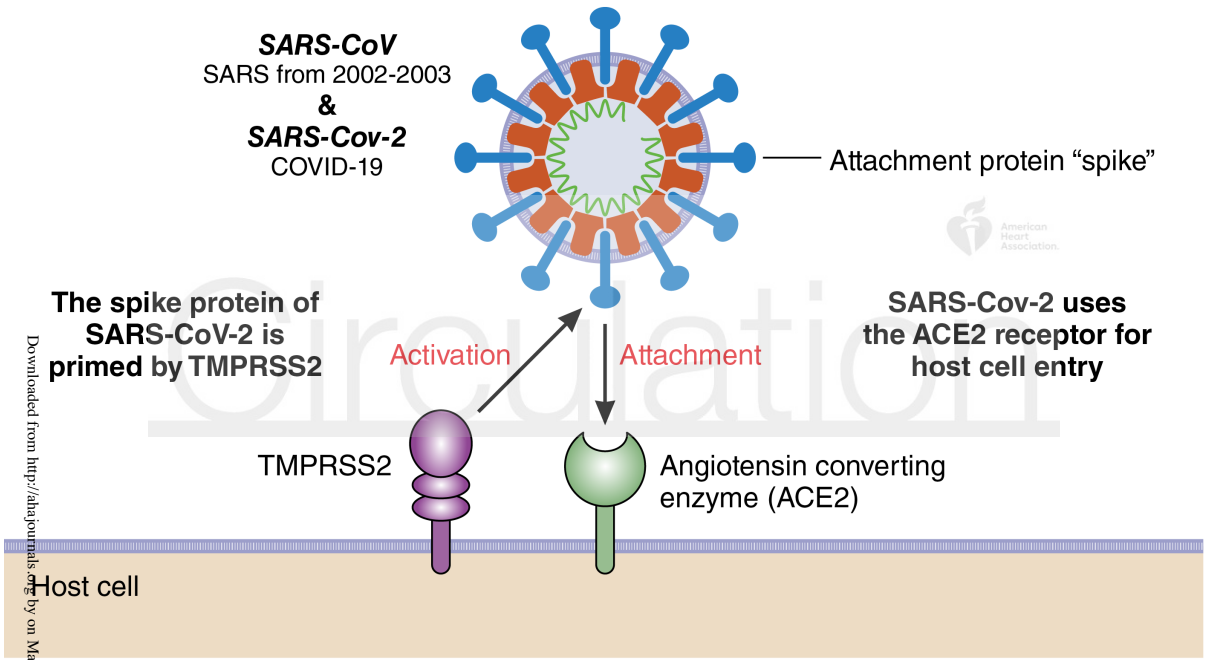
Coronavirus Disease 2019 (COVID-19) and The heart

Current outbreak was cause by coronavirus which as caused the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).

This is novel single-stranded enveloped RNA virus is the seventh known human coronavirus. SARS-CoV-2 is unlike the other coronaviruses known to cause the common cold (229E, OC43, NL63, and HKU1), but similar to the zoonotic severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 (SARS) and the Middle East respiratory syndrome coronavirus (MERS-CoV) from 2012 (MERS) – the latter had transferred from mammals to human.

Pathogenesis –

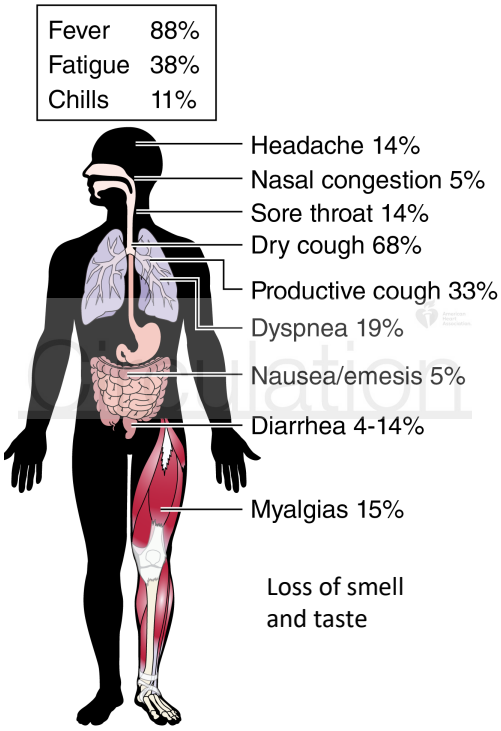
SARS-CoV-2 utilises the ACE-2 receptor for cell entry as shown below -



Although, ACE2 is expressed in the lung (principally Type II alveolar cells7) and appears to be the predominant portal of entry. The invasion to the alveolar epithelial cells, resulting in respiratory symptoms - After ligand binding, SARS-CoV2 enters cells via receptor-mediated endocytosis in a manner akin to human immunodeficiency virus (HIV).

We find that ACE2 is also expressed (highly) in the heart, counteracting the effects of angiotensin II in states with excessive activation of the renin-angiotensin system such as

hypertension (HTN), congestive heart failure (CHF), and atherosclerosis. We can find ACE2 expressed also in the intestinal epithelium, vascular endothelium, and the kidneys, providing a mechanism for the multi-organ dysfunction that can be seen with SARS-CoV-2 infection.

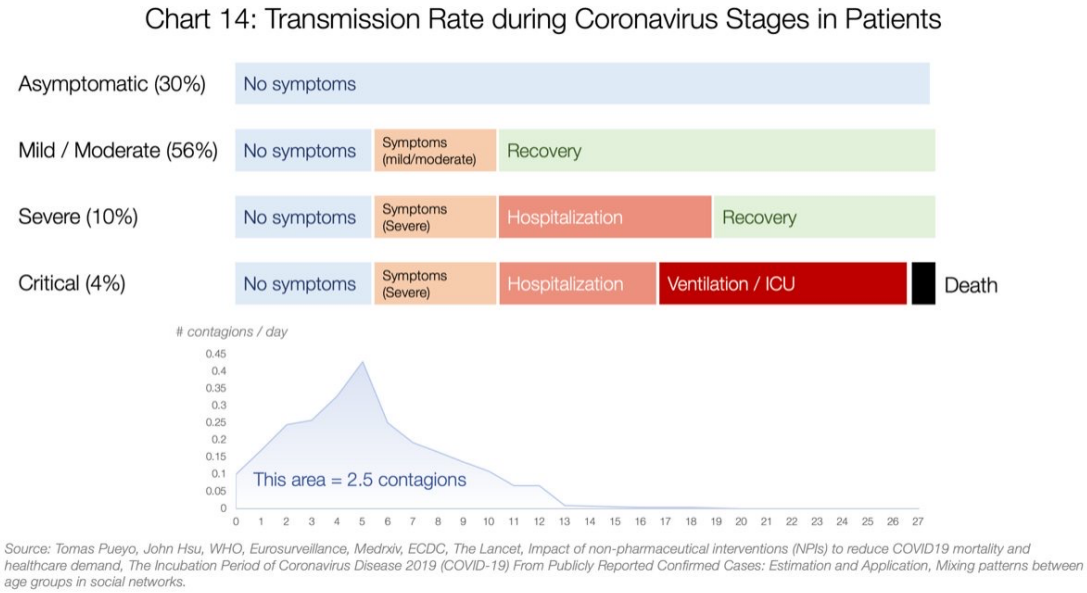


Clinical Presentation –

Symptoms vary from different publications, but the majority reporting those symptoms that are see in the figure attached →

In severe cases, COVID-19 may present as pneumonia, the acute respiratory distress syndrome (ARDS), with or without both distributive and cardiogenic shock.

The severity of the disease is listed below with a graph with the rate of contingency.

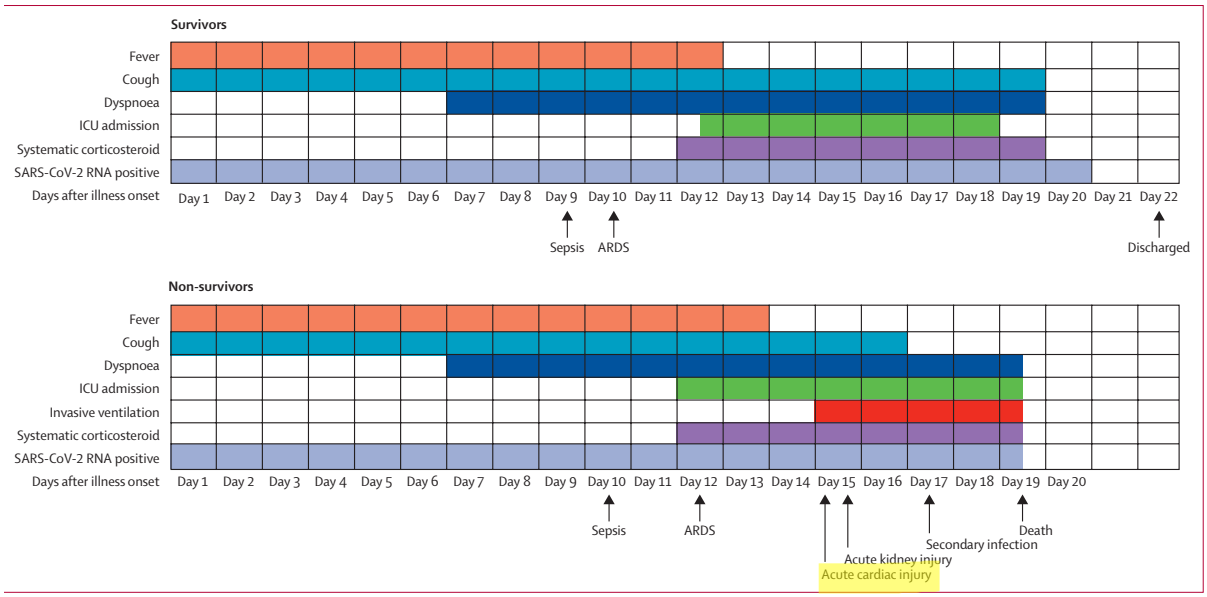


Source: Tomas Pueyo, John Hsu, WHO, Eurosurveillance, Medrxiv, ECDC, The Lancet, Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand, The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application, Mixing patterns between age groups in social networks.

Cardiovascular disease in the COVID-19 Patients

In a meta-analysis of six studies with a total of 1,527 patients with COVID-19 have shown: examined the prevalence of CVD and reported the prevalence of hypertension 17.1%, cardiac disease and cerebrovascular disease 16.4% , and diabetes 9.7%. The prevalence of

those co-morbidities has increased in the non-survivor group. Moreover, hospitalized patients have been suffering from cardiac complications, including new or worsening heart failure (52% 28/44), new or worsening arrhythmia (16%), or myocardial infarction. About 3% of patients with pneumonia have suffer cardiac arrest (Zhau et al. The Lancet 2020).
See below the time frame for the acute cardiac injury in those patient -

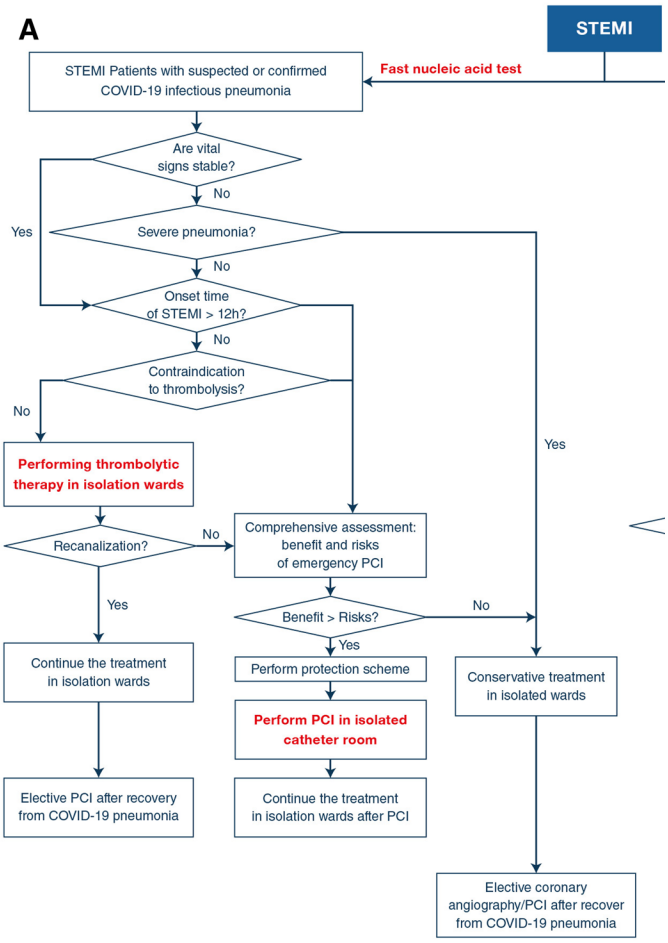


The evidence of acute myocardial injury is conveyed by the elevated cardiac troponin, elevated BNP and abnormal ECG (any, I haven't found a specific changes) – this was seen in up to 22% of patient's that required ICU (Wang et al, JAMA 2020). In this report the rate of new onset cardiomyopathy was 7% (7/21 patients).
Fulminant myocarditis was reported in two cases (Hu et al, EHJ 2020; Zeng et al, preprints 2020) both of them showed ST elevation on ECG, markers of myocardial injury (elevated troponin and CPK) and hemodynamic compromised. Coronary disease was ruled out by CT in the first case, the second case no coronary imaging was done due to the over clinic. Echo showed reduced LVEF in both cases (27% and 32% respectively) and improved after treatment with high dose steroids and IVIg. There is no good estimate for the occurrence of myocarditis.

Emphasizing - The majority of the existing analyses, including those related to CV complications of COVID-19 are based on retrospective and often single-center series, thus should be taken appropriately.

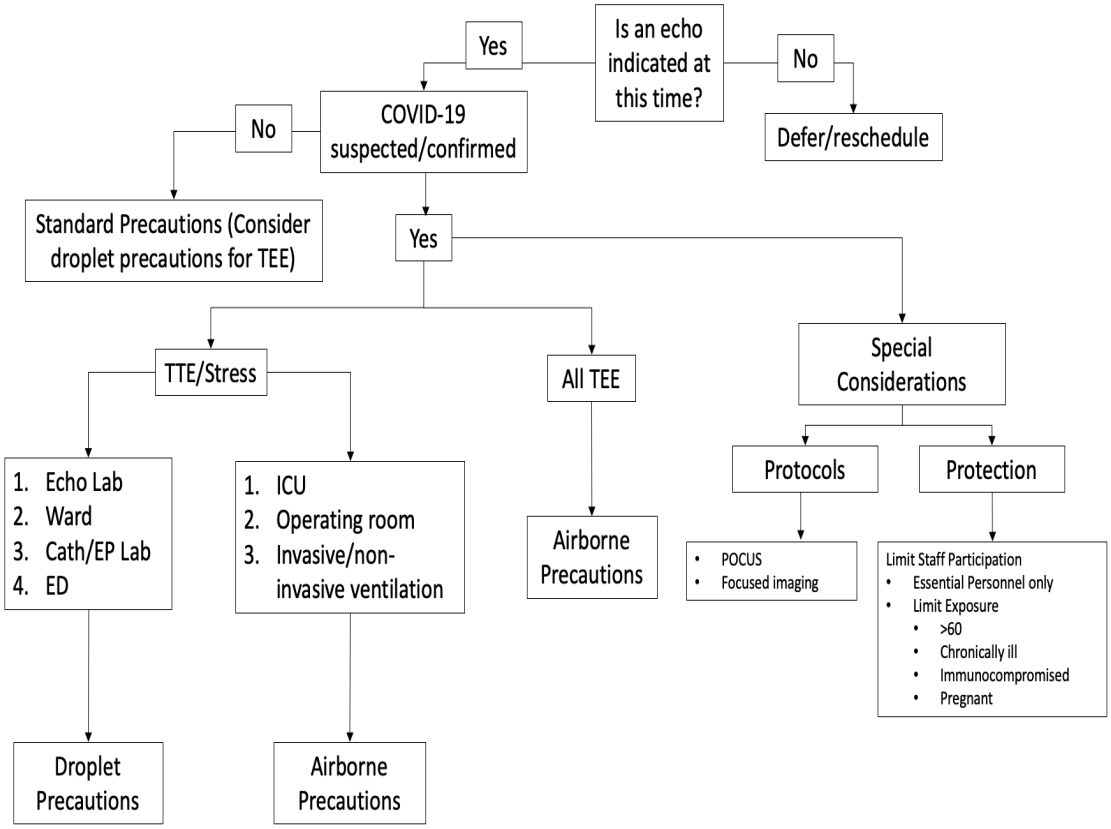
Imaging and Treating patients in the COVID-19 era

ACS –One report from China (Zeng et al Intensive care medicine 2020) have suggested this schema were thrombolytic therapy is done in the isolation wards. Other report by Tam et al (Circ Cardiovasc Qual Outcomes. 2020) have reported increased door-to-balloon time in all concerning aspect – time to medical assistance, door to device and even cath. team arrival to the device which was almost doubled. But we have to note that this report reported only 7 events of STEMI. NSTEMI patients in the previous report was treated conservative or with thrombolysis.



The SCAI and intervational council have issued their statement where they advise that “in the patient with known COVID-19 and STEMI, the balance of staff exposure and patient benefit will need to be weighed carefully. Fibrinolysis can be considered an option for the relatively stable STEMI patient with active COVID-19.” In regard to NSTEMI it “suggested that in appropriately selected cases of patients with known COVID-19 and NSTEMI, (e.g., particularly for patients with type 2 MI) conservative therapy may be sufficient based on the patient’s risk. It is important to note that recent reports suggest that acute cardiac injury is present in ~7% of patients with COVID-19 and may represent either type 2 MI or myocarditis.” (https://doi.org/10.1016/j.jacc.2020.03.021)

Echo. – ASE have released their recommendation in the era of COVID-19 First and most important (not only in COVID-19 era) echo “should only be performed if they are expected to provide clinical benefit.”



Second, “Regardless of the type of study (UAPE, POCUS, CCE or comprehensive echo), prolonged scanning can expose these clinicians to added risk. These studies should not be performed by a sonography student or any other novice/inexperienced practitioner, in order to minimize scanning time while obtaining images of the highest possible quality”. Third, is where the image should be and they are suggesting to perform the ECHO in the isolation room with proper personal protection. They summarize with this: “Carefully considering ‘Whom to Image’, ‘Where to Image’ and ‘How to Image’ has the potential to reduce the risks of transmission.” [https://www.asecho.org/covid-19-resources/]

Cardiac CT – the SCCT have released guideline paper for the COVID-19 time. The main massage is that “In patients under investigation (PUI) and with confirmed COVID-19, the benefit of CCT in most clinical scenarios will likely be lower than the risk of exposure and infection to healthcare personnel. These cases should be considered on a case-by-case basis.”

Medical treatment –

Although high postulated till now there is no recommendation to stop ACE or ARB treatment (doi:10.1093/eurheartj/ehaa235).

Furthermore, the cassation of these drug is not advised in patient with COVID-19 since there is a fear of increased cardiovascular mortality.

Recent reports from France have noticed that the use of NSAID have cause deterioration of symptoms in young healthy men. They have reported that 4 young man, with no known previous illness have used Ibuprofen in the early stage; this was resulted with increased severity of disease. British scientists have added their statement and claiming that the properties of ibuprofen's anti-inflammatory properties could "dampen down" the immune system, which could slow the recovery process. [BMJ 2020;368:m1086 doi: 10.1136/bmj.m1086 (Published 17 March 2020)] -> this is the only scientific paper about NSAID and COVID-19 with no clinical trials or evidence only some suggestions and speculations.

I have attached a table below with recommendations regarding dosing and adjustment in the setting of medication interactions between COVID-19 treatment and cardiovascular drugs.

Table 5. Recommendations Regarding Dosing and Adjustment in the Setting of Medication Interactions

Therapy	Specific Interaction	MOA of Drug Interaction and Specific Dose Adjustments	Other Notes
Ribavirin	**Anticoagulants** Warfarin	Unknown mechanism of action: No dosage adjustment recommended.	Monitor INR
Lopinavir/Ritonavir	**Anticoagulants** • Apixaban • Rivaroxaban	CYP3A4 inhibition: Apixaban should be administered at 50% of dose (do not administer if requirement 2.5 mg per day). Rivaroxaban should not be co-administered.	Dabigatran and warfarin can be administered with caution
	Antiplatelet • Clopidogrel • Ticagrelor	CYP3A4 inhibition: Diminished effect of clopidogrel. Do not co-administer. Increased effect of ticagrelor. Do not co-administer.	Consider prasugrel if no contraindications. If other agents used, consider a testing-guided approach (e.g. $P2Y_{12}$ platelet function assay).
	Statin • Atorvastatin • Rosuvastatin • Lovastatin • Simvastatin	OATTP1B1 and BCRP inhibition: Rosuvastatin should be adjusted to maximum dose 10 mg/day. CYP3A4 inhibition: Atorvastatin should be adjusted to maximum dose 20 mg/day Lovastatin and simvastatin should not be co-administered.	Start at lowest possible dose of rosuvastatin and atorvastatin and titrate up. Pravastatin and pitavastatin can also be considered.
	Antiarrhythmics • QT-prolonging medication • Digoxin	P-glycoprotein inhibition: Monitor digoxin level for possible dose reduction.	Use cautiously with antiarrhythmics

Chloroquine / Hydroxychloroquine	**<u>Beta Blockers</u>** • metoprolol, carvedilol, propranolol, labetalol **<u>Antiarrhythmics</u>** • QT-prolonging agents • Digoxin	CYP 2D6 inhibition: Dose reduction for beta blockers may be required. P-glycoprotein inhibition: Monitor digoxin level for possible dose reduction.	Use cautiously with antiarrhythmics
Fingolimod	**Bradycardia-Causing Agents:** • Beta blockers, Calcium channel blockers, Ivabradine **<u>Antiarrhythmics</u>** QT-Prolonging Medications: • Class 1A Antiarrhythmics • Class III Antiarrhythmics)	Sphingosine-1-phosphate receptor inhibition (on atrial myocytes): do not co-administer with class IA and III antiarrhythmics.	Use cautiously with other QT-prolonging drugs
Methylprednisolone	**<u>Anticoagulants</u>** • Warfarin	Unknown mechanism: Dose adjust based on INR.	Monitor INR

INR = international normalized ratio; MOA = mechanism of action