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

Cardiac Involvement of COVID-19: A Comprehensive Review

Wei-Ting Chang, MD[1,2,3], Han Siong Toh, MD, MSc[2,4], Chia-Te Liao, MD, MSc[1,5] and Wen-Liang Yu, MD[4,6]

[1] Division of Cardiology, Department of Internal Medicine, Chi-Mei Medical Center, Tainan, Taiwan; [2] Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [3] Department of Biotechnology, Southern Taiwan University of Science and Technology, Tainan, Taiwan; [4] Department of Intensive Care Medicine, Chi Mei Medical Center, Tainan, Taiwan; [5] Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [6] Department of Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

ABSTRACT

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. SARS-CoV-2 caused COVID-19 has reached a pandemic level. COVID-19 can significantly affect patients' cardiovascular systems. First, those with COVID-19 and preexisting cardiovascular disease have an increased risk of severe disease and death. Mortality from COVID-19 is strongly associated with cardiovascular disease, diabetes, and hypertension. Second, therapies under investigation for COVID-19 may have cardiovascular side effects of arrhythmia. Third, COVID-19 is associated with multiple direct and indirect cardiovascular complications. Associated with a high inflammatory burden related to cytokine release, COVID-19 can induce vascular inflammation, acute myocardial injury, myocarditis, arrhythmias, venous thromboembolism, metabolic syndrome and Kawasaki disease. Understanding the effects of COVID-19 on the cardiovascular system is essential for providing comprehensive medical care for cardiac and/or COVID-19 patients. We hereby review the literature on COVID-19 regarding cardiovascular virus involvement.

Key words: Coronavirus; Covid-19; Sars-cov-2; Myocardial injury; myocarditis. **[Am J Med Sci 2021;361(1):14–22.]**

EPIDEMIOLOGY

COVID-19 can cause viral pneumonia with additional cardiovascular complications. In early studies of patients admitted with COVID-19 in China, 32% - 46% of patients had underlying diseases, including hypertension (15% - 31%), cardiovascular disease (14.5% - 15%), and diabetes (10% - 20%).[2] Then, a meta-analysis of six COVID-19 studies reported the prevalence of hypertension, cardiac and cerebrovascular disease, and diabetes to be 17.1%, 16.4%, and 9.7%, respectively.[3] The prevalence of cardiovascular disease varied widely by the study scale of COVID-19 populations, ranging from 40% in a study of 99 COVID-19 patients[4] to 2% - 4% in large studies of more than 1000 COVID-19 patients.[5,6]

Furthermore, factors associated with mortality in COVID-19 patients include male sex, advanced age, and presence of hypertension, diabetes mellitus, cardiovascular diseases, and cerebrovascular diseases as well as complications of acute cardiac injury, cardiomyopathy, and heart failure.[7–9] In a large series of 44,672 COVID-19 patients, those with coronary heart disease had a fatality rate of 10.5% higher than the overall mortality rate of 2.3%.[10] The coexistence of coronary heart disease and the myocardial injury was associated with the highest mortality rate.[11]

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor to enter the host cell.[12,13] The cardiovascular disorders share an underlying renin-angiotensin system (RAS)-related pathophysiology and pharmacologic RAS inhibitors both increase ACE2 levels, which may increase the entry of SARS-CoV-2 into the lungs and heart.[14] Thus, the infection may have a direct impact on cardiovascular diseases (Fig. 1). The detailed cardiac events of comorbidity, complication, and relevant mortality are tabulated in Table 1.

MYOCARDITIS

Virus infection has been widely described as one of the most common causes of myocarditis. Complications of acute cardiac injury were recognized in 12% - 8% of the COVID-19 patients,[1,3] and the incidence was approximately 13 times higher in ICU/severe patients than non-ICU/severe patients.[3]

Among 150 patients with laboratory-confirmed COVID-19, patients who died had higher levels of troponin, myoglobin, C-reactive protein (CRP), serum

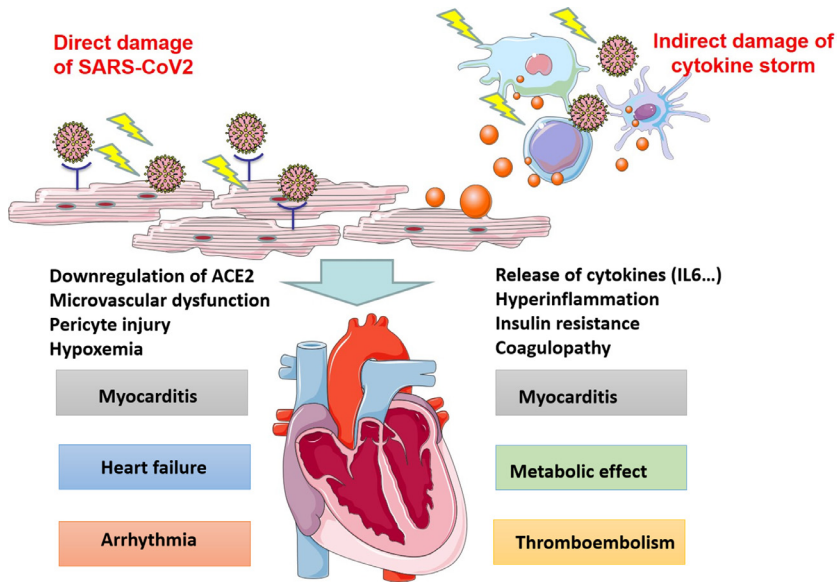

FIG. 1. Cardiovascular involvements by SRAS-CoV2 infection include direct damage (such as myocarditis, heart failure, and arrhythmia) and indirect damage (such as thromboembolism and metabolic disorder). Direct damage may be mediated through downregulation of ACE2, vascular endothelial cell dysfunction, microvascular dysfunction, pericyte injury, and hypoxemia. Indirect damage may be mediated through the release of cytokines (interleukin 6. . .), coagulopathy, and insulin resistance.

ferritin, and interleukin-6 (IL-6).[15] Some patients died of fulminant myocarditis or virus-activated "cytokine storm syndrome", suggesting a high inflammatory burden in COVID-19 and a possible increase in myocarditis-related cardiac events.[8] An extremely robust cytokine storm is also the core pathophysiological mechanism of fulminant myocarditis affected by COVID-19.[15]

Acute cardiac injury determined by elevated high-sensitivity troponin levels is commonly observed in severe cases. In a study of 120 SARS-CoV-2-infected patients, elevated levels of N-terminal pro-brain natriuretic peptides (NT-proBNP) (27.5%) and cardiac troponin T (TnT) (10%) were associated with dramatically increased plasma IL-6 levels.[16] Guo et al. reported 28% of 187 patients hospitalized with COVID-19 had an acute myocardial injury (defined as elevated TnT). Patients with high TnT levels also had higher inflammatory biomarkers, such as leukocytosis, lymphopenia, dimer, CRP, and procalcitonin.[11] Myocardial injury is an important prognostic factor in COVID-19 and is strongly associated with mortality.[11,17–19]

SARS-CoV-2 appears to affect the myocardium and cause myocarditis. Myocardial injury is likely associated with infection-related myocarditis and/or ischemia. Sporadic autopsy cases suggest infiltration of the myocardium by interstitial mononuclear inflammatory cells, especially in the cases of fulminant myocarditis.[20,21] Further evidence is needed to determine whether corticosteroids are useful for reducing myocardial inflammatory response.[22]

DOUBLE ROLES OF ACE2: "SKELETON IN THE CLOSET"?

Normally, angiotensin I is converted to angiotensin II via ACE, which could be inhibited by ACE inhibitors. ACE2 antagonizes the activation of the classical RAS and protects against organ damage, especially in patients with hypertension, diabetes, and cardiovascular disease.[23] The ACE2 converts angiotensin I to angiotensin 1–9 and angiotensin II to angiotensin 1–7, which have anti-inflammatory effects. The pro-inflammatory effects, vasoconstriction, and the genesis of atherosclerosis of angiotensin II are mediated through angiotensin type 1 (AT1) receptor, which is attenuated by AT1 receptor blockers (ARBs). Angiotensin II binding to the AT1 receptor allows ACE2 degradation. ARBs block angiotensin II binding to the AT1 receptor and prevent ACE2 degradation. Chronic use of ARBs would increase ACE2 expression and thus promote anti-inflammatory benefits by conversion angiotensin II to angiotensin 1–7 via the receptor Mas. Overall, by this pathway of ARBs or ACEI, the promotion of ACE2 benefits lung from anti-inflammation.[24]

The dual roles of ACE2 should be taken into serious consideration. On one hand, ACE2 activity is increased in patients with cardiovascular diseases and chronic use of pharmacologic RAS inhibitors. ACE2 is highly expressed in lung alveolar cells and plays a role in lung protection. On the other hand, however, ACE2 plays another role in viral pathogenicity. ACE2 is used by SARS-CoV-2 to initiate the COVID-19 infection, which may downregulate ACE2,

Table 1. Cardiac events (comorbidity, complication and relevant mortality) of patients with COVID-19.

	Reference	Patient no	Prevalence (%)	Mortality (%)	*p* (vs control)
Comorbidity					
Hypertension	Huang et al.[1]	41	14.6		
	Wang et al.[2]	138	31.2		
	Li et al.[3]	1527	17.1		
	Guan et al.[5]	1099	15.0		
	Guan et al.[6]	1590	16.9	10.4	< 0.00001
	Zhou et al.[9]	191	30	44.8	0.0008
	China Team[10]	44,672	12.8	6.0	
	Li et al.[59]	1178	30.7	21.3	< 0.00001
	Shi et al.[65]	671	29.7	18.6	< 0.001
Diabetes	Huang et al.[1]	41	19.5		
	Wang et al.[2]	138	10.1		
	Li et al.[3]	1527	9.7		
	Guan et al.[5]	1099	7.4		
	Guan et al.[6]	1590	8.2	10.0	< 0.00001
	Zhou et al.[9]	191	19	47.2	0.0051
	China Team[10]	44,672	5.3	7.3	
	Shi et al.[65]	671	14.5	17.5	0.004
CVD	Huang et al.[1]	41	14.6		
	Wang et al.[2]	138	14.5		
	Li et al.[3]	1527	16.4		
	Guan et al.[6]	1590	3.7	13.6	< 0.00001
	China Team[10]	44,672	4.2	10.5	
CAD	Guan et al.[5]	1099	2.5		
	Zhou et al.[9]	191	8.0	86.7	< 0.0001
	Shi et al.[65]	671	8.9	35	< 0.001
Complication					
Cardiomyopathy	Arentz et al.[7]	21*	33.3		
Myocardial injury (Myocarditis)	Huang et al.[1]	41	12.2		
	Li et al.[3]	1527	8.0		
	Zhou et al.[9]	191	17	97.0	< 0.0001
	Guo et al.[11]	187	27.8	59.6	< 0.001
	Chen et al.[16]	120	27.5		
	Shi et al.[18]	416	19.7	51.2	< 0.00001
Heart failure	Zhou et al.[9]	191	23	63.6	< 0.0001
Arrhythmia	Wang et al.[2]	138	16.7		
Thromboembolism	Wang et al.[37]	1026	40	3	
	Klok et al.[38]	184	31		

Note. *p*, comorbidity-related mortality vs patients without that comorbidity; CVD, cardiovascular disease; CAD, coronary artery disease; *critically ill patients.

leading to additional toxic overaccumulation of angiotensin II that induces acute respiratory distress syndrome and fulminant myocarditis.

RAS inhibition leads to upregulation of ACE2, which might make patients vulnerable to COVID-19 but could also mitigate the toxic effects caused by virus-induced ACE2 downregulation, thus, attenuating ARDS and myocarditis in COVID-19 patients.[14] Overall, RAS inhibitors such as ACEIs and ARBs potentially contribute to the improvement of clinical outcomes of COVID-19 patients with hypertension.[25]

HEART FAILURE

COVID-19 has the potential to cause heart failure in 23% of 191 inpatients from Wuhan, China.[9] Cases of severe myocarditis with reduced systolic function have been reported after COVID-19.[20] In a study of 113 deceased COVID-2019 patients, cardiac complications were common for acute cardiac injury (72/94; 77%) and heart failure (41/83; 49%).[26] Among 68 deaths in a case series of 150 patients with COVID-19, 7% were attributed to myocarditis with circulatory failure.[16] Whether heart failure is most commonly due to exacerbation of preexisting left ventricular dysfunction or new cardiomyopathy (either due to myocarditis or stress cardiomyopathy) must be further clarified.[27]

Cardiac pericytes with a high expression of ACE2 might act as the target cardiac cell of SARS-CoV-2.[23] Pericyte injury due to virus infection may result in capillary endothelial cell dysfunction, inducing microvascular dysfunction. Patients with basic heart failure showed

increased ACE2 expression in both mRNA and protein levels, meaning that if infected by the virus, these patients may have a higher risk of heart attack and critically ill condition. This study's finding explains the high rate of severe cases among COVID-19 patients with basic cardiovascular disease.[28]

For imaging features, in addition to ground-glass opacity and thickening of the interlobular septum, the ratio of central and gradient distribution was higher in patients with heart failure than that in those with COVID-19. In patients with heart failure, the ratio of the expansion of the small pulmonary veins was higher, and lung lesions significantly improved after effective anti-heart failure treatment. There are more diseases with rounded morphology in COVID-19.[29]

ARRHYTHMIAS

Among 187 patients with confirmed COVID-19, patients with elevated TnT levels had more frequent malignant arrhythmias. The impact of COVID-19 on cardiac arrhythmias originates from myocardial injury and subsequent cardiac dysfunction.[11] Cardiac arrhythmia was noted in 16.7% of patients hospitalized with COVID-19 and contributed to 44% of those transferred to the ICU.[2] Fulminant myocarditis with cardiogenic shock was associated with atrial and ventricular arrhythmias.[30–32] Additional concerns would be arrhythmia monitoring (mobile cardiac telemetry) and whether a need of an implantable cardioverter-defibrillator or wearable cardioverter-defibrillator after discharge.[33]

Hydroxychloroquine (HCQ) is known to block Kv11.1 (HERG) and can cause drug-induced LQT.[34] The clinical arrhythmic toxicity (syncope and torsade de pointes) is largely limited to chronic use (due to its long half-life of 40 days), use of multiple concomitant QT-prolonging medications (azithromycin), metabolic derangements, renal failure, or in an acute overdose setting.[35,36] Because the proposed HCQ therapy for COVID-19 is relatively short (5−10 days), the risk of arrhythmic toxicity is likely quite low. However, there are specific precautions to be considered for selected patients with congenital long QT, severe renal insufficiency, and electrolyte imbalances (hypokalemia and hypomagnesemia).

VENOUS THROMBOEMBOLISM

The increased risk of venous thromboembolism poses a considerable challenge to caring for 31% - 40% of critically ill COVID-19 patients.[37,38] Disseminated intravascular coagulation (DIC) occurred in 71.4% of patients who died of severe COVID-19. The DIC patients had high venous thromboembolism rates, elevated D-dimer levels, high fibrinogen levels, low antithrombin levels, and pulmonary congestion with microvascular thrombosis and occlusion. Fibrin deposition in the pulmonary microvasculature contributed to ARDS in patients with concomitant diagnoses of DIC.[39]

Panigada et al. described a severe inflammatory state with hypercoagulability rather than acute DIC among 24 ICU COVID-19 patients. The clinical characteristics were increased CRP, normal or increased platelet count, near-normal prothrombin time and activated partial thromboplastin time, increased fibrinogen, and dramatically increased D-dimer. Factor VIII and von Willebrand factor (n = 11) were increased. Antithrombin (n = 11) was marginally decreased and protein C (n = 11) was increased.[40] The hypercoagulable changes of microthrombi are noted in pulmonary capillary vessels, and are thought to represent megakaryocytes' overexpression and platelet adhesion. Thus, current recommendations are favoring platelet inhibitors. In Italy, antiplatelet therapy including acetylsalicylic acid, clopidogrel, tirofiban, and fondaparinux showed effective in improving hypoxemia and successful in weaning ventilator in COVID-19 patients with severe respiratory failure, bilateral pulmonary infiltrates and a D-dimer > 3 times the upper limit of normal.[41]

These data support antithrombotic prophylaxis for venous thromboembolism in some at-risk patients. Tang et al. reported lower 28-day mortality from heparin use than non-users in COVID-19 patients with a D-dimer more than 6 times the upper limit of normal (32.8% vs 52.4%, p = 0.017).[42] Furthermore, the thromboembolic diseases should be considered in critically ill COVID-19 patients who demonstrate worsening hypoxia and hemodynamic instability.

CYTOKINE RELEASE SYNDROME (CRS)

Inflammatory cytokines and chemokines, such as TNFα, IL-6, interleukin-1β (IL-1β), and monocyte chemoattractant protein-1 (MCP-1) were significantly elevated in severe COVID-19 patients.[43,44] The elevated cytokine levels may also contribute to the lethal complications of COVID-19. In severe COVID-19 patients with elevated inflammatory cytokines, postmortem pathology has revealed tissue necrosis and interstitial infiltrations with macrophage and monocyte in the lung, heart, and gastrointestinal mucosa.[20] The evidence of inferior outcomes of SARS patients treated with corticosteroids does not support corticosteroid treatment for COVID-19.[45] However, clinical trials have demonstrated that dexamethasone reduces mortality for advanced respiratory compromise. The RECOVERY trial showed that dexamethasone 6 mg once per day reduced deaths by one-third in ventilated patients (rate ratio 0.65; p = 0.0003) and by one fifth in other patients receiving oxygen only (p = 0.0021). There was no benefit among those patients who did not require respiratory support (p = 0.14).[46]

The immunomodulators may be a beneficial addition to antiviral therapy. Among the excessive cytokines, IL-6 is one of the key cytokines. Excessive IL-6 signaling leads to several biological effects such as increasing vessel permeability, cardiac arrhythmia, and reducing

myocardium contractility.[44,47] IL-6 blockade targeting the host immune system that may be effective for COVID-19. The drug tocilizumab is a recombinant humanized monoclonal anti-IL−6 receptor antibody. Tocilizumab has been approved in patients with COVID-19 pneumonia and elevated IL-6 in China.[48] Early diagnosis of CRS in COVID-19 patients and prompt initiation of immunomodulatory treatment may be beneficial. Timely intervention in patients with elevated serum IL-6 levels may prevent the progression of COVID-19. The CRP synthesized by IL-6-dependent hepatic biosynthesis is a reliable marker of IL-6 bioactivity and is used to predict CRS severity and monitor IL-6 blockade efficacy.[3]

METABOLIC SYNDROME

The conditions of BMI > 25 kg/m^2, elevated CRP and diabetes characterized metabolic syndrome in COVID-19 patients were at higher risk of developing severe ARDS and worsening cardiovascular conditions.[9,21,49] The presence of obesity and fatty liver disease in COVID-19 patients was associated with a ~ 6-fold increased risk of severe illness.[50] Patients with type-2 diabetes respond poorly to the infection with SARS-CoV-2, if inflammatory laboratory markers (such as IL-6, CRP, serum ferritin, lactate dehydrogenase, and D-dimer) are elevated.[1]

KAWASAKI DISEASE

Kawasaki disease (KD) is an acquired, acute, and self-limited vasculitis primarily affecting young children. As immune inability to fight inflammatory pathogens, KD can present acute inflammatory condition with fever, rash, alterations of the mucous membranes, conjunctiva infection, pharyngeal erythema, and adenopathy. This autoimmune disease can result in coronary artery aneurysmal abnormalities in a significant proportion of patients especially with missed diagnosis or delayed treatment, placing the patients at risk for coronary artery thrombosis, myocardial ischemia and infarction. Echocardiography is the imaging modality of choice for detection of coronary artery abnormalities and assessment of myocardial function.[51] Cardiac support, immunomodulation, and anticoagulation are the key aspects for the management of the acute phase.

There are some similarities between the inflammatory syndrome seen with COVID-19 and KD. On one hand, among the COVID-19 children, virus infection aggravates the condition of KD. Furthermore, KD may occasionally trigger macrophage activation syndrome, a condition of uncontrolled activation and proliferation of macrophages, leading to multiorgan system dysfunction.[52,53] On the other hand, SARS-Cov-2-associated multisystem inflammatory syndrome in children, similar to Kawasaki disease, often presented with fever, gastrointestinal symptoms, polymorphic rash, conjunctivitis, and mucosal changes. A subset of these patients also presented with shock from either acute myocardial dysfunction or systemic hyperinflammation. Elevated inflammatory markers and evidence of cytokine storm were frequently observed. Most importantly, delays of KD diagnosis and treatment while fighting against COVID-19 especially in children may result in deleterious cardiac events, including coronary artery dilation or aneurysm, and arrhythmias in the near future for children with COVID-19-related KD.[54, 55]

HYPERTENSION

Angiotensin-converting enzyme-2 (ACE2) is a key counterregulatory enzyme that degrades angiotensin II to angiotensin 1−7, thereby attenuating vasoconstriction.[56] ACE2 is also the receptor for the coronavirus SARS-CoV-2, which causes COVID-19. Therefore, it is concerned that ACEIs and ARB inhibitors would enhance ACE2 binding to SARS-CoV-2 when infected and thus increase COVID-19-associated morbidity and mortality.[57,58]

Among a total of 1178 hospitalized patients with COVID-19, ACEIs/ARBs were prescribed for 115 (31.8%) of 362 patients with hypertension and the in-hospital mortality was 21.3%. There were no differences between nonsurvivors and survivors in the use of ACEIs and/or ARBs.[59] Of a total of 6272 patients with severe SARS-CoV-2 infections at the Lombardy region in Italy in 2020, the use of ARBs or ACEIs did not show any association with the risk of COVID-19 or with a fatal outcome.[60] Similar results were found in New York that none of the antihypertensive medications, including ACEIs, ARBs, beta-blockers, calcium-channel blockers, and thiazide diuretics was associated with an increased likelihood of COVID-19 or in the risk of the severe illness of COVID-19.[61]

Among a total of 417 COVID-19 patients, 42 of 51 patients with hypertension receiving antihypertensive therapy were divided into two groups: the ACEI/ARB group (17 patients) and the non-ACEI/ARB group (25 patients).[25] The patients in the ACEI/ARB group had a trend toward a lower rate of severe diseases and lower IL-6 levels as well as a significantly lower peak viral load than that in the non-CEI/ARB group. The COVID-19 patients could benefit from the persistent usage of ACEI/ARB for antihypertensive therapy.[25]

The current evidence does not support the hypothesis that ACEIs/ARBs would enhance COVID-19-associated severity and mortality. American Heart Association and other major cardiology scientific associations recommend that patients with hypertension do not discontinue using ACEIs, ARBs, or other RAS antagonists in this setting except for clinical reasons rather than COVID-19.[62,63]

DIAGNOSIS OF COVID-19 CARDIAC COMPLICATIONS

The cardiac injury was defined as an elevated serum level of high-sensitivity cardiac troponin I (hs-TnI) greater

than the reference range's upper limit (>28 pg/mL).[64] Guo et al. reported acute myocardial injury defined as elevated troponin T (TnT) greater than the 99th percentile upper limit.[11] Shi et al. reported 15.8% of 671 COVID-19 patients with hs-TnI levels >40 pg/mL (normal range, 0 −40 pg/mL) and a significantly higher mean level of hs-TnI in non-survivors than that in the survivors (235 vs 6 pg/mL, $p < 0.001$).[65]

Cases of acute coronary syndrome in the COVID-19 setting have been identified, raising a difficulty in correctly differentiate the diagnosis of myocarditis from myocardial infarction.[66–68] Acute myocarditis in COVID-19 patients may develop transient ST elevation that resolved later without any intervention.[69,70] Endomyocardial biopsy may demonstrate myocardial inflammation and viral particles within the interstitial cells of the myocardium in a patient with acute myocarditis. Electron micrograph demonstrated a cytopathic inflammatory cell that contains viral particles with prominent spikes of the viral crown.[71] Among 104 endomyocardial biopsies from patients with suspected myocarditis or unexplained heart failure, five were confirmed with SARS-CoV-2 infections by the detection of SARS-CoV-2 genomes using reverse real-time transcriptase polymerase chain reaction.[72]

Another issue is that collateral damage may occur in the reduced rates of admission for ACS or acute myocardial infarction during fighting against the COVID-19 outbreak.[73,74] Particular attention will be dedicated to the infectious disease prevention measures adopted in the catheterization laboratory to protect the staff and to avoid further spread of the infection.[75,76]

If patients of COVID-19 with high troponin, acute heart failure, hemodynamic instability without clear explanation, and cardiac arrhythmia, echocardiography is indicated. It is clearly helpful to evaluate the myocardial function, the detection of regional wall contraction abnormalities, acute valvular disease, and for non-invasive hemodynamic assessments.[77] Typical signs of myocarditis may include diffuse myocardial hypokinesis and dyskinesia along with a decreased left ventricular ejection fraction,[78] but which might not be detected on echocardiography in an early stage.[79] Takotsubo or inverted takotsubo syndrome could be detected in the setting of COVID-19 infections.[80–83]

Szekely et al.[84] have published echocardiogram results from 100 COVID-19 patients studied within 24 h of admission and 32% of patients had a normal echocardiogram at baseline. Findings included decreased right ventricular (RV) function (dilatation and dysfunction) in 39% of patients and decreased left ventricular (LV) diastolic function in 16% of patients, and 10% with LV systolic dysfunction. Thus, LV systolic failure was a less common finding. Noteworthy, increased troponin with RV dysfunction in the early stage could predict a poorer clinical grading. The routine echocardiographic study was not recommended in the absence of clinical suspicion. However, echocardiographic follow-up is required for 20% of patients in clinical deterioration.[84]

The cardiac computed tomographic angiography with delayed myocardial imaging may serve to identify myocardial inflammatory patterns and exclude significant coronary artery disease.[85] The cardiac magnetic resonance imaging can show diffuse biventricular myocardial edema and late gadolinium enhancement consistent with acute myopericarditis,[24,30] including findings as follows:

- Increased wall thickness with diffuse biventricular hypokinesis
- Hypokinesis in the apical segments
- Severe left ventricular dysfunction (reduced left ventricular ejection fraction)
- Marked biventricular myocardial interstitial edema in T2-mapping sequences
- Diffuse late gadolinium enhancement involving the entire biventricular wall
- Circumferential pericardial effusion around the right cardiac chambers

ANTIVIRAL THERAPY

Considering the multiple ongoing clinical trials and rapid release of new findings, treatment recommendations for COVID-19 should be beyond the scope of the current review. We could only briefly discuss remdesivir as a therapeutic agent. Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA-dependent RNA polymerases, has been considered the most promising antiviral agent against SARS-CoV-2.[86] A global study of 1063 patients underwent randomization, remdesivir had a median recovery time of 11 days as compared with 15 days in the placebo group ($P<0.001$). Thus, remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 and lower respiratory tract infection.[87] A randomized, double-blind, placebo-controlled, multicentre trial of 237 adult patients admitted to hospital for severe COVID-19 at ten hospitals in Hubei, China, remdesivir was not associated with statistically significant clinical benefits in time to clinical improvement.[88] However, in a global cohort of 53 patients (22 were in the United States, 22 in Europe or Canada, and 9 in Japan) hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%).[89] Among 584 hospitalized patients with moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%) enrolled from 105 hospitals in the United States, Europe, and Asia, the primary end point of clinical status on day 11 for patients receiving standard care was statistically significantly worse than those in the 5-day remdesivir group, but was not significantly different to those in the 10-day remdesivir group.[90] As the authors acknowledge, the clinical importance of the results is uncertain. The more large-scale trials of randomized and placebo-controlled designs are required to further

clarify the uncertainties of remdesivir therapeutic efficacy and optimal use.

CONCLUSIONS

SARS-CoV-2 may either induce new cardiac pathologies and/or exacerbate underlying cardiovascular diseases as the high inflammatory burden of COVID-19. The presence of cardiac injury (defined by elevated troponin levels or TnT), heart failure (defined by elevated NT-proBNP), and myocarditis (suspected by echocardiographic findings of diffuse hypokinesis and dyskinesis) are independent factors associated with mortality. New onset of life-threatening tachyarrhythmias in an elevated troponin setting should raise a concern of myocarditis. Increased troponin associated with RV dysfunction in the early stage could predict poorer clinical grading. The severe and critical cases have more severe effects on the cardiovascular system due to a more robust inflammatory response (evidenced by elevated levels of CRP, procalcitonin, ferritin, and IL-6). The venous thromboembolism should be considered in critically ill patients who demonstrate the clinical deterioration of hypoxia and hemodynamic instability with a D-dimer more than 3~6 times the upper normal limit. Current therapy may include remdesivir, IL-6 blockade like tocilizumab, and anti-platelet therapy if indicated and keep maintenance on an ACEI or ARB therapy for patients with underlying cardiovascular disorders.

CONFLICT OF INTEREST DISCLOSURES

None reported.

FUNDING DISCLOSURES

None declared.

REFERENCES

1. **Huang C, Wang Y, Li X, et al.** Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
2. **Wang D, Hu B, Hu C, et al.** Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069.
3. **Li B, Yang J, Zhao F, et al.** Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020;109(5):531–538.
4. **Chen N, Zhou M, Dong X, et al.** Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507–513.
5. **Guan WJ, Ni ZY, Hu Y, et al.** China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720.
6. **Guan WJ, Liang WH, et al.** Comorbidity and its impact on 1590 patients with Covid-19 in China: a Nationwide Analysis. *Eur Respir J*. 2020;55:(5) 2000547.
7. **Arentz M, Yim E, Klaff L, et al.** Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA*. 2020;323 (16):1612–1614.
8. **Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O.** Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. 2020;5(7):831–840.
9. **Zhou F, Yu T, Du R, et al.** Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–1062.
10. **The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team.** [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41:145–151. [Chinese].
11. **Guo T, Fan Y, Chen M, et al.** Association of cardiovascular disease and myocardial injury with outcomes of patients hospitalized with 2019-coronavirus disease (COVID-19). *JAMA Cardiol*. 2020;5(7):811–818.
12. **Chan JF, Kok KH, Zhu Z, et al.** Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect*. 2020;9(1):221–236.
13. **Wan Y, Shang J, Graham R, Baric RS, Li F.** Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. *J Virol*. 2020;94(7). https://doi.org/10.1128/JVI.00127-20.
14. **Hanff TC, Harhay MO, Brown TS, Cohen JB, Mohareb AM.** Is there an association between COVID-19 mortality and the renin-angiotensin system-a call for epidemiologic investigations. *Clin Infect Dis*. 2020;71 (15):870–874.
15. **Ruan Q, Yang K, Wang W, Jiang L, Song J.** Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46(5):846–848.
16. **Chen C, Zhou Y, Wang DW.** SARS-CoV-2: a potential novel etiology of fulminant myocarditis. *Herz*. 2020;45(3):230–232.
17. **Deng Y, Liu W, Liu K, et al.** Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. *Chin Med J (Engl)*. 2020;133(11):1261–1267.
18. **Shi S, Qin M, Shen B, et al.** Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802–810.
19. **Han H, Xie L, Liu R, et al.** Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. *J Med Virol*. 2020;92(7):819–823.
20. **Xu Z, Shi L, Wang Y, et al.** Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8 (4):420–422.
21. **Liu Y, Yang Y, Zhang C, et al.** Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci*. 2020;63(3):364–374.
22. **Liu K, Fang YY, Deng Y, et al.** Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J (Engl)*. 2020;133(9):1025–1031.
23. **Cheng H, Wang Y, Wang GQ.** Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. *J Med Virol*. 2020;92(7):726–730.
24. **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(17):1653–1659.
25. **Meng J, Xiao G, Zhang J, et al.** Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect*. 2020;9(1):757–760.
26. **Chen T, Wu D, Chen H, et al.** Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. https://doi.org/10.1136/bmj.m1091.
27. **Buzon J, Roignot O, Lemoine S, et al.** Takotsubo cardiomyopathy triggered by influenza A virus. *Intern Med*. 2015;54(16):2017–2019.
28. **Chen L, Li X, Chen M, Feng Y, Xiong C.** The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res*. 2020;116(6):1097–1100.
29. **Zhu ZW, Tang JJ, Chai XP, et al.** [Comparison of heart failure and 2019 novel coronavirus pneumonia in chest CT features and clinical characteristics]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2020;48:E007.. [Chinese].

30. **Hu H, Ma F, Wei X, Fang Y.** Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J*. 2020: ehaa190. https://doi.org/10.1093/eurheartj/ehaa190.
31. **Driggin E, Madhavan MV, Bikdeli B, et al.** Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. *J Am Coll Cardiol*. 2020;75 (18):2352–2371.
32. **Lippi G, Lavie CJ, Sanchis-Gomar F.** Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. *Prog Cardiovasc Dis*. 2020;63(3):390–391.
33. **Lakkireddy DR, Chung MK, Gopinathannair R, et al.** Guidance for Cardiac Electrophysiology During the Coronavirus (COVID-19) Pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 2020;141(21):e823–e831.
34. **Traebert M, Dumotier B, Meister L, Hoffmann P, Dominguez-Estevez M, Suter W.** Inhibition of hERG K+ currents by antimalarial drugs in stably transfected HEK293 cells. *Eur J Pharmacol*. 2004;484(1):41–48.
35. **Demaziere J, Fourcade JM, Busseuil CT, Adeleine P, Meyer SM, Saissy JM.** The hazards of chloroquine self prescription in west Africa. *J Toxicol Clin Toxicol*. 1995;33(4):369–370.
36. **Cervera A, Espinosa G, Font J, Ingelmo M.** Cardiac toxicity secondary to long term treatment with chloroquine. *Ann Rheum Dis*. 2001;60(3):301.
37. **Wang T, Chen R, Liu C, et al.** Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *Lancet Haematol*. 2020;7(5):e362–e363.
38. **Klok FA, Kruip MJHA, van der Meer NJM, et al.** Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145–147.
39. **Wang J, Hajizadeh N, Moore EE, et al.** Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. *J Thromb Haemost*. 2020;18(7):1752–1755.
40. **Panigada M, Bottino N, Tagliabue P, et al.** Hypercoagulability of COVID-19 patients in intensive care unit. A report of thromboelastography findings and other parameters of hemostasis. *J Thromb Haemost*. 2020;18(7):1738–1742.
41. **Viecca M, Radovanovic D, Forleo GB, Santus P.** Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study. *Pharmacol Res*. 2020;158: 104950. https://doi.org/10.1016/j.phrs.2020.104950.
42. **Tang N, Bai H, Chen X, Gong J, Li D, Sun Z.** Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094–1099.
43. **Fu Y, Cheng Y, Wu Y.** Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. *Virol Sin*. 2020;35(3):266–271.
44. **Liu B, Li M, Zhou Z, Guan X, Xiang Y.** Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS). *J Autoimmun*. 2020;111: 102452. https://doi.org/10.1016/j.jaut.2020.102452.
45. **Russell CD, Millar JE, Baillie JK.** Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395 (10223):473–475.
46. **Mahase E.** Covid-19: demand for dexamethasone surges as RECOVERY trial publishes preprint. *BMJ*. 2020;369:m2512.
47. **Pathan N, Hemingway CA, Alizadeh AA, Stephens AC, Boldrick JC, Oragui EE.** Role of interleukin 6 in myocardial dysfunction of meningococcal septic shock. *Lancet*. 2004;363(9404):203–209.
48. **Chinese Clinical Trial Registry.** *A multicenter, Randomized Controlled Trial For the Efficacy and Safety of Tocilizumab in the Treatment of New Coronavirus Pneumonia (COVID-19)*. Feb 13, 2020. Available at: http://www.chictr.org.cn/showprojen.aspx?proj=49409. Accessed 6 March 2020.
49. **Peng YD, Meng K, Guan HQ.** [Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2020;48(6):450–455. [Chinese].
50. **Zheng KI, Gao F, Wang XB, et al.** Letter to the Editor: obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. *Metabolism*. 2020;108: 154244. https://doi.org/10.1016/j.metabol.2020.154244.
51. **McCrindle BW, Cifra B.** The role of echocardiography in Kawasaki disease. *Int J Rheum Dis*. 2018;21:50–55.
52. **Ronconi G, Teté G, Kritas SK, et al.** SARS-CoV-2, which induces COVID-19, causes kawasaki-like disease in children: role of pro-inflammatory and anti-inflammatory cytokines. *J Biol Regul Homeost Agents*. 2020 Jun 1;34(3). https://doi.org/10.23812/EDITORIAL-RONCONI-E-59.
53. **Loomba RS, Villarreal EG, Flores S.** COVID-19 and hyperinflammatory syndrome in children: kawasaki disease with macrophage activation syndrome in disguise. *Cureus*. 2020;12(8):e9515.
54. **Jiang L, Tang K, Levin M, et al.** COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis*. 2020 Aug 17. https://doi.org/10.1016/S1473-3099(20)30651-4. S1473-3099(20) 30651-4.
55. **Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A.** Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. *Eur J Pediatr*. 2020 Aug 15:1–16. https://doi.org/10.1007/s00431-020-03766-6.
56. **Brojakowska A, Narula J, Shimony R, Bander J.** Clinical implications of SARS-CoV-2 interaction with renin angiotensin system: JACC review topic of the week. *J Am Coll Cardiol*. 2020;75(24):3085–3095.
57. **Sriram K, Insel PA.** A hypothesis for pathobiology and treatment of COVID-19: the centrality of ACE1/ACE2 imbalance. *Br J Pharmacol*. 2020 Apr 24. https://doi.org/10.1111/bph.15082.
58. **Kai H, Kai M.** Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors-lessons from available evidence and insights into COVID-19. *Hypertens Res*. 2020;43(7):648–654.
59. **Li J, Wang X, Chen J, Zhang H, Deng A.** Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for Coronavirus Disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol*. 2020;5(7):825–830.
60. **Mancia G, Rea, Ludergnani F, Apolone M, Corrao G G.** Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *N Engl J Med*. 2020;382(25):2431–2440.
61. **Reynolds HR, Adhikari S, Pulgarin C, et al.** Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. *N Engl J Med*. 2020;382 (25):2441–2448.
62. **Rico-Mesa JS, White A, Anderson AS.** Outcomes in patients with COVID-19 infection taking ACEI/ARB. *Curr Cardiol Rep*. 2020;22(5):31. https://doi.org/10.1007/s11886-020-01291-4.
63. **American Heart Association.** HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. *J Card Fail*. 2020;26 (5):370. https://doi.org/10.1016/j.cardfail.2020.04.013.
64. **Yang X, Yu Y, Xu J, et al.** Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475–481.
65. **Shi S, Qin M, Cai Y, et al.** Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J*. 2020;41(22):2070–2079.
66. **Siddamreddy S, Thotakura R, Dandu V, Kanuru S, Meegada S.** Corona virus disease 2019 (COVID-19) presenting as acute ST elevation myocardial infarction. *Cureus*. 2020;12(4):e7782. https://doi.org/10.7759/cureus.7782.
67. **Yousefzai R, Bhimaraj A.** Misdiagnosis in the COVID era: when zebras are everywhere, don't forget the horses. *JACC Case Rep*. 2020;2 (10):1614–1619.
68. **Secco GG, Tarantini G, Mazzarotto P, et al.** Invasive strategy for COVID patients presenting with acute coronary syndrome: the first multicenter Italian experience. *Catheter Cardiovasc Interv*. 2020 May 12. https://doi.org/10.1002/ccd.28959.
69. **Loghin C, Chauhan S, Lawless SM.** Pseudo acute myocardial infarction in a young COVID-19 patient. *JACC Case Rep*. 2020;2(9):1284–1288.
70. **Asif T, Ali Z.** Transient ST segment elevation in two patients with COVID-19 and a normal transthoracic echocardiogram. *Eur J Case Rep Intern Med*. 2020;7:(5) 001672. https://doi.org/10.12890/2020_001672.
71. **Tavazzi G, Pellegrini C, Maurelli M, et al.** Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail*. 2020;22 (5):911–915.
72. **Escher F, Pietsch H, Aleshcheva G, et al.** Detection of viral SARS-CoV-2 genomes and histopathological changes in endomyocardial biopsies.

ESC Heart Fail. 2020 Jun 12. https://doi.org/10.1002/ehf2.12805. 10.1002/ehf2.12805.
73. **Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJ.** Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. *Eur Heart J*. 2020;41(19):1852–1853.
74. **De Filippo O, D'Ascenzo F, Angelini F, et al.** Reduced rate of hospital admissions for ACS during Covid-19 outbreak in northern Italy. *N Engl J Med*. 2020;383(1):88–89.
75. **Mahmud E, Dauerman HL, Welt FGP, et al.** Management of acute myocardial infarction during the COVID-19 pandemic: a Consensus Statement from the Society for Cardiovascular Angiography and Interventions (SCAI), the American College of Cardiology (ACC), and the American College of Emergency Physicians (ACEP). *Catheter Cardiovasc Interv*. 2020;96(2):336–345.
76. **Chieffo A, Stefanini GG, Price S, et al.** EAPCI Position statement on invasive management of acute coronary syndromes during the COVID-19 pandemic. *Eur Heart J*. 2020;41(19):1839–1851.
77. **Cosyns B, Lochy S, Luchian ML, et al.** The role of cardiovascular imaging for myocardial injury in hospitalized COVID-19 patients. *Eur Heart J Cardiovasc Imaging*. 2020;21(7):709–714.
78. **Zeng JH, Liu YX, Yuan J, et al.** First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. *Infection*. 2020 Apr 10:1–5. https://doi.org/10.1007/s15010-020-01424-5.
79. **Deng Q, Hu B, Zhang Y, et al.** Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. *Int J Cardiol*. 2020;311:116–121. https://doi.org/10.1016/j.ijcard.2020.03.087.
80. **Meyer P, Degrauwe S, Van Delden C, Ghadri JR, Templin C.** Typical takotsubo syndrome triggered by SARS-CoV-2 infection. *Eur Heart J*. 2020;41(19):1860. https://doi.org/10.1093/eurheartj/ehaa306.
81. **Minhas AS, Scheel P, Garibaldi B, et al.** Takotsubo syndrome in the setting of COVID-19 infection. *JACC Case Rep*. 2020;2(9):1321–1325.
82. **Solano-López J, Sánchez-Recalde A, Zamorano JL.** SARS-CoV-2, a novel virus with an unusual cardiac feature: inverted takotsubo syndrome. *Eur Heart J*. 2020;41(32):3106. https://doi.org/10.1093/eurheartj/ehaa390.
83. **Roca E, Lombardi C, Campana M, et al.** Takotsubo syndrome associated with COVID-19. *Eur J Case Rep Intern Med*. 2020;7:(5) 001665.
84. **Szekely Y, Lichter Y, Taieb P, et al.** The spectrum of cardiac manifestations in Coronavirus disease 2019 (COVID-19) - a systematic echocardiographic study. *Circulation*. 2020;142(4):342–353.
85. **Siripanthong B, Nazarian S, Muser D, et al.** Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm*. 2020;17(9):1463–1471.
86. **Jean SS, Lee PI, Hsueh PR.** Treatment Options for COVID-19: the reality and challenges. *J Microbiol Immunol Infect*. 2020;53(3):436–443.
87. **Beigel JH, Tomashek KM, Dodd LE, et al.** Remdesivir for the treatment of Covid-19 - Preliminary report. *N Engl J Med*. 2020 May 22. https://doi.org/10.1056/NEJMoa2007764.
88. **Wang Y, Zhang D, Du G, et al.** Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569–1578.
89. **Grein J, Ohmagari N, Shin D, et al.** Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med*. 2020;382(24):2327–2336.
90. **Spinner CD, Gottlieb RL, Criner GJ, et al.** Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048–1057.

Submitted May 18, 2020; accepted October 1, 2020.

Correspondence: Wen-Liang Yu, MD, Department of Intensive Care Medicine, Chi Mei Medical Center, 901 Chung Hwa Road, 710 Tainan City, Taiwan (E-mail: Yuleon_md@yahoo.com.tw).