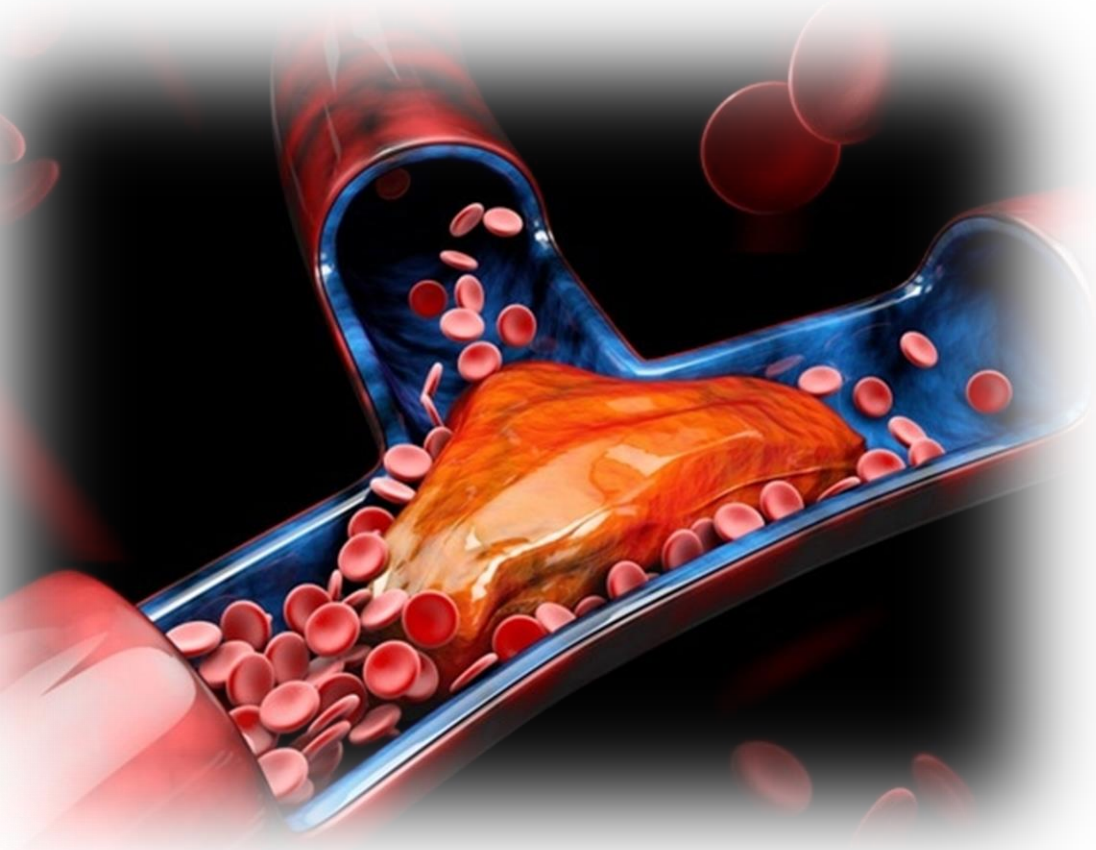
ΕΠΕΜΥ
Επιστημονική Εταιρεία
για τη Μυοσκελετική Υγεία

12° Πανελλήνιο Συνέδριο

Ολοκληρωμένη διαχείριση των Φλεγμονωδών και των Μυοσκελετικών Παθήσεων

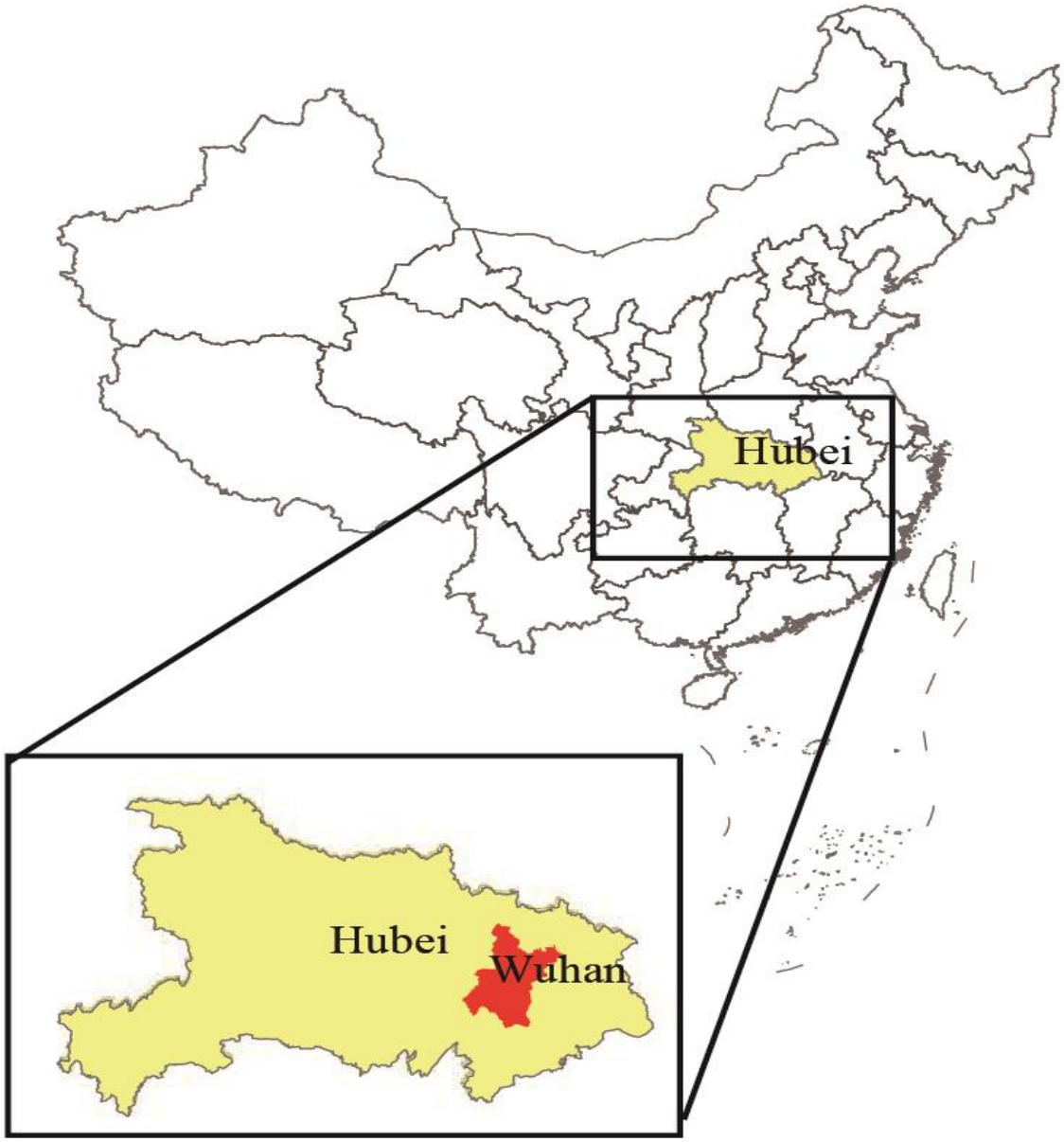


Φλεγμονή και θρόμβωση: τι μάθαμε από το Covid-19;

Σερταρίδου Ν. Ελένη, MD, MSc, PhD,
Χειρουργός – Εντατικολόγος,
Επιμ. Α' ΜΕΘ, ΠΓΝ Αλεξ/πολης

29 Οκτωβρίου - 01 Νοεμβρίου 2020
Ξενοδοχείο Valis
Βόλος
www.epemy.gr

December 31, 2019
14 counties in 1 province



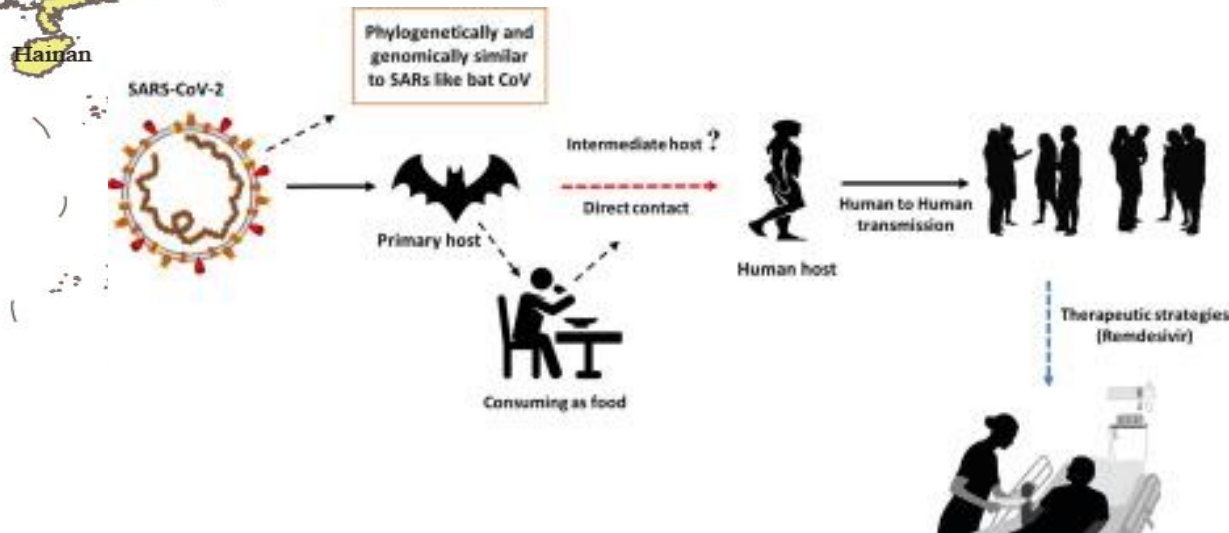
Pneumonia with unknown origin

January 10, 2020

113 counties in 20 provinces

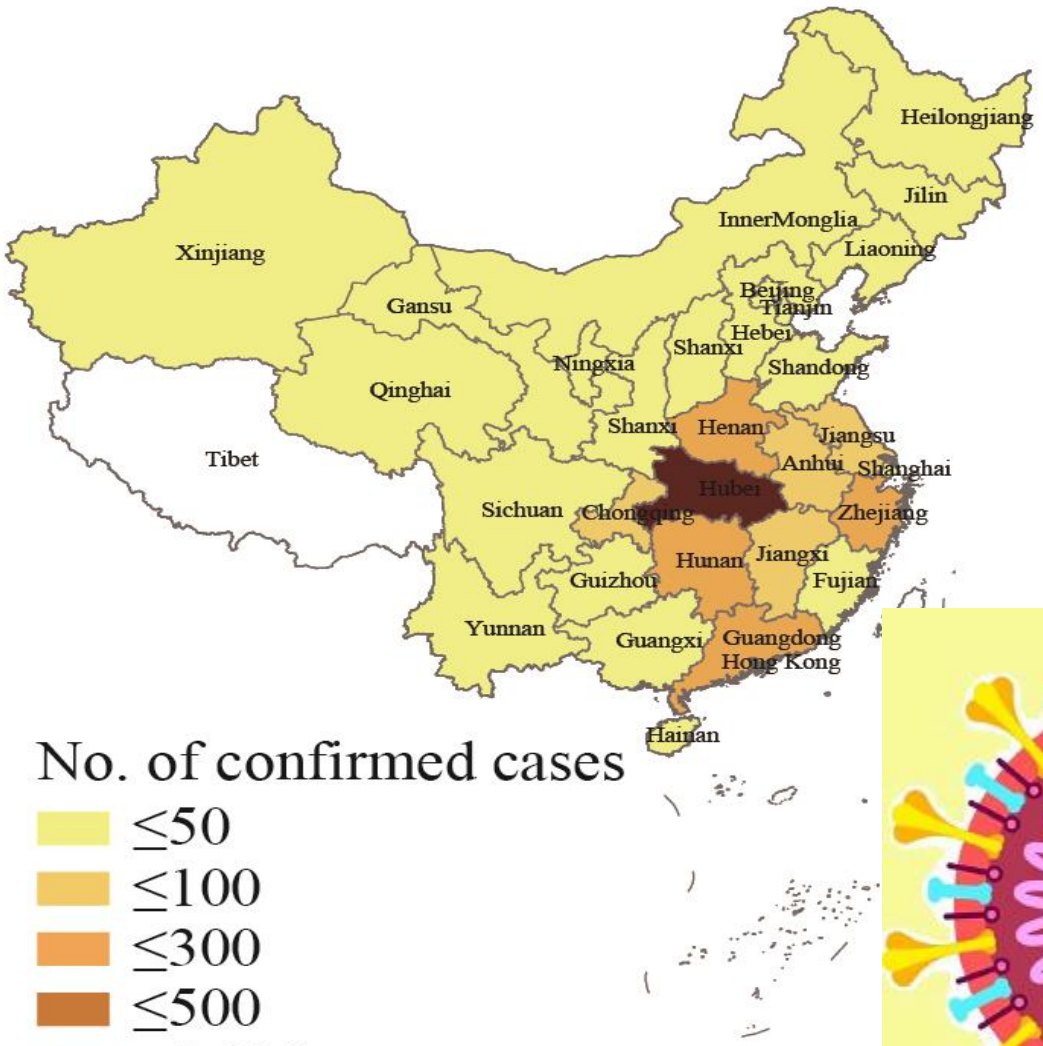
No. of confirmed cases

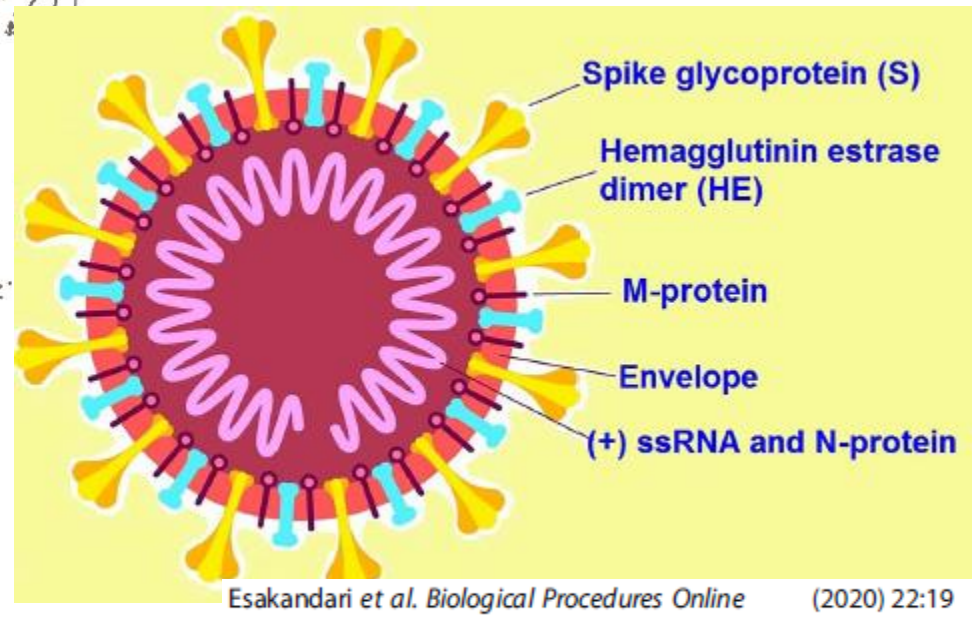
- ≤50
- ≤100
- ≤300
- ≤500
- ≤1,000
- >1,000
- No data



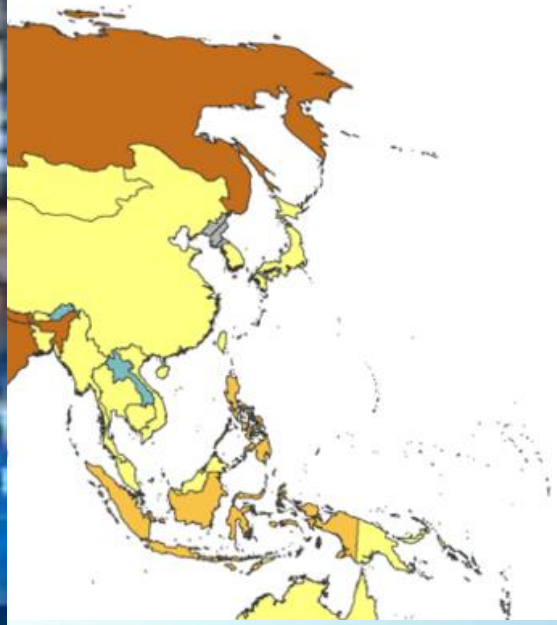
January 20, 2020

627 counties in 30 provinces





Esakandari *et al. Biological Procedures Online* (2020) 22:19

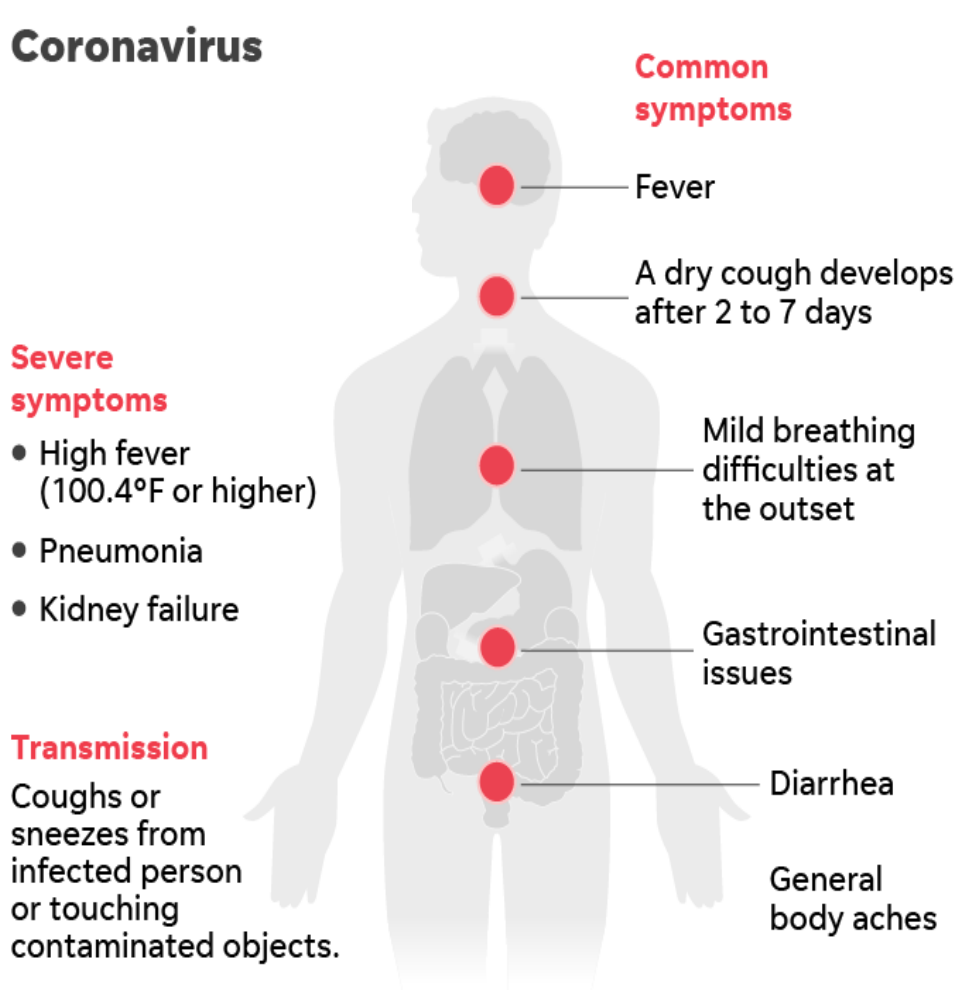


14-day COVID-19 case

< 20.0 20.0 - 59.

No cases rep

The boundaries and names shown on this map do not imply official endors



Mild disease: non-pneumonia and mild pneumonia (81%).

Severe disease: dyspnea, respiratory frequency ≥ 30/min, SpO2≤ 93%, PaO2/FiO2 < 300, and/or lung infiltrates > 50% within 24 to 48 hours (14%).

Critical disease: respiratory failure, septic shock, and/or MOD or MOF (5% of cases).

JAMA. 2020;323(13):1239-1242.

- ✓ *Bilateral pneumonia,*
- ✓ *systemic inflammation,*
- ✓ *endothelial dysfunction,*
- ✓ *coagulation activation,*
- ✓ *ARDS and MOF have been described as features of severe COVID-19*

Thrombosis research 2020;191:9-14

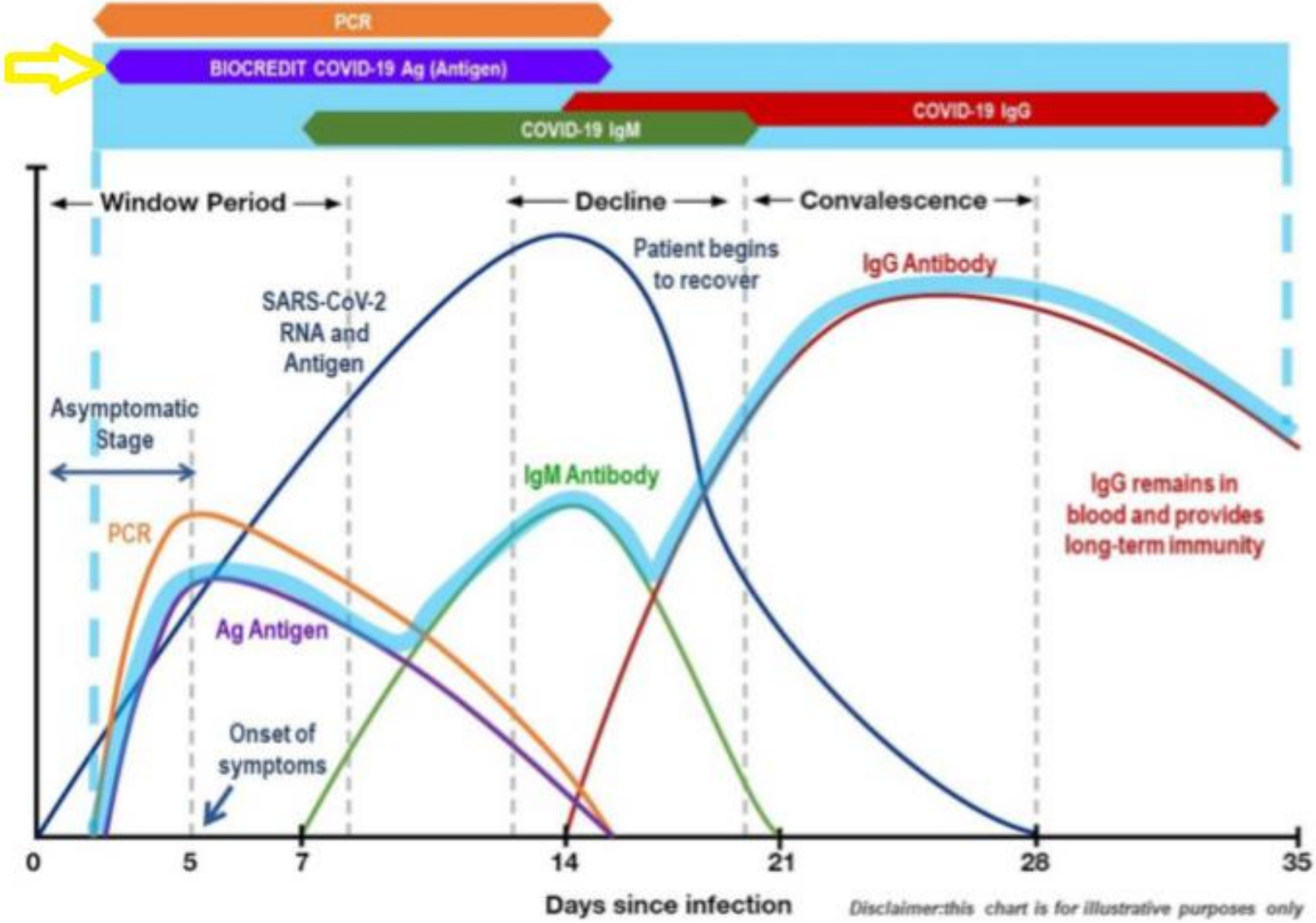
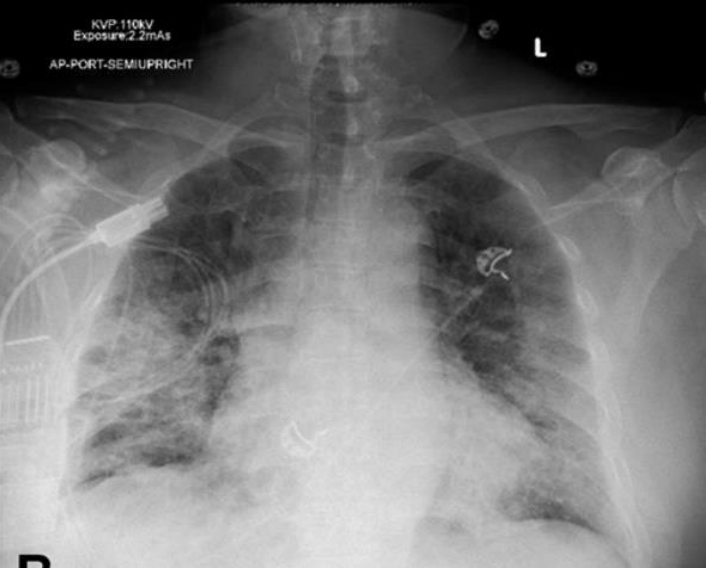
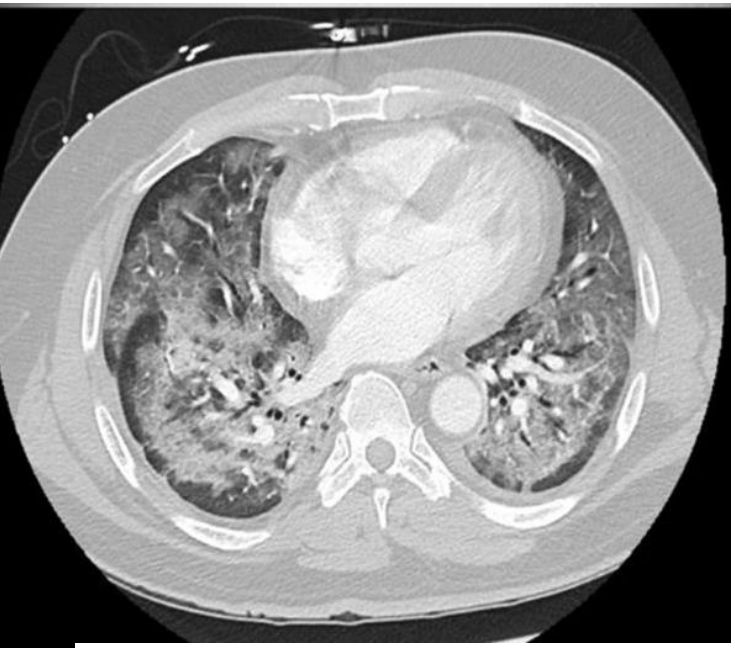


Figure 1: Variation of the Levels of SARS-CoV-2 RNA and Antigen, IgM and IgG after infection.



Another case with severe ARDS which need Mechanical Ventilation?



Similarity with seasonal flu ???

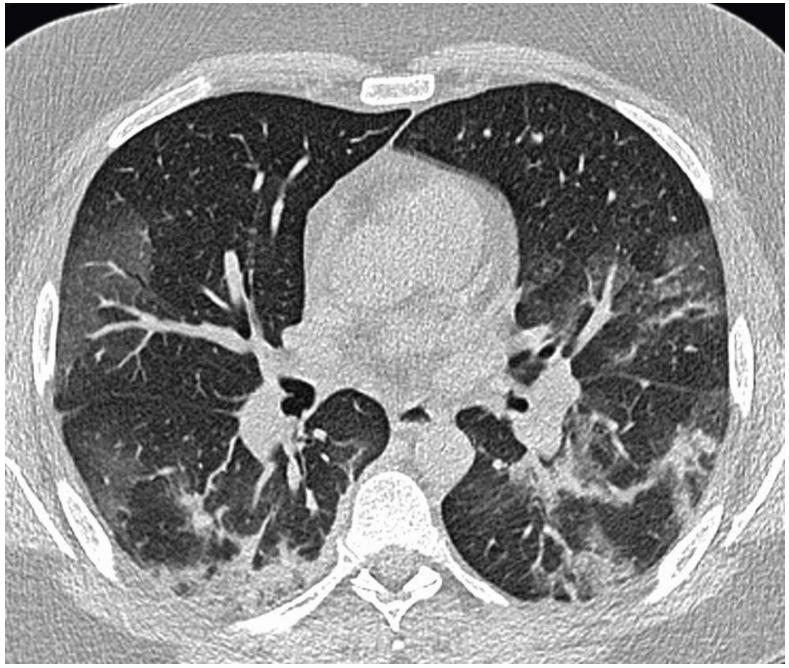
Συμπτώματα	Κορονοϊός συμπτώματα από ήπια έως σοβαρά	Κρυολόγημα σταδιακή έναρξη συμπτωμάτων	Γρίπη απότομη έναρξη συμπτωμάτων
Πυρετός	Συχνά	Σπάνια	Συχνά
Κούραση	Μερικές φορές	Μερικες φορές	Συχνά
Βήχας	Συχνά (ξηρός)	Ήπιος	Συχνά (ξηρός)
Φτέρνισμα	Όχι	Συχνά	Όχι
Μυικοί πόνοι	Μερικές φορές	Συχνά	Συχνά
Καταρροή	Σπάνια	Συχνά	Μερικες φορές
Πονόλαιμος	Μερικές φορές	Συχνά	Μερικές φορές
Διάρροια	Σπάνια	Όχι	Μερικές φορες (για παιδιά)
Πονοκέφαλος	Μερικές φορές	Σπάνια	Συχνά

Θνητότητα: 3-7% vs <1%

Sources: World Health Organization, Centers for Disease Control and Prevention

Not just ARDS

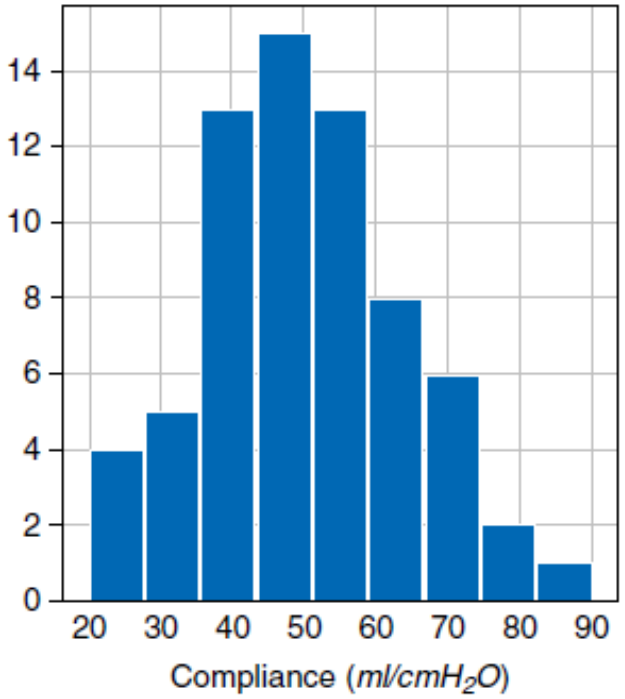
Not a usual ARDS



COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome

Am J Respir Crit Care Med. 2020;201(10):1299-1300.

- Dissociation between relatively well-preserved lung mechanics and severe hypoxaemia.
- High respiratory compliance and high shunt fraction.
- **Loss of lung perfusion regulation** and **hypoxic vasoconstriction**.
- The increases in oxygenation with high PEEP and/or prone positioning are not due to recruitment, but instead, result from the redistribution of perfusion in response to pressure and/or gravitational forces.



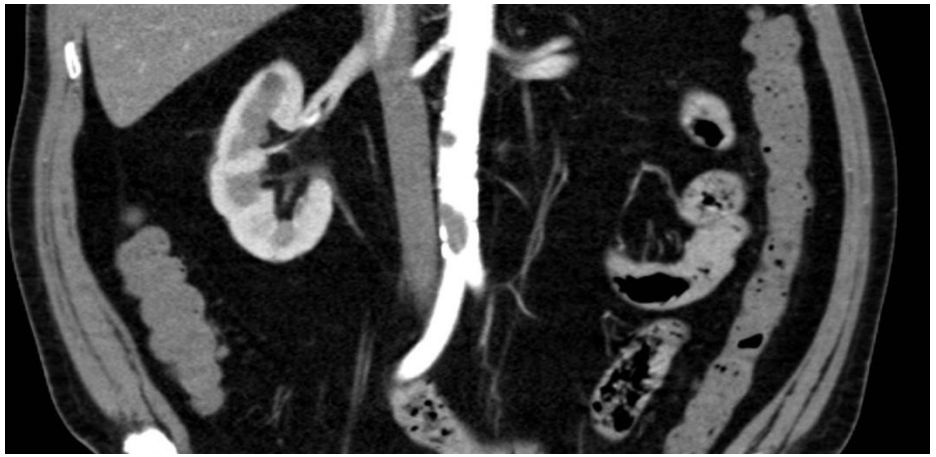
Τι είδαμε από την δική μας εμπειρία;

- “ARDS” syndrome, που δεν υπάκουε στους κανόνες προστατευτικού μηχανικού αερισμού που γνωρίζαμε
- Εμπύρετο (Θ>40^{o} C)
- Κυκλοφορική καταπληξία
- Καρδιογενές shock (↓ EF, αρρυθμίες)

Οι ασθενείς πέθαιναν με:

- υπερπυρεξία,
- AKI και
- ηπατική ανεπάρκεια

Extrapulmonary Manifestations and thrombotic complications



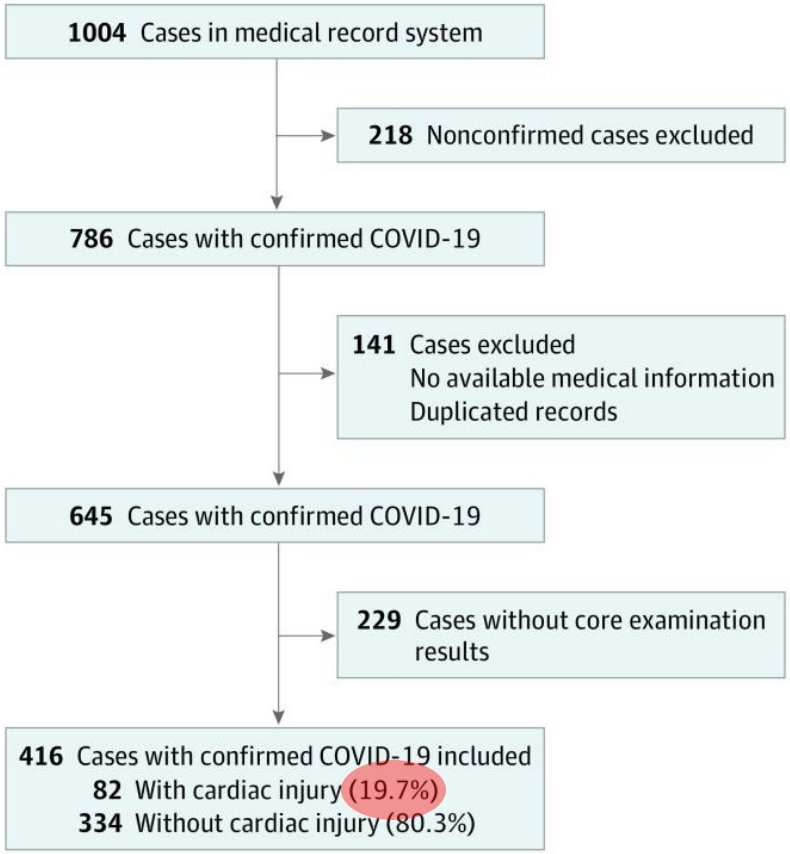
Προσβολή λοιπών οργάνων

Μυοκάρδιο:

- Mild myocardial hypertrophy changes and focal fibrosis are tissue changes seen in the heart biopsies of death COVID-19 patients.
- Severe and sudden inflammation of the heart muscle causes arrhythmias and impairs the heart's ability to efficiently pump blood.
- Fatty plaques in the arteries of the heart of people with or without symptoms of cardiovascular disease may become unstable due to fever and inflammation, leading to vascular obstruction and cardiovascular problems.

Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China

JAMA Cardiol. 2020 Jul; 5(7): 802–810.



- patients with cardiac injury were older (74 [34-95] vs 60 [21-90] years; *P* < .001),
- more likely to have chest pain

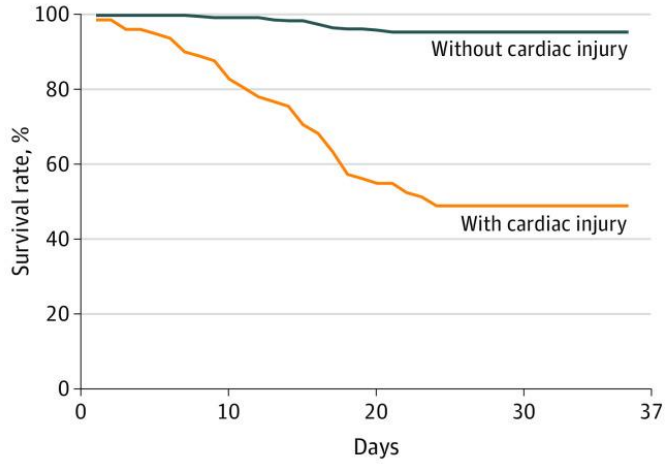
Comorbidities :

- hypertension (59.8% vs 23.4%),
- diabetes (24.4% vs 12.0%),
- coronary heart disease (29.3% vs 6.0%),
- cerebrovascular disease (15.9% vs 2.7%),
- chronic heart failure (14.6% vs 1.5%),
- chronic obstructive pulmonary disease (7.3% vs 1.8%], and
- cancer (8.5% vs 0.6%)

Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China

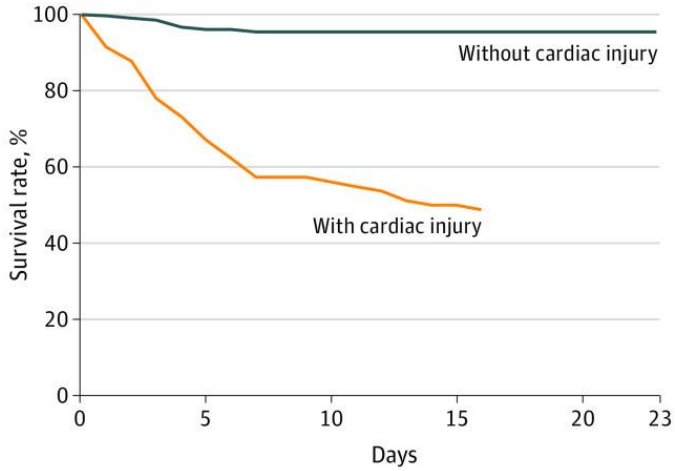
JAMA Cardiol. 2020 Jul; 5(7): 802–810.

A Time from symptom onset



No. at risk					
With cardiac injury	82	68	46	40	40
Without cardiac injury	334	329	323	320	319

B Time from admission



No. at risk						
With cardiac injury	82	55	46	41	0	0
Without cardiac injury	334	321	319	319	319	319

C Comparison of outcomes

	No. of events/ No. of patients	Time from symptom onset: Duration, mean (range), d	Time from symptom onset: *P* value log-rank	Time from admission: Duration, mean (range), d	Time from admission: *P* value log-rank
With cardiac injury	42/82	15.6 (1-37)	<.001	6.3 (1-16)	<.001
Without cardiac injury	15/334	16.9 (3-37)		7.8 (1-23)	

Προσβολή λοιπών οργάνων

Ήπαρ/ ΓΕΣ:

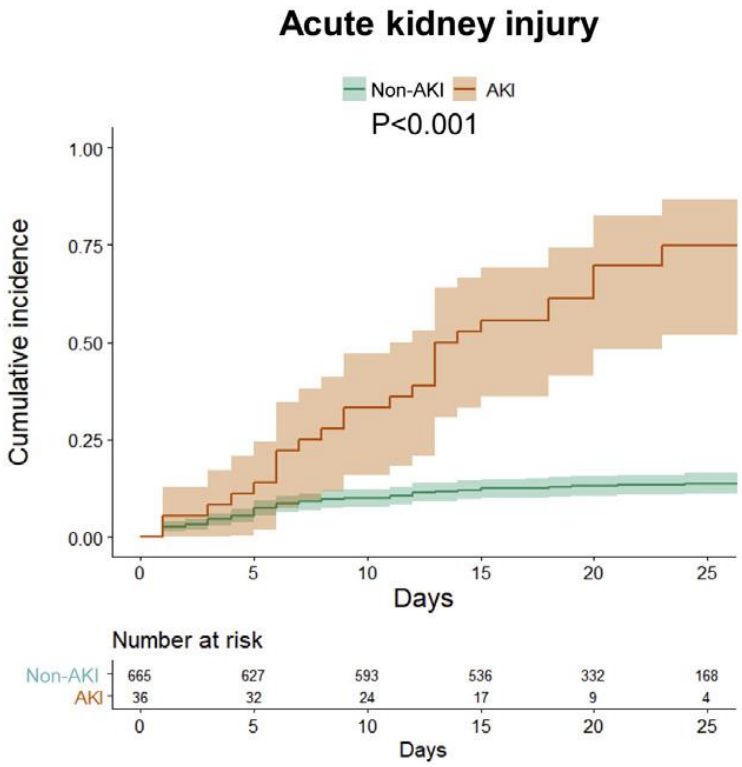
- Multifocal **hepatic** necrosis, mild lymphocytic infiltration, sinusoidal dilation, and steatosis are pathologic changes observed in the liver of COVID-19 patients with moderate to severe illness.
- vomiting, diarrhea, and other gastrointestinal disorders.

ΚΝΣ:

- losing the senses of smell, taste or vision,
- decreasing alertness,
- seizures,
- stroke, and
- acute necrotizing hemorrhagic encephalopathy

Νεφροί:

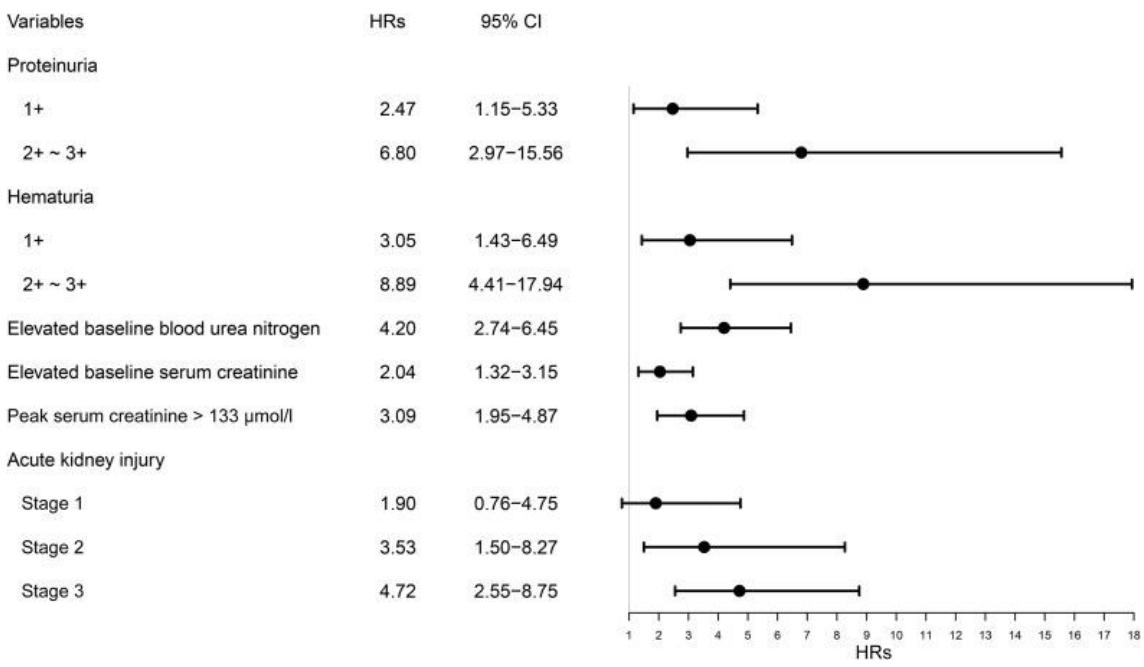
- Multifocal protein or blood in the urine, which indicates early renal damage



Kidney disease is associated with in-hospital death of patients with COVID-19

Kidney International (2020) 97, 829–838

- A prospective cohort study of 701 patients with COVID-19
- Mortality: 16.1%



Cytokine Storm syndrome

A **hyperinflammatory syndrome** characterised by a fulminant and fatal hypercytokinaemia with MOFs, which may contribute to the deterioration

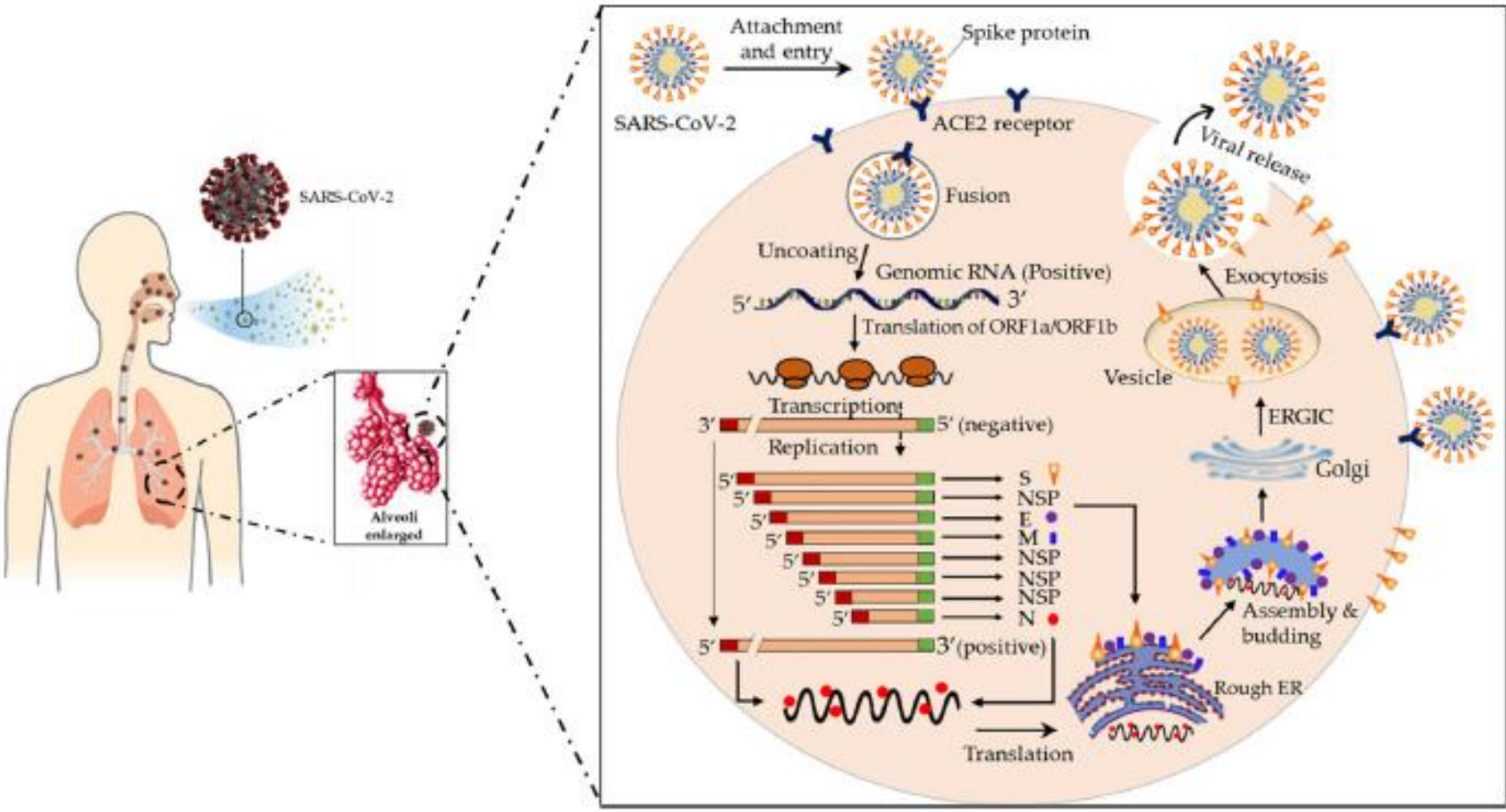
resulting in:

- Unremitting fever
- Elevation in C-reactive protein
- Elevation of LDH
- Elevation of D-dimer
- Cytopenia
- Hyperferritinaemia
- ARDS in 50%
- High levels of IL-2, 6, 7, GCSF, interferon – γ, TNF – α etc

HScore for secondary HLH, by clinical parameter

	Number of points
Temperature	
< 38.4 °C	0
38.4 °C - 39.4 °C	33
> 39.4 °C	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias*	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
< 1.5 mmol/L	0
1.5 - 4.0 mmol/L	44
> 4.0 mmol/L	64
Fibrinogen (g/L)	
> 2.5 g/L	0
≤ 2.5 g/L	30

	Number of points
Ferritin ng/ml	
< 2000 ng/ml	0
2000 - 6000 ng/ml	35
> 6000 ng/ml	50
Serum aspartate aminotransferase	
< 30 IU/L	0
≥ 30 IU/L	19
Haemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression†	
No	0
Yes	18



Infect Genet Evol. 2020 Sep;83:104327.

Thrombosis and COVID-19 pneumonia: the clot thickens!

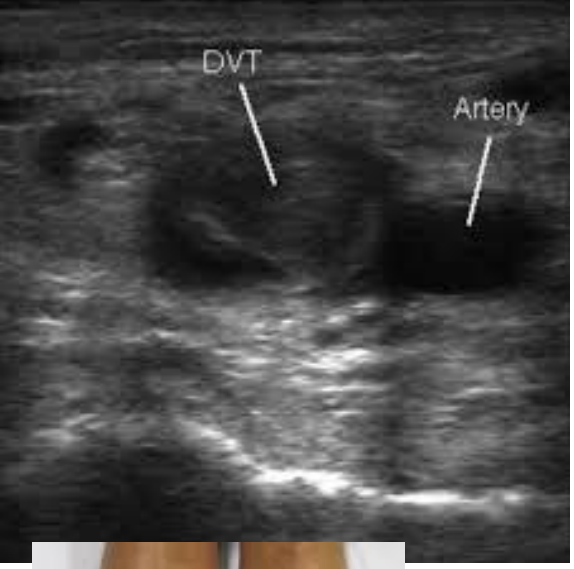
Eur Respir J 2020; 56: 2001608

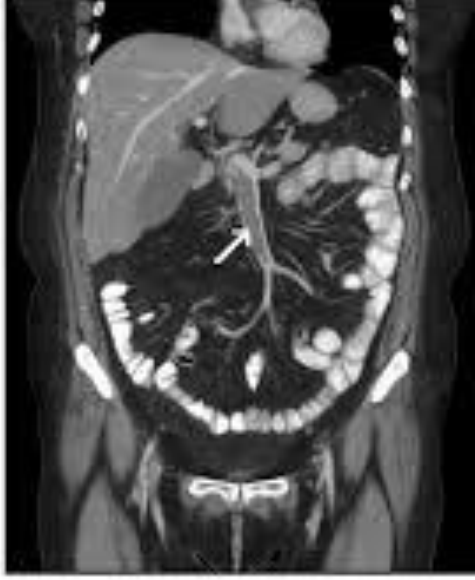
Relevant thrombosis factors:

- State of disease
- Where patient is tested (ward or ICU)
- Amount of anticoagulation

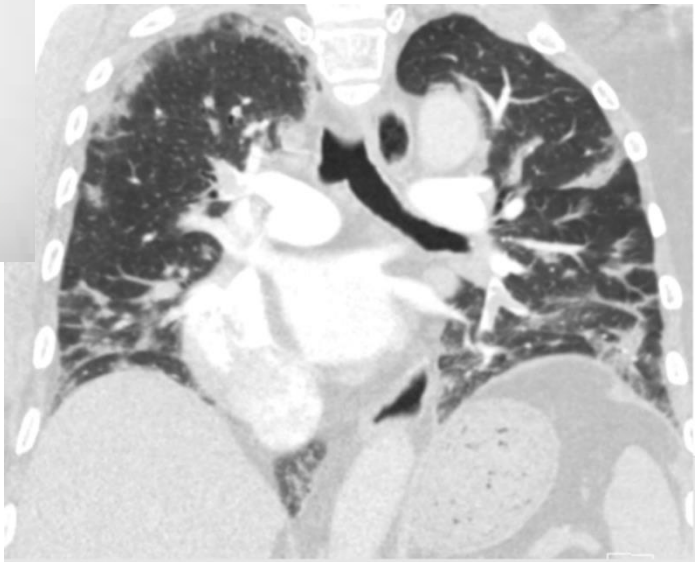
Proposed underlying mechanisms include:

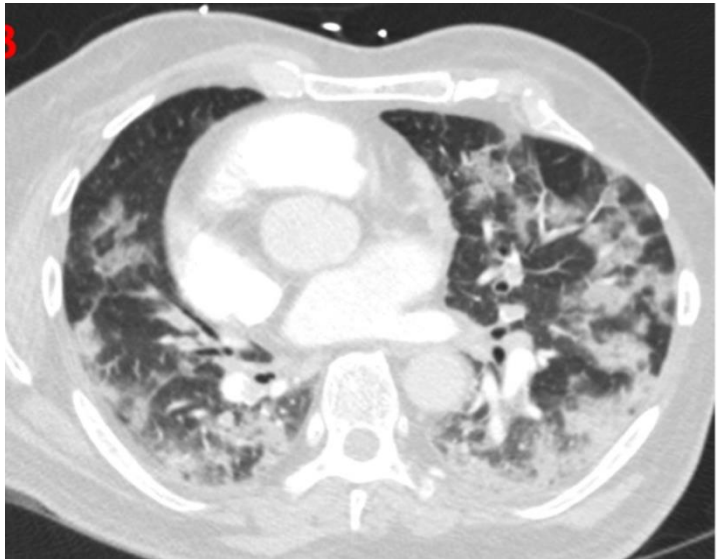
- an excessive immune response cytokine storm,
- endotheliopathy,
- angiogenesis and
- hypercoagulability





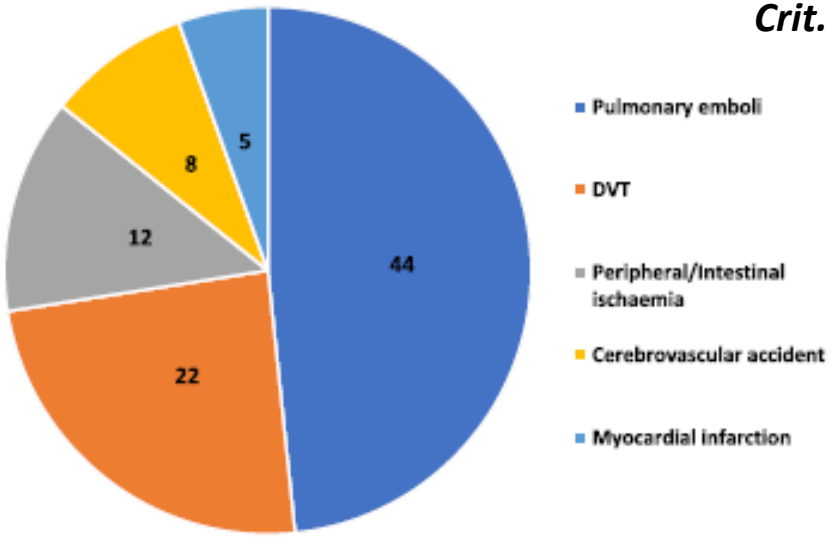
Are thrombosis rates in COVID-19 patients higher than we would expect?



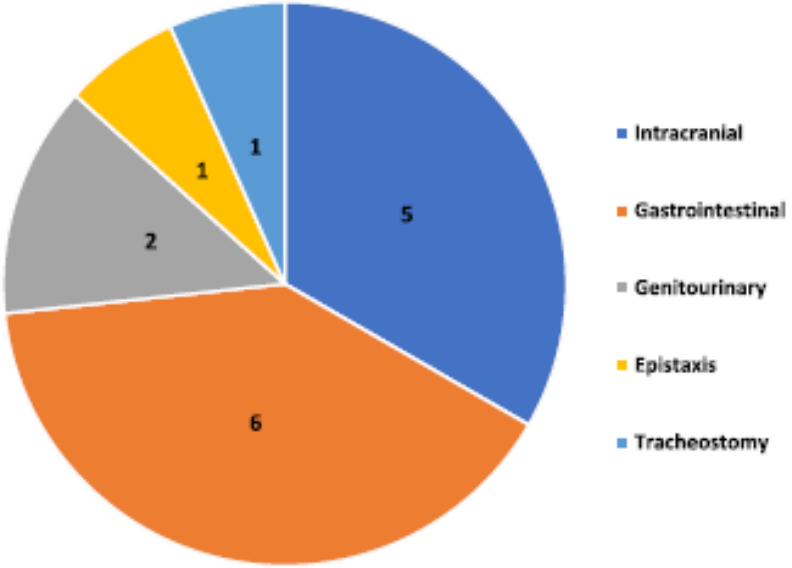


Thrombotic and hemorrhagic complications in critically ill patients with COVID-19: a multicenter observational study

Crit. Care 2020;24:561



Thrombotic complications (n=91)



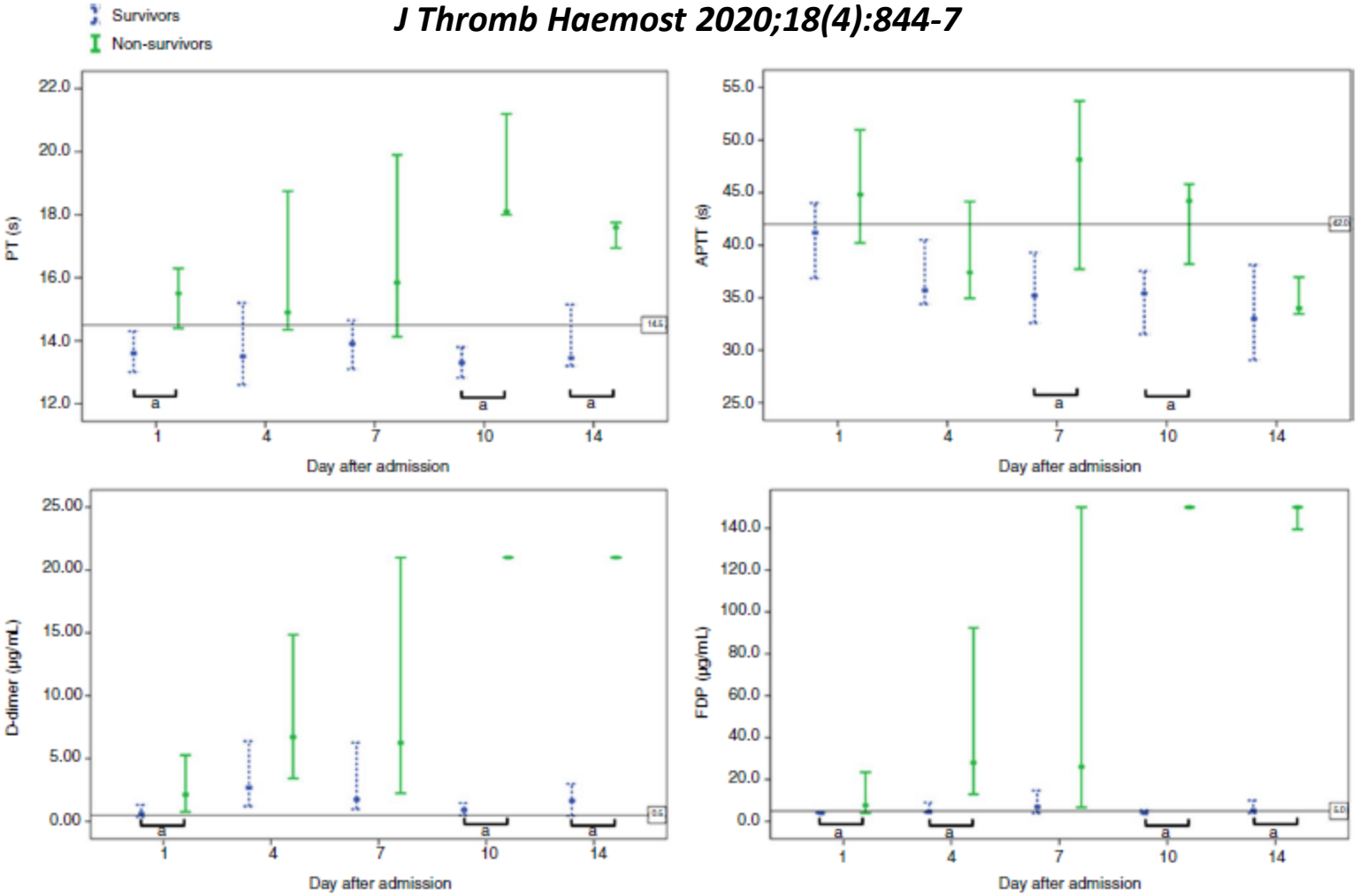
Haemorrhagic complications (n=15)

- A multicentre retrospective observational study evaluating 187 COVID-19 patients in 4 ICUs
- 100% thromboprophylaxis or therapeutic dose LWMH
- Overall ICU mortality: 31.6%.
- More patients with thrombosis died when compared with those without but this was not statistically significant (39.5% vs. 25.5%).
- ICU length of stay was longer in patients who developed thrombosis 17 (11–27) days vs. 12 (7–13) days).
- Thromboelastography: hypercoagulable profile
- Patients with thrombosis had:
  - *higher D-dimer,*
  - *ferritin,*
  - *troponin and*
  - *WBC count levels at ICU admission*

THROMBOINFECTION

Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

J Thromb Haemost 2020;18(4):844-7



- Conventional coagulation parameters of 183 patients with NCP were retrospectively analyzed.
- Abnormal coagulation results, are associated with poor prognosis.
- Existence of disseminated intravascular coagulation (DIC) is common in deaths with NCP (71.4%).

Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy.

Thrombosis Research 2020;191:9–14

Venous and arterial thromboembolic events in hospitalized COVID-19 patients **(N=388)**

	Intensive care unit			General ward		
Thromboembolic events	n	% of closed cases (n = 48) **(18%)**	% of imaging tests performed*	n	% of closed cases (n = 314)	% 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%)	–
VTE	4	8.3%	22%	12	3.8%	46%
PE (± DVT)	2	4.2%	25%	8	2.5%	36%
Isolated pDVT	1	2.1%	7%	3	1.0%	44%
Isolated dDVT	0	–	–	1	0.3%	13%
Catheter-related DVT	1	2.1%	50%	0	–	–
Ischemic stroke	3	6.3%	–	6	1.9%	–
ACS/MI	1	2.1%	–	3	1.0%	–

- Thromboembolic events occurred in 28% (29.6% ICU vs 9.6% general ward).
- Thromboprophylaxis was used in 100% of ICU patients and 75% of those on the general ward
- Half of the thromboembolic events were diagnosed within 24 h of hospital admission.

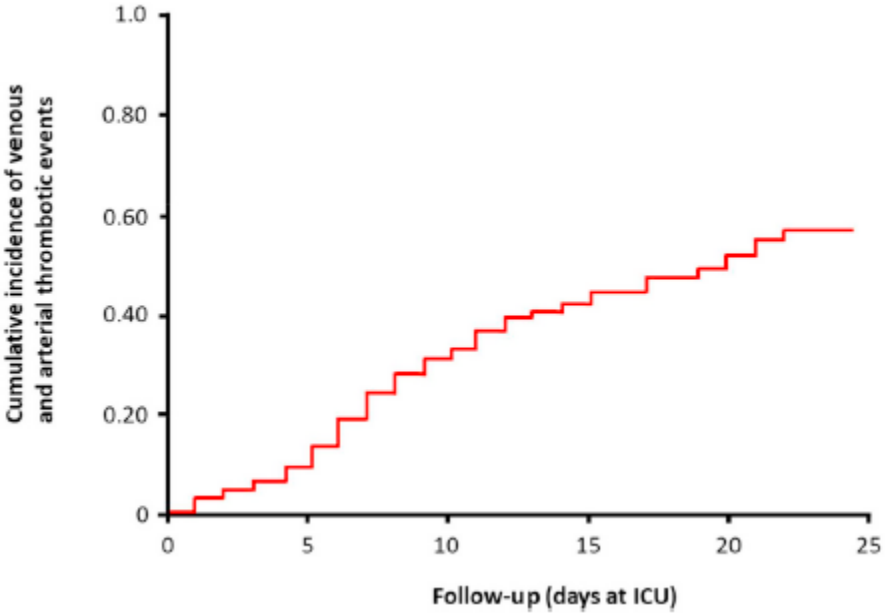
Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis.

Thrombosis Research 2020;191:148–150

- 184 ICU patients in 3 Dutch hospital, of whom a total of
- 41 died (22%) and 78 were discharged alive (43%).

Description of thrombotic complications.

Type of event	Number of cases
Pulmonary embolism	65
Other venous thromboembolic events	3
Arterial thrombotic events	7



- 31% (20-41%) PE
- The majority of thrombotic events were PE (65/75; 87%).
- All patients received pharmacological thromboprophylaxis.
- **Chronic anticoagulation therapy at admission was associated with a lower risk of the composite outcome** (Hazard Ratio [HR] 0.29, 95%CI 0.091–0.92).

High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study

Intensive Care Med. 2020 Jun;46(6):1089-1098.

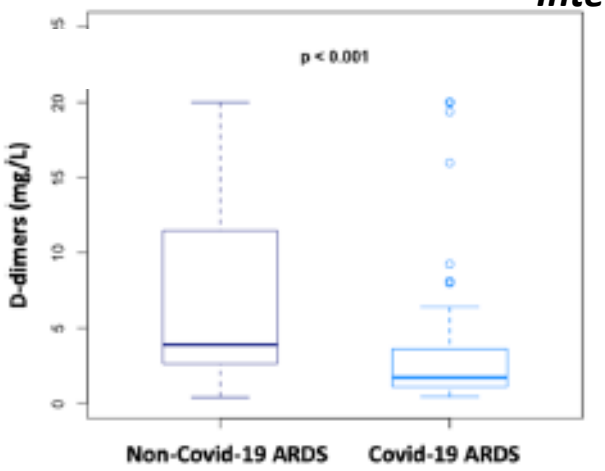
Outcomes of COVID-19 ARDS and non-COVID-19 ARDS

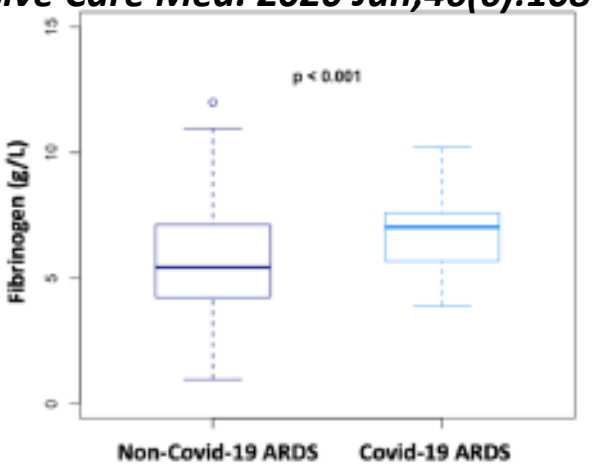
	Population before matching ($n=383$)				Population after matching ($n=222$)			
	Non-COVID-19-ARDS ($n=233$)	COVID-19-ARDS ($n=150$)	OR [95% IC]	*p*-value	Non-COVID-19-ARDS ($n=145$)	COVID-19-ARDS ($n=77$)	OR [95% IC]	*p*-value
Thrombo-embolic complications—*n* (%)	14 (6)	27 (18)	3.4 [1.7–7.3]	<0.001	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)	–	–

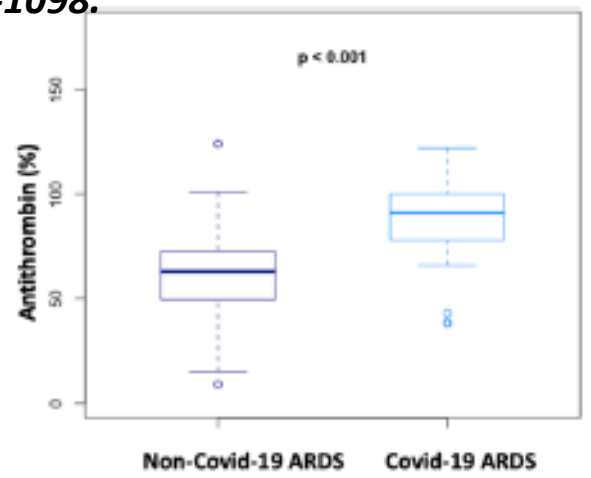
150 patients from 4 ICUs from 2 centers of a French tertiary hospital with ARDS

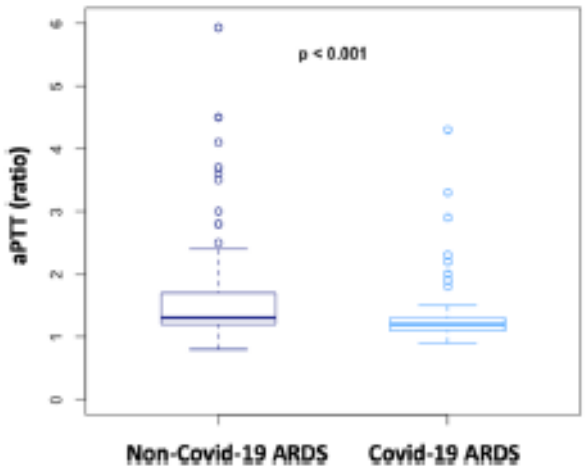
High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study

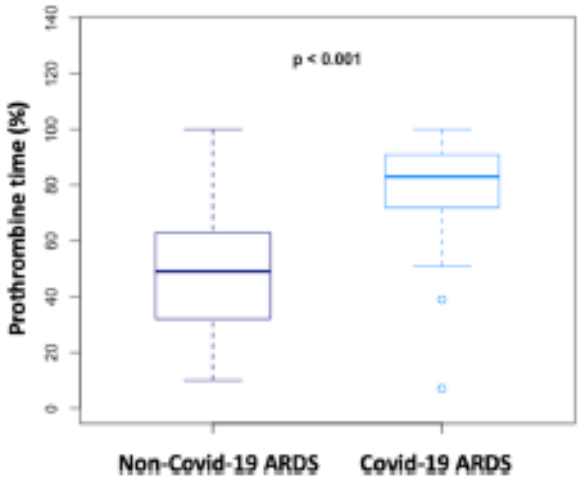
Intensive Care Med. 2020 Jun;46(6):1089-1098.

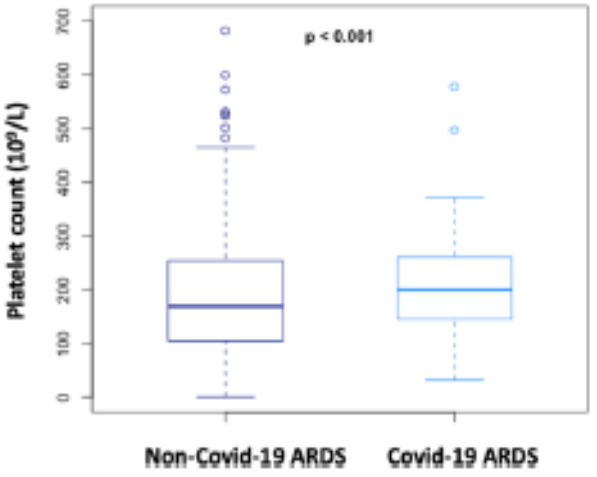






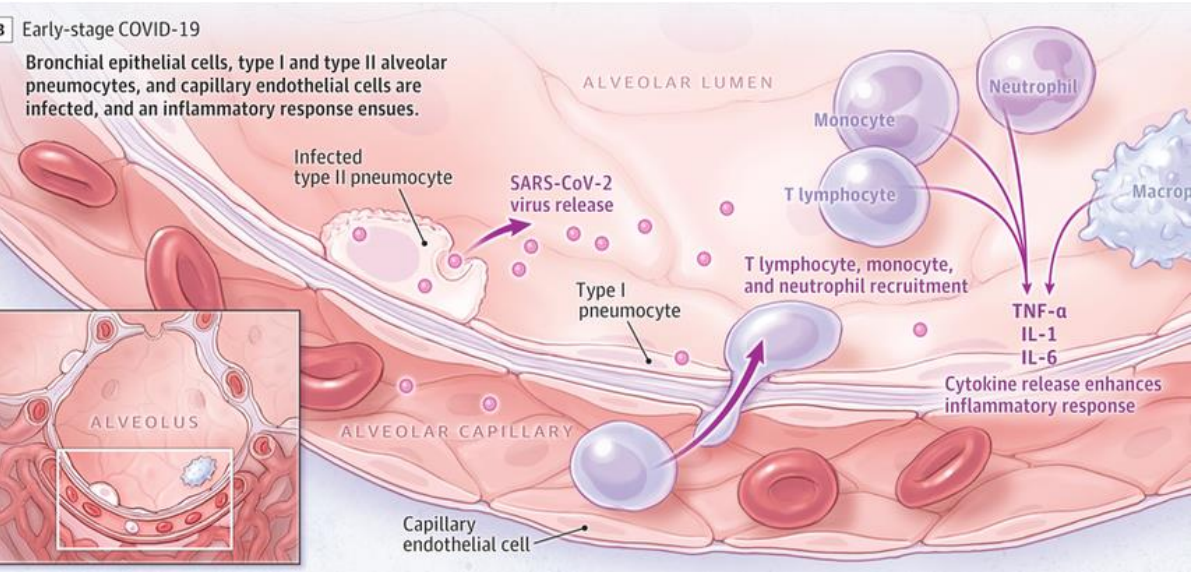






- These thrombotic complications occurred despite prophylactic or therapeutic anticoagulation
- A systemic inflammatory response syndrome, assessed by high fibrinogen, was present in all patients

Mechanisms of SARS-CoV-2-induced pneumonia



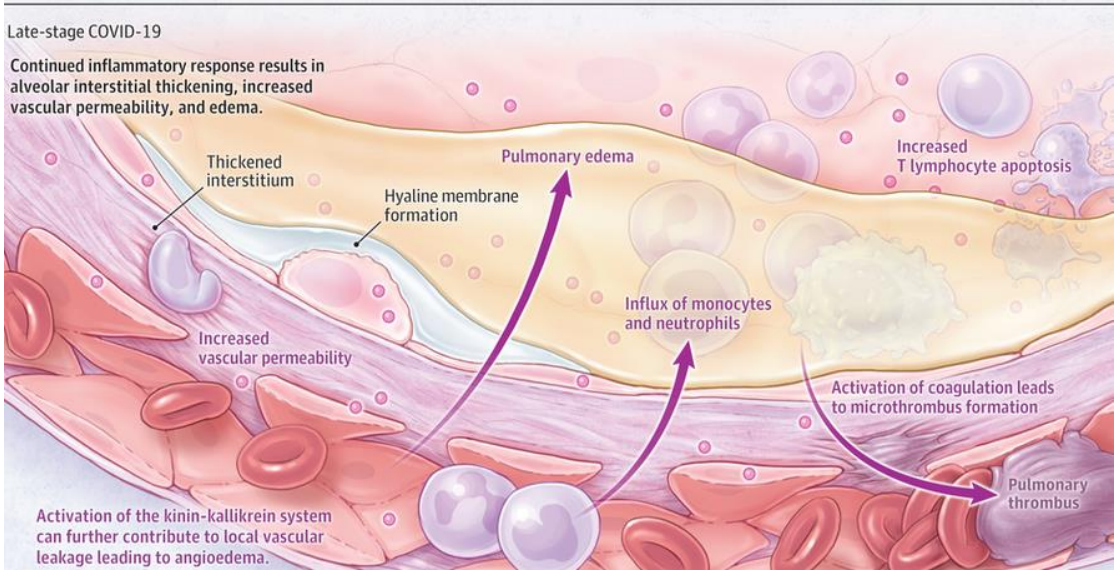
Diffuse Alveolar Disease with severe capillary congestion:

- Thrombotic microangiopathy,
- accumulations of CD4+ mononuclear cells around small thrombotic vessels, and
- hemorrhage appear

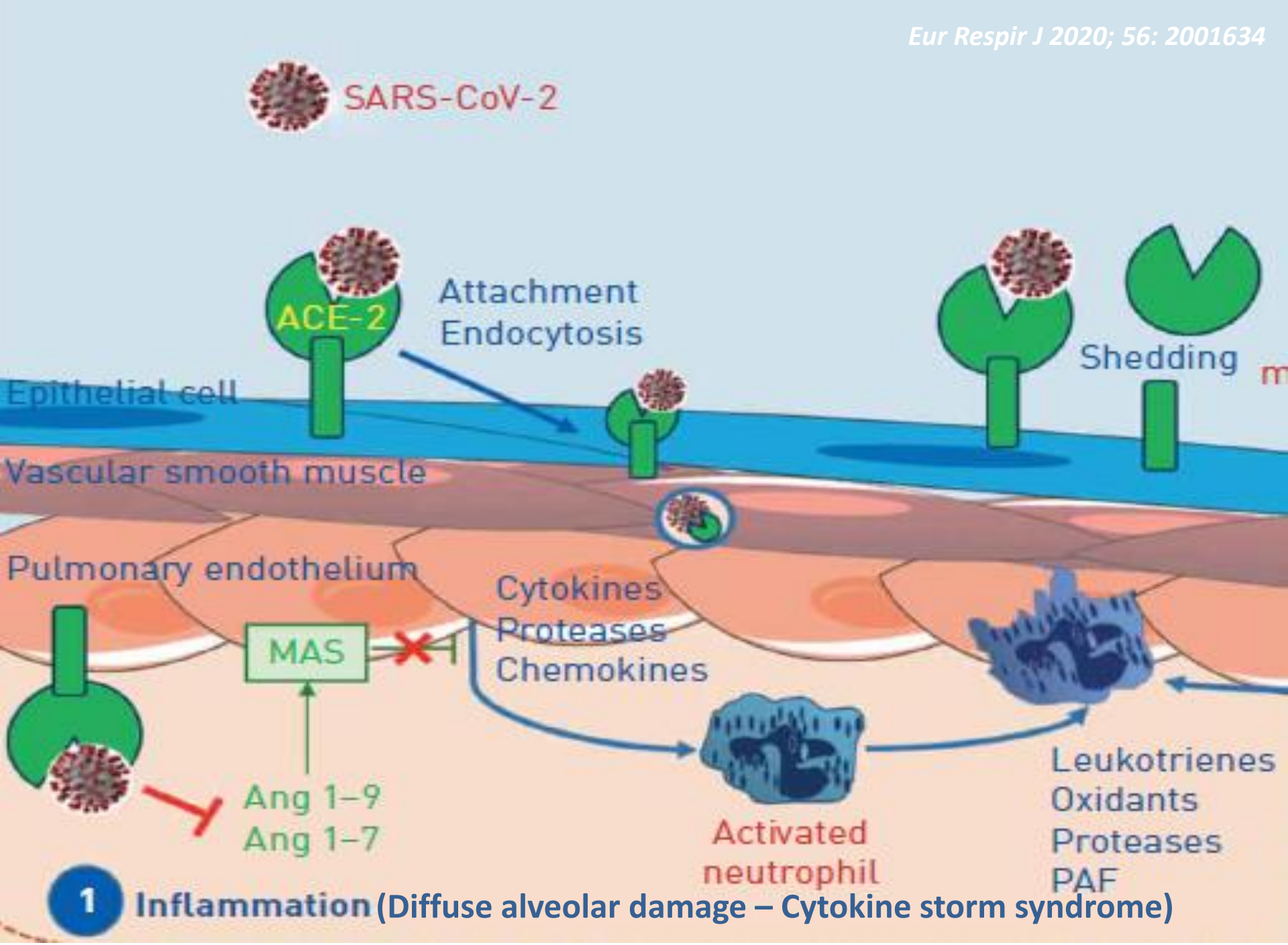
- Activated local megakaryocytes in the **lung**,
- platelet aggregation,
- fibrin deposition, and clot formation

are involved with the mentioned process.

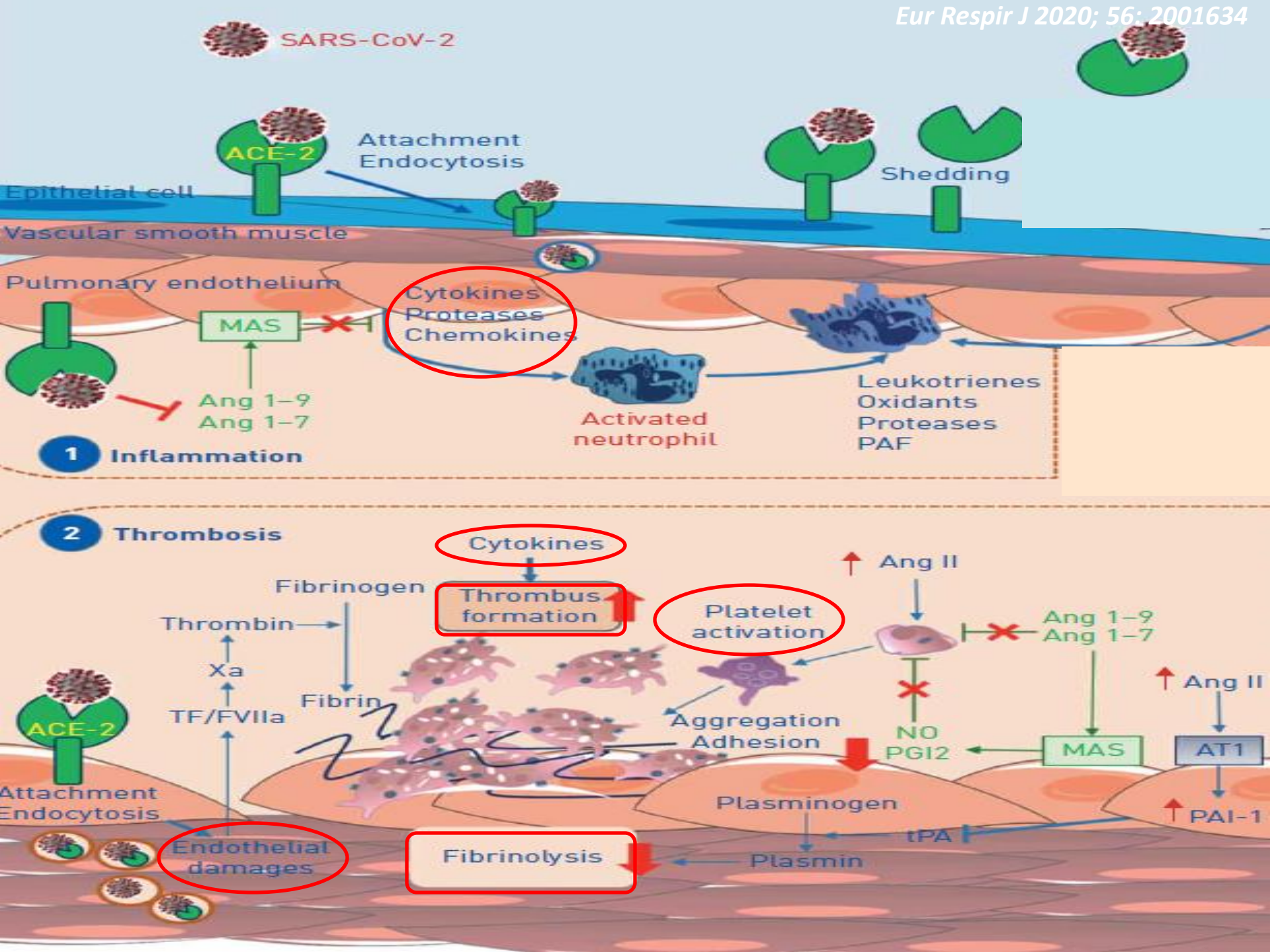
- capillary congestion,
- necrosis and hyperplasia of pneumocytes,
- interstitial edema.



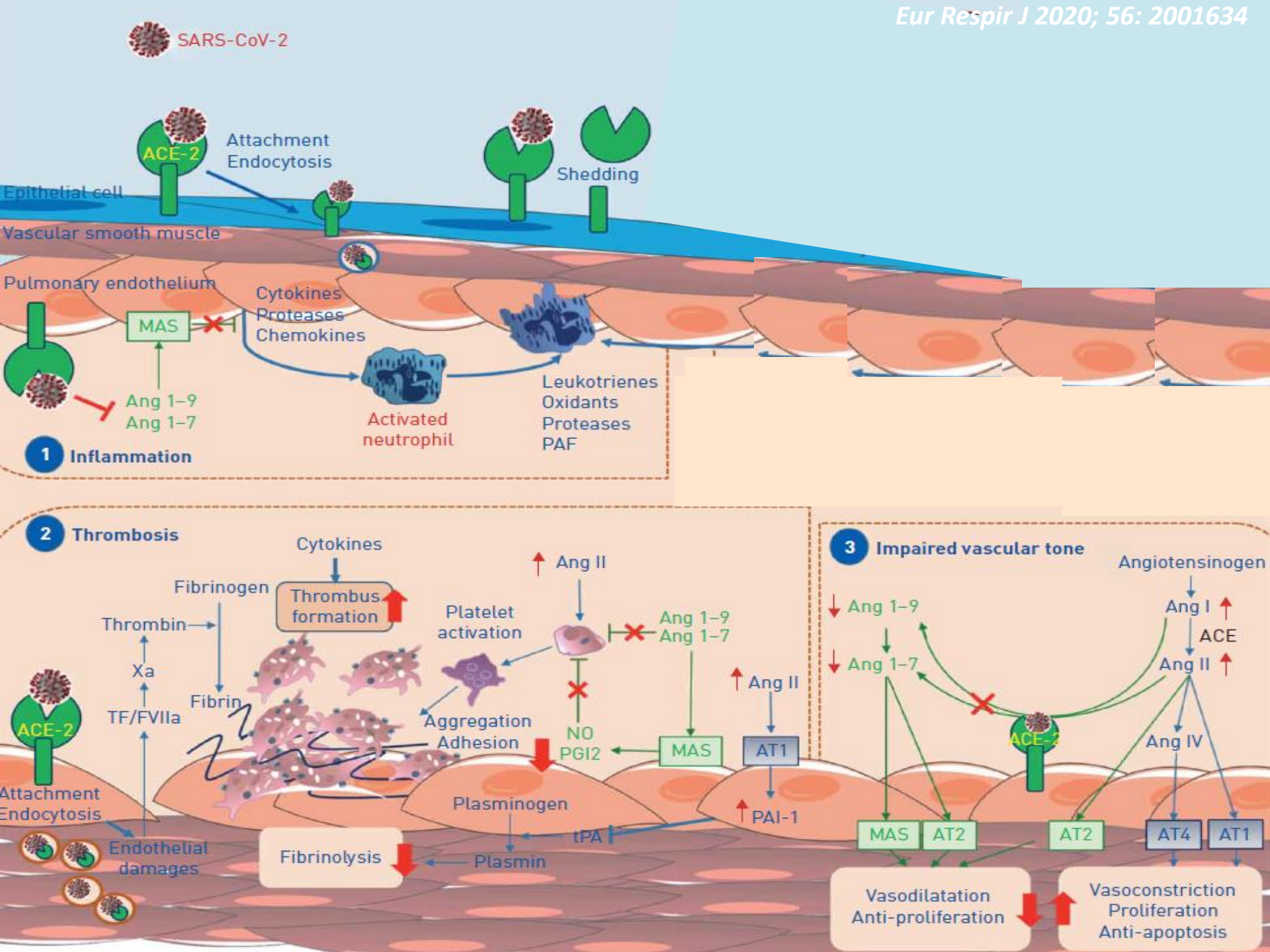
Eur Respir J 2020; 56: 2001634



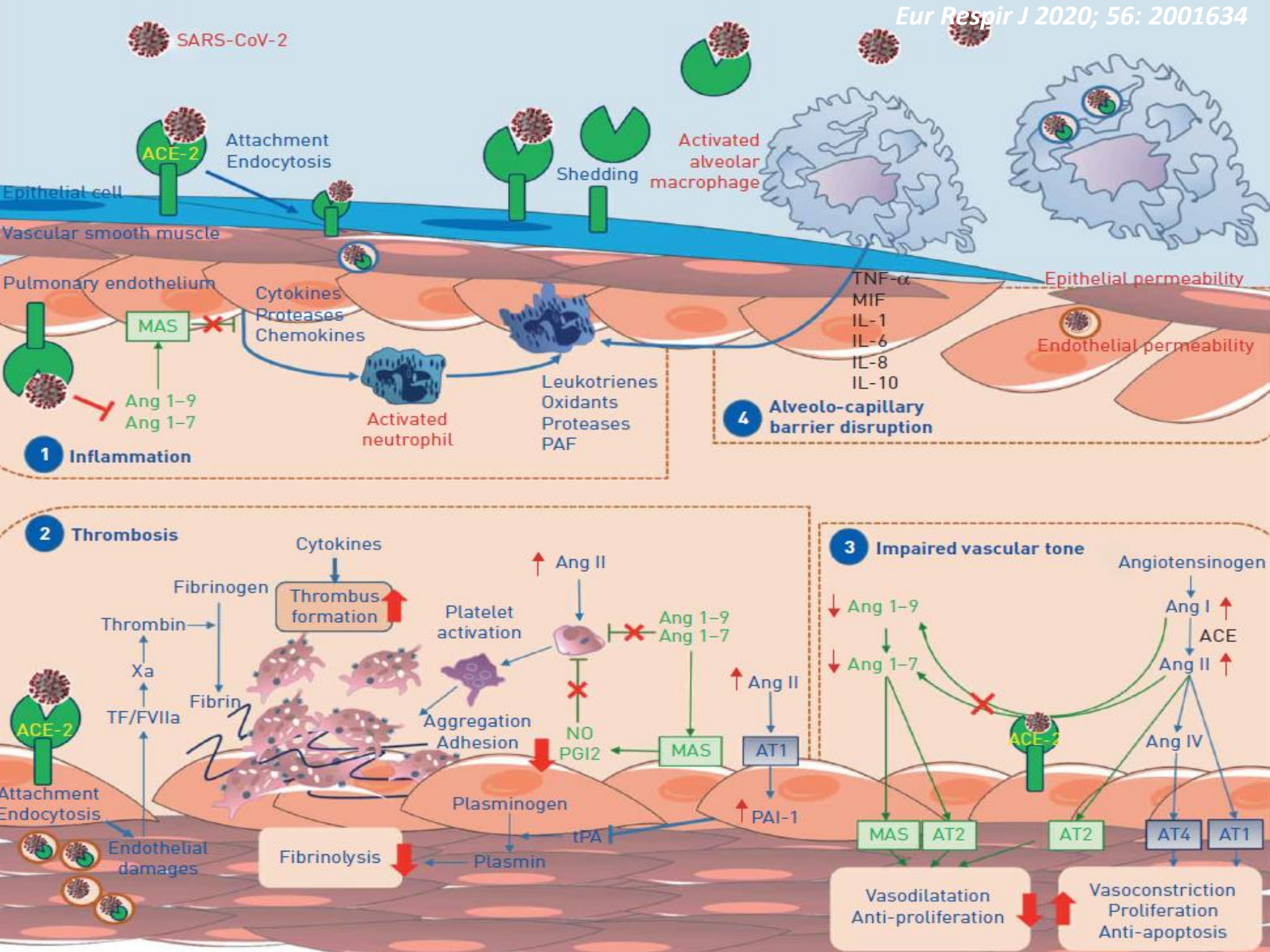
Eur Respir J 2020; 56: 2001634



Eur Respir J 2020; 56: 2001634

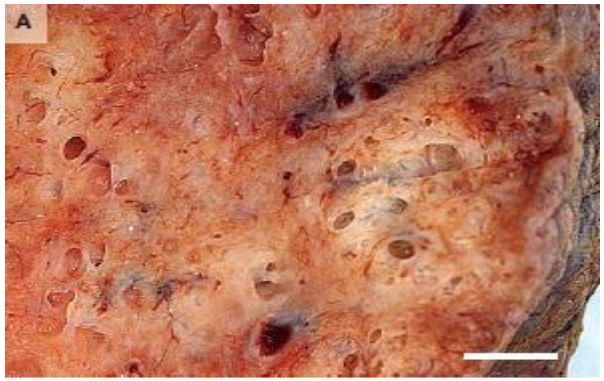


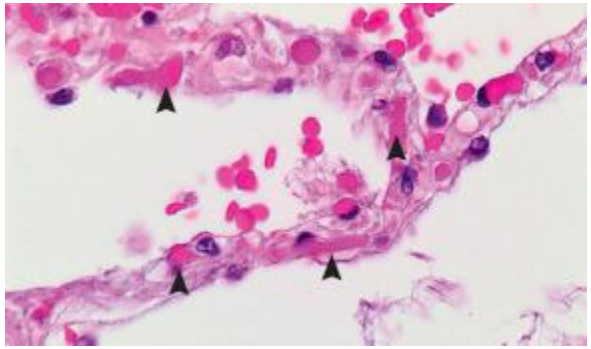
Eur Respir J 2020; 56: 2001634

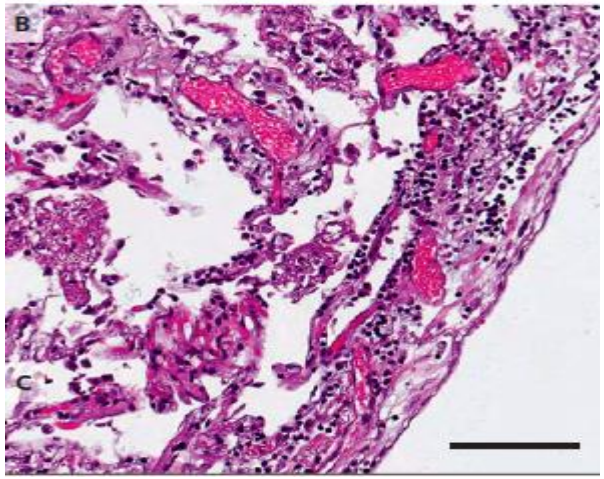


Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

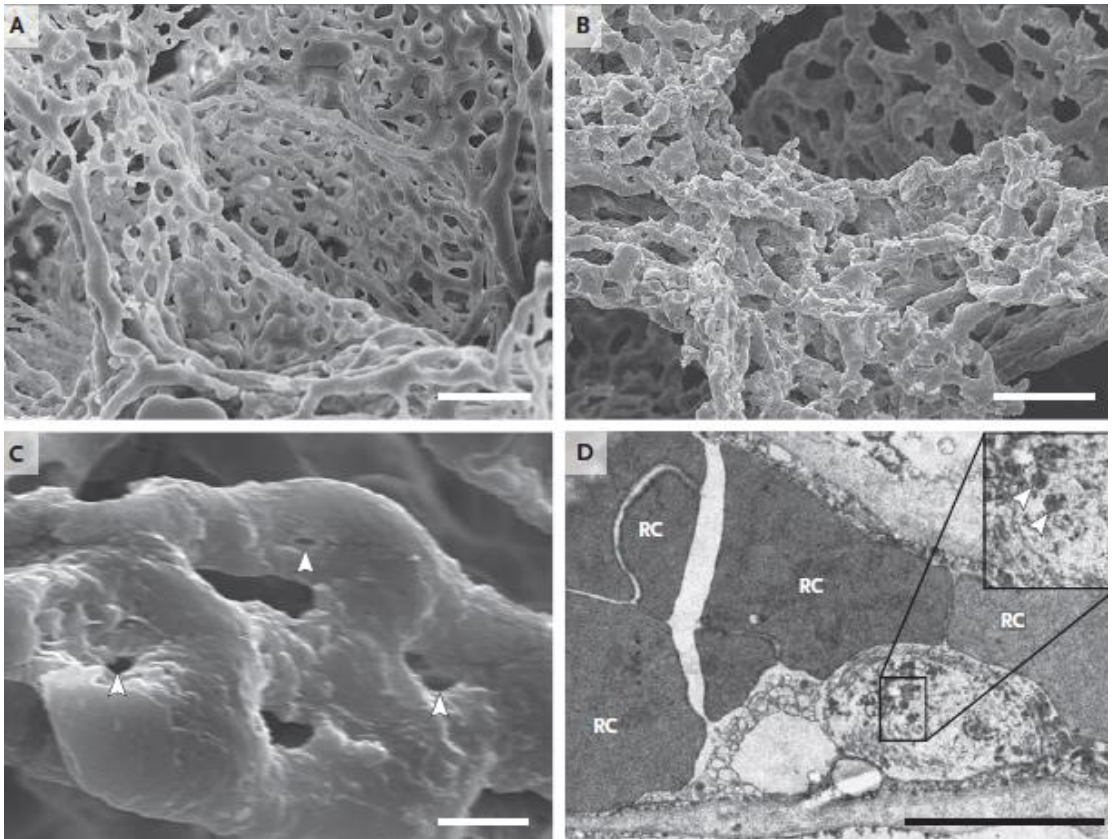
N Engl J Med. 2020 Jul 9;383(2):120-128.







- endothelial injury associated with intracellular SARS-CoV-2 virus and disrupted endothelial cell membranes,
- vascular thrombosis with
- microangiopathy and occlusion of alveolar capillaries
- new vessel growth through a mechanism of angiogenesis



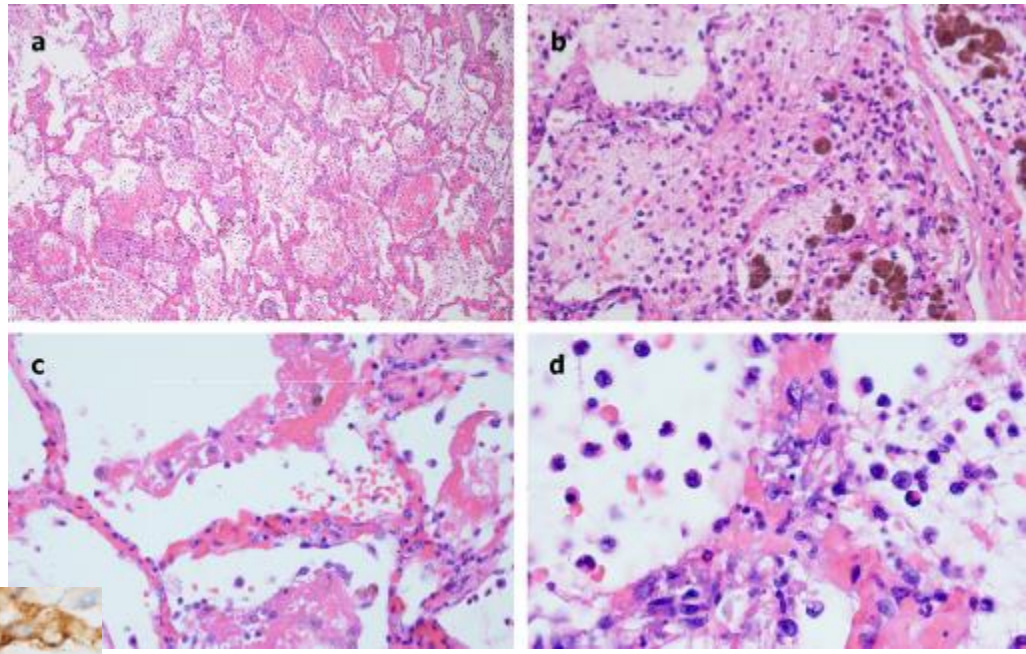
- diffuse alveolar damage with necrosis of alveolar lining cells,
- Perivascular lymphocytes
- pneumocyte type 2 hyperplasia, and
- intraalveolar fibrin deposition

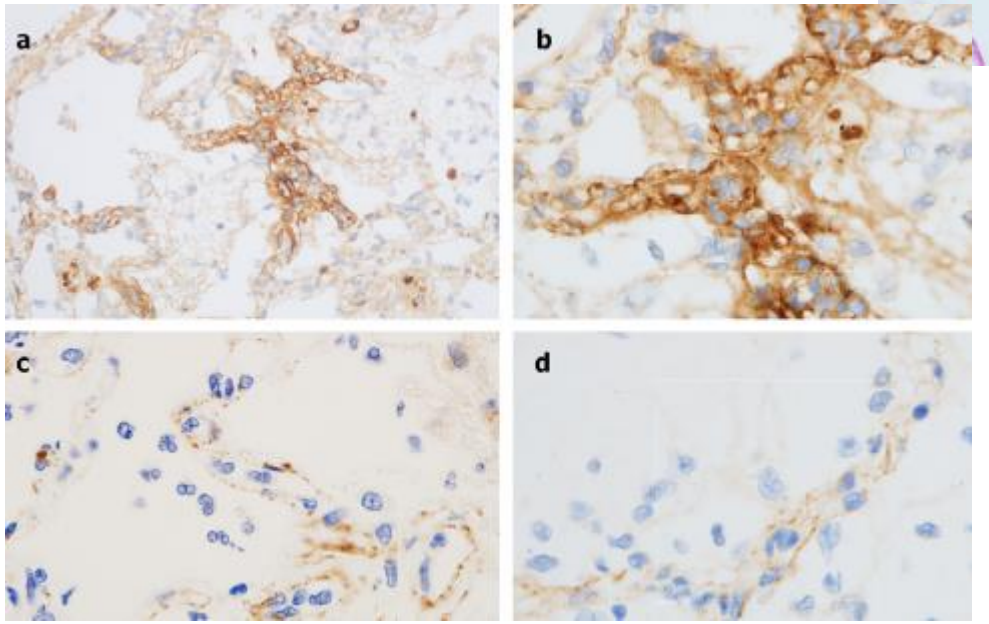
Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases

Translational Research 2020; 220:1-13

- A pattern of tissue damage consistent with complement-mediated microvascular injury was noted in the lung and/or skin.

- Demonstration of the striking deposition of C5b-9, C4d, and MASP2 in the microvasculature of 2 organ systems is consistent with profound and generalized activation of both alternative and lectin-based pathways.

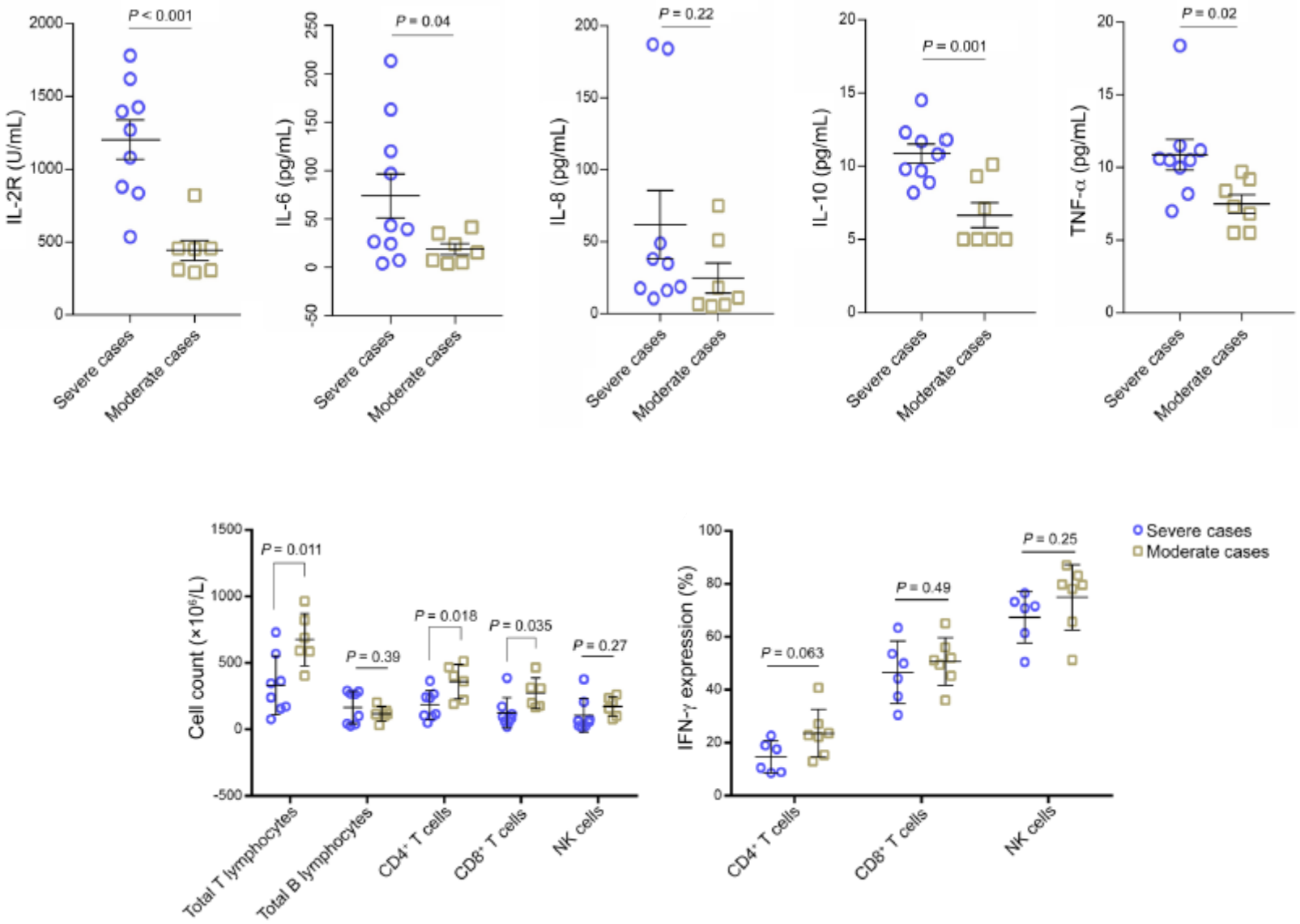




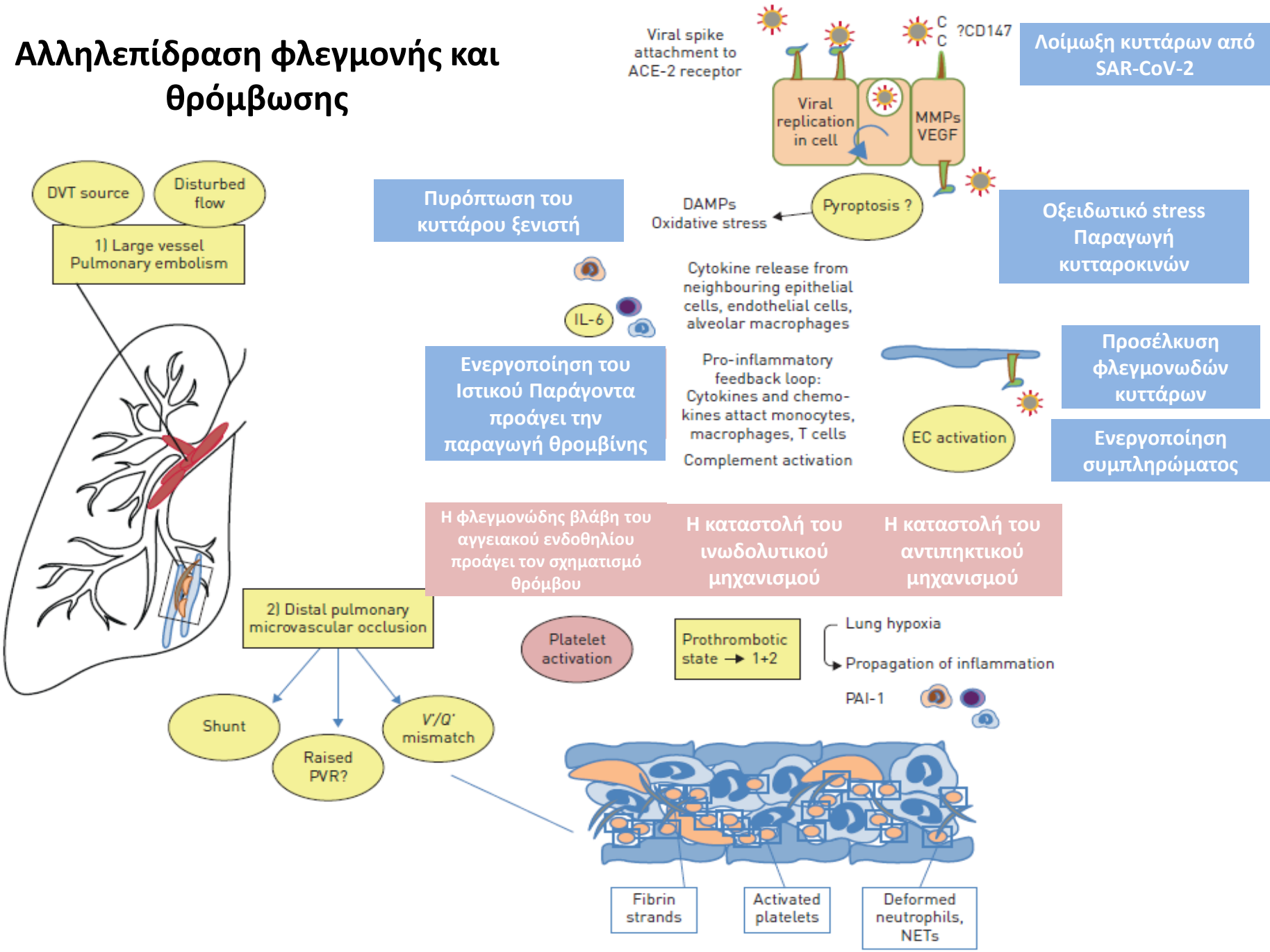
C4d, C5b-9 and C3d deposition throughout the lung parenchyma, with striking septal capillary localization

Clinical and immunological features of severe and moderate coronavirus disease 2019

J Clin Invest. 2020 May 1; 130(5): 2620–2629.



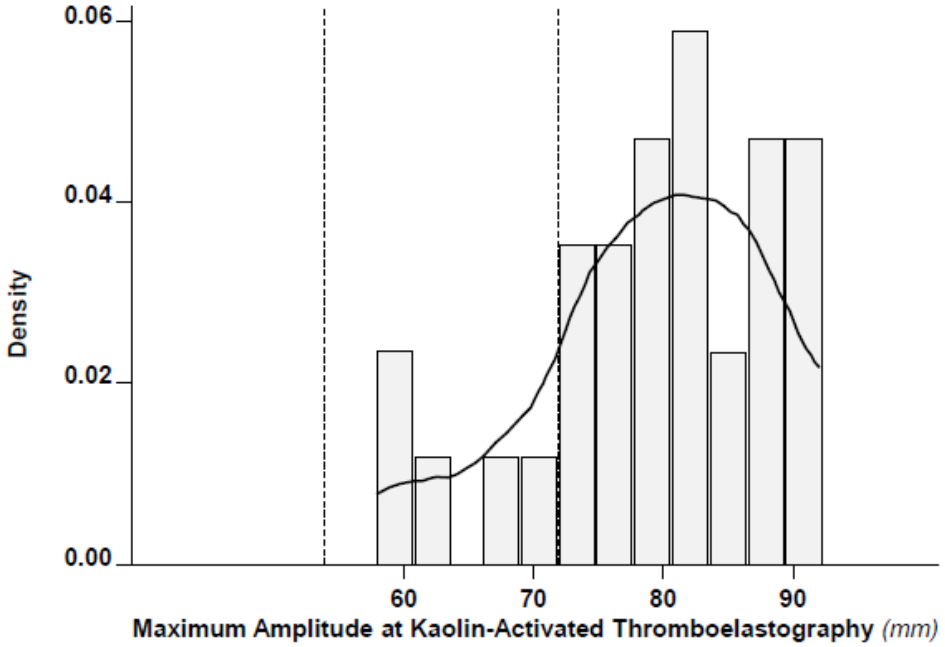
Αλληλεπίδραση φλεγμονής και θρόμβωσης



Eur Respir J 2020; 56: 2001608

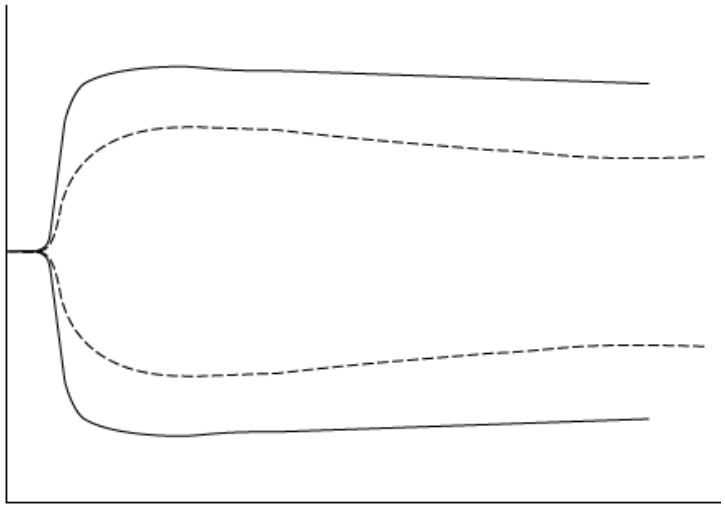
Hypercoagulability of COVID-19 patients in Intensive Care Unit. A Report of Thromboelastography Findings and other Parameters of Hemostasis

J Thromb Haemost 2020;18:1738-42



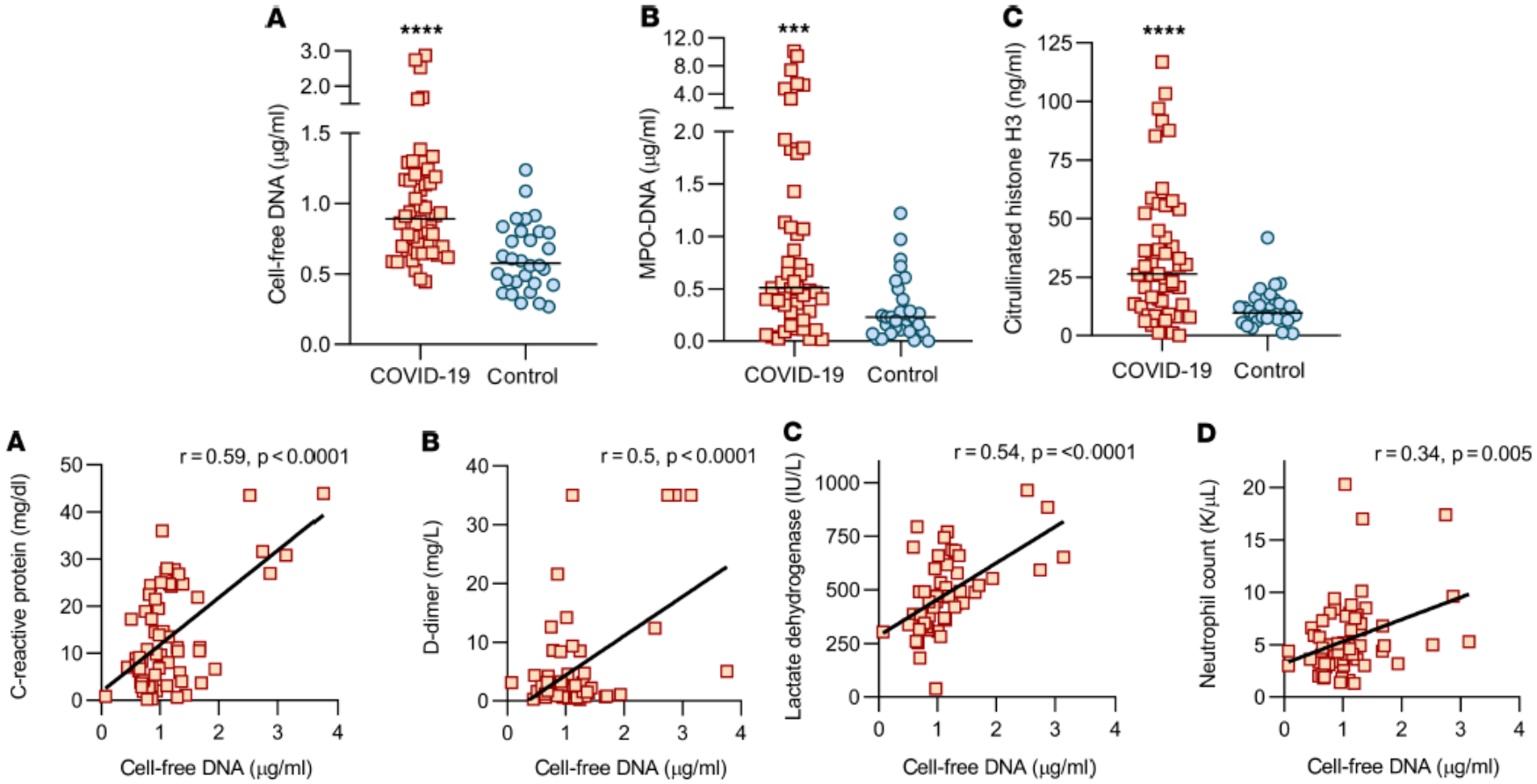
- Small studies describing thromboelastography in patients with COVID-19 suggest clot formation is extremely rapid and also resistant to breakdown.
- Solid and broken lines represent the univariate density estimation and the limits of the reference range, respectively.

- Typical TEG tracings. Broken and solid lines represent a healthy subject and a COVID-19 patient, respectively.



Neutrophil extracellular traps in COVID-19

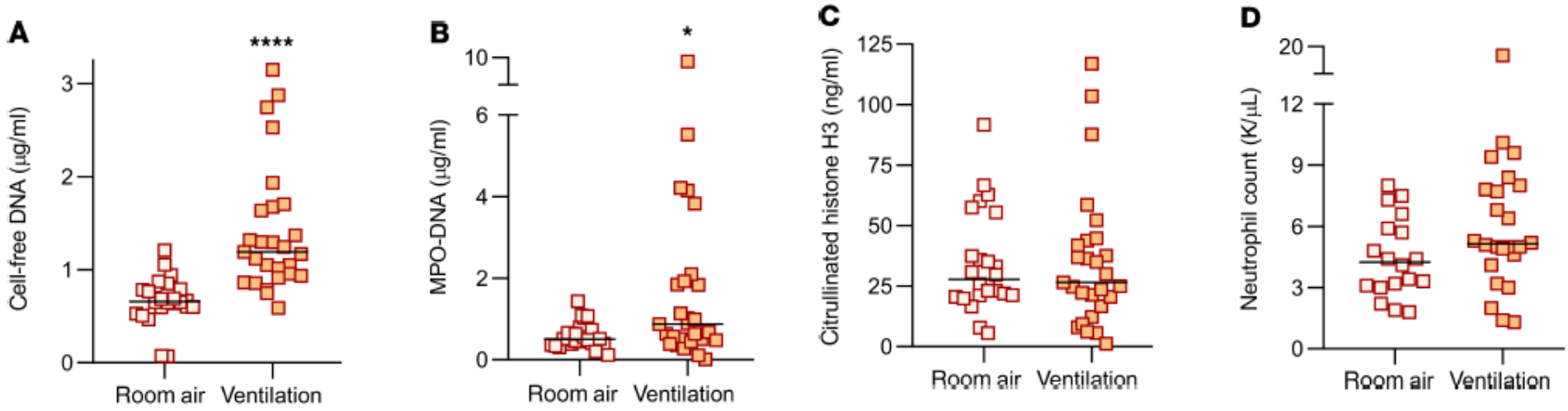
JCI Insight 2020;5:138999



- As compared with serum samples from 30 healthy controls, the 50 COVID-19 samples showed higher levels of cell-free DNA, MPO-DNA complexes, and citrullinated histone H3
- Hydroxychloroquine administration didn't change NET markers

Neutrophil extracellular traps in COVID-19

JCI Insight 2020;5:138999

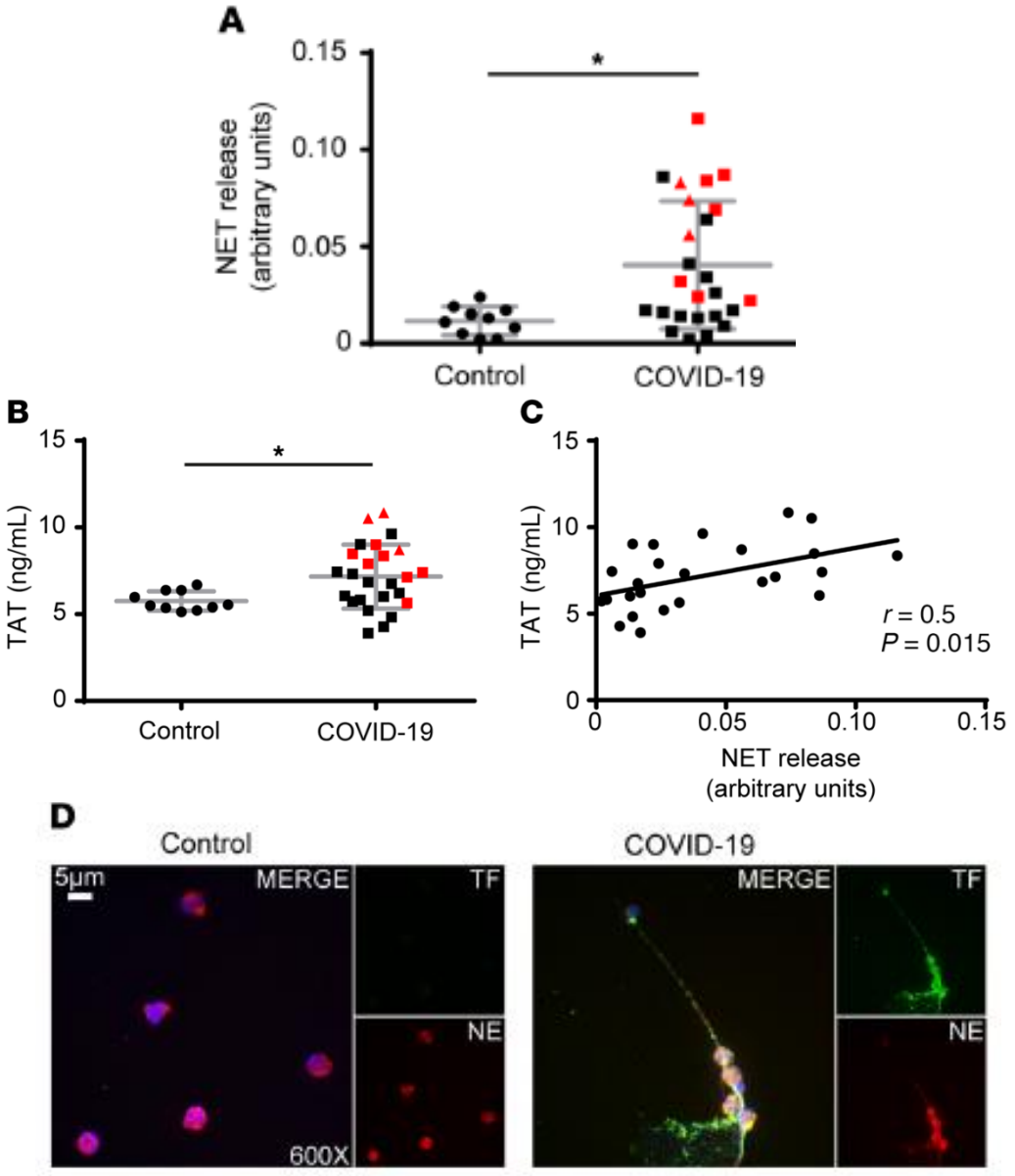


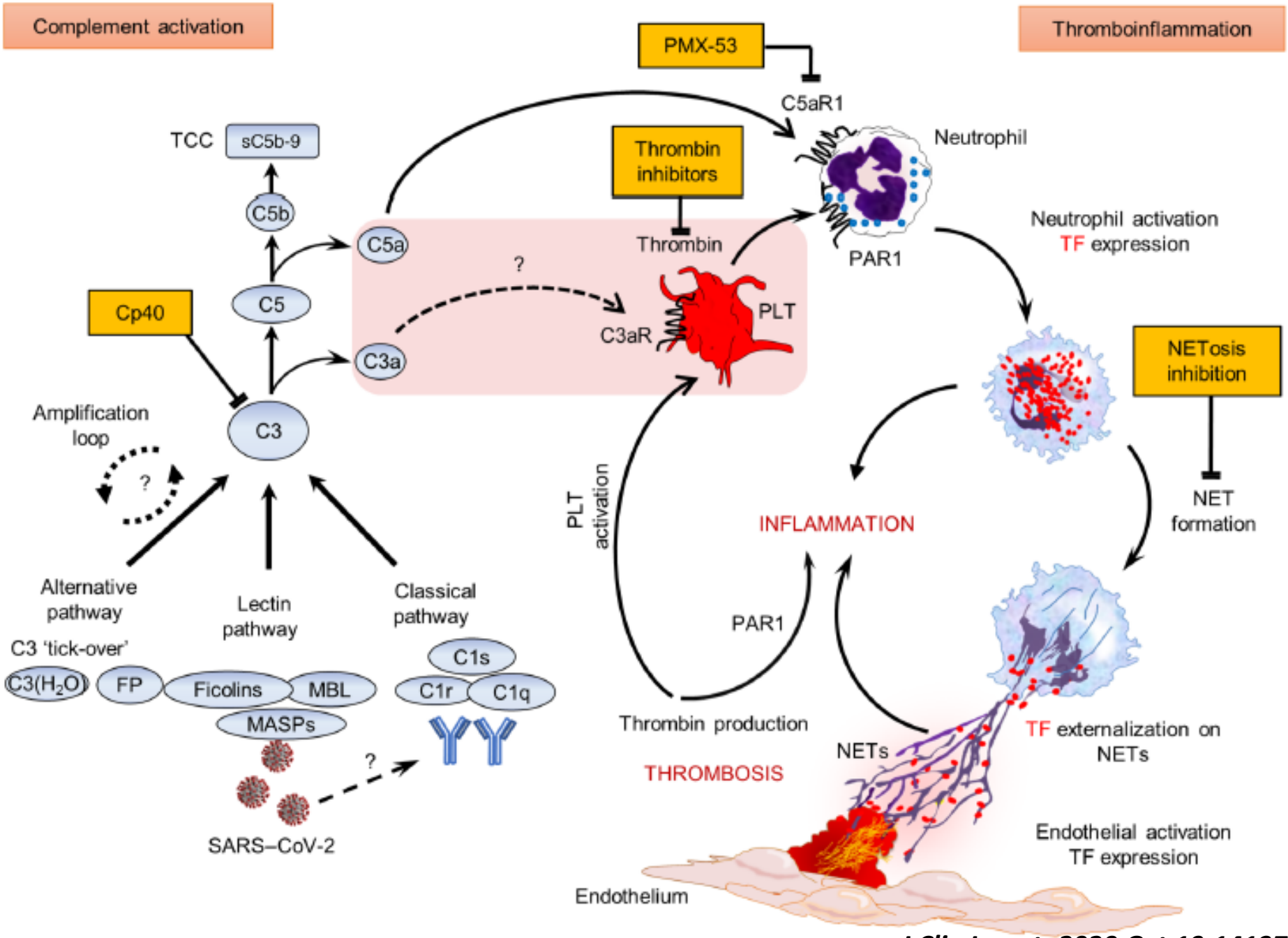
- As compared with patients breathing room air, patients requiring mechanical ventilation had significantly higher levels of cell-free DNA and MPO-DNA, while
- Cit-H3 and absolute neutrophil counts were not significantly higher the ventilated patients.
- There is a possible relationship between level of serum NETs and severity of COVID-19.

Complement and tissue factor–enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis

J Clin Invest. 2020 Oct 19;141374.

- significantly increased NETs levels in patients with COVID-19
- the levels of these complexes were positively correlated with thrombin-antithrombin (TAT) activity, indicating activation of the Tissue Factor (TF)/thrombin axis
- NET release is positively correlated with in vivo thrombotic potency in COVID-19





J Clin Invest. 2020 Oct 19;141374.

Στόχοι θεραπείας

- Effective therapy should not be limited only to the viral pathogen, but also the microangiopathic and thrombotic effects of the virus.
- The intimate association between inflammation and thrombosis would suggest an anti-inflammatory/anti-viral therapeutic approach should be considered in parallel to anticoagulation.

Antiviral agents:

- Remdesivir,
- Umifenovir,
- Lopinavir,
- Oseltamivir, and
- Favipiravir.

High dose low molecular weight heparin as thromboprophylaxis

Adjunctive agents:

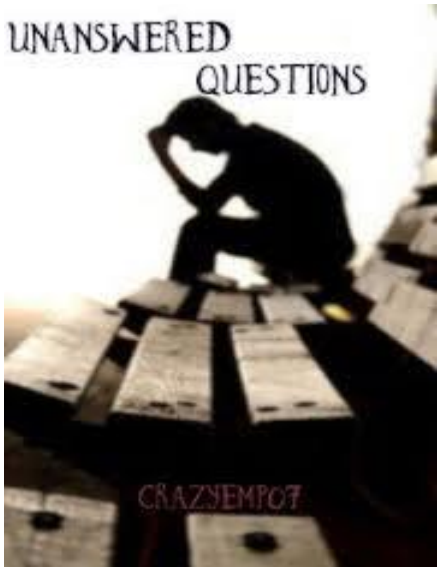
- Chloroquine, Hydroxychloroquine
- Tocilizumab,
- Hydroxychloroquine,
- Zinc,
- Vitamin D,
- Azithromycin,
- Ascorbic acid,
- Nitric oxide,
- Corticosteroids, and
- IL-6 antagonists.

Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): A case series

J Thromb Haemost 2020; 18: 1752–1755.

- a series of 3 critically ill, mechanically ventilated patients with severe COVID-19 respiratory failure who were treated with tPA.
- 25 mg **Alteplase** iv in 2 hours and 25 mg iv in 22 hours
- Heparine iv 10 IU/kg/h, aPTT: 60-80

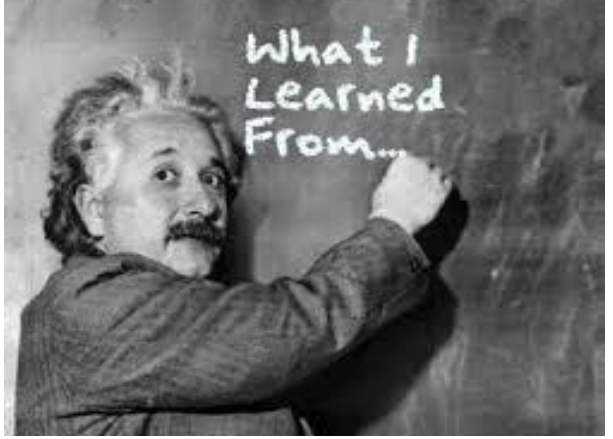
- In all 3 cases, the patients demonstrated an initial improvement in their P/F ratio



Questions remain to be answered

- What are the triggers for more intense anticoagulation where imaging is not available?
- Can this be done using D-dimer alone and
- what is the threshold to use?
- What do you do with patients when they are discharged?

Take home message



- A unique feature of COVID-19 respiratory failure is a relatively preserved lung compliance and high Alveolar-arterial oxygen gradient,
- with pathology reports consistently demonstrating diffuse pulmonary microthrombi on autopsy, and
- Endotheliitis.
- Many uncertainties remain with regard to both the virus-host interaction and the evolution of the pandemic, with specific reference to the times when it will reach its peak.

Ευχαριστώ για την προσοχή σας