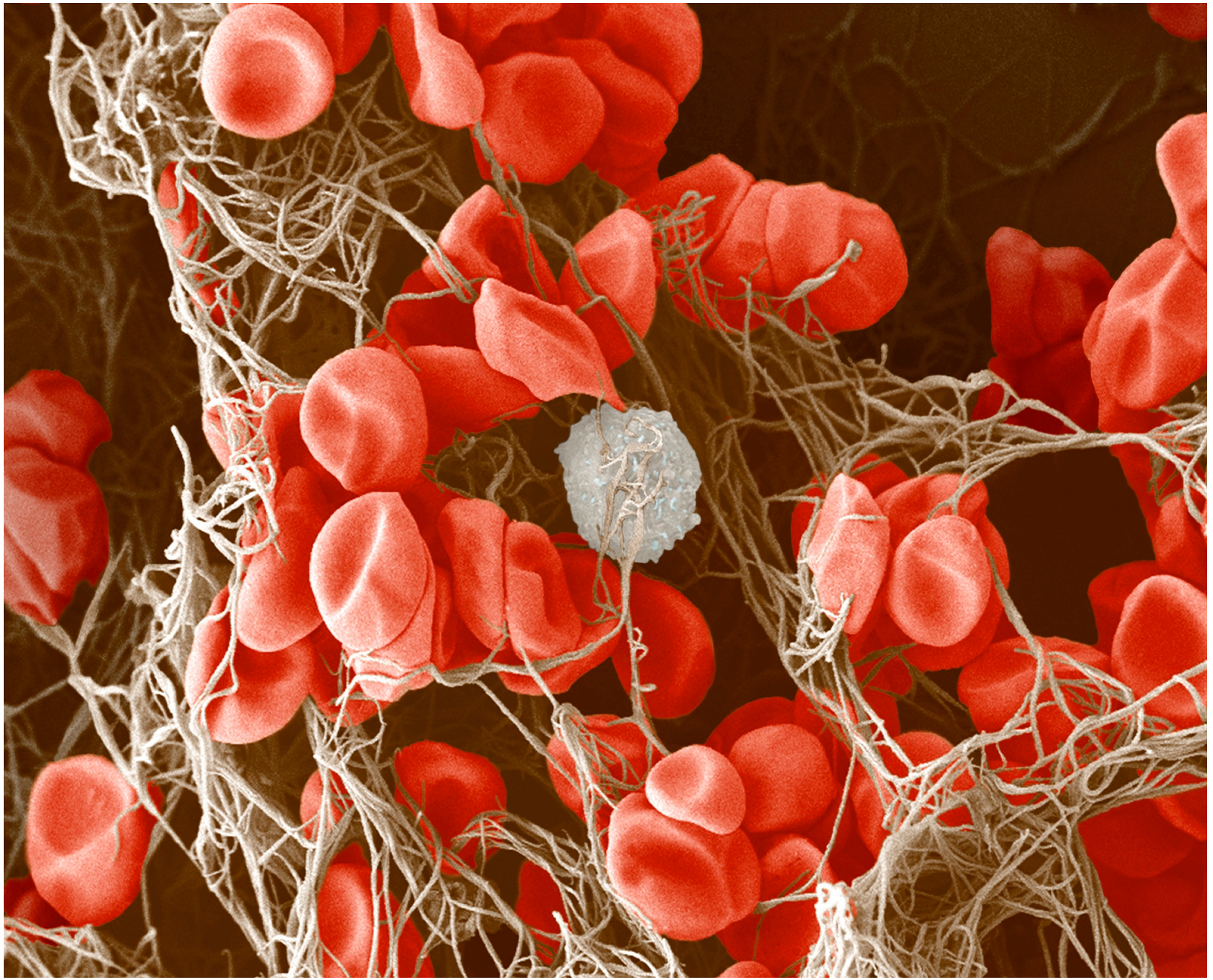

ANTICOAGULANTS IN THE MANAGEMENT OF COVID-19-ASSOCIATED THROMBOSIS

DIVYA JOSHI
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COVID-19

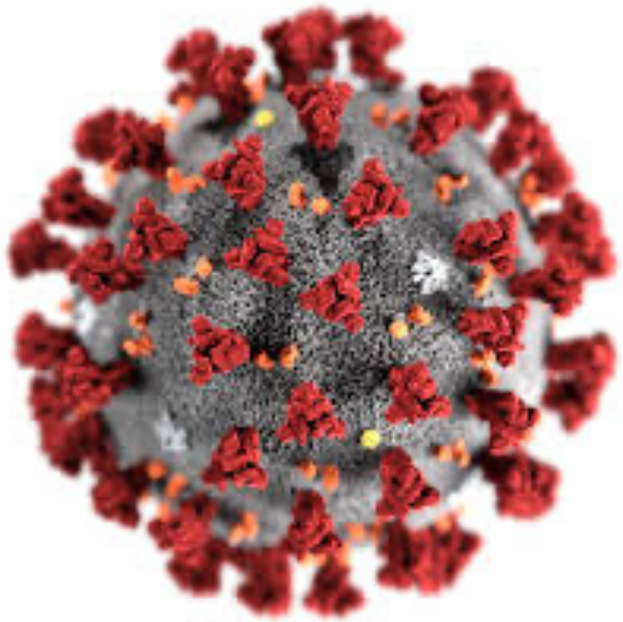
- The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus that has caused a global pandemic in 2020
- In late 2019, the virus was transmitted from an unknown animal to a human in the Huanan seafood market in Wuhan, China
- All coronaviruses are named for their appearance under a microscope: they all have crown-like spikes on the viral surface (corona means crown)
- Currently, there are three vaccines approved namely Pfizer, Moderna and Astra-Zeneca (Oxford)
- Total cases around the world have reached a total of 83 million with 2 million death, while in the US the total number of deaths due to the disease and its complications is over 350 thousand with over 20 million confirmed cases
- Patients are especially susceptible if they are of an advanced age, immunocompromised, or have comorbidities such as diabetes and liver disease
- Ethinic predisposition include higher prevalence in African-American and Southeast Asian populations

COVID-19

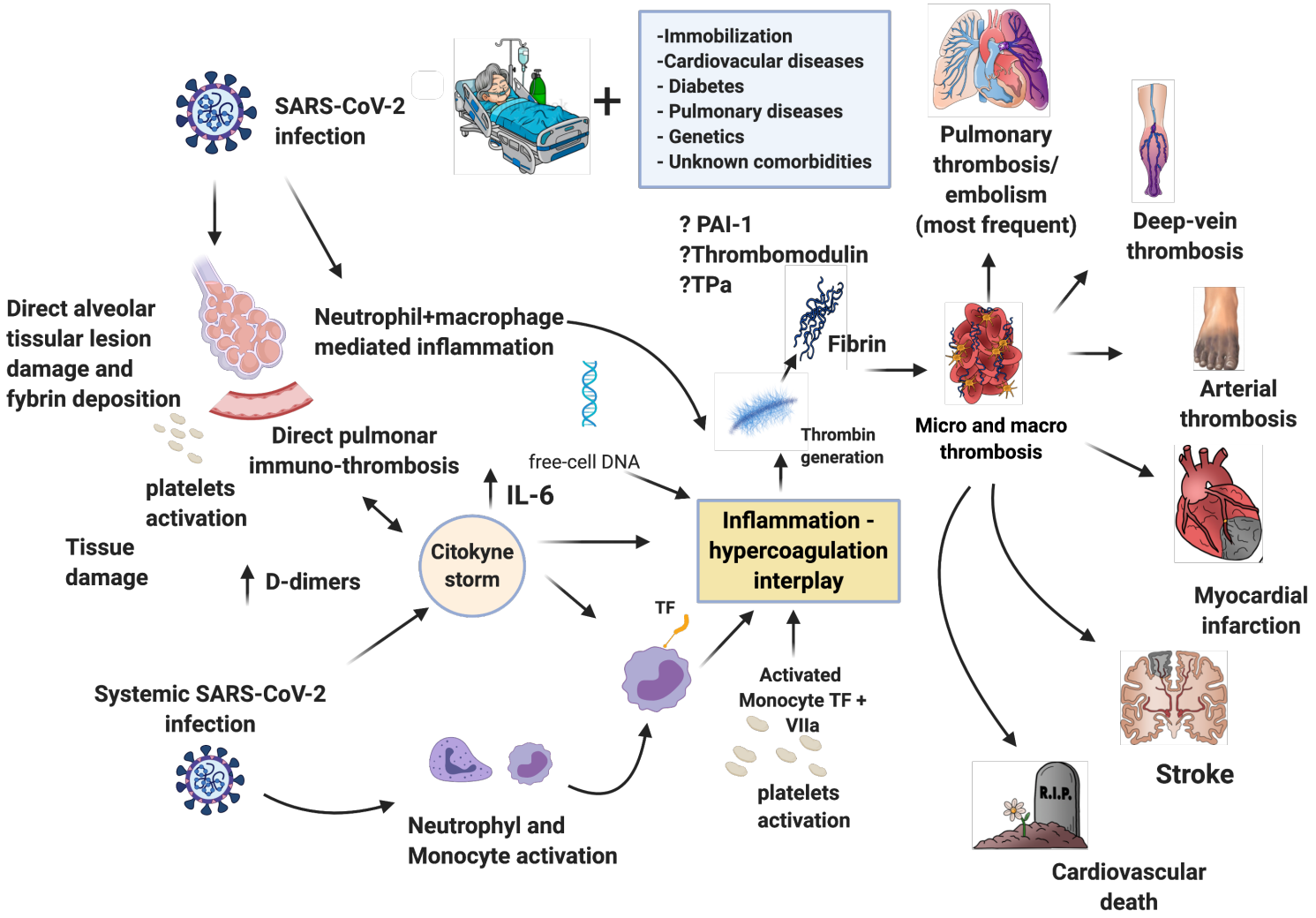
- SARS-CoV-2 mainly targets the upper and lower respiratory tract but also impacts other organ systems
- Respiratory droplets are the primary source of spread, it may also be spread by contact and surfaces
- The incubation period is 14 days
- Symptoms: fever/chills, cough, fatigue, shortness of breath, body aches, loss of taste or smell, sore throat, diarrhea, nausea/vomiting, and congestion
- Complications and comorbidities of SARS-CoV-2: pneumonia, ARDS, kidney failure, cytokine release syndrome, and viral sepsis
- Severe thrombotic complications including both the venous and arterial system and microvascular network have been observed

PATHOPHYSIOLOGY OF COVID-19

- The SARS-CoV-2 virus, like all viruses, is composed of a lipid and protein envelope structure
- The two host-cell receptors that allow SARS-CoV-2 to attach to cells are angiotensin converting enzyme-2 (ACE-2) and transmembrane protease serine 2 (TMPRSS2). The virus employs a spike protein to bind to the human host cells that express ACE-2 cell receptors
- After binding to one of these host cell receptors, the virus makes its way to the cell's nucleus where it hijacks the cell's ribosomes and begins producing viral proteins that in turn create trillions of more viruses
- These viruses primarily affect the lungs, causing inflammation and pneumonia, but also invade other tissues

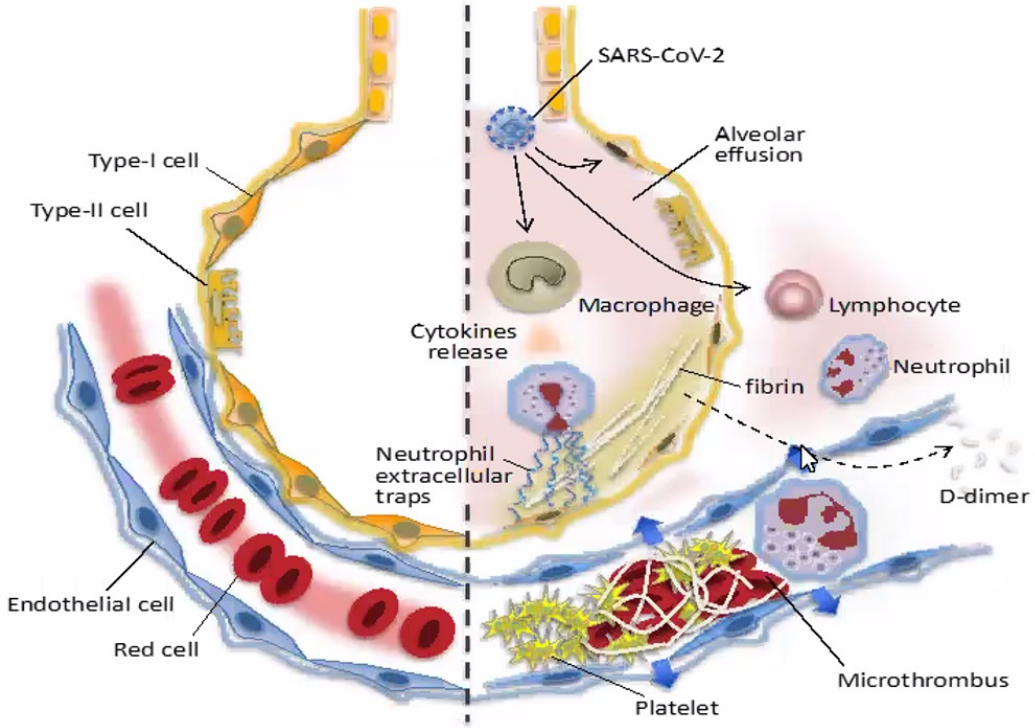


COVID-19 AND THROMBOTIC RISK



Ramacciotti et al - Evidence-based practical guidance for the antithrombotic management in patients with coronavirus disease (COVID-19) in 2020 – paper in press

COVID-19 AND THROMBOTIC RISK



Iba T, et al, 2020

Radiology: Cardiothoracic Imaging

IMAGES IN CARDIOTHORACIC IMAGING

COVID-19 Complicated by Acute Pulmonary Embolism

Yuanliang Xie, MD • Xiang Wang, MD • Pei Yang, MD • Shutong Zhang, MD

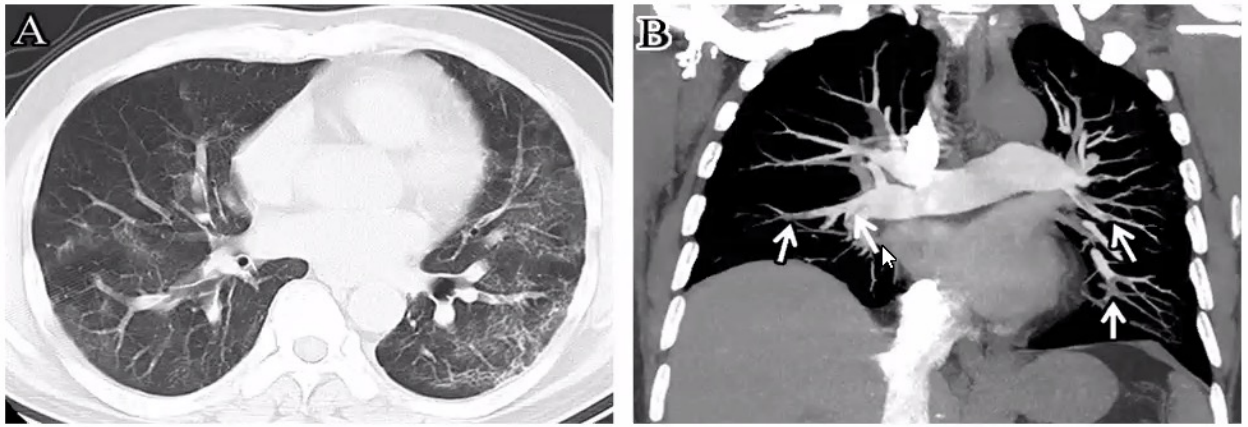
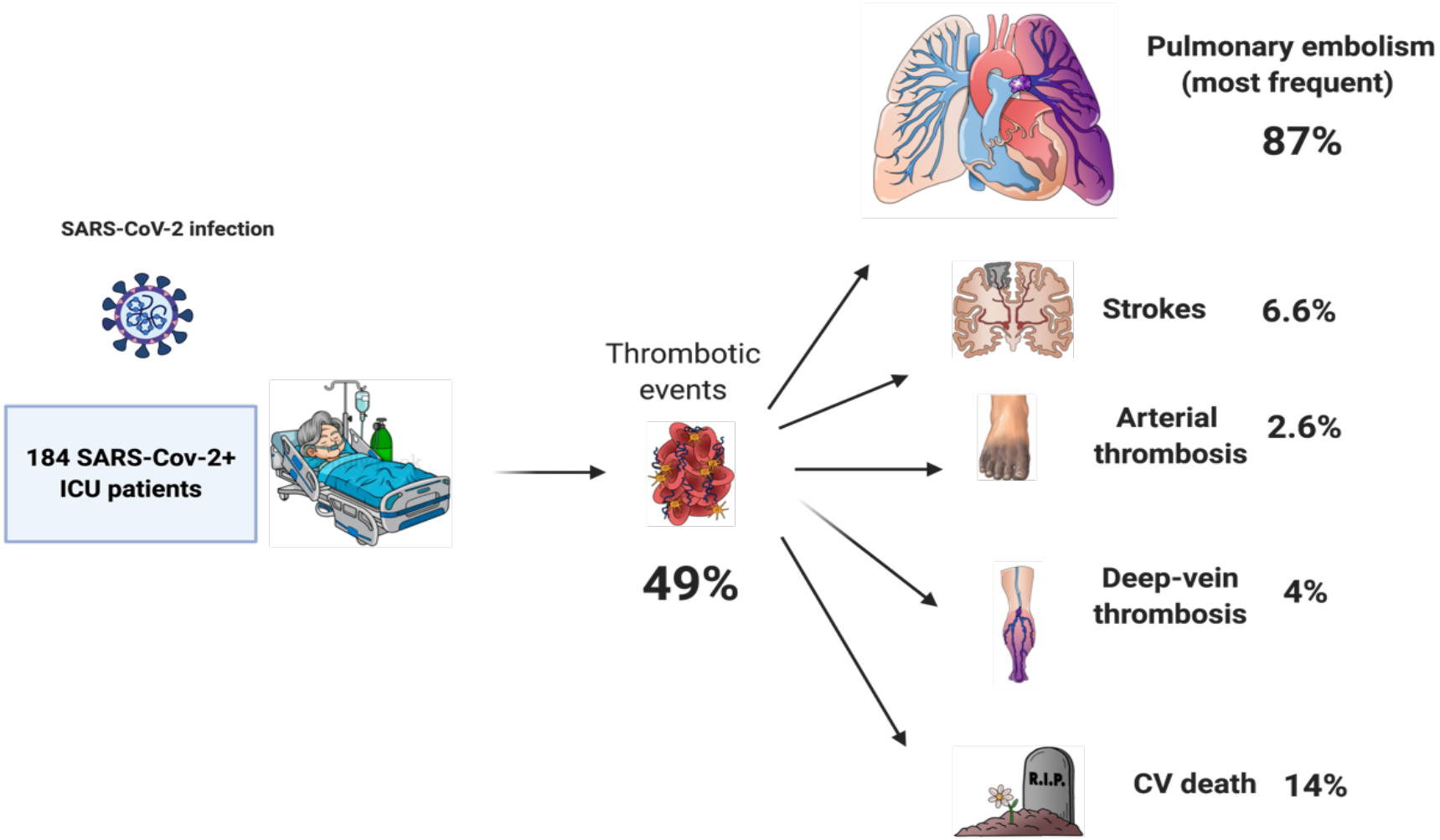


Figure 1: Images in a 57-year-old man with COVID-19 pneumonia. *A*, Axial unenhanced chest CT scan obtained on day 10 after the onset of symptoms shows bilateral areas of peripheral ground-glass opacities. *B*, Coronal thick maximum intensity projection slab of CT pulmonary angiography demonstrates multiple bilateral filling defects (white arrows) involving lobar, segmental, and subsegmental branches of the pulmonary artery.

Xie Y. Published Online: March 16, 2020
https://doi.org/10.1148/ryct.2020200067

Radiology: Cardiothoracic Imaging

COVID-19 AND THROMBOTIC COMPLICATIONS

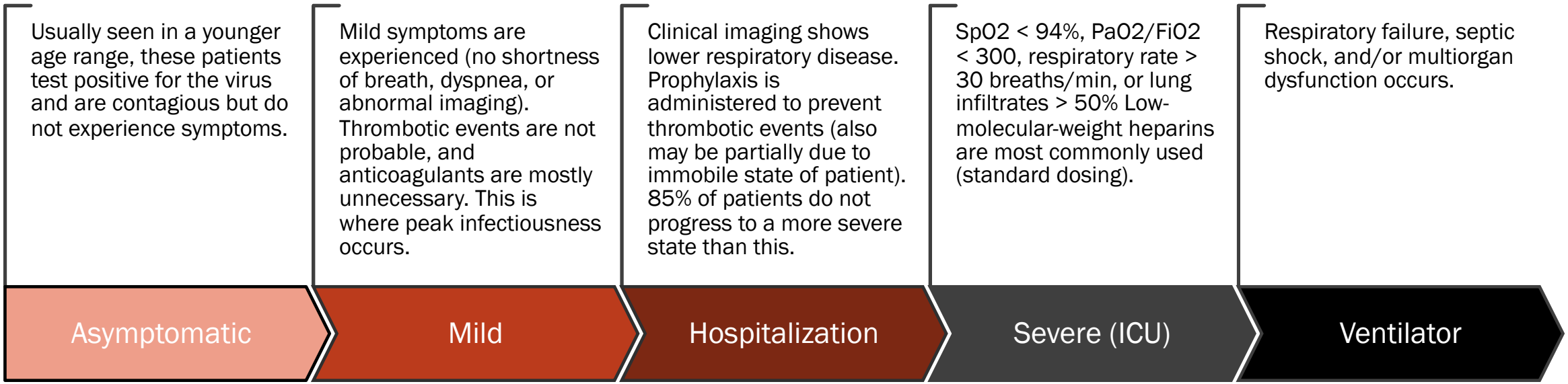


1. Klok FA Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thromb. Res 2020
2. Ramacciotti et al - Evidence-based practical guidance for the antithrombotic management in patients with coronavirus disease (COVID-19) in 2020 – paper in press

COAGULATION AND COVID-19

- There exist links between severe cases of SARS-CoV-2 and viral coagulopathy, causing thrombotic complications such as pulmonary embolism and venous/arterial/microvascular thrombosis that may lead to acute respiratory distress syndrome (ARDS)
- Due to the high concentration of ACE-2 receptors in endothelial cells, severe endothelial injury has also been observed in the lungs
- Unique features of coagulopathy in COVID-19 patients include no underlying lesions and association with DIC
- In order to prevent such thrombotic complications, it is necessary to administer anticoagulants to patients with severe cases of COVID-19, both immediately after being admitted to the hospital and also throughout their treatment
- Anticoagulation is also recommended after the hospital discharge of COVID-19 patients to avoid post COVID synderome

COVID-19 STAGES



- Thrombotic complications are observed during the hospitalization and the severity is increased in advanced stages

HEPARINS AND LOW MOLECULAR WEIGHT HEPARINS

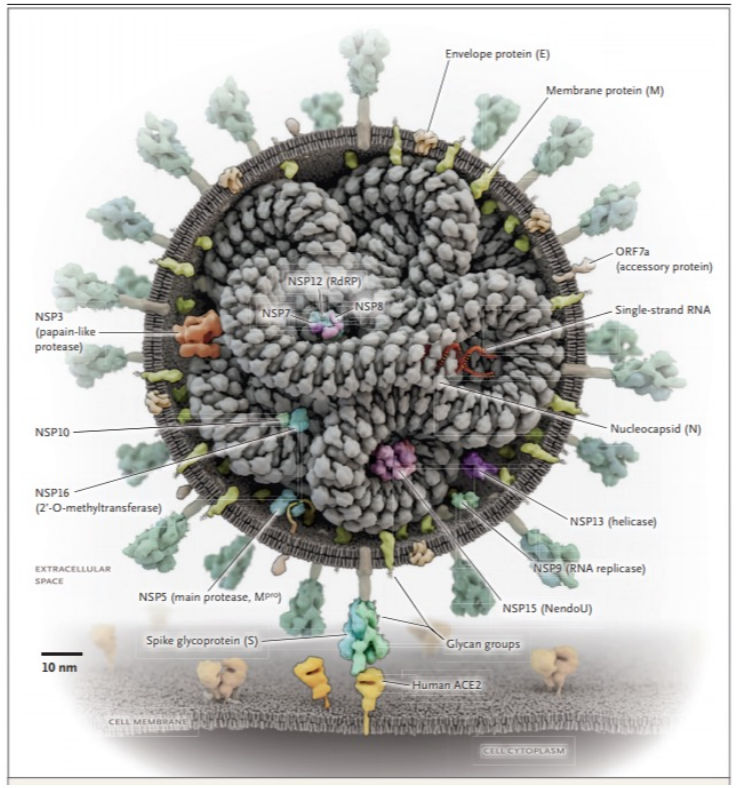
- Unfractionated heparin and low-molecular-weight heparins are the most common anticoagulant agents administered to patients
- They activate antithrombin III, which works to inhibit thrombin and factor Xa so that the coagulation cascade is hindered
- Heparins also produced the release of TFPI, which produces inhibition of tissue factor and mediates anti-inflammatory responses
- Unfractionated and low-molecular-weight heparins have already shown a marked decrease in the risk of thrombotic complications without an increase in the risk of bleeding in SARS-CoV-2 patients
- Currently, several studies are ongoing on heparins for their therapeutic effects in COVID-19

HEPARINS AS ANTI-INFLAMMATORY AGENTS

- In addition to their antithrombotic properties, heparins also act as anti-inflammatory (decreased lung inflammation and improved oxygenation) due to their binding to and neutralization of inflammatory molecules such as inflammatory cytokines
- Additionally, assuming the theory whereby inflammation and thrombin formation are directly correlated, heparin could decrease the inflammatory response by blocking thrombin generation
- As the levels of cytokines in COVID-19 patients (cytokine storm) has been observed to be roughly 50x higher than the amounts in patients of Zika and West Nile virus which may have increased COVID-19 deaths

HEPARINS AS ANTIVIRAL AGENTS

- Another potential attribute of low-molecular-weight heparin is its antiviral ability.
- Low-molecular-weight heparins have already been established as inhibiting production of HIV-1 in vitro from a T cell lymphoma line and phytohemagglutinin-stimulated lymphoblasts.
- A similar effect may be observed in patients with SARS-CoV-2, as unfractionated heparin has been shown to potentially decrease the infectivity of the Covid-19 virus by inhibiting binding between the virus's spike protein and the ACE2 cell receptor.



Recent report showed that the SARS-CoV-2 Spike S1 protein receptor binding domain (attaches to ACE2 cell receptor) interacts with heparin

www.biorxiv.org/content/10.1101/2020.02.29.971093v1

DOSING OF HEPARINS IN COVID-19 PATIENTS

- The optimal dosage of heparins in Covid-19 patients remains unknown, many trials have used a median dose of 60 mg of low-molecular-weight heparin (although some argue for a larger dose)
- To replace LMWH in critical cases, heparin 5000 units SQ BID may be used
- A study in two French intensive care units examined 26 consecutive patients with COVID-19 at a severe stage. 31% were treated with prophylactic anticoagulation, while 69% were treated with therapeutic anticoagulation. The overall rate of VTE was 69%, showing high rates of thrombosis in hospitalized COVID-19 patients
- Escalation of prophylaxis in some cases would require an assessment of the patient's BMI in order to establish a threshold for increased dosing
- Risk assessment (including risk of thrombotic complications and bleeding) has also been utilized in several institutions to determine dosing
- Both the ASH and ISTH documents recommend that all hospitalized COVID patients undergo prophylaxis, but the ASH document also suggest that "therapeutic anticoagulation is not required unless another indication for therapeutic anticoagulation is documented."
- The NIH sponsored study was designed to demonstrate the therapeutic befits of heparin, this study is being reviewed due to potential bleeding risk with heparins due to dosage issues

HEPARINS- IN HOSPITAL PROPHYLAXIS DOASES

UFH 5.000 IU SC q12/12hrs or q8/8 hrs

Enoxaparin 40 mg SC once-daily

Fondaparinux 2.5 mg SC once-daily

Kalodiki E, Fareed J, **Ramacciotti E,** A consensus conference on complex biologics and low molecular weight heparins. Int Angiol. 2010 Apr;29(2):193-6.

HEPARINS – VTE TREATMENT DOSES

UFH

Continous I.V. infusion:
- Inicial dose: 5.000 -10.000 units IV
-Maintenance: 20.000 - 40.000 IU IV (aPTT)

Enoxaparin

1 mg/kg BID
1.5 mg/kg SC OD

Fondaparinux

5 mg SC OD <50 Kg
7.5 mg SC OD 50-100 Kg
10 mg SC OD > 100 Kg

Kalodiki E, Fareed J, **Ramacciotti E,** A consensus conference on complex biologics and low molecular weight heparins. Int Angiol. 2010 Apr;29(2):193-6.

STUDY ON DOSAGE ESCALATION

- Although there is a lack of randomized trials related to elevation of prophylactic dosing, a retrospective study looked at 2,773 patients with laboratory-confirmed COVID.
- Out of the patients on the ventilator, the in-hospital mortality was 29.1% with a median survival of 21 days for those treated with full dose anticoagulation as compared to 62.7% with a median survival of 9 days in people who did not receive treatment dose anticoagulation.
- However, a direct link between anticoagulant dose and mortality rate cannot be established because patients on full-dose anticoagulation would almost certainly have already been given more aggressive therapy such as perhaps remdesivir and hydroxycholorquine, among other therapies.

OTHER HEPARIN RELATED AGENTS

- Danaparoid: It is mixture heparan sulfate, dermatan sulfate and chondroitin sulfate in amounts of approximately 84%, 12% and 4%, respectively
- Sulodexide: It is composed of low molecular weight heparin (LMWH) and dermatan sulfate (DS). This mixture contains 80% iduronyl glycosaminoglycan sulfate (IGS, known as fast-moving heparin [FMH] because of its electrophoretic mobility in the barium propane diamine system), and 20% DS. Sulodexide is orally effective
- Pantosan Polysulfate: It is a sulfated polymer, primarily composed of 5 member ring pentosan polysulfate
- Pentasaccharide: It represent a synthetic heparin oligosaccharide with strong anti-Xa activity. Pentasaccharide is free of viral contaminants and other biologic contaminants. Pentasacchairde may useful in the anticoagulant management of COVID-19 patients, specially in the outpatient settings

All of these agents are capable of interacting with the spike protein, release TFPI and produce antithrombotic actions

ADDITIONAL ANTICOAGULANT AND ANTIPLATELET AGENTS

- Warfarin and related oral anticoagulants
- DAOC's including both the anti-Xa and anti-IIa agents.

  Apixaban, Betrixaban, Edoxaban, Rivaroxaban and Dabigatran
- Direct antithrombin Agents

  Argatroban, Angiomax,
- Antiplatelet Drugs

  Aspirin, Clopedogrel, prasugrel, ticagrelor and cangrelor
- Defibrotide

EXTENDED MANAGEMENT WITH DOAC'S

RIVAROXABAN

21 Days | 6 Months | Extended

15mg twice daily → 20mg once daily → 20mg/ 10mg once daily

APIXABAN

7 Days | 6 Months | Extended

10mg twice daily → 5mg twice daily → 2.5mg twice daily

DABIGATRAN

5 Days | 6 Months | Extended

HNF / HBPM → 150mg twice daily → 150mg twice daily

EDOXABAN

5 Days | 6 Months | Extended

HNF / HBPM → 60mg once daily with dose adjustment to 30mg once daily

1. Ramacciotti et al - Evidence-based practical guidance for the antithrombotic management in patients with coronavirus disease (COVID-19) in 2020 – paper in press

ANTICOAGULANT IN COVID-19

- Anticoagulants will continue to play a crucial role in the management of COVID-19 associated vascular complications
- Heparins will remain crucial for the management of COVID-19 patient's, however dosage optimization and individualization of anticoagulation needs to be further refined
- Direct antithrombin agents may be useful in heparin compromised patients, specially those with HIT syndrome
- DOAC's will be useful in the long-term management of COVID-19 patients post hospital discharge
- Oher heparin like drugs including danaparoid and sulodexide will be beneficial for the management of COVID-19 patients. Specially sulodexide which can be administered orally
- Adjunct usage of other drugs including antiplatelet drugs and thrombolytic agents requires additional validation studies
- Novel formulation of anticoagulants including inhalers and other targeted delivery system will play a role