiotensin (Ang)I. AngI is further cleaved by the angiotensin-converting enzyme (ACE) to yield AngII, which then acts through angiotensin receptor types 1 and 2 (AT1, AT2). The AngII/AT1 receptor axis mediates vasoconstriction, while the effects of AT2 are often antagonistic to AT1 (Figure 1). Vasoconstriction of the pulmonary vasculature can lead to right ventricular hypertrophy [67,68]. AngII also increases blood pressure indirectly by stimulating aldosterone production, which increases sodium and water reabsorption [69].

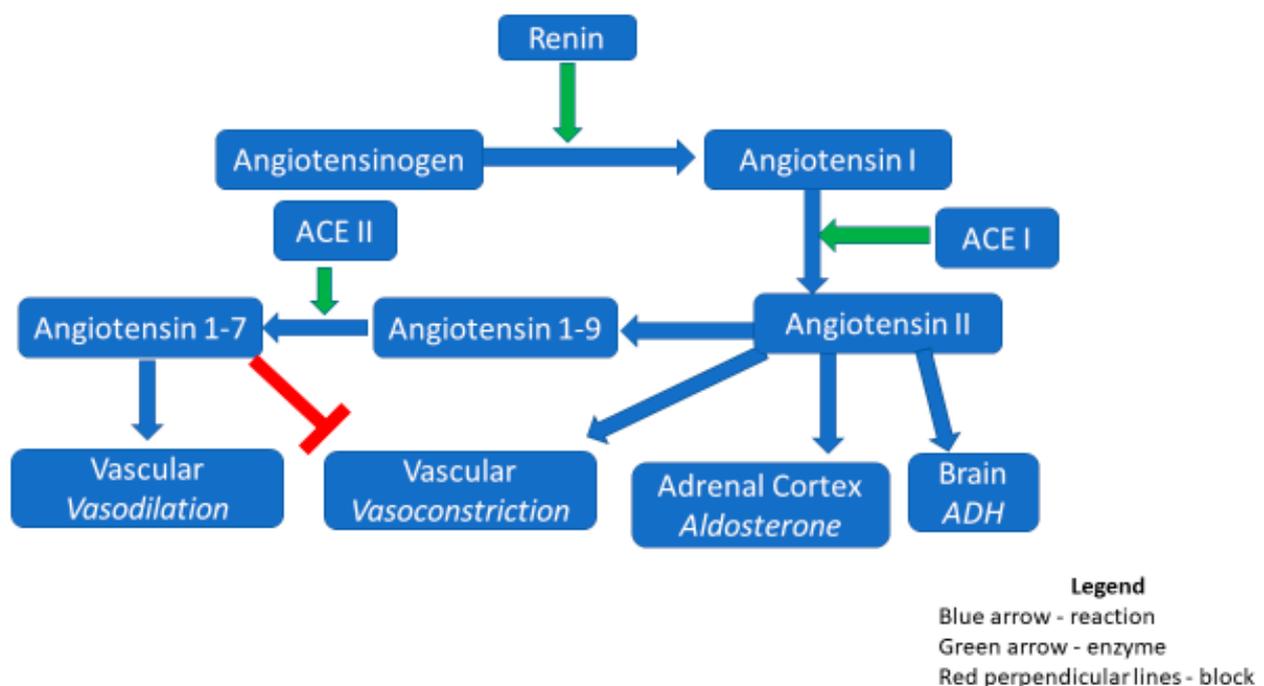


Figure 1. Renin–angiotensin–aldosterone system (RAS) and ACE inhibitors. The precursor molecule angiotensinogen is cleaved by renin to form angiotensin 1 in response to low sodium-chloride, as sensed by the macula densa. Angiotensin 1 is then further modified by the angiotensin-converting enzyme (ACE) to form angiotensin II. The ACE is the target of ACE inhibitors. Angiotensin II has direct effects on the vasculature, adrenal cortex, and brain, causing vasoconstriction and the secretion of aldosterone and the anti-diuretic hormone (ADH), respectively. An alternate pathway also exists, whereby angiotensin II is converted to angiotensins 1–9 and then angiotensins 1–7. A key enzyme in the formation of the latter is ACE2. Angiotensins 1–7, in contrast to angiotensin II, cause vasodilation and inhibit vasoconstriction.

ACE2, homologous to ACE, cleaves AngII via an alternative pathway to form Angiotensin 1–7. Angiotensin 1–7 has vasodilatory effects and protect against acute respiratory distress syndrome (ARDS) [70]. ACE2 is constitutively expressed in the lungs, kidney, gastrointestinal tract, and endothelium. The COVID-19 particle enters host cells via the full-length membrane-bound ACE2, which has an extracellular domain that acts as a receptor for the SARS-COV-2 spike protein [71]. The spike transmembrane glycoprotein is the target of many mRNA vaccines against COVID-19 [72].

Cleavage of the viral S-spike protein by host proprotein convertases generates S1 and S2 segments. The S1 (globular) subunit contains the receptor-binding domain that allows the attachment of COVID-19 to the ACE2 receptor. Once attached, COVID-19 fuses with the host cell membrane via the S2 subunit, enters the cell, and subsequently replicates in the cytoplasm [73,74]. Hypertension may also increase ACE2 enzyme concentration, which initially sparked concern that hypertension might increase viral entry into cells, amplifying the severity of infection [75]. Long-term use of ACE inhibitors (ACEIs) or ARBs can upregulate ACE enzymes. ACEIs are not known to increase pulmonary or serum ACE2 levels but do increase ACE2 in the brain, heart, and urine [76,77]. Overall, there exists no definitive evidence that ACEIs or ARBs increase COVID-19 risk [78–83]. In fact, a preponderance of evidence indicates ACEIs and ARBs are not harmful to COVID-19 patients and may even provide some benefit [84–86]. In a cohort from France of over 2 million hypertensive patients (mean age of 63 years), the outcome in patients with COVID-19 on ACEIs and ARBs was compared to those on calcium channel blockers. The ACEI and ARB groups showed a lower risk of COVID-19 hospitalization and a lower risk of intubation/death [87].

A retrospective single-center study from Long Island, New York, found that 614 of over 6000 COVID-19 patients were hypertensive and required hospitalization. These patients were categorized as taking and not taking ACEIs/ARBs prior to admission. Those who had been on ACEIs/ARBs and discontinued these medications during their hospital stay were twice as likely to be admitted to the ICU as those who continued their established treatment. The authors speculate that, although the medications may cause ACE2 receptor upregulation, discontinuing hypertensive medication can worsen illness because the benefits of controlling blood pressure outweigh other factors and, possibly, ACEIs/ARBs may mitigate the effects of cytokine storms [88]. This does not, however, indicate whether a change in medication prior to contraction of illness or onset of symptoms would confer benefit. Genetic variations in RAS genes and their expression profiles may also influence how pharmacotherapies affect COVID-19 outcomes; this is an area of active study [89,90].

The current recommendation is that patients should not change their regimen, as directed by the European and American Societies of Cardiology as well as the AHA [75,81,91–93].

4. Pulmonary Arterial Hypertension and Right Ventricular Hypertrophy

Pulmonary arterial hypertension (PAH), defined as a mean pressure above 25 mmHg in the pulmonary circulation at rest (normal = 24/12), confers susceptibility to vascular remodeling, fibrosis, and pulmonary edema [94]. Severe and sustained PAH can manifest as pulmonary edema and right-sided hypertrophy and/or heart failure. The incidence of COVID-19 in persons with PAH is comparable to that in the general population, and based on their documented propensity to worse outcomes during hospitalization in general, they may have greater mortality during COVID-19-related hospitalization [95,96]. In 24 COVID-19 patients with PAH, Pagnesi et al. determined that PAH specifically, and not right ventricular hypertrophy, was associated with more severe COVID-19 illness and worse clinical outcomes [97].

The RAS is of clinical importance in both PAH and COVID-19. Within the RAS, ACE2 may offer vasoprotective effects. ACE2 supplements are being considered as a treatment for several lung diseases [98]. Such supplements have ameliorating effects in PAH via increased Angiotensin 1–7 and nitric oxide bioavailability. Inhaled nitric oxide was shown to be effective in the 2003 SARS epidemic, causing the reversal of PAH and decreased lengths of

ventilator support. Clinical trials are evaluating this therapy in COVID-19 [99–111]. PAH is characterized by increased levels of the vasoconstrictor endothelin-1, and, therefore, along with increasing nitric oxide, the antagonism of the endothelin-1 receptor is effective PAH therapy that may be beneficial in COVID-19 infection [102]. Endothelin-1 may decrease ACE2, augmenting vasoconstriction via higher levels of AngII from lung epithelial cells [103–105]. Endothelin-1 may also promote endothelial dysfunction, platelet activation, and IL-6 secretion, all detrimental in the setting of COVID-19 [106,107].

Overall, COVID-19 is known to induce microthrombosis and hemorrhage in the alveoli and lung interstitium, and this may be exacerbated by pre-existing hypertension or increased vascular stress brought on by COVID-19-associated PAH. [108].

5. Coagulopathy in COVID-19: Mechanisms, Manifestations, and Treatment

A state of hypercoagulability frequently accompanies COVID-19, especially in severe disease [109,110]. Coagulopathy leaves patients vulnerable to thrombotic complications, including venous thromboembolism, pulmonary embolism, and disseminated intravascular coagulation [111–115].

Pro-inflammatory mediators produced during COVID-19 infection cause the release of tissue factor, an initiator of blood coagulation, from mononuclear cells [116,117]. IL-6, a key mediator elevated in the COVID-19 setting, can raise tissue factor levels and may also stimulate platelet production in bone marrow and lungs [118–120]. The panoply of inflammatory factors also activates endothelial cells, increasing their expression of adhesion molecules and leading to the release of the von Willebrand factor, thus promoting a procoagulant endothelial phenotype, excessive activity in the coagulation cascade, and multiple thrombotic complications.

Coagulation abnormalities are detected in laboratory tests as increased serum concentrations of the procoagulants fibrinogen and D-dimers as well as decreased antithrombin and prolonged prothrombin time (Table 2) [121,122].

Table 2. Early Markers Associated with Poor Outcomes in COVID-19 Patients.

Marker	Mean Level	Time of Measurement	Definition of Poor Outcome	Reference
IL-6	7.39 pg/mL	On admission	ARDS	[20]
Fibrinogen	5.16 g/L	On admission	Death	[113]
D-dimer	≥1 µg/mL	Outpatient	Death	[119]
LDH	445 µg/mL	On admission	Ventilation	[121]
CAC score	≥400	During hospitalization	Death	[123]
CRP	>40 mg/L	On admission	Death/ARDS	[124]
Ferritin	>950 ng/L	On admission	ARDS	[125]

ARDS: acute respiratory distress syndrome; CAC: coronary artery calcium; CRP: C-reactive protein; LDH: lactate dehydrogenase; IL-6: interleukin-6.

As a result of vascular injury, the propeptide fibrinogen is cleaved to fibrin, and high circulating fibrin levels are common in the early phase of COVID-19 infection. Either hyper- or hypofibrinolysis can occur in the setting of COVID-19, with hypofibrinolysis causing susceptibility to thrombus formation and hyperfibrinolysis causing susceptibility to bleeding [126]. The hypofibrinolytic state may be attributed to the elevated production of plasminogen activator inhibitor 1 (PAI-1) by epithelial and endothelial cells in the inflamed lung [127]. D-dimers, produced during the degradation of crosslinked fibrin, are below 0.5 µg/mL under normal physiologic conditions. An increase in fibrinogen and D-dimers is associated with the risk of microthrombus formation in COVID-19 patients and subsequent emboli and/or organ failure [128,129]. Fibrinogen levels were, on average, higher in patients who developed severe versus less severe illness (5.16 vs. 4.51 g/L) [130]. D-dimer levels over 1 µg/mL can identify patients with poorer prognoses early in the

course of disease and may signal the need for admission to critical care. Elevated D-dimer appears to be an independent risk factor for death [130,131]. In evaluating D-dimer levels, the implementation of age adjustment instead of a fixed cutoff may increase the accuracy of clinical assessment [132].

Sepsis-induced coagulopathy due to COVID-19 infection can lead to thrombotic stroke and myocardial infarction (MI) [133–136]. Losartan, previously mentioned for its ability to normalize levels of ACE2, is believed to be protective against strokes, offering another reason for its use in place of ACEIs [137].

Addressing the hypercoagulability risk at all levels of COVID-19 severity and in different age groups is challenging. Hypercoagulability may worsen in the setting of this pandemic via decreased activity, decreased exercise, and less movement in general under quarantine restrictions. Particularly affected are the elderly, with more limited movement capability due to age and co-morbidities. Venous stasis that accompanies inactivity, combined with hypercoagulability, sets the stage for two of three predisposing factors described in Virchow's triad for vascular thrombosis (blood flow alterations, endothelial injury, and hypercoagulability) [138]. Hypertension predisposes to endothelial injury, the last remaining factor in Virchow's triad. As discussed above, ACEIs should be used cautiously in COVID-19 patients. Anti-inflammatory drugs, cytokine inhibitors, and statins may be considered to protect the endothelium while simultaneously working against viral replication. Thromboprophylaxis with low molecular weight heparin could decrease D-dimer levels, and heparin can decrease fibrosis in those suffering from COVID-19-induced ARDS [130]. At this time, there are different approaches to coagulopathy in the field, with the evaluation of efficacy still ongoing. We await the results of major clinical trials regarding the dosage, class, and timeline of the use of anticoagulation therapy [139].

6. Myocardial Injury: Subclinical Atherosclerosis and Acute Coronary Syndrome

COVID-19 cardiac manifestations may include myocarditis, cardiac arrhythmias, and new or worsening heart failure, which may be particularly damaging to patients with a history of CVD [140,141]. The mechanisms underlying cardiac injury may be multifactorial (Figure 2). Inflammation and thrombosis are known culprits [142]. Infection increases overall metabolic demand and heart rate. This intensifies oxygen expenditure while shortening the filling time in the diastole and limiting coronary perfusion. Infection-mediated vasoconstriction and ventilation/perfusion mismatch negatively affecting blood oxygenation can exacerbate the oxygen deficit, leading to myocardial ischemia [143,144]. Internalized virus loads within cardiomyocytes may directly damage the heart.

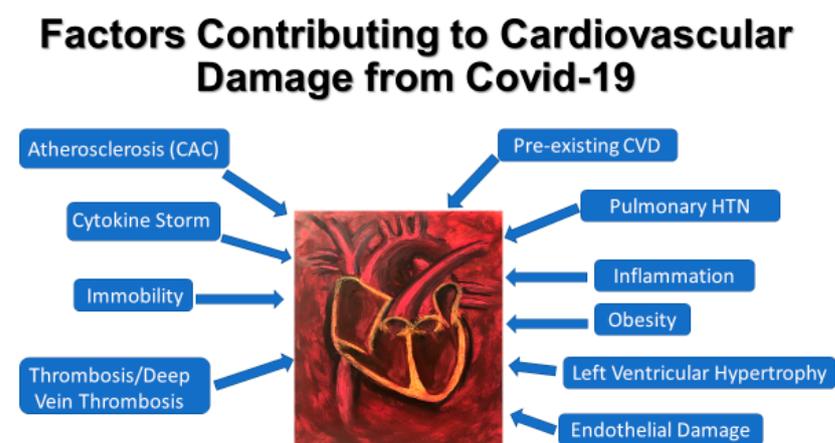


Figure 2. Factors contributing to cardiovascular damage in COVID-19. The white text in blue bubbles represents some of the pathologies that are associated with CVD in patients with COVID-19. Arrows are drawn from each factor to the central image of the heart and associated vasculature to emphasize their effect on the cardiovascular system specifically. CAC—Coronary Artery Calcium score; IL-6: interleukin-6; CVD: cardiovascular disease.

Immune-inflammatory-mediated injury to the heart from COVID-19 is more likely in severe cases and in those with HBP and can be monitored via the release of certain injury biomarkers, including cardiac-specific troponin and creatine kinase-MB [145–148]. Elevated lactate dehydrogenase (LDH) may be of cardiac origin but is nonspecific and can result from damage to other organs [149]. In COVID-19, LDH may be released from the lung since this is a key site for inflammatory processes [150]. LDH levels above 445 µg/mL on admission can be predictive of more severe COVID-19 [133,151–153]. An analysis of 353 COVID-19 patients, 79 (22.4%) of whom presented with myocardial injury, revealed more frequent elevations in LDH (mean level: 244 U/L (without MI) vs. 655 U/L (with MI) and creatinine (71 µmol/L (without MI) vs. 155 µmol/L (with MI) in the MI group during their hospitalization [154]. In addition to acute MI, differential diagnoses for increased serum cardiac biomarkers include stress-induced cardiomyopathy as well as myocarditis [155–157].

Evidence is accumulating that cardiac injury combined with COVID-19 infection, whether the myocardial injury is pre-existing or occurs during the infection, is associated with poorer outcomes [158–160]. A prospective, multicenter cohort study in Spain found that in patients with acute MI, COVID-19 is an independent risk factor for in-hospital mortality [161]. A small study of 77 COVID-19 patients who died in Wuhan, China, in early 2020 found that heart disease was present in 32%, and heart disease patients were more likely to be in the short-term survival group and to die within 14 days of COVID-19 onset [153].

COVID-19-associated coagulopathy can cause both large and small vessel embolic phenomena [123,162]. Postmortem histological evaluation has revealed signs of microvascular thrombosis in both skin and lungs [163]. Coronary arteries and coronary microvasculature may be affected by COVID-19 because this viral infection can directly activate the endothelium via inflammatory cytokines and indirectly by causing hypoxic conditions [124,164,165]. Further, the virus can directly infect endothelial cells, leading to an inflamed endothelium [166]. Coronary microvascular endothelial inflammation could lead to myocardial injury [125]. The potential for COVID-19 to compromise the patency of coronary bypass grafts has been suggested [167].

Subclinical atherosclerosis can impact the course of COVID-19. Coronary artery calcification (CAC), a specific imaging marker of coronary atherosclerosis that correlates with the plaque burden, can reveal previously undiagnosed CVD in COVID-19 patients [168]. In a cross-sectional study of 209 consecutively admitted COVID-19 patients without known CVD, assessed for CAC, CAC was detected in 106 (Table 2) (50.7%). Half of those positive patients required mechanical ventilation, extracorporeal membrane oxygenation, or died, whereas only 17.5% of patients negative for CAC had such poor outcomes [169]. A separate study by Nai Fovino et al. from Italy also found that high CAC as a surrogate for subclinical atherosclerosis was a marker for worse outcomes [170]. In this study, 75% of patients with high CAC either died or were admitted to the ICU, in contrast with only 20% of the group with lower CAC scores. Patients with a high score were also more likely to experience an MI.

C-reactive protein (CRP), an acute-phase reactant and marker of chronic low-grade systemic inflammation, has prognostic value as a predictor of cardiovascular risk. A number of studies have shown an association between elevated CRP and higher rates of COVID-19-related hospitalization and mortality (Table 2) [171,172]. While moderate CRP elevation in the 3–10 mg/L range is useful in cardiovascular risk prediction, CRP values in COVID-19 may exceed 40 mg/L, reflecting an acute inflammatory response unrelated to the heart [173,174]. Ferritin, critical for iron homeostasis, is also associated with a high risk of arterial hypertension and has utility in predicting the risk of ARDS in COVID-19 patients [175,176]. Ferritin is used to monitor systemic inflammation and may also be considered a marker of a hypercoagulable state [177]. Hypoxia is also a factor in elevating ferritin levels, and, thus, high ferritin may be a consequence of poor oxygenation [178].

Ferritin-targeted therapies are promising as a means of limiting the hypercoagulable state in the early phases of COVID-19 [179,180].

Patients with pre-existing CVD and atherosclerotic plaque containing inflammatory cells may be vulnerable to plaque activation upon exposure to cytokines such as IL-6 and IFN- γ [24,181–183]. Leukocyte infiltration and the activation of the endothelium contribute to the host synthesis of metalloproteinases and peptidases that break down collagen and weaken and destabilize plaque [184,185]. Furthermore, acute infection induces a prothrombotic, hypercoagulable state that can incite the formation of platelet thrombi [186].

7. Lifestyle

In response to the COVID-19 public health emergency, many governments imposed lockdown measures, stay-at-home orders, and quarantine. Curfews are in effect in many parts of the world, and social distancing is strongly recommended or mandated [187–190]. Quarantine refers to the separation of individuals or communities who may have been exposed to an infectious disease, while lockdown is a restriction in movement, with the closing of non-essential businesses and activities.

Quarantine and lockdown are effective in preventing disease transmission but can increase sedentary behavior both, directly through impeded access to exercise facilities and outdoor activities and the shutdown of interactive sports as well as indirectly through an increased prevalence of anxiety, depression, and insomnia that drain energy [191–195]. Sedentary behavior and low physical activity are of particular concern in those with CVD as these behaviors are highly associated with increased mortality in both males and females [196–198]. Physical activity has numerous favorable effects on the cardiovascular system, while lack of physical activity has long been linked to atherosclerosis [199,200]. Exercise delays the loss of age-associated endothelium-dependent vasodilation and reduces systemic inflammation and oxidative stress [201–204]. It also improves cardiac function and the lipid profile and decreases the resting heart rate [205–207]. Moderate to vigorous physical activity, 60 min per day, 5–7 days per week, is recommended to combat the physical and mental toll of COVID-19 isolation. Outdoor activities may include walking or jogging; if the workout is indoor only, home-based stairclimbing, walking with step-counts, or an exercise bicycle are good options [208,209].

Another lifestyle factor of concern for these patients during the pandemic is diet. To compound the issue, quality of diet and level of physical activity are linked, and people who spend a lot of time in front of screens also tend to eat more processed foods [210,211]. Pandemic constraints can lead to increased consumption of less healthy foods [212,213]. Boredom, anxiety, hesitation to venture outside, and fear of food shortages can drive the purchase of more salty, sugar-laden foods with high trans-fat content and longer shelf life. Poor dietary choices may result in weight gain and worsen pre-existing diabetes and hypertension [214]. A survey conducted in Italy found that 48% of participants noted weight gain during quarantine [215].

A balanced, nutritious diet containing fresh fruits and vegetables is important for the maintenance of healthy body weight, serum lipid profiles, glucose metabolism, and blood pressure levels [216–220]. Grocery delivery services are often available and particularly useful to susceptible populations, such as those suffering from CVD and the elderly. Of note, an anti-inflammatory diet, high in fiber from legumes, vegetables, and whole grains, can promote the production of short-chain fatty acids that may offer protection via the inhibition of cytokine production. Overall, this diet could potentially reduce the risk of cardiovascular complications of COVID-19 by promoting healthy weight, improving glucose control, and regulating metabolism [221]. Specific nutraceuticals of benefit to the cardiovascular system in COVID-19 are not yet defined, but the area is under study [222].

Quarantine may introduce stressors into life such as the loss of childcare resources, unemployment, death of a loved one, or strained relationships. Increased stress may lead to substance abuse. A study conducted in Poland showed that alcohol consumption in-

creased in 14.6% of survey respondents, and 45% of smokers acknowledged smoking more. Furthermore, 43% of respondents reported increased food consumption/snacking [223].

Lastly, quarantine and feelings of isolation can increase depression and anxiety [224]. Among 1593 participants, Lei et al. found the total prevalence of anxiety and depression to be approximately 8.3% and 14.6%, respectively, and the prevalence in the isolated group (12.9%, 22.4%) was significantly higher than that in the group that did not undergo quarantine (6.7%, 11.9%) [198]. The length of quarantine is also highly associated with the development of mental health issues, with persons under quarantine conditions for more than 10 days more likely to develop post-traumatic stress than those quarantined for less than 10 days [190]. Mental well-being can be impacted by fear of contracting the illness, fear of the financial burden associated with quarantine, restricted availability of food, lack of information regarding quarantine specifics, and excessive time spent on COVID-19 related news (>1 h) [225–227].

Quarantine can lead to increased suicide risk, particularly among the elderly, who are more likely to live alone and perceive themselves as a burden [228]. People with underlying CVD who are subjected to extended periods of quarantine may experience stress-related worsening of their cardiac status [229,230].

8. Delivering Care

Care delivery to patients with COVID-19 in office or hospital settings comes with the risk of transmission and spread to physicians, staff, and other patients. Telemedicine has been slowly gaining acceptance for the advantages it offers in access to care and cost-effectiveness. Now, the pandemic has accelerated its growth because it brings the key benefit of increased safety through the circumvention of direct physical contact [231]. This safety comes with a downside as fewer in-person visits to medical personnel can lead to decreased patient engagement [232]. The Technology Acceptance model states that the willingness of the patient to utilize technology depends on two key factors: perceived usefulness and perceived ease of use [233]. Therefore, barriers to use, such as lack of familiarity with technology, privacy concerns, or preference for in-person communication, may impact patient interaction and satisfaction with telemedicine [234,235].

Interestingly, in the case of hypertension, several studies have shown that virtual approaches are as effective or more effective than traditional treatments in achieving blood pressure goals [236–238]. ECG transmission systems may allow the detection of acute MI in real-time [239,240]. It is important to note that cardiac emergencies require in-person evaluation and treatment without delay.

9. Tailoring CVD Treatment and Vaccination in the Context of COVID-19

As of this writing, our understanding of the pathophysiologic mechanisms of Sars-Cov-2 infection is rapidly changing, and evidence thus far obtained continues to include potentially conflicting hypotheses [241,242]. As such, identifying targets for therapy remain elusive, and no definitive recommendations can be made. In addition, previously used therapies and some therapies under investigation may have adverse cardiovascular effects, while their clinical efficacy for combating COVID-19 is unconfirmed [243]. However, once specific cardiovascular complications have been identified, such as acute coronary syndromes, acute heart failure, or myocarditis, it is reasonable to employ standard treatments and therapies. Additionally, regardless of the exact mechanism(s) resulting in cardiovascular involvement, the severe inflammatory state associated with this disease pinpoints targeting this state as an important therapeutic goal. As demonstrated in their review, Samidurai and Das [244] note that the precise mechanisms linking CVD and worsened prognosis or higher mortality rate in COVID-19 patients remain unknown, but it is presumed that the pathophysiology of this virus' method of infection, because it may directly involve the cardiovascular system, predicts high rates of cardiovascular involvement and higher morbidity and mortality in patients with pre-existing CVD.

As noted previously, it is generally accepted within the medical community that ACE inhibitors and ARBs should be continued as treatment in hypertensive patients who have been diagnosed with COVID-19 [245,246]. In those with diabetes, COVID-19 may increase blood glucose levels, and, therefore, strict monitoring and blood sugar control may be indicated [247,248].

In those with CVD, who may be vulnerable to severe effects of COVID-19, prevention of illness by vaccination is preferable to treatment after infection. At the time of this writing, mRNA vaccines and adenoviral vaccines targeting the spike protein are being administered widely [249]. The American College of Cardiology recommends that persons with CVD be prioritized for vaccination and, thus far, the vaccine is well-tolerated by these patients [250,251]. A small study of 86 mostly young subjects from Rome found that hypertension, central obesity, and smoking were each associated with lower antibody titers in individuals vaccinated with the Pfizer-BioNTech mRNA vaccine and suggested that individuals with these risk factors may benefit from a booster vaccine dose [252].

One caveat is the possible link between COVID-19 mRNA vaccination and myocarditis, but this is largely seen in younger vaccine recipients with a median age of about 26 years [253,254]. A major concern is the diminished effectiveness of vaccination in those who have undergone solid organ transplants, including heart transplants. These patients may fail to mount a robust immune response to vaccination, and this lack of response is more likely in older persons above age 60. [255,256]. A booster vaccine dose may improve protection against illness in these patients [257].

10. Conclusions

For the reasons discussed above, the elderly with preexisting CVD are vulnerable to multiple cardiovascular manifestations that can lead to adverse outcomes. Table 3 highlights the most pressing issues facing older persons with CVD during the COVID-19 pandemic. It is our hope that with the release of highly effective vaccines, prevention will render treatment needs less urgent in the future, but as the virus evolves, new variants may prolong the pandemic [258]. Identification of effective therapies and novel therapeutic targets remain a central focus for research and development [259]. Preventive strategies such as advanced technological tools, including artificial intelligence and machine learning, can accelerate the diagnosis/screening of patients for the virus [260]. Rapid COVID-19 testing and self-testing are becoming more accessible [261]. In addition, analysis of available literature and identification of potential therapeutic targets and other specific clinical features can help address this contagion and perhaps form the foundation for addressing future pandemics.

Table 3. Summary of key issues for older COVID-19 patients with CVD.

Issue	Mitigating Actions
Hypertension	Blood pressure control, do not discontinue ACEI or ARB medications
Diabetes	Early glycemic control
Risk of coagulopathy	Consider pharmacological thromboprophylaxis, especially if hospitalized
Access to healthcare	Virtual approach as necessary, family involvement if possible
Consequences of isolation: sedentary, poor diet, depression, anxiety, stress	Vaccination, nutritious diet, exercise program, social engagement (virtual or in person), mental and behavioral healthcare and monitoring

Author Contributions: Conceptualization, A.B.R., J.D.L., and C.D.; writing—original draft preparation, A.B.R. and C.D.; writing review and editing, A.B.R. and J.D.L.; design of the figures, C.D. and A.B.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable. This study involved no humans or animals.

Informed Consent Statement: Not applicable.

Acknowledgments: The authors would also like to thank Charles Fuschillo, Bert E. Brodsky and The Alzheimer’s Foundation of America. We thank Robert Buescher and Edmonds Bafford. The original art in Figure 2 is by Samantha M. Steiner (oil pastel on heavy paper). This paper is dedicated to the memory of Bill E.C. Chester.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Benjamin, E.J.; Muntner, P.; Alonso, A.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Das, S.R.; et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: A report from the American Heart Association. *Circulation* **2019**, *139*, e56–e528. [[CrossRef](#)] [[PubMed](#)]
2. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **2016**, *388*, 1459–1544. [[CrossRef](#)]
3. Go, A.S.; Mozaffarian, D.; Roger, V.L.; Benjamin, E.J.; Berry, J.D.; Blaha, M.J.; Dai, S.; Ford, E.S.; Fox, C.S.; Franco, S.; et al. Heart Disease and Stroke Statistics-2014 update. *Circulation* **2014**, *129*, e28–e292. [[CrossRef](#)] [[PubMed](#)]
4. Savji, N.; Rockman, C.B.; Skolnick, A.H.; Guo, Y.; Adelman, M.A.; Riles, T.; Berger, J.S. Association between advanced age and vascular disease in different arterial territories: A population database of over 3.6 million subjects. *J. Am. Coll. Cardiol.* **2013**, *61*, 1736–1743. [[CrossRef](#)]
5. Rodgers, J.L.; Jones, J.; Bolleddu, S.I.; Vanthenapalli, S.; Rodgers, L.E.; Shah, K.; Karia, K.; Panguluri, S.K. Cardiovascular Risks Associated with Gender and Aging. *J. Cardiovasc. Dev. Dis.* **2019**, *6*, 19. [[CrossRef](#)]
6. Wu, Z.; McGoogan, J.M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* **2020**, *323*, 1239–1242. [[CrossRef](#)] [[PubMed](#)]
7. Neumann-Podczaska, A.; Chojnicki, M.; Karbowski, L.M.; Al-Saad, S.R.; Hashmi, A.A.; Chudek, J.; Tobis, S.; Kropinska, S.; Mozer-Lisewska, I.; Suwalska, A.; et al. Clinical characteristics and survival analysis in a small sample of older COVID-19 patients with defined 60-day outcome. *Int. J. Environ. Res. Public Health* **2020**, *17*, E8362. [[CrossRef](#)] [[PubMed](#)]
8. Grasselli, G.; Zangrillo, A.; Zanella, A.; Antonelli, M.; Cabrini, L.; Castelli, A.; Cereda, D.; Coluccello, A.; Foti, G.; Fumagalli, R.; et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* **2020**, *323*, 1574–1581. [[CrossRef](#)]
9. Yang, C.; Liu, F.; Liu, W.; Cao, G.; Liu, J.; Huang, S.; Zhu, M.; Tu, C.; Wang, J.; Xiong, B. Myocardial injury and risk factors for mortality in patients with COVID-19 pneumonia. *Int. J. Cardiol.* **2021**, *326*, 230–236. [[CrossRef](#)]
10. Nadkarni, G.N.; Lala, A.; Bagiella, E.; Chang, H.L.; Moreno, P.R.; Pujadas, E.; Arvind, V.; Bose, S.; Charney, A.W.; Chen, M.D.; et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. *J. Am. Coll. Cardiol.* **2020**, *76*, 1815–1826. [[CrossRef](#)]
11. Awortwe, C.; Cascorbi, I. Meta-analysis on outcome-worsening comorbidities of COVID-19 and related potential drug-drug interactions. *Pharmacol. Res.* **2020**, *161*, 105250. [[CrossRef](#)]
12. McQueenie, R.; Foster, H.M.E.; Jani, B.D.; Katikireddi, S.V.; Sattar, N.; Pell, J.P.; Ho, F.K.; Niedzwiedz, C.L.; Hastie, C.E.; Anderson, J.; et al. Multimorbidity, polypharmacy, and COVID-19 infection within the UK Biobank cohort. *PLoS ONE* **2020**, *15*, e0238091. [[CrossRef](#)] [[PubMed](#)]
13. Sánchez-Sánchez, E.; Ramírez-Vargas, G.; Avellaneda-López, Y.; Orellana-Pecino, J.I.; García-Marín, E.; Díaz-Jimenez, J. Eating habits and physical activity of the Spanish population during the COVID-19 pandemic period. *Nutrients* **2020**, *12*, 2826. [[CrossRef](#)] [[PubMed](#)]
14. Gao, Y.D.; Ding, M.; Dong, X.; Zhang, J.J.; Azkur, A.K.; Azkur, D.; Gan, H.; Sun, Y.L.; Fu, W.; Li, W.; et al. Risk factors for severe and critically ill COVID-19 patients: A review. *Allergy* **2021**, *76*, 428–455. [[CrossRef](#)] [[PubMed](#)]
15. Nolen, S.C.; Evans, M.A.; Fischer, A.; Corrada, M.M.; Kawas, C.H.; Bota, D.A. Cancer-Incidence, prevalence and mortality in the oldest-old. A comprehensive review. *Mech. Ageing Dev.* **2017**, *164*, 113–126. [[CrossRef](#)]
16. Quagliariello, V.; Bonelli, A.; Caronna, A.; Conforti, G.; Iovine, M.; Carbone, A.; Berretta, M.; Botti, G.; Maurea, N. SARS-CoV-2 Infection and Cardiology: From Cardiometabolic Risk Factors to Outcomes in Cancer Patients. *Cancers* **2020**, *12*, 3316. [[CrossRef](#)]

17. Huang, Y.; Hu, Z.; Hu, D.; Quan, Z.; Zhou, X.; Fan, G.; Chen, X.; Liu, X.; Zhang, Z.; Chen, G.; et al. Clinical characteristics, risk factors and cardiac manifestations of cancer patients with COVID-19. *J. Appl. Physiol.* **2021**. [[CrossRef](#)]
18. Gonçalves, T.; Gonçalves, S.; Guarnieri, A.; Riseigato, R.C.; Guimarães, M.P.; de Freitas, D.C.; Razuk-Filho, A.; Benedito Junior, P.B.; Parrillo, E.F. Prevalence of obesity and hypovitaminosis D in elderly with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin. Nutr. ESPEN* **2020**, *40*, 110–114. [[CrossRef](#)]
19. Vanderbeke, L.; Van Mol, P.; Van Herck, Y.; De Smet, F.; Humblet-Baron, S.; Martinod, K.; Antoranz, A.; Arijs, I.; Boeckx, B.; Bosisio, F.M.; et al. Monocyte-driven atypical cytokine storm and aberrant neutrophil activation as key mediators of COVID-19 disease severity. *Nat. Commun.* **2021**, *12*, 4117. [[CrossRef](#)]
20. Basso, C.; Leone, O.; Rizzo, S.; De Gaspari, M.; van der Wal, A.C.; Aubry, M.C.; Bois, M.C.; Lin, P.T.; Maleszewski, J.J.; Stone, J.R. Pathological features of COVID-19-associated myocardial injury: A multicentre cardiovascular pathology study. *Eur. Heart J.* **2020**, *41*, 3827–3835. [[CrossRef](#)]
21. Tai, S.; Tang, J.; Yu, B.; Tang, L.; Wang, Y.; Zhang, H.; Zhu, W.; Xiao, K.; Wen, C.; Tan, C.; et al. Association between cardiovascular burden and requirement of intensive care among patients with mild COVID-19. *Cardiovasc. Ther.* **2020**, *2020*, 9059562. [[CrossRef](#)]
22. Baradaran, A.; Ebrahimzadeh, M.H.; Baradaran, A.; Kachooei, A.R. Prevalence of comorbidities in COVID-19 patients: A systematic review and meta-analysis. *Arch. Bone Jt. Surg.* **2020**, *8*, 247–255. [[PubMed](#)]
23. Richardson, S.; Hirsch, J.S.; Narasimhan, M.; Crawford, J.M.; McGinn, T.; Davidson, K.W. Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* **2020**, *323*, 2052–2059. [[CrossRef](#)] [[PubMed](#)]
24. Ahrenfeldt, L.J.; Nielsen, C.R.; Möller, S.; Christensen, K.; Lindahl-Jacobsen, R. Burden and prevalence of risk factors for severe COVID-19 disease in the ageing European population—A SHARE-based analysis. *Z. Gesundh. Wiss.* **2020**, *11*, 1–10.
25. Wu, C.; Chen, X.; Cai, Y.; Xia, J.; Zhou, X.; Xu, S.; Huang, H.; Zhang, L.; Zhou, X.; Du, C.; et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern. Med.* **2020**, *180*, 934–943. [[CrossRef](#)]
26. Chen, Y.; Gong, X.; Wang, L.; Guo, J. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: A systematic review and meta-analysis. *medRxiv* **2020**. [[CrossRef](#)]
27. Liu, H.; Chen, S.; Liu, M.; Nie, H.; Lu, H. Comorbid chronic diseases are strongly correlated with disease severity among COVID-19 patients: A systematic review and meta-analysis. *Aging Dis.* **2020**, *11*, 668–678. [[CrossRef](#)] [[PubMed](#)]
28. Lippi, G.; Wong, J.; Henry, B.M. Hypertension in patients with coronavirus disease 2019 (COVID-19): A pooled analysis. *Pol. Arch. Intern. Med.* **2020**, *130*, 304–309.
29. Atkins, J.L.; Masoli, J.; Delgado, J.; Pilling, L.C.; Kuo, C.L.; Kuchel, G.A.; Melzer, D. Preexisting comorbidities predicting COVID-19 and mortality in the UK Biobank Community Cohort. *J. Gerontol. A Biol. Sci. Med. Sci.* **2020**, *75*, 2224–2230. [[CrossRef](#)]
30. Hernández-Galdamez, D.R.; González-Block, M.Á.; Romo-Dueñas, D.K.; Lima-Morales, R.; Hernández-Vicente, I.A.; Lumbreras-Guzmán, M.; Méndez-Hernández, P. Increased risk of hospitalization and death in patients with COVID-19 and pre-existing noncommunicable diseases and modifiable risk factors in Mexico. *Arch. Med. Res.* **2020**, *51*, 683–689. [[CrossRef](#)] [[PubMed](#)]
31. De Vito, A.; Geremia, N.; Fiore, V.; Princic, E.; Babudieri, S.; Madeddu, G. Clinical features, laboratory findings and predictors of death in hospitalized patients with COVID-19 in Sardinia, Italy. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 7861–7868. [[PubMed](#)]
32. Mani, V.R.; Kalabin, A.; Valdivieso, S.C.; Murray-Ramcharan, M.; Donaldson, B. At the epicenter of the American coronavirus outbreak—New York inner city hospital COVID-19 experience and current data: A retrospective analysis. *J. Med. Internet Res.* **2020**, *22*, e20548. [[CrossRef](#)] [[PubMed](#)]
33. Gupta, S.; Hayek, S.S.; Wang, W.; Chan, L.; Mathews, K.S.; Melamed, M.L.; Brenner, S.K.; Leonberg-Yoo, A.; Schenck, E.J.; Radbel, J.; et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *JAMA Intern. Med.* **2020**, *180*, 1436–1447. [[CrossRef](#)] [[PubMed](#)]
34. Bajgain, K.T.; Badal, S.; Bajgain, B.B.; Santana, M.J. Prevalence of comorbidities among individuals with COVID-19: A rapid review of current literature. *Am. J. Infect. Control* **2021**, *49*, 238–246. [[CrossRef](#)] [[PubMed](#)]
35. Atalla, E.; Kalligeros, M.; Giampaolo, G.; Mylona, E.K.; Shehadeh, F.; Mylonakis, E. Readmissions among patients with COVID-19. *Int. J. Clin. Pract.* **2021**, *75*, e13700. [[CrossRef](#)]
36. Zheng, M.; Gao, Y.; Wang, G.; Song, G.; Liu, S.; Sun, D.; Xu, Y.; Tian, Z. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell. Mol. Immunol.* **2020**, *17*, 533–535. [[CrossRef](#)]
37. Pan, W.; Zhang, J.; Wang, M.; Ye, J.; Xu, Y.; Shen, B.; He, H.; Wang, Z.; Ye, D.; Zhao, M.; et al. Clinical features of COVID-19 in patients with essential hypertension and the impacts of renin-angiotensin-aldosterone system inhibitors on the prognosis of COVID-19 patients. *Hypertension* **2020**, *76*, 732–741. [[CrossRef](#)]
38. Kreutz, R.; Algharably, E.A.E.; Azizi, M.; Dobrowolski, P.; Guzik, T.; Januszewicz, A.; Persu, A.; Prejbisz, A.; Riemer, T.G.; Wang, J.-G.; et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: Implications for COVID-19. *Cardiovasc. Res.* **2020**, *116*, 1688–1699. [[CrossRef](#)]
39. Caillon, A.; Schiffrin, E.L. Role of inflammation and immunity in hypertension: Recent epidemiological, laboratory, and clinical evidence. *Curr. Hypertens. Rep.* **2016**, *18*, 21. [[CrossRef](#)]
40. De Miguel, C.; Rudemiller, N.P.; Abais, J.M.; Mattson, D.L. Inflammation and hypertension: New understandings and potential therapeutic targets. *Curr. Hypertens. Rep.* **2015**, *17*, 507. [[CrossRef](#)]

41. Strioga, M.; Pasukoniene, V.; Characiejus, D. CD8+ CD28- and CD8+ CD57+ T cells and their role in health and disease. *Immunology* **2011**, *134*, 17–32. [[CrossRef](#)] [[PubMed](#)]
42. Barbaro, N.R.; Kirabo, A.; Harrison, D.G. A new role of Mister (MR) T in hypertension: Mineralocorticoid receptor, immune system, and hypertension. *Circ. Res.* **2017**, *120*, 1527–1529. [[CrossRef](#)] [[PubMed](#)]
43. Zhang, C.; Wang, F.S.; Silvestre, J.S.; Arenzana-Seisdedos, F.; Tang, H. Is aberrant CD8+ T cell activation by hypertension associated with cardiac injury in severe cases of COVID-19? *Cell. Mol. Immunol.* **2020**, *17*, 675–676. [[CrossRef](#)] [[PubMed](#)]
44. Norlander, A.E.; Madhur, M.S.; Harrison, D.G. The immunology of hypertension. *J. Exp. Med.* **2018**, *215*, 21–33. [[CrossRef](#)]
45. Trott, D.W.; Thabet, S.R.; Kirabo, A.; Saleh, M.A.; Itani, H.; Norlander, A.E.; Wu, J.; Goldstein, A.; Arendshorst, W.J.; Madhur, M.S.; et al. Oligoclonal CD8+ T cells play a critical role in the development of hypertension. *Hypertension* **2014**, *64*, 1108–1115. [[CrossRef](#)] [[PubMed](#)]
46. Pedersen, S.F.; Ho, Y.-C. SARS-CoV-2: A storm is raging. *J. Clin. Investig.* **2020**, *130*, 2202–2205. [[CrossRef](#)] [[PubMed](#)]
47. Tanaka, T.; Narazaki, M.; Kishimoto, T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. *Immunotherapy* **2016**, *8*, 959–970. [[CrossRef](#)]
48. Vázquez-Oliva, G.; Fernández-Real, J.M.; Zamora, A.; Vilaseca, M.; Badimón, L. Lowering of blood pressure leads to decreased circulating interleukin-6 in hypertensive subjects. *J. Hum. Hypertens.* **2005**, *19*, 457–462. [[CrossRef](#)]
49. Korn, T.; Bettelli, E.; Oukka, M.; Kuchroo, V.K. IL-17 and Th17 Cells. *Annu. Rev. Immunol.* **2009**, *27*, 485–517. [[CrossRef](#)] [[PubMed](#)]
50. Hirota, H.; Yoshida, K.; Kishimoto, T.; Taga, T. Continuous activation of gp130, a signal-transducing receptor component for interleukin 6-related cytokines, causes myocardial hypertrophy in mice. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 4862–4866. [[CrossRef](#)]
51. Fontes, J.A.; Rose, N.R.; Cihakova, D. The varying faces of IL-6: From cardiac protection to cardiac failure. *Cytokine* **2015**, *74*, 62–68. [[CrossRef](#)]
52. Tanase, D.M.; Gosav, E.M.; Radu, S.; Ouatu, A.; Rezus, C.; Ciocoiu, M.; Costea, C.F.; Floria, M. Arterial hypertension and interleukins: Potential therapeutic target or future diagnostic marker? *Int. J. Hypertens.* **2019**, *2019*, 3159283. [[CrossRef](#)]
53. Ruscica, M.; Macchi, C.; Iodice, S.; Tersalvi, G.; Rota, I.; Ghidini, S.; Terranova, L.; Valenti, L.; Amati, F.; Aliberti, S.; et al. Prognostic parameters of in-hospital mortality in COVID-19 patients—An Italian experience. *Eur. J. Clin. Investig.* **2021**, *51*, e13629. [[CrossRef](#)]
54. Liu, F.; Ji, C.; Luo, J.; Wu, W.; Zhang, J.; Zhong, Z.; Lankford, S.; Huang, H.; Lin, F.; Wang, Y.; et al. Clinical characteristics and corticosteroids application of different clinical types in patients with corona virus disease 2019. *Sci. Rep.* **2020**, *10*, 13689. [[CrossRef](#)] [[PubMed](#)]
55. Aziz, M.; Fatima, R.; Assaly, R. Elevated interleukin-6 and severe COVID-19: A meta-analysis. *J. Med. Virol.* **2020**, *92*, 2283–2285. [[CrossRef](#)] [[PubMed](#)]
56. Sivakorn, C.; Dechsanga, J.; Jamjumrus, L.; Boonak, K.; Schultz, M.J.; Dorndorp, A.M.; Phumratanaprapin, W.; Ratanarat, R.; Naorungroj, T.; Wattanawitichai, P.; et al. High mobility group box 1 and interleukin 6 at intensive care unit admission as biomarkers in critically ill COVID-19 Patients. *Am. J. Trop. Med. Hyg.* **2021**, *105*, 73. [[CrossRef](#)]
57. Zhang, Y.; Zhong, Y.; Pan, L.; Dong, J. Treat 2019 novel coronavirus (COVID-19) with IL-6 inhibitor: Are we already that far? *Drug Discov. Ther.* **2020**, *14*, 100–102. [[CrossRef](#)]
58. Meletiadis, J.; Tsioudras, S.; Tsirigotis, P. Interleukin-6 blocking vs. JAK-STAT inhibition for prevention of lung injury in patients with COVID-19. *Infect. Dis. Ther.* **2020**, *9*, 707–713. [[CrossRef](#)]
59. Pettit, N.N.; Nguyen, C.T.; Mutlu, G.M.; Wu, D.; Kimmig, L.; Pitrak, D.; Pursell, K. Late onset infectious complications and safety of tocilizumab in the management of COVID-19. *J. Med. Virol.* **2021**, *93*, 1459–1464. [[CrossRef](#)] [[PubMed](#)]
60. Montesarchio, V.; Parella, R.; Iommelli, C.; Bianco, A.; Manzillo, E.; Fraganza, F.; Palumbo, C.; Rea, G.; Murino, P.; De Rosa, R.; et al. Outcomes and biomarker analyses among patients with COVID-19 treated with interleukin 6 (IL-6) receptor antagonist sarilumab at a single institution in Italy. *J. Immunother. Cancer* **2020**, *8*, e001089. [[CrossRef](#)]
61. Selvaraj, V.; Khan, M.S.; Bavishi, C.; Dapaah-Afriyie, K.; Finn, A.; Lal, A.; Mylonakis, E. Tocilizumab in Hospitalized Patients with COVID-19: A Meta Analysis of Randomized Controlled Trials. *Lung* **2021**, *199*, 239–248. [[CrossRef](#)]
62. EMAP-CAP Investigators; Gordon, A.C.; Mouncey, P.R.; Al-Beidh, F.; Rowan, K.M.; Nichol, A.D.; Arabi, Y.M.; Annane, D.; Beane, A.; van Bentum-Puijk, W.; et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with COVID-19. *N. Engl. J. Med.* **2021**, *384*, 1491–1502.
63. McGonagle, D.; Sharif, K.; O'Regan, A.; Bridgewood, C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun. Rev.* **2020**, *19*, 102537. [[CrossRef](#)] [[PubMed](#)]
64. Cunningham, L.; Kimber, I.; Basketter, D.A.; McFadden, J.P. Why judiciously timed anti-IL 6 therapy may be of benefit in severe COVID-19 infection. *Autoimmun. Rev.* **2020**, *19*, 102563. [[CrossRef](#)] [[PubMed](#)]
65. McGonagle, D.; Sharif, K.; O'Regan, A.; Bridgewood, C. Re: Patiently waiting for the results of anti-IL 6 therapy in severe COVID-19 infection. *Autoimmun. Rev.* **2020**, *19*, 102560. [[CrossRef](#)] [[PubMed](#)]
66. Forrester, S.J.; Booz, G.W.; Sigmund, C.D.; Coffman, T.M.; Kawai, T.; Rizzo, V.; Scalia, R.; Eguchi, S. Angiotensin II signal transduction: An update on mechanisms of physiology and pathophysiology. *Physiol. Rev.* **2018**, *98*, 1627–1738. [[CrossRef](#)] [[PubMed](#)]
67. Pascaud, M.A.; Griscelli, F.; Raoul, W.; Marcos, E.; Opolon, P.; Raffestin, B.; Perricaudet, M.; Adnot, S.; Eddahibi, S. Lung overexpression of angiotensin aggravates pulmonary hypertension in chronically hypoxic mice. *Am. J. Respir. Cell. Mol. Biol.* **2003**, *29*, 449–457. [[CrossRef](#)]

68. De Man, F.S.; Tu, L.; Handoko, M.L.; Rain, S.; Ruiters, G.; Francois, C.; Schalij, I.; Dorfmüller, P.; Simonneau, G.; Fadel, E.; et al. Dysregulated renin-angiotensin-aldosterone system contributes to pulmonary arterial hypertension. *Am. J. Respir. Crit. Care Med.* **2012**, *186*, 780–789. [[CrossRef](#)]
69. Morizane, S.; Mitani, F.; Ozawa, K.; Ito, K.; Matsushashi, T.; Katsumata, Y.; Ito, H.; Yan, X.; Shinmura, K.; Nishiyama, A.; et al. Biphasic time course of the changes in aldosterone biosynthesis under high-salt conditions in Dahl salt-sensitive rats. *Arterioscler. Thromb. Vasc. Biol.* **2012**, *32*, 1194–1203. [[CrossRef](#)]
70. Chen, Y.; Zhao, W.; Liu, C.; Meng, W.; Zhao, T.; Bhattacharya, S.K.; Sun, Y. Molecular and cellular effect of angiotensin 1-7 on hypertensive kidney disease. *Am. J. Hypertens.* **2019**, *32*, 460–467. [[CrossRef](#)] [[PubMed](#)]
71. Zhou, P.; Yang, X.L.; Wang, X.G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.R.; Zhu, Y.; Li, B.; Huang, C.L.; et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **2020**, *579*, 270–273. [[CrossRef](#)]
72. Jackson, L.A.; Anderson, E.J.; Roupahel, N.G.; Roberts, P.C.; Makhene, M.; Coler, R.N.; McCullough, M.P.; Chappell, J.D.; Denison, M.R.; Stevens, L.J.; et al. An mRNA vaccine against SARS-CoV-2—Preliminary report. *N. Engl. J. Med.* **2020**, *383*, 1920–1931. [[CrossRef](#)]
73. Hasan, A.; Paray, B.A.; Hussain, A.; Qadir, F.A.; Attar, F.; Aziz, F.M.; Sharifi, M.; Derakhshankhah, H.; Rasti, B.; Mehrabi, M.; et al. A review on the cleavage priming of the spike protein on coronavirus by angiotensin-converting enzyme-2 and furin. *J. Biomol. Struct. Dyn.* **2021**, *39*, 3025–3033. [[CrossRef](#)]
74. Li, W.; Moore, M.J.; Vasilieva, N.; Sui, J.; Wong, S.K.; Berne, M.A.; Somasundaran, M.; Sullivan, J.L.; Luzuriaga, K.; Greenough, T.C.; et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* **2003**, *426*, 450–454. [[CrossRef](#)]
75. Sommerstein, R.; Kochen, M.M.; Messerli, F.H.; Gräni, C. Coronavirus Disease 2019 (COVID-19): Do angiotensin-converting enzyme inhibitors/angiotensin receptor blockers have a biphasic effect? *J. Am. Heart Assoc.* **2020**, *9*, e016509. [[CrossRef](#)] [[PubMed](#)]
76. Ferrario, C.M.; Jessup, J.; Chappell, M.C.; Averill, D.B.; Brosnihan, K.B.; Tallant, E.A.; Diz, D.I.; Gallagher, P.E. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* **2005**, *111*, 2605–2610. [[CrossRef](#)] [[PubMed](#)]
77. Furuhashi, M.; Moniwa, N.; Mita, T.; Fuseya, T.; Ishimura, S.; Ohno, K.; Shibata, S.; Tanaka, M.; Watanabe, Y.; Akasaka, H.; et al. Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker. *Am. J. Hypertens.* **2015**, *28*, 15–21. [[CrossRef](#)] [[PubMed](#)]
78. Chung, M.K.; Karnik, S.; Saef, J.; Bergmann, C.; Barnard, J.; Lederman, M.M.; Tilton, J.; Cheng, F.; Harding, C.V.; Young, J.B.; et al. SARS-CoV-2 and ACE2: The biology and clinical data settling the ARB and ACEI controversy. *EBioMedicine* **2020**, *58*, 102907. [[CrossRef](#)]
79. Raisi-Estabragh, Z.; McCracken, C.; Ardissino, M.; Bethell, M.S.; Cooper, J.; Cooper, C.; Harvey, N.C.; Petersen, S.E. Renin-angiotensin-aldosterone system blockers are not associated with coronavirus disease 2019 (COVID-19) hospitalization: Study of 1439 UK Biobank cases. *Front. Cardiovasc. Med.* **2020**, *7*, 138. [[CrossRef](#)]
80. Cheng, X.; Cai, G.; Wen, X.; Gao, L.; Jiang, D.; Sun, M.; Qin, S.; Zhou, J.; Zhang, D. Clinical characteristics and fatal outcomes of hypertension in patients with severe COVID-19. *Aging* **2020**, *12*, 23436–23449. [[CrossRef](#)]
81. Patel, A.B.; Verma, A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: What is the evidence? *JAMA* **2020**, *323*, 1769–1770. [[CrossRef](#)]
82. Nunes, J.P.L. Mortality and use of angiotensin-converting enzyme inhibitors in COVID 19 disease: A systematic review. *Porto Biomed. J.* **2020**, *5*, e085. [[CrossRef](#)]
83. Ren, L.; Yu, S.; Xu, W.; Overton, J.L.; Chiamvimonvat, N.; Thai, P.N. Lack of association of antihypertensive drugs with the risk and severity of COVID-19: A meta-analysis. *J. Cardiol.* **2021**, *77*, 482–491. [[CrossRef](#)] [[PubMed](#)]
84. Loader, J.; Lampa, E.; Gustafsson, S.; Cars, T.; Sundström, J. Renin-Angiotensin Aldosterone System Inhibitors in Primary Prevention and COVID-19. *J. Am. Heart Assoc.* **2021**, *10*, e021154. [[CrossRef](#)]
85. Jia, N.; Zhang, G.; Sun, X.; Wang, Y.; Zhao, S.; Chi, W.; Dong, S.; Xia, J.; Zeng, P.; Liu, D. Influence of angiotensin converting enzyme inhibitors/angiotensin receptor blockers on the risk of all-cause mortality and other clinical outcomes in patients with confirmed COVID-19: A systemic review and meta-analysis. *J. Clin. Hypertens.* **2021**. [[CrossRef](#)] [[PubMed](#)]
86. Ssentongo, A.E.; Ssentongo, P.; Heilbrunn, E.S.; Lekoubou, A.; Du, P.; Liao, D.; Oh, J.S.; Chinchilli, V.M. Renin-angiotensin-aldosterone system inhibitors and the risk of mortality in patients with hypertension hospitalised for COVID-19: Systematic review and meta-analysis. *Open Heart* **2020**, *7*, e001353. [[CrossRef](#)]
87. Semenzato, L.; Botton, J.; Drouin, J.; Baricault, B.; Vabre, C.; Cuenot, F.; Penso, L.; Herlemont, P.; Sbidian, E.; Weill, A.; et al. Antihypertensive Drugs and COVID-19 Risk: A Cohort Study of 2 Million Hypertensive Patients. *Hypertension* **2021**, *77*, 833–842. [[CrossRef](#)] [[PubMed](#)]
88. Lam, K.W.; Chow, K.W.; Vo, J.; Hou, W.; Li, H.; Richman, P.S.; Mallipattu, S.K.; Skopicki, H.A.; Singer, A.J.; Duong, T.Q. Continued in-hospital ACE inhibitor and ARB use in hypertensive COVID-19 patients is associated with positive clinical outcomes. *J. Infect. Dis.* **2020**, *222*, 1256–1264. [[CrossRef](#)] [[PubMed](#)]
89. Gemmati, D.; Tisato, V. Genetic Hypothesis and Pharmacogenetics Side of Renin-Angiotensin-System in COVID-19. *Genes* **2020**, *11*, 1044. [[CrossRef](#)]
90. Snyder, E.M.; Johnson, B.D. ACE2 and COVID-19: Using antihypertensive medications and pharmacogenetic considerations. *Pharmacogenomics* **2020**, *21*, 695–703. [[CrossRef](#)]

91. Spaccarotella, C.; Mazzitelli, M.; Migliarino, S.; Curcio, A.; De Rosa, S.; Torti, C.; Indolfi, C. Therapy with RAS inhibitors during the COVID-19 pandemic. *J. Cardiovasc. Med.* **2021**, *22*, 329–334. [[CrossRef](#)]
92. de la Cruz, A.; Ashraf, S.; Vittorio, T.J.; Bella, J.N. COVID-19 and renin-angiotensin system modulators: What do we know so far? *Expert Rev. Cardiovasc. Ther.* **2020**, *18*, 743–748. [[CrossRef](#)]
93. Vázquez-Cornejo, E. Considerations on the use of antihypertensive blockers of the renin-angiotensin system in adults and children in the face of the COVID-19 pandemic. *Bol. Med. Hosp. Infant Mex.* **2020**, *77*, 274–281. [[CrossRef](#)] [[PubMed](#)]
94. Hoepfer, M.M.; Bogaard, H.J.; Condliffe, R.; Frantz, R.; Khanna, D.; Kurzyna, M.; Langleben, D.; Manes, A.; Satoh, T.; Torres, F.; et al. Definitions and diagnosis of pulmonary hypertension. *J. Am. Coll. Cardiol.* **2013**, *62*, D42–D50. [[CrossRef](#)]
95. Lee, J.D.; Burger, C.D.; Delossantos, G.B.; Grinnan, D.; Ralph, D.D.; Rayner, S.G.; Ryan, J.J.; Safdar, Z.; Ventetuolo, C.E.; Zamanian, R.T.; et al. A Survey-based Estimate of COVID-19 Incidence and outcomes among patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension and impact on the process of care. *Ann. Am. Thorac. Soc.* **2020**, *17*, 1576–1582. [[CrossRef](#)] [[PubMed](#)]
96. Ryan, J.J.; Melendres-Groves, L.; Zamanian, R.T.; Oudiz, R.J.; Chakinala, M.; Rosenzweig, E.B.; Gomberg-Maitland, M. Care of patients with pulmonary arterial hypertension during the coronavirus (COVID-19) pandemic. *Pulm. Circ.* **2020**, *10*. [[CrossRef](#)] [[PubMed](#)]
97. Pagnesi, M.; Baldetti, L.; Beneduce, A.; Calvo, F.; Gramegna, M.; Pazzanese, V.; Ingallina, G.; Napolano, A.; Finazzi, R.; Ruggeri, A.; et al. Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19. *Heart* **2020**, *106*, 1324–1331. [[CrossRef](#)] [[PubMed](#)]
98. Farha, S.; Heresi, G.A. COVID-19 and pulmonary arterial hypertension: Early data and many questions. *Ann. Am. Thorac. Soc.* **2020**, *17*, 1528–1530. [[CrossRef](#)]
99. Zhang, J.; Dong, J.; Martin, M.; He, M.; Gongol, B.; Marin, T.L.; Chen, L.; Shi, X.; Yin, Y.; Shang, F.; et al. AMP-activated protein kinase phosphorylation of angiotensin-converting enzyme 2 in endothelium mitigates pulmonary hypertension. *Am. J. Respir. Crit. Care Med.* **2018**, *198*, 509–520. [[CrossRef](#)] [[PubMed](#)]
100. Alvarez, R.A.; Berra, L.; Gladwin, M.T. Home nitric oxide therapy for COVID-19. *Am. J. Respir. Crit. Care Med.* **2020**, *202*, 16–20. [[CrossRef](#)]
101. Adusumilli, N.C.; Zhang, D.; Friedman, J.M.; Friedman, A.J. Harnessing nitric oxide for preventing, limiting and treating the severe pulmonary consequences of COVID-19. *Nitric Oxide* **2020**, *103*, 4–8. [[CrossRef](#)] [[PubMed](#)]
102. Parikh, V.; Bhardwaj, A.; Nair, A. Pharmacotherapy for pulmonary arterial hypertension. *J. Thorac. Dis.* **2019**, *11*, S1767–S1781. [[CrossRef](#)]
103. Zhang, H.; Li, Y.; Zeng, Y.; Wu, R.; Ou, J. Endothelin-1 downregulates angiotensin-converting enzyme-2 expression in human bronchial epithelial cells. *Pharmacology* **2013**, *91*, 297–304. [[CrossRef](#)] [[PubMed](#)]
104. Wenzel, R.R.; Rütthemann, J.; Bruck, H.; Schäfers, R.F.; Michel, M.C.; Philipp, T. Endothelin-A receptor antagonist inhibits angiotensin II and noradrenaline in man. *Br. J. Clin. Pharmacol.* **2001**, *52*, 151–157. [[CrossRef](#)] [[PubMed](#)]
105. Badagliacca, R.; Sciomer, S.; Petrosillo, N. Endothelin receptor antagonists for pulmonary arterial hypertension and COVID-19: Friend or foe? *J. Heart Lung Transplant.* **2020**, *39*, 729–730. [[CrossRef](#)]
106. Mohammed El Tabaa, M.; Mohammed El Tabaa, M. Targeting Nephrylysin (NEP) pathways: A potential new hope to defeat COVID-19 ghost. *Biochem. Pharmacol.* **2020**, *178*, 114057. [[CrossRef](#)] [[PubMed](#)]
107. D’Alessandro, A.; Thomas, T.; Dzieciatkowska, M.; Hill, R.C.; Francis, R.O.; Hudson, K.E.; Zimring, J.C.; Hod, E.A.; Spitalnik, S.L.; Hansen, K.C. Serum proteomics in COVID-19 patients: Altered coagulation and complement status as a function of IL-6 level. *J. Proteome Res.* **2020**, *19*, 4417–4427. [[CrossRef](#)] [[PubMed](#)]
108. McGonagle, D.; O’Donnell, J.S.; Sharif, K.; Emery, P.; Bridgewood, C. Why the immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia are distinct from macrophage activation syndrome with disseminated intravascular coagulation. *Lancet Rheum.* **2020**, *2*, e437–e445. [[CrossRef](#)]
109. Terpos, E.; Ntanasis-Stathopoulos, I.; Elalamy, I.; Kastritis, E.; Sergentanis, T.N.; Politou, M.; Psaltopoulou, T.; Gerotziafas, G.T.; Dimopoulos, M. A Hematological findings and complications of COVID-19. *Am. J. Hematol.* **2020**, *95*, 834–847. [[CrossRef](#)]
110. Klok, F.A.; Kruip, M.J.H.A.; van der Meer, N.J.M.; Arbous, M.S.; Gommers, D.A.M.P.J.; Kant, K.M.; Kaptein, F.H.J.; van Paassen, J.; Stals, M.A.M.; Huisman, M.V.; et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb. Res.* **2020**, *191*, 145–147. [[CrossRef](#)]
111. Dobesh, P.P.; Trujillo, T.C. Coagulopathy, venous thromboembolism, and anticoagulation in patients with COVID-19. *Pharmacotherapy* **2020**, *40*, 1130–1151. [[CrossRef](#)] [[PubMed](#)]
112. Kermani-Alghoraishi, M.; Ghahramani, R. A review of venous thromboembolism phenomena in COVID-19 patients. *Curr. Probl. Cardiol.* **2020**, *46*, 100692. [[CrossRef](#)]
113. Benito, N.; Filella, D.; Mateo, J.; Fortuna, A.M.; Gutierrez-Alliende, J.E.; Hernandez, N.; Gimenez, A.M.; Pomar, V.; Castellvi, I.; Corominas, H.; et al. Pulmonary thrombosis or embolism in a large cohort of hospitalized patients with COVID-19. *Front. Med.* **2020**, *7*, 557. [[CrossRef](#)] [[PubMed](#)]
114. Voicu, S.; Delrue, M.; Chousterman, B.G.; Stépanian, A.; Bonnin, P.; Malissin, I.; Deye, N.; Neuwirth, M.; Ketfi, C.; Mebazaa, A.; et al. Imbalance between procoagulant factors and natural coagulation inhibitors contributes to hypercoagulability in the critically ill COVID-19 patient: Clinical implications. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 9161–9168. [[PubMed](#)]

115. Chen, J.; Wang, X.; Zhang, S.; Lin, B.; Wu, X.; Wang, Y.; Wang, X.; Yang, M.; Sun, J.; Xie, Y. Characteristics of acute pulmonary embolism in patients with COVID-19 associated pneumonia from the city of Wuhan. *Clin. Appl. Thromb. Hemost.* **2020**, *26*. [[CrossRef](#)]
116. Bouchard, B.A.; Tracy, P.B. The participation of leukocytes in coagulant reactions. *J. Thromb. Haemost.* **2003**, *1*, 464–469. [[CrossRef](#)] [[PubMed](#)]
117. Bautista-Vargas, M.; Bonilla-Abadía, F.; Cañas, C.A. Potential role for tissue factor in the pathogenesis of hypercoagulability associated with in COVID-19. *J. Thromb. Thrombolysis* **2020**, *50*, 479–483. [[CrossRef](#)]
118. Levi, M.; van der Poll, T. Inflammation and coagulation. *Crit. Care Med.* **2010**, *38*, S26–S34. [[CrossRef](#)] [[PubMed](#)]
119. Bester, J.; Matshailwe, C.; Pretorius, E. Simultaneous presence of hypercoagulation and increased clot lysis time due to IL-1beta, IL-6 and IL-8. *Cytokine* **2018**, *110*, 237–242. [[CrossRef](#)]
120. Roncati, L.; Ligabue, G.; Nasillo, V.; Lusenti, B.; Gennari, W.; Fabbiani, L.; Malagoli, C.; Gallo, G.; Giovannella, S.; Lupi, M.; et al. A proof of evidence supporting abnormal immunothrombosis in severe COVID-19: Naked megakaryocyte nuclei increase in the bone marrow and lungs of critically ill patients. *Platelets* **2020**, *31*, 1085–1089. [[CrossRef](#)]
121. Tang, N.; Li, D.; Wang, X.; Sun, Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J. Thromb. Haemost.* **2020**, *18*, 844–847. [[CrossRef](#)]
122. Zhang, L.; Yan, X.; Fan, Q.; Liu, H.; Liu, X.; Liu, Z.; Zhang, Z. D-dimer levels on admission to predict in-hospital mortality in patients with COVID-19. *J. Thromb. Haemost.* **2020**, *18*, 1324–1329. [[CrossRef](#)]
123. Bray, M.A.; Sartain, S.E.; Gollamudi, J.; Rumbaut, R.E. Microvascular thrombosis: Experimental and clinical implications. *Transl. Res.* **2020**, *225*, 105–130. [[CrossRef](#)]
124. Del Turco, S.; Vianello, A.; Ragusa, R.; Caselli, C.; Basta, G. COVID-19 and cardiovascular consequences: Is the endothelial dysfunction the hardest challenge? *Thromb. Res.* **2020**, *196*, 143–151. [[CrossRef](#)] [[PubMed](#)]
125. Montone, R.A.; Iannaccone, G.; Meucci, M.C.; Gurgoglione, F.; Niccoli, G. Myocardial and microvascular injury due to coronavirus disease 2019. *Eur. Cardiol.* **2020**, *15*, e52. [[CrossRef](#)] [[PubMed](#)]
126. Zuo, Y.; Warnock, M.; Harbaugh, A.; Yalavarthi, S.; Gockman, K.; Zuo, M.; Madison, J.A.; Knight, J.S.; Kanthi, Y.; Lawrence, D.A. Plasma tissue plasminogen activator and plasminogen activator inhibitor-1 in hospitalized COVID-19 patients. *Sci. Rep.* **2021**, *11*, 580. [[CrossRef](#)]
127. Whyte, C.S.; Morrow, G.B.; Mitchell, J.L.; Chowdary, P.; Mutch, N.J. Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19. *J. Thromb. Haemost.* **2020**, *18*, 1548–1555. [[CrossRef](#)] [[PubMed](#)]
128. Connors, J.M.; Levy, J.H. Thromboinflammation and the hypercoagulability of COVID-19. *J. Thromb. Haemost.* **2020**, *18*, 1559–1561. [[CrossRef](#)] [[PubMed](#)]
129. Iba, T.; Levy, J.H.; Levi, M.; Thachil, J. Coagulopathy in COVID-19. *J. Thromb. Haemost.* **2020**, *18*, 2103–2109. [[CrossRef](#)]
130. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; 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*, 1054–1062. [[CrossRef](#)]
131. Simadibrata, D.M.; Lubis, A.M. D-dimer levels on admission and all-cause mortality risk in COVID-19 patients: A meta-analysis. *Epidemiol. Infect.* **2020**, *148*, e202. [[CrossRef](#)]
132. Roncon, L.; Zuin, M.; Zonzin, P. Age-adjusted D-dimer cut-off levels to rule out venous thromboembolism in COVID-19 patients. *Thromb. Res.* **2020**, *190*, 102. [[CrossRef](#)]
133. Li, X.; Xu, S.; Yu, M.; Wang, K.; Tau, Y.; Zhou, Y.; Shi, J.; Zhou, M.; Wu, B.; Yang, Z.; et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J. Allergy Clin. Immunol.* **2020**, *146*, 110–118. [[CrossRef](#)] [[PubMed](#)]
134. Oxley, T.J.; Mocco, J.; Majidi, S.; Kellner, C.P.; Shoirah, H.; Singh, I.P.; De Lacey, R.A.; Shigematsu, T.; Ladner, T.R.; Yaeger, K.A.; et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. *N. Engl. J. Med.* **2020**, *382*, 360. [[CrossRef](#)]
135. Cantador, E.; Núñez, A.; Sobrino, P.; Espejo, V.; Fabia, L.; Vela, L. Incidence and consequences of systemic arterial thrombotic events in COVID-19 patients. *J. Thromb. Thrombolysis* **2020**, *50*, 543–547. [[CrossRef](#)]
136. Rey, J.R.; Caro-Codón, J.; Pineda, D.P.; Merino, J.L.; Iniesta, A.M.; López-Sendón, J.L. Arterial thrombotic complications in hospitalized patients with COVID-19. *Rev. Esp. Cardiol. (Engl. Ed.)* **2020**, *73*, 769–771. [[CrossRef](#)]
137. Hess, D.C.; Eldahshan, W.; Rutkowski, E. COVID-19-related stroke. *Transl. Stroke Res.* **2020**, *11*, 322–325. [[CrossRef](#)] [[PubMed](#)]
138. Kumar, D.R.; Hanlin, E.; Glurich, I.; Mazza, J.J.; Yale, S.H. Virchow’s contribution to the understanding of thrombosis and cellular biology. *Clin. Med. Res.* **2010**, *8*, 168–172. [[CrossRef](#)]
139. Sharma, A.; Sharma, C.; Raina, S.; Singh, B.; Dadhwal, D.S.; Dogra, V.; Gupta, S.; Bhandari, S.; Sood, V. A randomized open-label trial to evaluate the efficacy and safety of triple therapy with aspirin, atorvastatin, and nicorandil in hospitalised patients with SARS Cov-2 infection: A structured summary of a study protocol for a randomized controlled trial. *Trials* **2021**, *22*, 451. [[CrossRef](#)]
140. Khateri, S.; Mohammadi, H.; Khateri, R.; Moradi, Y. The prevalence of underlying diseases and comorbidities in COVID-19 patients; an updated systematic review and meta-analysis. *Arch. Acad. Emerg. Med.* **2020**, *8*, e72.
141. Long, B.; Brady, W.J.; Koefman, A.; Gottlieb, M. Cardiovascular complication in COVID-19. *Am. J. Emerg. Med.* **2020**, *38*, 1504–1507. [[CrossRef](#)] [[PubMed](#)]
142. Sriram, K.; Insel, P.A. Inflammation and thrombosis in COVID-19 pathophysiology: Proteinase-activated and purinergic receptors as drivers and candidate therapeutic targets. *Physiol. Rev.* **2021**, *101*, 545–567. [[CrossRef](#)]

143. Musher, D.M.; Abers, M.; Corrales-Medina, V.F. Acute infection and myocardial infarction. *N. Engl. J. Med.* **2019**, *380*, 171–176. [[CrossRef](#)] [[PubMed](#)]
144. Kim, I.C.; Kim, H.A.; Park, J.S.; Nam, C.W. Updates of cardiovascular manifestations in COVID-19: Korean experience to broaden worldwide perspectives. *Korean Circ. J.* **2020**, *50*, 543–554. [[CrossRef](#)] [[PubMed](#)]
145. Walker, C.; Deb, S.; Ling, H.; Wang, Z. Assessing the elevation of cardiac biomarkers and the severity of COVID-19 infection: A meta-analysis. *J. Pharm. Pharm. Sci.* **2020**, *23*, 396–405. [[CrossRef](#)]
146. Kim, I.C.; Song, J.E.; Lee, H.J.; Park, J.H.; Hyun, M.; Lee, J.Y.; Kim, H.A.; Kwon, Y.S.; Park, J.S.; Youn, J.C.; et al. The implication of cardiac injury score on in-hospital mortality of coronavirus disease 2019. *J. Korean Med. Sci.* **2020**, *35*, e349. [[CrossRef](#)]
147. Fan, Z.X.; Yang, J.; Zhang, J.; He, C.; Wu, H.; Yang, C.J.; Zheng, T.; Ma, C.; Xiang, Z.J.; Zhai, Y.H.; et al. Analysis of influencing factors related to elevated serum troponin I level for COVID-19 patients in Yichang, China. *Cardiovasc. Diagn. Ther.* **2020**, *10*, 678–686. [[CrossRef](#)]
148. Danwang, C.; Endomba, F.T.; Nkeck, J.R.; Wouna, D.L.A.; Robert, A.; Noubiap, J.J. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). *Biomark. Res.* **2020**, *8*, 37. [[CrossRef](#)] [[PubMed](#)]
149. Li, X.; Pan, X.; Li, Y.; An, N.; Xing, Y.; Yang, F.; Tian, L.; Sun, J.; Gao, Y.; Shang, H.; et al. Cardiac injury associated with severe disease or ICU admission and death in hospitalized patients with COVID-19: A meta-analysis and systematic review. *Crit. Care* **2020**, *24*, 468. [[CrossRef](#)]
150. Henry, B.M.; Aggarwal, G.; Wong, J.; Benoit, S.; Vikse, J.; Plebani, M.; Lippi, G. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. *Am. J. Emerg. Med.* **2020**, *38*, 1722–1726. [[CrossRef](#)]
151. Setiati, S.; Harimurti, K.; Safitri, E.D.; Ranakusuma, R.W.; Saldi, S.R.F.; Azwar, M.K.; Marsigit, J.; Pitoyo, Y.; Widyaningsih, W. Risk factors and laboratory test results associated with severe illness and mortality in COVID-19 patients: A systematic review. *Acta. Med. Indones.* **2020**, *52*, 227–245. [[PubMed](#)]
152. Zhu, Y.; Du, Z.; Zhu, Y.; Li, W.; Miao, H.; Li, Z. Evaluation of organ function in patients with severe COVID-19 infections. *Med. Clin. (Engl. Ed.)* **2020**, *155*, 191–196. [[PubMed](#)]
153. Wang, K.; Qiu, Z.; Liu, J.; Fan, T.; Liu, C.; Yian, P.; Wang, Y.; Ni, Z.; Zhang, S.; Luo, J.; et al. Analysis of the clinical characteristics of 77 COVID-19 deaths. *Sci. Rep.* **2020**, *10*, 16384. [[CrossRef](#)] [[PubMed](#)]
154. Fan, Q.; Zhu, H.; Zhao, J.; Zhuang, L.; Zhang, H.; Xie, H.; Zhang, R.; Granada, J.F.; Xiang, X.; Hu, W.; et al. Risk factors for myocardial injury in patients with coronavirus disease 2019 in China. *ESC Heart Fail.* **2020**, *7*, 4108–4117. [[CrossRef](#)]
155. Bangalore, S.; Sharma, A.; Slotwiner, A.; Yatskar, L.; Harari, R.; Shah, B.; Ibrahim, H.; Friedman, G.H.; Thompson, C.; Alviar, C.L.; et al. ST-Segment elevation in patients with COVID-19—A case series. *N. Engl. J. Med.* **2020**, *382*, 2478–2480. [[CrossRef](#)]
156. Bavishi, C.; Bonow, R.O.; Trivedi, V.; Abbott, J.D.; Messerli, F.H.; Bhatt, D.L. Special article—Acute myocardial injury in patients hospitalized with COVID-19 infection: A review. *Prog. Cardiovasc. Dis.* **2020**, *63*, 682–689. [[CrossRef](#)]
157. Hendren, N.S.; Drazner, M.H.; Bozkurt, B.; Cooper, L.T., Jr. Description and proposed management of the acute COVID-19 cardiovascular syndrome. *Circulation* **2020**, *9*, 1903–1914. [[CrossRef](#)]
158. Guo, H.; Shen, Y.; Wu, N.; Sun, X. Myocardial injury in severe and critical coronavirus disease 2019 patients. *J. Card. Surg.* **2020**, *36*, 82–88. [[CrossRef](#)]
159. Shi, S.; Qin, M.; Shen, B.; Cai, Y.; Liu, T.; Yang, F.; Gong, W.; Liu, X.; Liang, J.; Zhao, Q.; et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* **2020**, *5*, 802–810. [[CrossRef](#)]
160. Gu, Z.C.; Zhang, C.; Kong, L.C.; Shen, L.; Li, Z.; Ge, H.; Lin, H.W.; Pu, J. Incidence of myocardial injury in coronavirus disease 2019 (COVID-19): A pooled analysis of 7,679 patients from 53 studies. *Cardiovasc. Diagn. Ther.* **2020**, *10*, 667–677. [[CrossRef](#)]
161. Solano-López, J.; Zamorano, J.L.; Pardo Sanz, A.; Amat-Santos, I.; Sarnago, F.; Gutiérrez Ibañes, E.; Sanchis, J.; Rey Blas, J.R.; Gómez-Hospital, J.A.; Santos Martínez, S.; et al. Risk factors for in-hospital mortality in patients with acute myocardial infarction during the COVID-19 outbreak. *Rev. Esp. Cardiol. (Engl. Ed.)* **2020**, *73*, 985–993. [[CrossRef](#)]
162. Suh, Y.J.; Hong, H.; Ohana, M.; Bompard, F.; Revel, M.P.; Valle, C.; Gervaise, A.; Poissy, J.; Susen, S.; Hékimian, G.; et al. Pulmonary embolism and deep vein thrombosis in COVID-19: A systematic review and meta-analysis. *Radiology* **2020**, *298*, E70–E80. [[CrossRef](#)]
163. Menter, T.; Haslbauer, J.D.; Nienhold, R.; Savic, S.; Hopfer, H.; Deigendes, N.; Frank, S.; Turek, D.; Willi, N.; Pargger, H.; et al. Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. *Histopathology* **2020**, *77*, 198–209. [[CrossRef](#)]
164. Lodigiani, C.; Iapichino, G.; Carenzo, L.; Cecconi, M.; Ferrazzi, P.; Sebastian, T.; Kucher, N.; Studt, J.D.; Sacco, C.; Bertuzzi, A.; et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb. Res.* **2020**, *191*, 9–14. [[CrossRef](#)]
165. Zaher, N.; Sattar, Y.; Mahmood, S.; Vacek, T.; Alraies, M.C. COVID-19 infection complicated by a complete occlusion of the left circumflex artery with acute restenosis after drug-eluting stent placement. *Cureus* **2020**, *12*, e10708. [[PubMed](#)]
166. Varga, Z.; Flammer, A.J.; Steiger, P.; Haberecker, M.; Andermatt, R.; Zinkernagel, A.S.; Mehra, M.R.; Schuepbach, R.A.; Ruschitzka, F.; Moch, H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* **2020**, *395*, 1417–1418. [[CrossRef](#)]
167. Topal, G.; Loesch, A.; Dashwood, M.R. COVID-19—Endothelial axis and coronary artery bypass graft patency: A target for therapeutic intervention? *Braz. J. Cardiovasc. Surg.* **2020**, *35*, 757–763. [[CrossRef](#)] [[PubMed](#)]
168. Budoff, M.J.; Mayrhofer, T.; Ferencik, M. Prognostic value of coronary artery calcium in the PROMISE study (prospective multicenter imaging study for evaluation of chest pain). *Circulation* **2017**, *136*, 1993–2005. [[CrossRef](#)] [[PubMed](#)]

169. Dillinger, J.G.; Benmessaoud, F.A.; Pezel, T.; Voicu, S.; Sideris, G.; Chergui, N.; Hamzi, L.; Chauvin, A.; Leroy, P.; Gautier, J.F.; et al. COVID Research Group of Lariboisiere Hospital. Coronary artery calcification and complications in patients with COVID-19. *JACC Cardiovasc. Imaging* **2020**, *13*, 2468–2470. [[CrossRef](#)] [[PubMed](#)]
170. Fovino, L.N.; Cademartiri, F.; Tarantini, G. Subclinical coronary artery disease in COVID-19 patients. *Eur. Heart J. Cardiovasc. Imaging* **2020**, *21*, 1055–1056. [[CrossRef](#)]
171. Wang, H.; Xing, Y.; Yao, X.; Li, Y.; Huang, J.; Tang, J.; Zhu, S.; Zhang, Y.; Xiao, J. Retrospective study of clinical features of COVID-19 in inpatients and their association with disease severity. *Med. Sci. Monit.* **2020**, *26*, e927674. [[PubMed](#)]
172. Hodges, G.; Pallisgaard, J.; Schjerning Olsen, A.M.; McGettigan, P.; Andersen, M.; Krogager, M.; Kragholm, K.; Køber, L.; Gislason, G.H.; Torp-Pedersen, C.; et al. Association between biomarkers and COVID-19 severity and mortality: A nationwide Danish cohort study. *BMJ Open* **2020**, *10*, e041295. [[CrossRef](#)]
173. Ridker, P.M. A test in context: High-sensitivity c-reactive protein. *J. Am. Coll. Cardiol.* **2016**, *67*, 712–723. [[CrossRef](#)] [[PubMed](#)]
174. Aksel, G.; Islam, M.M.; Algin, A.; Eroğlu, S.E.; Yaşar, G.B.; Ademoğlu, E.; Dölek, C.U. Early predictors of mortality for moderate to severely ill patients with COVID-19. *Am. J. Emerg. Med.* **2020**, *45*, 290–296. [[CrossRef](#)] [[PubMed](#)]
175. Kim, M.K.; Baek, K.H.; Song, K.H.; Kang, M.I.; Choi, J.H.; Bae, J.C.; Park, C.Y.; Lee, W.Y.; Oh, K.W. Increased serum ferritin predicts the development of hypertension among middle-aged men. *Am. J. Hypertens.* **2012**, *25*, 492–497. [[CrossRef](#)] [[PubMed](#)]
176. Liang, M.; He, M.; Tang, J.; He, X.; Liu, Z.; Feng, S.; Chen, P.; Li, H.; Xue, Y.; Bai, T.; et al. Novel risk scoring system for predicting acute respiratory distress syndrome among hospitalized patients with coronavirus disease 2019 in Wuhan, China. *BMC Infect. Dis.* **2020**, *20*, 960. [[CrossRef](#)]
177. Venter, C.; Bezuidenhout, J.A.; Laubscher, G.J.; Lourens, P.J.; Steenkamp, J.; Kell, D.B.; Pretorius, E. Erythrocyte, Platelet, Serum Ferritin, and P-Selectin Pathophysiology Implicated in Severe Hypercoagulation and Vascular Complications in COVID-19. *Int. J. Mol. Sci.* **2020**, *21*, 8234. [[CrossRef](#)]
178. Lee, J.; Park, H.K.; Kwon, M.J.; Ham, S.Y.; Kim, J.M.; Lim, S.Y.; Song, J.U. Decreased lung function is associated with elevated ferritin but not iron or transferrin saturation in 42,927 healthy Korean men: A cross-sectional study. *PLoS ONE* **2020**, *15*, e0231057. [[CrossRef](#)]
179. Perricone, C.; Bartoloni, E.; Bursi, R.; Cafaro, G.; Guidelli, G.M.; Shoenfeld, Y.; Gerli, R. COVID-19 as part of the hyperferritinemic syndromes: The role of iron depletion therapy. *Immunol. Res.* **2020**, *68*, 213–224. [[CrossRef](#)]
180. Habib, H.M.; Ibrahim, S.; Zaim, A.; Ibrahim, W.H. The role of iron in the pathogenesis of COVID-19 and possible treatment with lactoferrin and other iron chelators. *Biomed. Pharmacother.* **2021**, *136*, 111228. [[CrossRef](#)]
181. Bonow, R.O.; Fonarow, G.C.; O’Gara, P.T.; Yancy, C.W. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. *JAMA Cardiol.* **2020**, *5*, 751–753. [[CrossRef](#)]
182. Corrales-Medina, V.F.; Madjid, M.; Musher, D.M. Role of acute infection in triggering acute coronary syndromes. *Lancet Infect. Dis.* **2010**, *10*, 83–92. [[CrossRef](#)]
183. Ramji, D.P.; Davies, T.S. Cytokines in atherosclerosis: Key players in all stages of disease and promising therapeutic targets. *Cytokine Growth Factor Rev.* **2015**, *26*, 673–685. [[CrossRef](#)]
184. Galis, Z.S.; Khatri, J.J. Matrix metalloproteinases in vascular remodeling and atherogenesis: The good, the bad, and the ugly. *Circ. Res.* **2002**, *90*, 251–262. [[CrossRef](#)]
185. Libby, P. Collagenases and cracks in the plaque. *J. Clin. Investig.* **2013**, *123*, 3201–3203. [[CrossRef](#)]
186. Libby, P.; Loscalzo, J.; Ridker, P.M.; Farkouh, M.E.; Hsue, P.Y.; Fuster, V.; Hasan, A.A.; Amar, S. Inflammation, immunity, and infection in atherothrombosis: JACC review topic of the week. *J. Am. Coll. Cardiol.* **2018**, *72*, 2071–2081. [[CrossRef](#)]
187. Maghdid, H.S.; Ghafoor, K.Z. A smartphone enabled approach to manage COVID-19 lockdown and economic crisis. *SN Comput. Sci.* **2020**, *1*, 271. [[CrossRef](#)] [[PubMed](#)]
188. Wilder-Smith, A.; Freedman, D.O. Isolation, quarantine, social distancing and community containment: Pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. *J. Travel Med.* **2020**, *27*, 1–4. [[CrossRef](#)] [[PubMed](#)]
189. Naser, A.Y.; Al-Hadithi, H.T.; Dahmash, E.Z.; Alwafi, H.; Alwan, S.S.; Abdullah, Z.A. The effect of the 2019 coronavirus disease outbreak on social relationships: A cross-sectional study in Jordan. *Int. J. Soc. Psychiatry* **2020**. [[CrossRef](#)]
190. Brooks, S.K.; Webster, R.K.; Smith, L.E.; Woodland, L.; Wessely, S.; Greenberg, N.; Rubin, G.J. The psychological impact of quarantine and how to reduce it: Rapid review of the evidence. *Lancet* **2020**, *395*, 912–920. [[CrossRef](#)]
191. Lei, L.; Huang, X.; Zhang, S.; Yang, J.; Yang, L.; Xu, M. comparison of prevalence and associated factors of anxiety and depression among people affected by versus people unaffected by quarantine during the COVID-19 epidemic in southwestern China. *Med. Sci. Monit.* **2020**, *26*, e924609. [[CrossRef](#)] [[PubMed](#)]
192. Lei, H.; Wu, X.; Wang, X.; Xu, M.; Xie, Y.; Du, X.; Cowling, B.J.; Li, Y.; Shu, Y. Different transmission dynamics of COVID-19 and influenza suggest the relative efficiency of isolation/quarantine and social distancing against COVID-19 in China. *Clin. Infect. Dis.* **2020**. [[CrossRef](#)]
193. Rogers, N.T.; Waterlow, N.R.; Brindle, H.; Enria, L.; Eggo, R.M.; Lees, S.; Roberts, C.H. Behavioral change towards reduced intensity physical activity is disproportionately prevalent among adults with serious health issues or self-perception of high risk during the UK COVID-19 lockdown. *Front. Public Health* **2020**, *8*, 575091. [[CrossRef](#)] [[PubMed](#)]
194. Bourdas, D.I.; Zacharakis, E.D. Impact of COVID-19 lockdown on physical activity in a sample of Greek adults. *Sports* **2020**, *8*, E139. [[CrossRef](#)] [[PubMed](#)]

195. Hawryluck, L.; Gold, W.L.; Robinson, S.; Pogorski, S.; Galea, S.; Styra, R. SARS control and psychological effects of quarantine, Toronto, Canada. *Emerg. Infect. Dis.* **2004**, *10*, 1206–1212. [[CrossRef](#)] [[PubMed](#)]
196. Warren, T.Y.; Barry, V.; Hooker, S.P.; Sui, X.; Church, T.S.; Blair, S.N. Sedentary behaviors increase risk of cardiovascular disease mortality in men. *Med. Sci. Sports. Exerc.* **2010**, *42*, 879–885. [[CrossRef](#)]
197. Chomistek, A.K.; Manson, J.E.; Stefanick, M.L.; Lu, B.; Sands-Lincoln, M.; Going, S.B.; Garcia, L.; Allison, M.A.; Sims, S.T.; LaMonte, M.J.; et al. Relationship of sedentary behavior and physical activity to incident cardiovascular disease. *J. Am. Coll. Cardiol.* **2013**, *61*, 2346–2354. [[CrossRef](#)]
198. Arena, R.; Bond, S.; Calvo, I.R.; Lebowicz, L.; Ozemek, C.; Severin, R.; Laddu, D.; Faghy, M.A.; Lavie, C.J.; Carbone, S.; et al. Shelter from the cytokine storm: Healthy living is a vital preventative strategy in the COVID-19 era. *Prog. Cardiovasc. Dis.* **2021**. [[CrossRef](#)]
199. Schnohr, P.; O’Keefe, J.H.; Lange, P.; Jensen, G.B.; Marott, J.L. Impact of persistence and non-persistence in leisure time physical activity on coronary heart disease and all-cause mortality: The Copenhagen City Heart Study. *Eur. J. Prev. Cardiol.* **2017**, *24*, 1615–1623. [[CrossRef](#)]
200. Anderson, L.; Oldridge, N.; Thompson, D.R.; Zwisler, A.D.; Rees, K.; Martin, N.; Taylor, R.S. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J. Am. Coll. Cardiol.* **2016**, *67*, 1–12. [[CrossRef](#)]
201. DeSouza, C.A.; Shapiro, L.F.; Clevenger, C.M.; Dinunno, F.A.; Monahan, K.D.; Tanaka, H.; Seals, D.R. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation* **2000**, *102*, 1351–1357. [[CrossRef](#)]
202. Ertek, S.; Cicero, A. Impact of physical activity on inflammation: Effects on cardiovascular disease risk and other inflammatory conditions. *Arch. Med. Sci.* **2012**, *8*, 794–804. [[CrossRef](#)]
203. Laufs, U.; Werner, N.; Link, A.; Endres, M.; Wassmann, S.; Jürgens, K.; Miche, E.; Böhm, M.; Nickenig, G. Physical training increases endothelial progenitor cells, inhibits neointima formation, and enhances angiogenesis. *Circulation* **2004**, *109*, 220–226. [[CrossRef](#)] [[PubMed](#)]
204. Mohammadi, H.R.; Khoshnam, M.S.; Khoshnam, E. Effects of different modes of exercise training on body composition and risk factors for cardiovascular disease in middle-aged men. *Int. J. Prev. Med.* **2018**, *9*, 9.
205. Aadahl, M.; Kjaer, M.; Jørgensen, T. Associations between overall physical activity level and cardiovascular risk factors in an adult population. *Eur. J. Epidemiol.* **2007**, *22*, 369–378. [[CrossRef](#)]
206. Igarashi, Y.; Nogami, Y. Response of lipids and lipoproteins to regular aquatic endurance exercise: A meta-analysis of randomized controlled trials. *J. Atheroscler. Thromb.* **2019**, *2*, 14–30. [[CrossRef](#)]
207. Ogura, A.; Izawa, K.P.; Tawa, H.; Kureha, F.; Wada, M.; Harada, N.; Ikeda, Y.; Kimura, K.; Kondo, N.; Kanai, M.; et al. Older phase 2 cardiac rehabilitation patients engaged in gardening maintained physical function during the COVID-19 pandemic. *Heart Vessels* **2021**. [[CrossRef](#)]
208. Jiménez-Pavón, D.; Carbonell-Baeza, A.; Lavie, C.J. Physical exercise as therapy to fight against the mental and physical consequences of COVID-19 quarantine: Special focus in older people. *Prog. Cardiovasc. Dis.* **2020**, *63*, 386–388. [[CrossRef](#)]
209. Füzéki, E.; Groneberg, D.A.; Banzer, W. Physical activity during COVID-19 induced lockdown: Recommendations. *J. Occup. Med. Toxicol.* **2020**, *15*, 20. [[CrossRef](#)] [[PubMed](#)]
210. Werneck, A.O.; Silva, D.R.; Malta, D.C.; Gomes, C.S.; Souza-Júnior, P.R.B.; Azevedo, L.O.; Barros, M.B.A.; Szwarcwald, C.L. Associations of sedentary behaviors and incidence of unhealthy diet during the COVID-19 quarantine in Brazil. *Public Health Nutr.* **2020**, *24*, 1–12.
211. Maricarmen, V.; Buman, M.; DesRoches, T.; Wharton, C. From TVs to tablets: The relation between device-specific screen time and health-related behaviors and characteristics. *BMC Public Health* **2020**, *20*, 1295.
212. Zachary, Z.; Brianna, F.; Brianna, L.; Garrett, P.; Jade, W.; Alyssa, D.; Mikayla, K. Self-quarantine and weight gain related risk factors during the COVID-19 pandemic. *Obes. Res. Clin. Pract.* **2020**, *14*, 210–216. [[CrossRef](#)]
213. Poelman, M.P.; Gillebaart, M.; Schlinkert, C.; Dijkstra, S.C.; Derksen, E.; Mensink, F.; Hermans, R.C.J.; Aardening, P.; de Ridder, D.; de Vet, E. Eating behavior and food purchases during the COVID-19 lockdown: A cross-sectional study among adults in the Netherlands. *Appetite* **2020**, *157*, 105002. [[CrossRef](#)]
214. Pearl, R.L. Weight stigma and the “Quarantine-15”. *Obesity* **2020**, *28*, 1180–1181. [[CrossRef](#)]
215. Di Renzo, L.; Gualtieri, P.; Pivari, F.; Soldati, L.; Attinà, A.; Cinelli, G.; Leggeri, C.; Caparello, G.; Barrea, L.; Scerbo, F.; et al. Eating habits and lifestyle changes during COVID-19 lockdown: An Italian survey. *J. Transl. Med.* **2020**, *18*, 229. [[CrossRef](#)]
216. Migliaccio, S.; Brasacchio, C.; Pivari, F.; Salzano, C.; Barrea, L.; Muscogiuri, G.; Savastano, S.; Colao, A.; Obesity Programs of nutrition, Education, Research and Assessment (OPERA) Group. What is the best diet for cardiovascular wellness? A comparison of different nutritional models. *Int. J. Obes. Suppl.* **2020**, *10*, 50–61. [[CrossRef](#)] [[PubMed](#)]
217. Abubakar, I.I.; Tillmann, T.; Banerjee, A. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **2015**, *385*, 117–171.
218. Alissa, E.M.; Ferns, G.A. Dietary fruits and vegetables and cardiovascular diseases risk. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 1950–1962. [[CrossRef](#)] [[PubMed](#)]
219. Aune, D.; Giovannucci, E.; Boffetta, P.; Fadnes, L.T.; Keum, N.; Norat, T.; Greenwood, D.C.; Riboli, E.; Vatten, L.J.; Tonstad, S. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality—a systematic review and dose-response meta-analysis of prospective studies. *Int. J. Epidemiol.* **2017**, *46*, 1029–1056. [[CrossRef](#)] [[PubMed](#)]

220. Mattioli, A.V.; Sciomer, S.; Cocchi, C.; Maffei, S.; Gallina, S. Quarantine during COVID-19 outbreak: Changes in diet and physical activity increase the risk of cardiovascular disease. *Nutr. Metab. Cardiovasc. Dis.* **2020**, *30*, 1409–1417. [[CrossRef](#)] [[PubMed](#)]
221. Quagliariello, V.; D’Aiuto, G.; Iaffaioli, R.V.; Berretta, M.; Buccolo, S.; Iovine, M.; Paccone, A.; Cerrone, F.; Bonanno, S.; Nunnari, G.; et al. Reasons why COVID-19 survivors should follow dietary World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommendations: From hyper-inflammation to cardiac dysfunctions. *Eur. Rev. Med. Pharmacol. Sci.* **2021**, *25*, 3898–3907.
222. Ruscica, M.; Penson, P.E.; Ferri, N.; Sirtori, C.R.; Pirro, M.; Mancini, G.; Sattar, N.; Toth, P.P.; Sahebkar, A.; Lavie, C.J.; et al. Impact of nutraceuticals on markers of systemic inflammation: Potential relevance to cardiovascular diseases—A position paper from the International Lipid Expert Panel (ILEP). *Prog. Cardiovasc. Dis.* **2021**. [[CrossRef](#)]
223. Sidor, A.; Rzymiski, P. Dietary choices and habits during COVID-19 lockdown: Experience from Poland. *Nutrients* **2020**, *12*, 1657. [[CrossRef](#)]
224. Yildirim, H.; Işık, K.; Aylaz, R. The effect of anxiety levels of elderly people in quarantine on depression during COVID-19 pandemic. *Soc. Work Public Health* **2021**, *7*, 1–11.
225. Antonova, E.; Schlosser, K.; Pandey, R.; Kumari, V. Coping With COVID-19: Mindfulness-Based Approaches for Mitigating Mental Health Crisis. *Front Psychiatry* **2021**, *12*, 563417. [[CrossRef](#)]
226. Li, J.; Yang, Z.; Qiu, H.; Wang, Y.; Jian, L.; Ji, J.; Li, K. Anxiety and depression among general population in China at the peak of the COVID-19 epidemic. *World Psychiatry* **2020**, *19*, 249–250. [[CrossRef](#)]
227. Lu, H.; Nie, P.; Qian, L. Do quarantine experiences and attitudes towards COVID-19 affect the distribution of mental health in China? A quantile regression analysis. *Appl. Res. Qual. Life* **2020**, 1–18. [[CrossRef](#)]
228. Zalsman, G.; Stanley, B.; Szanto, K.; Clarke, D.E.; Carli, V.; Mehlum, L. Suicide in the time of COVID-19: Review and recommendations. *Arch. Suicide Res.* **2020**, *24*, 477–482. [[CrossRef](#)] [[PubMed](#)]
229. Mattioli, A.V.; Nasi, M.; Cocchi, C.; Farinetti, A. COVID-19 outbreak: Impact of the quarantine-induced stress on cardiovascular disease risk. *Future Cardiol.* **2020**, *16*, 539–542. [[CrossRef](#)] [[PubMed](#)]
230. Mazza, M.; Marano, G.; Antonazzo, B.; Cavarretta, E.; Di Nicola, M.; Janiri, L.; Sani, G.; Frati, G.; Romagnoli, E. What about heart and mind in the COVID-19 era? *Minerva Cardiol. Angiol.* **2021**, *69*, 222–226. [[CrossRef](#)]
231. Monaghesh, E.; Hajizadeh, A. The role of telehealth during COVID-19 outbreak: A systematic review based on current evidence. *BMC Public Health* **2020**, *20*, 1193. [[CrossRef](#)]
232. Reiss, A.B.; De Leon, J.; Dapkins, I.P.; Shahin, G.; Peltier, R.; Goldberg, E.R. A telemedicine approach to COVID-19 assessment and triage. *Medicina* **2020**, *56*, 461. [[CrossRef](#)]
233. Davis, F.D. Perceived usefulness, perceived ease of use, and user acceptance of information technology. *MIS Quart.* **1989**, *13*, 319–340. [[CrossRef](#)]
234. Lupton, D. The digitally engaged patient: Self-monitoring and self-care in the digital health era. *Soc. Theory Health* **2013**, *11*, 256–270. [[CrossRef](#)]
235. Scott Kruse, C.; Karem, P.; Shifflett, K.; Vegi, L.; Ravi, K.; Brooks, M. Evaluating barriers to adopting telemedicine worldwide: A systematic review. *J. Telemed. Telecare* **2018**, *24*, 4–12. [[CrossRef](#)]
236. Milani, R.V.; Lavie, C.J.; Bober, R.M.; Milani, A.R.; Ventura, H.O. Improving hypertension control and patient engagement using digital tools. *Am. J. Med.* **2017**, *130*, 14–20. [[CrossRef](#)]
237. Omboni, S.; McManus, R.J.; Bosworth, H.B.; Chappell, L.C.; Green, B.B.; Kario, K.; Logan, G.; Magid, D.J.; McKinstry, B.; Margolis, K.L.; et al. Evidence and recommendations on the use of telemedicine for the management of arterial hypertension: An international expert position paper. *Hypertension* **2020**, *76*, 1368–1383. [[CrossRef](#)]
238. Pan, F.; Wu, H.; Liu, C.; Zhang, X.; Peng, W.; Wei, X.; Gao, W. Effects of home telemonitoring on the control of high blood pressure: A randomised control trial in the Fangzhuang Community Health Center, Beijing. *Aust. J. Prim. Health* **2018**, *24*, 398–403. [[CrossRef](#)]
239. De Waure, C.; Cadeddu, C.; Gualano, M.R.; Ricciardi, W. Telemedicine for the reduction of myocardial infarction mortality: A systematic review and a meta-analysis of published studies. *Telemed. e-Health* **2012**, *18*, 323–328. [[CrossRef](#)]
240. Mahmoud, W.; Vestergaard, L.D.; Schneider, I.R.; Hansen, V.B. Evaluation of telemedicine in patients suspected of acute coronary syndrome at a non-invasive centre. *Dan. Med. J.* **2020**, *67*, A10190570.
241. Lindner, D.; Fitzek, A.; Brauning, H.; Aleshcheva, G.; Edler, C.; Meissner, K.; Scherschel, K.; Kirchhof, P.; Escher, F.; Schultheiss, H.P.; et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. *JAMA Cardiol.* **2020**, *5*, 1281–1285. [[CrossRef](#)]
242. Sharma, A.; Garcia, G., Jr.; Wang, Y.; Plummer, J.T.; Morizono, K.; Arumugaswami, V.; Svendsen, C.N. Human iPSC-derived cardiomyocytes are susceptible to SARS-CoV-2 infection. *Cell. Rep. Med.* **2020**, *1*, 100052. [[CrossRef](#)]
243. Giudicessi, J.R.; Noseworthy, P.A.; Friedman, P.A.; Ackerman, M.J. 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*, 1213–1221. [[CrossRef](#)]
244. Samidurai, A.; Das, A. Cardiovascular complications associated with COVID-19 and potential therapeutic strategies. *Int. J. Mol. Sci.* **2020**, *21*, 6790. [[CrossRef](#)] [[PubMed](#)]
245. Simko, F.; Baka, T. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers: Potential allies in the COVID-19 pandemic instead of a threat? *Clin. Sci.* **2021**, *135*, 1009–1014. [[CrossRef](#)] [[PubMed](#)]

246. Bauer, A.; Schreinlechner, M.; Sappeler, N.; Dolejsi, T.; Tilg, H.; Aulner, B.A.; Weiss, G.; Bellmann-Weiler, R.; Adolf, C.; Wolf, D.; et al. Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): A prospective, parallel group, randomised, controlled, open-label trial. *Lancet Respir. Med.* **2021**, *9*, 863–872. [[CrossRef](#)]
247. Lim, S.; Bae, J.H.; Kwon, H.S.; Nauck, M.A. COVID-19 and diabetes mellitus: From pathophysiology to clinical management. *Nat. Rev. Endocrinol.* **2021**, *17*, 11–30. [[CrossRef](#)]
248. Carrasco-Sánchez, F.J.; López-Carmona, M.D.; Martínez-Marcos, F.J.; Pérez-Belmonte, L.M.; Hidalgo-Jiménez, A.; Buonaiuto, V.; Suárez Fernández, C.; Freire Castro, S.J.; Luordo, D.; Pesqueira Fontan, P.M.; et al. Admission hyperglycaemia as a predictor of mortality in patients hospitalized with COVID-19 regardless of diabetes status: Data from the Spanish SEMI-COVID-19 Registry. *Ann. Med.* **2021**, *53*, 103–116. [[CrossRef](#)]
249. Bok, K.; Sitar, S.; Graham, B.S.; Mascola, J.R. Accelerated COVID-19 vaccine development: Milestones, lessons, and prospects. *Immunity* **2021**, *54*, 1636–1651. [[CrossRef](#)]
250. Junapudi, S.S.; Junapudi, S.; Ega, K.; Chidipi, B. Major cardiac concerns in therapy and vaccinations for COVID-19. *Metab. Open* **2021**, *11*, 100102. [[CrossRef](#)]
251. Martins, W.A.; Oliveira, G.; Brandão, A.A.; Mourilhe-Rocha, R.; Mesquita, E.T.; Saraiva, J.; Bacal, F.; Lopes, M. Vaccinating patients with heart disease against COVID-19: The reasons for priority. *Arq. Bras. Cardiol.* **2021**, *16*, 213–218. [[CrossRef](#)] [[PubMed](#)]
252. Watanabe, M.; Balena, A.; Tuccinardi, D.; Tozzi, R.; Risi, R.; Masi, D.; Caputi, A.; Rossetti, R.; Spoltore, M.E.; Filippi, V.; et al. Central obesity, smoking habit, and hypertension are associated with lower antibody titres in response to COVID-19 mRNA vaccine. *Diabetes Metab. Res. Rev.* **2021**, e3465. [[CrossRef](#)]
253. Gargano, J.W.; Wallace, M.; Hadler, S.C.; Langley, G.; Su, J.R.; Oster, M.E.; Broder, K.R.; Gee, J.; Weintraub, E.; Shimabukuro, T.; et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices—United States, June 2021. *MMWR Morb. Mortal. Wkly. Rep.* **2021**, *70*, 977–982. [[CrossRef](#)]
254. Mansour, J.; Short, R.G.; Bhalla, S.; Woodard, P.K.; Verma, A.; Robinson, X.; Raptis, D.A. Acute myocarditis after a second dose of the mRNA COVID-19 vaccine: A report of two cases. *Clin. Imaging* **2021**, *78*, 247–249. [[CrossRef](#)]
255. Crespo-Leiro, M.G.; Barge-Caballero, E.; Gustafsson, F. Efficacy of the COVID-19 vaccine in heart transplant recipients: What we know and what we ignore. *Eur. J. Heart Fail.* **2021**. [[CrossRef](#)]
256. Hall, V.G.; Ferreira, V.H.; Ierullo, M.; Ku, T.; Marinelli, T.; Majchrzak-Kita, B.; Yousuf, A.; Kulasingam, V.; Humar, A.; Kumar, D. Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA-1273 vaccine in solid organ transplant recipients. *Am. J. Transplant.* **2021**. [[CrossRef](#)]
257. Boyarsky, B.J.; Werbel, W.A.; Avery, R.K.; Tobian, A.; Massie, A.B.; Segev, D.L.; Garonzik-Wang, J.M. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. *JAMA* **2021**, *325*, 2204–2206. [[CrossRef](#)]
258. Callaway, E. Delta coronavirus variant: Scientists brace for impact. *Nature* **2021**, *595*, 17–18. [[CrossRef](#)] [[PubMed](#)]
259. Rappuoli, R.; De Gregorio, E.; Del Giudice, G.; Phogat, S.; Pecetta, S.; Pizza, M.; Hanon, E. Vaccinology in the post-COVID-19 era. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2020368118. [[CrossRef](#)]
260. He, W.; Zhang, J.; Li, W. Information technology solutions, challenges, and suggestions for tackling the COVID-19 pandemic. *Int. J. Inf. Manag.* **2020**, *57*, 102287. [[CrossRef](#)]
261. Stohr, J.; Zwart, V.F.; Goderski, G.; Meijer, A.; Nagel-Imming, C.; Kluytmans-van den Bergh, M.; Pas, S.D.; van den Oetelaar, F.; Hellwich, M.; Gan, K.H.; et al. Self-testing for the detection of SARS-CoV-2 infection with rapid antigen tests for people with suspected COVID-19 in the community. *Clin. Microbiol. Infect.* **2021**. [[CrossRef](#)] [[PubMed](#)]