

# Coagulopathy of COVID-19

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# COVID-19: A global crisis



# Objectives

- To describe the hypercoagulable state in COVID-19
- To discuss the pathophysiology of the prothrombotic milieu
- To provide guidance on use of D-dimer and anticoagulation prophylaxis and treatment



# Risk of thrombosis in pneumonia/ ARDS

- Venous thromboembolism (VTE) risk is increased in pneumonias
- Associations noted with SARS-CoV-1 and MERS-CoV
- Risk factors: immobility, mechanical ventilation, central venous access devices, inflammation and infection

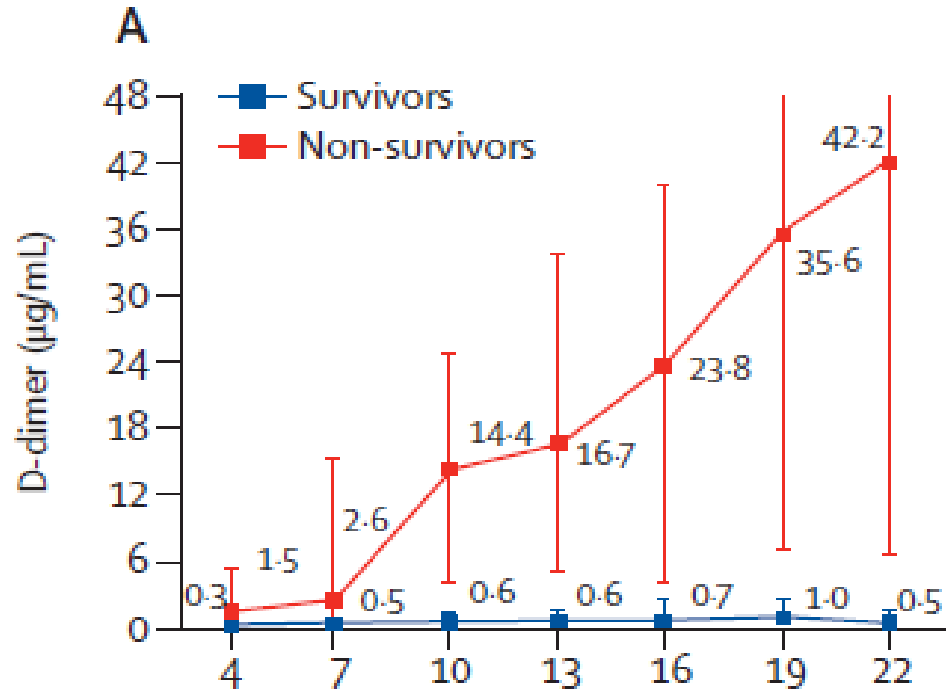


# Evidence for a hypercoagulable state in COVID-19

- D-dimer as a poor prognostic marker was first brought to notice by Zhou et al (Lancet, March 9<sup>th</sup>, 2020)
- DIC in COVID-19 patients more frequent in non-survivors (71%) than survivors (0.6%)
- Initially considered a prognostic parameter, warranting enhanced vigilance
- Hypothesis that DIC may not be a concomitant finding but more a pathophysiological process contributing to circulatory and organ failure, especially pulmonary damage



# Coagulation parameters in COVID-19

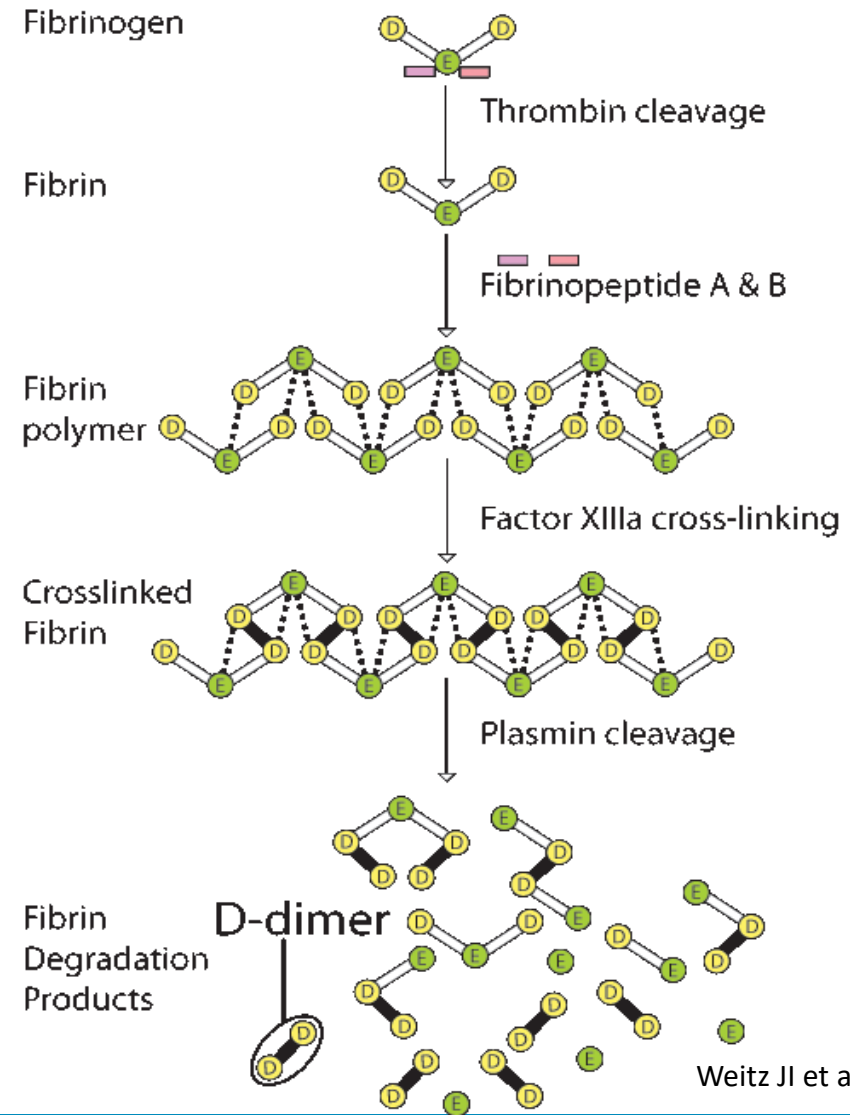


Parameters	Normal range	Total (n=183)	Survivors (n=162)	Non-survivors (n=21)	p value
PT (sec)	11.5-14.5	13.7 (13.1-14.6)	13.6 (13.0-14.3)	15.5 (14.4-16.3)	<0.001
aPTT (sec)	29.0-42.0	41.6 (36.9-44.5)	41.2 (36.9-44.0)	44.8 (40.2-51.0)	0.096
Fibrinogen (g/L)	2.0-4.0	4.55 (3.66-5.17)	4.51 (3.65-5.09)	5.16 (3.74-5.69)	0.149
D-dimer (µg/mL)	<0.5	0.66 (0.38-1.50)	0.61 (0.35-1.29)	2.12 (0.77-5.27)	<0.001
FDP (µg/mL)	<5.0	4.0 (4.0-4.9)	4.0 (4.0-4.3)	7.6 (4.0-23.4)	<0.001
AT (%)	80-120	91 (83-97)	91 (84-97)	84 (78-90)	0.096



# What is a D-dimer?

## Generation of D-dimer from cross-linked fibrin



Weitz JI et al. JACC 2017;70:2411-2420



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Location (first author)	Sample size	D-dimer cut-off for risk assessment	Outcome of interest
Wuhan, China (Zhou et al)	191	> 1mcg/ml	Mortality
Wuhan, China (Yao et al)	248	>2.14 mg/L	Mortality
Wuhan, China (Zhang et al)	343	>2 mcg/ml	Mortality
Wuhan, China (Tang et al)	183	N/A (continuous variable)	Mortality
Mainland China (Guan et al)	1099	N/A (continuous variable)	Severe disease; Primary composite endpoint was admission to ICU/ mechanical ventilation or death
Wuhan, China (Huang et al)	41	N/A (continuous variable)	ICU admission
Wuhan, China (Wang et al)	138	N/A (continuous variable)	ICU admission
Wuhan, China (Wu et al)	201	N/A (continuous variable)	ARDS; mortality
Milan, Italy (Lodigiani et al)	388	N/A (continuous variable)	ICU; mortality
Beijing, China (Cui et al)	81	>1.5 mcg/ml	VTE
Strasbourg, France (Leonard-Lorant et al)	106	>2660 mcg/L	Pulmonary embolism





# High Risk of Thrombosis in Patients with Severe SARS-CoV-2 Infection

- 4 ICUs at 2 centers in France
- 150 patients (122 males, median age 63), all received anticoagulation (70% prophylactic, 30% therapeutic)
- 64 clinically relevant thrombotic complications
  - 16.7% Pulmonary Embolism
  - 28/29 (96.6%) clotting CRRT circuits
  - 3 thrombotic occlusions of ECMO circuits in 2/12 patients
  - 15% stroke on CT/MRI; 1 acute limb ischemia, 1 mesenteric ischemia
- COVID ARDS (n=77) vs. non-COVID ARDS (n=145)
  - PE: 11.7% vs 2.1% OR 6.2 (1.6-23.4) p<0.008
  - VTE: 11.7% vs 4.6% OR 2.6 (1.1-6.1) p=0.035

Helms et al. Intensive Care Medicine, May 2020

**Despite anticoagulation, a high number of patients with ARDS secondary to COVID-19 developed life-threatening thrombotic complications. Higher anticoagulation targets than usual should probably be suggested**



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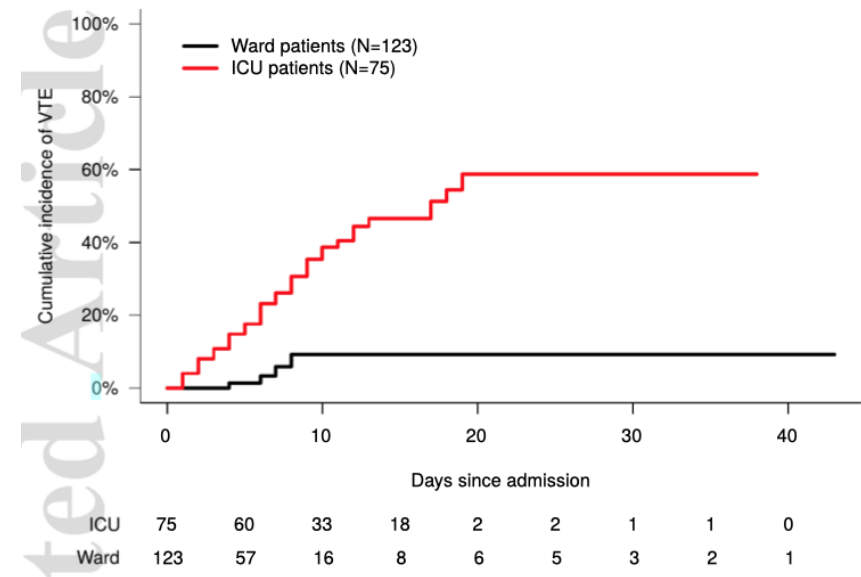
# High incidence of VTE despite thromboprophylaxis

- 198 hospitalized patients, 38% direct ICU admissions
- ALL patients received VTE prophylaxis, weight adjusted (100kg)
- Cumulative incidence of **symptomatic** VTE:

Day 7: 10% (85% CI 5.8-16)

Day 14: 21% (95% CI 14-30)

Day 21: 25% (95% CI 16-36)



Middledorp et al. JTH 2020

## Anticoagulation = Improved outcomes

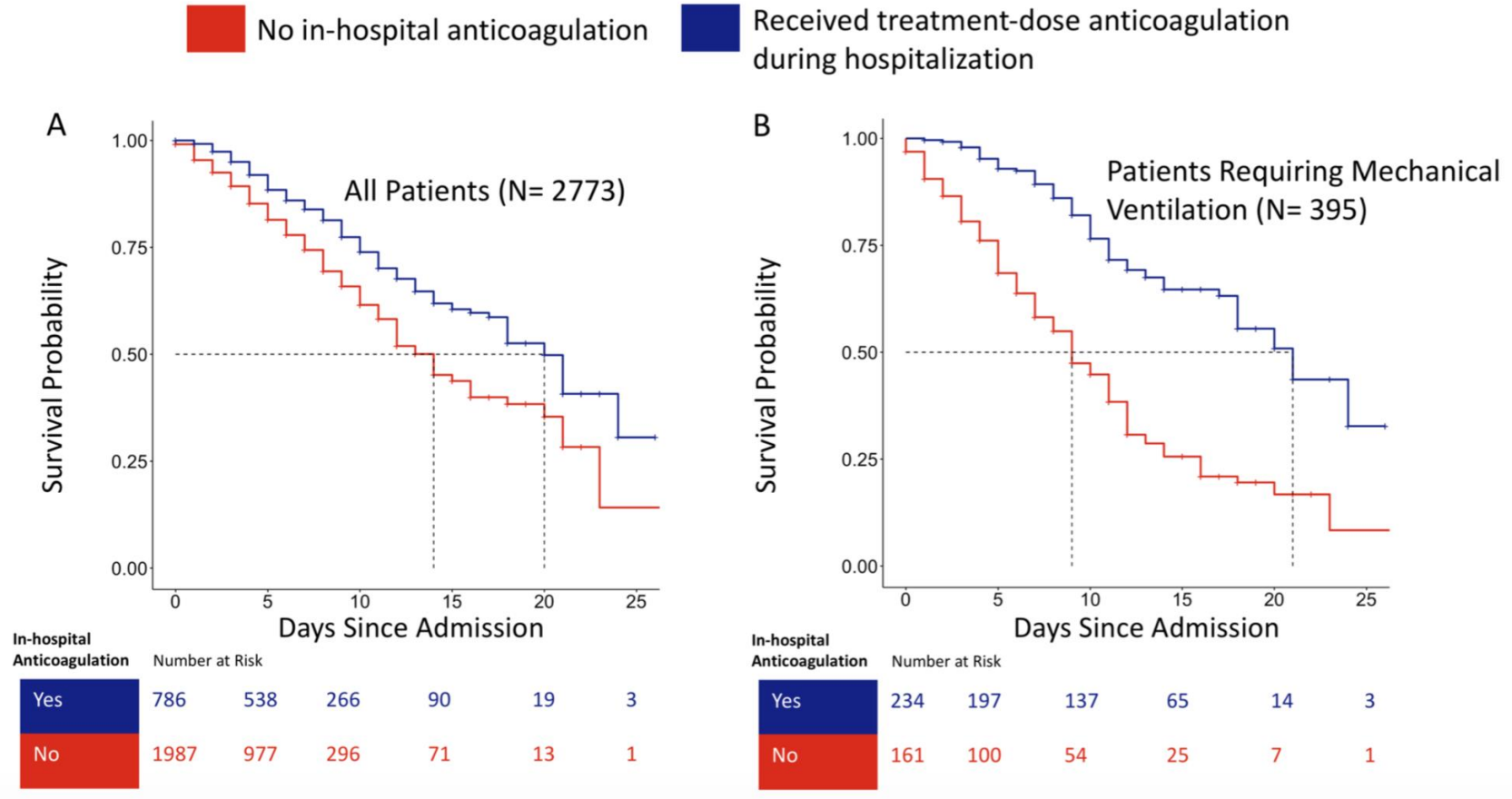
- 2,773 hospitalized patients in NY
- In hospital mortality 29% on anticoagulation vs 62% without anticoagulation in the mechanically ventilated patients
- Major bleeding 3% versus 1.9%

Paranjpe et al. JACC May 6th, 2020



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# Anticoagulation = Improved outcomes



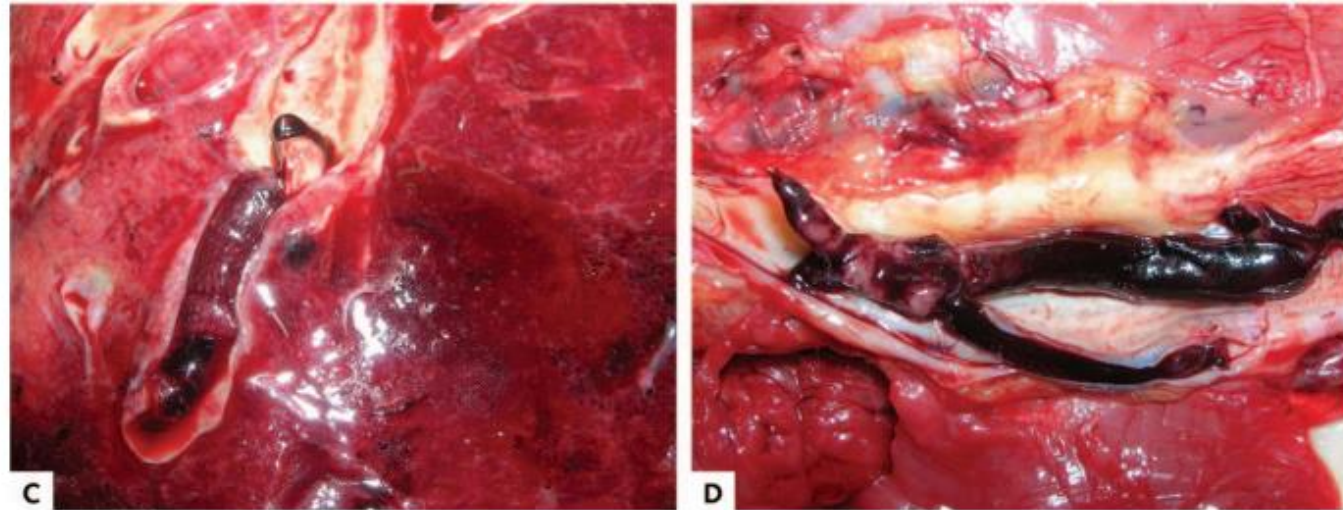
Paranjpe et al. JACC. May 6. Mt Sinai, NY



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Location (first author)	Type of study	Sample size	Use of thromboprophylaxis	VTE incidence	Arterial thrombosis incidence
Wuhan, China (Cui et al)	Retrospective; hospitalized patients	81	No	VTE 25%; all lower extremity thrombi	None
Netherlands (Klok et al)	Retrospective; multicenter; hospitalized patients	184	Yes (nadroparin at different doses)	VTE (n=28) 27%; of those PE (n=25) was most common finding in 81%	Ischemic strokes (n=3) 3.7%
Netherlands (Middeldorp et al)	Retrospective; single center; hospitalized patients	198	Yes (nadroparin 2850 units daily for <100 kg and 5700 units daily for >100 kg)	7-day incidence of VTE (15%) and 14-day incidence of VTE (34%)	None
Italy (Lodigiani et al)	Retrospective; single center; hospitalized patients	388	Yes (LMWH) Ward: 75% used (41% prophylactic dose, 21% intermediate dose; 23% therapeutic dose) ICU: 100% used	VTE 21% (cumulative rate) ICU 27.6% and general ward 6.6%	Ischemic stroke 2.5% and ACS/MI 1.1%
France (Llitjos et al)	Retrospective study; 2 ICUs	26	Yes (31% with prophylactic dose and 69% with therapeutic dose)	VTE 69%	None
France (Helms et al)	Prospective study; COVID-19 ARDS patients at 4 ICUs in 2 centers	150	Yes (LMWH)	PE 16.7%; DVT 2%	Ischemic stroke 1.3%; limb ischemia 0.7%; mesenteric ischemia 0.7%
France (Poissy et al)	Retrospective case series; ICU	107	Yes	PE (20.6%)	None
Netherlands (Beun et al)	Retrospective; ICU	75	Unknown	PE (26.6%; 21.3% subsegmental and 5.3% central); DVT 4%	Ischemic stroke 2.7%

# Post-mortem evidence of thrombosis in COVID-19



Wichmann De et al. Annal Int Med 2020



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# Increased incidence of arterial thrombosis

- Arterial events occur as well
- 5 patients (<50 years) presented with sudden large vessel strokes
- Klok FA et al. VTE 27% and 3.7 % arterial events



Oxley TJ et al. NEJM April 28 2020  
Klok et al. Thromb Res, 2020  
Bellosta et al. J Vasc Surg. 2020 Apr 29  
Qian e al. JCVA. doi:10.1053/j.jcva.2020.03.063

# Increased incidence of arterial thrombosis

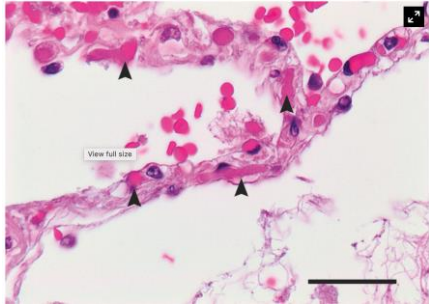
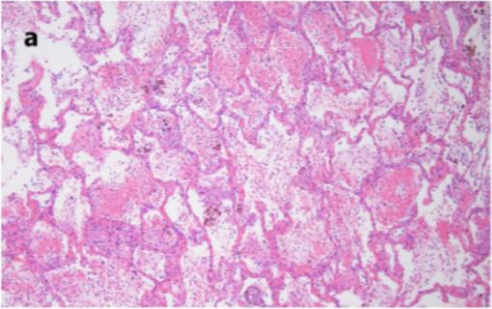
Location (first author)	Type of study	Sample size	Use of thromboprophylaxis (Yes/No/Unknown; drug used, if any)	Arterial thrombosis incidence (w/ type or site)
New York, USA (Oxley et al)	Case series	5	No	Ischemic stroke 5 young patients in 2 week period
Beijing, China (Zhang et al)	Case series	3	Unknown	Ischemic strokes in 3 patients
Italy (Bellosta et al)	Observational cohort study	20	25% were on anticoagulation at baseline due to atrial fibrillation	Acute limb ischemia in 20 patients (16.3%)



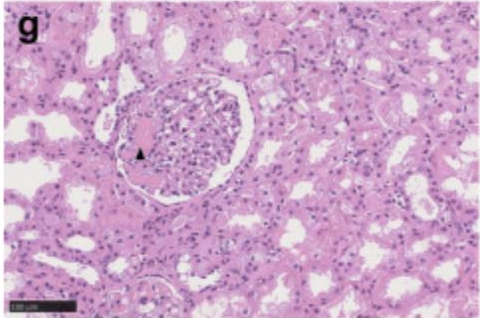


# Microvascular thrombosis

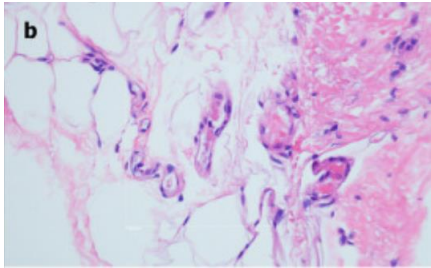
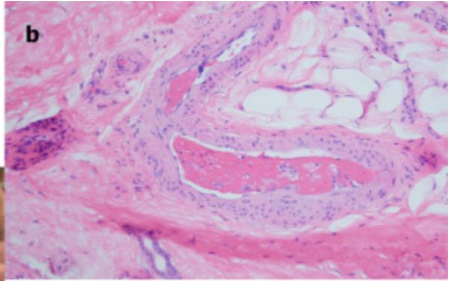
Pulmonary



Renal



Dermal microvasculature

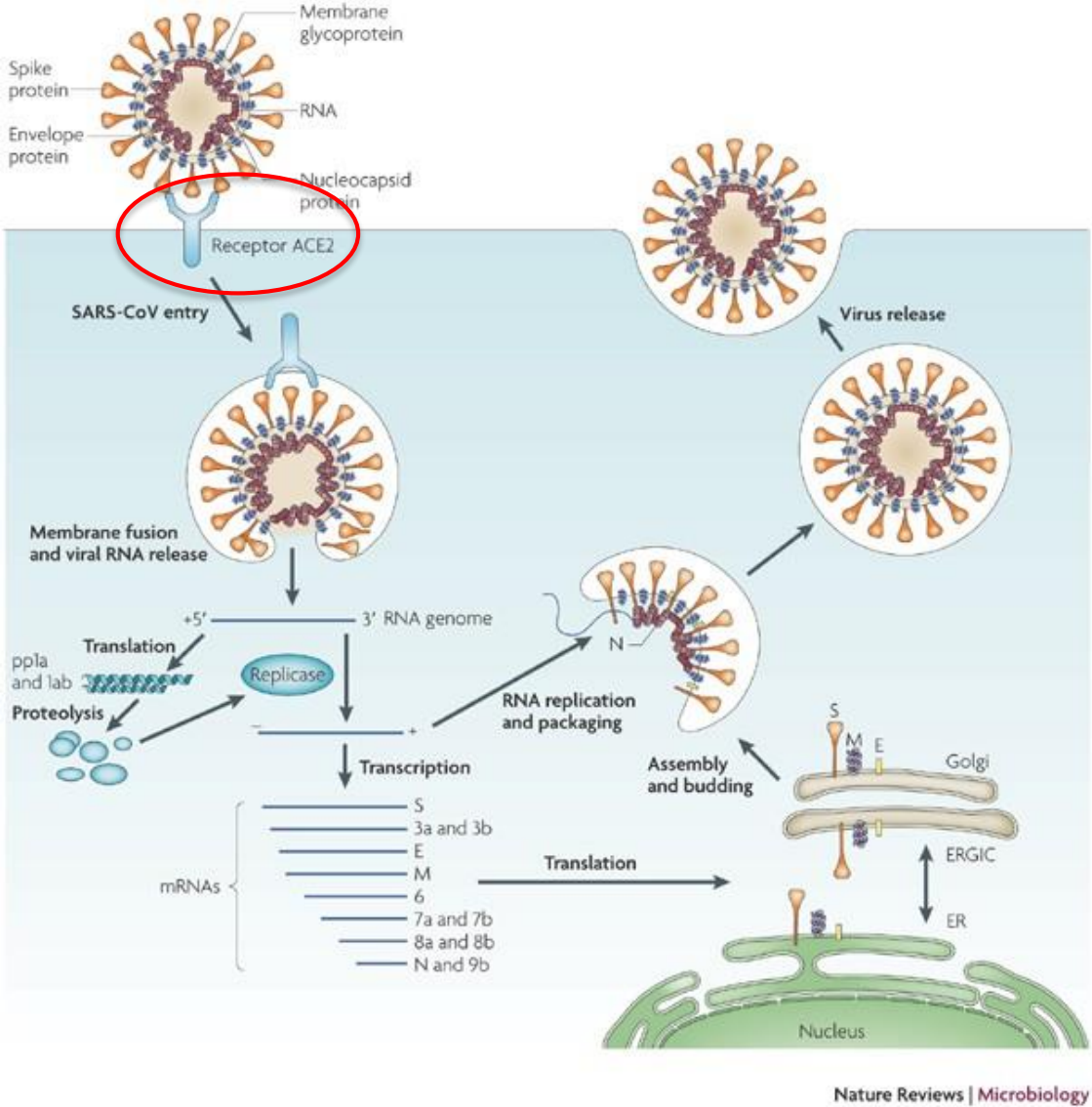


Magro et al. Transl Res. 2020 April 15  
Su H et al. Kidney Int. April 9 2020  
Ackermann M et al. NEJM 2020

# Pathophysiology of hypercoagulable state in COVID-19



# SARS-CoV-2 uses ACE2 for cell entry



Nature Reviews | Microbiology



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# ACE2 expression is ubiquitous

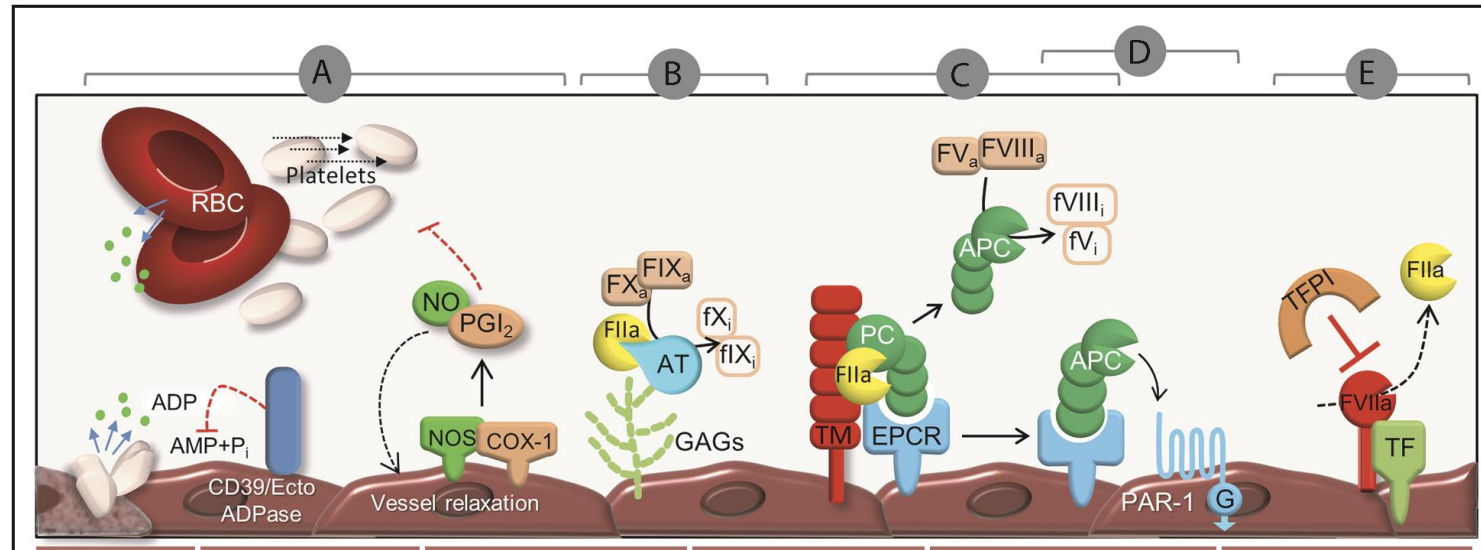
ACE receptor well described
Type II pneumocytes
Enterocytes of small bowel
Nasal and oral mucosa
Kidney
Myocardium
Smooth muscle cells and <b>endothelium</b> of vessels

Lukassen S, et al. *EMBO* 2020



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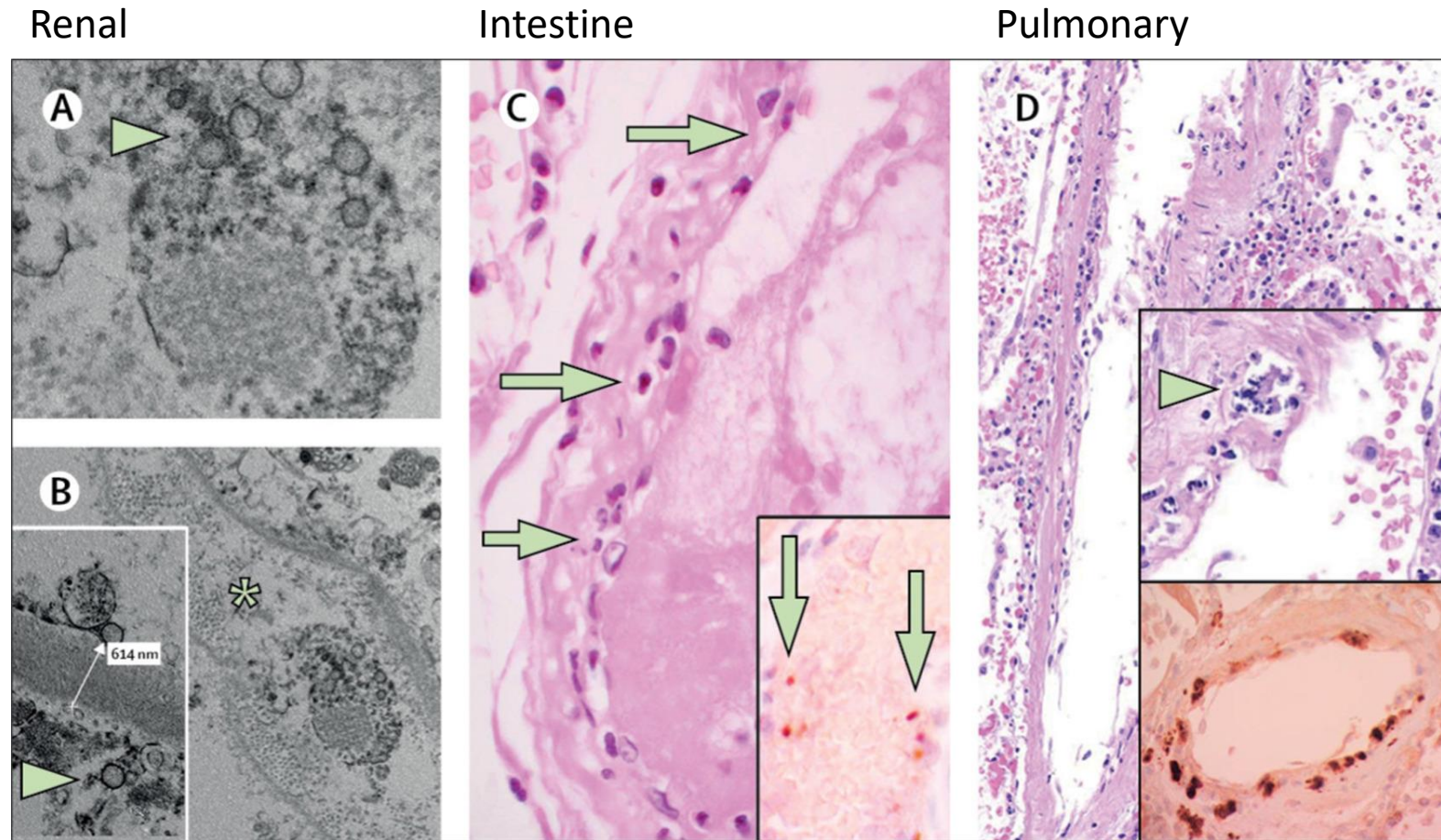
# Physiologic role of endothelium



*Blood* (2019) 133 (9): 906–918



# 1. Endotheliitis is an early process leading to thrombosis

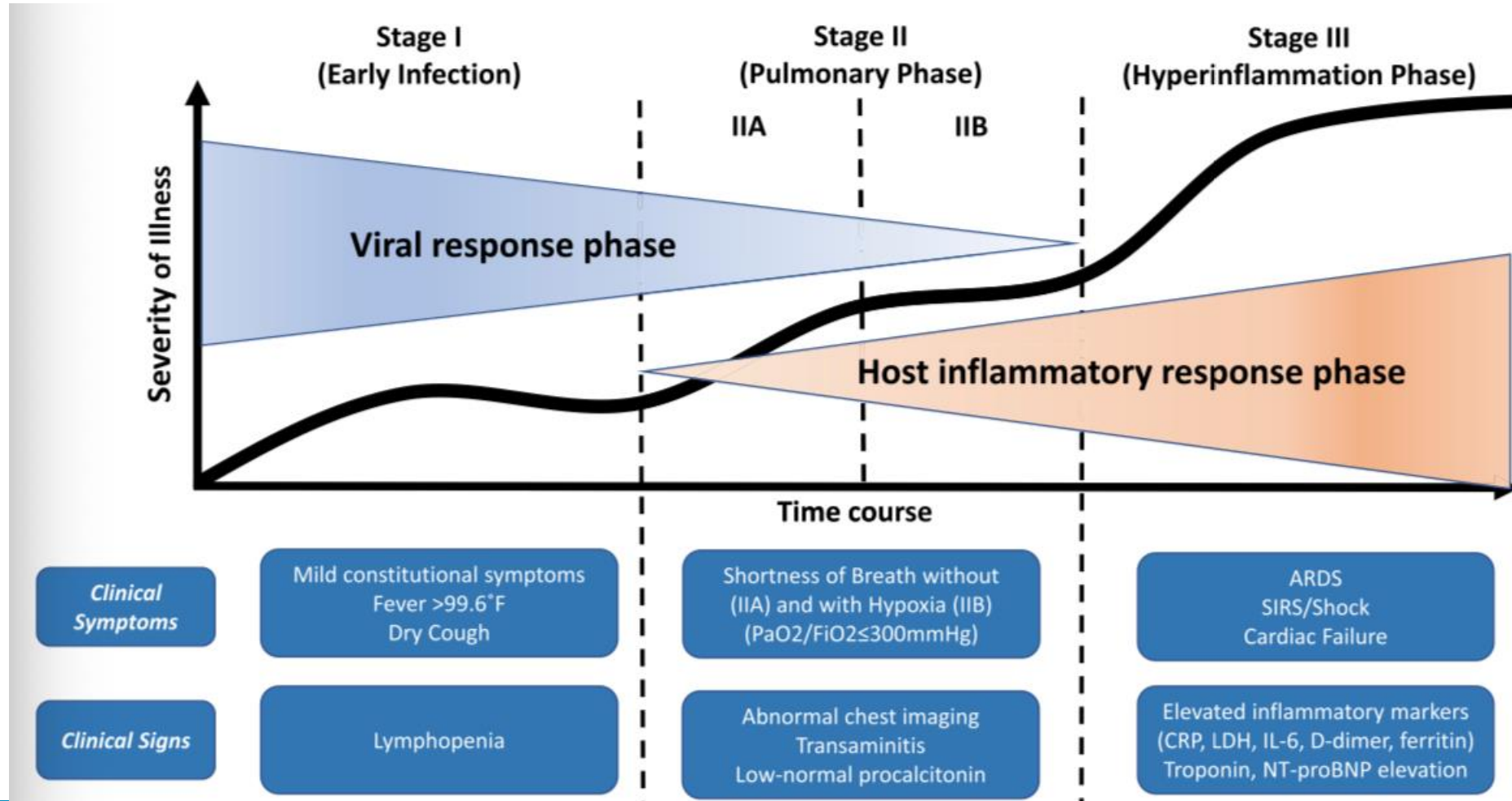


Varga et al. Lancet 2020 <https://doi.org/10.1016/>



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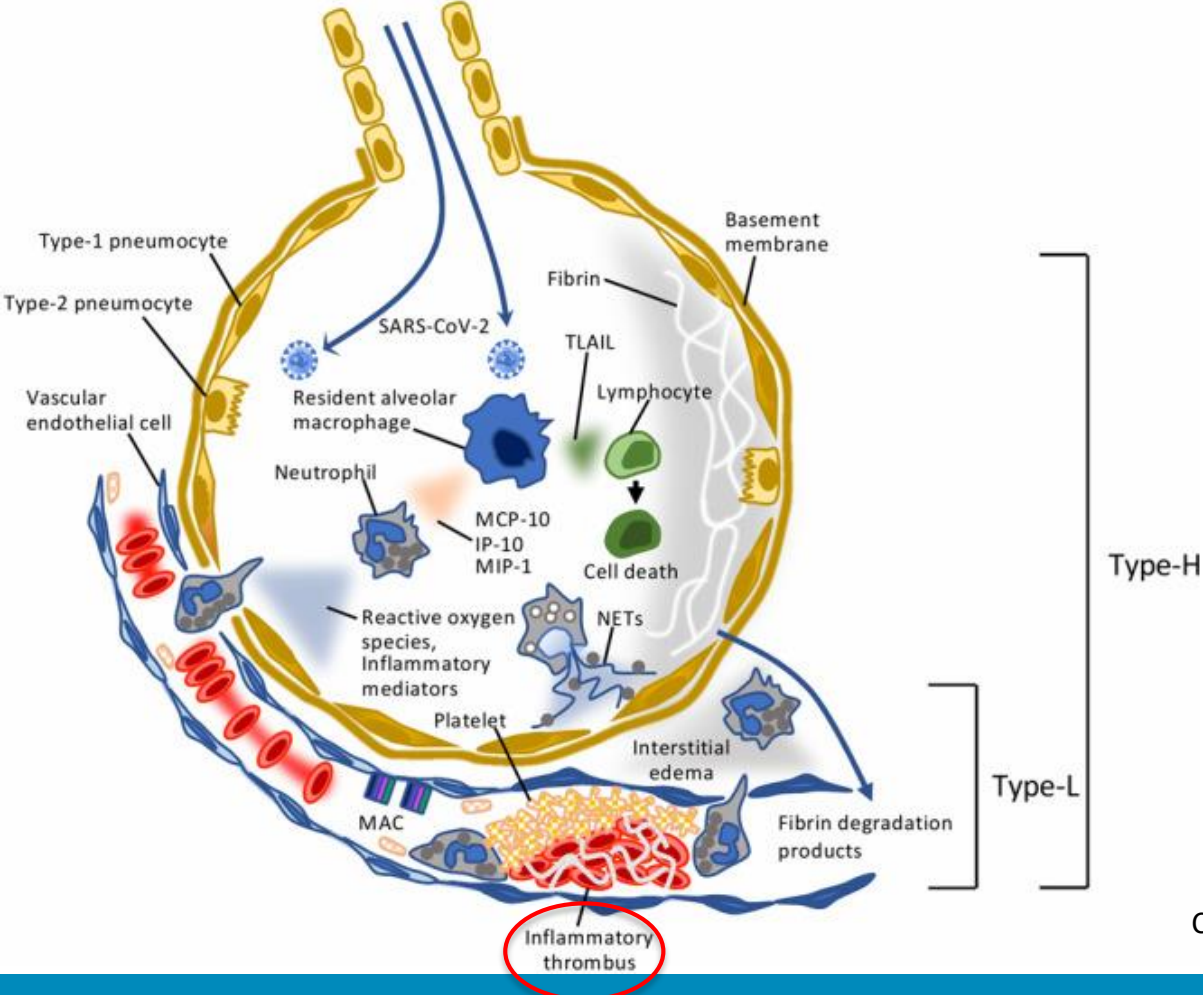
## 2. Hyperinflammation in severe COVID-19 leads to immunothrombosis



Siddiqui et al. JHLT May 2020



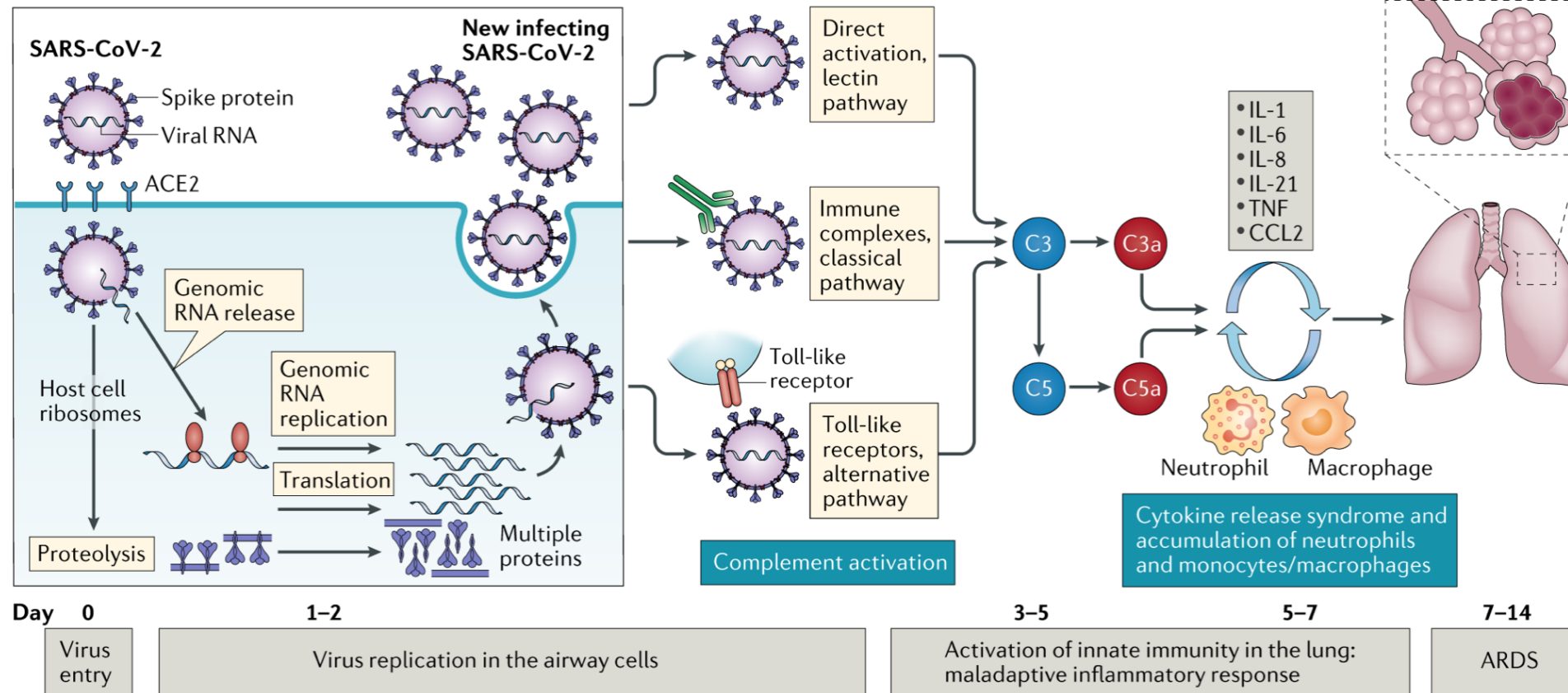
# The lung as the epicenter of COVID-19 induced coagulopathy



Crit Care Med. 2020 May 27; 1097/CCM



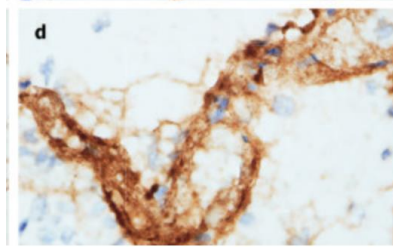
# 3. Complement activation in COVID-19



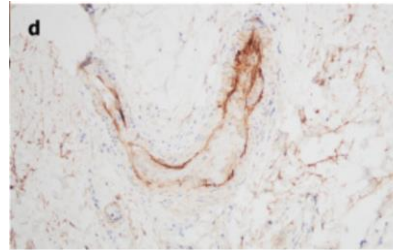
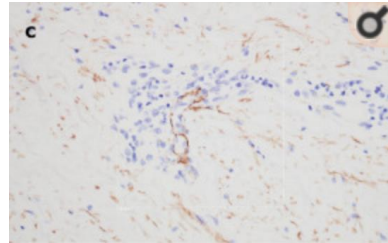
Risitano et al Nat Rev Immun. 20, 343-344 2020

# Complement-mediated microvascular injuries

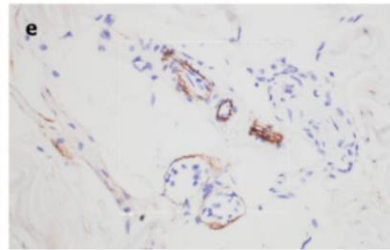
Pulmonary



Dermal



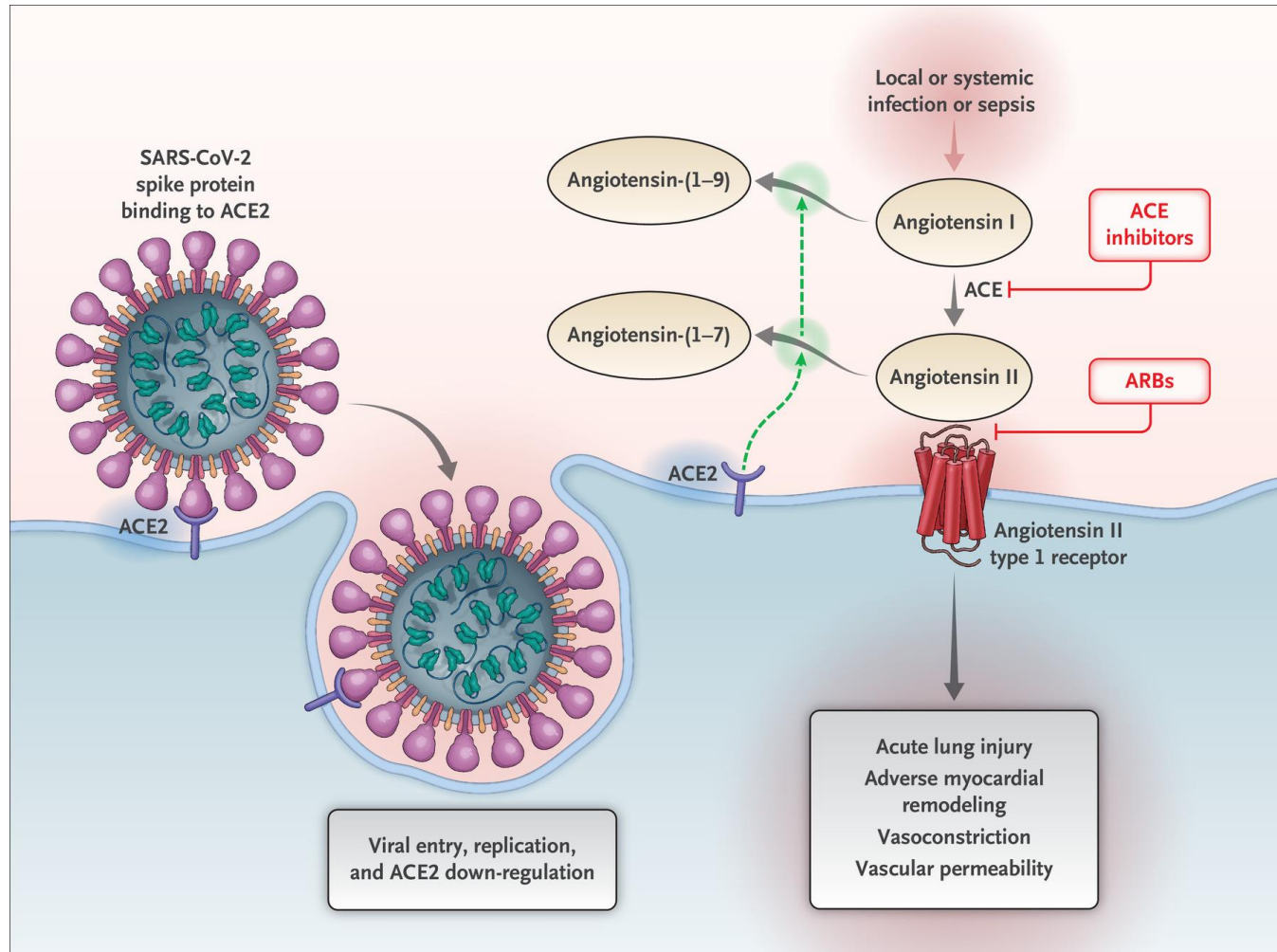
Normal adjacent muscle



C5b-9 deposition

Magro et al. Transl Res. 2020 April 15

# 4. Dysregulated renin-angiotensin (RAS)



Vaduganathan et al. NEJM 382"1653-1659

# Management: Current guidelines

- ASH (Expert Panel)
- ISTH
- Recommendations are to give prophylactic anticoagulation to all patients (medical, surgical and obstetric) that are admitted with COVID-19.
- Intermediate dose and therapeutic AC in ICU patients is controversial
- Paucity of high quality data; individual institutional protocols have gone into effect.



# Management

- For patients already on DOACs:
  - Continue DOACs as outpatient
  - Switch to shorter acting parenteral agents if admitted due to clinical status
  - Important to note significant drug interactions of DOACs with some of the treatments for COVID-19

# Management: post discharge

- Routine post-discharge VTE prophylaxis not recommended
- Certain high-risk populations:
  - Modified IMPROVE-VTE score  $\geq 4$  OR
  - Modified IMPROVE-VTE score  $\geq 2$  and D-dimer  $>2X$  normal OR
  - Age  $>60$  years, D-dimer  $>2$  times normal, and previous VTE or cancer
- Also consider individual patient risk factors, mobility, bleeding risks



# Outpatient management of mild COVID-19

- No routine VTE prophylaxis is recommended
- Case by case discussion of the high risk patients should again be considered

# IMPROVE RISK SCORE

VTE risk factor	VTE risk score
Previous VTE	3
Known thrombophilia <sup>a</sup>	2
Current lower limb paralysis or paresis <sup>b</sup>	2
History of cancer <sup>c</sup>	2
ICU/CCU stay	1
Complete immobilization <sup>d</sup> $\geq$ 1 d	1
Age $\geq$ 60 y	1

Abbreviations: CCU, cardiac care unit; ICU, intensive care unit; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; NIH, National Institutes of Health; VTE, venous thromboembolism.

<sup>a</sup>A congenital or acquired condition leading to excess risk of thrombosis (e.g., factor V Leiden, lupus anticoagulant, factor C or factor S deficiency).

<sup>b</sup>Leg falls to bed by 5 seconds, but has some effort against gravity (taken from NIH stroke scale).

<sup>c</sup>Cancer (excluding nonmelanoma skin cancer) present at any time in the past 5 years (cancer must be in remission to meet eligibility criteria).

<sup>d</sup>Immobilization is being confined to bed or chair with or without bathroom privileges.

- $\geq$ 4 OR
- 2-3 with D-dimer  $\geq$ 2 X ULN

Spyropolous et al. TH Jan 2020



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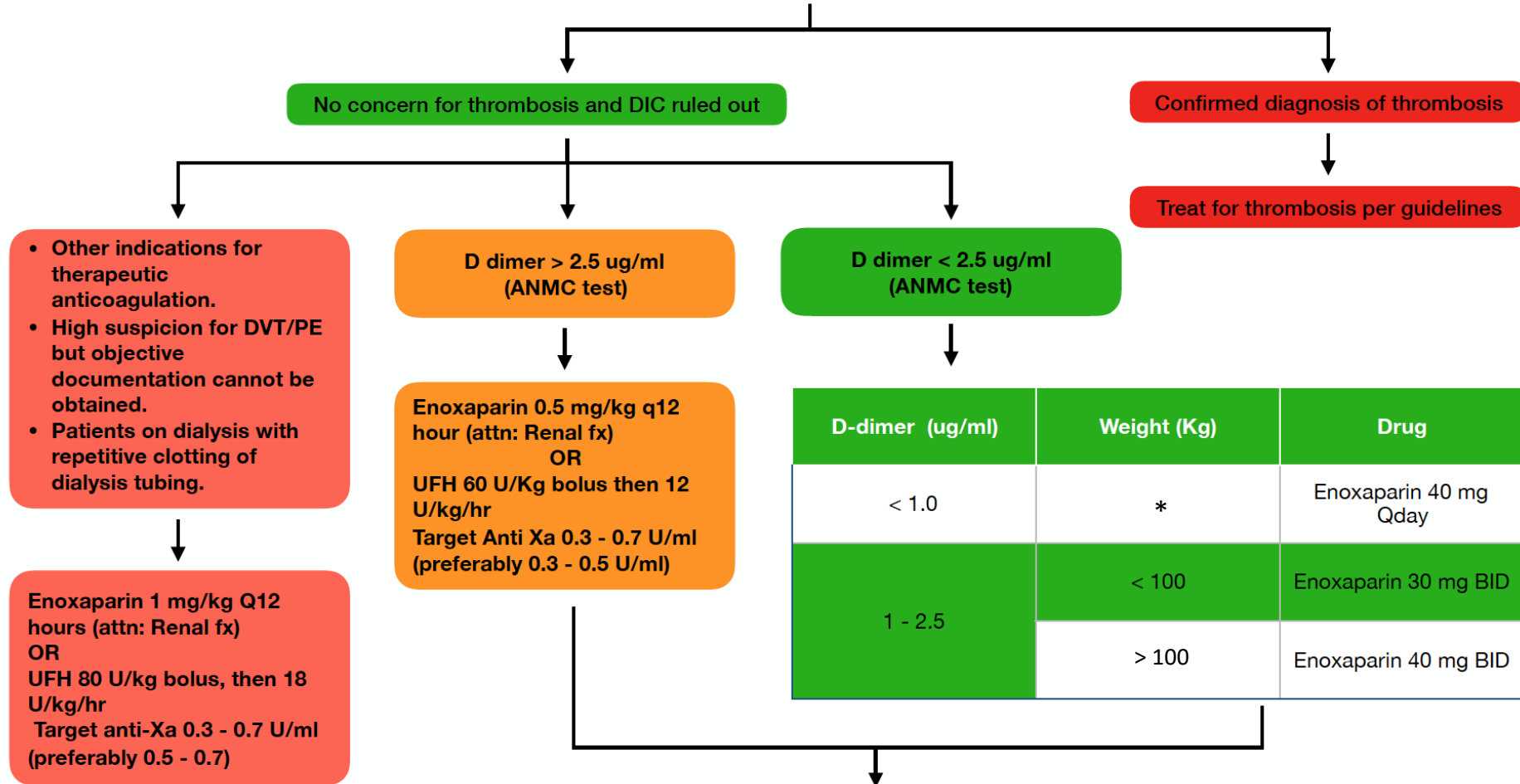
# Management: Testing

- All inpatients admitted with COVID-19 should get the following tests daily:
  - CBC with diff
  - PT, INR, PTT
  - D-dimer
  - Fibrinogen
- Institutional protocols are based on D-dimer levels



# ANMC COVID19 Thromboprophylaxis Guidelines (5.14.2020)

**History:** Symptoms suggestive of arterial or venous thrombosis  
**Physical exam:** Look for signs of arterial or venous thrombosis  
**Labs:** Check PT, PTT, Fibrinogen and D-dimer daily



**Post discharge:**

- Consider Apixaban 2.5 mg BID or Rivaroxaban 10 mg once daily for 30 days or until mobile.
- Educate patient about symptoms of DVT (swelling, pain, redness, warmth) and PE (SOB, CP, tachycardia, cough/hemoptysis)

**\*Please consult hematology for any questions\***

**THANK YOU!**

**QUESTIONS?**



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