EVMS
MEDICAL GROUP

EVMS CRITICAL CARE COVID-19 MANAGEMENT PROTOCOL

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URGENT! Please circulate as widely as possible. It is crucial that every pulmonologist, every critical care doctor and nurse, every hospital administrator, every public health official receive this information immediately.

This is our recommended approach to COVID-19 based on the best (and most recent) available literature including the Shanghai Management Guideline for COVID. We should not re-invent the wheel, but learn from the experience of others around the world. It is important to recognize that COVID-19 does not cause your "typical ARDS"… this disease must be treated differently and it is likely we are exacerbating this situation by causing ventilator induced lung injury. This is a very fluid situation; therefore, we will be updating the guideline as new information emerges. Please check on the EVMS website for updated versions of this protocol.

EVMS COVID website: https://www.evms.edu/covid-19/medical_information_resources/
Short url: evms.edu/covidcare

"If what you are doing ain't working, change what you are doing"

Dr AB (NYC).

"We have zero success for patients who were intubated. Our thinking is changing to postpone intubation to as long as possible, to prevent mechanical injury from the ventilator. These patients tolerate arterial hypoxia surprisingly well. Natural course seems to be the best."

This is not your "typical ARDS". Mechanical Ventilation may be doing harm. We need to think of alternative treatment strategies.

Suggested approach to prophylaxis and treatment of COVID-19

Prophylaxis

While there is very limited data (and none specific for COVID-19), the following "cocktail" may have a role in the prevention/mitigation of COVID-19 disease, especially amongst the most vulnerable citizens in our community; i.e. those over the age of 60 years and those with medical comorbidities. While there is no high level evidence that this cocktail is effective; it is cheap, safe and should be readily available. So what is there to lose?

- Vitamin C 500 mg BID and Quercetin 250-500 mg BID
- Zinc 75-100 mg/day (acetate, gluconate or picolinate). Zinc lozenges are preferred. After 1-2 months, reduce the dose to 30-50 mg/day.
- Melatonin (slow release): Begin with 0.3mg and increase as tolerated to 1-2 mg at night
- Vitamin D3 1000-4000 u/day (optimal dose unknown). Likely that those with baseline low 25-OH vitamin D levels and those > living at 40^{o} latitude will benefit the most.

Mildly Symptomatic patients (on floor):

- Vitamin C 500mg BID and Quercetin 250-500 mg BID (if available)
- Zinc 75-100 mg/day
- Melatonin 6-12 mg at night (the optimal dose is unknown)
- Vitamin D3 1000-4000 u/day
- Enoxaparin 40-60mg day (if not contraindicated; dose adjust with CrCl < 30ml/min)
- *Optional* (and if available): Chloroquine 500 mg PO BID for 5 days or hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days
- Observe closely.
- N/C 2L /min if required (max 4 L/min; consider early t/f to ICU for escalation of care).
- Avoid Nebulization and Respiratory treatments. Use "Spinhaler" or MDI and spacer if required.
- **Avoid non-invasive ventilation**
- T/f EARLY to the ICU for increasing respiratory signs/symptoms.

Respiratory symptoms (SOB; hypoxia- requiring N/C ≥ 4 L min: admit to ICU):

Essential Treatment

1. Chloroquine 500 mg PO BID for 5 days or hydroxychloroquine 400mg BID day 1 followed by 200mg BID for 4 days.
2. Ascorbic acid (Vitamin C) 3g IV q 6 hourly until extubated or for at least 7 days. Early termination may result in a rebound effect (see Figure below): Also see dosage adjustment and caution with POC glucose testing (below).
3. Anticoagulation. Unless contraindicated we suggest FULL anticoagulation (on admission to the ICU) with enoxaparin, i.e 1 mg kg s/c q 12 hourly (dose adjust with Cr Cl < 30mls/min). Heparin is suggested with CrCl < 15 ml/min. Alternative approach: Half-dose rTPA: 25mg of tPA over 2 hours followed by a 25mg tPA infusion administered over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg followed by full anticoagulation. On transfer to floor, consider reducing enoxaparin to 40-60 mg /day.
4. Corticosteroids: Hydrocortisone 50 mg q 6 for 7 days or methylprednisolone 60mg IV daily for 7 days.

Optional Treatment Components (the Full Monty)

5. Thiamine 200mg q 12 (PO or IV).
6. Azithromycin 500 mg day 1 then 250 mg for 4 days (has immunomodulating properties including downregulating IL-6; in addition Rx of concomitant bacterial pneumonia).
7. Melatonin 6-12 mg at night (the optimal dose is unknown).
8. Zinc 75-100 mg daily.
9. Magnesium: 2 g stat IV. Keep Mg between 2.0 and 2.4 mmol/l. Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc).
10. Broad-spectrum antibiotics if superadded bacterial pneumonia is suspected based on procalcitonin levels and resp. culture (no bronchoscopy).
    Co-infection with other viruses appears to be uncommon, however a full respiratory viral panel is still recommended. Superadded bacterial infection is reported to be uncommon (however, this may not be correct).
11. Maintain *EUVOLEMIA* (this is not non-cardiogenic pulmonary edema). Due to the prolonged "replicative phase" with flu-like symptoms (6-8 days) patients may be volume depleted. Cautious rehydration with 500 ml boluses of Lactate Ringers may be warranted, ideally guided by non-invasive hemodynamic monitoring. Diuretics should be avoided unless the patient has obvious intravascular volume overload.
12. Early norepinephrine for hypotension. While the angiotenin II agonist Giapreza ™ has a limited role in septic shock, this drug may uniquely be beneficial in patients with COVID-19 (downregulates ACE-2).
13. *Optional:* Atorvastatin 40-80 mg/day. Of theoretical but unproven benefit. Statins have been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. Statins have pleotropic anti-inflammatory, immunomodulatory, antibacterial and antiviral effects. In addition, statins decrease expression of PAI-1.
14. *Optional:* Tocilizumab (if available) may have a role in cytokine storm (specific IL-6 inhibitor).
15. Corticosteroids:
    a. The only study on the use of corticosteroids and COVID-19 (from Wuhan) demonstrates a marked mortality reduction with methylprednisolone (60mg daily for 7 days). It appears that BOTH corticosteroids AND vitamin C are required to down-regulate the cytokine storm.
    b. During the early viral replicative stage, corticosteroids should be avoided.
    c. During the hyperimmune/hypercoagulable phase (day 6-8 onward) in patients with hypoxia: Hydrocortisone 50mg IV q 6 or methylprednisolone for 7 days is suggested.
    d. Patients may evolve into an HLH/cytokine vortex phase, marked by increasing ferrin, CRP, IL-6 and worsening oxygenation. These patients may benefit from high dose methylprednisolone. (dose?? 200-500 mg q 12).
16. Consider plasma exchange for cytokine storm/HLH picture. The use of CVVH filters that remove cytokines should also be considered.

17. Escalation of respiratory support (steps); ***Try to avoid intubation if at all possible***
    - Accept "permissive hypoxemia" (keep O2 Saturation > 86%)
    - N/C 1-6 L/min
    - High Flow Nasal canula (HFNC) up to 60-80 L/min
    - Trial of inhaled Flolan (epoprostenol)
    - Attempt proning (cooperative proning; see Figure)
    - Intubation … by Expert intubator; Rapid sequence. No Bagging; Full PPE. Crash/emergency intubations should be avoided.
    - Volume protective ventilation; Lowest driving pressure and lowest PEEP as possible. Keep driving pressures < 15 cmH_2O.
    - Moderate sedation to prevent self-extubation
    - Trial of inhaled Flolan (epoprostenol)
    - Prone positioning
    - ?? ECMO < 60 yrs. and no severe commodities/organ failure.

    There is widespread concern that using HFNC could increase the risk of viral transmission. There is however, no evidence to support this fear. HFNC is a better option for the patient and the health care system than intubation and mechanical ventilation. CPAP/BiPAP may be used in select patients, notably those with COPD exacerbation or heart failure.

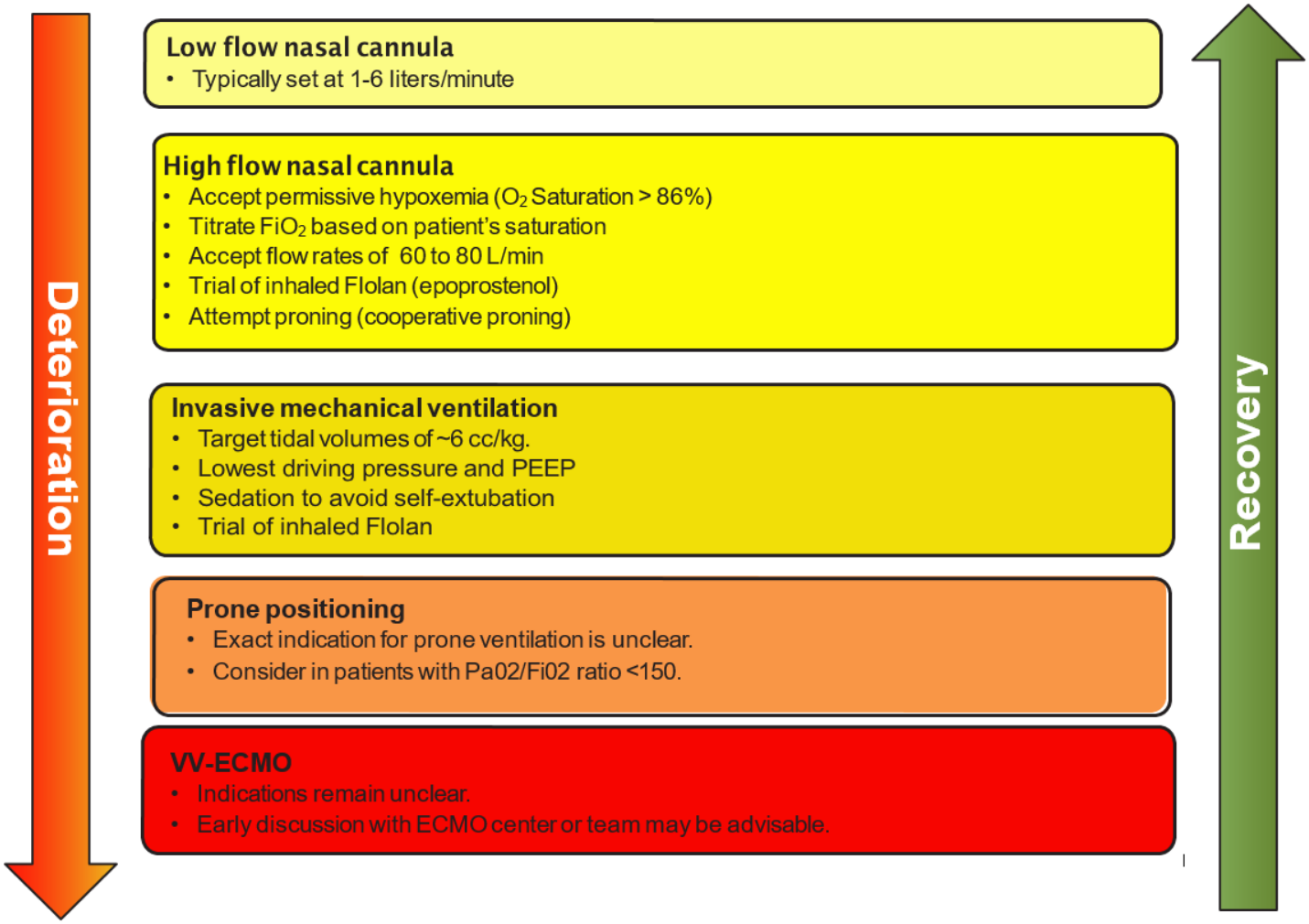
    A group of patients with COVID-19 deteriorates very rapidly (see graphic below). Intubation and mechanical ventilation may be required in these patients.

18. Monitoring

- Daily: PCT, CRP, IL-6, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer, Mg, CRP and Ferritin are good biomarkers and track disease severity. Thromboelastogram (TEG) on admission and repeated as indicated.
- In patients receiving IV vitamin C, the Accu-Chek™ POC glucose monitor will result in spuriously high blood glucose values. Therefore, a laboratory glucose is recommended to confirm the blood glucose levels.
- Monitor QTc interval if using chloroquine/hydrochloroquine and azithromycin and monitor Mg++ (torsades is uncommon in monitored ICU patients)
- No routine CT scans, follow CXR and chest ultrasound.
- Follow ECHO closely; Pts develop a severe cardiomyopathy.

General schema for respiratory support in patients with COVID-19

Try to avoid intubation if possible

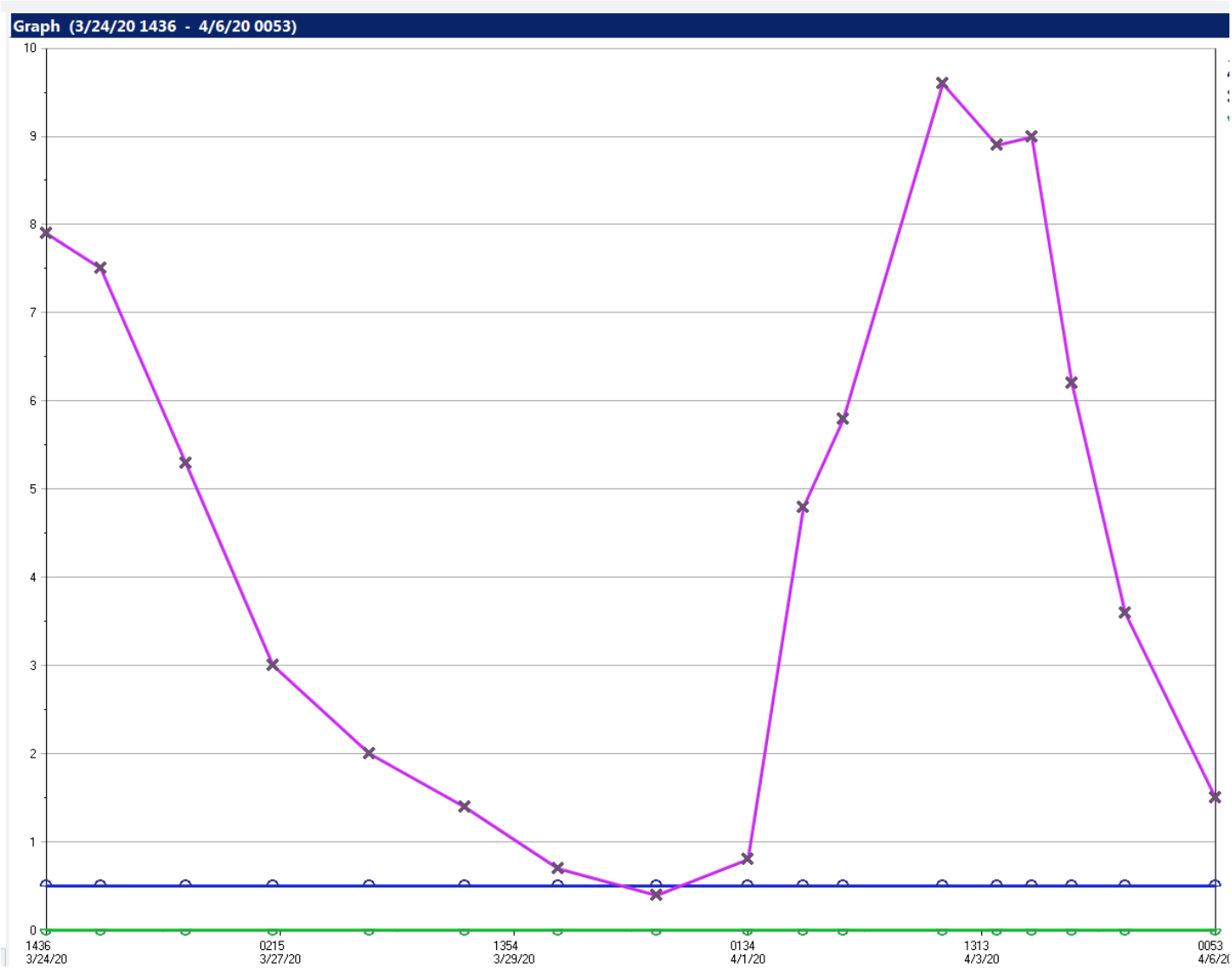


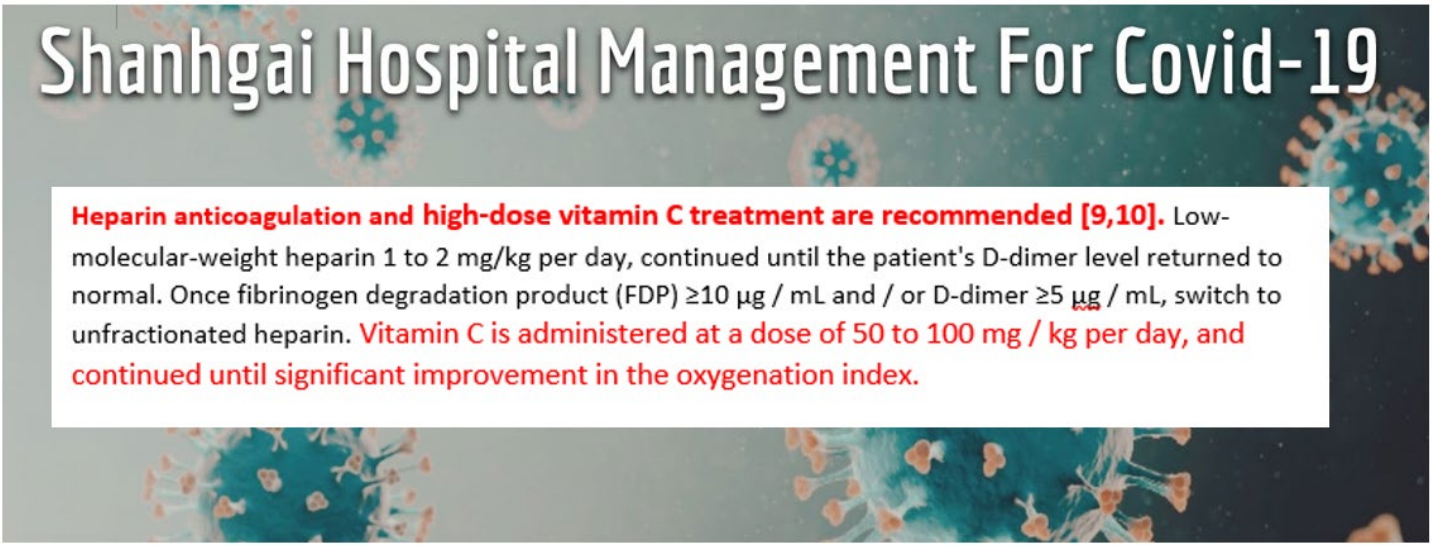
A few General thoughts:

1. We are facing a Global Health Crisis of unimaginable magnitude. We are all in this together. We need to break down the barriers to solving this crisis. We need to act decisively and immediately; there is no time to lose. Patients are dying needlessly.
2. The attack rate of COVID-19 is calculated using mathematical models; estimates of the basic reproduction number (R0) of 2–3, suggests that 50–60% of the entire world population will eventually be infected because most humans are naive to the new virus; this is a sobering and frightening statistic.
3. COVID-19 results in a dysregulated and exuberant immune response. Patients requiring intensive care have significantly higher levels of IL-6, IL-10 and TNFα and fewer CD4+ and CD8+ T cells. Downregulating the **cytokine storm** is an essential component of the treatment of severe COVID-19 disease.
4. COVID-19 patients developed a severe hypercoagulable state (see Figures). This likely results in pulmonary micro- and macrovascular disease which may lead to hypoxia/pulmonary shunting. These patients also have an increased risk of pulmonary and cerebral emboli (see Figure).
5. The course of the disease is quite predictable. Acute respiratory failure occurs on day 6-8 concomitant with the cytokine storm and hypercoagulable state. In those patients requiring supplemental oxygen, we need to be very aggressive to prevent disease progression and mechanical ventilation. Once intubated, the mortality is high.
6. This is not your "typical" ARDS… but something else (weird). Chest CT shows bilateral, discreet, irregular, multilobar "ground-glass" infiltrates and not the typical dependent air-space consolidation ("sponge lung/baby lung") characteristic of "typical" ARDS. Physiologically "COVID-19 ARDS" is different; our preliminary data suggests that lung water (EVLWI) is normal or only marginally increased (therefore by definition this is NOT ARDS). Furthermore, lung compliance is quite good yet there is severe hypoxia (due to shunting). This suggest microvascular and/or macrovascular disease… or some other alternative explanation. In addition, pulmonary embolism appears to be very common in these patients and may be the cause of sudden death (see Figure). The typical ARDS that develops over time (see Figures) is due mechanical ventilator induced lung injury and/or superadded bacterial pneumonia.
7. The World Health Organization has now launched the SOLIDARITY trial to investigate four potential treatments: remdesivir, chloroquine/hydroxychloroquine; lopinavir and ritonavir; and lopinavir and ritonavir plus interferon-β. It will likely take many months before this study is completed and the results are available; many tens of thousands of patients will die from COVID-19 related complications in the intervening time.
8. Good medical practice and the best interests of the patient require that physicians use legally available drugs according to their best knowledge and judgement. If physicians use a product for an indication not currently approved, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.
9. It is important to stress that there is no known drug/treatment that has been proven unequivocally to improve the outcome of COVID-19. This, however, does not mean we should adopt a nihilist approach and limit treatment to "supportive care". Furthermore, it is likely that there will not be a single "magic bullet" to cure COVID-19. Rather, we should be using multiple drugs/interventions that have synergistic and overlapping biological effects that are safe, cheap and "readily" available. The impact of COVID-19 on middle- and low-income countries will be enormous; these countries will not be able to afford expensive designer molecules.

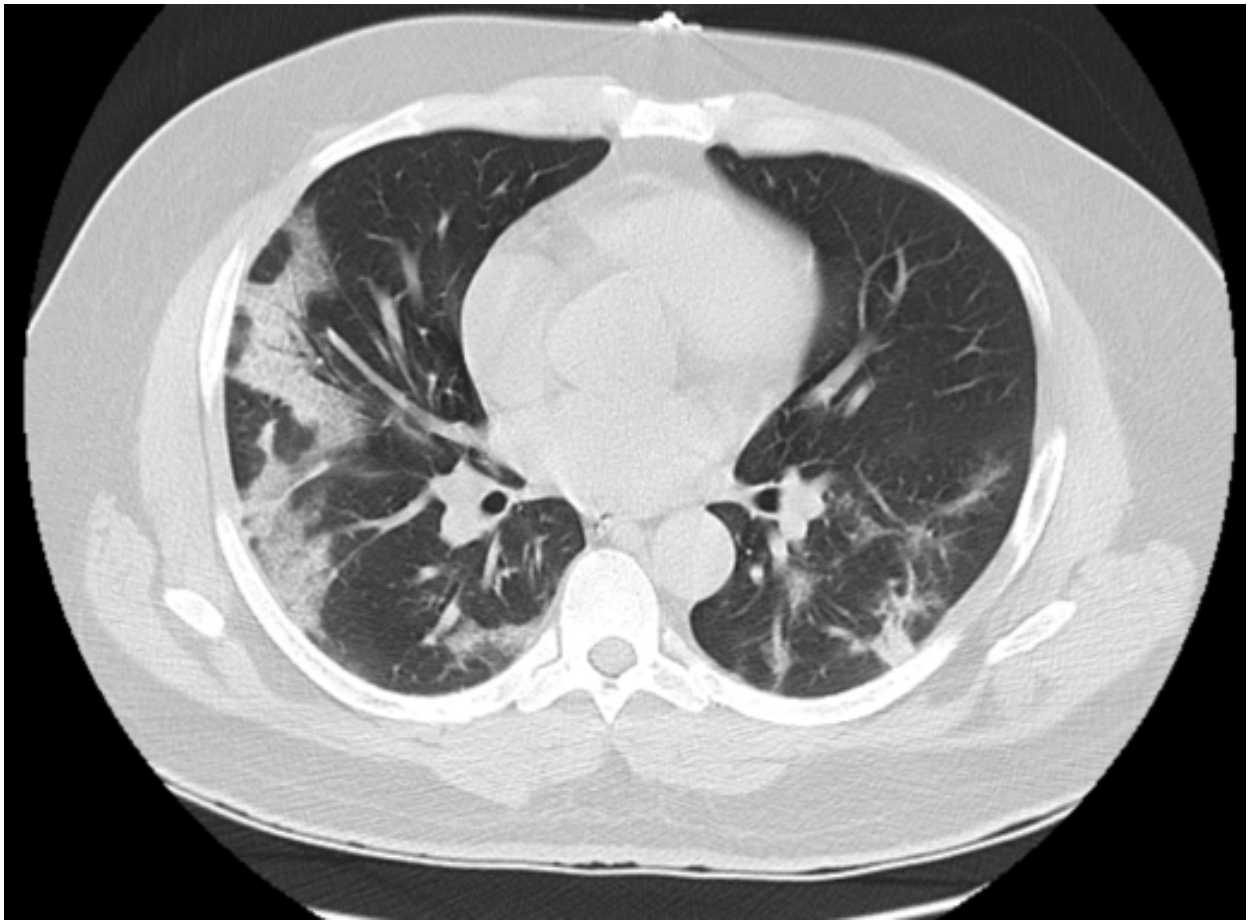
10. Preliminary data suggests that chloroquine and hydroxychloroquine decrease the duration of viral shedding. In addition, chloroquine has favorable immunomodulating properties including inhibition of PAI-1 expression. These agents are now FDA approved for the treatment of COVID-19. These agents (if available) could be used to mitigate/curtail the spread of this virus and could be used in elderly patients with comorbidities at risk of progression and death.
11. Zinc (Zn^{++}) inhibits viral RNA dependent RNA polymerase (replicase). Chloroquine and hydroxychloroquine are potent Zn ionophores that increase intracellular Zn concentrations.
12. Ascorbic acid has numerous proven biological properties (anti-inflammatory, anti-oxidant, immune enhancing, antiviral) that are likely to be of benefit in patients with COVID-19 disease. Furthermore, it is important to stress that ascorbic acid has proven synergistic effects when combined with corticosteroids. Therefore, steroids are recommended in patients with COVID-19 and respiratory failure. The benefit of ascorbic acid (without corticosteroids) in patients with severe respiratory failure appears to be limited. While the optimal dose of ascorbic acid is unknown, we suggest 3 g IV q 6 hourly. It should be noted that in the presence of free iron (released from ferritin) ascorbic acid may potentially have pro-oxidant effects. Therefore, the trends in CRP and ferritin need to be closely monitored; in those patients who ferritin AND CRP are increasing, reducing the dose to 1.5g q 6 hourly should be considered.
13. Very recent data suggests that in addition to being a potent anti-oxidant, melatonin may have direct antiviral effects against COVID-19. In healthy people, melatonin levels plummet after the age of 40 years. This may partly explain the increased risk of death in patients with COVID-19 who are over the age of 40. Melatonin may therefore have a role in both the prevention and treatment of COVID-19.
14. Vitamin D has important immune-enhancing effects. Much of the population, especially the elderly have sub-optimal vitamin D levels, particularly during the winter months. Low vitamin D levels have been shown to increase the risk of developing viral upper respiratory tract infections. Therefore, prophylactic vitamin D should be considered especially in the elderly.
15. Quercetin is a plant phytochemical. Experimental and early clinical data suggests that this compound has broad antiviral properties (including against coronavirus) and acting at various steps in the viral life cycle. Quercetin is a potent inhibitor of heat shock proteins (HSP 40 and 70) which are required for viral assembly. This readily available and cheap plant-derived compound may play a role in the prophylaxis of COVID-19 in high-risk populations.

Premature discontinuation of Corticosteroids and Vitamin C (after 4 days), and the effect of reinitiation of this Vital Combination on CRP. Clinical course followed CRP profile.

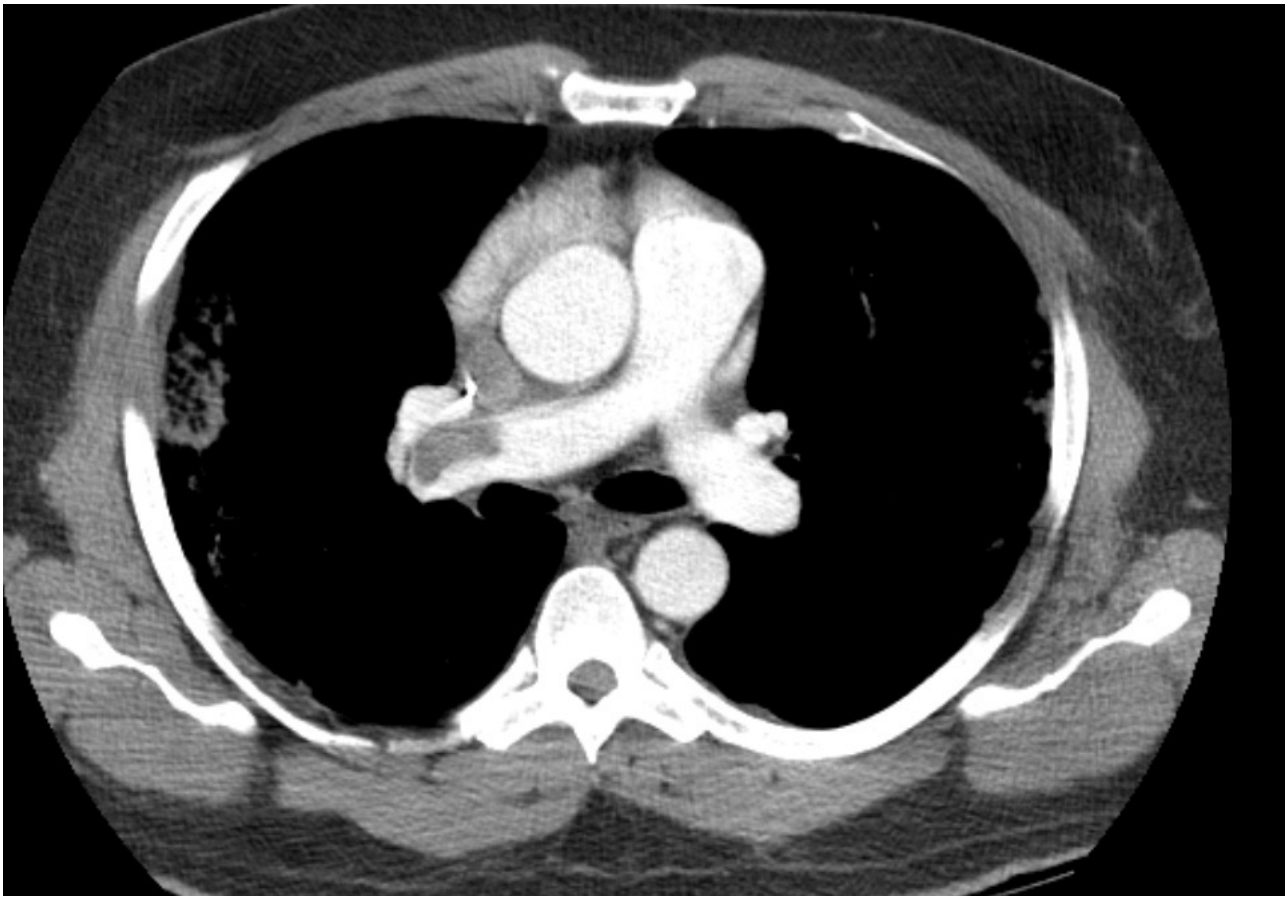




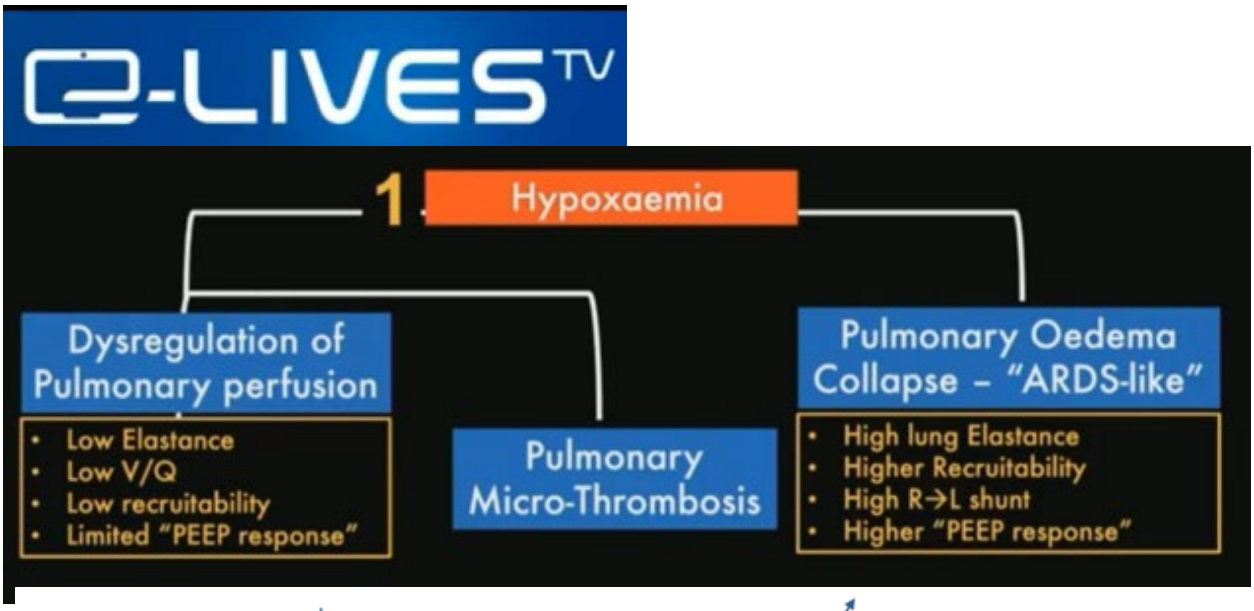
CT scan of Typical COVID-19 Patient



CTPA of 44 yr. old COVID + patient (with no risk factor for DVT/PE) presenting with severe tachycardia



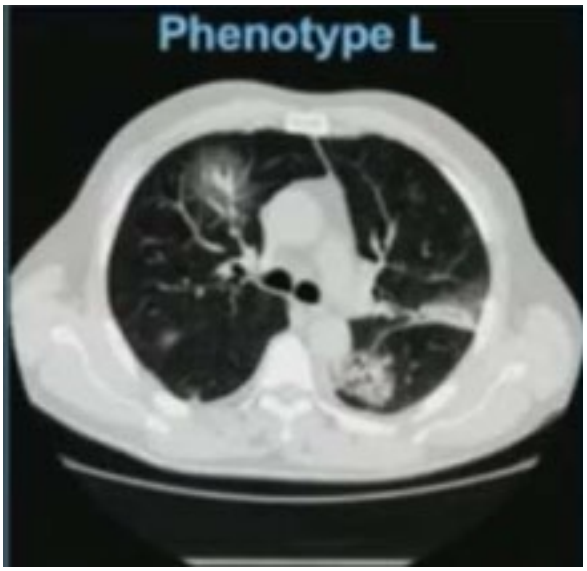
“Cooperative” proning of non-intubated patient

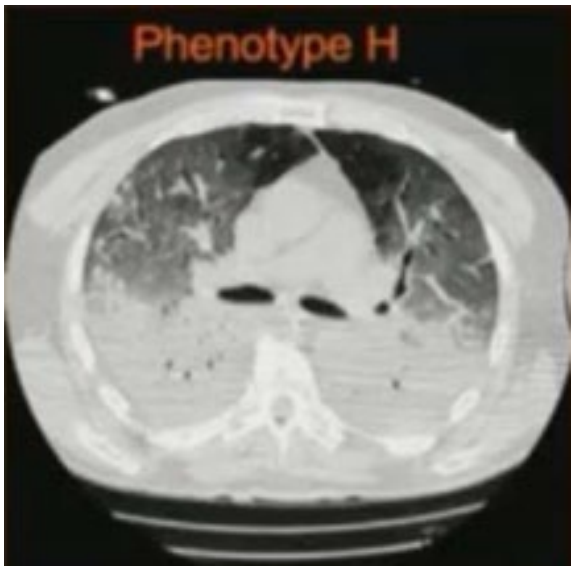


Ventilator induced lung injury/ bacterial pneumonia

L - phenotype

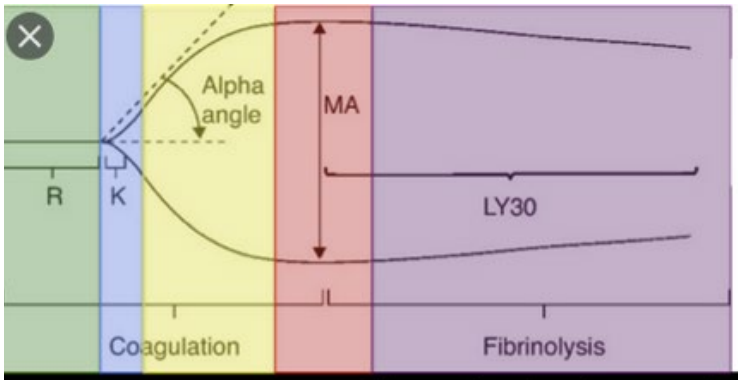
H - phenotype ("typical ARDS")






e-LIVES TV
Disease Course and late "failures"
Severity
Hyperacute:
severe hypoxaemia and breathlessness leading to immediate intubation;
Indolent (improving):
moderate or severe hypoxaemia but only moderate work of breathing.
Biphasic: initial indolent course followed – typically after 5 - 7 days– by an acute deterioration with hyper-inflammation, worsening respiratory failure with bilateral infiltrates and consolidation
Days

Thromboelastogram (TEG) of COVID-19 patient on admission to ICU
Demonstrating marked hypercoagulable state



R.E.B.E.L.EM

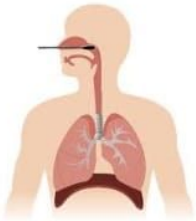
rebelem.com

Thromboelastogram (TEG)

Components	Definition	Normal Values	Problem with...	Treatment
R Time	Time to start forming clot	5 – 10 minutes	Coagulation Factors	FFP
K Time	Time until clot reaches a fixed strength	1 – 3 minutes	Fibrinogen	Cryoprecipitate
Alpha angle	Speed of fibrin accumulation	53 – 72 degrees	Fibrinogen	Cryoprecipitate
Maximum Amplitude (MA)	Highest vertical amplitude of the TEG	50 – 70 mm	Platelets	Platelets and/or DDAVP
Lysis at 30 Minutes (LY30)	Percentage of amplitude reduction 30 minutes after maximum amplitude	0 – 8%	Excess Fibrinolysis	Tranexemic Acid and/or Aminocaproic Acid

Covid-19 shedding

No. of samples positive for SARS-CoV-2 by RT-PCR/ total no. of samples in aggregated studies (%)

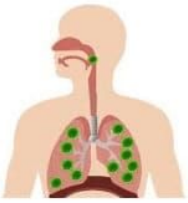


Nasopharyngeal swabs: 31/35 (88.6%)

Zou L et al, NEJM, 2020
Kujawski et al, medRxiv, 2020
Chan JF et al, Lancet

Conjunctival swabs: 2/188 (1.1%)

Xu L et al, medRxiv, 2020
Zhang X et al, medRxiv, 2020
Sun X et al, medRxiv, 2020



Sputum: 48/49 (97.9%)

Pan Y et al, Lancet Infect Dis, 2020
Kujawski et al, medRxiv, 2020
Chen L et al, Am J Gastroenterol, 2020
Lin C et al, medRxiv, 2020
Chan JF et al, Lancet, 2020

Throat swabs: 45/75 (60%)
Post. throat saliva: 31/35 (88.6%)
Oral swabs: 7/15 (46.7%)

Pan Y et al, Lancet Infect Dis, 2020
Zou L et al, NEJM, 2020
Kujawski et al, medRxiv, 2020
Chen L et al, Am J Gastroenterol, 2020
Lin C et al, medRxiv, 2020
To KKW et al, Lancet Infect Dis, 2020
To KKW et al, Clin Infect Dis, 2020
Chan JF et al, Lancet, 2020

Stool: 34/48 (70.8%)
Anal swabs: 16/78 (20.5%)
Rectal swabs: 4/23 (17.4%)

Cui P et al, medRxiv, 2020
Chen W et al, Emerg Microbes Infect
Pan Y et al, Lancet Infect Dis, 2020
To KKW et al, Lancet Infect Dis, 2020
Kujawski et al, medRxiv, 2020
Xie C et al, IJID, 2020
Young BE et al, JAMA, 2020
Zhang J et al, JMV, 2020

Urine: 0/76 (0%)

Pan Y et al, Lancet Infect Dis, 2020
To KKW et al, Lancet Infect Dis, 2020
Kujawski et al, medRxiv, 2020
Xie C et al, IJID, 2020
Young BE et al, JAMA, 2020
Wolfel R et al, medRxiv, 2020

Blood: 20/162 (12.3%)

Chen W et al, Emerg Microbes Infect, 2020
To KKW et al, Lancet Infect Dis, 2020
Kujawski et al, medRxiv, 2020
Xie C et al, IJID, 2020
Young BE et al, JAMA, 2020
Chan JF et al, Lancet, 2020
Wolfel R et al, medRxiv, 2020

Vaginal swabs: 0/35 (0%)

Cui P et al, medRxiv, 2020

Found on Internet, source unknown (thank you author)

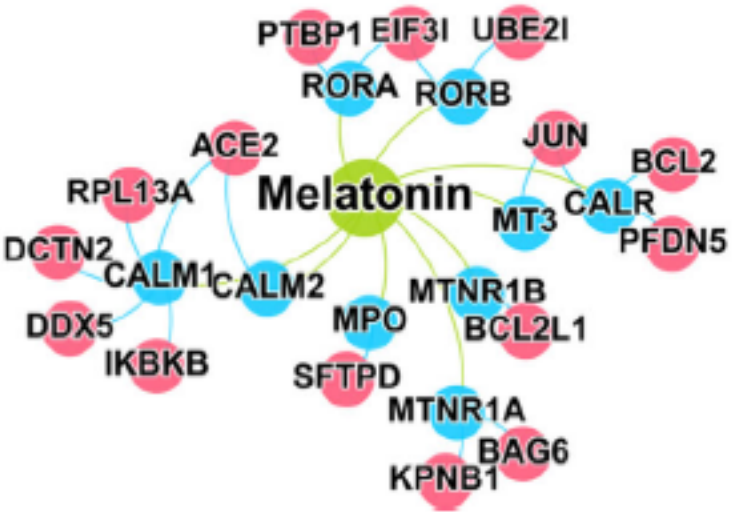
Zhou et al. *Cell Discovery* (2020)6:14
https://doi.org/10.1038/s41421-020-0153-3

Cell Discovery
www.nature.com/celldisc

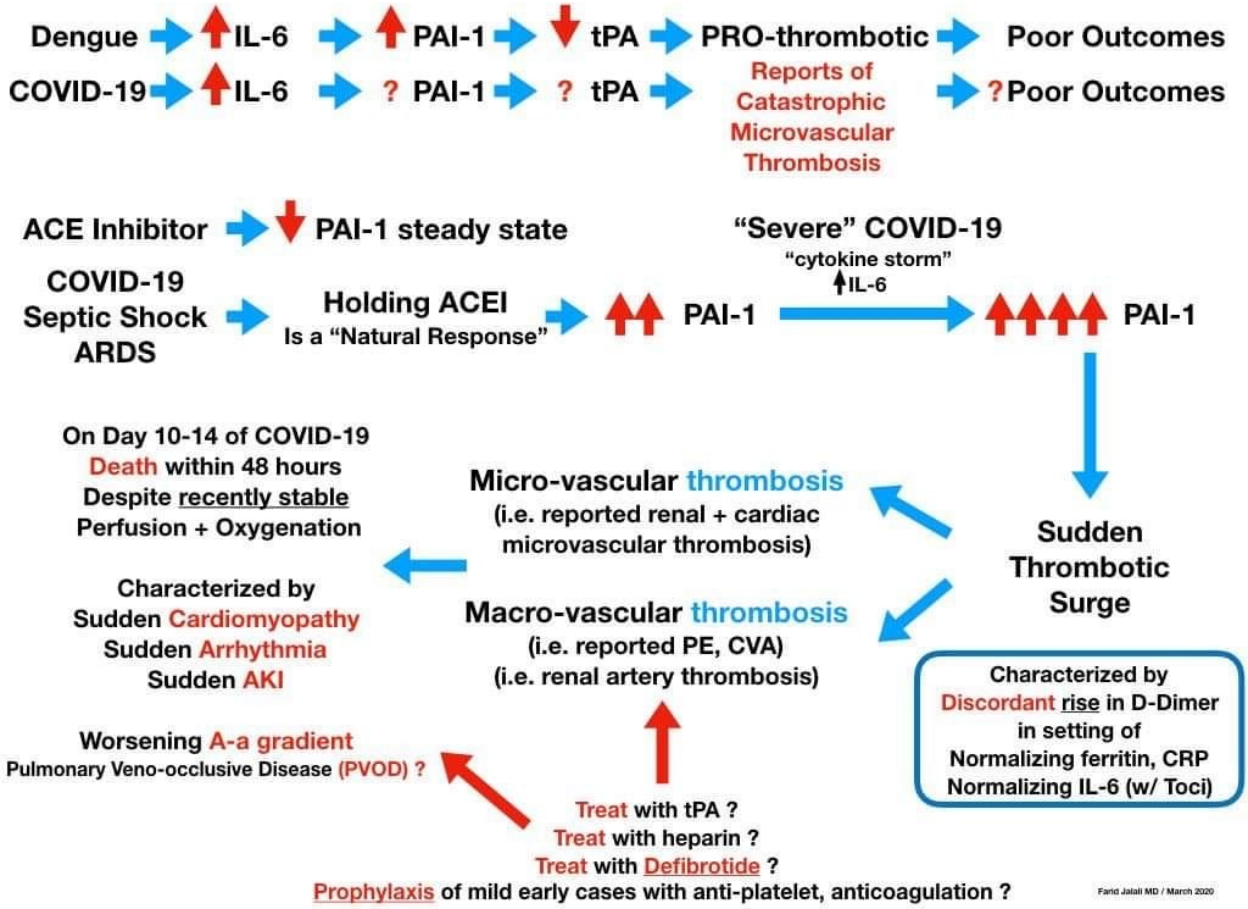
ARTICLE Open Access

Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2

Yadi Zhou[1], Yuan Hou[1], Jiayu Shen[1], Yin Huang[1], William Martin[1] and Feixiong Cheng[1,2,3]



Proposed mechanism of hypercoagulable state.



Courtesy of Farid Jalali, MD Gastroenterologist, California

Do not forget these are our Brothers and Sisters