COVID-19 AND IT’S IMPACT ON CARDIOVASCULAR SYSTEM

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Introduction:
The Severe Acute Respiratory Syndrome (SARS) Coronaviruses (CoVs), namely SARS-CoV2 (COVID-19), pandemic has pushed global health system to its limit. Till 27 August 2021, total cases of COVID-19 infection crossed 214 million; with over 4.4 million deaths since the beginning of the pandemic.¹ Evidence suggests that adults with cardiovascular disease (CVD) are at a higher risk of in-hospital mortality with COVID-19 infection.² Evidence suggests that higher age, male sex, black or African American ethnicity, underlying health conditions including CVD and cardiovascular risk factors (e.g. hypertension, diabetes mellitus, and chronic kidney disease) increase risk of severe COVID-19 or mortality with COVID-19.³-¹¹ Although, COVID-19 mainly affects respiratory system, severe COVID-19 may involve multiple organs including cardiovascular system. There is a both way relationship between covid 19 and CVS risk factors. Covid19 can adversely affect CVS directly or indirectly by various mechanisms and on the other hand, patients having CVS risk factors when infected by covid19 are at higher risk of poor outcome.Meta analysis by Harrison SL et al. showed that the cardiovascular complications in hospitalized covid19 infected patients were acute heart failure (2%), myocardial infarction (4%), deep vein thrombosis (7%), myocardial injury (10%), angina (10%), arrhythmias (18%), pulmonary embolism (19%), and venous thromboembolism (25%).¹² Research is going on for better understanding of the impact of covid19 in different systems of human body and finding better clinical solution to reduce the morbidity and mortality.

Pathophysiological effects of covid on CVS:
Entry of Covid19 virus into the body is mediated by binding of viral spike proteins with the angiotensin converting enzyme-2 (ACE-2) receptor expressed on type 2 pneumocytes and ciliated bronchial epithelial cells.¹³-¹⁶ ACE-2 is expressed also in other tissues like lung, gut, kidney epithelial cells, cardiomyocytes, arterial and venous endothelial cells, testis and to lesser extent in the breast, skin and on cells of haematopoietic origin.¹⁷ ACE-2 enzyme is a negative regulator of RAAS (Renin-Angiotensin-Aldosterone system) that serves as a protective mechanism against heart failure, myocardial infarction, lung disease, hypertension, vascular permeability by it’s beneficial effects like anti-inflammatory (reducing vascular inflammation and plaque destabilization), anti-fibrotic (preventing ventricular remodeling), vasodilatation effect,¹⁸,¹⁹ Following Covid19 binding, the activity of ACE-2 is reduced due to endocytosis and proteolytic cleavage.²⁰ There is increase in the level of Angiotensin II in these patients which accelerates

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the accumulation of inflammatory cells in the endothelium, rendering to endothelial inflammation/injury, vasoconstriction, pro-inflammatory and pro-oxidative state 21.

CARDIAC EFFECTS:
COVID-19 is associate with a wide spectrum of cardiovascular sequelae, including myocardial injury22, myocarditis23, ischemic injury caused by cardiac microvascular dysfunction, small vessel cardiac vasculitis24, endothelitis25 or epicardial coronary artery disease (with plaque rupture or demand ischemia), oxygen supply and demand imbalance, acute-onset heart failure, arrhythmias, cardiac arrest, stress (takotsubo) cardiomyopathy26,27, right heart strain (acute cor pulmonale), with causes including pulmonary embolism28, adult respiratory distress syndrome 29 and pneumonia); and systemic inflammatory response syndrome (cytokine storm) 30,31.

Most patients with Covid19 with cardiac abnormalities have typical symptoms of Covid-19, including cough, fever, myalgia, fatigue, headache and dyspnea. A minority of patients present with symptoms suggestive of heart disease (such as palpitations31 or chest pain 33). These symptoms may or may not be accompanied by prior or concurrent symptoms typical of COVID-19 infection30,34. Dyspnea and chest pain are non specific, symptoms which may occur due to non-cardiac and/or cardiac causes. Approximately 20% of patients admitted with Covid-19 have clinically significant cardiac involvement35, occult involvement may be even commoner36. Various pathophysiological mechanisms have been proposed, including viral infiltration, inflammation and microthrombi, and down-regulation of ACE-2 receptors.

a. Type I Myocardial infarction (MI):
The incidence of MI is high in this group of patients. The large amount of inflammatory mediators seg. Interleukins (IL-1, IL-6, and IL-8), tumor necrosis factor-alpha (TNF-á) generated due to covid19 infection stimulates the release of macrophages and T-cells inside the atherosclerotic plaques37. These cells activate matrix metalloproteinase and peptidase causing degradation of extracellular matrix and oxidative burst occurs and releasing phospholipids, tissue factor, collagen and platelet-adhesive matrix elements which contribute to plaque instability and thrombus formation. Besides this, COVID produces a hypercoagulable state, increased thrombus burden in culprit arteries, increased need for heparin and GP IIbIIIa inhibitors and increased morbidity and mortality in the patients with MI with COVID1938.

The diagnosis of MI may go unnoticed in critically ill patients with acute respiratory failure39.

b. Type II Myocardial Infarction:
Type 2 MI can be induced by imbalance between oxygen supply and demand provoked by different clinical etiologies such as hypoxemia due to Covid19 associated respiratory failure and sepsis40,41. The risk of myocardial ischemia is 17 folds higher in patients with acute respiratory infections, mainly due to disruption in ventilation-perfusion ratios, loss of hypoxic vaso-constrictive reflex, activation of the sympathetic nervous system which all together puts stress on myocardial oxygen demand leading to myocardial infarction42. Moreover, respiratory viruses have been associated with an increased risk of MI due to susceptible gene expression that stimulates platelet activation39. The clinical manifestations of type 2 MI include atypical signs and symptoms such as dyspnea43.

c. Myocarditis:
Covid19 has been found to cause myocarditis and myopericarditis. Lindner and colleagues performed autopsies on 39 decedents (median age 85 years) who died of covid19 infection and 24 of them (61.5%) had SARS-CoV-2 in their cardiac tissues. Viral loads above 1000 copies per iq RNA were documented in 16 cases (41.0%). Proinflammatory gene upregulation was present in each decedent with high viral loads44. Clinical feature of myocarditis is variable ranging from minimal symptoms to fulminant heart failure, cardiogenic shock and arrhythmias. Subclinical myocarditis may portend a particularly high risk for sudden. Puntmann and colleagues showed that approximately 80% of patients with severe COVID-19 have cardiac involvement and nearly 25% have evidence of ongoing myocardial inflammation three months after diagnosis. So these patients would require careful monitoring and follow up.

d. Arrhythmia:
Cardiac arrhythmias are common in COVID-19 infected patients. It may occur during the ongoing covid19 infection or after recovery. This may be due to preexisting cardiac illness, newly developed MI i, myocarditis, pericarditis, hypoxia, drug interaction or electrolyte imbalance45. Patients taking remdesivir may experience sinus bradycardia46 and those treated with hydroxychloroquine and azithromycin may experience ventricular arrhythmia due to their QT prolonging effect. Fever due to covid19 can unmask cases of cardiac channelopathies such as Brugada syndrome and long QT syndrome47.48. Study from Italy revealed nearly 60 percent increase in the rate of
out-of-hospital cardiac arrest during the peak of the 2020 COVID-19 pandemic (when compared with the same time frame from 2019)\textsuperscript{49}.

e. **TakoTsubo syndrome:**
Stress (takotsubo) cardiomyopathy has been reported in patients with COVID-19\textsuperscript{50}. During the COVID-19 pandemic, the incidence of TakoTsubo syndrome (TTS) has risen 4.5-fold\textsuperscript{51}. Even individuals without COVID-19 infection are at increased risk of TTS. This is probably due to increased emotional stress. TTS associated with COVID-19 is known as secondary TTS and this secondary TTS has got worse prognosis than primary TTS\textsuperscript{52}. Patients with TTS are at risk for a repeat episode of stress-induced cardiomyopathy; the largest study reported a recurrence rate of 1.8% per patient-year\textsuperscript{53,54}.

f. **Nonischemic myocardial injury:**
Non ischaemic myocardial injury may occur in COVID-19 infected patients for various reasons such as hypoxia, acute RV strain as a result of pulmonary embolism, covid pneumonia, ARDS, systemic inflammatory response syndrome (cytokine storm), direct myocardial damage by virus, small vessel inflammation. In a retrospective study on 416 COVID-19-affected patients, myocardial injury (transient increase of hs-Troponin values) was associated with significantly higher mortality than the subgroup without myocardial injury (51% vs 4.4%, respectively; \( p < 0.001 \))\textsuperscript{55}.

g. **DVT/Thrombosis:**
A high frequency of thrombosis and thromboembolism has been reported in COVID-19-affected patients\textsuperscript{56-58}. Arterial and venous endothelial cells express ACE-2 receptor which makes them prone to get infected by COVID19 with subsequent development of endothelitis, endothelial cell damage, systemic vasculitis and disseminated intravascular coagulation (DIC). COVID-19-affected patients present a severe hypercoagulability rather than consumptive coagulopathy with massive endothelial stimulation and damage with release of von Willebrand Factor from Weibel–Palade bodies\textsuperscript{59}. Significantly higher levels of D-dimer and fibrin degradation products along with longer prothrombin and activated thromboplastin times were observed in COVID19 infected subjects\textsuperscript{59}. Unlike acute DIC, COVID-19 patients have high fibrinogen and high factor VIII activity, suggesting that major consumption of coagulation factors does not occur\textsuperscript{61}.

h. **Multisystem inflammatory syndrome in adults (MIS-A):**
Multisystem inflammatory syndrome (MIS) was initially described in children (MIS-C) with recent COVID-19 infection which presents as a Kawasaki-like illness (fever, gastrointestinal symptoms, shock, LV systolic dysfunction, and elevated inflammatory markers). Similar cases of MIS have been described in young to middle-aged adults (MIS-A)\textsuperscript{62,63}. Many of these patients had history of recent COVID-19 and had positive COVID-19 antibody tests, with fewer having positive COVID-19 rT-PCR tests. MIS-A should be considered in young adults presenting with inflammatory shock. This syndrome seems to be highly responsive to parenteral steroids.

Management implications:
The overall management principles for patients presenting with COVID-19 who develop CV complications or who have pre-existing CVD are same as for any other patient without COVID-19. However, there are a few important points that need consideration.

1. All healthcare personnel involved in the care of COVID-19 patients should use personal protective equipment (PPE) and they should be trained for proper donning, usage and doffing of PPEs according to practice guidelines.
2. The cardiology ward should be arranged into a COVID-free zone, a COVID-19 zone and a grey zone hosting suspected of having COVID-19. The cardiology department should develop and rehearse working protocols for rapid diagnosis, triage, isolation, and management of COVID-19 patients with CV complications.
3. Patients with acute MI need rapid assessment followed by transfer from emergency room to CCU or cath lab to avoid the risk of acquiring infection as well as minimizing delay. There are reports of delays in acute cardiac care due to extra precautions taken in view of COVID-19\textsuperscript{64}.
4. Patients with COVID-19 who present with ST-segment elevation myocardial infarction (STEMI) within 12 hours of symptom onset, may be managed by primary PCI if there is a dedicated cath lab for COVID-19 positive cases. Where dedicated cath lab is not available, a fibrinolysis-first strategy is recommended. National Clinical Guidance for the management of cardiac patients in the COVID-19 pandemic, Bangladesh\textsuperscript{65} also supported conservative management by fibrinolysis with tenecteplase for STEMI presenting within 12 hours in the absence of
dedicated cath lab and if the risk of transmission is greater than the patient’s possible benefit.66

5. Unwarranted diagnostic tests (e.g. cardiac troponin, natriuretic peptides, echocardiography, etc.)67 should be avoided in these patients. The American College of Cardiology has urged clinicians to perform these assays only when they would meaningfully add to the management of the patients with COVID-19. The American Society of Echocardiography has also issued a similar advisory regarding the use of echocardiography in these patients68.

6. Thrombo-prophylaxis with heparin has been recommended for all hospitalized patients of COVID-19. It prevents pulmonary vascular thrombo-embolism, decrease dead space ventilation and mortality. International Society on Thrombosis and Hemostasis recommend at least six weeks of anticoagulation in high risk patients following discharge57.

7. Heart failure (HF) patients may be treated with guideline directed HF therapy including beta-blockers, ACEI/ARB/ARNI and aldosterone antagonists69. There was theoretical concerns regarding increased levels of ACE2 and the risk of acute COVID-19 with the use of RAAS inhibitors but they are now shown to be safe and should be continued in those with stable cardiovascular disease 70,71. Instead, abrupt cessation of RAAS inhibitors may be potentially harmful 72.

8. Patients with postural orthostatic tachycardia syndrome (POTS) can be managed by adequate hydration, betablocker and minimizing the dose of drugs which can exaggerate the condition73. Inappropriate sinus tachycardia may benefit from a low-dose beta blocker for heart rate management and reducing adrenergic activity73. Attention is warranted to the use of drugs such as anti-arrhythmic agents (for example, amiodarone) in patients with fibrotic pulmonary changes after COVID-1974.

Discharge and Follow-Up:
ACS patients during pandemic who have tested negative for COVID-19 disease should be discharged as early as the condition of the patient allows.75 It is recommend for very early discharge for NSTEMI cases within less than 24 hours and less than 48 hours for ST elevation myocardial infarction patients. ACS patients who have tested positive for COVID-19 disease with mild illness can be discharged within the same timeframes. After discharge, patients should self-isolate for at least 14 days or until full recovery from COVID-19, whichever is longer.76 Patients with positive COVID-19 and ACS who have a moderate to severe presentation such as pneumonia, severe pneumonia, Acute Respiratory Distress Syndrome, or even sepsis with or without septic shock should be managed primarily for the viral illness as inpatients for as long as the condition requires.75 All face-to-face follow-up appointments in outpatient department should be postponed.76 To avoid unnecessary patient contamination tele-consultation services for follow-up should be established and encouraged.77

Cardiac presentation of Post COVID-19 Syndrome
Evidence is evolving on the long-term effects of COVID-19, which can affect multiple organ systems.78 Persistence of symptoms such as fatigue, palpitations, dyspnea, chest pain, cognitive disturbances etc. beyond 4 weeks from the onset of acute symptoms of covid19 is defined as post covid syndrome79,80. Long-term CV sequelae may include increased cardiometabolic demand, myocardial fibrosis or scarring (detectable via cardiac MRI), arrhythmias, stress cardiomyopathy81 and autonomic dysfunction. Management of post covid syndrome includes serial clinical and imaging evaluation with electrocardiogram and echocardiogram at 4–12 weeks, identification and treatment of the CVS pathology 82,83. Current evidence does not support the routine utilization of advanced cardiac imaging, and this should be considered on a case-by-case basis. Recommendations for competitive athletes with cardiovascular complications related to COVID-19 include abstinence from competitive sports or aerobic activity for 3–6 months until resolution of myocardial inflammation by cardiac MRI or troponin normalization69,84.

Conclusion:
COVID-19 is more of a systemic disease than respiratory disease. Cardiovascular disease and certain cardiovascular risk factors are associated severe COVID-19 and/or increased mortality with COVID-19. Heart disease management scenario is changed in COVID era. Diagnostic dilemma limits the therapeutic plan. International global registry and randomized trials from a global perspective can help to develop a standardized approach for diagnosis and treatment to optimize the early morbidity and mortality along with documentation of actual prevalence of ACS and other cardiac complications. Clinicians and policy makers should consider primary and secondary prevention strategies to improve cardiovascular health and outcomes for people following COVID-19.

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References:
1. WHO coronavirus (COVID-19) Dashboard [Internet]. World Health Organization. World Health Organization; [cited 2021Aug28]. Available from: https://covid19.who.int/
2. Figliozzi S, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, et al. Predictors of ADVERSE prognosis in COVID 19: A systematic review and meta analysis. European Journal of Clinical Investigation. 2020;50(10). https://doi.org/10.1111/eci.13362. PMid: 32726868
3. Yang X, Yu Y, Xu J, Shu H, Xia J, Lui H, et al. Clinical course and outcomes of critically ill patients with SARS-COV-2 pneumonia in Wuhan, China: A single-centered, retrospective, Observational Study. The Lancet Respiratory Medicine. 2020;8(5):475-81. https://doi.org/10.1016/s2213-2600(20)30079-5.
4. Yancy CW. Covid-19 and African Americans. JAMA. 2020;323(19):1891. https://doi.org/10.1001/jama.2020.6548. PMid:32293639
5. Rimmer A. Covid-19: two thirds of healthcare workers who have died were from ethnic minorities. BMJ 2020;369:m1621. https://doi.org/10.1136/bmj.m1621. PMid:32327412
6. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with covid-19 in the New York City area. JAMA. 2020;323(20):2052. https://doi.org/10.1001/jama.2020.6775. PMid:32320003 PMCid:PMC7177629
7. Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-COV-2: A prospective cohort study. European Respiratory Journal. 2020;55(5):2000524. https://doi.org/10.1183/13993003.50524-2020. PMid:32973076 PMCid:PMC8410236
8. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiology. 2020;5(7):802. https://doi.org/10.1001/jamacardio.2020.0950. PMid:32211816 PMCid:PMC7097841
9. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. International Urology and Nephrology. 2020;52(6):1193-4. https://doi.org/10.1007/s11255-020-02451-9. PMid:32222883 PMCid:PMC7103107
10. Clark A, Jit M, Warren-Gash C, Guthrie B, Wang HH, Mercer SW, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: A modelling study. The Lancet Global Health. 2020;8(8): e1003-e1017. https://doi.org/10.1016/S2214-109X(20)30264-3.
11. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430-436. https://doi.org/10.1038/s41586-020-2521-4. PMid:32640463 PMCid:PMC7611074
12. Harrison SL, Buckley BJR, Rivera-Caravaca JM, Zhang J, Lip GYH. Cardiovascular risk factors, cardiovascular disease, and COVID-19: An Umbrella review of systematic reviews. European Heart Journal - Quality of Care and Clinical Outcomes. 2021Oct;7(4):330-9. https://doi.org/10.1093/ehjqco/qcab029 PMid:34107535 PMCid:PMC8294691
13. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger 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(2). https://doi.org/10.1016/j.cell.2020.02.045. PMid:32275855 PMCid:PMC7144619
14. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-COV-2 by full-length human ACE2. Science. 2020;367(6485):1444-8. https://doi.org/10.1126/science.abb2762. PMid:32132184 PMCid:PMC7164635
15. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3. https://doi.org/10.1038/s41586-020-2012-7.
16. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and functional basis of SARS-COV-2 entry by using human ACE2. Cell. 2020;181(4). https://doi.org/10.1016/j.cell.2020.03.045. PMid:32275855 PMCid:PMC7144619
17. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology. 2004;203(2):631-7. https://doi.org/10.1002/path.1570. PMid:15141377 PMCid:PMC7167720
18. Chen L, Hao G. The role of angiotensin-converting enzyme 2 in coronaviruses/influenza viruses and...
cardiovascular disease. Cardiovascular Research. 2020;116(12):1932-6. https://doi.org/10.1093/cvr/cvaa093. PMid:32267499 PMCid:PMC7184394.

19. Batlle D, Wysocki J, Khan MS. Vascular angiotensin-converting enzyme 2. Circulation Research. 2010;107(7):822-4. https://doi.org/10.1161/CIRCRESAHA.110.229831. PMid:20884883 PMCid:PMC2953869

20. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nature Medicine. 2005;11(8):875-9. https://doi.org/10.1038/nm1267. PMid:16007097 PMCid:PMC7095783

21. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. European Journal of Clinical Investigation. 2009;39(7):618-25. https://doi.org/10.1111/j.1365-2362.2009.02153. PMid:19453650 PMCid:PMC7163766

22. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe covid-19 patients. National Science Review. 2020;7(6):998-1002. https://doi.org/10.1093/nsr/nwaa041. PMid:34676125 PMCid:PMC7279731

23. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiology. 2020;5(7):802.https://doi.org/10.1001/jamacardio.2020.0950. PMid:32211816 PMCid:PMC7097841

24. Fox SE, Lameira FS, Rinker EB, Vander Heide RS. Cardiac endotheliitis and multisystem inflammatory syndrome after COVID-19. Annals of Internal Medicine. 2020;173(12):1025-7. https://doi.org/10.7326/m20-1175. PMid:32706743

25. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. The Lancet. 2020;395(10234):1417-8. https://doi.org/10.1016/s0140-6736(20)30937-5.

26. Giustino G, Croft LB, Oates CP, Rahman K, Lerakis S, Reddy VY, et al. Takotsubo cardiomyopathy in covid-19. Journal of the American College of Cardiology. 2020;76(5):628-9. https://doi.org/10.1016/j.jacc.2020.05.068. PMid:32517962 PMCid:PMC7279731

27. Tsao CW, Strom JB, Chang JD, Manning WJ. Covid-19-associated stress (takotsubo) cardiomyopathy. Circulation: Cardiovascular Imaging. 2020;13(7). https://doi.org/10.1161/circimaging.120.011222.

28. Creel-Bulos C, Hockstein M, Amin N, Melhem S, Truong A, Sharifpour M. Acute CorPulmonale in critically ill patients with covid-19. New England Journal of Medicine. 2020;382(21).https://doi.org/10.1056/nejm2010459. PMid:32374956 PMCid:PMC7281714

29. Huette P, Beyls C, Guilbart M, Haye G, Najid F-Z, Mestan B, et al. Acute CorPulmonale in covid-19-related Ards. JACC: Case Reports. 2020;2(9):1311-4.https://doi.org/10.1016/j.jaccr.2020.06.011. PMid:32835274 PMCid:PMC7296301

30. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. Covid-19 and the cardiovascular system. Nature Reviews Cardiology. 2020;17(5):259-60.https://doi.org/10.1038/s41569-020-0360-5. PMid:32139904 PMCid:PMC7095524

31. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with coronavirus disease 2019: Possible mechanisms. Journal of Cardiac Failure. 2020;26(6):470-5. https://doi.org/10.1016/j.cardfail.2020.04.009. PMid:32315733 PMCid:PMC7166030

32. Liu K, Fang Y-Y, Deng Y, Liu W, Wang M-F, Ma J-P, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chinese Medical Journal. 2020;133(9):1025-31. https://doi.org/10.1097/cm9.0000000000000744. PMid:32044814 PMCid:PMC7147277

33. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. The Lancet. 2020;395(10223):507-13. https://doi.org/10.1016/s0140-6736(20)30211-7.

34. Dong N, Cai J, Zhou Y, Liu J, Li F. End-stage heart failure with covid-19. JACC: Heart Failure. 2020;8(6):515-7. https://doi.org/10.1016/j.jchf.2020.04.001. PMid:32265149 PMCid:PMC7141452

35. Kreutz R, Algharably EA, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, et al. Erratum to: Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: Implications for covid-19: European Society of Hypertension covid-19 task force review of evidence. Cardiovascular Research. 2021; https://doi.org/10.1093/cvr/cvab224. PMid:34269396 PMCid:PMC8344701

36. Yancy CW, Fonarow GC. Coronavirus disease 2019 (covid-19) and the heart—is heart failure the next chapter? JAMA Cardiology. 2020;5(11):1216. https://doi.org/10.1001/jamacardio.2020.3575. PMid:32730614
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37. Crea F, Liuzzo G. Pathogenesis of acute coronary syndromes. Journal of the American College of Cardiology. 2013;61(1):1-11. https://doi.org/10.1016/j.jacc.2012.07.064. PMid:23158526

38. Choudry FA, Hamshere SM, Rathod KS, Akhtar MM, Archbold RA, Guttmann OP, et al. High thrombus burden in patients with covid-19 presenting with st-segment elevation myocardial infarction. Journal of the American College of Cardiology. 2020;76(10):1168-76. https://doi.org/10.1016/j.jacc.2020.07.022. PMid:32679155 PMCid:PMC7833185.

39. Arlati S, Brenna S, Prencipe L, Marocchi A, Casella GP, Lanzani M, et al. Myocardial necrosis in ICU patients with acute non-cardiac disease: A prospective study. Intensive Care Medicine. 2000;26(1):31-7. https://doi.org/10.1007/s001340050008. PMid:10663277

40. Mushar DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction. New England Journal of Medicine. 2019;380(2):171-6. https://doi.org/10.1056/nejmra1808137. PMid:30625066

41. Sandoval Y, Smith SW, Sexter A, Schulz K, Apple FS. Use of objective evidence of myocardial ischemia to facilitate the diagnostic and prognostic distinction between type 2 myocardial infarction and myocardial injury. European Heart Journal: Acute Cardiovascular Care. 2018;9(1):62-9. https://doi.org/10.1177/204887261787796. PMid:29979092

42. Ruane L, Buckley T, Hoo SY, Hansen PS, McCormack C, Shaw E, et al. Triggering of acute myocardial infarction by respiratory infection. Internal Medicine Journal. 2017;47(5):522-9. https://doi.org/10.1111/imj.13377. PMid:28105763

43. Lippi G, Sanchis-Gomar F, Cervellin G. Chest pain, dyspnea and other symptoms in patients with type 1 and 2 myocardial infarction. A literature review. International Journal of Cardiology. 2016;215:20-2. https://doi.org/10.1016/j.ijcard.2016.04.045. PMid:27107538

44. Lindner D, Fitzek A, Bräuning H, Aleshcheva G, Edler C, Meissner K, et al. Association of cardiac infection with SARS-COV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiology. 2020;5(11):1281. https://doi.org/10.1001/jamacardio.2020.3551. PMid:32730555 PMCid:PMC7385672

45. Dherange P, Lang J, Qian P, Oberfeld B, Sauer WH, Koplan B, et al. Arrhythmias and covid-19. JACC: Clinical Electrophysiology. 2020;6(9):1193-204. https://doi.org/10.1016/j.jacep.2020.08.002. PMid:32972561 PMCid:PMC7417167

46. Touafchia A, Bagheri H, Carriè D, Durrieu G, Sommet A, Chouchana L, et al. Serious bradycardia and Remdesivir for coronavirus 2019 (COVID-19): A new safety concerns. Clinical Microbiology and Infection. 2021;27(5). https://doi.org/10.1016/j.cmi.2021.02.013. PMid:33647441 PMCid:PMC7910147

47. Amin AS, Herfat Lij, Delisle BP, Klemens CA, Rook MB, Bezzina CR, et al. Fever-induced QTC prolongation and ventricular arrhythmias in individuals with type 2 congenital long QT syndrome. Journal of Clinical Investigation. 2008; https://doi.org/10.1172/jci35337. PMid:18551196 PMCid:PMC2423868

48. Chang D, Saleh M, Garcia-Bengo Y, Choi E, Epstein L, Willner J. Covid-19 infection unmasking Brugada Syndrome. HeartRhythm Case Reports. 2020; 6(5):237-40. https://doi.org/10.1016/j.hrcr.2020.03.012. PMid:32292696 PMCid:PMC7138191

49. Baldi E, Sechi GM, Mare C, Canevari F, Brancaglione A, Primi R, et al. Out-of-hospital cardiac arrest during the COVID-19 outbreak in Italy. New England Journal of Medicine. 2020;383(5):496-8. https://doi.org/10.1056/nejmc2010418. PMid:32348640 PMCid:PMC7204428

50. Shojaei F, Habibi Z, Goudarzi S, Firouzabadi FD, Montazerin SM, Najafi H, et al. Covid-19: A double threat to takotsubo cardiomyopathy and spontaneous coronary artery dissection? Medical Hypotheses. 2021;146:110410. https://doi.org/10.1016/j.mehy.2020.110410. PMid:33267999 PMCid:PMC7680528

51. Jabri A, Kalra A, Kumar A, Alameh A, Adroja S, Bashir H, et al. Incidence of stress cardiomyopathy during the coronavirus disease 2019 pandemic. JAMA Network Open. 2020;3(7).https://doi.org/10.1001/jamanetworkopen.2020.14780. PMid:32644140 PMCid:PMC7348683

52. Ahmad Alhiyari M, Ata F, Islam Alghizzawi M, Bint I Bilal A, SalihAbdulhadi A, Yousaf Z. Post covid-19 fibrosis, an emerging complication of SARS-COV-2 infection. IDCases. 2021;23. https://doi.org/10.1016/j.idcr.2020.e01041. PMid:33425682 PMCid:PMC7785952

53. Boedinghaus J, Nestelberger T, Kaiser C, Twerenbold R, Fahri G, Bingisser R, et al. Effect of covid-19 on acute treatment of st-segment elevation and non-st-segment elevation acute coronary syndrome in northwestern Switzerland. IJC Heart & Vasculature. 2021;32:100686. https://doi.org/10.1016/j.ijcha.2020.100686. PMid:33335974 PMCid:PMC7734221

54. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataisou DR, Jaguszewski M, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. Journal of Clinical Investigation. 2008;123(11):4963-74. https://doi.org/10.1172/jci35337. PMid:18551196 PMCid:PMC2423868

55. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan,
COVID-19 and It’s Impact on Cardiovascular System

63. Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-COV-2 infection - United Kingdom and United States, March-August 2020. https://doi.org/10.1001/jamachest.2020.0950. PMid:3221816 PMCID:PMC7097841

64. Tam C-CF, Cheung K-S, Lam S, Wong A, Yung A, Sze M, et al. Impact of coronavirus disease 2019 (covid-19) outbreak on st-segment-elevation myocardial infarction care in Hong Kong, China. Circulation: Cardiovascular Quality and Outcomes. 2020;13(4).https://doi.org/10.1161/circoutcomes.120.006631. PMid:32182131 PMCID:PMC7147280

65. A clinical guidance for the management of cardiac patients in the COVID-19 pandemic [Internet]. Bangladesh Society of Cardiac Intervention; 2020 [cited 2021Aug29]. Available from: https://dghs.gov.bd/images/docs/Notice/13_05_2020_cardiovascular_guideline.pdf

66. Zhang L, Fan Y, Lu Z. Experiences and lesson strategies for cardiology from the COVID-19 outbreak in Wuhan, China, by ‘on the scene’ cardiologists. European Heart Journal. 2020;41(19):1788-90. https://doi.org/10.1093/eurheartj/ehaa266. PMid:32242895 PMCID:PMC7529146

67. ACC Clinical Bulletin focuses on cardiac implications of coronavirus (COVID-19) [Internet]. American Society of Echocardiography. 2020 [cited 2021Aug29]. Available from: https://www.asecho.org/latest-in-cardiology/articles/2020/02/13/12/42/acc-clinical-bulletin-focuses-on-cardiac-implications-of-coronavirus-2019-ncov

68. ASE statement on covid-19 [Internet]. American Society of Echocardiography. 2020 [cited 2021Aug29]. Available from: https://www.asecho.org/ase-stateMENT-covid-19/

56. Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: A random association? European Heart Journal. 2020;41(19):1858. https://doi.org/10.1093/eurheartj/eaa254. PMid:32227120 PMCID:PMC7184406

57. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. Covid-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up. Journal of the American College of Cardiology. 2020;75(23):2950-73. https://doi.org/10.1016/j.jacc.2020.04.031. PMid:32311448 PMCID:PMC7164881

58. Spiezia L, Leclerc M, Chocchois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID 19 patients. Journal of Thrombosis and Haemostasis. 2020;18(7):1743-6. https://doi.org/10.1111/jth.14850. PMid:3230517 PMCID:PMC7264774

59. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis. 2020;120(06):998-1000. https://doi.org/10.1111/jth.14768. PMid:32316063 PMCID:PMC7295272

60. Spiezia L, Boscolo A, Poletto F, Cerruti L, Monsallier JM, et al. Hypercoagulability of Covid 19 patients in Intensive Care Unit: A report of thromboelastography findings and other parameters of hemostasis. Journal of Thrombosis and Haemostasis. 2020;18(7):1738-42. https://doi.org/10.1111/jth.14869. PMid:32211806 PMCID:PMC7164881

61. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of Covid 19 patients in Intensive Care Unit: A report of thromboelastography findings and other parameters of hemostasis. Journal of Thrombosis and Haemostasis. 2020;18(7):1738-42. https://doi.org/10.1111/jth.14850. PMid:32302438

62. Chau VQ, Giustino G, Mahmood K, Oliveros E, Neibart E, Oloomi M, et al. Cardiogenic shock and hyperinflammatory syndrome in young males with covid-19. Circulation: Heart Failure. 2020;13(10). https://doi.org/10.1161/circheartfailure.120.007485. PMid:32844662

63. Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-COV-2 infection - United Kingdom and United States, March-August 2020. MMWR Morbidity and Mortality Weekly Report. 2020;69(40):1450-6. https://doi.org/10.15585/mmwr.mm6940e1. PMid:33031361 PMCID:PMC7561225

64. Tam C-CF, Cheung K-S, Lam S, Wong A, Yung A, Sze M, et al. Impact of coronavirus disease 2019 (covid-19) outbreak on st-segment-elevation myocardial infarction care in Hong Kong, China. Circulation: Cardiovascular Quality and Outcomes. 2020;13(4).https://doi.org/10.1161/circoutcomes.120.006631. PMid:32182131 PMCID:PMC7147280

65. A clinical guidance for the management of cardiac patients in the COVID-19 pandemic [Internet]. Bangladesh Society of Cardiac Intervention; 2020 [cited 2021Aug29]. Available from: https://dghs.gov.bd/images/docs/Notice/13_05_2020_cardiovascular_guideline.pdf

66. Zhang L, Fan Y, Lu Z. Experiences and lesson strategies for cardiology from the COVID-19 outbreak in Wuhan, China, by ‘on the scene’ cardiologists. European Heart Journal. 2020;41(19):1788-90. https://doi.org/10.1093/eurheartj/ehaa266. PMid:32242895 PMCID:PMC7529146

67. ACC Clinical Bulletin focuses on cardiac implications of coronavirus (COVID-19) [Internet]. American Society of Echocardiography. 2020 [cited 2021Aug29]. Available from: https://www.asecho.org/latest-in-cardiology/articles/2020/02/13/12/42/acc-clinical-bulletin-focuses-on-cardiac-implications-of-coronavirus-2019-ncov

68. ASE statement on covid-19 [Internet]. American Society of Echocardiography. 2020 [cited 2021Aug29]. Available from: https://www.asecho.org/ase-stateMENT-covid-19/

57/69. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. Covid-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up. Journal of the American College of Cardiology. 2020;75(23):2950-73. https://doi.org/10.1016/j.jacc.2020.04.031. PMid:32311448 PMCID:PMC7164881

69. Hendren NS, Drazner MH, Bozkurt B, Cooper LT. Description and proposed management of the acute COVID-19 cardiovascular syndrome. Circulation. 2020;141(23):1903-14. https://10.1161/circulationaha.120.047349. PMid:32297796 PMCID:PMC714493
COVID-19 and Its Impact on Cardiovascular System

71. Lopes RD, Macedo AV, de Barros E Silva PG, Moll-Bernardes RJ, dos Santos TM, Mazza L, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with covid-19. JAMA. 2021;325(3):254. https://doi.org/10.1001/jama.2020.25864

72. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with covid-19. New England Journal of Medicine. 2020;382(17):1653-9.https://doi.org/10.1056/NEJMsr2005760. PMid:32227760 PMCid:PMC7121452

73. Raj SR, Black BK, Biaggioni I, Paranjape SY, Ramirez M, Dupont WD, et al. Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome. Circulation. 2009;120(9):725-34. https://doi.org/10.1161/circulationaha.108.846501. PMid:19687359 PMCid:PMC2758650

74. Kociol RD, Cooper LT, Fang JC, Mosleh DJ, Pang PS, Sabe MA, et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. Circulation 141, e69-e92 (2020).https://doi.org/10.1161/cir.0000000000000745. PMid:31902242

75. European Society of Cardiology .Covid-19 and Cardiology [Internet]. European Society of Cardiology. [cited 2021Aug29]. Available from:https://www.escardio.org/Education/COVID-19-and-Cardiology

76. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. Journal of the American College of Cardiology. 2020;75(18):2352-71. https://doi.org/10.1016/j.jacc.2020.03.031. PMid:32201335 PMCid:PMC7198856

77. American College of Cardiology. ACC’s Covid-19 Hub. [cited 2021Aug29]Available at https://www.acc.org/latest-in-cardiology/features/accs-coronavirus-disease-2019-covid-19-hub.

78. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehraut TS, et al. Extrapulmonary manifestations of covid-19. Nature Medicine. 2020;26(7):1017-32.https://doi.org/10.1038/s41591-020-0968-3. PMid:32651579

79. Datta SD, Talwar A, Lee JT. A proposed framework and timeline of the spectrum of disease due to SARS-COV-2 infection.JAMA. 2020;324(22):2251.https://doi.org/10.1001/jama.2020.22717. PMid:33206133

80. Greenhalgh T, Knight M, A’Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020;;m3026. PMid:32784198

81. Jabri A, Kalra A, Kumar A, Alameh A, Adroja S, Bashir H, et al. Incidence of stress cardiomyopathy during the coronavirus disease 2019 pandemic. JAMA Network Open. 2020;3(7). https://doi.org/10.1001/jamanetworkopen.2020.14780. PMid:32644140 PMCid:PMC7346863

82. George PM, Barratt SL, Condliffe R, Desai SR, Devaraj A, Forrest I, et al. Respiratory follow-up of patients with covid-19 pneumonia. Thorax. 2020;75(11):1009-16. https://doi.org/10.1136/thoraxjnl-2020-215314. PMid:32839287 PMCid:PMC7447111

83. Desai AD, Bourisiquot BC, Melki L, Wan EY. Management of arrhythmias associated with covid-19. Current Cardiology Reports. 2020;23(1). PMid:33231782 PMCid:PMC7685181

84. Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NAM, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 3: Hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis. Circulation. 2015;132(22). https://doi.org/10.1161/CIR.0000000000000239