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Current Perspectives on Coronavirus Disease 2019 and Cardiovascular Disease: A White Paper by the *JAHA* Editors

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ABSTRACT: Coronavirus Disease 2019 (COVID-19) has infected more than 3.0 million people worldwide and killed more than 200,000 as of April 27, 2020. In this White Paper, we address the cardiovascular co-morbidities of COVID-19 infection; the diagnosis and treatment of standard cardiovascular conditions during the pandemic; and the diagnosis and treatment of the cardiovascular consequences of COVID-19 infection. In addition, we will also address various issues related to the safety of healthcare workers and the ethical issues related to patient care in this pandemic.

Key Words: cardiovascular disease ■ cardiovascular risk factors ■ coronavirus disease 2019 ■ COVID-19 ■ management ■ SARS-CoV-2 ■ treatment

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Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has infected >3.0 million people worldwide and killed >200 000 as of April 27, 2020, making it the most lethal pandemic since the Spanish flu of 1918.[1,2] COVID-19 may preferentially infect individuals with cardiovascular conditions, is more severe in subjects with cardiovascular comorbidities, may directly or indirectly affect the heart, and may interact with cardiovascular medications.[3] In addition, the widespread effects of the pandemic on the global healthcare system affect the routine and emergency cardiac care for patients who are, may be, or are not infected with COVID-19. In this White Paper authored by the Physicians and Scientists on the Editorial Board of the *Journal of the American Heart Association* (*JAHA*), we address the cardiovascular comorbidities of COVID-19 infection; the diagnosis and treatment of standard cardiovascular conditions during the pandemic; and the diagnosis and treatment of the cardiovascular consequences of COVID-19 infection. In addition, we will touch on the safety of healthcare workers (HCWs) and on ethical issues related to patient care in the COVID-19 era.

COVID-19 DISEASE AND TROPONIN

Take-Home Points

1. Elevated troponin levels are frequently seen in patients with COVID-19 disease; and are associated with increased severity of disease and risk of death.

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2. In the absence of a specific cause, elevated levels of troponins are likely attributable to myocardial injury from inflammation or a direct effect of SARS-CoV-2 infection.

Research Questions

1. The role of troponin in clinical risk stratification, and as a prognostic factor of disease severity and mortality, needs to be further explored, particularly after accounting for other confounders.
2. Mechanistic studies are needed to evaluate the cause of myocardial injury, and whether there is a potential for therapeutic options.

Between 7% and 27.8% of COVID-19 patients may have elevated troponin levels.[4–7] In this section, we discuss the implications of elevated troponins, both in terms of cause and clinical interpretation.

Foremost, even during the ongoing COVID-19 pandemic, the basic clinical tenets do not change: common causes of elevated troponin, such as type 1 myocardial infarction (MI),[8] should be clinically excluded in all patients. If clinical suspicion for spontaneous MI arises, the modified pathways for ST-segment–elevation MI (STEMI) and acute coronary syndrome (ACS) in the COVID-19 pandemic era can provide guidance to clinicians.[9] It is also vital to understand that in the setting of SARS-CoV-2 infection, there is a greater possibility of type 2 MI, because of a mismatch between myocardial oxygen demand and supply. Aside from these causes, COVID-19 patients should be clinically evaluated to exclude other common causes of troponin elevation, such as decompensated heart failure, arrhythmia, renal failure, hypoxemia, and hypotension (Figure 1).

SARS-CoV-2 infection is associated with systemic inflammation, and that may, in theory, contribute to the excess risk of type 1 MI by destabilization of coronary atheromatous plaques, increased platelet aggregation, and higher risk of stent thrombosis. However, to date, there are no reports of an increase in STEMI risk associated with COVID-19 disease, although increased risk of MI has been demonstrated in similar respiratory viral infections, such as influenza.[10]

Other reasons for elevated troponin levels, more specific to SARS-CoV-2 infection, are as follows. First, the virus appears to evoke a cytokine storm, resulting in intense activation of inflammatory proteins.[6] An association of high troponin levels has been seen with the elevated inflammatory markers in several cohorts,[6,7] suggesting direct myocardial inflammatory damage attributable to myocarditis.[4] This could also reflect a hypercoagulable state causing microvascular thrombi and secondary MI.[11] Second, it is also possible that the elevated troponin levels are attributable to coronary microvascular ischemia mediated by SARS-CoV-2 binding of the endothelial angiotensin-converting enzyme 2 (ACE2) receptor. Third, it could be attributable to direct myocarditis through cardiac viral infection (Figure 1). A specific section is dedicated to this issue in this article.

Elevated troponin levels also have a strong prognostic implication in those with COVID-19 disease. Several studies have shown that those with elevated troponin levels at baseline have a greater

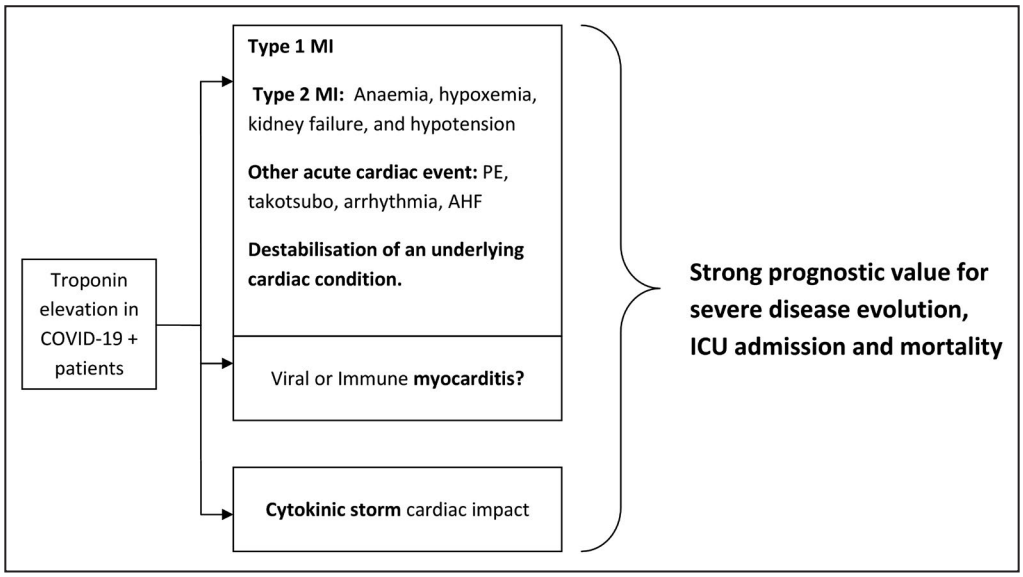

Figure 1. Cause of troponin elevation in patients with severe acute respiratory syndrome coronavirus-2 infection and its prognostic implication.
AHF indicates acute heart failure; COVID-19, coronavirus disease 2019; ICU, intensive care unit; MI, myocardial infarction; and PE, pulmonary embolism.

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risk of having a severe disease,[11] increased intensive care unit (ICU) admissions, and significantly higher mortality.[6,7] In a cohort study,[7] presence of elevated troponin levels was second to the presence of acute respiratory distress syndrome (ARDS) in the strength of association with mortality: hazard ratios (HR) were 4.26 (95% CI, 1.92–9.49) and 7.89 (95% CI, 3.73–16.66), respectively. Guo et al, in a single-center retrospective analysis of 187 COVID-19 patients, studied the relationship of baseline troponin levels and other comorbidities with mortality.[6] They reported that the risk of death can be stratified according to the presence of elevated troponin and/or history of cardiovascular disease (CVD). The risk of death in these patients increased linearly, with 7.62% of those dying with no history of CVD compared with 13.3% of those with presence of only history of CVD, 37.5% in those with presence of elevated troponin levels only, and 69.4% in those with both elevated troponin levels and history of CVD. Notably, elevated troponin level carried a strong prognostic value even in the absence of CVD history. In addition, the authors reported that in survivors, during the hospitalization period, the troponin levels remained stable and within normal limits. On the other hand, nonsurvivors showed a trend of gradual and progressive increase in troponin levels. This suggests that troponin elevation may reflect progression of the disease to a severe stage,[12] notably through a continual inflammatory surge.

If troponin elevation occurs in the absence of clinical symptoms, ECG changes, and other indications, extensive investigations, such as echocardiography and coronary angiography, are not recommended routinely to exclude acute coronary event. Similarly, although it is crucial to ensure adherence to long-term prescribed cardiovascular therapies, it is unclear whether isolated elevation of troponin warrants any cardiovascular therapy. This topic is discussed extensively in a separate section.

In conclusion, elevated troponin levels are frequently seen in patients with COVID-19 disease. The reasons are multifactorial, and routine causes should be excluded in the first step. In the absence of specific cause, SARS-CoV-2 infection–induced inflammation with myocardial injury may be the cause. Elevated troponin levels are associated with higher risk of severe disease and death. Several gaps in knowledge persist, and it will be interesting to evaluate whether there is a linear association of troponin levels with risk of death, after adjusting for other confounders and elevated inflammatory response. Mechanistic studies are needed to evaluate for the cause of myocardial injury, and whether there is a potential therapeutic option available. The role of troponin as a prognostic factor and in stratification of risk needs further elaboration.[13]

COVID-19 AND HYPERTENSION

Take-Home Points

1. Hypertension is associated with a higher risk of severe COVID-19 disease and greater mortality rates.
2. Until further studies reveal the impact of preexisting or de novo renin-angiotensin system (RAS) blockade on COVID-19 disease progression or severity, there is no justification to omit RAS blockers in COVID-19 patients.

Research Questions

1. What is the association of a preexisting hypertension diagnosis and/or blood pressure level itself with COVID-19 susceptibility and prognosis in fully adjusted analyses?
2. What is the association of preexisting or de novo RAS blockade with COVID-19 outcomes in both hypertensive and nonhypertensive patients?

Early, epidemiological analyses have suggested an association between COVID-19 disease (and its associated mortality) and cardiovascular risk factors, such as hypertension. This focused section summarizes current understanding and key missing information about hypertension and COVID-19 disease.

SARS-CoV-2, similar to SARS-CoV that caused SARS in 2003, enters cells through an endosomal pathway, with its spike protein binding to ACE2.[14] ACE2 is a monocarboxypeptidase that cleaves and generates several peptides within the RAS, including angiotensin II. It is widely expressed in different tissues, including lungs, heart, and kidneys, and SARS-Cov-2 internalization downregulates surface expression of ACE2, resulting in increased angiotensin II signaling. Although animal models have shown that ACE inhibitors and angiotensin receptor blockers (ARBs) can increase ACE2 tissue mRNA levels, poor evidence exists in human tissues and there are no consistent clinical data. RAS is fundamental in the pathogenesis and continuation of human hypertension (and as a target for first-line therapeutics) and, therefore, concern has arisen about the possibility of hypertension as a risk factor for, and predictor of, negative outcomes with COVID-19. Furthermore, scrutiny has been placed on the widespread concomitant use of RAS drugs (eg, ACE inhibitors and ARBs) in patients with CVD and/or hypertension and the effects thereof on outcomes from COVID-19 disease.

Various reports have shown that between 15% and 35% of patients with COVID-19 have coexisting hypertension[15,16] (Table 1). A meta-analysis of 8 recent reports, including 46 248 confirmed COVID-19 patients, suggests that hypertension is the most common

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Table 1. Prevalence of Hypertension in Case Series Studies of Patients With COVID-19 Disease

Article	Total No. of Patients	Proportion of Patients With Hypertension at Baseline, %	Proportion of Those in ICU With Hypertension, %	Proportion of Those With Severe Disease or ARDS With Hypertension, %	Deaths Among Those With Hypertension, %	Composite of Death, ICU Admission, or Intubation in Those With Hypertension, %	Notes
Huang C et al[12]	41	15	15	···	···	···	Two thirds were exposed to the Huanan seafood market
Zang J et al[17]	140	30	···	37.9	···	···	Severe vs nonsevere disease
Wu C et al[18]	201	19.4	···	27.4	36.4	···	ARDS and deaths
Shi S et al[7]	416	30.5	···	···	···		Cardiac injury and mortality
Guan W et al[19]	1590	16.9	···	32.7	···	35.8	Comorbidities and outcomes
Chen T et al[20]	274	34	···	···	48	···	Clinical characteristics of deceased patients
Guan W et al[15]	1099	15	···	23.7	···	35.8	Patients across mainland China
Wang et al[5]	138	31.2	58.2	···	···	···	Critically ill vs noncritically ill patients
Liu K et al[21]	137	9.5	···	···	···	···	Patients admitted in 9 tertiary hospitals in Hubei Province (Dec 2019–Jan 2020)
Du Y et al[22]	85	···	···	···	37.6	···	Clinical features of fatal cases
Wang L et al[23]	339	40.8	···	···	50	···	Consecutive cases aged >60 y
Zhou F et al[2]	191	30	···	···	48	···	Risk factors associated to in-hospital death
Mo P et al[24]	155	23.9	···	···	···	···	Study on refractory COVID-19 patients
Cao J et al[25]	102	27.5	···	···	64.7	···	Short-term outcomes
Summary, total/mean (SD)	4908	24.9 (9.1)	36.5	30.4 (6.2)	47.4 (10.2)	35.8	

ARDS indicates acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; and ICU, intensive care unit.

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comorbidity (18%) seen in these patients.[26] Similar relationships between preexisting hypertension and other novel coronavirus infections, such as SARS and Middle East respiratory syndrome, have been identified previously. For example, meta-analysis of >600 Middle East respiratory syndrome cases revealed hypertension prevalence of up to 50%[27]; thus, to date, the prevalence of hypertension in the COVID-19 pandemic appears to be lower.

This apparent association of COVID-19 with hypertension could be confounded by 2 factors: (1) the high prevalence of hypertension in the general population, as in China at least 23% of the adult population is hypertensive[28]; and (2) the association of hospitalized COVID-19 patients with age. For example, in a study on 191 COVID-19 patients (30% of them hypertensive), after multivariable adjustments for all other demographic and clinical parameters, hypertension was no longer an independent risk factor.[2]

A background of hypertension seems to correlate with severity of the disease and mortality. Wu et al found that, among COVID-19 patients, hypertension was twice more common in those with ARDS and, among these, more common among those who died (HR, 1.82 and 1.70, respectively).[18] A review of 3200 Italian COVID-19 hospital deaths reported hypertension was present in 73.8% of cases.[29] In another large study, hypertension was an independent risk factor, associated with 50% excess risk of ICU admission or death, even after controlling for age and smoking status.[19]

It is unclear how hypertension itself, or blood pressure level, could correlate with severity of COVID-19 disease. Some hypertensive patients may have high ACE2 tissue expression (thus facilitating the virus entry in target cells), to counteract RAS activation and high angiotensin II level (the latter contributes to the lung injury with inflammation and fibrosis and causes direct myocardial damage).[30]

Indeed, if the above hypothesis is true, then it is possible that ARBs may be protective.[31,32] Recent retrospective data may be consistent with this hypothesis.[33] In this study, the use of ARBs in hypertensive patients with COVID-19 was associated with lower risk of adverse outcomes (odds ratio [OR] of severe disease, 0.343). Another study in its retrospective evaluation reported that among COVID-19 patients, those with hypertension and on ACE inhibitor or ARB treatment (compared with the hypertensive patients on other treatments) were associated with numerically lower ICU admissions and deaths.[34] However, both reports are retrospective and have not had a peer review yet (preprints), and clearly have several issues with confounding and bias. Pending further evidence, for now, it is difficult to be certain in which direction coexistent treatment with ARBs or even starting ARBs de novo would lead to in COVID-19 disease given the potential opposing effects of ACE2 upregulation on viral entry and RAS blockade preventing further lung and cardiac injury. This is under investigation in at least one randomized controlled trial (NCT04312009). To date, all international hypertension and cardiac societies have recommended continuation of RAS drugs in COVID-19 disease in patients with CVD and/or hypertension.

The current knowledge gap about the role of hypertension as a risk factor independent from age or other comorbidities will require large epidemiological studies, including nonhospitalized patients with milder forms of COVID-19 infections, and a comparison with the prevalence in the general population, which may also reveal the impact of concomitant RAS blocking drugs on infection incidence and progression. There is currently a knowledge gap on both the effect of human RAS blockade on ACE2 expression and the effect of ACE2 or other RAS genotype (ie, low renin status) variations that may alter angiotensin II levels, and thereby predispose to viral infection and/or to more severe lung disease. Another question that needs further elaboration is whether prevalent blood pressure level per se has an independent role on severity of infection or not. Last, the impact of RAS blocking drugs in COVID-19 affected patients with or without hypertension needs to be urgently investigated.

COVID-19 INFECTION AND THE RISK OF VASCULAR EVENTS

Take-Home Points

1. Vascular events appear to be a common complication of COVID-19 infection.
2. The increased burden of vascular comorbidities among people with severe infection is only a partial explanation of such increased risk of events.

As the COVID-19 pandemic strains the medical system of the United States and other countries, there exists a need to understand the cause of inpatient mortality in this population. The risk of severe COVID-19 is associated with older age and cardiovascular comorbidities, including hypertension, coronary artery disease, stroke, and diabetes mellitus.[2] In addition, COVID-19 may in turn cause CVD. The SARS-CoV-2 uses the ACE2 receptor to enter cells, which is highly expressed in the heart, potentially explaining the increased risk of poor outcomes among people with CVD as well as increasing the risk of myocardial injury and CVD after infection. Recent reports indicate up to 22% of COVID-19 patients who required ICU care had evidence of myocardial injury, and 12% of patients who did not have prior CVD had elevated troponin levels or cardiac arrest during their hospitalization.[3] Acute cardiac injury is a predictor of mortality and

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occurs in a significant proportion of COVID-19 patients.[3] In a study of 187 patients confirmed to have COVID-19, a third of the patients had prior CVD. There exists a biological gradient between history of cardiac disease and plasma evidence of T-troponin, including a much higher mortality noted among patients with elevated plasma levels of T-troponin and prior CVD.[6] Interestingly, in this study, there was a linear association between elevated troponin levels and the inflammatory biomarker CRP (C-reactive protein). Increased levels of T-troponin, leukocytosis, and elevated D-dimer are markers of increased mortality in this population.[20] To date, there is one study on risk of stroke after COVID-19.[35] Stroke occurred in ≈6% of severe COVID-19 patients, and patients with CVD were at higher risk for stroke after COVID-19, similar to other studies on stroke risk after infections.

There is a paucity of good quality data on the rates of vascular disease in the setting of acute COVID-19 infection. A small case series from Washington state reported that up to one third of those severely affected with COVID-19 had an acute vascular event.[36] To date, among the 932 deaths from COVID-19 in New York City, 748 patients had an underlying illness, including diabetes mellitus, lung disease, cancer, immunodeficiency, heart disease, hypertension, asthma, kidney disease, and gastrointestinal/liver disease. One of our top priorities is to investigate the predictors and rates of vascular events in New York City, given the increased risk of death among COVID-19 patients with vascular events and the unfortunate role of New York City as the latest epicenter of the pandemic in the world.

Infections have long been identified as risk factors and/or triggers for stroke and MI. The role of sepsis as a risk factor for stroke, MI, and new-onset atrial fibrillation has been described, and illustrated that patients with concomitant coagulopathy, congestive heart failure, renal failure, and other circulation disorders had increased the risk of stroke after sepsis with the risk remaining up to a year after the sepsis event.[37] More common infections, such as respiratory tract infections or influenza-like illness, have been identified as both a potential long-term risk factor and a short-term trigger for stroke and MI. Moreover, risk of infections and stroke/MI share several similarities. First, endothelial dysfunction plays an important role in both stroke and sepsis pathophysiological characteristics.[38] Second, higher baseline biomarkers of inflammation are related to both an increased risk of infections and stroke.[39,40] Third, independent risk factors for stroke are similar to independent risk factors for infections, with increased inflammatory biomarker activity during a baseline stable phase of health associated with future risk of both stroke and sepsis.[39,40]

The data to date available for acute COVID-19 infection suggest a role for acute systemic inflammation in the pathophysiological characteristics of the myocardial injury. The inflammatory response to the virus causes a short-term influx of inflammatory cytokines, which in turn activates the endothelium and may cause widespread vascular damage.[41] At this time, there seem to be 2 patterns of myocardial injury with COVID-19: cytokine storm mediated or secondary hemophagocytic lymphohistiocytosis versus viral myocarditis or stress cardiomyopathy.[42] The specific mechanism of cardiac involvement is also still under investigation, but is potentially ACE2 mediated. It is imperative to better understand the pathophysiological characteristics of COVID-19–related vascular events so that adequate therapies may be implemented to curb the associated vascular morbidity and mortality.

COVID-19 AND MYOCARDIAL INJURY: POSSIBLE MECHANISMS

Take-Home Point

1. Broad elevations of chemokines and cytokines occur in SARS-CoV2 infection, similar to cytokine release syndrome seen in cancer patients on immune-modulating therapy. Yet, some overlap with troponin elevation has been seen.

Research Questions

1. Could the elevation in inflammatory markers (eg, interleukin-6) play a role in COVID-19 associated cardiac toxicity? And if so, could this be a potential target for treatment?

A growing number of reports have described cardiac injury, absent of coronary obstruction, during severe COVID-19 infection.[43,44] In a recent single-center study of 416 patients with confirmed COVID-19, cardiac troponin I elevation was seen in 19.7% and corresponded to higher in-hospital mortality.[7] Similarly, in another study of 187 confirmed COVID-19 patients, 52 (27.8%) had evidence of myocardial injury, reflected by elevated troponin T.[6] In addition to elevations in troponin, a study of 138 hospitalized COVID-19 patients also revealed a high prevalence of arrhythmias, occurring in 16.7% (n=23) of patients.[5] Despite these observations, the exact mechanism(s) by which COVID-19 induces cardiac damage (Figure 2) remain unclear.

Viral myocarditis with inflammatory infiltrates or myocyte necrosis and injury by a systemic inflammatory response have been implicated as potential causes of cardiac injury. Herein, we used the criteria for clinically suspected myocarditis by the European Society of Cardiology[45] for a critical appraisal of reports on cardiac injury by SARS, Middle East respiratory syndrome, and

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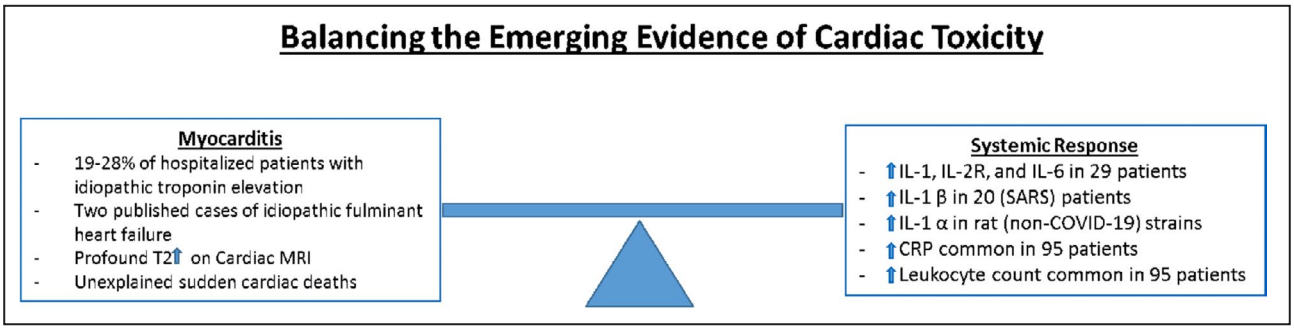

Figure 2. Balance of the evidence to guide current understanding of mechanisms of clinical cardiac events after coronavirus disease 2019 (COVID-19) infection.
CRP indicates C-reactive protein; IL, interleukin; MRI, magnetic resonance imaging; and SARS, severe acute respiratory syndrome.

other coronavirus infections as well as emerging data on COVID-19. Moreover, we discuss the concept of broad systemic inflammatory response as an alternative or additional mechanism for myocardial injury in COVID-19.

Coronaviruses are not regarded as cardiotrophic viruses, and reports on cardiac involvement with coronavirus-induced respiratory illness are rare. The criteria for clinically suspected myocarditis were met in one patient with coronavirus OC43 infection (chest pain, ECG changes, pericardial effusion; Table 2).[46] In one patient with Middle East respiratory syndrome who presented with chest pain and dyspnea, the diagnosis was corroborated by elevated cardiac biomarkers, diagnostic ECG changes, and findings by echocardiography and cardiac magnetic resonance imaging.[47] Of note, left ventricular (LV) dysfunction persisted at 3 months after diagnosis. In the literature on SARS, we identified no cases of myocarditis or evidence of other major cardiac involvement. In one SARS patient with LV dysfunction, myocyte necrosis or inflammatory infiltrates were absent at autopsy,[48] whereas SARS-CoV RNA and macrophages were detected in 7 of 20 autopsy samples in another report.[49]

The 2 viruses causing SARS (SARS-CoV) and COVID-19 (SARS-CoV-2) both attach to ACE2 as the cellular entry receptor.[14] It may be reasonable to postulate that those with elevated ACE2 receptors are at increased risk for infection and more severe disease response, including arrhythmic events. In most studies on COVID-19, cardiac injury was defined by laboratory parameters, such as troponin and creatinine kinase-MB. As of this writing, few studies have reported additional ECG or cardiac imaging data needed to apply the European Society of Cardiology criteria. To date, 2 cases of myocarditis have been reported, each supported by biomarkers, LV dysfunction with pericardial effusion, and normal coronary anatomical features.[43,44] The patients symptomatically improved on guideline-directed heart failure treatment. No substantial pathological feature was seen in the myocardium of another patient at autopsy,[50] raising concerns over this hypothesized mechanism of COVID-19–associated myocardial injury.

Concurrently, increasing data have shown the presence of a broad systemic inflammatory response after COVID-19 confirmation.[50–53] Notably, similar presentations have been observed among cancer patients with cytokine release syndrome following initiation of novel immune-modulating therapies, even manifesting with heart failure and arrhythmias.[54,55] In these patients, high levels of circulating cytokines, including interleukin-6, have been observed.[55] In patients with severe cytokine release syndrome, elevation of ACE2 and other markers (eg, interferon) has been linked to organ toxicity manifestations.[56] Among COVID-19 patients, broad elevation of chemokines and cytokines has also been reported, with emerging reports suggesting potential efficacy with interleukin-6 blockade after infection.[57,58] In accordance to a phase 3 study, randomizing patients to the interleukin-6 receptor antagonist, tocilizumab, after COVID-19 infection is currently underway.[59] These observations raise the potential that much of the troponin release may actually be driven by a broader inflammatory response.

In summary, the pathophysiological characteristics of COVID-19 induced cardiac clinical manifestations remain unknown, and may relate to a direct viral-induced myocarditis, a broader systemic inflammatory response, or even another process not described herein, such as hypoxia or catecholamine-induced cardiac injury. Given the tsunami of COVID-19 infections and the potential profound implications on cardiovascular health, additional studies are needed.

COVID-19 AND CARDIAC ARRHYTHMIAS

Take-Home Points

1. COVID-19 is associated with a high inflammatory burden that may cause arrhythmias attributable

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Table 2. COVID-19–Associated Myocarditis

Author	Year	Age/Sex	Symptoms	Cardiac Biomarkers	ECG	Imaging	Virology
Riski[46]	1980	46/Male	Chest pain, fatigue	Not provided	ST-segment elevations, T-wave inversions	Pericardial effusion (TTE)	CoV OC43 titer
Alhogbani[47]	2016	60/Male	Chest pain, fever, dyspnea	Troponin T, NT-proBNP	Sinus tachycardia with T-wave inversions	Severely decreased LVEF, pericardial effusion (TTE); LGE and T2w images: interstitial edema (CMR)	MERS sputum RT-PCR
Hu[43]	2020	37/Male	Chest pain, diarrhea, dyspnea	Troponin T, CK-MB, BNP	Inferior ST-segment elevations	LVEF 27%, pericardial effusion (TTE)	SARS-CoV-2 sputum RT-PCR
Inciardi[44]	2020	53/Female	Fatigue, fever, cough	Troponin T, NT-proBNP	Diffuse ST-segment elevations	LVEF 27%, biventricular diffuse hypokinesis (TTE); LGE and T2w images: interstitial edema (CMR)	SARS-CoV-2 sputum RT-PCR

BNP indicates B-type natriuretic peptide; CMR, cardiac magnetic resonance imaging; CoV, coronavirus; COVID-19, coronavirus disease 2019; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MERS, Middle East respiratory syndrome; NT-proBNP, N-terminal pro-BNP; RT-PCR, reverse transcription–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; and TTE, transthoracic echocardiogram.

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to increased metabolic demand, hypoxia, and/or sympathetic stimulation in patients with and without preexisting CVD.

2. New-onset ventricular arrhythmias combined with elevated troponin T levels in the setting of COVID-19 should raise suspicion of myocarditis.
3. Antiviral therapy for COVID-19 may lead to electrical disturbances (most often corrected QT interval prolongation) and increased arrhythmic risk.

Although cardiovascular complications of COVID-19 are increasingly recognized, the incidence of cardiac arrhythmias in affected patients is infrequently reported. Given the paucity of data, it is tempting to assess precedent among similar viruses, including SARS-CoV. Yu et al described that 87 (72%) of 121 hospitalized SARS-CoV patients had tachycardia, which could not be solely explained by hypotension, whereas transient bradycardia occurred in 18 (15%) patients.[60] Apart from one patient with atrial fibrillation, no arrhythmias were observed, but the cohort existed mostly of relatively young (mean age, 38 years) and healthy HCWs. For COVID-19 (SARS-CoV-2), a literature search to determine the prevalence of arrhythmias yielded 3 reports (date of search April 4, 2020), which are summarized in Table 3. All studies were retrospective case series in hospital settings in China, with arrhythmias reported in 6% to 60% of patients. Wang et al were the first to report that 23 (17%) of 138 COVID-19 patients developed arrhythmias, although the types of arrhythmia were not specified.[5] In addition, these authors showed that 16 (44%) of 36 ICU admissions experienced arrhythmias as a complication. A lower prevalence of arrhythmias was reported by Guo et al, who showed that 11 (6%) of 187 COVID-19 patients developed ventricular tachycardia or fibrillation, most often (n=9/11) in the setting of myocardial injury (defined as troponin T >99th percentile of normal).[6] Indeed, it seems likely that the occurrence of arrhythmias is related to severity of disease, as the proportion of patients with reported arrhythmias was much higher (n=51 [60%]) in a study of 85 fatal COVID-19 cases.[22] Of note, none of these reports compares the prevalence of arrhythmias among CVD-naïve versus cardiac comorbid patients.

As with all viral infections, the high inflammatory burden caused by COVID-19 stresses the heart and vascular system. This leads to increased metabolic demand, hypoxia, and neurohumoral stress, which (alone or in combination) may trigger arrhythmias. In addition to such “indirect” proarrhythmic effects, COVID-19 infection may also directly affect the myocardium. For instance, COVID-19–induced myocarditis may set the stage for arrhythmias; the latter may also occur in the absence of overt respiratory failure (ie, either in the initial phase of the disease or after improvement of respiratory failure). Indeed,

Table 3. Summary of Clinical Reports Describing Arrhythmias in COVID-19 Patients

Reference	Location	Type of Study	Setting	Total No.	No. (%) With Arrhythmia	Remarks
Guo et al[6]	Wuhan, China	Single-center retrospective case series	Hospitalized patients	187	11 (6) VT/VF	Only VT/VF reported. Almost all (9/11 patients with VT/VF) had increased troponin-T levels.
Du et al[22]	Wuhan, China	Multicenter retrospective case series	Fatal cases	85	51 (60) type of arrhythmia unknown	Report on 85 fatal cases. No information on type of arrhythmia.
Wang et al[5]	Wuhan, China	Single-center retrospective case series	Hospitalized patients	138	23 (17) type of arrhythmia unknown	No information on type of arrhythmia. Arrhythmic occurrence relates to severity of disease: 44% of 36 ICU patients had arrhythmias.

Search strategy: ("SARS-CoV-2" OR "COVID-19" OR "novel coronavirus") AND ("arrhythmia" OR "tachycardia" OR "bradycardia" OR "cardiac arrest"), date of search was April 4, 2020. COVID-19 indicates coronavirus disease 2019; ICU, intensive care unit; VF, ventricular fibrillation; and VT, ventricular tachycardia.

some publications have reported sudden cardiac arrest early in the disease course (eg, immediately after hospital admission),[4] and anecdotal reports in the media describe relatively young and healthy individuals who died suddenly and were later found to test positive for SARS-CoV-2. Whether these sudden deaths are the consequence of myocarditis, other COVID-19–related effects on the heart, or massive pulmonary embolism remains elusive. In rare cases, it is possible that the presence of SARS-CoV-2 uncovers an underlying cardiac condition. For instance, fever associated with COVID-19 infection may unmask Brugada syndrome, an inherited disorder associated with increased arrhythmia risk.[61] Accordingly, specific COVID-19–related recommendations have been proposed for patients with inherited arrhythmia syndromes.[62]

Last, several of the proposed drugs for COVID-19 have proarrhythmic potential. In addition to a modest effect on the QT interval and increased risk of torsade de pointes, (hydroxy)chloroquine may induce conduction abnormalities, particularly atrioventricular conduction problems, which may be consequent to sodium channel inhibition.[63] Lopinavir/ritonavir is also reported to potentially affect repolarization, although QT prolongation was only rarely observed (n=1/99 [1%]) in a recent open-label trial in COVID-19 patients.[64] Nonetheless, both (hydroxy)chloroquine and lopinavir/ritonavir should be avoided in patients with congenital or acquired long-QT syndrome, and particular care should be taken to prevent electrolyte disturbances (especially hypokalemia) and the concomitant use of other QT-interval prolonging drugs.[62] The combination of (hydroxy)chloroquine with azithromycin or lopinavir/ritonavir may prove particularly harmful because these all inhibit CYP3A4 and potentially affect (hydroxy)chloroquine metabolism. In addition, other proposed drugs for COVID-19, such as remdesivir, interferon, and ribavarin, may have cardiac adverse effects.[65] Given that the level of evidence for a potential beneficial effect of these drugs in COVID-19 patients is as yet limited, caution should be exercised when prescribing these medications to those with preexisting CVD.

COVID-19 AND THE USE OF STATIN AND OTHER CARDIOVASCULAR PROTECTIVE THERAPIES

Take-Home Points

1. A significant proportion of patients with COVID-19 have evidence of myocardial injury, which portends a higher risk of ICU admission and death.
2. All patients with COVID-19, where clinically indicated, should be commenced on statins and antiplatelet therapy, if not already on them. Currently, there is no

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Table 4. Summary of Studies Showing the Evidence of Myocardial Injury in COVID-19 Patients and Subsequent Outcomes

Article	Total No. of Patients	Median (Mean) Age, y	Proportion of Patients With the Evidence of Myocardial Injury, N (%)	Overall Death, N %	Patients With Increased Troponin, N (%)		Death Categorized by Troponin Level, N (%)	
					Non-ICU/Survivors*	ICU/Nonsurvivors*	Normal	Elevated
Huang et al[12]	41	49	5 (12.0)†	6 (15.0)	1/28 (4)	4/13 (31)	NA	NA
Zhou et al[2]	191	56	24 (17.0)	54 (28.0)	1/95 (1)*	23/50 (46)*	NA	NA
Wang et al[5]	138	56	10 (7.2)	6 (4.3)	2/102 (2)	8/36 (22)	NA	NA
Zhang et al[68]	48	(71)	13 (27.1)	17 (35.4)	3/31 (9.7)*	10/17 (59)*	NA	NA
Yang et al[4]	52	(60)	12 (23.0)	32 (61.5)	3/20 (15)	9/32 (28)	NA	NA
Chen et al[20]	274	62	83/203 (41.0)‡	113 (41.2)	15/109 (14)	68/94 (72)	NA	NA
Shi et al[7]	416	64	82 (19.7)	57 (13.7)	NA	NA	15 (5)	42 (51)
Guo et al[6]	187	(59)	52 (27.8)	43 (21.0)	NA	NA	12 (9)	31 (60)

COVID-19 indicates coronavirus disease 2019; ICU, intensive care unit and NA, not available.
*Survivors or nonsurvivors.
†Defined as hypersensitive troponin I >28 pg/mL or new abnormalities on ECG or echocardiogram.
‡NB. most proportions are rounded off to the nearest integer. Defined as >15.6 pg/mL.

evidence to stop cardioprotective therapy, assuming no contraindications.

Research Questions

1. Is there a role for early use of the cardioprotective therapies in patients with COVID-19 who have either cardiovascular risk factors or evidence of myocardial injury?
2. What are the pathophysiological characteristics of troponin increase in the patients with COVID-19? Is there an argument for increased plaque rupture and microvascular thrombosis, on top of the hypothesized direct myocardial infiltration and inflammation?

Early observations from China found a higher prevalence of cardiovascular comorbidities among nonsurvivors and patients requiring ICU, with hypertension, diabetes mellitus, and cardiocerebrovascular disease increasing overall case fatality rates of 2.3% to 6%, 7.3%, and 10.5%, respectively.[66] Other studies suggest that serum troponin is an independent predictor of prognosis, showing patients with preexisting CVD but normal troponins had lower mortality rate (13.3%) compared with patients with no known cardiovascular comorbidities and elevated troponin (37.5%).[6] A review of serum troponin in critically ill patients with a wide range of presentations previously suggested an association between elevated serum troponin and increased mortality (OR, 2.5; 95% CI, 1.9–3.4; $P<0.001$) and length of ICU stay.[67] A list of published studies suggesting myocardial injury in patients with COVID-19 is summarized in Table 4.[2,4–7,12,20,68]

Although it is reasonable to assume that patients with preexisting cardiovascular comorbidities are more susceptible to COVID-19–related myocardial injury, only 30% and 15% of patients with cardiac injury had coronary heart disease and chronic heart failure, respectively.[7] This suggests that the elevated troponin may be a marker of overall disease severity, regardless of underlying cardiovascular status. Data are lacking in this regard as <27% of patients with troponin elevation had ECGs in one study,[7] and there are few studies linking imaging correlates of myocardial injury (echocardiography and cardiac magnetic resonance) with troponin elevation.[43,44] Troponin elevation itself also correlated strongly with other systemic inflammatory markers, such as interleukin-6, CRP, and ferritin, as well as aggressive disease on chest radiography, findings that support the notion that troponin may be one of many markers of disease severity.

Furthermore, there is accumulating evidence that patients with severe COVID-19 may have a cytokine storm syndrome and that mortality may be attributable to virally driven hyperinflammation. This is supported

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by observations of patients admitted to ICU recording higher plasma cytokine levels, including interleukin-2, interleukin-7, interleukin-10, and granulocyte colony-stimulating factor.[12] The close correlation between troponin levels, inflammatory markers, and triglyceride levels (akin to secondary hemophagocytic lymphangiohistiocytosis) may support indirect effect of SARS-CoV-2 on the myocardium through immune-mediated mechanisms. Whether there is a role for standard therapies for troponin elevation, such as statin or dual antiplatelet therapy, is unknown.

Development of new therapeutic agents to a novel disease, such as COVID-19, is unrealistic in a timely manner. Instead, many have used existing pharmaceuticals, such as corticosteroids, hydroxychloroquine, azithromycin, and tocilizumab, primarily addressing the systemic inflammatory response. Given that myocardial injury is a strong predictor of severe disease, one may reasonably consider maximal optimization of treatment options, particularly in those with previous CVD or who are at a higher cardiovascular risk, as a potential therapeutic target. To date, there is no evidence on the effect of statins in COVID-19 independent of coronary artery disease or otherwise. One possible mechanism for myocardial injury in COVID-19 could be through plaque instability and rupture triggered by the profound cytokine activity and inflammation. Past clinical trials have shown that statins reduce cardiovascular events, with evidence suggesting this is mediated through reduction of inflammation and plaque stabilization.[69,70] That may suggest a preventative role of statin therapy.

From a theoretical perspective, statins play a role in regulating the innate immune response through post-translational modification of intracellular signaling molecules. This leads to suppression of the transcription factor nuclear factor-κB, decreased chemokine levels, including interleukin-1β, tumor necrosis factor-α, and interleukin-6, and decreased monocyte activation.[71] This reduces inflammatory cell infiltrates and macrophage accumulation in atherosclerotic plaques. This is relevant in SARS-like infections, which preclinically seem to upregulate a proinflammatory gene, *MYD88*, which results in activation of the nuclear factor-κB pathway, leading to marked inflammation. Transgenic mice with an attenuated nuclear factor-κB pathway were more likely to survive a SARS infection. Statins play a role in regulating *MYD88* expression levels in stress conditions, and early, high-dose statins appeared to suppress nuclear factor-κB activation.[72] However, the use of statins in COVID-19 without any obvious clinical indication may be problematic, given their interactions with supportive treatment, including macrolides and potential antiretrovirals, such as lopinavir and ritonavir combination.

The increased risk of plaque rupture in severe illness poses the question if antiplatelets and other cardioprotective therapies, such as β blockers, are beneficial. A retrospective study including 20000 patients in ICUs showed that patients taking aspirin, β blockers, and/or statins had a 30-day mortality reduction in a troponin-dependent manner. In particular, aspirin and β blockers reduced 30-day mortality only if the serum troponin was elevated.[73] The utility of continuation or de novo commencement of RAS blockers in these patients has been discussed in the section on hypertension in this article.

There have been reports of COVID-19 patients presenting with chest pain and dyspnea with ST-segment elevation on electrocardiography, later found to have nonobstructed coronary arteries. This has led to the proposition of widespread microvascular thrombosis, although myocarditis remains a possibility.[43,44] The role of aspirin and β blocker in fulminant myocarditis is, however, conflicting. Historic experimental data have shown selected β blockers were cardioprotective through suppression of inflammatory cytokines in autoimmune myocarditis, whereas others had deleterious effects.[74]

Indeed, studies have suggested high levels of D-dimer (>1 μg/mL) are associated with higher mortality risk, indicating a hypercoagulable state.[2] This is supported by findings of small-vessel lumen stenosis and occlusion on lung dissections in COVID-19 patients.[75] Furthermore, a recent retrospective study found better prognosis associated with heparin anticoagulation.[76] However, whether there is a similar role of oral anticoagulants and/or antiplatelets in those with less severe disease, who are treated in outpatient or ambulatory settings, is unknown.

In summary, we need a better understanding of the mechanisms underlying cardiac injury in COVID-19. Further histopathological studies may distinguish between plaque rupture, microvascular thrombosis, or direct myocardial infiltration and inflammation as a cause of troponin elevation. Moving forward, prospective, randomized clinical trials are needed to determine the role of cardioprotective therapies and anticoagulation in COVID-19 patients.

Pending these, patients on preexisting cardioprotective therapies should continue on them if possible. Patients with COVID-19 who meet conventional indications for these cardiovascular therapies should be commenced on them in the absence of contraindications. At present, there are no data to support expanding the role of these protective therapies to other COVID-19 patients, but that may change with rapidly evolving studies.

ACS IN THE COVID-19 PANDEMIC ERA: HOW TO TRIAGE AND WHEN TO RESORT TO INVASIVE STRATEGIES

Take-Home Points

1. Timely primary percutaneous coronary intervention (PCI) remains the mainstay treatment for STEMI.

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2. In case of patient- or system-related delays in mechanical reperfusion in the contemporary COVID-19 era, fibrinolytic therapy within door-to-balloon time of 30 minutes may be an alternative treatment for STEMI in the absence of contraindications.
3. An invasive strategy is highly recommended for patients with non–ST-segment–elevation ACS (NSTE-ACS) who are at high risk.
4. In the COVID-19 era, and especially when the local community outbreak is increasing and the healthcare system is overwhelmed, moderate- and low-risk patients with NSTE-ACS can be treated with an ischemia-guided approach.

ACSs encompass a spectrum of clinical entities ranging from STEMI to non–ST-segment–elevation MI and unstable angina. The latter 2, often coined collectively as NSTE-ACS, differ in their pathophysiological characteristics from STEMI in that they predominantly result from an acute nonocclusive thrombus overlying a disrupted plaque.[77] On the other hand, STEMI is usually attributable to an acute thrombosis overlying a disrupted plaque, which is completely occlusive of the epicardial coronary artery.[78] STEMI manifests with an acute myocardial injury pattern on ECG and needs to be aborted immediately to prevent irreversible myocardial damage. Therefore, a timely reperfusion strategy is the mainstay treatment after STEMI.[78] Of the 2 available reperfusion modalities, primary PCI is preferable to fibrinolytic therapy because it is safer and more effective.[79] On the other hand, moderate- and high-risk NSTE-ACS patients who are medically stabilized can be treated with an urgent, but not necessarily emergent, invasive strategy (ie, coronary angiography with intent to revascularize).[77]

The swiftly spreading COVID-19 pandemic in the United States is placing an unparalleled pressure on the healthcare system. There is currently a rapid depletion of resources in many medical centers, including shortages of hospital and ICU beds, personal protective equipment (PPE), and even HCWs. Hospitalized patients and HCWs are at increased risk of infection with SARS-CoV-2. Revisiting the modality of reperfusion after STEMI and the merits of an invasive strategy and its timing after NSTE-ACS is therefore critically important.

The initial assessment of any patient with suspected ACS should include a history, a physical examination, and a 12-lead ECG. Measurements of cardiac biomarkers of necrosis (eg, troponins) should be performed serially, but reperfusion therapy should be decided upfront based on the clinical presentation and ECG. In the COVID-19 era, a focused but meticulous history and physical examination should be conducted assuming that every patient may be, at a minimum, an asymptomatic SARS-CoV-2 carrier.

In the current section, we propose categorizing ACS patients into 3 categories: critically ill ACS patients and noncritically ill STEMI and NSTE-ACS patients. In the COVID-19 era, triaging patients to optimal medical therapy alone versus invasive approach (added to optimal medical therapy) will depend on many factors, including patients' ACS category, their COVID-19 status, and safety issues (eg, PPE availability and shortage of HCWs).

All ACS patients who are critically ill (eg, cardiogenic shock, mechanical complications, and refractory heart failure) should undergo emergent coronary angiography with intent to revascularize (Figure 3). In general, this life-saving strategy should take place irrespective of the patients' COVID-19 status and other considerations.

For STEMI patients who are not critically ill, timely primary PCI remains the treatment of choice (Figure 3). Mechanical reperfusion, within a first medical contact-to-device time of 90 minutes when presenting to a PCI-capable hospital, is highly recommended.[80] Timely reperfusion is critically important to salvaging myocardium. However, in a small cohort of 7 STEMI patients from Hong Kong undergoing primary PCI in the COVID-19 era, longer median times in all components of STEMI care were observed.[81] Difficulty of achieving timely mechanical reperfusion, especially in geographies severely affected by COVID-19, should be recognized.

Accordingly, it is reasonable to administer fibrinolytic therapy, in the absence of contraindications,[82] to appropriate STEMI patients in COVID-19–affected communities (Figure 3). This is particularly relevant to STEMI patients who do not have high-risk features and are either known or suspected to have COVID-19. A bedside echocardiogram can be readily available and will add incremental value for risk stratification. An example of a STEMI patient eligible for fibrinolytic would be the case of a COVID-19 (+) patient who is hemodynamically stable and who is presenting with ST elevation in aVL alone and echocardiographic evidence of small lateral hypokinesis. Experts from the Sichuan Provincial People's Hospital in China proposed the use of fibrinolytic therapy in COVID-19 (+) patients who are presenting with STEMI, are hemodynamically stable, and have no contraindication to fibrinolysis.[83] Fibrinolytic therapy is most effective when administered within the first 2 to 3 hours of symptom onset. When chosen, timely pharmacological reperfusion within door-to-needle time of 30 minutes and preferably using the newer-generation tenecteplase is recommended.[80] In case of failed fibrinolytic reperfusion, rescue PCI is a reasonable subsequent strategy.[84] As for STEMI patients presenting to non-PCI capable hospitals, timely pharmacologic reperfusion is strongly

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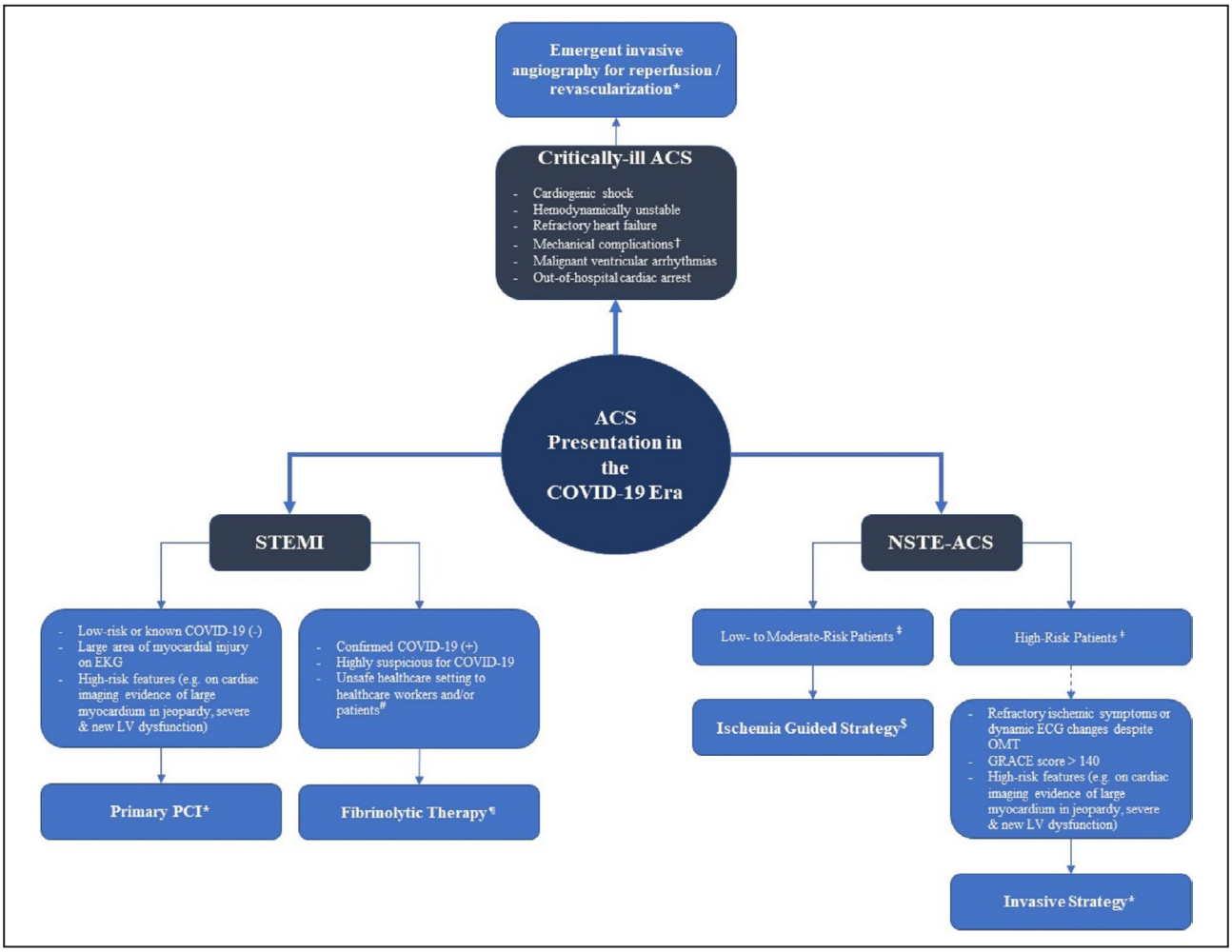

Figure 3. Invasive therapies for acute coronary syndrome (ACS) patients in the coronavirus disease 2019 (COVID-19) era. *When pursuing an invasive approach, appropriate personal protective equipment (eg, gowns, face shield/goggles, and N95 masks) and setup (eg, negative pressure room) must be available for the safety of healthcare workers and patients. Otherwise, defaulting to the alternative approach (pharmacologic reperfusion or ischemia-guided strategy) after deliberation between the heart team members, invoking the ethics team when appropriate, and in a process of shared decision making with the patient and family. †Acute myocardial infarction with mechanical complications is best treated with surgical revascularization and concomitant repair (with adjunctive percutaneous ventricular assist devices). ‡Risk stratification after non–ST-segment–elevation ACS (NSTE-ACS) can be performed using an objective risk score (eg, GRACE [Global Registry of Acute Coronary Events] or TIMI [Thrombolysis in Myocardial Infarction]). §Patients treated with an ischemia-guided strategy may cross over to an invasive strategy in case of significant spontaneous or inducible ischemia, or any evidence of hemodynamic or electrical instability. ¶Fibrinolytic therapy should be administered within door-to-needle time of 30 minutes. On failure of pharmacologic reperfusion, rescue percutaneous coronary intervention (PCI) is recommended. #Unsafe healthcare setting can be attributed to a myriad of factors (eg, lack of personal protective equipment, lack of ventilators, shortage of healthcare workers, or negative pressure catheterization laboratory not available). LV indicates left ventricular; OMT, optimal medical therapy; and STEMI, ST-segment–elevation myocardial infarction.

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encouraged, especially when the receiving PCI center is tackling a COVID-19 surge. In our opinion, transfer of successfully reperfused STEMI patients to a PCI-capable hospital, as part of a pharmacoinvasive approach, should not be routinely implemented but rather individualized, depending on many factors (eg, status of the receiving hospital and outbreak in the community).

For NSTE-ACS patients who are not critically ill, we believe most of those may be safely treated with an ischemia-guided strategy in the COVID-19 era (Figure 3). A routine invasive strategy is superior to an ischemia-guided strategy after NSTE-ACS and reduces the risk of recurrent MI.[85] However, the largest benefit appears to be confined to high-risk patients, and only modest benefit was observed in moderate-risk patients.[85] These studies were largely done more than a decade ago when dual antiplatelet therapy (especially the novel P_2Y_{12} receptor inhibitors), intensive lipid lowering, and optimal medical therapy were

not routinely implemented or available. We therefore believe that treating moderate-risk NSTE-ACS patients in COVID-19–affected medical communities with an ischemia-guided strategy is reasonable. All NSTE-ACS patients need to be risk stratified adequately using objective risk scores.[86] Those treated with an ischemia-guided approach may cross over to an invasive strategy if they manifest significant spontaneous or provoked ischemia or become unstable despite optimal medical therapy.[87] On the other hand, high-risk NSTE-ACS patients should still receive an invasive strategy.[85] An early invasive strategy within ≤24 hours is preferred, as it usually reduces recurrent ischemia compared with a delayed invasive strategy.[88] This is best done if COVID-19 testing is achieved before the procedure. Otherwise, when high level of suspicion for COVID-19 exists, a delayed invasive strategy (24–72 hours) may be selectively implemented in a controlled setting until the test result is available.

There are several considerations that need to be accounted for when entertaining invasive therapy in an ACS patient in the contemporary COVID-19 era. All patients should undergo clinical screening for COVID-19. Ideally, every ACS patient undergoing nonemergent invasive therapy should get tested for COVID-19 before the procedure. If not feasible, at least patients with high clinical suspicion should be tested. All procedures for patients with confirmed or suspected COVID-19 should be performed, if possible, in a dedicated/repurposed cardiac catheterization laboratory with optimal protection strategies for HCWs and patients.[9] Evaluation of the patient's airway should be assessed before transfer to the catheterization laboratory. In patients with concerning respiratory distress, intubation should be performed before arrival of the patient to the catheterization laboratory, if possible.[89] All patients should be outfitted with a face mask. Proper protection of HCWs with appropriate PPE is essential, including appropriate face mask (N95 respirator), face shield, or goggles for eye protection and gowns.[90]

When the healthcare setting is not safe for HCWs and patients (eg, lack of PPE and shortage of ventilators), the risks and benefits of an invasive strategy should be revisited, irrespective of the ACS category. Members of the heart team should deliberate and engage the patient and family in a process of shared decision making and, if necessary, invoke the ethics committee. This also applies to critically ill patients whose instability is attributable to advanced COVID-19 illness rather than the ACS itself, and in whom an invasive therapy is likely futile.

Overall, the aforementioned recommendations and proposed clinical algorithm provide general clinical guidance. In the absence of robust data specific to the COVID-19 era, they represent our opinion and complement guidance provided by other societies.[9,89] As such, they should be tailored to local medical institutions and communities. These recommendations are dynamic and should be constantly revised as the burden of the outbreak and the availability of resources continue to change over time.

EXTRACORPOREAL MEMBRANE OXYGENATION IN THE COVID-19 PANDEMIC ERA

Take-Home Points

1. Venovenous and venoarterial extracorporeal membrane oxygenation (ECMO) may be used as salvage therapies in COVID-19 patients with refractory respiratory or cardiorespiratory failure, respectively.
2. When needed, it is best to institute ECMO early before multiorgan failure ensues.
3. ECMO is a complex therapeutic modality that requires advanced expertise and intensive resource use. In the absence of definitive evidence supporting its utility, it should be used judiciously after careful assessment of the benefits and risks by a multifaceted medical team and with shared decision making with patient and family.

The clinical presentation of patients with COVID-19 is variable.[15] Hypoxemic respiratory failure requiring ICU admission occurs in 5% to 6% of patients, of whom most will require mechanical ventilation.[91] The most common cause for respiratory failure in these patients is ARDS.[18] Mortality rates are significantly high in patients who require mechanical ventilation and are reported to be 50%.[18,91] Furthermore, COVID-19 patients on mechanical ventilation require prolonged duration of respiratory support, with a median of 17 days of ventilation.[92] COVID-19 can also cause cardiovascular complications, including cardiac injury, myocarditis, heart failure, cardiogenic shock, tamponade, and pulmonary embolism.[93–95] Patients with underlying CVD are more likely to experience myocardial injury with COVID-19, and this combination (underlying CVD and myocardial injury) portends the highest mortality (70%).[6]

Venovenous and venoarterial ECMO can offer respiratory or cardiorespiratory support for patients with refractory respiratory or cardiorespiratory failure, respectively.[96] ECMO is also used in cases of cardiac arrest in conjunction with cardiopulmonary resuscitation.[97] Thus, ECMO could potentially offer a life-saving treatment to sick COVID-19 patients, as it did in prior coronavirus epidemics.[98] ECMO is a complex therapeutic modality that requires intensive resource use and is usually offered in tertiary and quaternary centers

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with a full ECMO team. It is therefore important to understand its benefits and limitations, especially when resources are stretched and healthcare systems are overwhelmed, as is the case in the current COVID-19 pandemic.[96,98]

There are conflicting reports about preliminary outcomes of ECMO use in sick COVID-19 patients. In one study, patients treated with ECMO had a mortality rate of 86%.[4] In another study, 50% of patients treated with ECMO died, whereas 37.5% were successfully weaned off ECMO but remained on mechanical ventilation.[99] A potential marker of poor prognosis in COVID-19 with ECMO is lymphopenia. Lymphopenia also occurred in prior coronavirus epidemics and was caused by lymphocyte apoptosis.[100] Lymphopenia occurs in 70% of symptomatic COVID-19 patients, and the degree of lymphopenia is associated with more severe disease and ICU admission.[5,12] ECMO use is associated with a decline in lymphocytic count, and this potentially confounds the clinical course in COVID-19 patients.[101] One possible explanation of poor prognosis is the significant increase in cytokines and inflammatory biomarkers, although there are conflicting opinions on whether it is an association or implicated in the causal pathway.[102] In COVID-19 patients, the cytokine release syndrome is associated with lower probability of survival.[16]

Given the limited evidence for ECMO use in COVID-19 patients with ARDS, and the extensive resources and experience required to provide ECMO support, the Extracorporeal Life Support Organization released a guidance document.[96] Several important issues should be taken into account when considering ECMO for COVID-19 patients (Table 5). First, it should be determined early which kind of support that patient would need, whether respiratory support only or whether there is evidence of myocardial dysfunction and cardiogenic shock requiring cardiorespiratory support. If ECMO is needed, it should be provided early in the course of mechanical ventilation, as prognosis is usually worse with longer duration on mechanical ventilation. Second, if ECMO is likely to be required, the consensus recommendation is to insert it early before multiorgan failure ensues. Third, ECMO may be futile in elderly patients with significant comorbidities in whom survival is unlikely. This is important at a time when resources are limited and the healthcare system is strained, as is the case in the current COVID-19 outbreak in several parts of the United States, Italy, and Spain. Fourth, a strong relationship between ECMO volume and outcome has been documented.[103] It is highly advisable to refer COVID-19 patients who might require ECMO support to experienced centers, as the best survival outcomes were reported in centers performing at least 30 ECMO procedures annually.[103] Fifth, given the risk of significant aerosolization and disease transmission during cardiopulmonary resuscitation, and the number of personnel required in the room for ECMO-assisted cardiopulmonary resuscitation, it is probably ill advised to use ECMO in COVID-19 patients with

Table 5. Clinical and Procedural Considerations in COVD-19 Patients Undergoing ECMO

Cannulation place	Preferably bedside percutaneous cannulation using adequate PPE to avoid moving the patient to the OR with dislodgment of cannula and potential transmission of the infection.
Resuscitation	Avoid doing ECMO-assisted CPR given poor prognosis, limited PPE resources, and high potential for aerosol generation and infecting healthcare staff.
Timing	Attempt to implement ECMO placement as early as possible and before end-organ damage occur. Also, avoid in patients with prolonged (usually >7 d) mechanical ventilation.
Patient selection	Consider avoiding in elderly patients with significant burden of comorbidities because of to futility.
Shared decision making	Patient- and family-centered discussions, early in the hospital course before clinical deterioration and continually, about goals of care, and extent of invasiveness desired by the patient.
Center referral	May not be advisable for centers to start an ECMO program during the pandemic. Preferably, a centralized approach of referring COVID-19 cases for ECMO care early to high-volume experienced centers should be considered.
Reporting	Participation and reporting to ELSO network are encouraged, to generate evidence about the safety and effectiveness of ECMO in sick COVID-19 patients.
Capacity consideration	Providing advanced ECMO care to critically ill COVID-19 patients should be balanced with the limitations of intensive care unit capacity in a pandemic.
Blood-borne transmission	There is no evidence of possible blood transmission of COVID-19 yet. However, standard precautions with blood-borne pathogens should be always observed.
Type of support	Given reported cases of severe cardiac dysfunction and cardiogenic shock in some COVID-19 cases, early placement of venoarterial ECMO or upgrade of venovenous ECMO to venoarterial ECMO should be considered if end-organ hypoperfusion becomes evident.
Laboratory consideration	Monitor blood counts, kidney and liver functions, electrolytes, D-dimers, and cardiac and proinflammatory markers, including interleukin-6 and ferritin. Standardized transfusion protocols should be used.

COVID-19 indicates coronavirus disease 2019; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; OR, operating room; and PPE, personal protective equipment.

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cardiac arrest. Finally, in COVID-19 patients with severe LV dysfunction (eg, myocarditis and takotsubo cardiomyopathy) complicating their ARDS, increased LV wall stress and consequent myocardial ischemia from ECMO may exacerbate cardiac dysfunction. In these patients, venting the heart using an intra-aortic balloon pump or a percutaneous ventricular assist device (eg, Impella) may be a reasonable strategy, as it has been successfully used in cardiogenic shock patients. However, this should be only performed judiciously with consideration of available resources and expertise in the middle of a pandemic.

It is probably too early in the pandemic to fully judge the utility of ECMO in the COVID-19 era. Currently, it remains an indispensable therapeutic modality in the armamentarium of clinicians attempting to salvage a decompensated COVID-19 patient with ARDS. It is laudable that the Extracorporeal Life Support Organization encouraged early entry of COVID-19 patients treated with ECMO into its registry by participating hospitals and waived membership fees during the pandemic.[96] This will help the medical community examine the role of ECMO and inform clinical practice with critically needed evidence.

COVID-19 INFECTION AND THE HEALTHCARE PROFESSIONAL: MITIGATING THE RISK

Take-Home Points

1. Cardiovascular healthcare professionals are at risk of contracting COVID-19, and best practices should be implemented to reduce the risk of patient-provider and provider-provider exposure.
2. Future research efforts should focus on reducing COVID-19 transmission, optimizing communication of risk, and understanding the long-term physical and psychosocial consequences of exposure.

The protection of healthcare providers from COVID-19 exposure during this pandemic is of paramount importance. Cardiovascular physicians, nurses, technicians, and other healthcare professionals will be increasingly called on to assist in the clinical care of patients with suspected or confirmed COVID-19, particularly those patients with underlying CVD or those who develop cardiac complications. To best serve these patients, cardiovascular healthcare professionals must use best practices to protect their own physical health and emotional well-being.

In China, 3.8% of patients infected with COVID-19 were HCWs, whereas in Italy, HCWs accounted for 9% of total COVID-19 cases.[66,104] The clinical spectrum of COVID-19 infection ranges from asymptomatic infection to severe viral pneumonia with respiratory failure. Transmission risk occurs from both asymptomatic and symptomatic patients, with infection rates ranging from 1% to 5%.[105] Cardiovascular healthcare professionals are at increased risk because COVID-19 is more prevalent in patients with cardiovascular comorbidities. The most common coexisting medical conditions in patients hospitalized with COVID-19 are hypertension (31%), CVD (14%), and diabetes mellitus (10%).[5] In addition, cardiovascular procedures place providers at increased risk because of the close contact needed with the patient and the potential for generation of respiratory droplets.

Precautions are needed at the societal, institutional, departmental, and administrator levels to protect cardiovascular healthcare professionals from COVID-19. Many societal professional meetings have been cancelled or converted to virtual platforms, including the American College of Cardiology 2020 Annual Scientific Session in Chicago, IL. Several healthcare institutions have also significantly restricted nonessential travel for faculty. To reduce COVID-19 exposure at the departmental level, the overall number of nonessential in-person patient-provider encounters should be limited. Routine cardiology consultations and outpatient visits should be conducted virtually (eg, telemedicine) whenever possible. Elective cardiology studies and procedures should be postponed to minimize exposure and preserve PPE and resources. The performance of essential cardiology studies and procedures, particularly those involving suspected or confirmed COVID-19 patients, should be limited to essential personnel. At the administrator level, adequate supplies of PPE should be obtained and local COVID-19–related updates should be relayed in a timely and transparent manner to all HCWs.

Precautions are also necessary at the personal level to protect cardiovascular healthcare professionals from COVID-19. Consideration should be given to limiting exposure of staff who may be particularly susceptible to the complications of COVID-19, including those with an age >60 years, those with chronic medical conditions, and those who are immunocompromised or pregnant. Although cardiovascular medical education remains important, restrictions should be placed on students and trainees who are not essential to direct clinical care to minimize exposure, and online platforms for learning (eg, teleconferences) should be used when possible.

When direct in-person patient care with COVID-19 patients is required, cardiovascular healthcare providers should strictly adhere to the latest Centers for Disease Control and Prevention (CDC) recommended guidelines.[106] Current CDC guidelines indicate that COVID-19 is spread by both close contact (within 6 feet) and respiratory droplets (eg, coughing or sneezing). Contact

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precautions include the use of a gown and gloves, and droplet precautions include the use of a face mask. To further minimize the risk of exposure when treating patients with suspected or confirmed COVID-19, the CDC recommends the use of eye protection (eg, goggles or face shield) and a respirator (eg, N95 or powered air-purifying respiratory systems) instead of a face mask when possible, particularly for procedures that are likely to generate respiratory aerosols (eg, transesophageal echocardiograms). Therefore, all cardiovascular staff should be fit tested for N95 respirator masks and receive training on the proper use of PPE, including doffing and donning techniques, before participating in the direct clinical care of COVID-19 patients. In contrast to the CDC guidelines, the World Health Organization and Public Health England currently recommend reserving respirators for aerosol-generating procedures.[90,107]

To reduce exposure risk during cardiac procedures, cardiac laboratories should be converted to a negative-pressure ventilation system whenever possible for optimal infection isolation and be thoroughly disinfected after procedures. To minimize the potential for cardiovascular staff shortages in the case of a procedural exposure, the separation of individuals with overlapping cardiovascular procedural skill sets should be considered. Specific procedural protocols for the management of acute cardiovascular conditions (eg, acute MI) should be developed for both patients with and without COVID-19. Because of the infectious risks in transporting hospitalized patients to cardiac laboratories, certain cardiac procedures (eg, transesophageal echocardiogram and pulmonary artery catheter placement) should be considered to be performed at the bedside. For PPE recommendations on specific cardiovascular aerosol-generating and non–aerosol-generating procedures, we recommend following subspecialty guidelines.[108–110]

In addition to appropriate patient-provider precautions, direct interactions with other healthcare providers should be conducted at a distance in accordance with social distancing. Staff rooms used by multiple healthcare providers should be frequently cleaned, with surface decontamination of commonly touched surfaces. Thorough and frequent handwashing is essential after visiting any public space, touching a common surface, touching of the face, and before and after eating. Cardiovascular providers should also clean personal items, such as stethoscopes and mobile telephones, with hospital-provided disinfectants or alcohol-based disinfectants to prevent potential viral transmission. In accordance with social distancing, nonessential travel and large gatherings of people should be avoided to minimize exposure risk.

It is also essential to recognize the psychological stress of COVID-19 exposure on cardiovascular healthcare providers. The pandemic has created newly unemployed spouses, difficulties finding child care during school closures, loved ones at increased risk of disease, and a feeling of uncertainty. Among Chinese HCWs exposed to COVID-19, women, nurses, and frontline workers reported more severe symptoms of depression, anxiety, insomnia, and distress.[111] Transparent and thoughtful communication from hospital leadership, local and state health departments, and the CDC is essential during this time. Interventions to promote psychosocial and emotional well-being should also be encouraged, including telemedicine therapy, mindfulness and meditation practices, and relaxation techniques.

Despite the above measures to minimize COVID-19 exposure, the risk cannot be fully eliminated. Cardiovascular healthcare professionals must self-monitor, report signs of illness, and undergo self-quarantine or medical evaluation as needed. Antibody testing may help identify cardiovascular HCWs exposed to COVID-19 infection who are safe to return to work and potentially immunized against future COVID-19 disease, although there is still an ongoing debate about how long, if at all, this immunity lasts for, and how good are these tests. As the medical community gains more experience with the COVID-19 pandemic, it will be essential to effectively communicate any updates in best practices to better protect cardiovascular healthcare professionals. When testing, vaccination, and treatments become (increasingly) available, the entire healthcare workforce should be considered a priority for evaluation and treatment.

ETHICAL ISSUES DURING THE COVID-19 PANDEMIC: TRIAGE, RESOURCE ALLOCATION, AND PATIENT RIGHTS

Take-Home Points

1. Internationally and in the United States, serious ethical concerns have arisen as healthcare providers address triaging suspected COVID-19 patients; determining allocation of scarce resources; and honoring patients' rights.
2. Following recommendations based on ethical and process principles may help those infected, their families, their caregivers, and society cope with the growing tragedy of the COVID-19 pandemic.

Research Questions

1. Are COVID-19 triage principles accurate in predicting which patients are most likely to survive?
2. Do vulnerable populations, as defined by Institutional Review Board criteria, have poorer outcomes following treatment for COVID-19 compared with nonvulnerable defined populations?

The COVID-19 pandemic is unprecedented in the modern era. Numerous ethical concerns have arisen

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as internationally and, in the United States, healthcare providers struggle to address grave issues: triaging suspected COVID-19 patients while preventing SARS-CoV-2 viral transmission to themselves, patients, and personnel; determining allocation of scarce resources; and honoring patients' rights and preferences. Life-and-death decisions are required, in some cases, with no existing guidelines and no time to establish best practices, leading to the question: How can human and capital resources be fairly and equitably allocated during this pandemic?

Public health emergencies require health care grounded in ethical principles. Herein, we examine 3 ethical principles and present recommendations for practice during the COVID-19 pandemic (Table 6). *Deontology* is an ethical value proposing that an action should be based on whether it is right or wrong under a series of rules. This may include the assessment of preexisting conditions, risk stratification, prognosis, and protection of vulnerable groups.[114] *Utilitarianism* suggests that actions are right if they are useful or benefit the majority. This is represented by saving the most lives, provisioning required resources, evaluating quality of life years, and saving those viewed as the most valuable to society[115] (eg, giving priority care to first responders and HCWs). *Egalitarianism* is an ethical precept meaning that all people are equal and deserve equal opportunities. Examples include the equal right to care, principle of first come first served, access to clinical trials, or lottery systems.[116] Understanding ethical principles can be useful to effectively develop processes to address crucial issues of triage, allocation of scare resources, and support of patients' rights.

Arguably, one of the most dangerous jobs in a pandemic is that of triage personnel in the emergency department. In normal times, most individuals coming to the emergency department are undifferentiated and expose emergency department staff to unknown threats. In the pandemic milieu, both triage personnel and patients require adequate PPE to remain free of disease or to prevent disease transmission. It is imperative that triage protocols with standardized triage acuity categories be applied fairly and equitably.[115] Commonly used triage indexes may need to be modified to protect staff and patients; however, the care of presumptive COVID-19 patients should not supersede the treatment of other patients presenting to the emergency department with life-threatening conditions, such as acute MI or stroke.

Of all the care that will be rationed, the most difficult will be the use of ventilators.[117] There are ≈62 000 full function ventilators in the United States,[117] which is wholly insufficient if millions of Americans become infected, as expected. The PPE is being rationed or reused at great risk to first responders, hospital staff, and the uninfected.[116] Medications may also be rationed as hospitalizations increase. There are already reported shortages of hydroxychloroquine following unsubstantiated reports by government officials that it is an effective COVID-19 treatment. Deficiencies in available and reliable testing have also become a critical issue because infected carriers may be asymptomatic for weeks and go on to infect others.[3] Finally, without large-scaled testing, it is impossible to track true disease prevalence. Numerous authors have suggested frameworks for the allocation of scarce resources in the face of disasters, such as a pandemic,[118,119] with process principles to improve the likelihood of equitable care and as a means to mitigate the moral distress experienced by frontline care providers. Recommended processes include a "triage officer," central monitoring committee, and triage algorithm.[120]

Maintaining patients' rights to high quality care, autonomy, and privacy in the midst of a public health emergency is challenging.[121] For example, the use of ventilators is not just a resource allocation issue. Who decides to initiate or terminate mechanical ventilation: the patient, the family, or a committee? Crushing decisions as to who lives and dies on the basis of individual and/or institutional criteria amid the surge are already taking place. Lack of transparency may also leave patients uninformed and suppress autonomy when their care is rationed because of scarce resources. Restricted visitation policies have caused great anguish for families by limiting or prohibiting presence at the bedside of their critically ill loved ones. Clinical trials and access to investigational products present another ethical challenge when patients are not offered opportunities to participate or compassionate use (expanded access) studies have been discontinued in the patients' most dire hour. Meanwhile, we may see critical drug shortages as increased demands disrupt pharmaceutical supply chains.

The thought of rationing health care is anathema to the general public, and healthcare decisions are fraught with ethical and moral dilemmas that, by definition, may have no right or wrong answer. For triage, we recommend the use of a specific algorithm on the basis of exclusion criteria and mortality risk; the use of a triage officer not involved in direct patient care; and fair and transparent decisions on care. For allocation of scarce resources, provide ventilators to those with greatest short- and long-term chance for survival; provide PPE to all personnel caring for the infected; prescribe medications approved for a specific use; and distribute resources on the basis of equal access. To preserve patients' rights, limit visitation and provide for virtual visitation, facilitate transparent discussion with patients and families on their right to receive or decline care, and convene a task force for expediting research. Following recommendations based on generally accepted ethical and process principles may help those infected, their families, their caregivers, and society as a whole cope with the growing tragedy of the COVID-19 pandemic and better prepare for the next pandemic.

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Table 6. Ethical principles and recommendations for practice during the COVID-19 pandemic

Ethical Concept	Ethical Principle of Interest	Recommendations for Application During COVID-19 Pandemic
Deontology: an action should be based on whether it is right or wrong under a series of rules (rule based or policy based)	1. Preexisting conditions 2. Risk stratification 3. Prognosis 4. Protecting vulnerable groups	Triage 1. Develop triage algorithm on the basis of exclusion criteria and assessment of mortality risk (eg, SOFA score)[4] and review regularly on the basis of outcome measures and new knowledge of pandemic 2. Use of a triage officer/committee not involved in direct patient care to triage those presenting to the ED
		Allocation of Scarce Resources 1. Provide ventilators to those with greatest short- and long-term chance for survival 2. Provide PPE to all personnel caring for the infected 3. Prescribe medication as approved for use, not for off-label use
		Patients' Rights 1. Create standards for emergency use of experimental treatments 2. Restrict visitation to reduce transmission of infection 3. Provide remote visitation via telephone or tablet
Utilitarianism: actions are right if they are useful or benefit the majority (balance or good vs bad consequences)	1. Saving the most lives 2. Required resources 3. Quality of life years 4. Saving function of society	Triage 1. Employ triage officer/committee not involved in direct patient care to decide priority for care
		Allocation of Scarce Resources 1. Direct critical resources to those who will benefit the most 2. Ventilators to those most likely to survive 3. Provide intensive care and medications for those most likely to survive
		Patients' Rights 1. Transparent discussion with patients and families about their right to decline care or request care
Egalitarianism: all people are equal and deserve equal opportunities	1. Equal rights 2. Unbiased selection 3. Research 4. First come, first served 5. Lottery	Triage 1. Include vulnerable populations 2. Make decisions based on fairness and transparency 3. Triage to appropriate level of care and resources
		Allocation of Scarce Resources 1. Distribute resources on the basis of equal access (nondiscrimination) 2. Provide equal opportunity for all patients to experience the stages of life from childhood to old age, and prioritize resources according to this life-cycle principle[112]
		Patients' Rights 1. Develop task forces for expediting all forms of research, ensuring access to data, informed consent, expedient IRB reviews, and inclusion of all populations[113] 2. Compassionate use of PPE by family members for patients at the end of life,[112] if possible, or provide videoconferencing technology to connect patients and families

COVID-19 indicates coronavirus disease 2019; ED, emergency department; IRB, institutional review board; PPE, personal protective equipment; and SOFA, Sequential Organ Failure Assessment.

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CONCLUSIONS

The novel coronavirus pandemic is a unique event during our lifetimes. Prior pandemics, including HIV and H1N1 influenza, had cardiac sequelae but differed significantly: HIV was initially highly lethal but less contagious than COVID-19, whereas H1N1 was highly contagious but had lower lethality than COVID-19. For both HIV and H1N1, however, the cardiac effects were less clearly apparent early during the course of the pandemic.

The ramifications of the COVID-19 pandemic are tragic, when considering the millions of infected patients, the strain on the healthcare system, and the effects on the world's economy. This Perspective Article and many others like it highlight how little we currently understand about COVID-19 and its cardiac effects. The intense study of the virus and its effects on the heart should correct this deficit. Both the National Institutes of Health and the American Heart Association have solicited grants to study cardiac effects of the virus. *JAHA* has already received dozens of articles related to COVID-19. It is likely that we will soon understand much more about the effects of the virus on the heart and the role of CVD in modulating viral infection. In addition, these studies will likely teach us something fundamental about cardiovascular physiological and pathophysiological characteristics that transcend the current pandemic.

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REFERENCES

1. John Hopkins University of Medicine Coronavirus Resource Center. Available at: https://coronavirus.jhu.edu/. Accessed April 27, 2020.
2. 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. DOI: 10.1016/S0140-6736(20)30566-3. Epub March 11, 2020.
3. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17:259–260. DOI: 10.1038/s41569-020-0360-5. [Epub ahead of print]
4. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8:475-481.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061–1069.
6. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020. DOI: 10.1001/jamacardio.2020.1017. [Epub ahead of print].
7. 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. DOI: 10.1001/jamacardio.2020.0950. [Epub ahead of print]. Published online March 25, 2020. Accessed April 6, 2020.
8. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72:2231–2264.
9. Welt FGP, Shah PB, Aronow HD, Bortnick AE, Henry TD, Sherwood MW, Young MN, Davidson LJ, Kadavath S, Mahmud E, et al.; American College of Cardiology's (ACC) Interventional Council and the Society of Cardiovascular Angiography and Intervention (SCAI). Catheterization laboratory considerations during the coronavirus (COVID-19) pandemic: from ACC's Interventional Council and SCAI. *J Am Coll Cardiol*. 2020;S0735-1097(20)34566-6. DOI: 10.1016/j.jacc.2020.03.021. [Epub ahead of print]. Published online March 17, 2020. Accessed April 6, 2020.
10. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, Katz K, Ko DT, McGeer AJ, McNally D, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med*. 2018;378:345–353.
11. 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.
12. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;6736:1–10. 31986264.
13. He XW, Lai JS, Cheng J, Wang MW, Liu YJ, Xiao ZC, Xu C, Li SS, Zeng HS. Impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients [in Chinese]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2020;48:E011. DOI: 10.3760/cma.j.cn112148-20200228-00137. [Epub ahead of print]. (Abstract Only)
14. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271–280.e8.
15. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, Liu L, Shan H, Lei C-L, Hui DSC, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–1720. DOI: 10.1056/NEJMoa2002032. [Epub ahead of print].
16. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846–848.
17. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020. DOI: 10.1111/all.14238. Published online February 19, 2020. Accessed April 6, 2020.
18. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Du C, Zhang Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020. DOI: 10.1001/jamainternmed.2020.0994. [Epub ahead of print]. Published online March 13, 2020.
19. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, Liu XQ, Chen RC, Tang CL, Wang T, et al.; China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020;55:2000547. DOI: 10.1183/13993003.00547-2020.
20. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.
21. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, Xiao W, Wang YN, Zhong MH, Li CH, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)*. 2020;133:1025–1031.
22. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, Wang X, Hu C, Ping R, Hu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. *Am J Respir Crit Care Med*. 2020; DOI: 10.1164/rccm.202003-0543OC. [Epub ahead of print]. Accessed April 8, 2020.
23. Wang L, He W, Yu X, Hu D, Bao M, Liu H, Zhou J, Jiang H. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020;80:639–645.
24. Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, Xiong Y, Cheng Z, Gao S, Liang K, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis*. 2020;ciaa270. DOI: 10.1093/cid/ciaa270. [Epub ahead of print]. Published online March 16, 2020. Accessed April 6, 2020.

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25. Cao J, Tu WJ, Cheng W, Yu L, Liu YK, Hu X, Liu Q. Clinical features and short-term outcomes of 102 patients with corona virus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020. [Epub ahead of print]. Published online April 2, 2020. Accessed April 6, 2020.
26. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91–95. DOI: 10.1016/j.ijid.2020.03.017. [Epub ahead of print].
27. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int J Infect Dis*. 2016;49:129–133.
28. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, Shao L, Tian Y, Dong Y, Zheng C, et al.; China Hypertension Survey Investigators. Status of hypertension in China: results from the China Hypertension Survey, 2012–2015. *Circulation*. 2018;137:2344–2356.
29. COVID-19 Surveillance Group. Istituto Superiore della Sanita'. Characteristics of COVID-19 patients dying in Italy report based on available data on March 20th, 2020. Available at: https://www.epicentro.iss.it/en/coronavirus/bollettino/Report-COVID-2019_14_May_2020.pdf. Accessed April 6. 2020.
30. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med*. 2020;382:1653–1659. DOI: 10.1056/NEJMsr2005760. Epub March 30, 2020.
31. Sommerstein R, Kochen MM, Messerli FH, 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. DOI: 10.1161/JAHA.120.016509.
32. Guo J, Huang Z, Lin L, Lv J. Coronavirus disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. *J Am Heart Assoc*. 2020;9:e016219. DOI: 10.1161/JAHA.120.016219.
33. Liu Y, Huang F, Xu J, Yang P, Qin Y, Cao M, Wang Z, Li X, Zhang S, Ye L, et al. Anti-hypertensive angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. *medRxiv*. 2020; Last accessed April 4, 2020. 2020.03.20.20039586.
34. Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, Cai J, Yang R, Han J, Huang Y, et al. Angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors usage is associated with improved inflammatory status and clinical outcomes in COVID-19 patients with hypertension. *medRxiv*. 2020;Last accessed April 4, 2020. 2020.03.31.20038935.
35. Mao L, Wang M, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Li Y, Jin H, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *JAMA Neurol*. 2020 Apr 10. DOI: 10.1001/jamaneurol.2020.1127. [Epub ahead of print]. Accessed April 1, 2020.
36. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA*. 2020 Mar 19. DOI: 10.1001/jama.2020.4326. [Epub ahead of print]. Accessed April 1, 2020.
37. Shao IY, Elkind MSV, Boehme AK. Risk factors for stroke in patients with sepsis and bloodstream infections. *Stroke*. 2019;50:1046–1051.
38. Aird WC. Endothelium as a therapeutic target in sepsis. *Curr Drug Targets*. 2007;8:501–507.
39. Wang HE, Shapiro NI, Griffin R, Safford MM, Judd S, Howard G. Inflammatory and endothelial activation biomarkers and risk of sepsis: a nested case-control study. *J Crit Care*. 2013;28:549–555.
40. Luna JM, Moon YP, Liu KM, Spitalnik S, Paik MC, Cheung K, Sacco RL, Elkind MS. High-sensitivity C-reactive protein and interleukin-6-dominant inflammation and ischemic stroke risk: the Northern Manhattan study. *Stroke*. 2014;45:979–987.
41. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, Kritas SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020;34:1. DOI: 10.23812/CONTI-E. [Epub ahead of print]
42. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burkhoff D, Kumaraiah D, Rabbani L, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. *Circulation*. 2020. DOI: 10.1161/CIRCULATIONAHA.120.046941. [Epub ahead of print]. Accessed April 1, 2020.
43. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J*. 2020;ehaa190. DOI: 10.1093/eurheartj/ehaa190. [Epub ahead of print]. Published online March 16, 2020.
44. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020; DOI: 10.1001/jamacardio.2020.1096. [Epub ahead of print]. Published online March 27, 2020. Accessed April 6, 2020.
45. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, et al.; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;34:2636–2648, 2648a-2648d.
46. Riski H, Hovi T, Frick MH. Carditis associated with coronavirus infection. *Lancet*. 1980;2:100–101.
47. Alhogbani T. Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus. *Ann Saudi Med*. 2016;36:78–80.
48. Li SS, Cheng CW, Fu CL, Chan YH, Lee MP, Chan JW, Yiu SF. Left ventricular performance in patients with severe acute respiratory syndrome: a 30-day echocardiographic follow-up study. *Circulation*. 2003;108:1798–1803.
49. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, Butany J. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest*. 2009;39:618–625.
50. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8:420–422.
51. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, Deng Y, Wei S. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia [in Chinese]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2020;43:203–208.
52. Miura TA, Wang J, Holmes KV, Mason RJ. Rat coronaviruses infect rat alveolar type I epithelial cells and induce expression of CXC chemokines. *Virology*. 2007;369:288–298.
53. Zhang G, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. *Respir Res*. 2020;21:74.
54. Alvi RM, Frigault MJ, Fradley MG, Jain MD, Mahmood SS, Awadalla M, Lee DH, Zlotoff DA, Zhang L, Drobni ZD, et al. Cardiovascular events among adults treated with chimeric antigen receptor T-cells (CAR-T). *J Am Coll Cardiol*. 2019;74:3099–3108.
55. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, Kochanek M, Böll B, von Bergwelt-Baildon MS. Cytokine release syndrome. *J Immunother Cancer*. 2018;6:56.
56. Mackall CL, Miklos DB. CNS endothelial cell activation emerges as a driver of CAR T cell-associated neurotoxicity. *Cancer Discov*. 2017;7:1371–1373.
57. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration UK. COVID- 19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395:1033–1034.
58. Zhang X, Song K, Tong F, Fei M, Guo H, Lu Z, Wang J, Zheng C. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv*. 2020;4:1307–1310.
59. Henriksen M. Anti-il6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure (TOCIVID). https://clinicaltrials.gov/ct2/show/NCT04322773. Accessed April 7, 2020.
60. Yu CM, Wong RS, Wu EB, Kong SL, Wong J, Yip GW, Soo YO, Chiu ML, Chan YS, Hui D, et al. Cardiovascular complications of severe acute respiratory syndrome. *Postgrad Med J*. 2006;82:140–144.
61. Chang D, Saleh M, Garcia-Bengo Y, Evan Choi E, Epstein L, Jonathan Willner J. COVID-19 infection unmasking Brugada syndrome. *HeartRhythm Case Rep*. 2020. DOI: doi.org/10.1016/j.hrcr.2020.03.012. Accessed April 8, 2020.
62. Wu CI, Postema PG, Arbelo E, Behr ER, Bezzina CR, Napolitano C, Robyns T, Probst V, Schulze-Bahr E, Remme CA, et al. SARS-CoV-2, COVID-19 and inherited arrhythmia syndromes. *Heart Rhythm*. 2020;S1547-5271(20)30285-X. DOI: 10.1016/j.hrthm.2020.03.024. [Epub ahead of print]. Acessed April 8 2020.
63. White NJ. Cardiotoxicity of antimalarial drugs. *Lancet Infect Dis*. 2007;7:549–558. DOI: 10.1016/S1473-3099(07)70187-1.

Downloaded from http://ahajournals.org by on April 27, 2022

64. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med*. 2020;382:1787–1799.
65. Sakabe M, Yoshioka R, Fujiki A. Sick sinus syndrome induced by interferon and ribavirin therapy in a patient with chronic hepatitis C. *J Cardiol Cases*. 2013;8:173–175. DOI: 10.1016/j.jccase.2013.08.002. eCollection 2013 Dec.
66. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Centre for Disease Control and Prevention. *JAMA*. 2020;Last accessed April 5, 2020. DOI: 10.1001/jama.2020.2648.
67. Lim W, Qushmaq I, Devereaux PJ. Elevated cardiac troponin measurements in critically ill patients. *Arch Intern Med*. 2006;166:2446–2454.
68. Zhang F, Yang D, Li J, Gao P, Chen T, Cheng Z, Cheng K, Fang Q, Pan W, Yi C. Myocardial injury is associated with in-hospital mortality of confirmed or suspected COVID-19 in Wuhan, China: a single center retrospective cohort study. *medRxiv*. Preprint online March 24, 2020. DOI: 10.1101/2020.03.21.20040121.
69. Albert MA, Danielson E, Rifai N, Ridker PM; PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA*. 2001;286:64–70. DOI: 10.1001/jama.286.1.64.
70. Ridker P.M., Danielson E., Fonseca F.A., Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, et al.; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207. DOI: 10.1056/NEJMoa0807646.
71. Diamantis E, Kyriakos G, Quiles-Sanchez LV, Farmaki P, Troupis T. The anti-inflammatory effects of statins on coronary artery disease: an updated review of the literature. *Curr Cardiol Rev*. 2017;13:209–216. DOI: 10.2174/1573403X13666170426104611.
72. Yuan S. Statins may decrease the fatality rate of Middle East respiratory syndrome infection. *mBio*. 2015;6:e01120. DOI: 10.1128/mBio.01120-15.
73. Rothernberg FG, Clay MB, Jamali H, Vandivier-Pletsch RH. Systematic review of β-blocker, aspirin and statin in critically ill patients: importance of severity of illness and cardiac troponin. *J Investig Med*. 2017;65:747–753. DOI: 10.1136/jim-2016-000374.
74. Yuan Z, Shioji K, Takenaka H, Onozawa Y, Kishimoto C. Cardioprotective effects of carvedilol on acute autoimmune myocarditis: anti-inflammatory effects associated with antioxidant property. *Am J Physiol Heart Circ Physiol*. 2004;286:H83–H90. DOI: 10.1152/ajpheart.00536.2003.
75. Luo W, Yu H, Gou J, Li X, Sun Y, Li J, Liu L. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). *Preprints*. 2020, 2020020407.
76. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 with coagulopathy. *J Thromb Haemost*. 2020. DOI: 10.1111/jth.14817. Accessed April 6, 2020.
77. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, et al. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2354–2394.
78. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, De Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:529–555.
79. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361:13–20.
80. Jneid H, Addison D, Bhatt DL, Fonarow GC, Gokak S, Grady KL, Green LA, Heidenreich PA, Ho PM, Jurgens CY. 2017 AHA/ACC clinical performance and quality measures for adults with ST-elevation and non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes*. 2017;10:e000032. DOI: 10.1161/HCQ.0000000000000032.
81. Tam C-CF, Cheung K-S, Lam S, Wong A, Yung A, Sze M, Lam Y-M, Chan C, Tsang T-C, Tsui M. Impact of coronavirus disease 2019 (COVID-19) outbreak on ST-segment–elevation myocardial infarction care in Hong Kong, China. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006631. DOI: 10.1161/CIRCOUTCOMES.120.006631. [Epub ahead of print]
82. O'Connor RE, Brady W, Brooks SC, Diercks D, Egan J, Ghaemmaghami C, Menon V, O'Neil BJ, Travers AH, Yannopoulos D. Part 10: acute coronary syndromes: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2010;122:S787–S817.
83. Zeng J, Huang J, Pan L. How to balance acute myocardial infarction and COVID-19: the protocols from Sichuan Provincial People's Hospital. *Intensive Care Med*. 2020. DOI: 10.1007/s00134-020-05993-9. [Epub ahead of print]. Accessed April 6, 2020.
84. Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, Foody JM, Krumholz HM, Phillips CO, Kashani A, You JJ, Tu JV, Ko DT. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. *J Am Coll Cardiol*. 2007;49:422–430.
85. Fox KAA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JGP, Lagerqvist B, Wallentin L; Collaboration FIR. Long-term outcome of a routine versus selective invasive strategy in patients with non–ST-segment elevation acute coronary syndrome: a meta-analysis of individual patient data. *J Am Coll Cardiol*. 2010;55:2435–2445.
86. de Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. *Eur Heart J*. 2005;26:865–872.
87. Jneid H. Invasive strategy after non–ST-segment elevation acute coronary syndrome. *JACC Cardiovasc Interv*. 2016;9:2277–2279.
88. Bonello L, Laine M, Puymirat E, Lemesle G, Thuny F, Paganelli F, Michelet P, Roch A, Kerbaul F, Boyer L. Timing of coronary invasive strategy in non–ST-segment elevation acute coronary syndromes and clinical outcomes: an updated meta-analysis. *JACC Cardiovasc Interv*. 2016;9:2267–2276.
89. Szerlip M, Anwaruddin S, Aronow HD, Cohen MG, Daniels MJ, Dehghani P, Drachman DE, Elmariah S, Feldman DN, Garcia S. Considerations for cardiac catheterization laboratory procedures during the COVID-19 pandemic perspectives from the Society for Cardiovascular Angiography and Interventions Emerging Leader Mentorship (SCAI ELM) Members and Graduates. *Catheter Cardiovasc Interv*. 2020. DOI: 10.1002/ccd.28887. [Epub ahead of print]. Accessed April 6, 2020.
90. World Health Organization (WHO). Rational Use of Personal Protective Equipment for Coronavirus Disease 2019 (COVID-19). World Health Organization; 2020:1-1–7.
91. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, et al. COVID-19 in critically ill patients in the Seattle region—case series. *N Engl J Med*. 2020. DOI: 10.1056/NEJMoa2004500. [Epub ahead of print].
92. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507–513.
93. Fried JA, Ramasubbu K, Bhatt R, Topkara VK, Clerkin KJ, Horn E, Rabbani L, Brodie D, Jain SS, Kirtane A, et al. The variety of cardiovascular presentations of COVID-19. *Circulation*. 2020. DOI: 10.1161/CIRCULATIONAHA.120.047164. [Epub ahead of print].
94. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? *Eur Heart J*. 2020;ehaa254. DOI: 10.1093/eurheartj/ehaa254. [Epub ahead of print].
95. Hua A, O'Gallagher K, Sado D, Byrne J. Life-threatening cardiac tamponade complicating myo-pericarditis in COVID-19. *Eur Heart J*. 2020;ehaa253. DOI: 10.1093/eurheartj/ehaa253. [Epub ahead of print].
96. Bartlett RH, Ogino MT, Brodie D, McMullan DM, Lorusso R, MacLaren G, Stead CM, Rycus P, Fraser JF, Belohlavek J, et al. Initial ELSO guidance document: ECMO for COVID-19 patients with severe cardiopulmonary failure. *ASAIO J*. 2020;66:472–474. DOI: 10.1097/MAT.0000000000001173. [Epub ahead of print]
97. Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest. *Circ Heart Fail*. 2018;11:e004905. DOI: 10.1161/CIRCHEARTFAILURE.118.004905.

Downloaded from http://ahajournals.org by on April 27, 2022

98. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, MacLaren G, Brodie D, Shekar K. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med*. 2020;8:518-526.
99. Li X, Guo Z, Li B, Zhang X, Tian R, Wu W, Zhang Z, Lu Y, Chen N, Clifford SP, et al. Extracorporeal membrane oxygenation for coronavirus disease 2019 in Shanghai, China. *ASAIO J*. 2020;66:475–481. DOI: 10.1097/MAT.0000000000001172. [Epub ahead of print]
100. Chu H, Zhou J, Wong BH, Li C, Chan JF, Cheng ZS, Yang D, Wang D, Lee AC, Li C, et al. Middle East respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways. *J Infect Dis*. 2016;213:904–914.
101. Henry BM. COVID-19, ECMO, and lymphopenia: a word of caution. *Lancet Respir Med*. 2020;8:e24.
102. Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. *Crit Care*. 2016;20:387.
103. Barbaro RP, Odetola FO, Kidwell KM, Paden ML, Bartlett RH, Davis MM, Annich GM. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality: analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med*. 2015;191:894–901.
104. Anelli F, Leoni G, Monaco R, Nume C, Rossi RC, Marinoni G, Spata G, De Giorgi D, Peccarisi L, Miani A, et al. Italian doctors call for protecting healthcare workers and boosting community surveillance during COVID-19 outbreak. *BMJ*. 2020;368:m1254.
105. World Health Organization. Report of the WHO-China joint mission on coronavirus disease 2019. 2016. Available at: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed April 8, 2020.
106. Centers for Disease Control. Interim infection prevention and control recommendations for patients with suspected or confirmed COVID-19 in healthcare settings. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html. Accessed April 8, 2020.
107. Public Health England. COVID-19 personal protective equipment (PPE). 2020. Available at: https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control/covid-19-personal-protective-equipment-ppe. Accessed April 8, 2020.
108. Lakkireddy DR, Chung MK, Gopinathannair R, Patton KK, Gluckman TJ, Turagam M, Cheung J, Patel P, Sotomonte J, Lampert R, et al. Guidance for cardiac electrophysiology during the coronavirus (COVID-19) pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 2020;. DOI: 10.1161/CIRCULATIONAHA.120.047063. [Epub ahead of print]. Accessed April 8, 2020.
109. Shah PB, Welt FGP, Mahmud E, Phillips A, Kleiman NS, Young MN, Sherwood M, Batchelor W, Wang DD, Davidson L, et al.; American College of Cardiology (ACC); Society for Cardiovascular Angiography and Interventions (SCAI). Triage considerations for patients referred for structural heart disease intervention during the coronavirus disease 2019 (COVID-19) pandemic: an ACC/SCAI Consensus Statement. *JACC Cardiovasc Interv*. 2020;S1936-8798(20)30867-0. DOI: 10.1016/j.jcin.2020.04.001. [Epub ahead of print]. Accessed April 8, 2020.
110. American Society of Echocardiography. ASE statement on protection of patients and echocardiography service providers during the 2019 novel coronavirus outbreak. 2020. Available at: URL: https://www.asecho.org/ase-statement-covid-19/. Accessed April 8, 2020.
111. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, Wu J, Du H, Chen T, Li R, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. *JAMA Netw Open*. 2020;3:e203976.
112. White DB, Lo B. A framework for rationing ventilators and critical care beds during the COVID-19 pandemic. *JAMA*. 2020. DOI: 10.1001/jama.2020.5046. [Epub ahead of print] No abstract available. Accessed April 4, 2020.
113. Papadimos TJ, Marcolini EG, Hadian M, Hardart GE, Ward N, Levy MM, Stawicki SP, Davidson JE. Ethics of outbreaks position statement, part 1: therapies, treatment limitations, and duty to treat. *Crit Care Med*. 2018;46:1842–1855.
114. Shamoo AE, Resnik DB. *Responsible Conduct of Research*. England: Oxford University Press; 2009.
115. Ghanbari V, Ardalan A, Zareiyan A, Nejati A, Hanfling D, Bagheri A. Ethical prioritization of patients during disaster triage: a systematic review of current evidence. *Int Emerg Nurs*. 2019;43:126–132.
116. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A, Zhang C, Boyle C, Smith M, Phillips JP. Fair allocation of scarce medical resources in the time of COVID-19. *N Engl J Med*. 2020. DOI: 10.1056/NEJMsb2005114. [Epub ahead of print]. Accessed April 4, 2020.
117. Truog RD, Mitchell C, Daley GQ. The toughest triage—allocating ventilators in a pandemic. *N Engl J Med*. 2020. DOI: 10.1056/NEJMp2005689. [Epub ahead of print]. Accessed April 4, 2020.
118. Daugherty Biddison EL, Faden R, Gwon HS, Mareiniss DP, Regenberg AC, Schoch-Spana M, Schwartz J, Toner ES. Too many patients…a framework to guide statewide allocation of scarce mechanical ventilation during disasters. *Chest*. 2019;155:848–854.
119. Douglas White, Scott D. Halpern. University of Pittsburgh Department of Critical Care Medicine SoM. Allocation of scarce critical care resources during a public health emergency: executive summary. 2020. Available at: http://bioethics.pitt.edu/sites/default/files/Univ%20Pittsburgh%20-%20Allocation%20of%20Scarce%20Critical%20Care%20Resources%20During%20a%20Public%20Health%20Emergency.pdf. Accessed April 4, 2020.
120. Rosenbaum L. Facing COVID-19 in Italy—ethics, logistics, and therapeutics on the epidemic's front line. *N Engl J Med*. 2020. DOI: 10.1056/NEJMp2005492. [Epub ahead of print]. Accessed April 4, 2020.
121. American Hospital Association. The patient care partnership. Chicago, IL: 2003. https://www.aha.org/other-resources/patient-care-partnership. Accessed April 1, 2020.

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