Asian J. Exp. Sci., Vol. 35, No. 2, 2021; 37-42

Online available on : www.ajesjournal.com, ISSSN : 0971-5444

Pathological Basis and Clinical Presentations in COVID-19

Nitesh Arora*, B. S. Yadav, Rajeev Gupta, A. Sharma, R. S. Meena, R. K. Singh, A. Jain
[1]Department of Cardiology, Gandhi Medical College Bhopal- 462001
*Corresponding author's Email: drnitesharora@icloud.com

Received: June 4, 2021; Revised: June 24, 2021; Accepted: June 26, 2021

Abstract: Heart and cardiovascular system is the second most common target organ in patients with COVID-19 after the lungs with 12% acute cardiac injury and 44% arrhythmias and a higher mortality rate in patients with pre-existing heart disease and hypertension. This article reviews the cardiac manifestations and complications in COVID-19 and highlights the major cardiovascular manifestations including myocardial infarction, heart failure, myocarditis, arrythmias, pulmonary thromboembolism which contribute to morbidity & mortality in these patients and may have a long-term impact on their health, which yet needs to be determined.

Key Words: COVID 19, heart, Myocardial infarction, Arrythmia, heart failure, cardiac biomarkers, NT ProBNP, Troponin I, VTE (Venous Thromboembolism).

Introduction

Heart and cardiovascular system has been attributed to be the second most common target organ in patients with COVID 19 after the lungs with 12% acute cardiac injury and 44% arrhythmias (Yang *et al*., 2020; Wang *et al.,* 2020) and a higher mortality rate in patients with pre-existing heart disease and hypertension (Rabi *et al.,* 2020).

Pathophysiological basis of Cardiovascular involvement and role of ACE-2 Receptors

SARS COV2 virus and its variants utilizes angiotensin-converting enzyme 2 receptors abundantly present in type 2 pneumocytes of lungs to gain entry into the host cells, which when recognized by the innate immune system produces a variety inflammatory response in the host mediating inflammatory state and inflammation induced damage to the tissues (Rabi *et al.,* 2020). The ACE-2 receptors are expressed abundantly by cardiomyocytes (7.5%), intestinal cells, vascular endothelium and kidneys (Zou *et al.,* 2020), thus increasing the target cells for the virus and the multisystem involvement of the disease.

In cardiovascular system the ACE-2 mediated internalization of virus into the host cell leads to down regulation of the ACE-2 receptors, and thus hyperstimulation of ACE-1 pathway leading to vasoconstriction, fibrosis, inflammation and unpropitious remodeling of myocardial tissue (Guo *et al.*, 2019; Kuba *et al.*, 2020; Vaduganathan *et al*., 2020). There have been multiple schools of thought regarding overexpression of ACE-2 receptors in hypertensives on long term ACEi/ARB and its association with severity of the disease. In animal studies, it has been found that overexpression of ACE-2 protein and mRNA is a rare phenomenon in rats treated with ACE-1/ARBS (Kai *et al.,* 2021) and human studies have reported no effect on ACE-2 receptors with use of ACEi/ARBS (Ferrario *et al.,* 2005). The retrospective studies of patients on ACEi/ARBs have either found mortality benefit (Zhang, 2020) or no increase in severity of the disease (Mancia *et al.,* 2020; Reynolds *et al.,* 2020; Fosbøl *et al.,* 2020). The BRACE-CORONA (NCT04364893) (Lopes *et al.,* 2021) trial suggests that continuing ACEi/ARB as opposed to withholding ACEi/ARB therapy does not change clinical outcomes in patients with COVID-19.

Myocardial Infarction in COVID

The mechanisms of STEMI in patients of COVID-19 have been attributed to the underlying CAD with susceptible plaque rupture due to inflammatory state resulting in type 1 MI, secondly to oxygen supply-demand mismatch resulting from hypoxia, underlying inflammation, increased core body temperature and increased heart rate leading to type 2 MI (Musher *et al.*, 2019). The current evidence from systematic review (Diaz *et al.*, 2021) suggests that 17% patients with STEMI in COVID-19 patients had non obstructive CAD on coronary angiography and a high in-hospital mortality of 30% was noted in patients with both obstructive and non-obstructive CAD. The data from the study (Rodriguez *et al.*, 2021) from Spanish national registry indicates that STEMI patients, later diagnosed to be suffering from COVID-19 patients had more heart failure on arrival (31.9% vs 18.4%, p=0.002). Mechanical thrombectomy (44% vs 33.5%, p=0.046) and GP IIb/IIIa inhibitor administration (20.9% vs 11.2%,

p=0.007) were more frequent in COVID-19 patients, who had an increased in-hospital mortality (23.1% vs 5.7%, p<0.0001), that remained consistent after adjustment for age, sex, Killip class and ischemic time (OR 4.85, 95% CI: 2.04-11.51; p<0.001). COVID-19 patients had an increase of stent thrombosis (3.3% vs 0.8%, p=0.020) and cardiogenic shock development after PCI (9.9% vs 3.8%, p=0.007).

Markers of Acute Cardiac Injury in CAD

In initial study by Yang *et al*, (2020) patients of COVID-19, cardiac injury using highly sensitive troponin I (> 28 ng/L) was noted in 29% of patients. A meta-analysis by Lippi *et al,* (2020). using data from China revealed that cTnI values are abnormally elevated (more than 99th percentile) in 8-12% of patients hospitalized for COVID and was independently associated with poor prognosis and a tenfold higher mortality in patients with elevated hs-troponin I, However, the rise in troponin I in hospitalized patients was not necessarily observed due to only ischemic cardiac injury. In the study by Zhou *et al*, (2020) Troponin I was noted to be mainly associated as a marker of multi-organ failure and pulmonary hypertension associated with acute respiratory distress syndrome (ARDS) more than acute myocardial damage. The acute rise in troponins {>99th percentile, then an increase of at least 50% of the 99th percentile or a change >20% from baseline *in* hospitalized patients is found to be associated with myocarditis, pro-inflammatory state, stress cardiomyopathy, pulmonary embolism (orbjørn et al., 2021) other than the ischemic causes. Thus, the current evidence suggests that troponins should be interpreted with caution in patients of COVID with respect to the clinical settings, and can be utilized as an independent prognostic marker in hospitalized patients.

Heart Failure and COVID-19

Acute heart failure (AHF) was found to develop in 2.5% of hospitalized patients. On critical analysis of data from this study by Rey *et al.* (2020) which included 3080 patients with a median follow up of 30 days, it was noted that incidence of AHF patients without prior evidence of chronic heart failure was 2.1%, whereas in patients with pre-existing CHF it was 11.2%. A higher mortality and increased need for hospital admission was noted in patients of AHF with pre-existing CHF. Risk of development was more in olderage (78.6±12.6), hypertensives, diabetics, those with underlying dyslipidemia, peripheral artery disease, ischemic stroke, COPD, chronic heart failure and chronic kidney disease patients, however no significant higher risk was noted with obesity, smoking, coronary artery disease. The patients who developed acute heart failure had a higher incidence of hospital admissions (98.9% Vs 70.4%, p<0.001) and deaths (46.5%) however, no difference in ICU admissions, and increased need for mechanical ventilation was noted in patients of AHF. Atrial fibrillation/flutter during admission (14.3% Vs 2.5%, p<0.0001) was higher in patients with AHF, however no increase in ventricular arrythmias was noted (p=0.243).

In patients with pre existing evidence of chronic heart failure required higher hospital admissions (92% vs71.1%, p<0.001) and had a higher mortality (48.7% Vs 19.0, p < 0.001), significantly higher number of patients with pre-existing CHF were diagnosed with AHF, than those without pre-existing CHF(11.7%vs 2.1%, p <0.001), however, no increase in incidence of atrial fibrillation, ventricular arrhythmias, pulmonary embolism was noted in patients with CHF.

In the same study a significantly higher values of NT-Pro BNP were noted in patients of both CHF and AHF, however markedly elevated values were also noted in patients without any evidence of heart failure. On further investigating into the matter, a number of studies including the preliminary studies determining clinical characteristics of COVID-19 (Gao L2020) a higher value of NT pro-BNP (cut off 88.6 pg/ml) was associated with lower survival and was considered as an independent prognostic marker in patients of COVID.

In a special reference to heart failure with preserved ejection fraction, the current evidence (Hadzibegovic *et al.*, 2021) suggests that COVID-19 patients have a higher likelihood of HFpEF than the normal subjects. These observations were based on evaluation of patients using heart failure with preserved ejection fraction scores, which were found to be significantly higher in patients of COVID-19. The underlying mechanism for this higher likelihood of HFpeF with COVID 19 is yet to be explored, however it is considered that COVID-19 infection might be a risk factor which may unmask underlying HFpEF (Freaney *et al.*, 2020).

Arrhythmia and COVID 19

In the study by Wang *et al*, (2020) 16.7% of hospitalized and 44.4% of intensive care unit patients with COVID-19 had arrhythmias. In a multicentric survey (Ellie J*et al.*, 2021) from 4 continents which included 4526 patients from 4 continents 827 patients (18%) had arrhythmias. On critical analysis of the data from the study, cardiac comorbidities were found to be common in patients with arrhythmias: 69% hypertension, 42% diabetes, 30% had heart

failure, and 24% had coronary artery disease. Most had no prior history of arrhythmia. Atrial arrhythmias (81.8%) were more common than the ventricular arrhythmias (20.7%) and 22.6% patients had bradyarrhythmia. Atrial fibrillation was noted less in Asia than in other continents (34% vs 63%), 43% of patients who developed arrythmias were mechanically ventilated and 51% survived to hospital discharge.

In supraventricular arrhythmias, atrial fibrillation was noted in 61.5 %, atrial flutter in 10.4%, SVT in 9.7% and NSVT in9.4% of COVID patients. In ventricular arrhythmias VT was noted in 8.1% patients, of which 3.6 % were monomorphic VT, whereas 4% were polymorphic VT, 3.4% of VF. Bradyarrhythmia included Sinus bradycardia (12.8%), AV Block (8.6%), pause >3 sec (1.2%). In Patients who died (31.3%), VT or VF was noted in 2.4% at time of death, bradycardia in 2.7% cases, PEA in 5.5% cases, asystole in 15.5%. The remainder did not have any rhythm monitoring during death. For the management of arrhythmias 4.8 percent patients were required pacemaker.

Pulmonary thrombo-embolism in COVID-19

Incidence of pulmonary embolism in patients of COVID-19 is reported to be 1.9 to 8.9% (Grillet *et al.,* 2020; Lodigiani *et al.,* 2020; Stoneham *et al.,* 2020) with a higher incidence of 26.6% to 33.3 %in patients requiring ICU admissions (Beun *et al.,* 2020). Amongst patients admitted to ICU, PE has been found in 13.6% (34) to 16.7% (Helms *et al.,* 2020) despite receiving adequate thromboprophylaxis. A higher incidence of pulmonary embolism in same study was found to be associated more with severity of disease and ARDS (Klok *et al.,* 2020). A twofold increase in frequency of PE in patients with ARDS due to COIVD 19 was noted, as compared to ARDS due to other causes (Poissy *et al.,* 2020). The paucity of DVT in the studies (Helms, 2020) suggest the occurrence of in-situ pulmonary thrombosis rather than embolism at least in some cases, and currently two phenotypes of pulmonary thromboembolism are accepted, the first one with ordinary VTE following DVT, and secondly pulmonary microthombosis, with the latter, being more commonly associated with COVID 19. The Underlying mechanisms for Pulmonary thromboembolism include a prothrombotic and hypercoagulable state in COVID 19 infection suggested by rise in Fibrin degradation products, D-Dimer, and fibrinogen levels (Rouhezamin *et al.,* 2020; Bikdeli *et al.,* 2020; Tang *et al.,* 2020) as well as an associated poor prognosis with these abnormalities this has been attributed to systemic inflammation as well as direct virus mediated prothrombotic state (Oudkerk *et al.,* 2020). Indeed, Lionard *et al,* (2020) showed that D-dimer greater than 2660 μg/L is highly sensitive (100%, 95% CI 88–100) but not specific (67%, 95% CI 52–79) to detect PE in COVID-19 patients. Therefore, routine screening for VTE based on elevated D-dimer levels was not recommended in the most recent guidelines of the ISTH.The second mechanism contributing to pulmonary microthrombosis is high inflammatory state and cytokine storm which cause secondary development of hemophagocytic lymphohistiocytosis with activation of blood coagulation, increased risk of intravascular microthrombosis and secondary local consumption coagulopathy (Thachil *et al.,* 2020). In agreement with this assumption, Middeldorp *et al,* (2020) found that white blood cell count, higher neutrophil-to-lymphocyte ratio and a higher D-dimer level are independent risk factors associated with VTE. The American Society of Hematology (ASH) have recently recommended that a prophylactic dose of LMWH (40 mg qd) or subcutaneous un-fractionated heparin (5000 IU tid) should be started in all suspected or confirmed COVID-19 patients admitted to hospital (Bikdeli *et al.,* 2020; Thachil *et al.,* 2020; Kollias *et al.,* 2020; Spyropoulos *et al.,* 2020). In patients with known heparin-induced thrombocytopenia, fondaparinux (Obi *et al.,* 2020; Witt *et al.,* 2020; Keshari e*t al.,* 2020) can be used. If pharmacological prophylaxis is contraindicated, mechanical VTE prophylaxis (e.g., intermittent pneumatic compression) should be considered in immobilized patients (Bikdeli *et al.,* 2020) combined pharmacologic and mechanical prophylaxis is not recommended. Thromboprophlaxis should be considered in pregenancy and has shown to be beneficial. The use of and intermediate dose of LMWH (e.g., enoxaparin 4000 IU subcutaneously every 12 h) can be considered on an individual basis in patients with multiple risk factors for VTE (Keshari *et al.*, 2020) and in critically ill patients due to the higher incidence of PE in this population. As recommended by the Italian Society on Thrombosis and Haemostasis (SISET), prophylactic anticoagulation should be maintained at home for 7–14 days after hospital discharge or in the pre-hospital phase during home self-isolation, in case of pre-existing or persisting VTE risk factors (i.e., reduced mobility, body mass index (BMI) > 30, previous VTE, active cancer, etc.) (Marietta *et al.*, 2020). Extended post-hospital VTE prophylaxis should be considered in patientswith COVID-19 (up to 45 days). Experience from the MAGELLAN, APEX and MARINER studies suggest that in select patients without COVID-19, post-discharge thrombo-prophylaxis (particularly with a DOAC) may be beneficial if bleeding risk can be minimized.

While no data specific to COVID-19 exist, it is reasonable to employ individualized risk stratification of thrombotic and bleeding risk, to consider patients with elevated risk of VTE [e.g. Reduced mobility, active cancer, prior DVT, elevated D-dimer (>2 ULN)]. VTE options include Apixaban 2.5 bid, rivaroxaban 10 mg daily or Enoxaparin SQ daily (prevention dose adjusted for weight).

Conclusion

COVID-19 has major cardiovascular manifestations including myocardial infarction, heart failure, myocarditis, arrhythmias, which contribute to morbidity and mortality in patients of COVID-19 and may have a long-term impact on their health, which yet needs to be determined. The cardiac Biomarkers including cardiac troponins and NT pro-BNP not only depict underlying ischemia or heart failure but are also found to be independent prognostic markers.

References

Beun R. Kusadasi N. Sikma M. Westerink J. *et al.* (2020). Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. *Int J Lab Hematol.* 42:19–20.

Bikdeli B. Madhavan M.V. Jimenez D. *et al.* (2020). COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. 75(2950):2973.Circulation 111, 2605–10 https://doi.org/10.1161/CIRCULATIONAHA.104.510461

Diaz-Arocutipa C. Torres-Valencia J. Saucedo-Chinchay J. *et al.* (2021). ST-segment elevation in patients with COVID-19: a systematic review. *J Thromb Thrombolysis* https://doi.org/10.1007/s11239-021-02411-9

Ellie J. Coromilas MD. Stephanie Kochav. (2021). Worldwide Survey of COVID-19–Associated Arrhythmias. Arrhythmia and *Electrophysiology*.14:e009458

Freaney P.M. Shah S.J. Khan S.S. *et al*. (2020). COVID-19 and Heart Failure with preserved ejection fraction. *JAMA*. ;324(15):1499–1500. doi:10.1001/jama.2020.17445

Ferrario C.M. Jessup J. Chappell M.C. *et al*. (2005). Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2.

Fosbøl E.L. Butt J.H. Østergaard L. *et al*. (2020). Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. JAMA 324, 168–177

Gao L. Jiang D. Wen XS. *et al*. (2020). Prognostic value of NT-proBNP in patients with severe COVID-19. Respir Res;21:83. doi: 10.1186/s12931-020-01352-w

Grillet F. Behr J. Calame P. *et al.* (2020). Acute pulmonary embolism associated with COVID-19 pneumonia detected by pulmonary CT angiography. Radiology; 296:E186–8.

Guo J. Huang Z. Lin L. *et al.* (2020). Coronavirus disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. *J Am Heart Assoc;***9***:*e016219

Hadzibegovic S. Lena A. Churchill. (2021). Heart Failure with preserved ejection fraction according to the HFA-PEFF score in COVID-19 patients: clinical correlates and echocardiographic findings. Eur J Heart Fail. Accepted Author Manuscript. https://doi.org/10.1002/ejhf.2210

Helms J. Tacquard C. Severac F. *et al*. (2020). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. https://doi.org/10.1007/s00134-020-06062-x.

Kai. H. Kai. M. Niiyama H. *et al*. (2021). Overexpression of angiotensin-converting enzyme 2 by renin-angiotensin system inhibitors. Truth or myth? A systematic review of animal studies. *Hypertens Res* https://doi.org/10.1038/s41440-021-00641-1

Keshari R.S. Silasi R. Popescu N.I. *et al*. (2020). Fondaparinuxpentasaccharide reduces sepsis coagulopathy and promotes survival in the baboon model of Escherichia coli sepsis. J ThrombHaemost.;18(1):180–90.

Klok F.A. Kruip M. Van der Meer N.J.M. *et al. (*2020). Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res;191:145–7.

Kollias A. Kyriakoulis K.G. Dimakakos E. *et al.* (2020). Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol. ;189:846–7.

Kuba K. Imai Y. Rao S. *et al.* (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*

*;***11**:875–9.

Leonard-Lorant I. Delabranche X.Severac F. Helms J.*et al.* (2020). Acute pulmonary embolism in COVID-19 patients on CT angiography and relationship to D-dimer levels. Radiology.;296:E189–91.

Lodigiani C. Iapichino G.Carenzo L. *et al.* (2020). Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan. Italy. ThrombRes.;191:9–14

Lippi G. Lavie C.J. Sanchis-Gomar F. *et al.* (2020). Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. Prog Cardiovasc Dis ;63:390–1

Lopes R.D. Macedo A.V.S. de Barros E. Silva PGM. *et al*. (2020). 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: A Randomized Clinical Trial. *JAMA*. 19;325(3):254-264. doi: 10.1001/jama.2020.25864.

Mancia G. Rea F. Ludergnani M.Apolone G. *et al.* (2020). Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N. Engl. J. Med. 382, 2431–2440 https://doi.org/10.1056/NEJMoa2006923

Marietta M. Ageno W. Artoni A. *et al.* (2020). COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). Blood Transfus. ;18:167–9.

Musher M.D. Abers M.S. Corrales V.F. *et al.* (2019). Acute infection and myocardial infarction. N Engl J Med ;380:171–6.

Middeldorp S. Coppens M. van Haaps T.F. *et al.* (2020) Incidence of venous thromboembolism in hospitalized patients with COVID-19. J ThrombHaemost. ;18:1995–2002

Obi A.T. Barnes G.D. Wakefield T.W. *et al.* (2020). Practical diagnosis and treatment of suspected venous thromboembolism during COVID-19 pandemic. J VascSurg Venous LymphatDisord.;8:526–34

Oudkerk M. Buller H.R. Kuijpers D. *et al.* (2020). Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: report of the National Institute for Public Health of the Netherlands. Radiology. https://doi.org/10.1148/radiol.2020201629

OrbjørnOmland. Nicholas L. Mills. Christian Mueller. *et.al.* (2021). On behalf of the Study Group on Biomarkers of the ESC Association for Acute Cardiovascular Care, Cardiovascular biomarkers in COVID-19, *European Heart Journal. Acute Cardiovascular Care*, zuab 037.

Poissy J. Goutay J. Caplan M. *et al.* (2020). Pulmonary embolism in COVID-19 patients: awareness of an increased prevalence. Circulation.;14:184–6.

Rabi F.A. Al Zoubi M.S. Kasasbeh G.A. *et al.* (2020). SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far. Pathogens [Internet]. MDPI AG; Mar 20;9(3):231. Available from: http://dx.doi.org/10.3390/pathogens9030231

Rey J.R. Caro-Codón J..Rosillo S.O. *et al.* (2020). Heart failure in COVID-19 patients: prevalence, incidence and prognostic implications. Eur J Heart Fail. Dec;22(12):2205-2215. doi: 10.1002/ejhf.1990. Epub 2020 Oct 7. PMID: 32833283; PMCID: PMC7461427.

Reynolds H.R. Adhikari S. Pulgarin C.M. *et al.* (2020). Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. N. Engl. J. Med. 382, 2441–2448

https://doi.org/10.1056/NEJMoa2008975

Rodriguez-Leor O. Cid Alvarez A.B. *et al.* (2020). In-hospital outcomes of COVID-19 ST-elevation myocardial infarction patients. EuroIntervention. 2021 Apr 20;16(17):1426-1433. doi: 10.4244/EIJ-D-20-00935. PMID: 33164893.

Rouhezamin M.R. Haseli S. (2020). Diagnosing pulmonary thromboembolism in COVID-19: a stepwise clinical and imaging approach. AcadRadiol.;27:896–7.

Stoneham S.M. Milne K.M. Nuttal E. *et al* (2020).Thrombotic risk in COVID-19: a case series and case-control study. Clin Med. ;20:e76–81.

Spyropoulos A.C. Levy J.H. Ageno W. et al. (2020). Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J ThrombHaemost*. 18:1859–65

Tang N. Li D. Wang X. Sun Z. (2020). Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J ThrombHaemost*. 18:844–7

Thachil J. Tang N. GandoS. *et al.* (2020). ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J

ThrombHaemost.;18:1023–6.

Vaduganathan M. Vardeny O. Michel T. *et al.* (2020). Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med ;*382*:*1653–9.

Wang D. Hu B. Hu C. *et al.* (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan. *China Jama*. ;323:1061–1069. doi:10.1001/jama.1585

Witt D.M. Nieuwlaat R. Clark N.P. *et al*. (2018). American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv.;2(22):3257–91

Yang X. Yu Y. Xu J. (2020). 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.*;8:475–481. doi: 10.1016/s2213-2600(20)30079-5.

Zhou F. Yu T. Du R. *et al*.(2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62. [Erratum in: Lancet;395(10229):1038]. doi: 10.1016/S0140-6736(20)30566-3

Zhang P. Zhu L. Cai J. *et al*. (2020). Correction to: 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. 127, e147, https://doi.org/10.1161/CIRCRESAHA.120.317134

Zou X. Chen K. Zou J. *et al*. (2020). Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med;14:185–92. doi: 10.1007/s11684-020-0754-0