VOLUME - 10, ISSUE - 05, MAY- 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Cardiology

UPDATE ON CARDIOVASCULAR IMPLICATIONS OF COVID 19

Prof Dr Pradeep Kumar Radhakrishnan	MS, MCh CTVS AIIMS, Postdoctoral Fellow CTVS, Post doctoral Fellow ECMO, FACC, FIACS, CPDH, Mentor World Innovation Hub, Chief Division of Cardiothoracic and Vascular Surgery GIMSR Gitam University.
Gayathri Ananyajyothi Ambat*	Medical Student GIMSR Gitam University. *Corresponding Author
Dr Roshini Ambat	MD, Senior Consultant KIMS.
Syed Ilas Basha	PhD Prof Pharmacology, GIMSR Gitam University.
Prof Dr Hema Prakash	MD, GIMSR Gitam University.
Prof Jyothi Padmaja	MD, GIMSR Gitam University.
Prof Raju	MD, GIMSR Gitam University.
Dr Padmakumar	MD, Broad meadow Centre, NSW Australia.
Prof Arun Vijay Kumar	MD, Fellow in Cardiac Anesthesiology, Travancore Medical College, India.
Dr U S Murugan	Asst. Prof. MD CTVS, Travancore Medical College, India.
Prof Y A Nazer	MS MCh AIIMS, Director Travancore Medical College, India.
Prof Venugopal V	MS MCh AIIMS,Previous Director AIIMS Advisor AIIMS New Delhi India.

ABSTRACT On March 11 2020 WHO declares corona viral disease as a global pandemic .COVID 19 pandemic has taken the world by storm and many countries like India is now experiencing a second surge due to mutant strains. Global health emergency has been precipitated by this corona virus disease caused by SARS CoV2.Acute and intermediate effects on cardiovascular system are becoming obvious with progression of time. SARS-CoV-2-related endothelial dysfunction results in an augmented risk for venous thromboembolism, systemic vasculitis, endothelial cell apoptosis, and inflammation in various organs. Acute infections have troponin elevation more due to indirect cardiac damage though definite patterns of direct damage do exist. Intermediate evaluation in patients with resolved infections shows increased incidence of exercise induced arrhythmias and residual cardiovascular symptoms. The virus with its zoonotic origin based upon its genomic identity to bat derived SARS corona virus has a human to human transmission mode.ACE 2 receptors facilitate cellular entry and has been implicated in direct and indirect myocardial damage. Myocarditis, acute myocardial injury, arrhythmias and thromboembolism dominates the clinical picture. Role of imaging must be defined in relation to relevant clinical findings. With arrival of vaccine and widespread vaccination global programs, we can look forward to understanding and managing long term complications of this disease. Prognostic implications of a resolved disease need to be evaluated by future studies.

KEYWORDS : SARS CoV2- Severe Acute Respiratory Syndrome Corona Virus 2, ACE 2 angiotensin converting enzyme 2, WHO world health organization, CSG corona virus study group, TMPRSS2, NT-proBNP, CRP

INTRODUCTION

WHO on Jan 12 2020 named corona virus as the 2019 novel corona virus (2019 n Co V) and then on Feb 11 2020 Corona Virus Study Group proposed the name as SARS Co V[1].Chinese studies initially reported troponin elevation in about 20-40% of affected patients [2,3].Ability of virus to bind to ACE 2 protein receptors on myocardial cells suggested direct myocardial injury as a cause of this phenomenon which has been refuted by the studies by Linder as none of these cases met the criteria of definition of myocarditis [4,5].

In fact a lesser incidence when compared with other viral illness was reported by Metkus [6].The elevation of other inflammatory markers suggested that the damage could be indirect associated with a widespread cytokine storm. But it should be remembered that in the coronaviridae family alpha, beta, delta and gamma which account for 5-10% of acute respiratory infections 2% are health carriers of the virus [7, 8].On January 7 2020 scientists deciphered the genomic sequencing of this virus [9]. Suggested cellular entry of the virus is as follows. Key points in cardiac complications of COVID 19 as per ESC is summarized in Table 3 and Figure 2.

TMPRSS2, a host transmembrane serine protease helps the virus access the cells by two diverse mechanisms. On the cell membrane surface, spike S1 subunit binds to the ACE2 and the ACE2 receptor is cleaved .TMPRSS2 causes irreversible conformational change by acting on the S2 subunit causing viral fusion to the cell membrane [10, 11, and 12]. After the initial viral infection in 2 -14 days' severe cases show respiratory, hepatic, gastrointestinal and cardiovascular complications which could be fatal [13].

Supply demand mismatch in the coronary circulation could result from hypoxia, hypoperfusion, tachycardia, microvascular thrombosis or inflammation related injury.

Acute plaque rupture, stress, myocarditis, arrhythmias could result from a secondary insult due to ongoing inflammatory cascade. Higher troponin values are associated with poorer outcome [14].It could serve as a marker of disease severity. Isolated elevations may not be very useful from the cardiovascular point of view but when associated with echocardiographic or angiographic abnormalities are predictive of mortality [15].

CMR should be restricted to evaluation of new left ventricular dysfunction and angina symptoms after CAD has been ruled out and very high clinical suspicion of myocarditis persist [16].With the stage set for multiple vaccines in market resolved infection evaluation for persistent arrhythmias may augment role of CMR for detection of inflammation and scar foci [17,18].In fact if CMR confirms myocarditis a 3-6 month holiday from strenuous activities and sports would be ideal.

The so termed long COVID has lingering cardiovascular and neurological symptoms. In fact residual symptoms are reported to be as high as 60%.Surprisingly these have been reported in young patients without co morbidities also [19]. Older persons with pre existing cardiovascular disease and reduced ACE2 levels will be expected to be more susceptible to the exaggerated inflammation with further reduction in ACE2 expression in the context of COVID-19, exhibiting greater disease severity. ACE2 receptors are involved in neurohumoral regulation of cardiovascular system also. The binding of SARS-CoV-2 to ACE2 causes acute myocardial and lung injury through the alternation in ACE2 signaling pathways [24].Besides this, diabetes and hyperlipidemia, alters the immune functions [20-23] adding on to morbidity and mortality. Infection affects cardiac relevant biochemical pathways such as the ACE2 signaling pathway, cardiac muscle integrity, fibrinogen pathways, redox homeostasis, and induces a break in plaque associated with the stent, and finally, aggravates a myocardial injury and dysfunction[25]. In addition to effect of ACE2 on coagulation patients with a history of diabetes, hypertension, and stroke on ventilators who underwent serological testing, showed the presence of anticardiolipin IgA antibodies and anti □2glycoprotein I IgA and IgG antibodies. These antiphospholipid antibodies abnormally target phospholipid proteins, rarely leading to thrombotic events [26].D-dimer levels (>1 g/L) was often associated with in-hospital death [27].Higher risk of venous thromboembolism has also been reported. 71.4% of non-survivors fit the clinical guidelines for disseminated intravascular coagulation (DIC) [28].Aortic and microvascular embolism is also noted in these patients. Direct oral anticoagulants and antiviral treatments, unfractionated heparin/low molecular weight heparins, or mechanical prevention are advocated strongly for this group.

Myocardial infarction type 2 is also noted in patients with non obstructive physiology [29].Those with obstructive physiology are more prone for infarction due to proinflammatory procoagulant state induced by the virus [30]. This condition leads to a drastic increase in myocardial demand during infection or critical systemic inflammatory stress that could lead to atherosclerotic plaque instability, rupture, vascular andmyocardial inflammation [31]. Systemic inflammation can also result in coronary plaque rupture in CVD patients and cause stent thrombosis [32]. Viral inflammation and degranulation of endothelial cells was demonstrated by scanning electron microscopy. Inflammation of vascular endothelial cells (endotheliitis) leads to degranulation and exocytosis of Weibel Palade Bodies (WPBs) containing von Willebrand factor, which promotes recruitment of platelets, as well as platelet-to-platelet aggregates through the glycoprotein 1b receptor. Circulating blood IgG in patients with COVID-19 promotes a procoagulant phenotype and thrombocytopenia through platelet apoptosis by stimulating platelet Fc gamma receptor IIA The post-receptor signal transduction pathway that increases platelet reactivity and promotes thrombosis .Endothelial cell damage may cause blood vessel inflammation, leading to plaque rupture and heart attack .Serial measurements of troponins and N-terminal pro-B-type natriuretic peptide (NT-proBNP) show a rising trend in those who do not survive compared to those who survive. Patients with myocardial injury also have confirmation of more severe systemic inflammation, including greater leukocyte counts and higher levels of CRP, procalcitonin, and high levels of other biomarkers of myocardial injury and stress, such as elevated creatine kinase, myoglobin, and NT-proBNP. Increased blood levels of procalcitonin, a peptide hormone produced by the thyroid gland, lungs, and intestine, are associated with more severe forms of COVID-19. Low platelet counts are also associated with an increased risk of severe disease and mortality in COVID-19 patients.

Myocardial injury occurs via diverse mechanisms, mainly mediated through ACE2 and other proposed mechanisms of cardiac participation comprising cytokine storm, arbitrate among subtypes of T helper cells and severe pneumonia causes hypoxia. Management guidelines of STEMI and NSTEMI in COVID 19 are given in Figure 3 and 4 according to ESC guidelines. Fibrinolyitc therapy indications are outlined in Table 4.This leads to ischemic cardiac tissue, which increases intracellular calcium leading to the apoptosis of cardiac myocyte [33]. This causes a troponin leak and an elevated BNP level. In experimental animals the virus can induce acute cardiac failure. Mutant human strains may do so in future and one has to be on guard against this possibility. The factors promoting endothelial dysfunction are discrepancies between reactive oxygen species production and nitric oxide reduction, remodeling of the left ventricle, fibrosis by differentiation of fibroblasts into myofibroblasts following monocytes secretion of transforming growth factor-beta (TGF□) [34].Data from various studies support the continued use of ACE inhibitors or ARBs in patients with hypertension hospitalized with COVID-19 [35]. All clinicians are advised to continue ACE inhibitors and ARB blockers for patients who are already on these drugs for their blood pressure. Postural Orthostatic Tachycardia Syndrome (POTS)-like syndrome emerging among COVID-19 survivors.

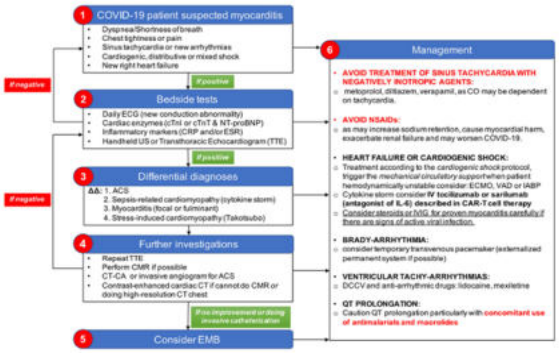
VITT- Vaccine Induced Thrombotic Thrombocytopenia is characterized by the presence of two conditions concurrently: thrombosis (often in unusual sites like the cerebral sinus veins or splanchnic veins) and thrombocytopenia. Early mechanistic evaluations have identified antibodies to the platelet factor 4 (PF4)-heparin complex, similar to HIT antibodies. Detection of the PF4 antibodies can be done using a HIT ELISA test, but not reliably with other HIT laboratory tests.

Routine use of VTE prophylaxis is strongly recommended for all patients hospitalized with COVID-19. For most patients, use of standard doses of low-molecular-weight heparin (e.g., enoxaparin 40 mg once daily) or unfractionated heparin (e.g., 5,000 units three times daily) is recommended by most society guidelines and guidance documents. For patients with critical illness in moderate or intensive care units, consideration can be made for intensifying the prophylactic regimen (e.g., enoxaparin 30-40 mg twice daily, unfractionated heparin 7,500 units three times daily). Spironolactone may also provide protection through concurrent actions in the modulation of ACE2 expression and increasing angiotensin 1–7 levels. Moreover, as an anti-androgenic agent, it can decrease viral priming through TMPRSS2 activity. Spironolactone seems to be an ideal drug candidate that reduces the harmful effects of the over expression of angiotensin II-AT-1 axis, and more importantly, is

pharmacologically safe in the treatment of COVID-19 patients with heart failure. Inclusion of new medicines such as SGLT2 inhibitors may help to maximize the efficacy of anti-heart failure treatments and minimize the negative impacts of other drugs on heart function but further studies supporting the same are needed. World heart federation guidelines for those with co morbidities are listed in table 1. Low dose radiation therapy (LDRT) has been evaluated as a potential therapeutic modality for COVID-19 pneumonia. However, due to heterogeneity in disease manifestation and inter-individual variations, effective planning for LDRT is limited for this large-scale event. 2-deoxy-D-glucose (2-DG) has emerged as a polypharmacological agent for COVID-19 treatment due to its effects on the glycolytic pathway, anti-inflammatory action, and interaction with viral proteins. Ivermectin, an FDA-approved anti-parasitic previously shown to have broad-spectrum anti-viral activity *in vitro*, is an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2 h post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h. Table 2 summarizes mechanism of action of most drugs used in treatment of COVID 19. Cardiac toxicity of antiviral drugs should be kept in mind. In NOAC-eligible patients (i.e. those without mechanical prosthetic heart valves, moderate to severe mitral stenosis or antiphospholipid syndrome), NOACs are preferred over VKAs owing to their better safety and fixed dosing without the need for laboratory monitoring of anticoagulant effect (hence no direct contact), notwithstanding the importance of proper NOAC dosing and adherence to treatment; Whereas apixaban, rivaroxaban or edoxaban can be given as oral solutions or crushed tablets (via enteral tubes), severely ill COVID-19 patients may be switched to parenteral anticoagulation, which has no clinically relevant drug-drug interactions with COVID19 therapies (with the exception of azithromycin, which should not be co-administered with UFH).

CONCLUSION

Theoretically, these predicted increases in ANG II levels could be countered by delivering maximal doses of ACE inhibitors and AT_1 receptor blockers. In the absence of supporting evidence, such an approach is unwarranted and needs to be studied. Innate immunity may be the key to defeat SARS-CoV-2 infection. It serves as the first line of antiviral defense and could participate in a significant role in the progression of the cytokine storm. Viral invasion leads to type I interferon (IFN-I) expression and other proinflammatory cytokines that defend against viral infection at the entry points. The activation and accumulation of monocytes and macrophages generate abandoned cytokine storms that lead to the modification of the M1 to M2 phenotype of alveolar macrophages resulting in inflammatory injuries and fibrosis of respiratory tracts. Some habits such as smoking carries added risk both to COVID infection and cardiovascular complications for obvious reasons. Impact COVID-19 activity is due to the renin-angiotensin system's over-activation, and the virus can activate a disintegrin and metalloproteases-17 (ADAM-17), which is a crucial regulator of tissue and plasma ACE2 and can cleave tissue ACE2 and increases plasma ACE2, which is more harmful. The presence of an excessive amount of ACE2 in plasma induces cardiac toxicity via renin-angiotensin overactivity. The reduction of ACE2 in tissue amplifies cardiovascular complications significantly, and therefore the inhibition of ADAM-17 is useful to protect COVID-19 patient's hearts. Higher shedding of ACE2 in women and could, at least partially, explain the reduced incidence of COVID-19 in women compared to men. Serine protease inhibitors or metabolic inhibitors may show the way forward in future. Symptomatic management till then would be steroids and cytokine storm inhibitors. Drug induced complications should be carefully avoided in all patient subsets. Effectiveness of vaccines would lead to surfacing of long term complications which should be carefully watched for with appropriate long term screening measures. Sustainable telehealth measures would go a long way supporting acute and long term care of these cardiovascular patients.



Courtesy: ACC

Figure 1 Management Of Myocarditis

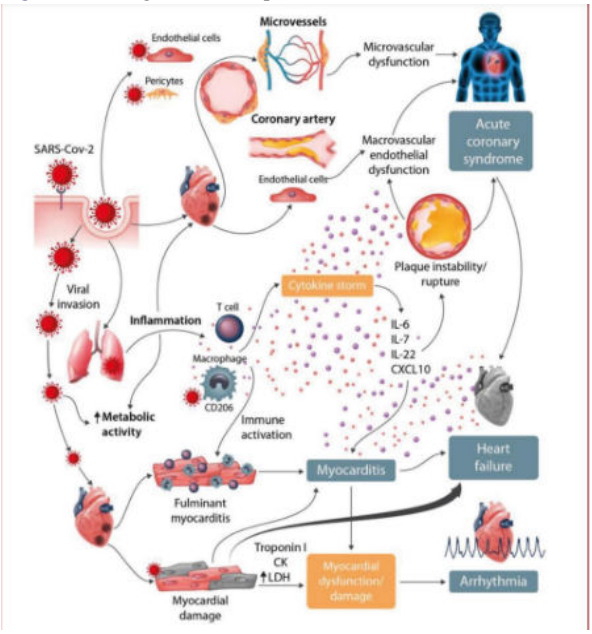


Figure 2 Key Cardiovascular System Involvement And Mechanisms As Per ESC

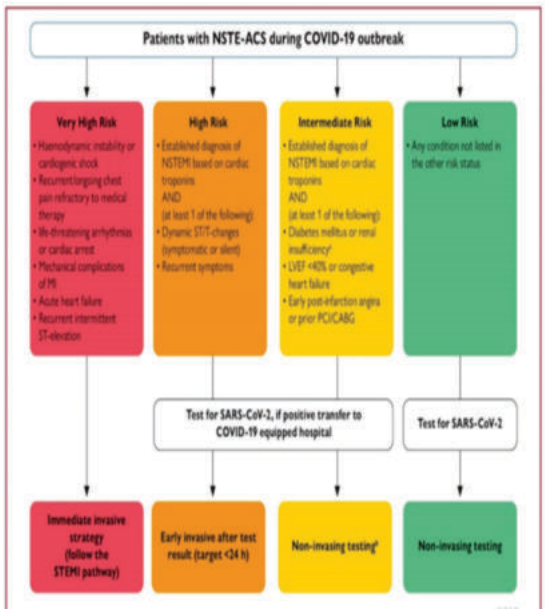


Figure 3 NSTEMI Management In COVID 19- ESC

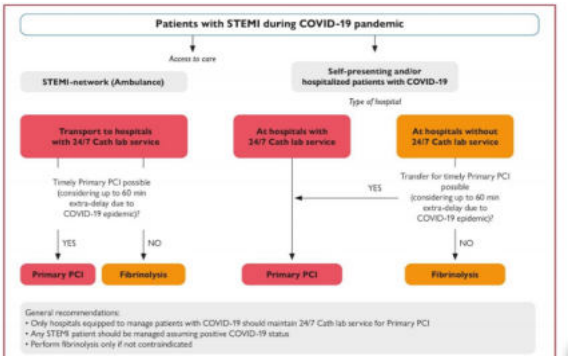


Figure 4 STEMI Guidelines In COVID 19 ESC

Table 1 World Heart Federation Guidelines For Those With Risk Factors

To avoid infection, we recommend you to:

- **Continue to take your medication** and follow medical advice
- **Secure a one month supply** of your medication or longer if possible
- Keep a distance of **at least one metre** from people with a cough, cold or flu
- **Wash your hands** often with soap and water for at least 20 seconds
- **Stay at home if possible**
- **Follow the instructions of the Department of Health** and local authorities in your country

Courtesy: WHF

Table 2 Anti COVID Agents Attempted

Corticosteroids (Dexamethasone	Inhibits the enzyme phospholipase A2 and blocks the synthesis of the inflammatory mediators
Chloroquine/hydroxychloroquine	Inhibition of endosomal acidification (early endosomal pathway)
Azitromycin (Zithromax)	Enhancement of the anti-SARS-CoV-2 activity of hydroxychloroquine
Camostat mesylate	Inhibition of spike protein on SARS-CoV-2 (non-endosomal pathway)
Remdesevir	Inhibition of the RNA-dependent RNA polymerase
Oseltamivir	Targeting the neuraminidase distributed on the surface of the virus
Umifenovir (Arbidol)	Blocking the virus-cell membrane fusion through incorporation into cell membranes
Lopinavir/ritonavir	Inhibition of papain-like protease and 3C-like protease
Sarilumab	Inhibiting the interleukin-6 (IL-6) pathway through binding and blocking the IL-6 receptor
Tocilizumab	Inhibiting the interleukin-6 (IL-6) pathway through binding and blocking the IL-6 receptor
Baicitinib	JAK1 and JAK2 inhibitor, reducing SARS-CoV-2 endocytosis
Vitamin C	Development and maturation of T-lymphocytes, inhibition of ROS production, remodulation of the cytokine network typical of systemic inflammatory syndrome
Vitamin D	Strengthens innate immunity, prevents an overactive immune response
Colchicine	Antithrombotic and anti-inflammatory
Favipiravir	Inhibition of the RNA-dependent RNA polymerase
Anakinra	IL-1 receptor antagonist
2 deoxy D glucose	effects on the glycolytic pathway, anti-inflammatory action, and interaction with viral proteins
Ivermectin	Inhibit viral replication

Table 3 (ESC)

· The pathobiology of coronavirus infection involves SARS-CoV-2 binding to the host receptor angiotensin-converting enzyme 2 (ACE2) to mediate entry into cells;

· ACE2, which is expressed in the lungs, heart and vessels, is a key member of the renin angiotensin system (RAS) important in the pathophysiology of CVD;

· CVD associated with COVID-19, likely involves dysregulation of the RAS/ACE2 system due to SARS-CoV-2 infection and due to comorbidities, such as hypertension;

· CVD may be a primary phenomenon in COVID-19, but may be secondary to acute lung injury, which leads to increased cardiac workload, potentially problematic in patients with pre existing HF;

· Cytokine release storm, originating from imbalance of T cell activation with dysregulated release of interleukin (IL)-6, IL-17 and other cytokines, may contribute to CVD in COVID-19. IL-6 targeting is being tested therapeutically;

· Immune system activation along with immunometabolism alterations may result in plaque instability, contributing to development of acute coronary events.

Table 4 Current Fibrinolyitc Therapy Guidelines Of ESC In COVID 19 With Cardiovascular Complications

Recommendations	Class[a]	Level[b]
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended	I	B
A half-dose of tenecteplase should be considered in patients ≥75 years of age	IIa	B
Antiplatelet co-therapy with fibrinolysis		
Oral or i.v. aspirin is indicated	I	B
Clopidogrel is indicated in addition to aspirin	I	A
DAPT (in the form of aspirin plus a $P2Y_{12}$ inhibitor) is indicated for up to 1 year in patients undergoing fibrinolysis and subsequent PCI.	I	C
Anticoagulation co-therapy with fibrinolysis		
Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The anticoagulant can be:	I	A
• Enoxaparin i.v. followed by s.c. (preferred over UFH)	I	A
• UFH given as a weight-adjusted i.v. bolus followed by infusion.	I	B
• In patients treated with streptokinase: fondaparinux i.v. bolus followed by an s.c. dose 24 h later.	IIa	B
Interventions following fibrinolysis		
Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock	I	A
Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis	I	B

[a]Class of recommendation.
[b]Level of evidence.

REFERENCES

1. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on corona virus disease 2019 (COVID-19) outbreak—an update on the status. Mil Med Res. 2020; 7:11.
2. 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; 5:802-10.
3. Bavishi C, Bonow RO, Trivedi V, Abbott JD, Messerli FH, Bhatt DL. Special Article - Acute myocardial injury in patients hospitalized with COVID-19 infection: a review. Prog Cardiovasc Dis 2020; 63:682-89
4. Atri D, Siddiqi HK, Lang JP, Nauffal V, Morrow DA, Bohula EA. COVID-19 for the cardiologist: basic virology, epidemiology, cardiac manifestations, and potential therapeutic strategies. JACC Basic Transl Sci 2020; 5:518-36
5. Metkus TS, Sokoll LJ, Barth AS, et al. Myocardial injury in severe COVID-19 compared with non-COVID-19 acute respiratory distress syndrome. Circulation 2021; 143:553-65.
6. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with Corona virus Disease 2019 (COVID-19). JAMA Cardiol 2020; 5:811-18
7. Chan JF, To KK, Tse H, Jin DY, Yuen KY. Interspecies transmission and emergence of novel viruses: lessons from bats and birds. Trends Microbiol. 2013; 21:544–55.
8. Chen Y, Liu Q, Guo D. Emerging corona viruses: genome structure, replication, and pathogenesis. J Med Virol. 2020; 92:418–23.
9. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterization and epidemiology of 2019 novel corona virus: implications for virus origins and

receptor binding. Lancet. 2020; 395: 565–74.
10. HoffmannM, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181:271–80.
11. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS corona virus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci U S A. 2009; 106:5871–6.
12. Matsuyama S, Nagata N, Shirato K, Kawase M, Takeda M, Taguchi F. Efficient activation of the severe acute respiratory syndrome corona virus spike protein by the transmembrane protease TMPRSS2. J Virol. 2010; 84:12658–64.
13. World Health Organization. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations.
14. Lala A, Johnson KW, Januzzi JL, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. J Am Coll Cardiol 2020; 76:533-46
15. Giustino G, Croft LB, Stefanini GG, et al. Characterization of myocardial injury in patients with COVID-19. J Am Coll Cardiol 2020; 76:2043-55.
16. Rudski L, Januzzi JL, Rigolin VH, et al. Multimodality imaging in evaluation of cardiovascular complications in patients with COVID-19: JACC Scientific Expert Panel. J Am Coll Cardiol 2020; 76:1345-57
17. Huang L, Zhao P, Tang D, et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. JACC Cardiovasc Imaging 2020; 13:2330-39.
18. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from Corona virus Disease 2019 (COVID-19). JAMA Cardiol 2020; 5:1265-73
19. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States, March-June 2020. MMWR Morb Mortal Wkly Rep 2020; 69:993-98.
20. ZidarDA, Al-Kindi SG, LiuY, Krieger NI, Perzynski AT, OsnardM, et al. Association of lymphopenia with risk of mortality among adults in the US general population. JAMA Netw Open. 2019; 2:e1916526.
21. Libby P, Ridker PM, Hansson GK. Leducq Transatlantic Network on Atherothrombosis, Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009; 54:2129–38.
22. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nat Rev Immunol. 2015; 15:104–16.
23. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest. 2017; 127:1–4.
24. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS corona virus. Nature. 2003; 426:450–4.
25. Bansal M. Cardiovascular disease and COVID-19. Diabetes Metab Syndr. 2020; 14:247–50.
26. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020; 382(17):e38
27. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054–62.
28. Tang N, Li D,Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel corona virus pneumonia. J Thromb Haemost. 2020; 18:844–7
29. BöhmM, Frey N, Giannitsis E, Sliwa K, Zeiher AM. Corona virus disease 2019 (COVID-19) and its implications for cardiovascular care: expert document from the German Cardiac Society and the World Heart Federation. Clin Res Cardiol. 2020; 27:1–14.
30. Nan J, Jin YB, Myo Y, Zhang G. Hypoxia in acute cardiac injury of corona virus disease 2019: lesson learned from pathological studies. J Geriatr Cardiol. 2020; 17(4):221–3.
31. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of corona virus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol. 2020.
32. Xiong TY, Redwood S, Prendergast B, Chen M. Corona viruses and the cardiovascular system: acute and long-term implications. Eur Heart J. 2020; 41(19):1798–1800.
33. Zheng YY,Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020; 17:259–60.
34. Riehle C, Bauersachs J. Key inflammatory mechanisms underlying heart failure. Herz. 2019; 44:96–106.
35. Zhang P, Zhu L, Cai J, Fang L, Qin JJ, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res.2020; 126(12):1671–1681.