COVID-19 and Pulmonary Embolism: Lessons from Pandemic (December 5th, 2021)

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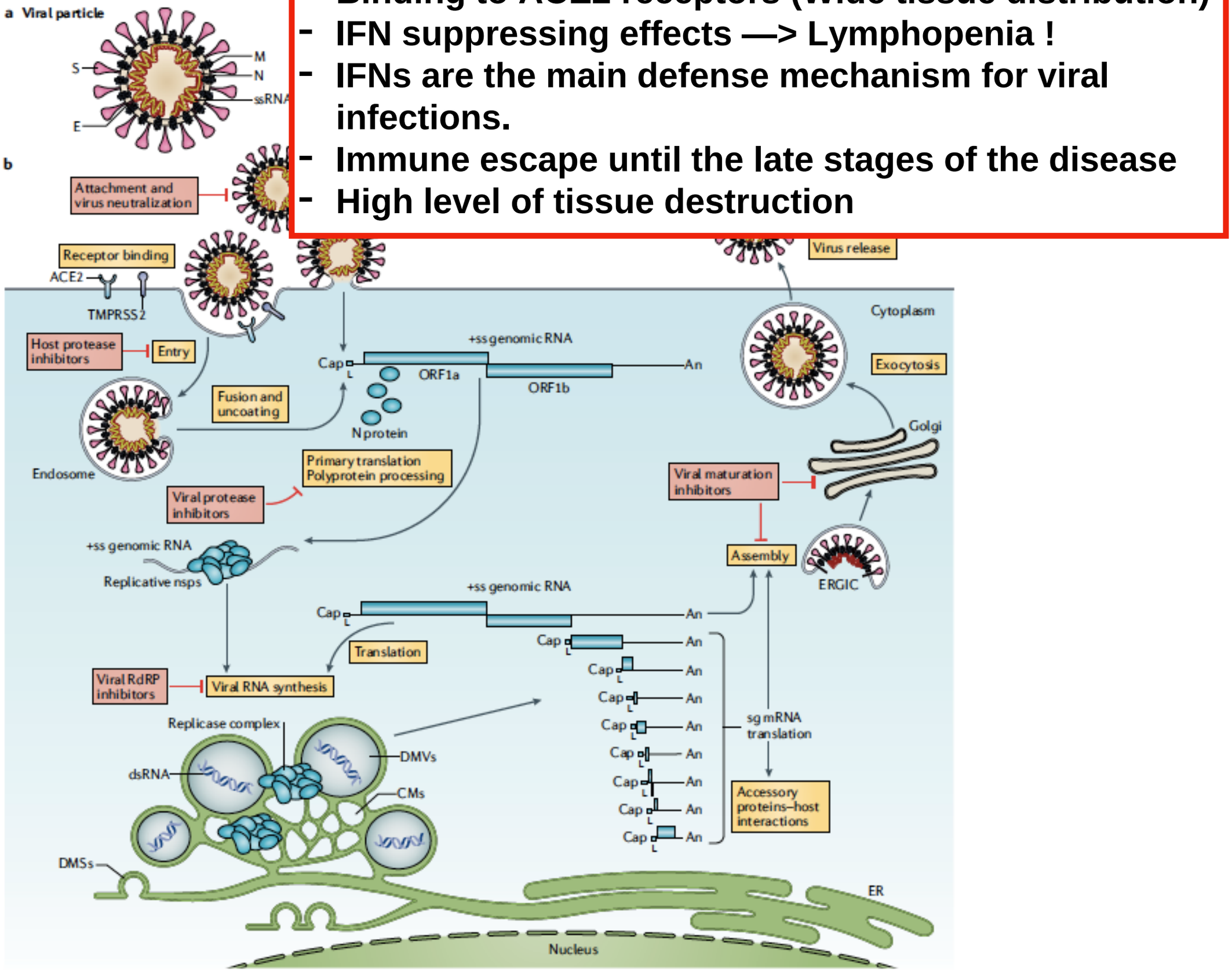
SARS-CoV-2 Pathophysiology

- SARS-CoV-2 is a **single-stranded positive-sense RNA virus** (Betacoronavirus genus).
- The first step of coronavirus infection is the binding of the coronavirus spike (S) protein to the cellular entry receptor **angiotensin converting enzyme 2 (ACE2).**
- Besides receptor binding, the proteolytic cleavage of coronavirus S proteins by host cell-derived proteases is essential to permit this fusion. SARS-CoV-2 has been shown to use the **cell-surface serine protease TMPRSS2** for priming and entry of the virus.
- **ACE2 is expressed in various human organs** including oral and nasal epithelium, nasopharynx, lung, small intestine, kidney, spleen, liver, colon, brain and also the vascular endothelium. However, its expression in the lungs is relatively lower when it is compared to other organs.
- **In fact, TMPRSS2 is mainly expressed in the human respiratory tract** and thus strongly contributes to both SARS-CoV-2 spread and pathogenesis.
- After entry of the SARS-CoV-2 into the host cells, it starts to express and replicate its genomic RNA to produce full-length copies that are incorporated into newly produced viral particles.

- **Binding to ACE2 receptors (Wide tissue distribution)**
- **IFN suppressing effects —> Lymphopenia !**
- **IFNs are the main defense mechanism for viral infections.**
- **Immune escape until the late stages of the disease**
- **High level of tissue destruction**



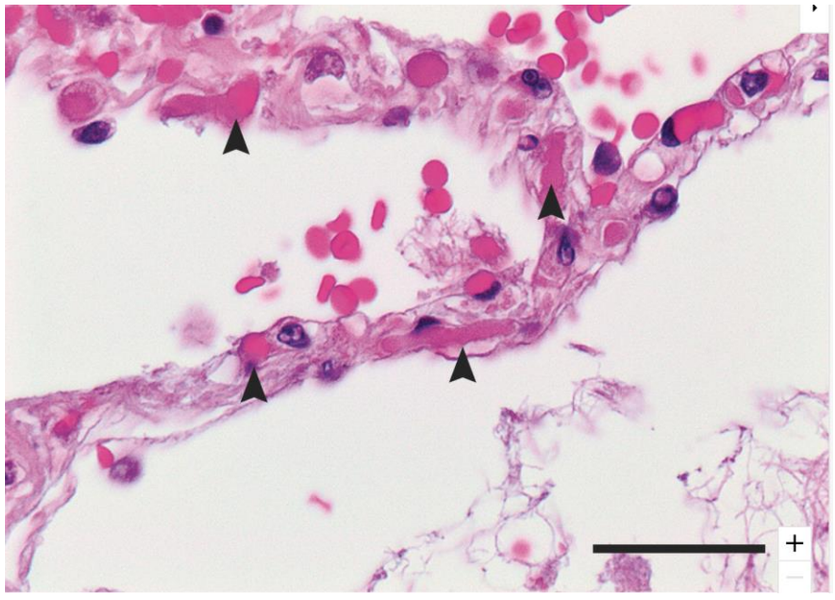
V'kovski P, et al. Nat Rev Microbiol. 2021 Mar;19(3):155-170.

Thrombosis in COVID-19

ORIGINAL ARTICLE

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., Tobias Welte, M.D., Florian Laenger, M.D., Arno Vanstapel, Ph.D., Christopher Werlein, M.D., Helge Stark, Ph.D., Alexandar Tzankov, M.D., William W. Li, M.D., Vincent W. Li, M.D., Steven J. Mentzer, M.D., and Danny Jonigk, M.D.



- Severe endothelial injury + intracellular virus
- Thrombosis with microangiopathy.
- Microthrombi were 9 times > H1N1
- New vessel growth — 2.7 times >H1N1

Ackermann M, et al. N Engl J Med. 2020 Jul 9;383(2):120-128.

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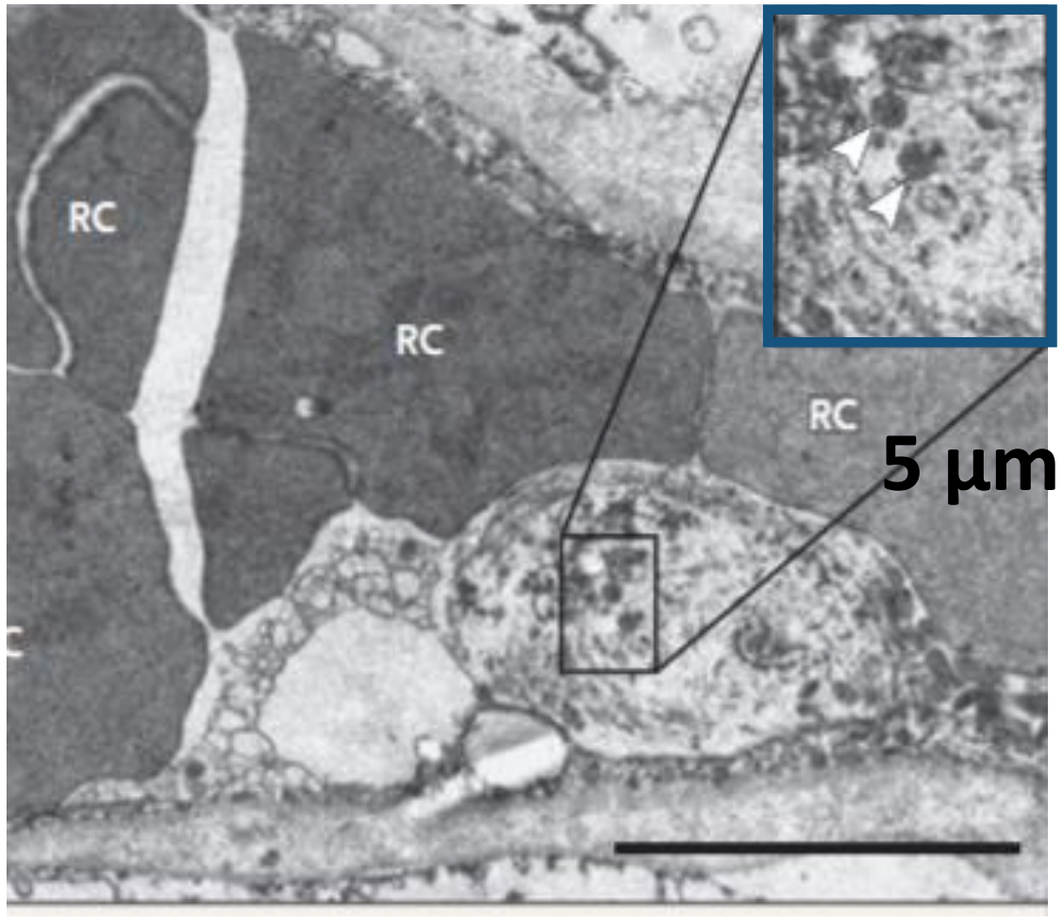


Transmission Electron Micrograph

Endothelial cell destruction and SARS-CoV-2 visible within the cell

White arrows indicate Coronavirus

Ackermann M, et al. N Engl J Med. 2020 Jul 9;383(2):120-128.

Thrombosis in COVID-19

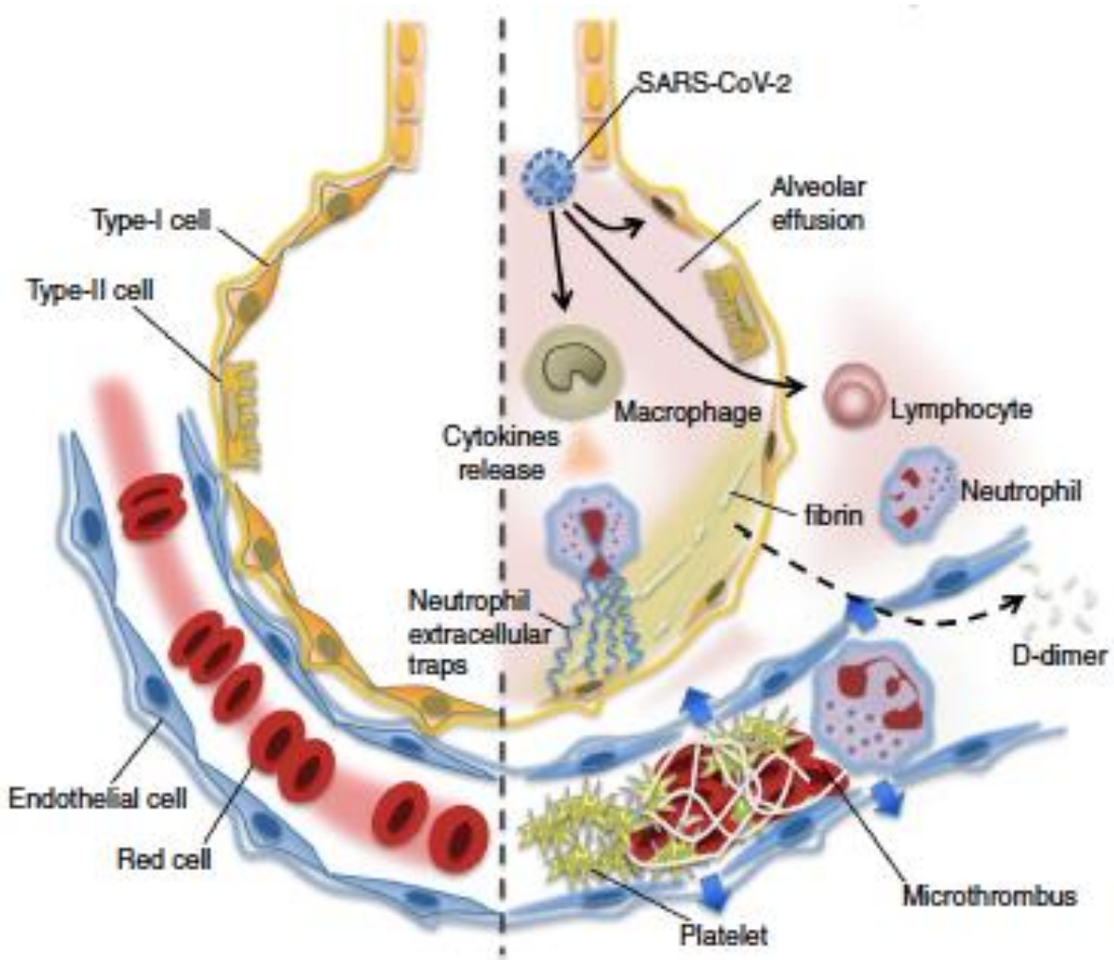
Coronavirus disease 2019 morbid pulmonary pathology: What did we learn from autopsy examinations?

Table 1. Summary of the 13 COVID-19 case series of autopsy findings

References	Date	Country	No. of cases	Tissue examination tools	Pulmonary findings	Comments
[17]	July 2020	USA	14	Macroscopy, light microscopy (H&E), IHC, EM, qRT-PCR	DAD Thrombosis	Complete autopsy, both macroscopic and microscopic examination for major body organs
[21]	June 2020	Germany	4	Macroscopy, histology (H&E), IHC, EM, RNA studies for SARS-CoV-2 RNA and IL-1β and IL-6 mRNA detection	DAD Thrombosis	Autopsy for lungs only
[18]	May 2020	USA	10	Macroscopy, microscopy (H&E), IHC, RNA labelling EM	DAD Thrombosis	Autopsy examination for lungs and heart
[13]	May 2020	UK	9	Macroscopy, microscopy (H&E)	DAD	Autopsy with microscopic histology for lungs and heart only
[19]	June 2020	Italy	38	Macroscopy, light microscopy (H&E), IHC, EM	DAD Thrombsis	Autopsy for lung tissue only
[14]	May 2020	Austria	11	Macroscopy, microscopy (H&E)+IHC for RT-PCR for SARS-CoV-2 in tissue		Complete autopsy
[15]	May 2020	Germany	12	Macroscopy, microscopy (H&E)+IHC for RT-PCR for SARS-CoV-2 in tissue	DAD Thrombosis	Complete autopsy
[16]	June 2020	USA	7	Autopsy/immunohistochemistry and electron microscopy	DAD Thrombo-embolism	Complete autopsy for major body organs
[23]	September 2020	Iran	7	Microscopy	DAD	Postmortem core needle biopsies from lung, heart, and liver
[24]	March 2020	China	4	Microscopy (H&E), IHC, RT-PCR for SARS-CoV-2 in tissue	DAD	Postmortem Core biopsy for lungs, liver and heart
[20]	May 2020	Germany	7	Macroscopy, histology (H&E/trichrome), IHC, SEM, corrosion casting, direct multiplexed measurement of gene expression	DAD Thrombo- embolism	7- lungs from autopsy of COVID-19 cases compared with 7 lungs from autopsy of (ARDS) cases secondary to influenza A (H1N1) and 10 age-matched, uninfected control lungs
[22]	Aug./Sept. 2020	Italy and USA	6			Only lung tissue studied
[25]	Aug./Sept. 2020	China	3			Core biopsy lung heart liver and LNs

Zulfu A, et al. J Clin Transl Res. 2021 Aug 4;7(4):479-484.

COVID-19 and the Risk of Thrombosis



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

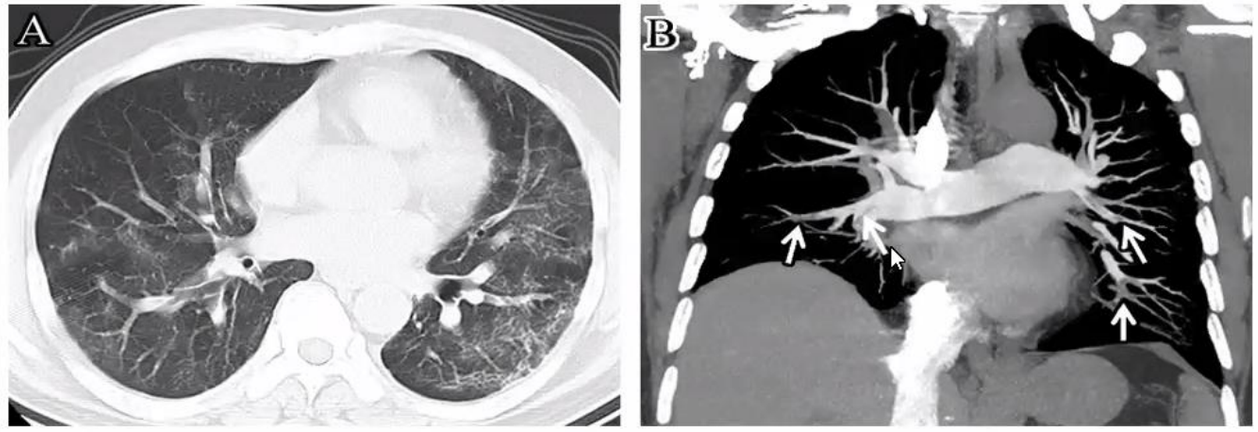
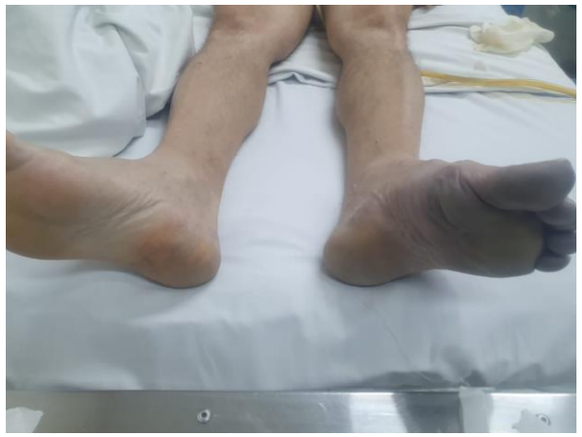


Figure 1: Images in a 57-year-old man with COVID-19 pneumonia. *A*, Axial unenhanced chest CT scan obtained on day 10 after the onset of symptoms shows bilateral areas of peripheral ground-glass opacities. *B*, Coronal thick maximum intensity projection slab of CT pulmonary angiography demonstrates multiple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

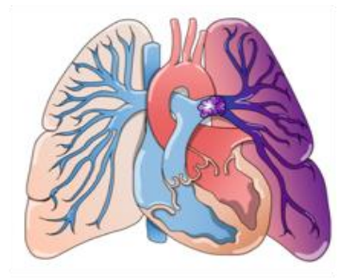
Xie Y. Published Online: March 16, 2020
https://doi.org/10.1148/ryct.2020200067

Radiology: Cardiothoracic Imaging

Thrombotic Events in COVID-19



Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis.



Pulmonary embolism (most frequent)

87%

SARS-CoV-2 infection

184 SARS-Cov-2+ ICU patients

Thrombotic events

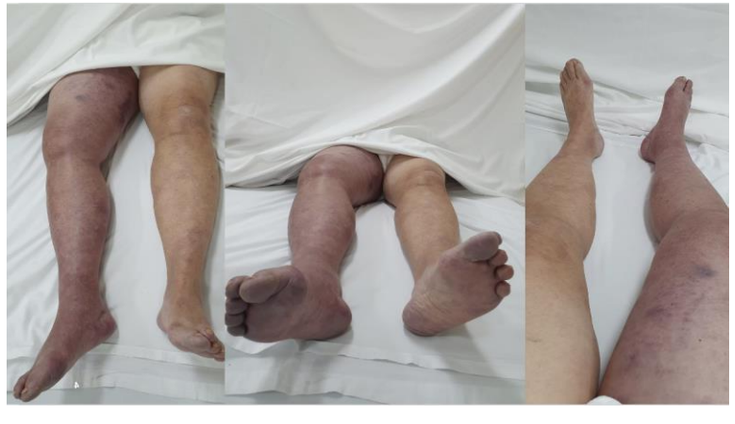
49%

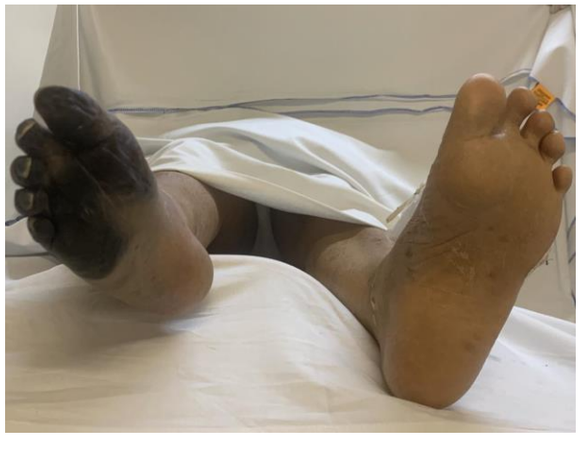
Strokes **6.6%**

Arterial thrombosis **2.6%**

Deep-vein thrombosis **4%**

CV death **14%**





Klok FA, et al. Thromb Res. 2020 Jul;191:148-150.

Laboratory Abnormalities in COVID-19

- Lymphopenia (anti-IFN properties and high level of tissue damage)
- Increased LDH
- Increased inflammatory markers
  - C-reactive protein
  - D-dimer (correlates with poor prognosis)
  - Ferritin
  - Interleukin-6 (IL-6) - (correlates with poor prognosis)
  - Fibrinogen

Coagulation Abnormalities in COVID-19

- Thrombocytopenia
- Prolongation of the PT
- Relatively normal aPTT
- Increased vWF and increased thrombomodulin (endothelial damage)

Auto-immune Antibody Formation in COVID-19

- Some of the antibodies that have been reported during the course of COVID-19:
    - Anticardiolipin (aCL),
    - Lupus anticoagulant(LAC),
    - Beta2 glycoprotein I (b 2GPI),
    - Antinuclear antibodies (ANA),
    - p-ANCA,
    - c-ANCA,
    - Anti-CCP and
    - Antiheparin- PF4 (aPF4) antibodies

Coagulation Abnormalities in COVID-19

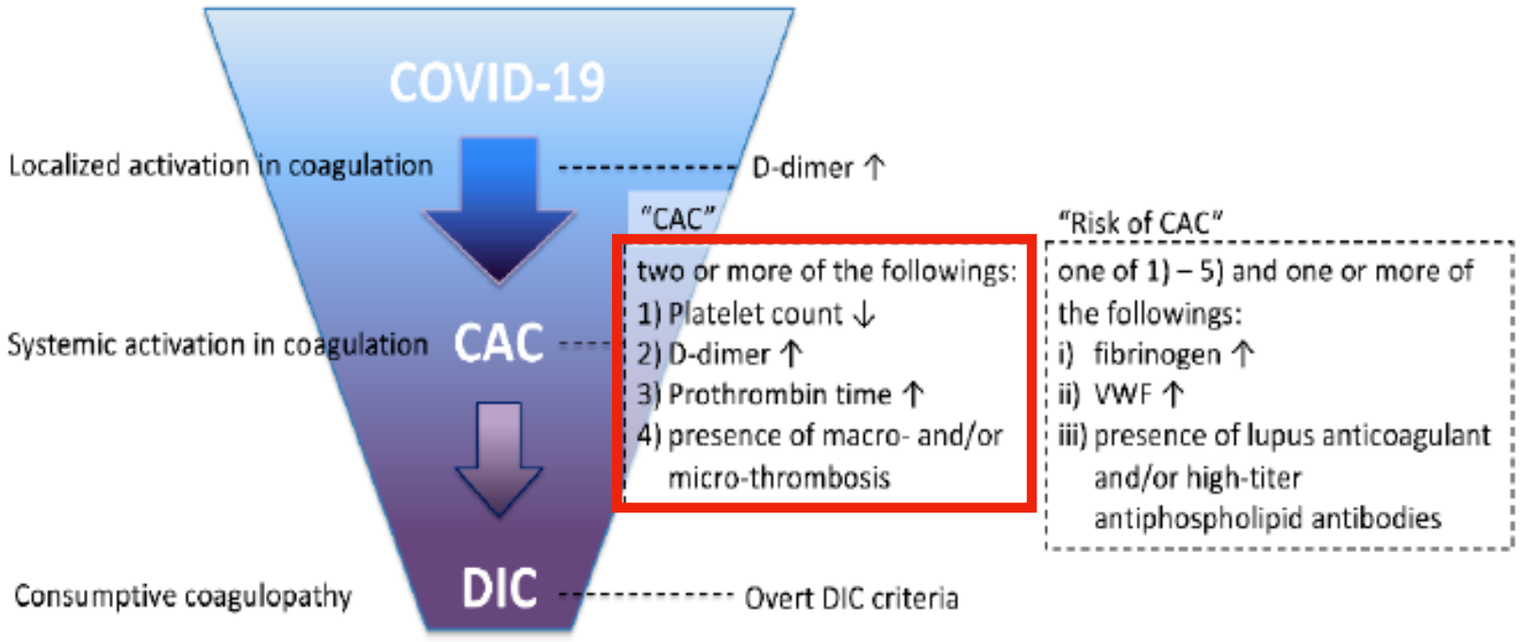
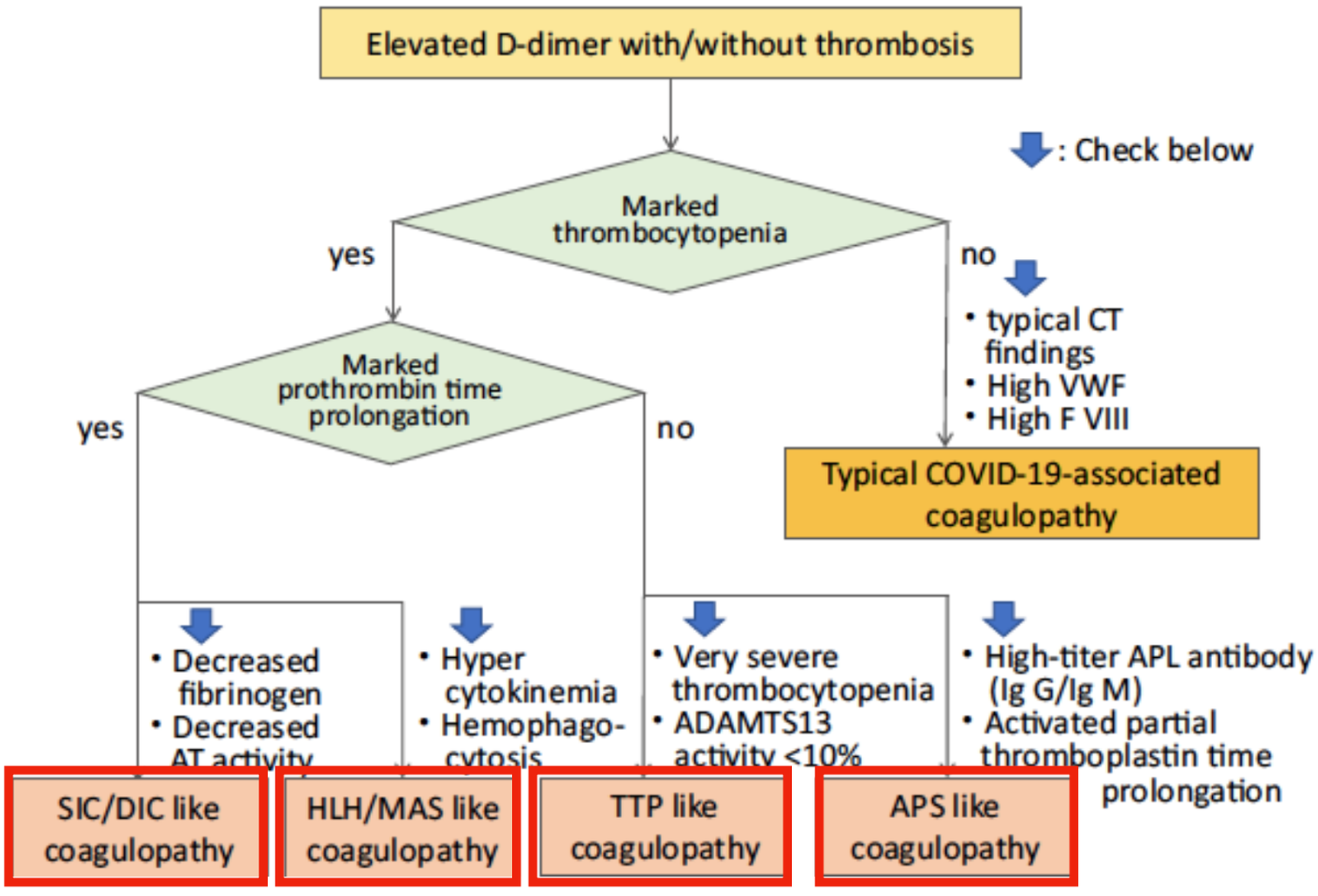


Figure 1. The progression from COVID-19-associated coagulopathy to disseminated intravascular coagulation (DIC). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) elicits thrombotic property by damaging the vascular endothelial cells. Activation in coagulation is initially localized in the lung microcirculation, however, when it expands systemically, it is called COVID-19-associated coagulopathy (CAC). The diagnostic criteria of CAC are proposed as (A) proven COVID-19 and (B) two or more of the following criteria: (1) decrease in platelet count (less than 150×10^9/L); (2) increase in D-dimer (more than two times the upper limit of normal); (3) >1 s prolonged prothrombin time or International Normalized Ratio (INR) > 1.2; (4) decrease in fibrinogen level; (5) presence of thrombosis (macrothrombosis including deep vein thrombosis/venous thromboembolism, thrombotic stroke, acute coronary syndrome, limb artery thrombosis, mesenteric artery thrombosis, etc., and/or microthrombosis including skin, acral lesions, etc.). "Risk of CAC" is defined as one of above five criteria and one of following criteria: (i) increase in fibrinogen level; (ii) increased von Willebrand factor (VWF) (more than two times the upper normal limit); (iii) presence of lupus anticoagulant and/or high-titer antiphospholipid antibodies. CAC and risk of CAC can progress to disseminated intravascular coagulation (DIC) when the disease progresses.

Coagulation Abnormalities in COVID-19



Anticoagulation in COVID-19

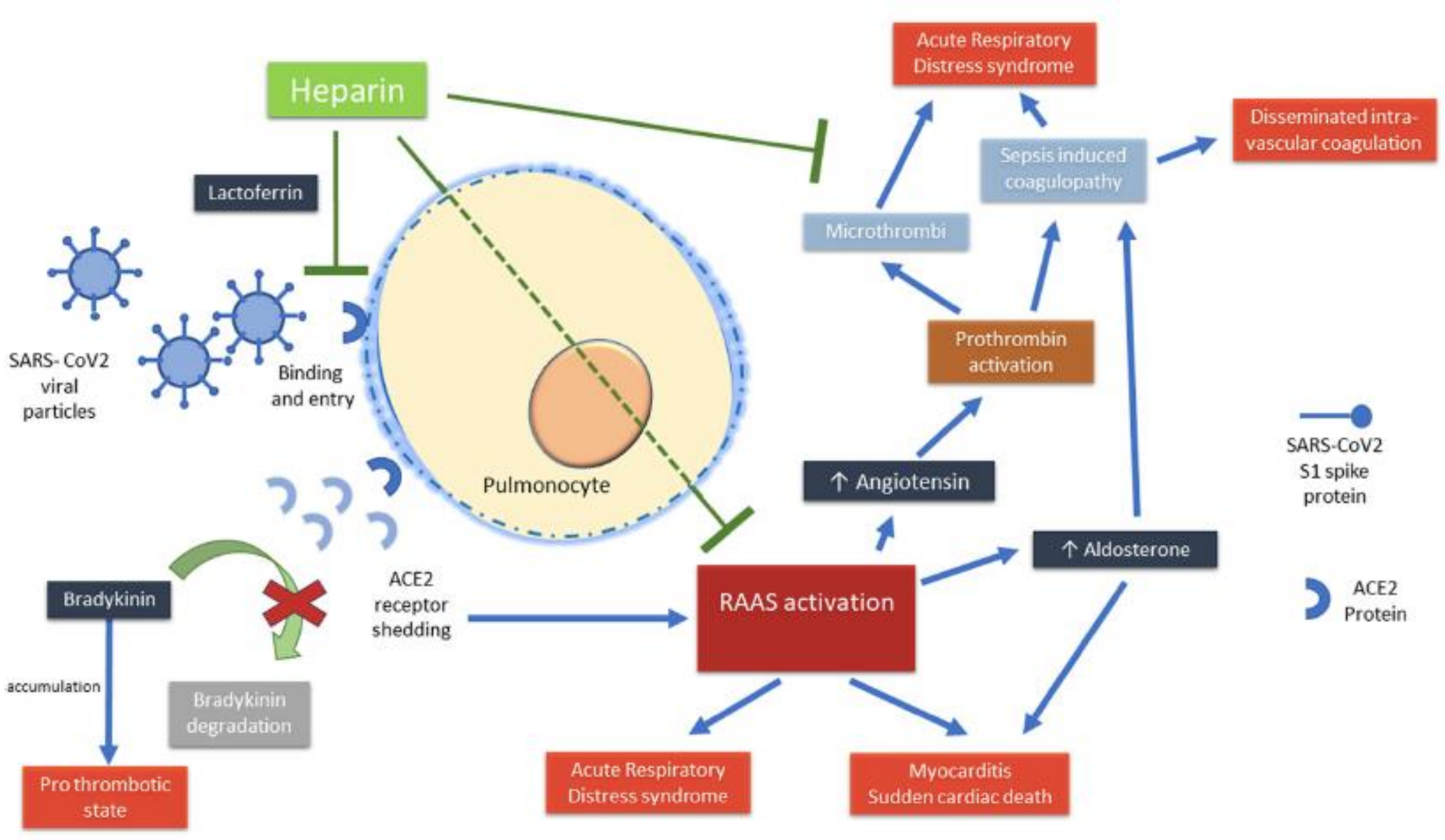


Fig. 1 Potential mechanisms of action of heparin in COVID-19. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; RAAS, renin-angiotensin-aldosterone system

coagulation in COVID-19

ASH Recommendations

COVID-19 and VTE/Anticoagulation: Frequently Asked Questions

(Version 12.0; last updated November 2, 2021)

Input from Drs. Lisa Baumann Kreuziger, MD; Agnes Y. Y. Lee, MD, MSc; David Garcia, MD; Maria DeSancho, MD; and Jean M. Connors, MD.

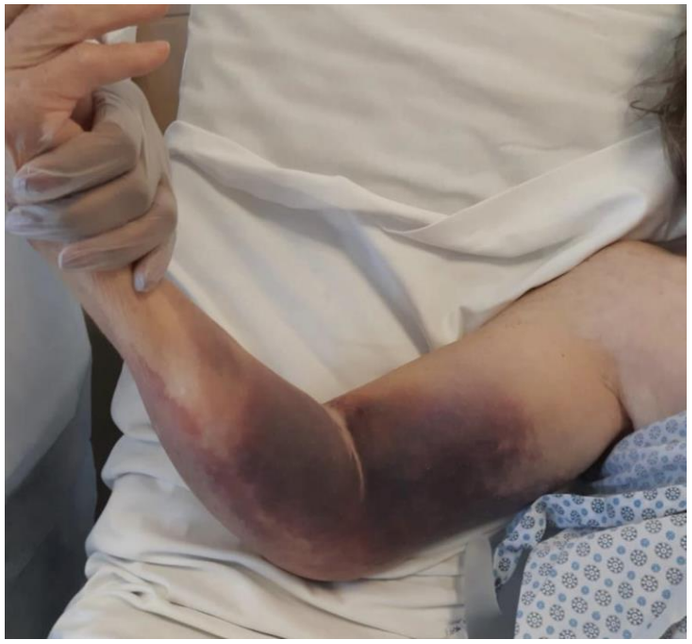
Is COVID-19 associated with an increased risk for venous thromboembolism (VTE)?

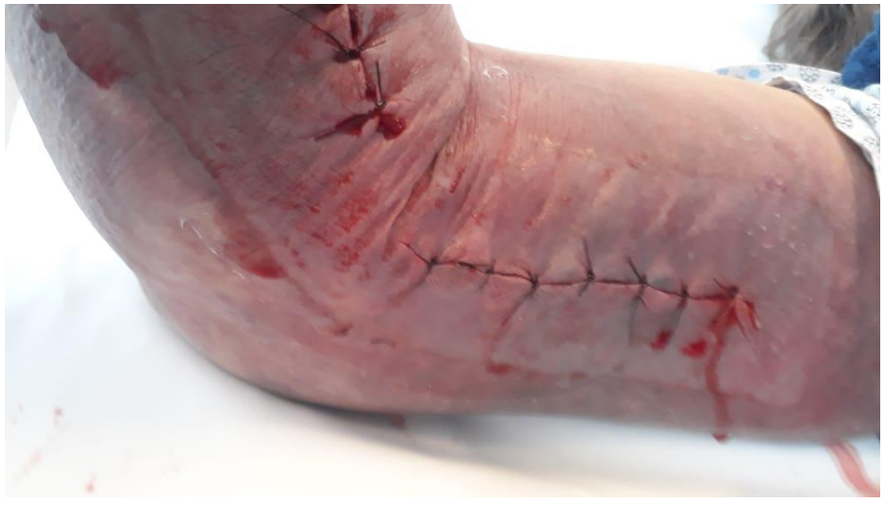
The incidence of VTE in COVID-19 patients varies depending on the patient population. In a meta-analysis of 66 observational studies through August 2020, the overall prevalence of VTE in hospitalized patients was 9.5 percent without screening ultrasound (US), and 40 percent with screening US; and higher in intensive-care-unit (ICU) patients at 18.7 percent without, and 45.6 percent with US. As with other medical patients, those with more severe disease, especially in the setting of additional risk factors (e.g., age, being male, obesity, cancer, history of VTE, comorbid diseases, ICU care), have a higher risk of VTE than those with mild or asymptomatic disease.

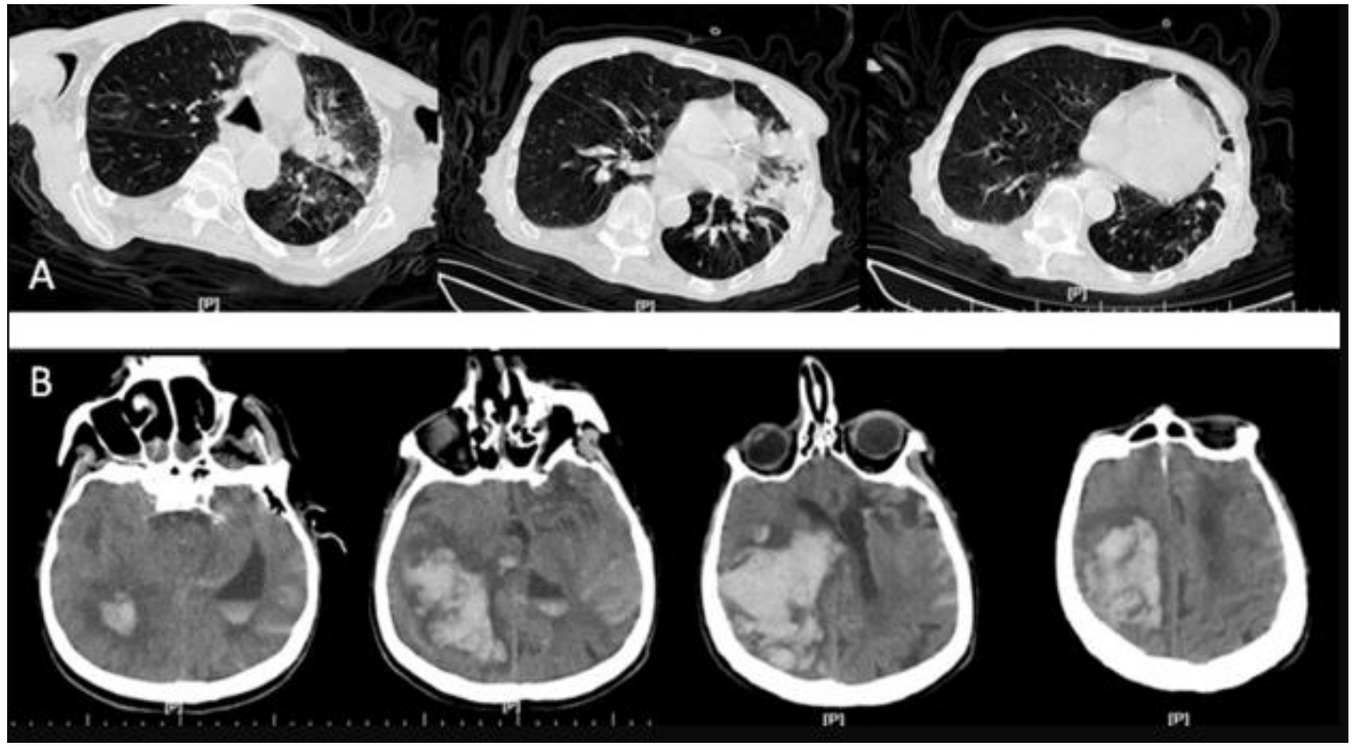
Summary of US and International Guidance on Anticoagulant Dosing in Patients Hospitalized with COVID-19

VTE prophylaxis	ACC[1]	ASH[2]	CHEST[3]	ISTH[4]	NIH[5]	WHO[6]
Ward patients	Prophylactic dose	Prophylactic dose	Prophylactic dose	Prophylactic dose	Prophylactic dose	Prophylactic dose
ICU patients	Prophylactic dose	Prophylactic dose	Prophylactic dose	Prophylactic/ intermediate* dose	Prophylactic dose	Prophylactic dose
Post-discharge thromboprophylaxis	Dependent on patient type		Inpatient prophylaxis only	14-30 days	Inpatient prophylaxis only	
VTE treatment						
Confirmed VTE		Therapeutic dose	Therapeutic dose	Therapeutic dose	Therapeutic dose	
Length of therapy			3 months	3 months		

Anticoagulation in COVID-19







A. Sharifi-Razavi, N. Karimi, N. Rouhani,COVID-19 and intracerebral haemorrhage: causative or coincidental?, New Microbes and New Infections, Volume 35, 2020

- Thank you.