Ενδοθηλιακή βλάβη και θρόμβωση σε βαρέως πάσχοντες ασθενείς με COVID-19 λοίμωξη

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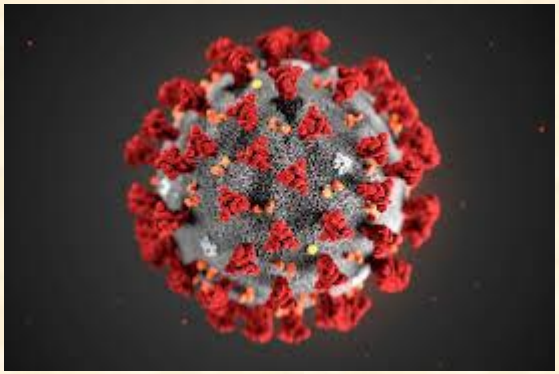
ΠΓΝ «ΑΤΤΙΚΟΝ»

COVID-19



- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- 20 Jan 2020: International public health emergency
- 11 March 2020: Pandemic
- 131 millions cases/ 2 millions deaths
- Pulmonary and cardiovascular disease: adverse outcomes

Disease severity classification: NIH criteria

MILD	MODERATE	SEVERE	CRITICAL
Individuals who have various signs and symptoms of COVID-19 (ANY): ☐ Fever ☐ Cough ☐ Sore throat ☐ Malaise ☐ Headache ☐ Muscle pain ☐ Nausea, vomiting, diarrhea ☐ Loss of taste and smell **BUT who do NOT have (ANY):** ☐ Shortness of breath ☐ Dyspnea ☐ Abnormal chest imaging (if obtained)	**Individuals who show evidence of lower respiratory disease during (ANY):** ☐ Clinical assessment ☐ Imaging **AND who have:** ☐ SpO2 ≥94% on room air at sea level (in those with normal baseline SpO2 at rest)	**Individuals who have (ANY):** ☐ SpO2 <94% on room air at sea level (in those with normal baseline SpO2 at rest) ☐ Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg (if ABG obtained) ☐ RR >30 breaths/min ☐ Lung infiltrates >50%	**Individuals with (ANY):** ☐ Respiratory failure ☐ Septic shock ☐ Multiorgan dysfunction or failure

SEVERE and **CRITICAL** Severity - Skip to Step 4 (**Diagnostic Testing**) on Page 2

Coagulation abnormalities in COVID -19

- Coagulopathy associated with increased risk of death
- Venous, arterial, microvascular thrombosis
- VTE: 25-49%, AMI, ischemic stroke
- 5-fold increase in all cause mortality
- Different than sepsis DIC
- DIC score usually negative
- High LDH and ferritin
- No signs of hemolysis or schistocytes

M. Levy et al. Lancet Hematology. Vol 7.June 2020

Coagulation characteristics of COVID-19

Platelet count: Mildly to moderate reduced in the most severe pts

PT: Mild prolongation in a minority of pts

High fibrinogen: in all pts

D-Dimers: elevated in non survivors

	Survivors	Non-survivors
Platelet count <150x10⁹/L	30-70%	45-80%
Platelet count <100x10⁹/L	0-1%	3-5%
Prothrombin time > 3 sec. prolonged	0-5%	15-25%
Fibrinogen < 1.0 g/L	0%	5-10%
Fibrinogen > 4.0 g/L	80-100%	80-100%
D-dimer > 1 mg/L (2x ULN)	15-25%	80-90%
D-dimer > 3 mg/L (6x ULN)	1-5%	50-70%
Antithrombin < 80%	0%	0-2%

M.Levi, B.Hunt. *Res Pract Thromb Haemost* 2020;4(5):744-751

JAMA Internal Medicine | Original Investigation

JAMA Intern Med. doi:10.1001/jamainternmed.2020.0994
Published online March 13, 2020.

Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China

Chaomin Wu, MD; Xiaoyan Chen, MD; Yanping Cai, MD; Jia'an Xia, MD; Xing Zhou, MD; Sha Xu, MD;

Table 4. Bivariate Cox Regression of Factors Associated With ARDS Development or Progression From ARDS to Death

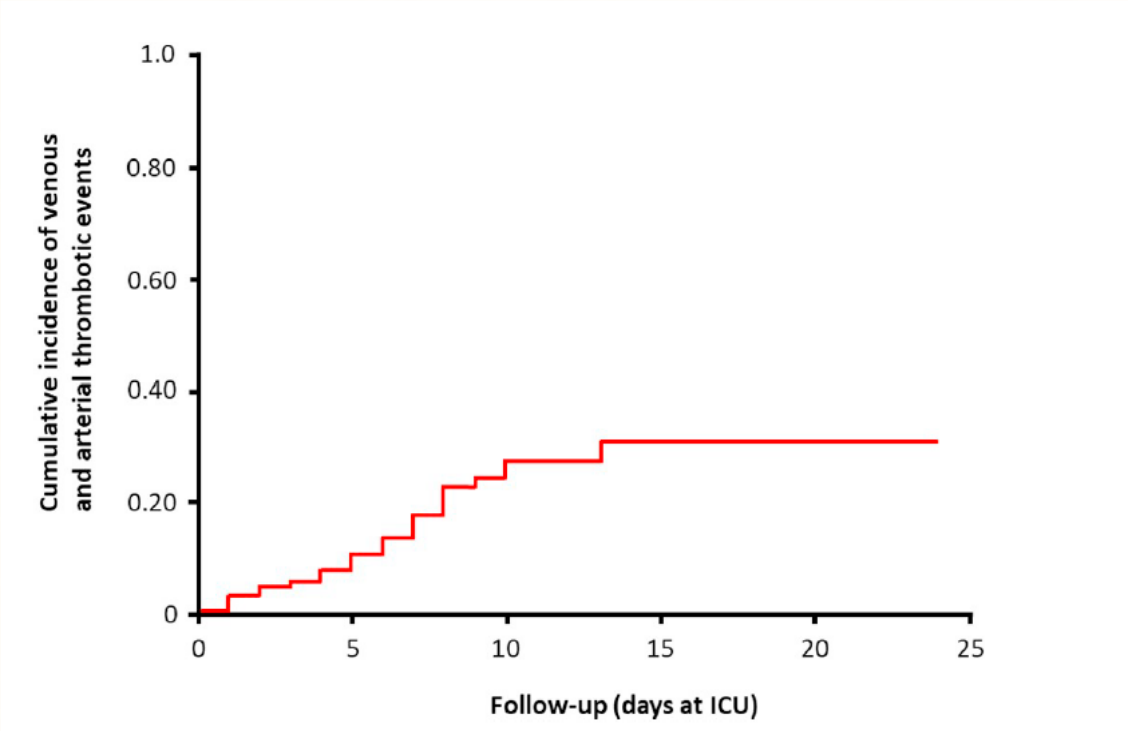
	ARDS		Death	
Patient characteristics and findings	HR (95% CI)	*P* value	HR (95% CI)	*P* value
IL-6, pg/L	1.02 (1.00-1.05)	.09	1.03 (1.01-1.05)	.01
Coagulation function				
PT, s	1.56 (1.32-1.83)	<.001	1.08 (0.84-1.38)	.54
APTT, s	0.97 (0.94-1.01)	.13	0.96 (0.91-1.00)	.06
D-dimer, μg/mL	1.03 (1.01-1.04)	<.001	1.02 (1.01-1.04)	.002

Incidence of thrombotic complications in critically ill ICU patients with COVID-19

F.A. Klok[a,*], M.J.H.A. Kruip[b], N.J.M. van der Meer[c], M.S. Arbous[d], D.A.M.P.J. Gommers[e],

Thrombosis Research 191 (2020) 145–147

- 3 Dutch Hospitals
- 183 pts COVID-19pneumonia ICU
- 31% thrombotic complications
- VTE 27%
- Arterial thromobosis: 3.7%



Pathophysiology of hemostatic disorders in COVID-19

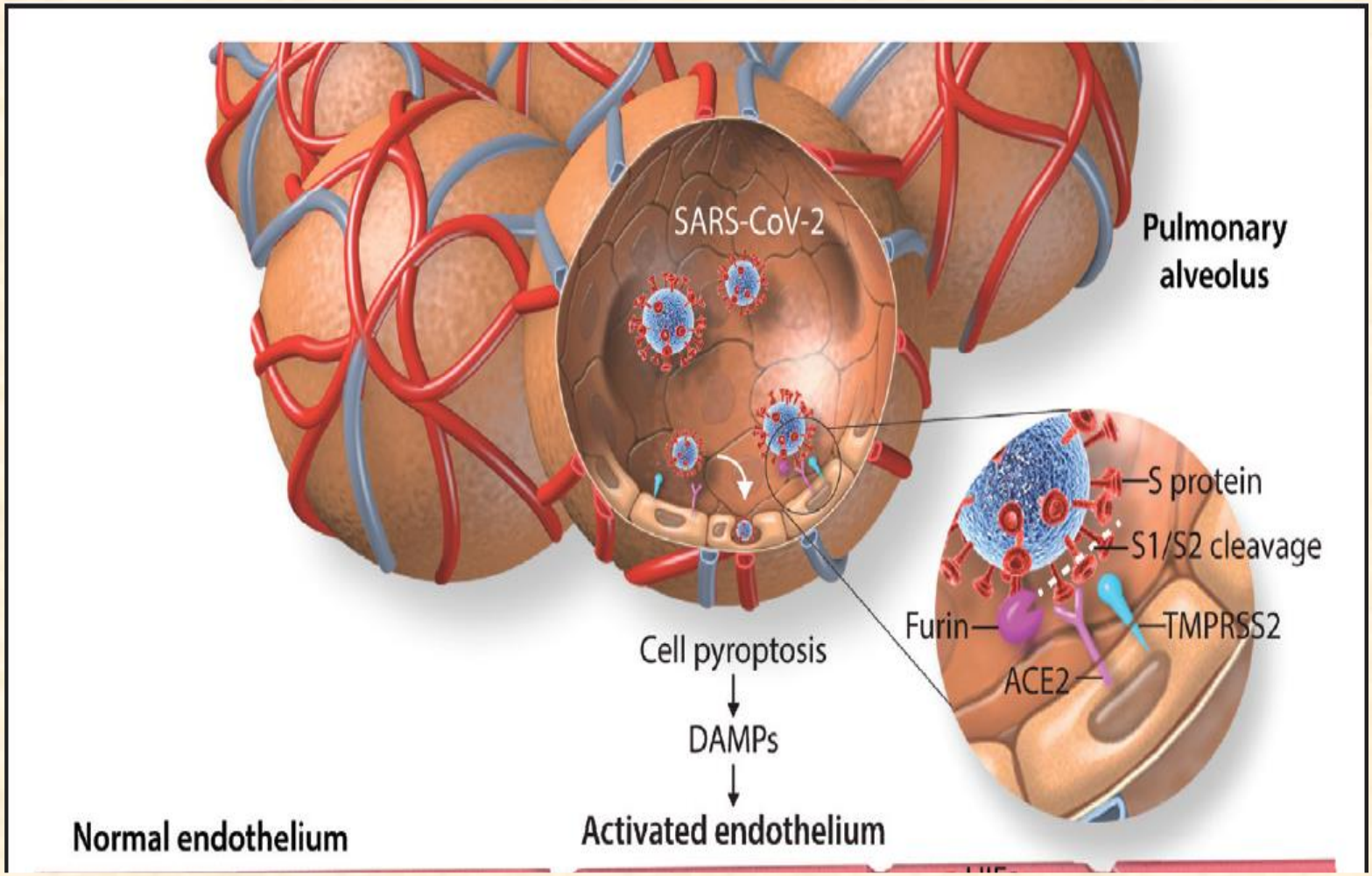
- Local tissue damage caused by SARS-CoV2
- Systemic inflammation and viremia
- Endotheliopathy - Immunothrombosis

Connors JM et al. Blood 2020;135:2032-40

Local tissue damage

- S1 attaches ACE-2 on lung alveolar type II cell
- Pyroptosis
- PRR detect PAMPs and DAMPs
- Chemokines and cytokines
- ARDS
- Alveolar fibrin deposition-Local fibrinolysis-High D-Dimers
- Endothelial damage

J.D.McFadyen et al. *Circulation Research*;127(4):571-587



J.D.McFadyen et al. Circulation Research;127(4):571-587

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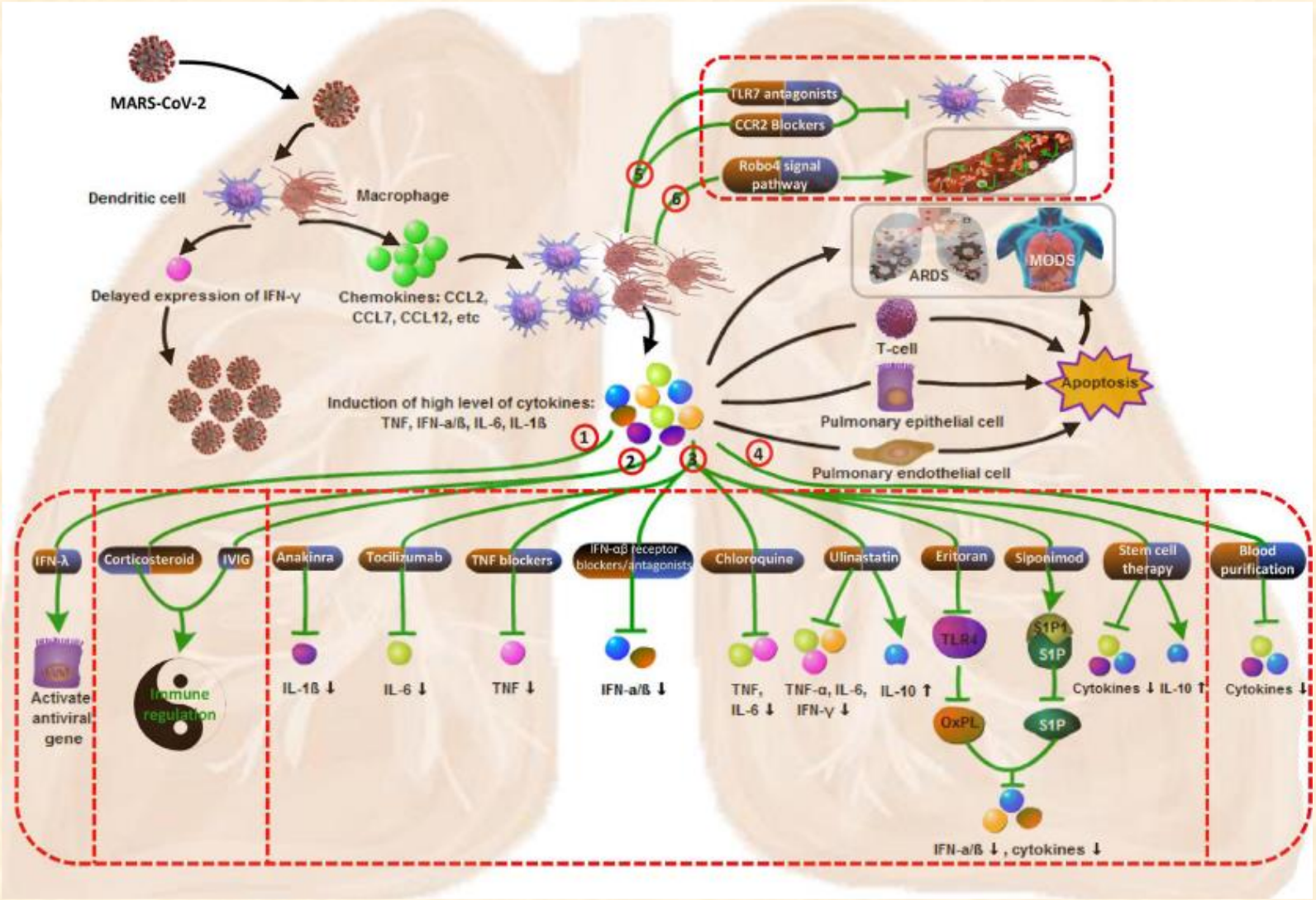
Connors JM et al. Blood 2020;135:2032-40

Uncontrolled systemic inflammation

- Viremia
- Detection of viral RNA at most tissues
- CRP, Ferritin, neutrophil to lymphocyte ratio, fibrinogen
- Cytokine storm, Macrophage activation syndrome
- IL-6, TNF-a, IL1β
- IL-6, TNF-a strongly associated with survival



Ye Q et al. *Journal of Infection*;80,2020:607-613

nature medicine

ARTICLES

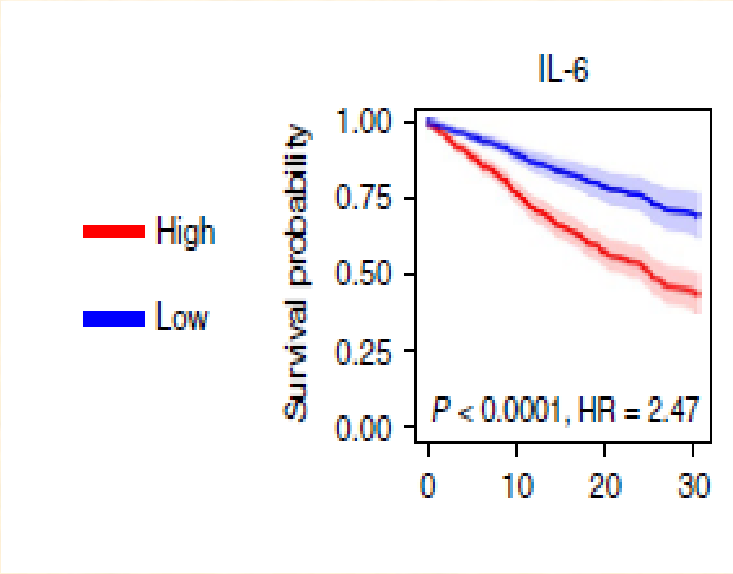
https://doi.org/10.1038/s41591-020-1051-9

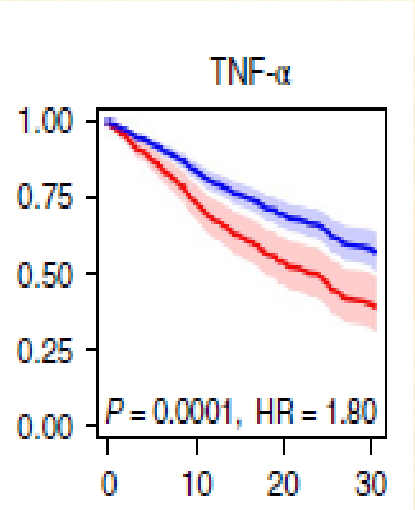
Check for updates

An inflammatory cytokine signature predicts COVID-19 severity and survival

Diane Marie Del Valle[1,2,3,14], Seunghee Kim-Schulze[1,2,3,4,14], Hsin-Hui Huang[5,6,7,14], Noam D. Beckmann[8],

1484 pts, New York city, March 21-April 28 2020





IL-6, TNFa: independent and significant predictors of disease severity and death

Pathophysiology of hemostatic disorders in COVID-19

- Local tissue damage caused by SARS-CoV2
- Systemic inflammation and viremia
- Endotheliopathy - Immunothrombosis

Connors JM et al. Blood 2020;135:2032-40

Endotheliopathy

- Viral attack of endothelial cells-ACE2
- Cytokines: Activation of neutrophils and endothelial cells
- Procoagulant phenotype: Upregulation of adhesion molecules, release of VWF, recruitment of platelets and leucocytes
- Upregulation of tissue factor
- Downregulation of natural anticoagulants
- Thrombin generation-Micro and macro vascular thrombosis

J.D.McFadyen et al. Circulation Research;127(4):571-587

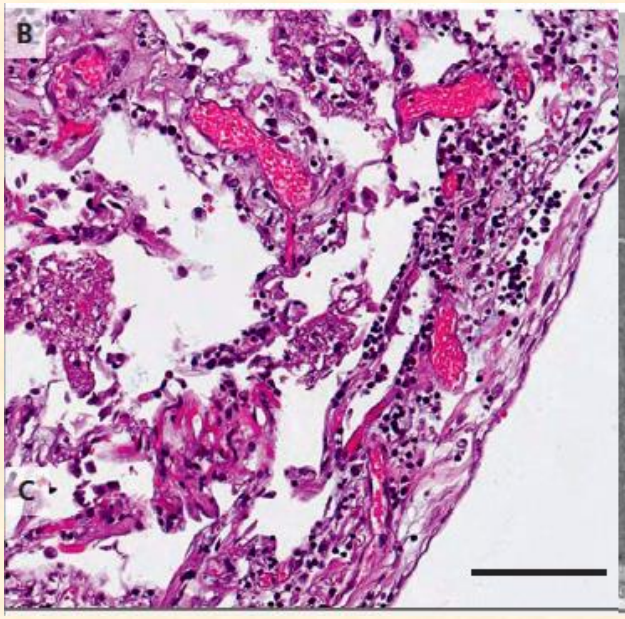
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

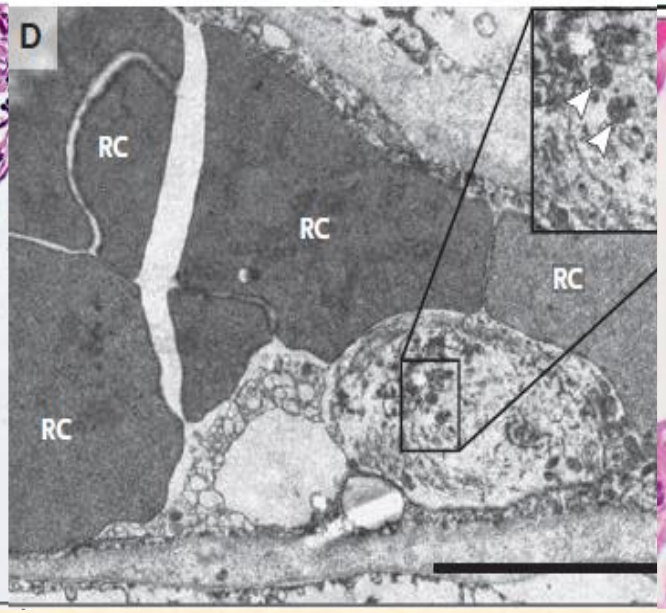
Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D.,

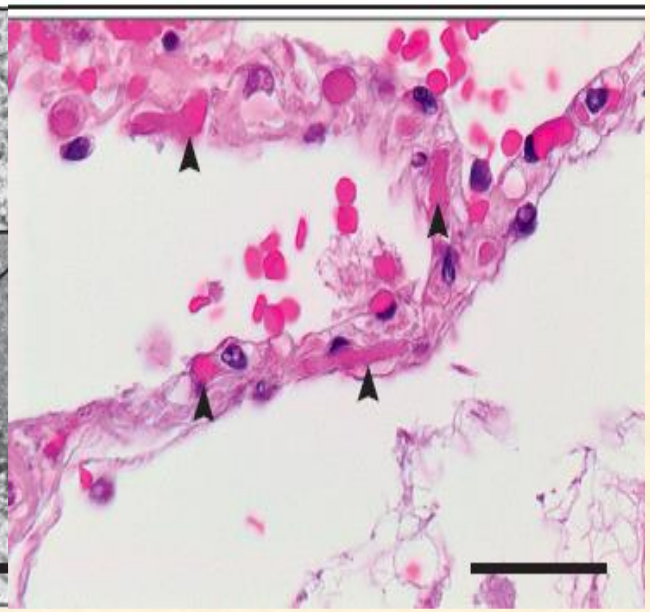
Autopsy
7 lungs from COVID-19 pts
7 lungs H1N1
10 control



T-lymphotic inflammation



SARS-CoV-2 within the cell membrane

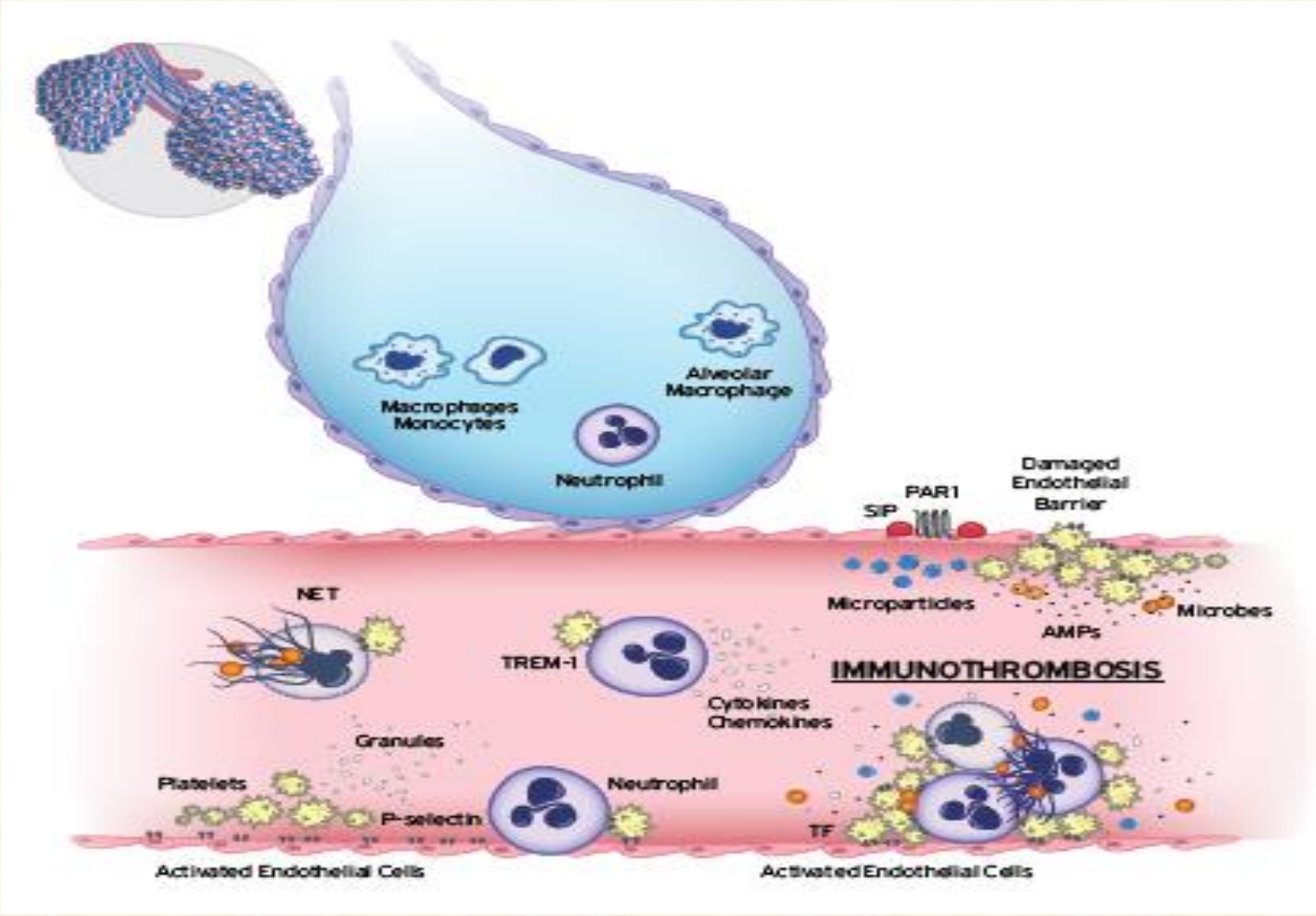


Microthrombi in the alveolar capillaries

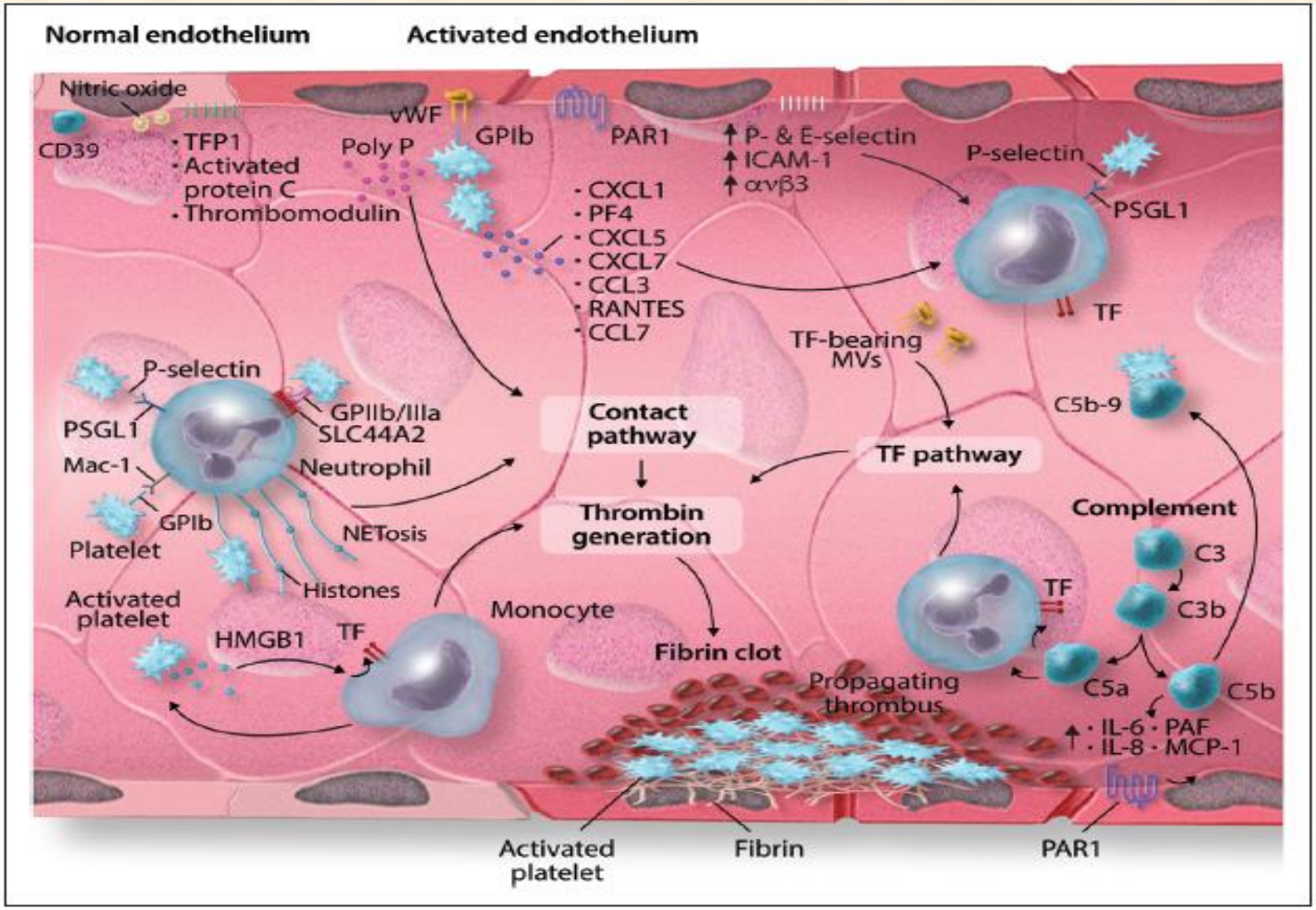
Immunothrombosis

- The pathophysiological role of coagulation in the innate host response to endothelial damage
- Organized recruitement of innate cells and platelets at the site of endothelial damage, regulated by coagulation proteases and inflammatory mediators
- Microthrombi: Complex with antimicrobiotic properties-inflammatory response, TF expression

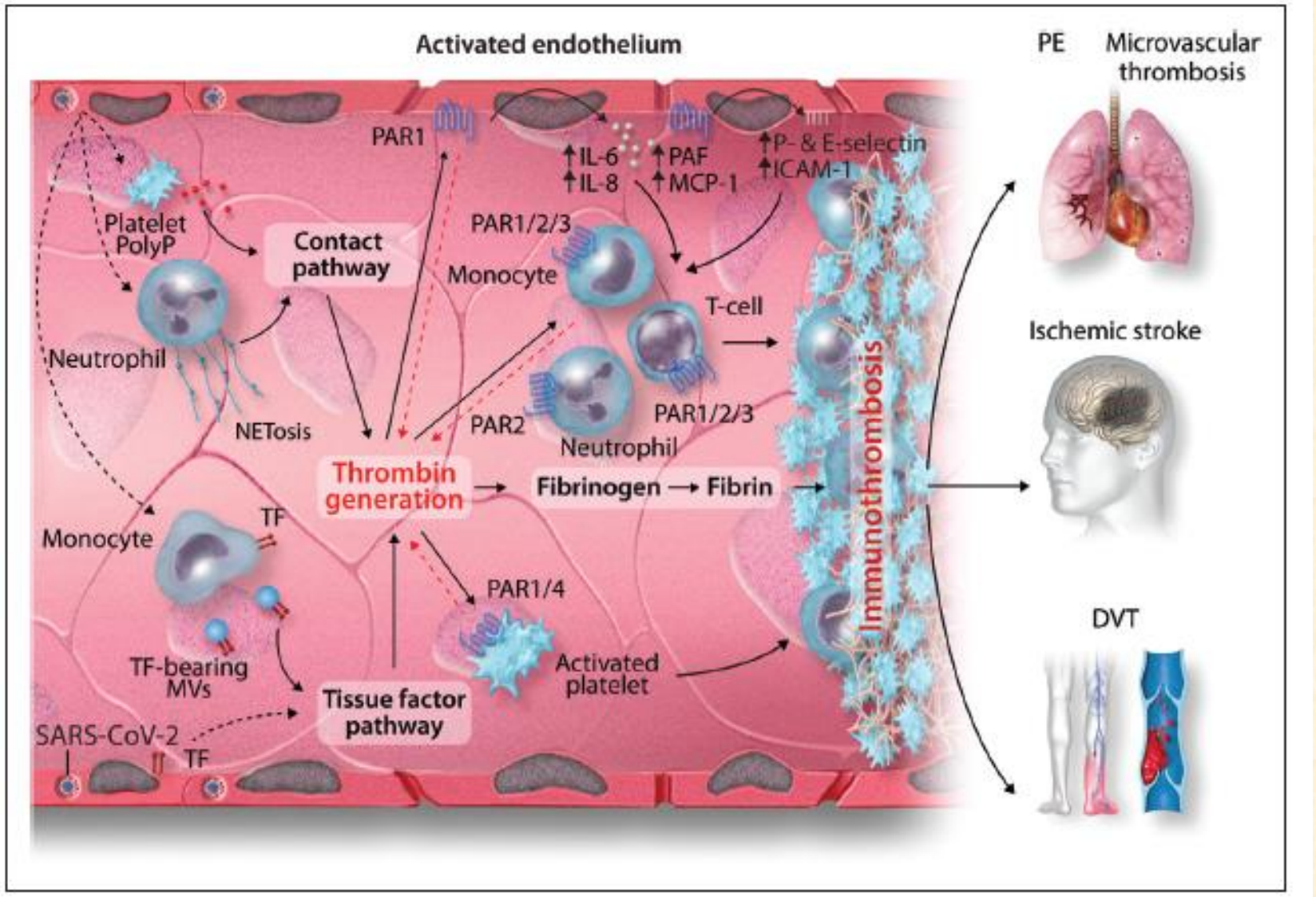
Engelmann B et al. *Nat Rev Immunol* 2013;13(1):34-45



Frantzeskaki F et al. *Respiration 2017*



J.D.McFadyen et al. Circulation Research;127(4):571-587



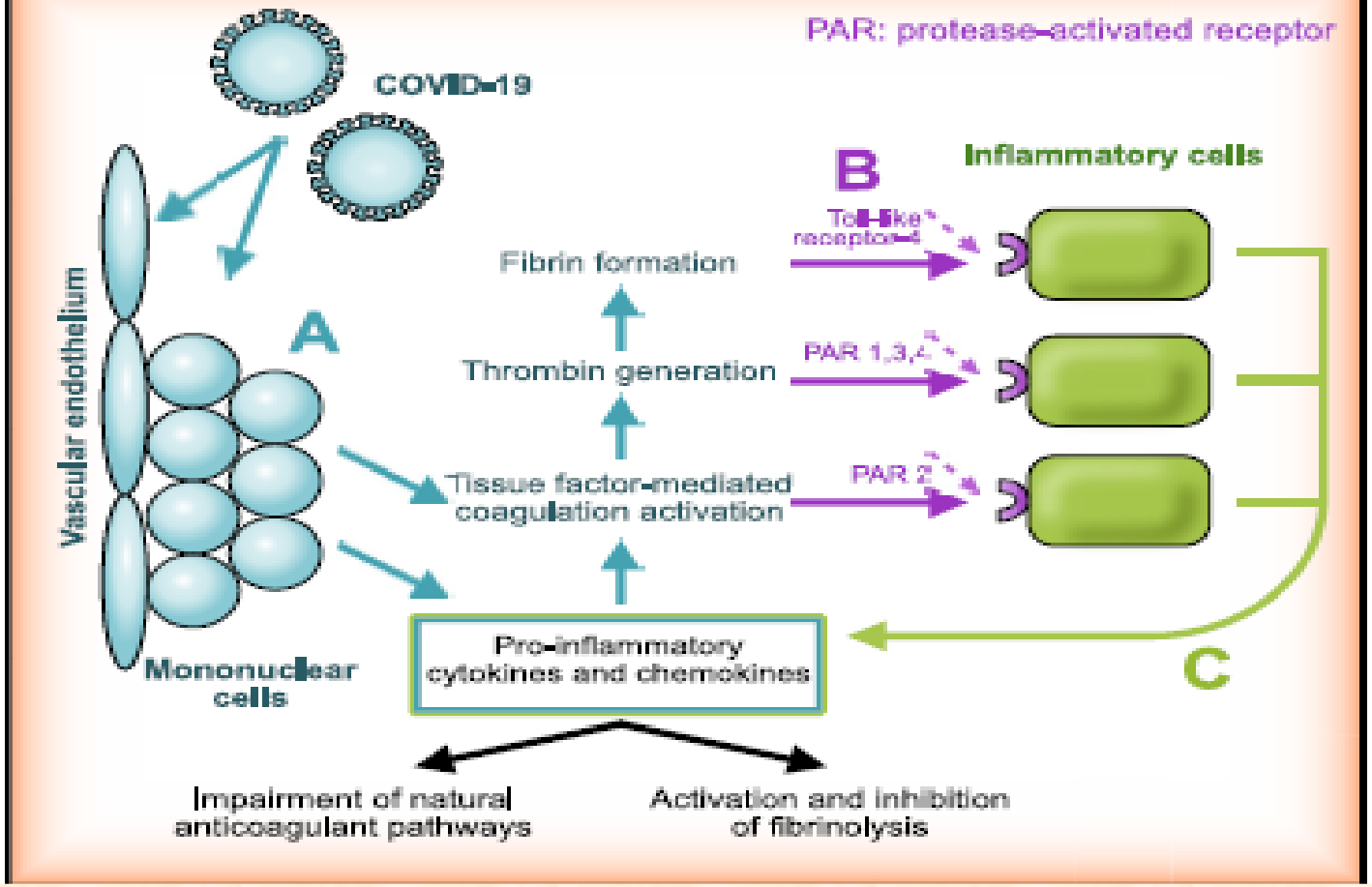
J.D.McFadyen et al. Circulation Research;127(4):571-587

Thrombin: In the heart of thrombosis and inflammation

- Enzymatic cleavage of fibrinogen to fibrin
- Proinflammatory effects
- PARs: platelets, epithelial cells, immune cells and astrocytes
- A strong platelet agonist
- Activation of leukocytes: cytokines and growth factors (IL-6, IL-8, PAF, ICM-1, P-selectin)
- Modulation of immune response to viruses

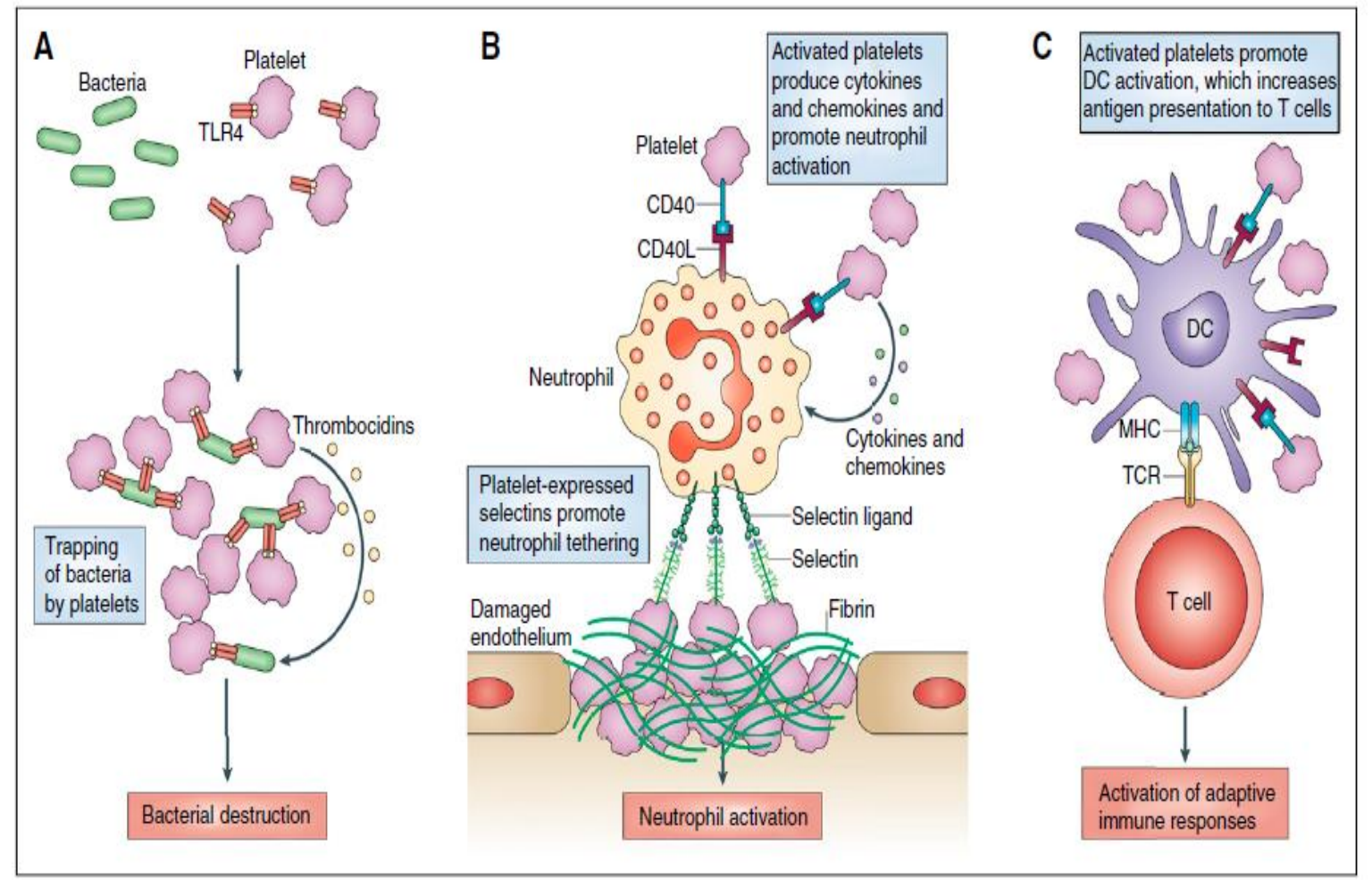
J.D.McFadyen et al. Circulation Research;127(4):571-587

Like many other infections, there is significant cross-talk between inflammation and coagulation



M.Levi, B.Hunt. *Res Pract Thromb Haemost* 2020;4(5):744-751

Platelets: The first defense

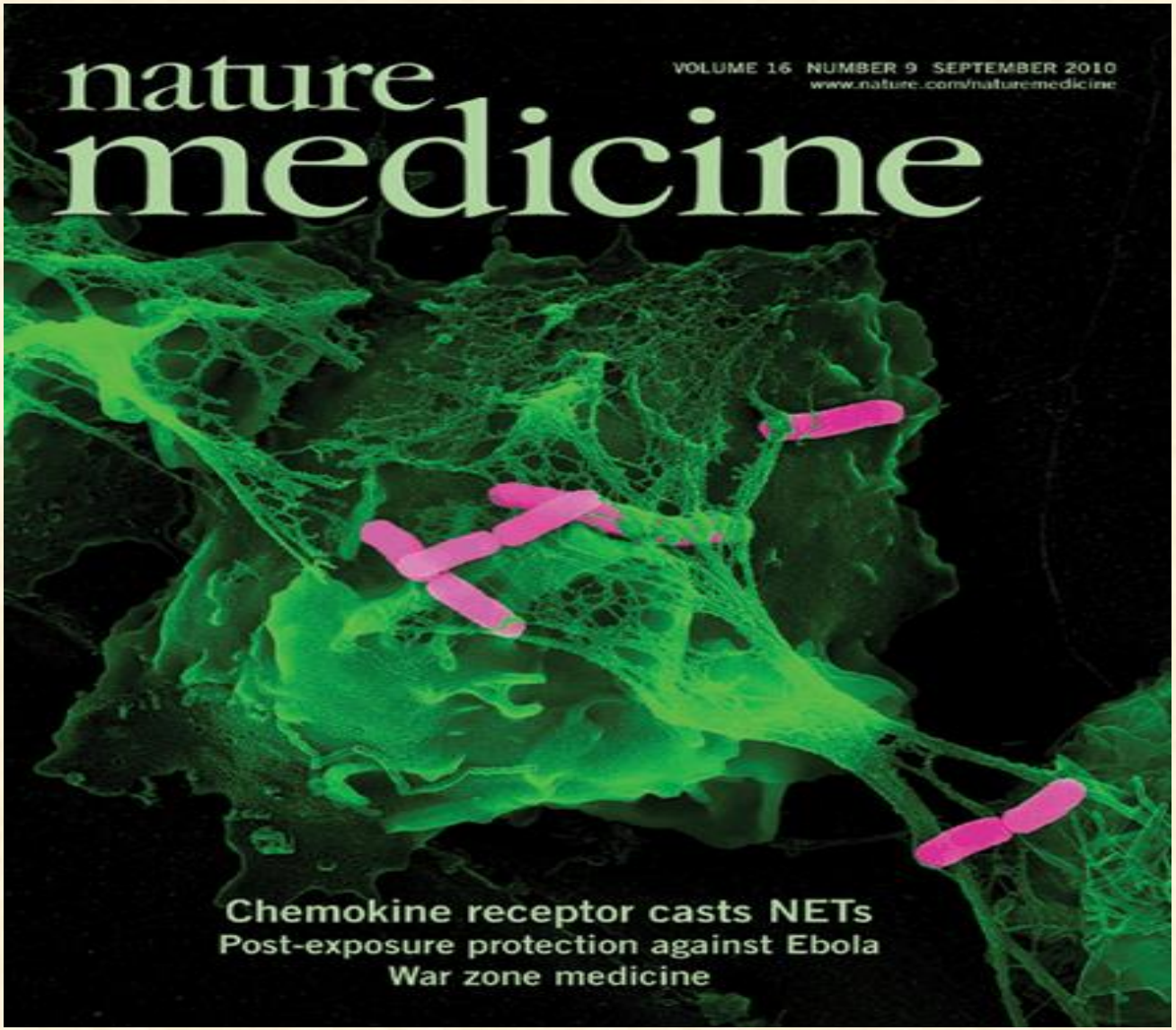


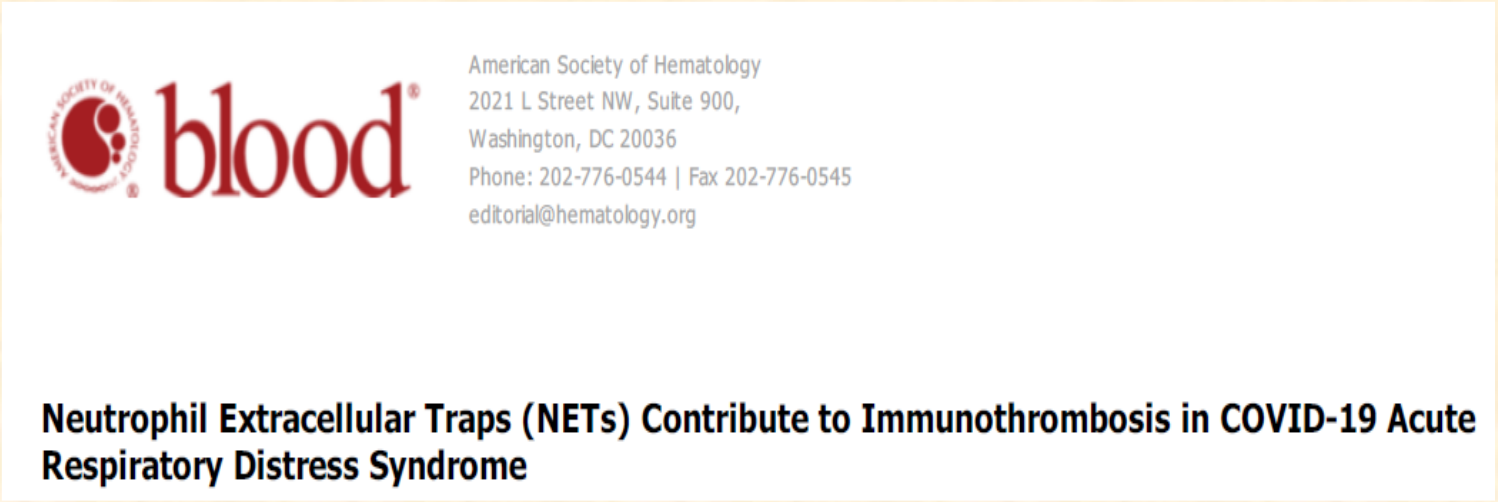
Graham S et al. *Blood* 2016;127(24)

Neutrophil extracellular traps (NETs)

- Released from activated neutrophils
- Chromatine and proteins of activated neutrophils, MPO, NE
- Antimicrobial properties-trapping microorganisms
- Procoagulant activities: arterial and venous thrombosis
- Activation of platelets and contact system (FXII)
- Excessive inflammatory response
- TRALI, ARDS, SLE, DIC

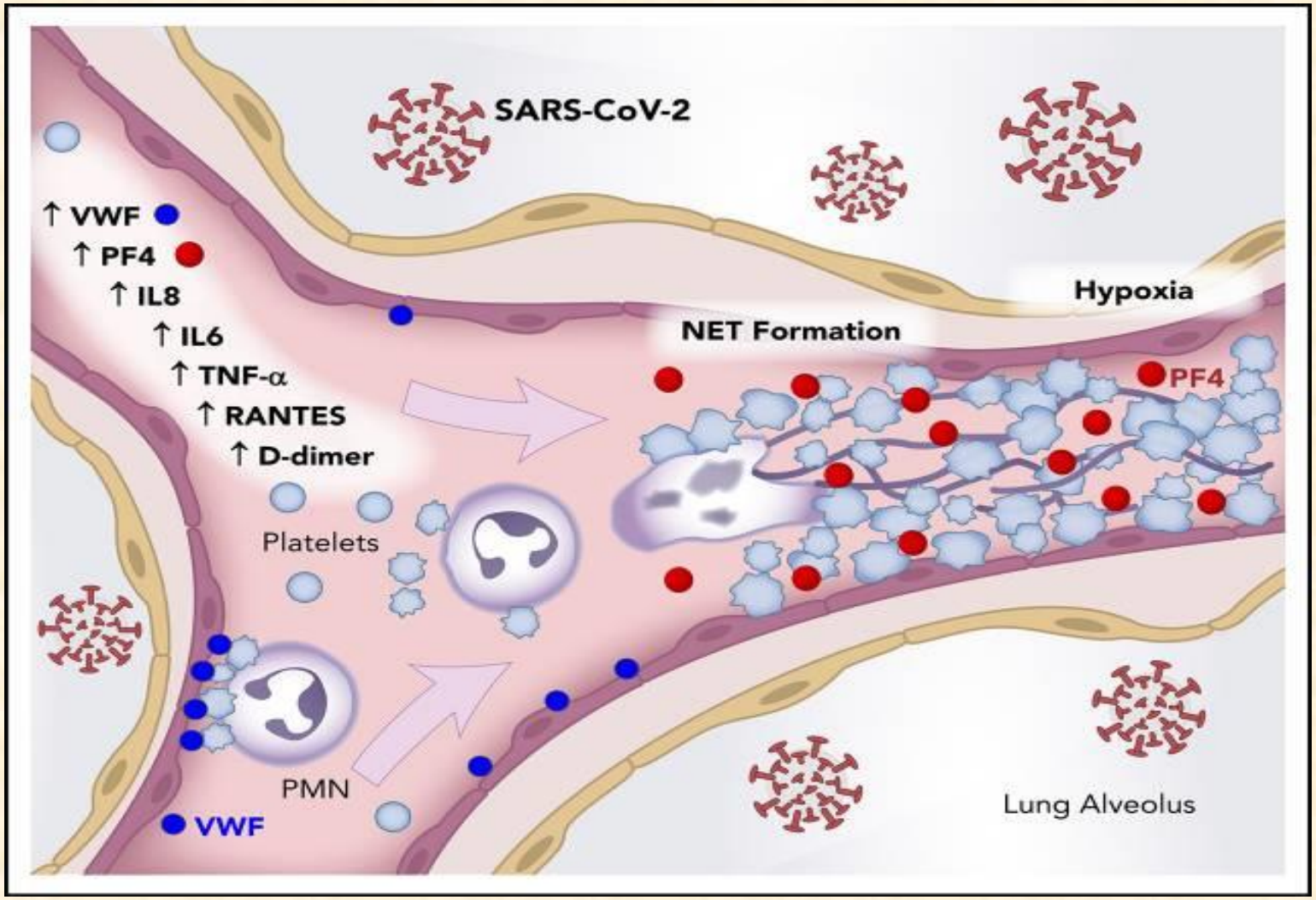
Kaplan et al. *Journal of immunology* 2012. Sep 15;189 (6) 2689-95


nature
medicine
VOLUME 16 NUMBER 9 SEPTEMBER 2010
www.nature.com/naturemedicine
Chemokine receptor casts NETs
Post-exposure protection against Ebola
War zone medicine

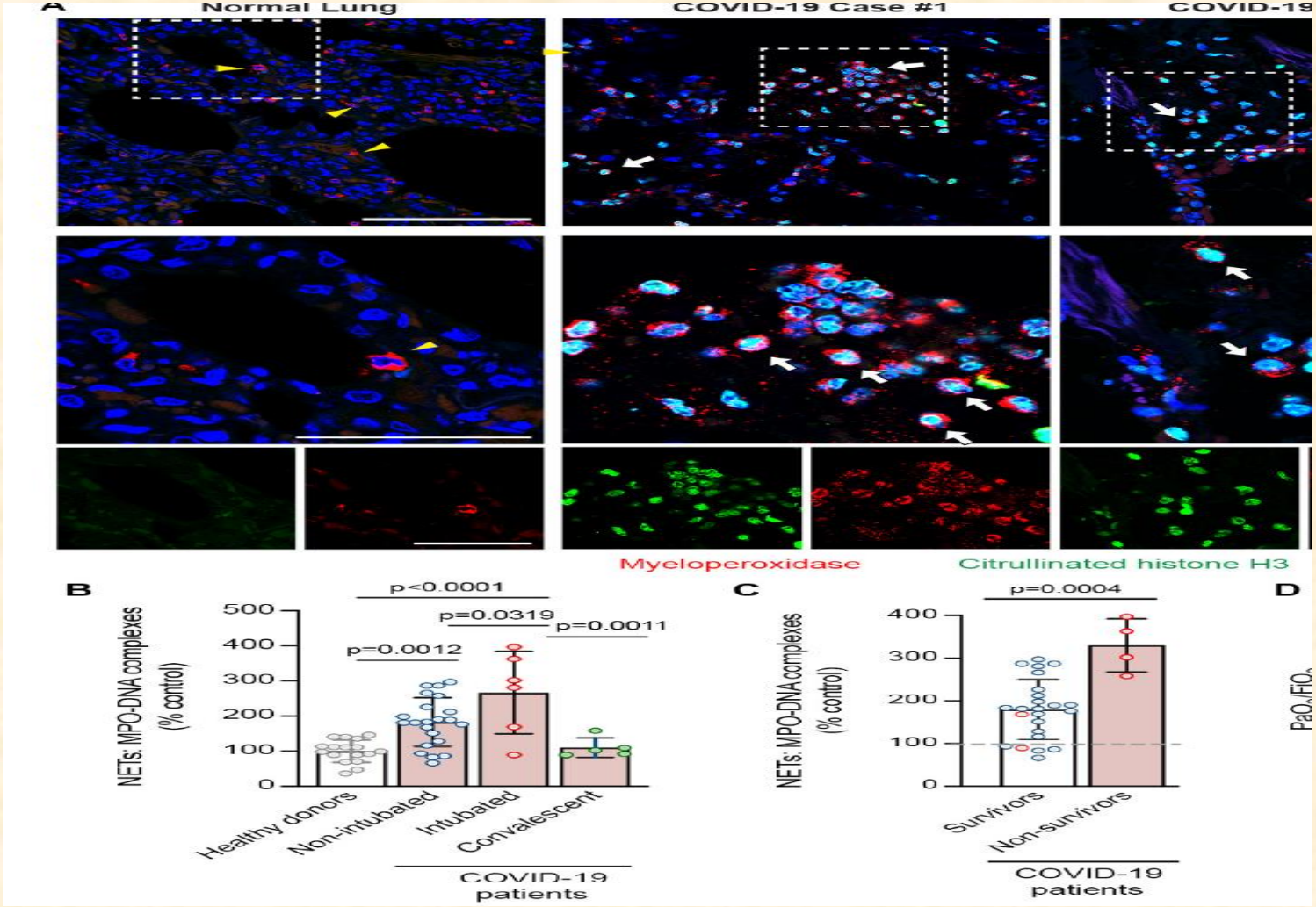


- Prospective cohort study in 33 COVID-19 pts
- NETs, PF-4, cytokines
- NETs increased in COVID-19 intubated pts compared to controls
- Correlation between NETs and respiratory disease severity
- Interaction with platelets in lung vessels
- Potential therapeutic target

E. Middleton et al. Blood 2020, 130 (10)

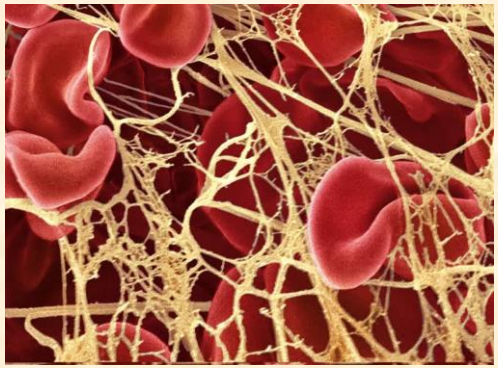


E.Middleton et al. *Blood* 2020, 130 (10)



E.Middleton et al. *Blood* 2020, 130 (10)

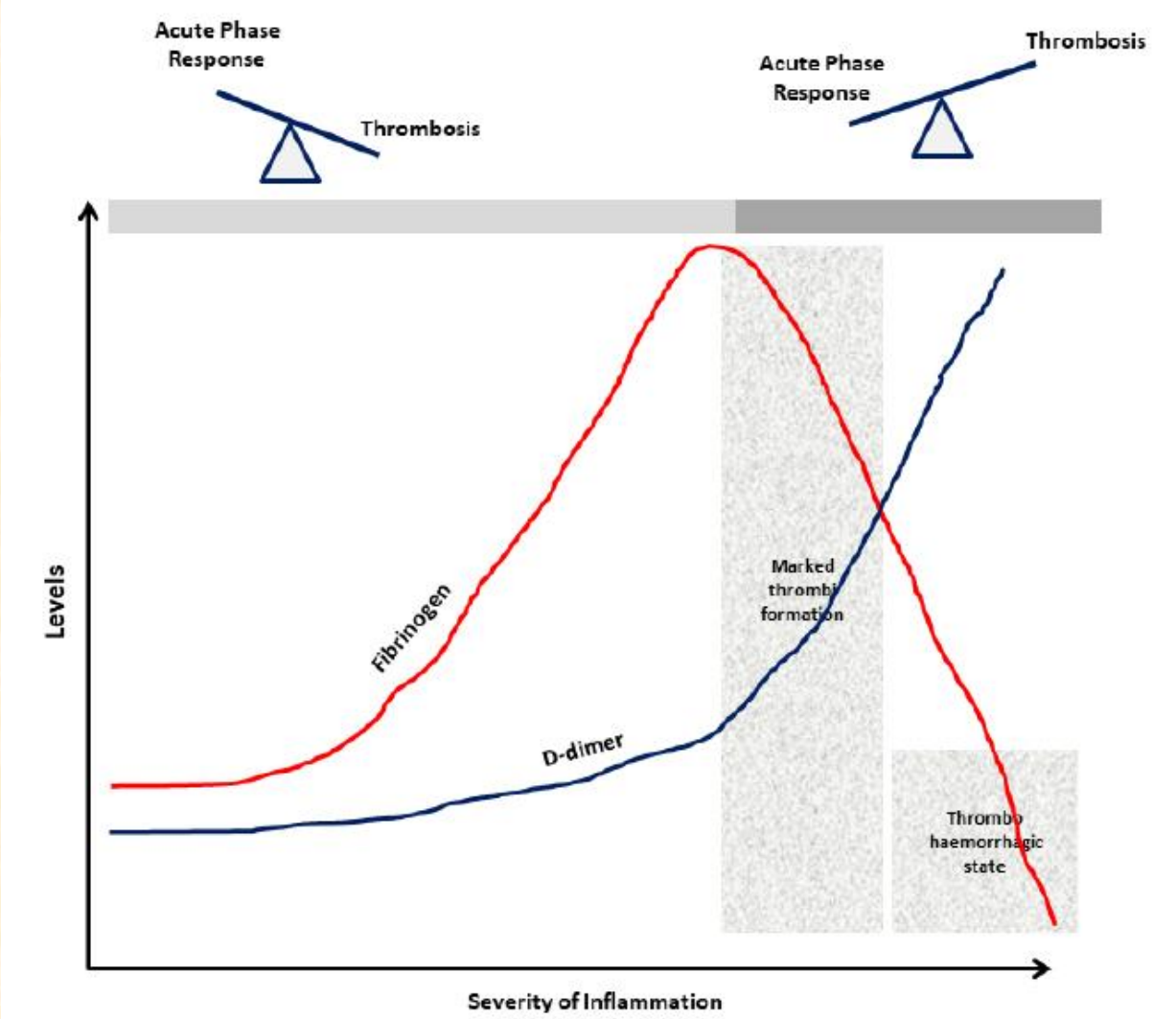
Fibrinolysis



- Initially: acute release of plasminogen activators
- Local fibrinolysis in alveoli (D-Dimers)
- Increase in PAI-1
- Fibrin(ogen) fundamental to survive infection
- Fibrin formation: pathogen entrapment
- Bacteria: Fibrinolysis activators (omptins)
- Dysplasminogenemia: Enhanced survival during infection with *Y.pestis*, *streptococci*, *S.aureus*

Delabranche X et al. *Ann Intensive Care* (2017) 7;117

Forum article: The protective rather than prothrombotic fibrinogen in COVID-19 and other inflammatory states



Jecko Thachil. *J Thromb and Hemostasis*; 2020 Aug;18(8)

Management of coagulation disorders

- LMWH reduces mortality in COVID-19 pts with elevated D-Dimers
- Heparin: AT mediated inhibition of FXa and thrombin
- Heparin: anti-inflammatory effects
- Heparin: antiviral properties

binding spike protein

inhibiting binding of virus to cells

Tang N et al. *J Thromb and Haemost* 2020;18
Milewska A et al. *J Virol* 2014;88

Received: 23 April 2020 | Accepted: 21 May 2020

DOI: 10.1111/jth.14929

RECOMMENDATIONS AND GUIDELINES

Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19

Alex C. Spyropoulos[1] | Jerrold H. Levy[2] | Walter Ageno[3] | Jean Marie Connors[4] | Beverley J. Hunt[5] | Toshiaki Iba[6] | Marcel Levi[7] | Charles Marc Samama[8] | Jecko Thachil[9] | Dimitrios Giannis[10] | James D. Douketis[11] | on behalf of the Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis

VTE prophylaxis in non-ICU hospitalized COVID-19 patients:

1. A universal strategy of routine thromboprophylaxis with standard-dose UFH or LMWH should be used after careful assessment of bleed risk, with LMWH as the preferred agent. Intermediate-dose LMWH may also be considered (30% of respondents).
2. VTE prophylaxis recommendations should be modified based on extremes of body weight, severe thrombocytopenia (ie platelet counts of $50\,000 \times 10^9$ per liter or $25\,000 \times 10^9$ per liter) or deteriorating renal function.

VTE prophylaxis in sick ICU hospitalized COVID-19 patients:

1. Routine thromboprophylaxis with prophylactic-dose UFH or LMWH should be used after careful assessment of bleed risk. Intermediate-dose LMWH (50% of respondents) can also be considered in high risk patients. Patients with obesity as defined by actual body weight or BMI should be considered for a 50% increase in the dose of thromboprophylaxis. Treatment-dose heparin should not be considered for primary prevention until the results of randomized controlled trials are available.
2. Multi-modal thromboprophylaxis with mechanical methods (ie, intermittent pneumonic compression devices) should be considered (60% of respondents).

JAMA | Original Investigation

Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit

The INSPIRATION Randomized Clinical Trial

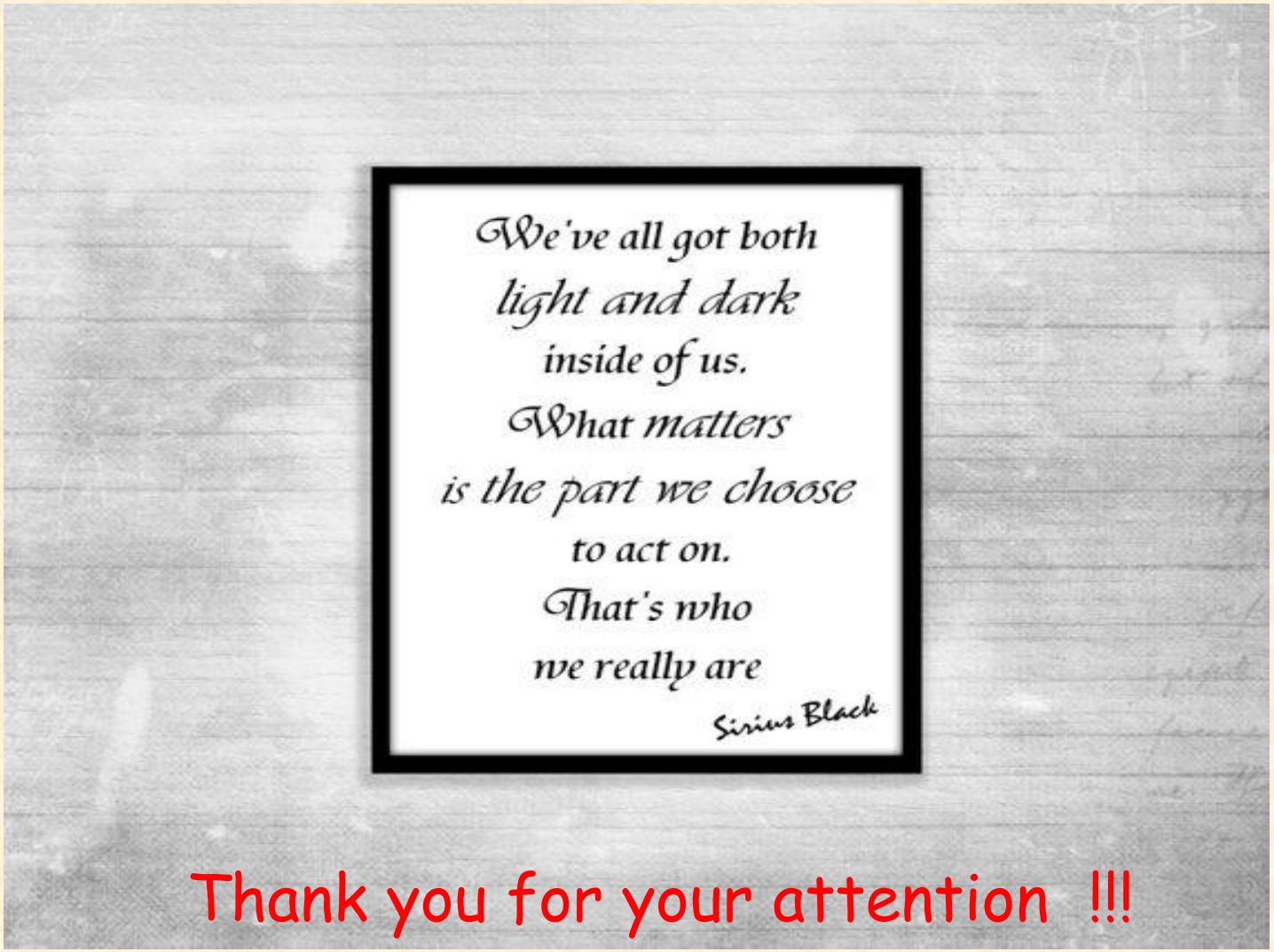
INSPIRATION Investigators

INTERVENTIONS Intermediate-dose (enoxaparin, 1 mg/kg daily) (n = 276) vs standard prophylactic anticoagulation (enoxaparin, 40 mg daily) (n = 286), with modification according to body weight and creatinine clearance. The assigned treatments were planned to be continued until completion of 30-day follow-up.

CONCLUSIONS AND RELEVANCE Among patients admitted to the ICU with COVID-19, intermediate-dose prophylactic anticoagulation, compared with standard-dose prophylactic anticoagulation, did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days. These results do not support the routine empirical use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the ICU with COVID-19.

Coagulopathy and inflammation in COVID-19

- Local inflammation
- Viremia and systemic inflammation
- Endotheliopathy
- Immunothrombosis concept
- Arterial and venous thrombosis
- Uncertainties on anticoagulation
- Need for RCT on therapeutic strategies



Thank you for your attention !!!