Webinar: Trombosis i anticoagulació: com impactarà en la pràctica clínica la pandèmia COVID-19?

Coagulopatia induïda per COVID-19: que coneixem?

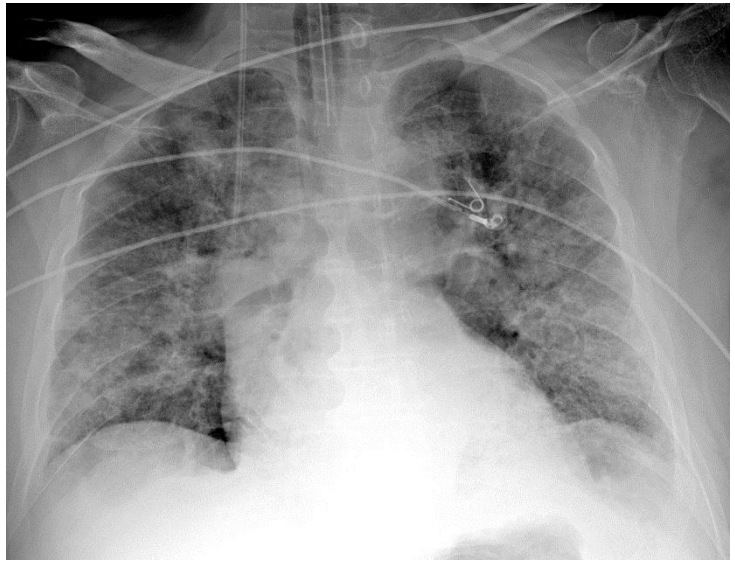
Alessandro Sionis
Intensive Cardiac Care Unit
Cardiology Department
Hospital de la Santa Creu i Sant Pau
Universitat Autònoma de Barcelona
Spain

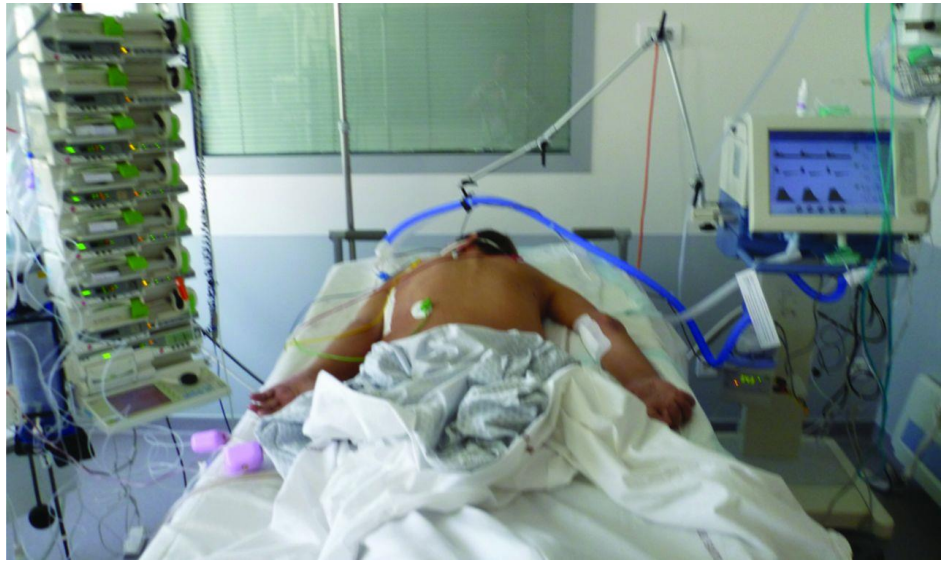
Disclosures (last 5 years)

- Advisory: Ferrer, Maquet, Orion-Pharma, Sanofi
- Speaker: Abiomed, Amgen, Astra-Zeneca, Bayer, Daichii-Sankyo, Ferrer, Maquet, Novartis, Orion-Pharma, Sanofi, Servier, Singulex
- Clinical trials: Bayer, Cardiorentis, DalCor, Esperion, Ferrer, Janssen, Novartis, Orion-Pharma, Singulex, Zoll
- Research grants: Novartis, Orion-Pharma, Singulex
- Royalties: No

Case 1

- 64-year-old man with a previous history of hypertension and dyslipidaemia treated with valsartan and atorvastatin
- He was admitted to the ICU on 15 March 2020 with severe respiratory failure (Pa/FiO2: 90) and underwent intubation for invasive mechanical ventilation ventilation with lung protective strategy

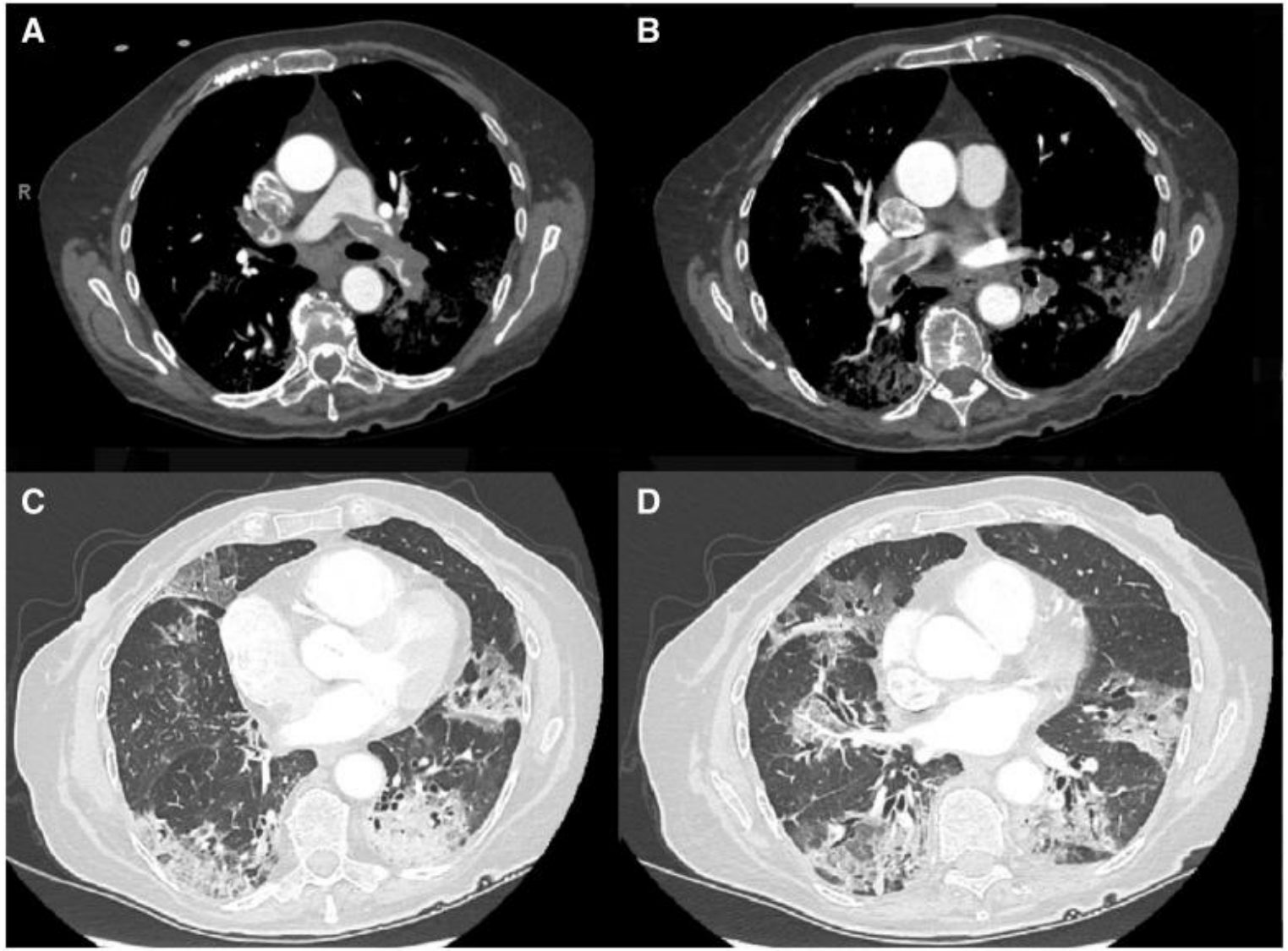




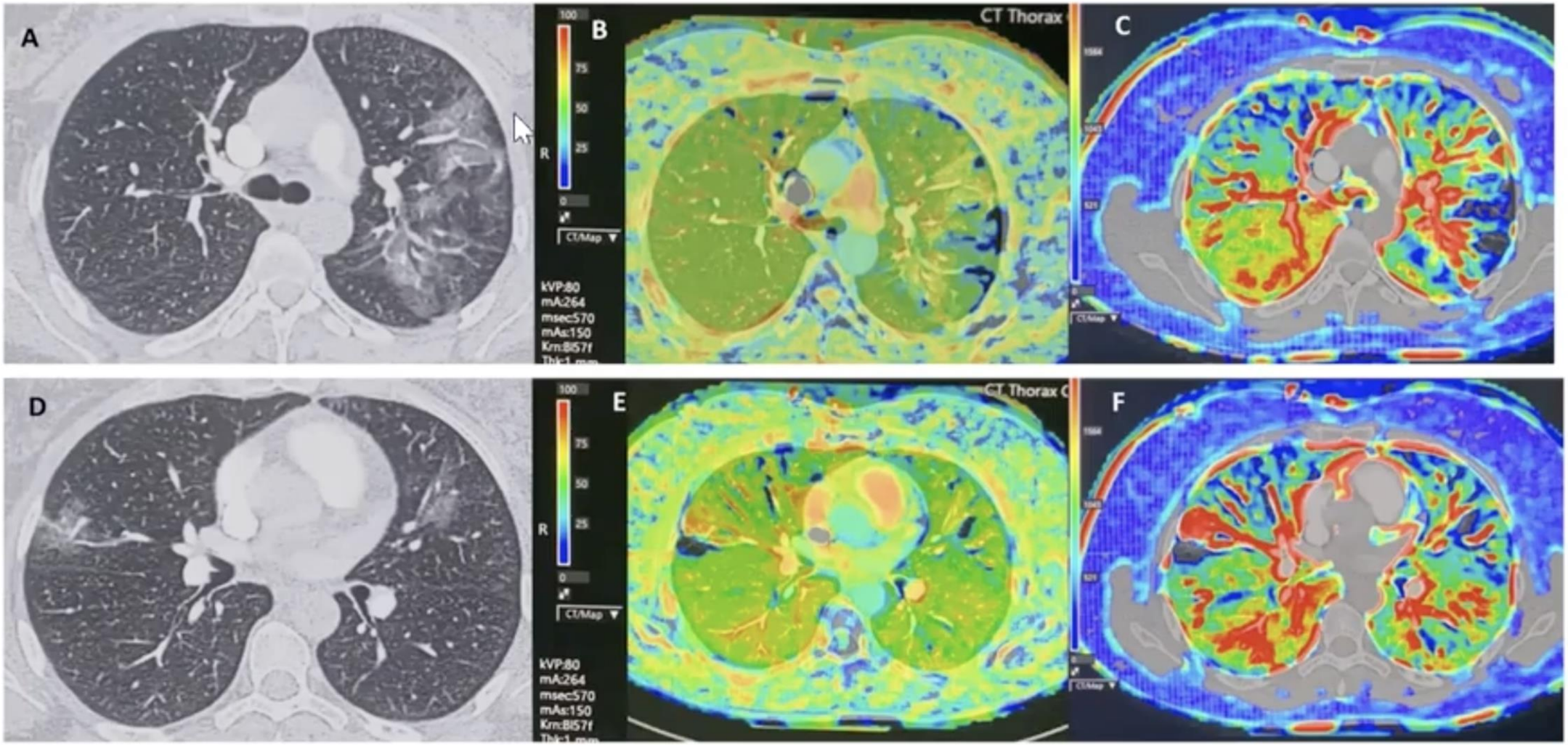
Case 1

- 64-year-old man with a previous history of hypertension and dyslipidaemia treated with valsartan and atorvastatin
- He was admitted to the ICU on 15 March 2020 with severe respiratory failure (Pa/FiO2: 90) and underwent intubation for invasive mechanical ventilation with lung protective strategy
- He improved after 3 cycles of prone-positioning (Pa/FiO2: 170) and was switched to pressure support ventilation
- On day 6 oxygenation worsened suddenly with a steep rise in pCO2. Lab results were remarkable for increased D-dimer (from 700 to 12,000 ng/mL)
- A chest CT scan was performed showing acute pulmonary embolism

Case 1



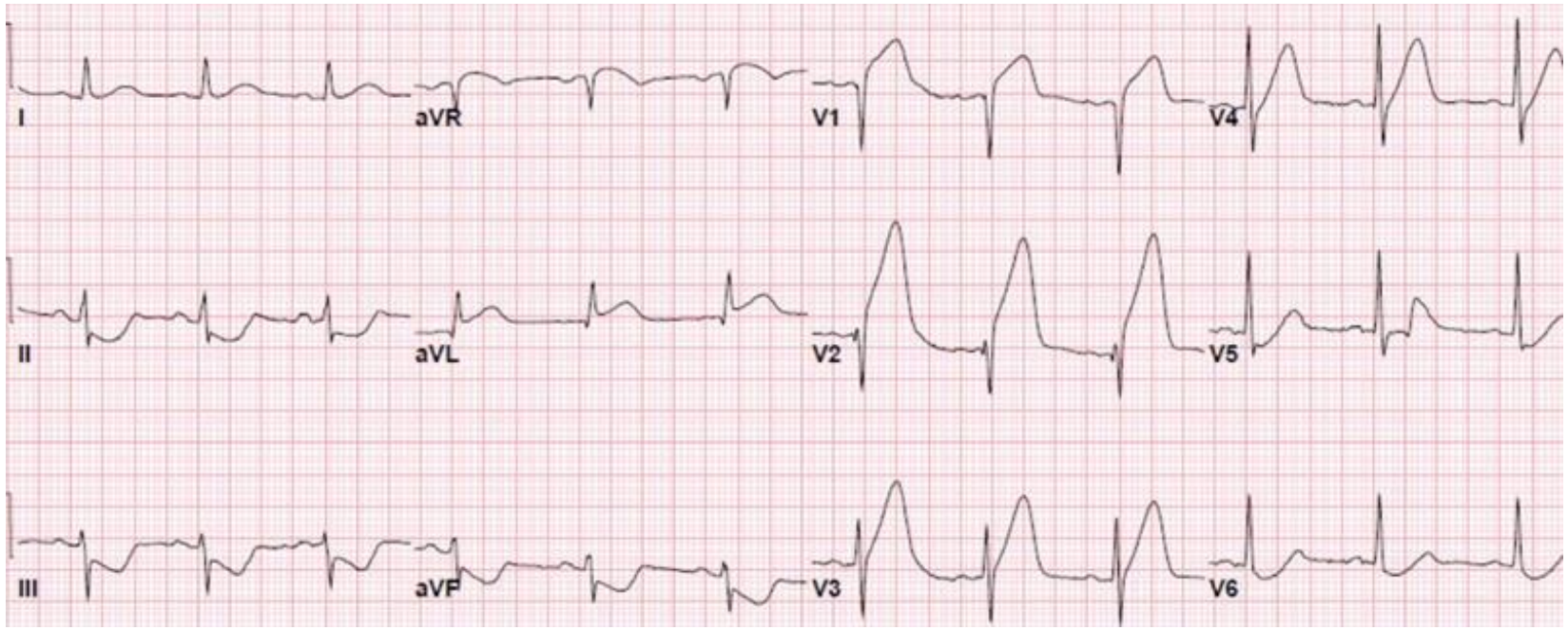
Lung CT Perfusion Scan: Microvascular Obstruction



Courtesy: Hidalgo A. Hospital de Sant Pau

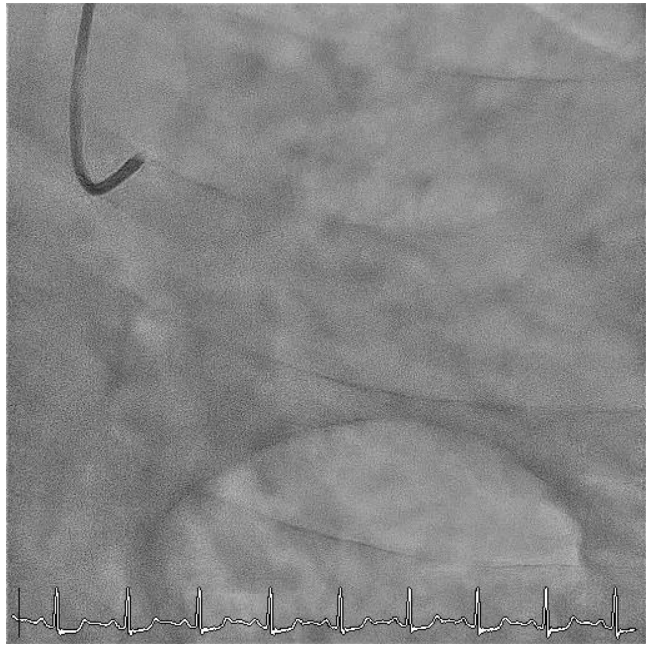
Case 2

- 52-year-old man with a previous history of obesity and type 2 diabetes
- On 21 March 2020 he presented to the emergency department with chest pain



Case 2

- 52-year-old man with a previous history of obesity and type 2 diabetes
- On 21 March 2020 he presented to the emergency department with chest pain
- He underwent immediate coronary angiography that showed a thrombus in the proximal LAD that was removed with an aspiration catheter



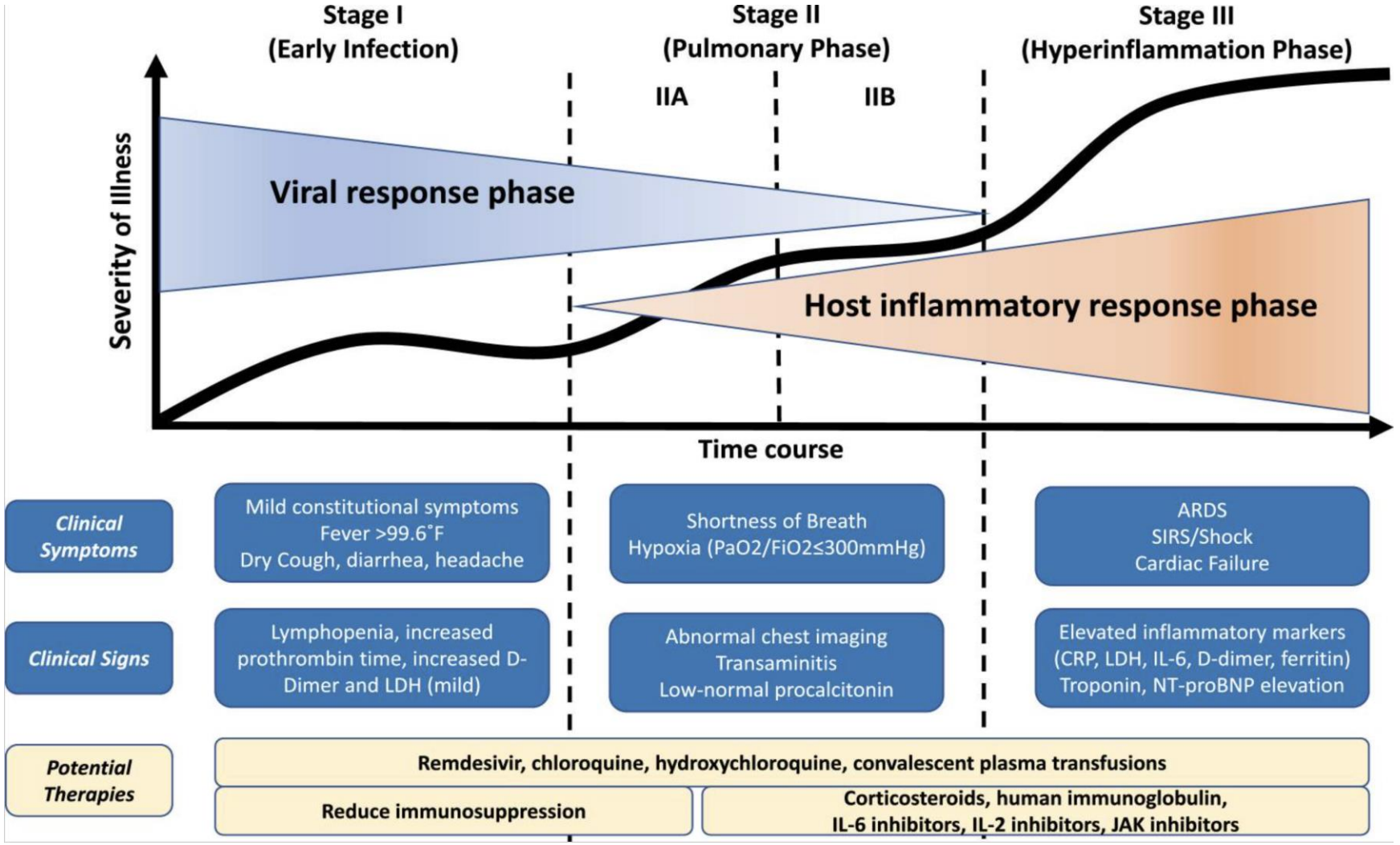
Case 2

- 52-year-old man with a previous history of obesity and type 2 diabetes
- On 2 April 2020 he presented to the emergency department with chest pain
- He underwent immediate coronary angiography that showed a thrombus in the proximal LAD that was removed with an aspiration catheter
- OCT did not demonstrated an underlying plaque rupture
- His PCR was positive for SARS-CoV-2 infection
- He had normal chest x-ray and ABG.

Background

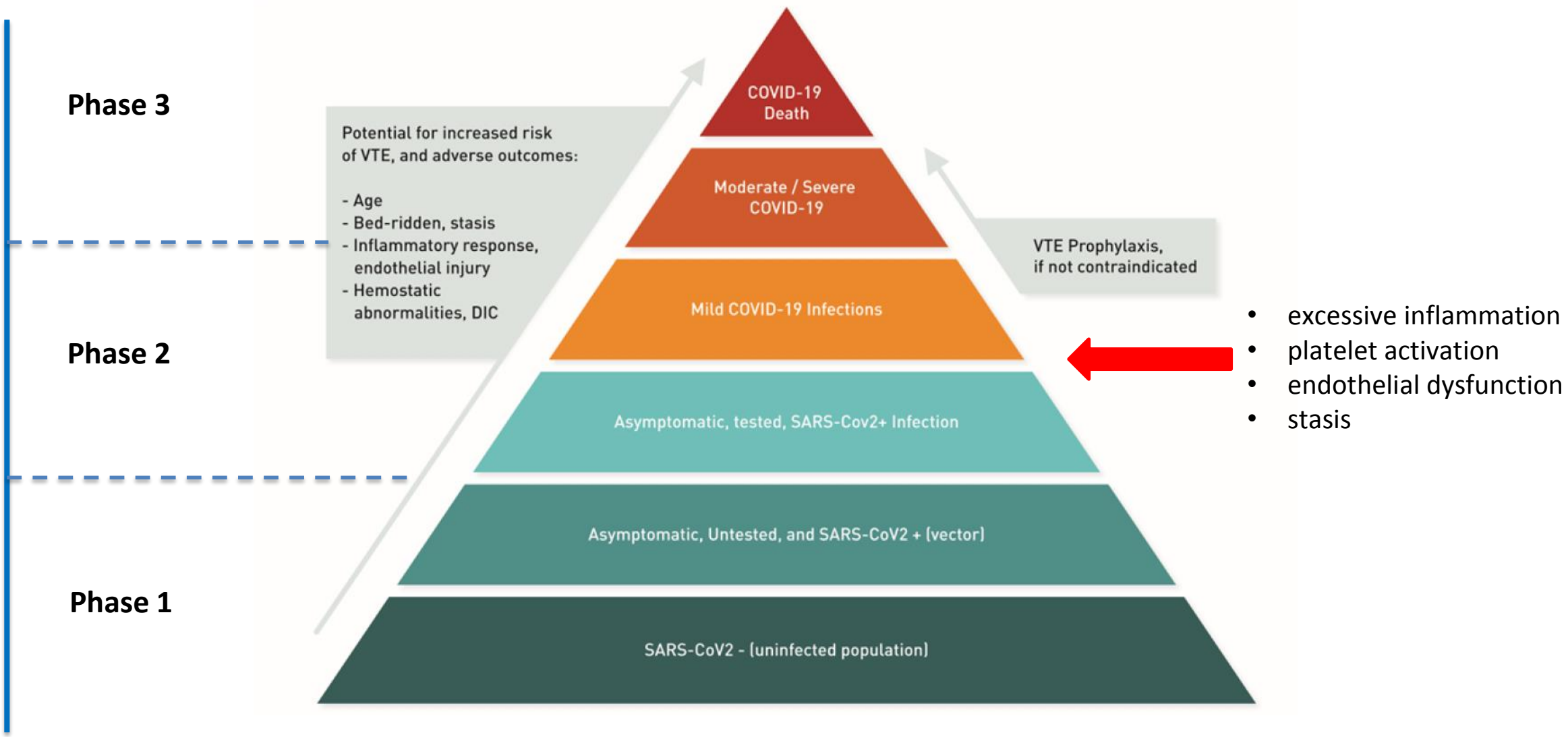
- Almost 6.5 million people have been affected by the SARS-CoV-2 pandemic
- The clinical spectrum appears to be wide encompassing asymptomatic infection, mild respiratory tract illness to severe viral pneumonia with respiratory failure and death
- So far it has caused almost 400,000 deaths worldwide with reported mortality rates between 3 and 1%
- The pathophysiology of SARS-CoV-2 infection is still largely poorly understood but one of its hallmarks is COVID-19 associated coagulopathy (CAC) in which a severe prothrombotic state predominates
- This presentation focuses on the main features of CAC

Classification of COVID-10 Disease States



Siddiqi HK et al. Heart Lung Transplant. 2020 May;39(5):405-407

Risk of Thrombotic Disease in COVID-19



- excessive inflammation
- platelet activation
- endothelial dysfunction
- stasis

Bikdeli B et al. J Am Coll Cardiol 2020; https://doi.org/10.1016/j.jacc.2020.04.031

Abnormal Coagulation Parameters and Prognosis in COVID-19

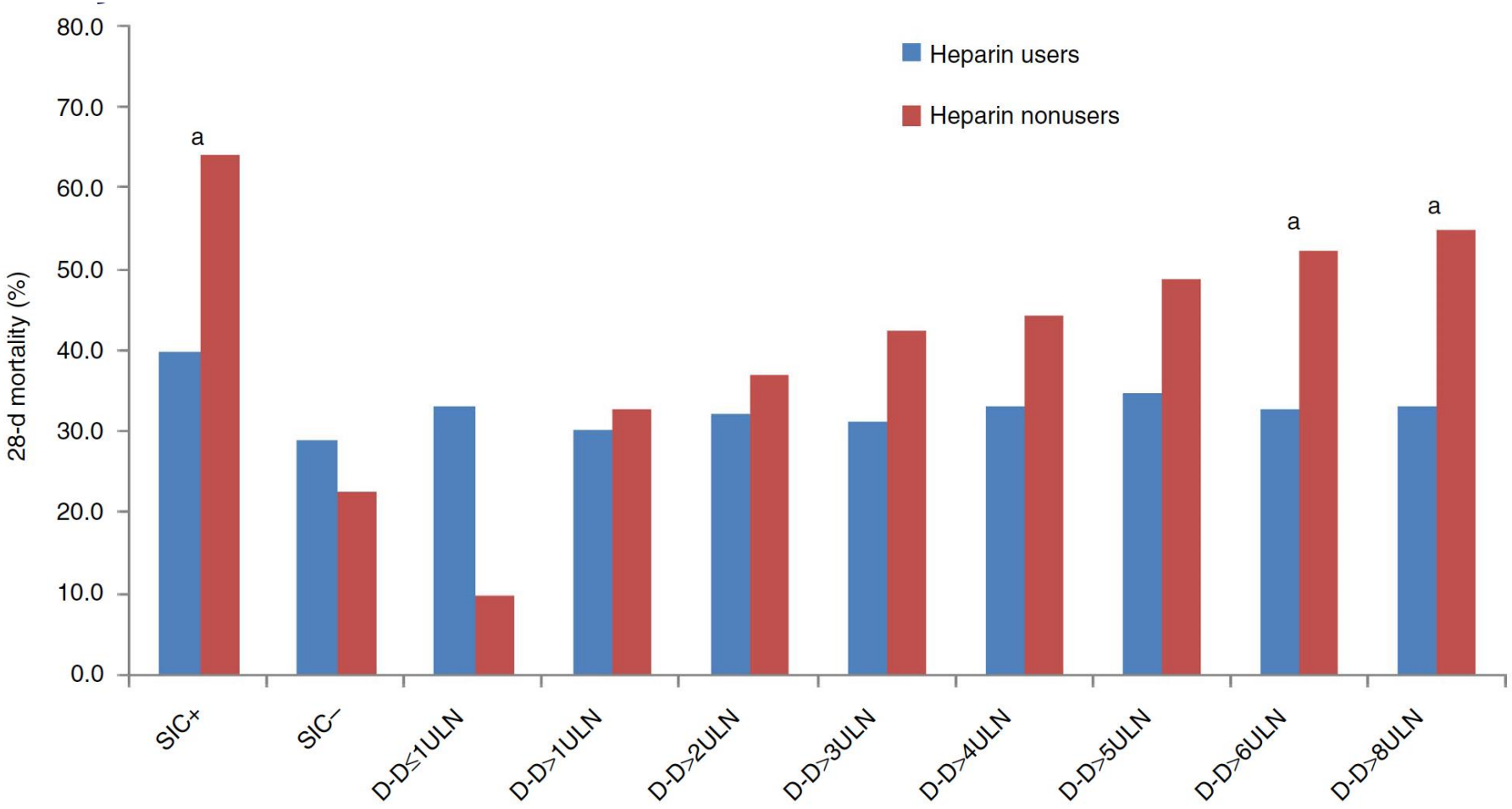
Coagulation Parameters on Admission

Parameters	Normal range	Total (n = 183)	Survivors (n = 162)	Non-survivors (n = 21)	*P* values
Age (years)		54.1 ± 16.2	52.4 ± 15.6	64.0 ± 20.7	<.001
Sex (male/female)		98/85	82/80	16/5	.035
With underlying diseases		75 (41.0%)	63 (38.9%)	12 (57.1%)	.156
On admission					
PT (sec)	11.5-14.5	13.7 (13.1-14.6)	13.6 (13.0-14.3)	15.5 (14.4-16.3)	<.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)	.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)	.149
D-dimer (μg/mL)	<0.50	0.66 (0.38-1.50)	0.61 (0.35-1.29)	2.12 (0.77-5.27)	<.001
FDP (μg/mL)	<5.0	4.0 (4.0-4.9)	4.0 (4.0-4.3)	7.6 (4.0-23.4)	<.001
AT (%)	80-120	91 (83-97)	91 (84-97)	84 (78-90)	.096

Mortality 11.5%; 71.4% of non-survivors met ISTH criteria for DIC

Tang N et al. J Thromb Haemost 2020 Apr;18(4):844-847.

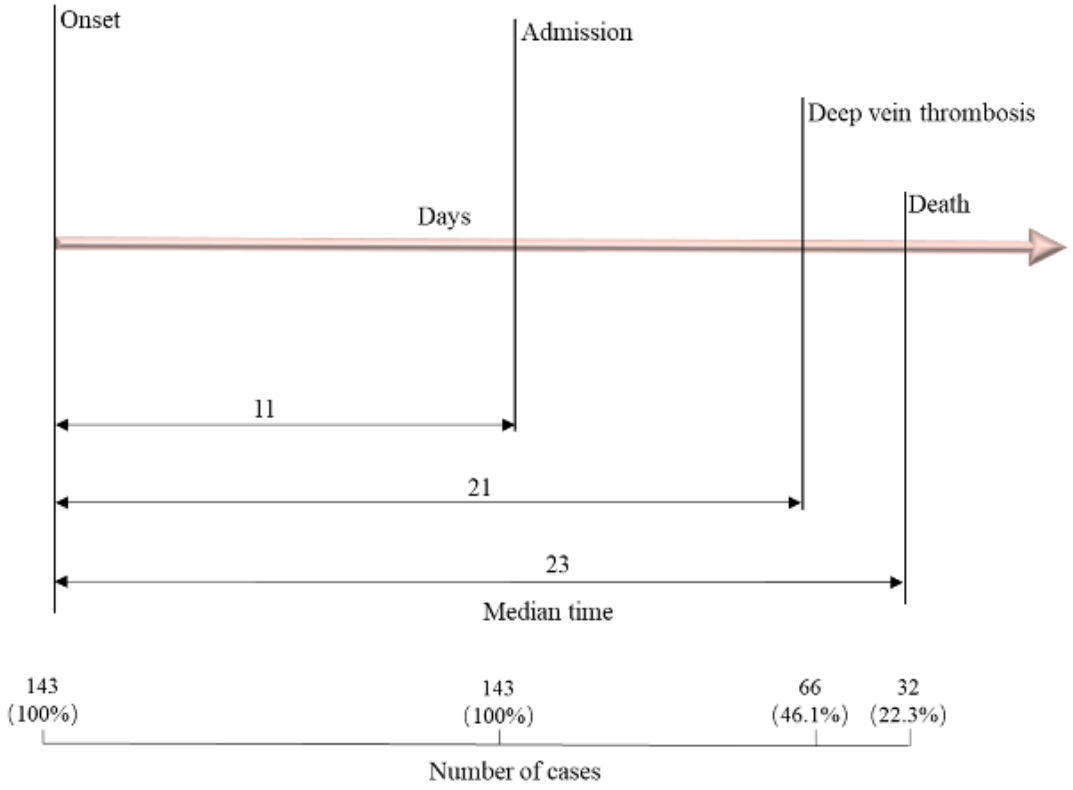
Anticoagulation Improves Prognosis in COVID-19

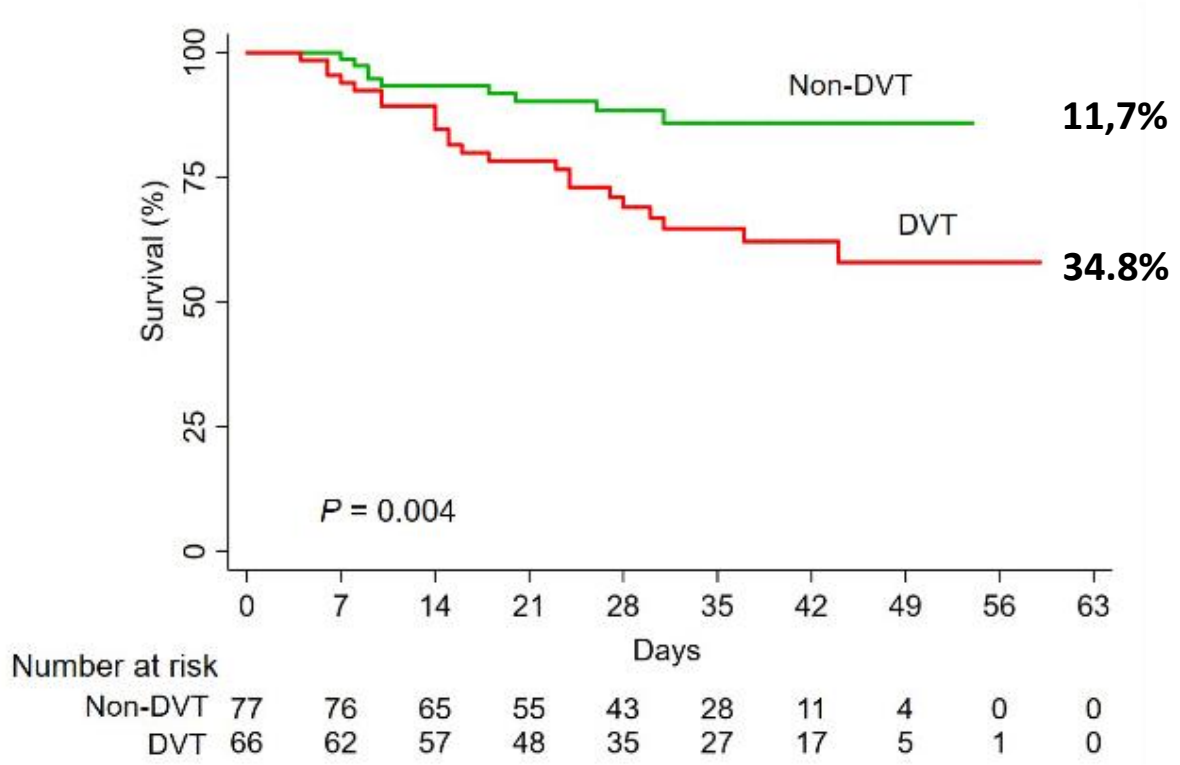


Mortality: SIC score ≥4 (40.0% vs 64.2%, P = .029), or D-dimer >6-fold of upper limit of normal (32.8% vs 52.4%, P = .017).

Tang N et al. J Thromb Haemost 2020 May;18(5):1094-1099.

Deep Vein Thrombosis (DVT) in COVID-19





DVT 46.1% (65.2% distal); CURB-65 score 3-5 (OR = 6.122, *P* = 0.031), Padua prediction score ≥ 4 (OR = 4.016, *P* = 0.04), and D-dimer >1.0 (µg/ml) (OR = 5.818, *P* < 0.014) with a sensitivity of 88.5% for DVT; BUT low prophylaxis rate (37.1%)

Zhang L et al. Circulation. 2020 May 18. doi: 10.1161/CIRCULATIONAHA.120.046702

Thrombotic Complications in COVID-19

Venous and arterial thromboembolic events in hospitalized COVID-19 patients.

	Intensive care unit			General ward			Total		
Thromboembolic events	n	% of closed cases (n = 48)	% of imaging tests performed*	n	% of closed cases (n = 314)	% of imaging tests performed*	n	% of closed cases (n = 362)	% of imaging tests performed
At least one thromboembolic event	8	16.7% (95%CI 8.7%–29.6%)	–	20	6.4% (95%CI 4.2%–9.6%)	–	28	7.7% (95%CI 5.4%–11.0%)	–
VTE	4	8.3%	22%	12	3.8%	46%	16	4.4%	36%
PE (± DVT)	2	4.2%	25%	8	2.5%	36%	10	2.8%	33%
Isolated pDVT	1	2.1%	7%	3	1.0%	44%	4	1.1%	21%
Isolated dDVT	0	–	–	1	0.3%	13%	1	0.3%	13%
Catheter-related DVT	1	2.1%	50%	0	–	–	1	0.3%	50%
Ischemic stroke	3	6.3%	–	6	1.9%	–	9	2.5%	–
ACS/MI	1	2.1%	–	3	1.0%	–	4	1.1%	–

ACS, acute coronary syndrome; DVT, deep vein thrombosis; MI, myocardial infarction; pDVT, proximal deep vein thrombosis; dDVT, distal DVT; PE, pulmonary embolism; VTE, venous thromboembolism.

388 patients; mortality 26%; 100% thromboprophylaxis; 7.7% thromboembolic events; DIC 2.2%
Confirmed by imaging: DVT 36.6%; 33.3% PE; ACS 2.5%; stroke 1.1%.

Lodigiani C et al. Thromb Research 2020; 191:9-14.

COVID-19 Thrombotic Complications in the ICU (update)

184 patients; mortality 22%; 100% thromboprophylaxis

Description of thrombotic complications.

Type of event	Number of cases	Relevant details
Pulmonary embolism	65	– 46 patients with PE in segmental or more proximal arteries, 19 patients with PE limited to subsegmental arteries
Other venous thromboembolic events	3	– 1 patient with proximal DVT of the leg – 2 patients with catheter related upper extremity thromboses
Arterial thrombotic events	7	– 5 patients with ischemic strokes – 2 patients with systemic arterial embolisms

PE/DVT/stroke/MI/SE 49%; higher risk of death (HR 5.4; 95%CI 2.4–12); no DIC.

Klok FA et al. Thromb Research 2020; Apr 30;S0049-3848(20)30157-2.

COVID-19 Thrombotic Complications in the ICU

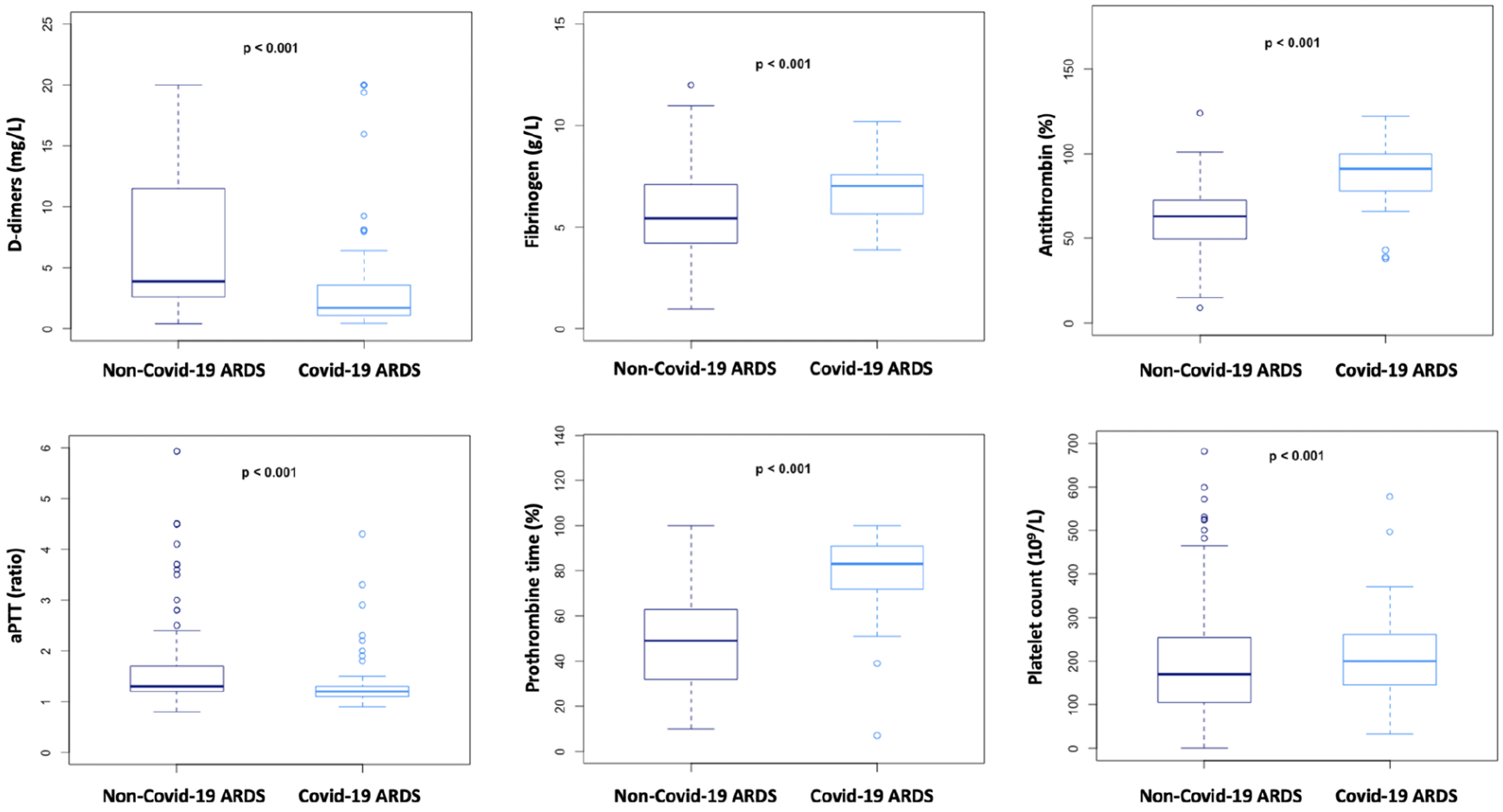
150 patients; 42.6% thrombotic events (16.7% PE)

	Population before matching ($n = 383$)				Population after matching ($n = 222$)			
	Non-COVID-19-ARDS ($n = 233$)	COVID-19-ARDS ($n = 150$)	OR [95% IC]	*p*-value	Non-COVID-19-ARDS ($n = 145$)	COVID-19-ARDS ($n = 77$)	OR [95% IC]	*p*-value
Thrombo-embolic complications—*n* (%)	14 (6)	27 (18)	3.4 [1.7–7.3]	< 0.001	7 (4.8)	9 (11.7)	2.6 [1.1–6.1]	0.04
Pulmonary embolisms—*n* (%)	3 (1.3)	25 (16.7)	15.2 [4.5–80.4]	< 0.001	3 (2.1)	9 (11.7)	6.2 [1.6–23.4]	0.01
Deep vein thrombosis—*n* (%)	3 (1.3)	3 (2)	1 [0.1–9.2]	1	2 (1.4)	0 (0)	–	–
Myocardial infarction—*n* (%)	6 (2.6)	0 (0)	0 [0–1.3]	0.09	2 (1.4)	0 (0)	–	–
Cerebral ischemic attack—*n* (%)	1 (0.4)	2 (1.3)	3.1 [0.2– 185.5]	0.68	0 (0.0)	0 (0)	–	–
Limb ischemia—*n* (%)	0 (0)	1 (0.7)	Inf [0.0–Inf]	0.78	0 (0.0)	0 (0)	–	–
Mesenteric ischemia—*n* (%)	3 (1.3)	1 (0.7)	0.5 [0.0–6.5]	0.98	2 (1.4)	1 (1.3)	0.96 [0.09–9.8]	0.97
Nb of RRT filter per dialyzed patient—median, IQR	1 [2–1]	3 [2–7]	–	< 0.001	2.0 [1.0–2.5]	3.0 [2.0–6]	–	0.03
Nb of RRT filter per day of RRT—median, IQR	0.3 [0.3; 0.5]	0.7 [0.5; 1]	–	< 0.001	0.3 [0.3; 0.4]	0.7 [0.5; 1]	–	< 0.001
ECMO oxygenator thrombosis—*n* (%)	1/10 (10)	2/12 (16.7)	–	0.59	1/7 (14.3)	0/4 (0)	–	–
Hemorrhagic complications—*n* (%)	1 (1.8)	4 (2.7)	2.4 [0.27–28.5]	0.6	2 (1.4)	0 (0)	–	–

Helms J et al. Intensive Care Med . 2020 May 4;1-10. doi: 10.1007/s00134-020-06062-x.

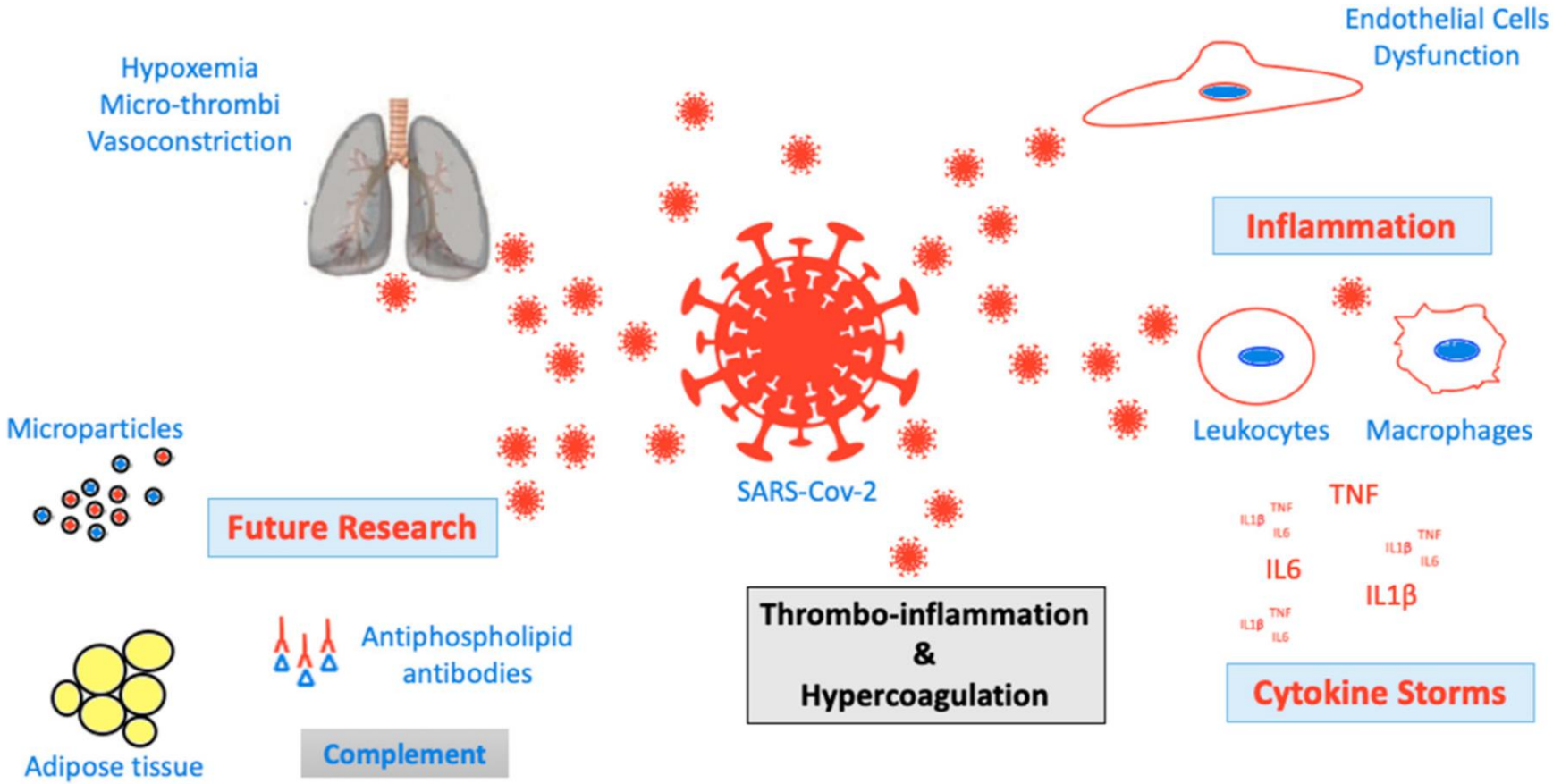
COVID-19 Thrombotic Complications in the ICU

Coagulation Parameters



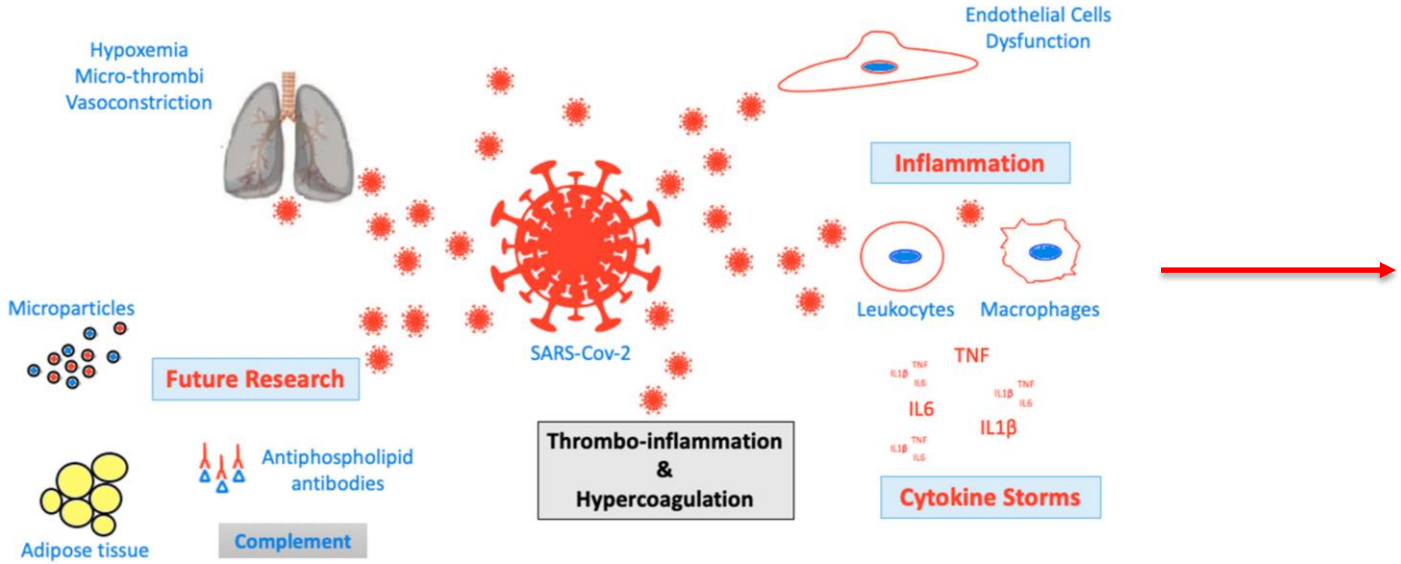
Helms J et al. Intensive Care Med . 2020 May 4;1-10. doi: 10.1007/s00134-020-06062-x.

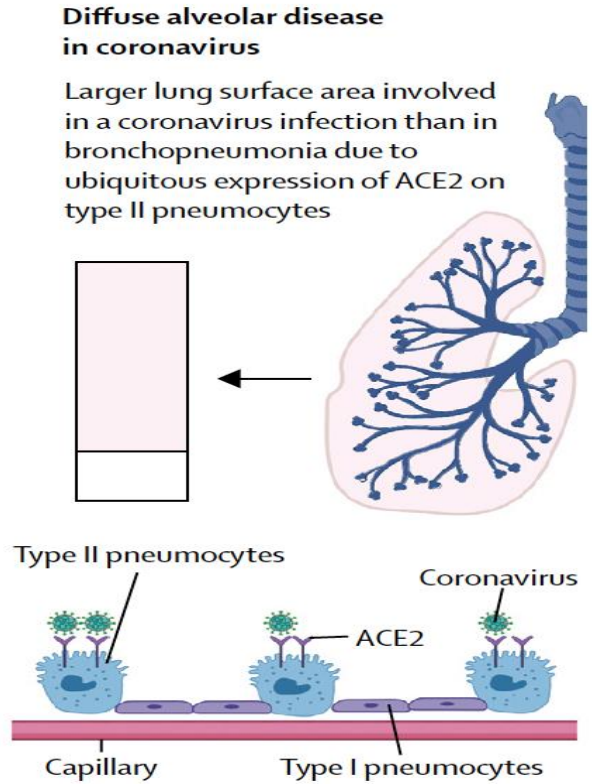
COVID-19 Coagulopathy: Key Mechanisms



Marchandot B et al. J. Clin. Med. 2020, 9(6), 1651 0-02134-33

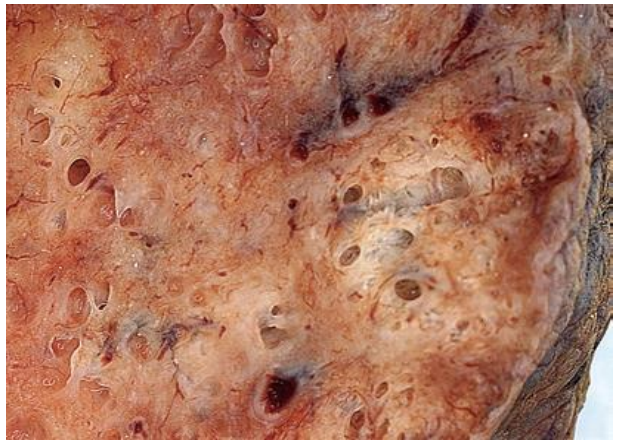
COVID-19 Coagulopathy: Key Mechanisms

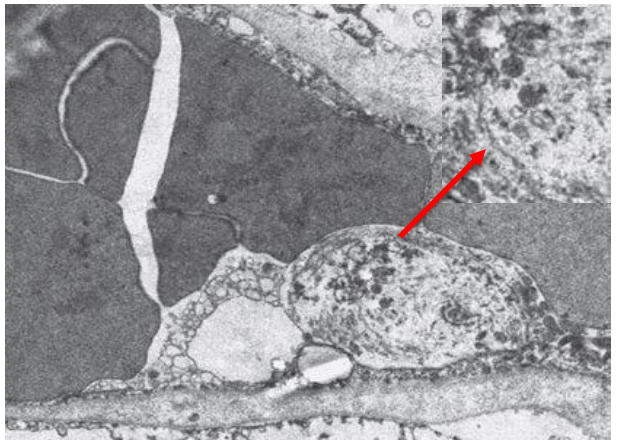


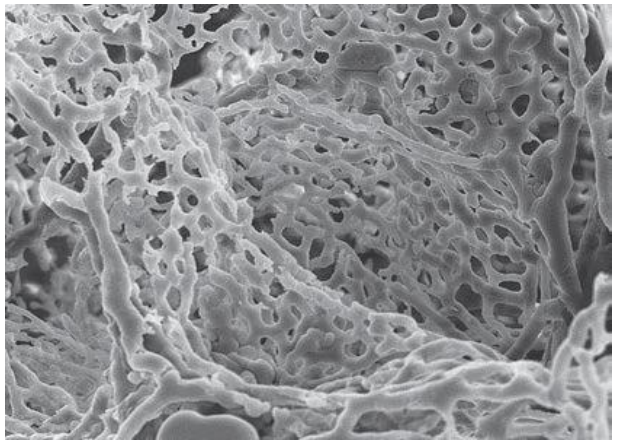


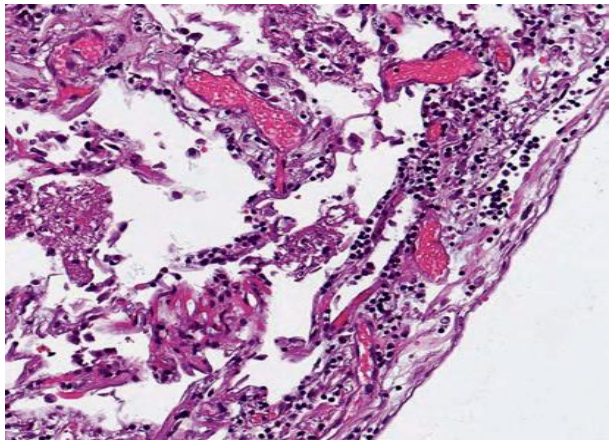
Marchandot B et al. J. Clin. Med. 2020, 9(6), 1651 0-02134-33

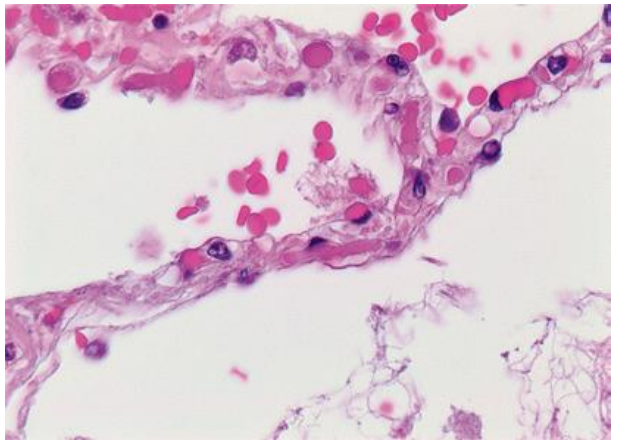
COVID-19: Autopsy Findings in Lungs

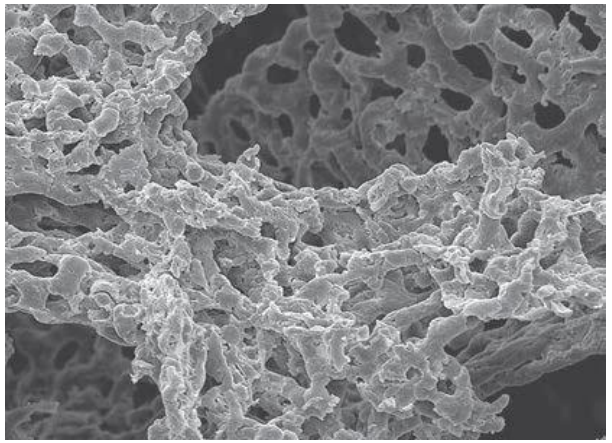












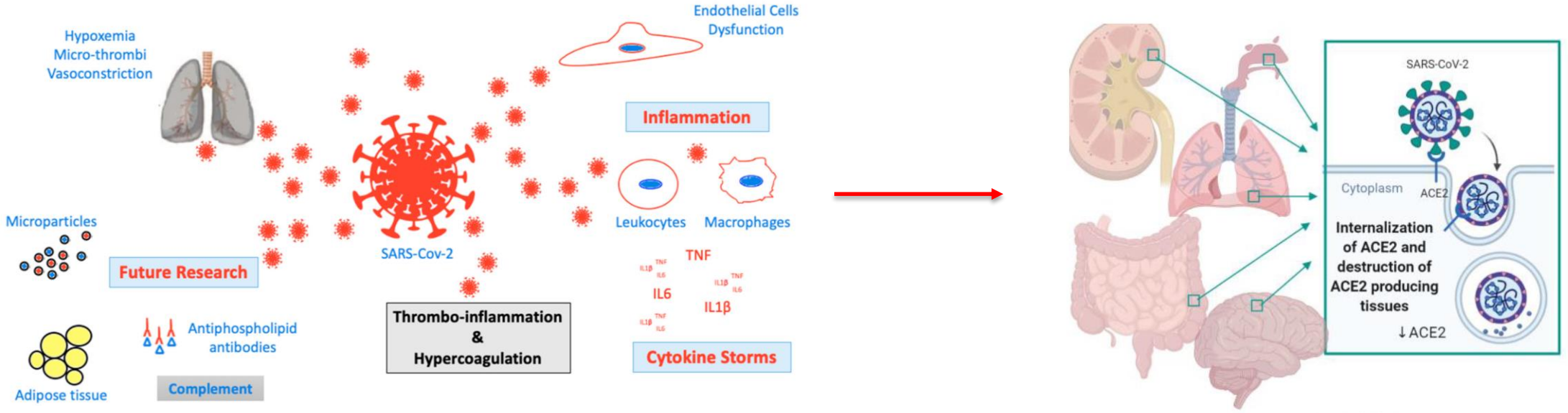
Limphocytic inflammation (endothelialitis)

Microthrombi in interalveolar septa

Microvascular corrosion (healthy vs COVID-19)

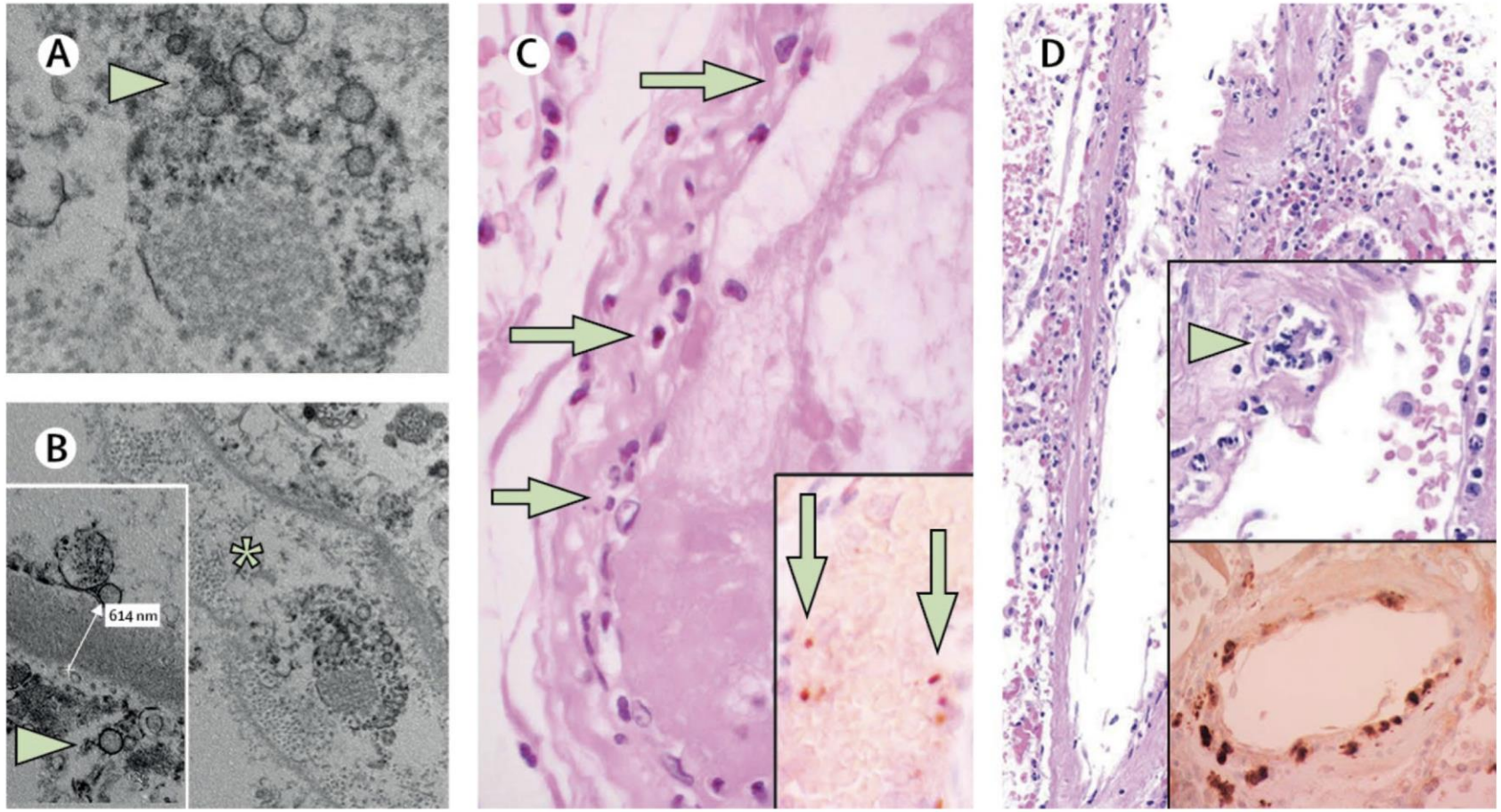
Ackermann M et al. N Engl J Med 2020; May 21, 2020 DOI: 10.1056/NEJMoa2015432

COVID-19 Coagulopathy: Key Mechanisms



Marchandot B et al. J. Clin. Med. 2020, 9(6), 1651 0-02134-33

COVID-19 Coagulopathy: Not Only the Lungs



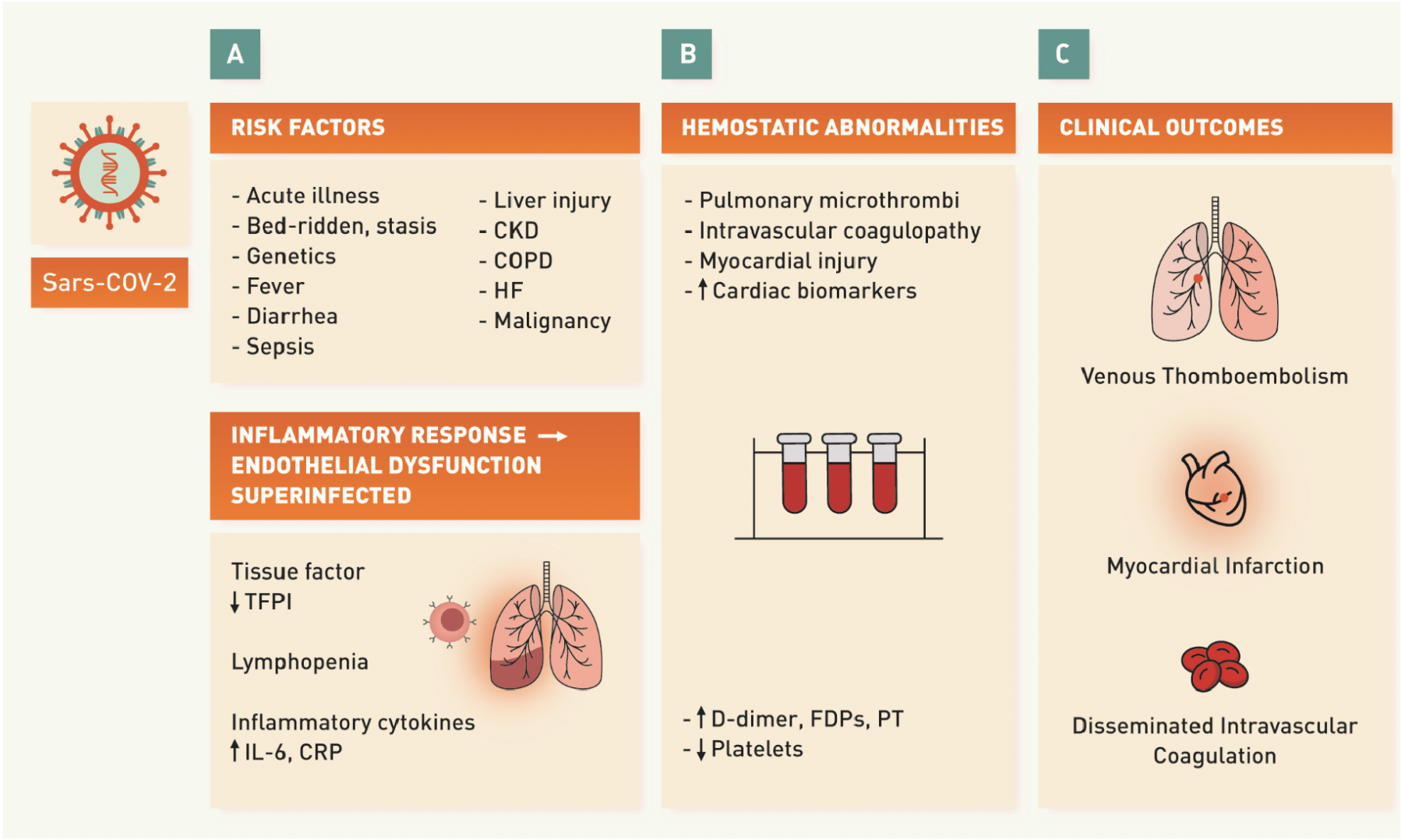
Glomerular capillary loops

Small intestine

Apoptotic endotelial cells

Becker RC. J Thromb Haemost 2020; doi.org/10.1007/s11239-020-02134-33

Pathogenesis of Thrombosis in COVID-19



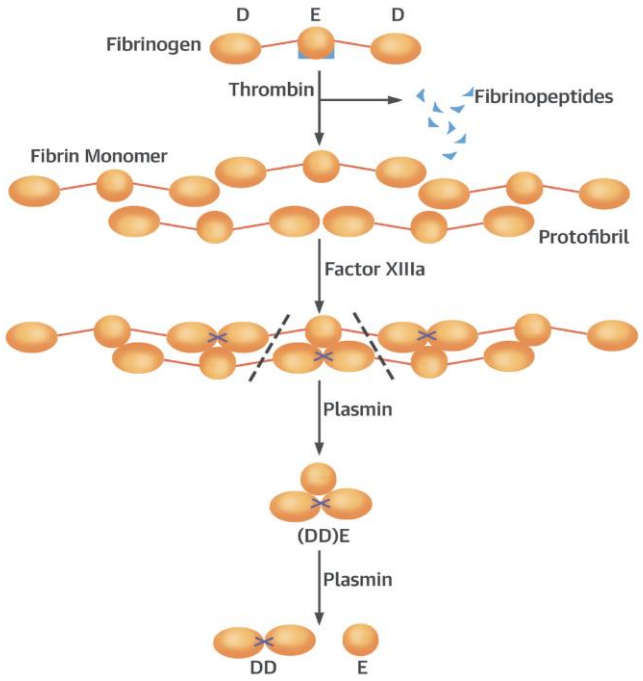
Bikdeli B et al. J Am Coll Cardiol 2020; https://doi.org/10.1016/j.jacc.2020.04.031

Take Home Messages

- COVID associated coagulopathy (CAC) is one of the clinical hallmarks of SARS-CoC-2 infection
- CAC presents with prominent elevation of D-dimer and fibrin/fibrinogen degradation products that often predate thrombotic events
- Thrombotic events are common in severe cases and are associated with worse prognosis
- The pathophysiology of CAC is complex and pivots around inflammation, endothelial dysfunction and severe hypoxaemia
- The lungs are the target organs for infection and thus pulmonary intravascular coagulopathy is the clinically predominant feature but other organs are frequently affected
- Rapidly emerging information from clinical observations, autopsy-based findings as well as in vivo and in vitro studies have increased our knowledge and changed therapeutic management but many questions remain unanswered

asionis@santpau.cat
@sionis_a

What is D-dimer? Where Does It Come From In COVID-19?



- Thrombosis activation leads to generation of thrombin, which converts soluble fibrinogen to fibrin monomers
- Factor XIIIa cross links the D-domains of fibrin, leading to formation of D-dimer polymers
- Plasminogen is cleaved by tissue plasminogen activator which creates plasmin that degrades the fibrin network resulting into soluble fragments D-dimer and fragment E
- D-dimer is cleared by the kidneys and reticuloendothelial cells (half-life 8 hours)
- D-dimer is a marker of thrombotic activity (ELISA tests)

Key factors in D-dimer generation in COVID-19 infection:

- Excess thrombin generation and early fibrinolysis shutdown secondary to viral triggered endothelial activation
- Severe hypoxaemia stimulates thrombosis through increased blood viscosity and hypoxia-inducible transcription factors
- Local pulmonary thrombotic phenomena (microthrombosis)

Weitz Ji et al. J Am Coll Cardiol 2017;70:2411-2420