COVID!

Tom DeLoughery, MD MACP FAWM @bloodman

Oregon Health & Science University

GENERAL HEMATOLOGY
OHSU

DISCLOSURE

Current Relevant Financial Relationship(s)

None

Talk

- Thrombosis incidence
- Mechanisms of thrombosis
- Testing
- Treatment

- Convalescent plasma
- Blood groups

COVID

- New infection
- Pneumonia primary feature
- Coagulation issues soon recognized as a major feature

Coagulopathy in COVID-19

- Very common!
- Most patients with
  - Abnormal coagulation
  - Very high D-dimers
  - Very high fibrinogen
- Thrombosis >>> bleeding

D-Dimer

- Marked elevation in all patients
- Major prognostic indicator
- May be a sign of thrombosis
- Cause
  - Widespread coagulation activation
  - Pulmonary thrombosis

D-Dimer

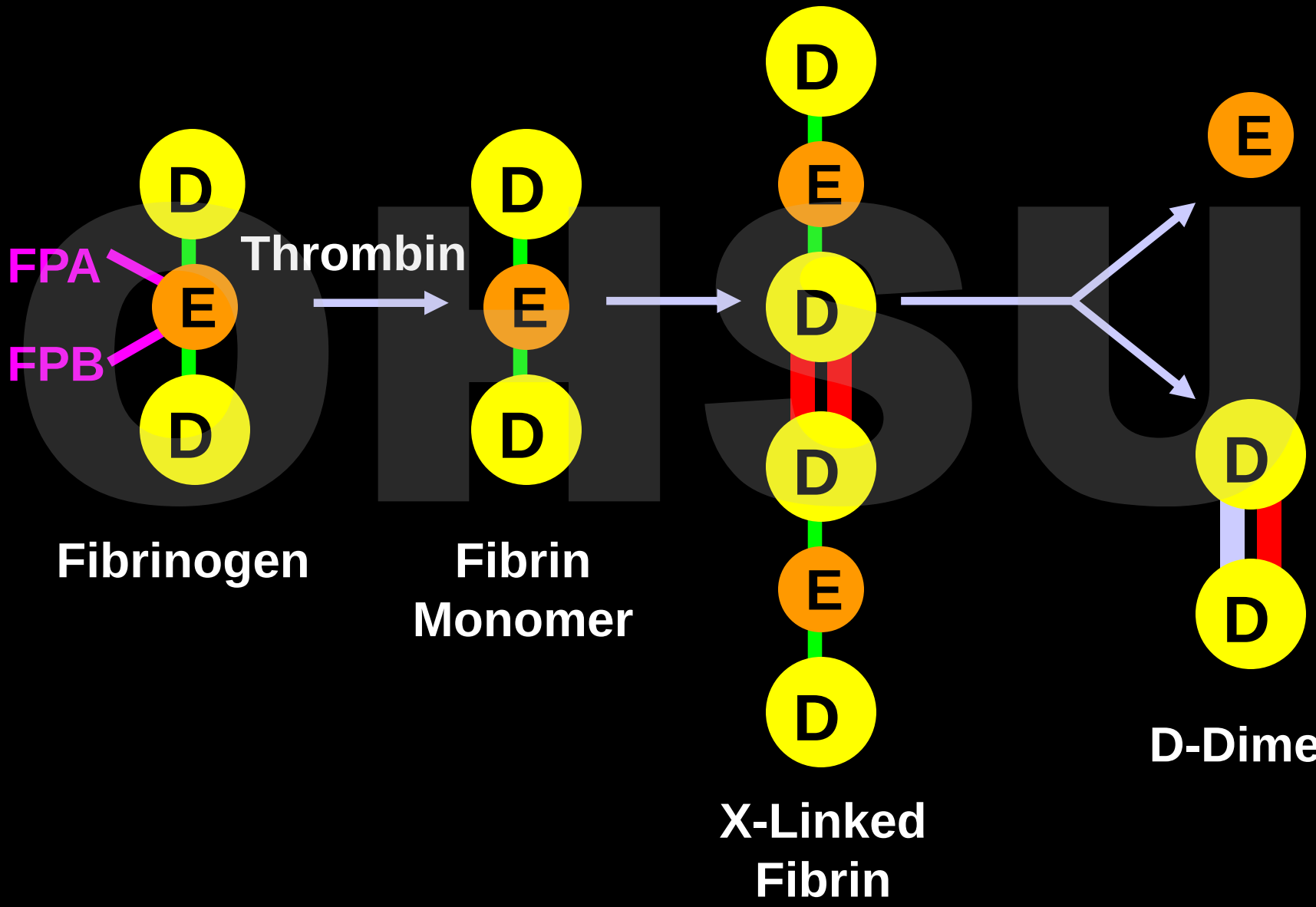
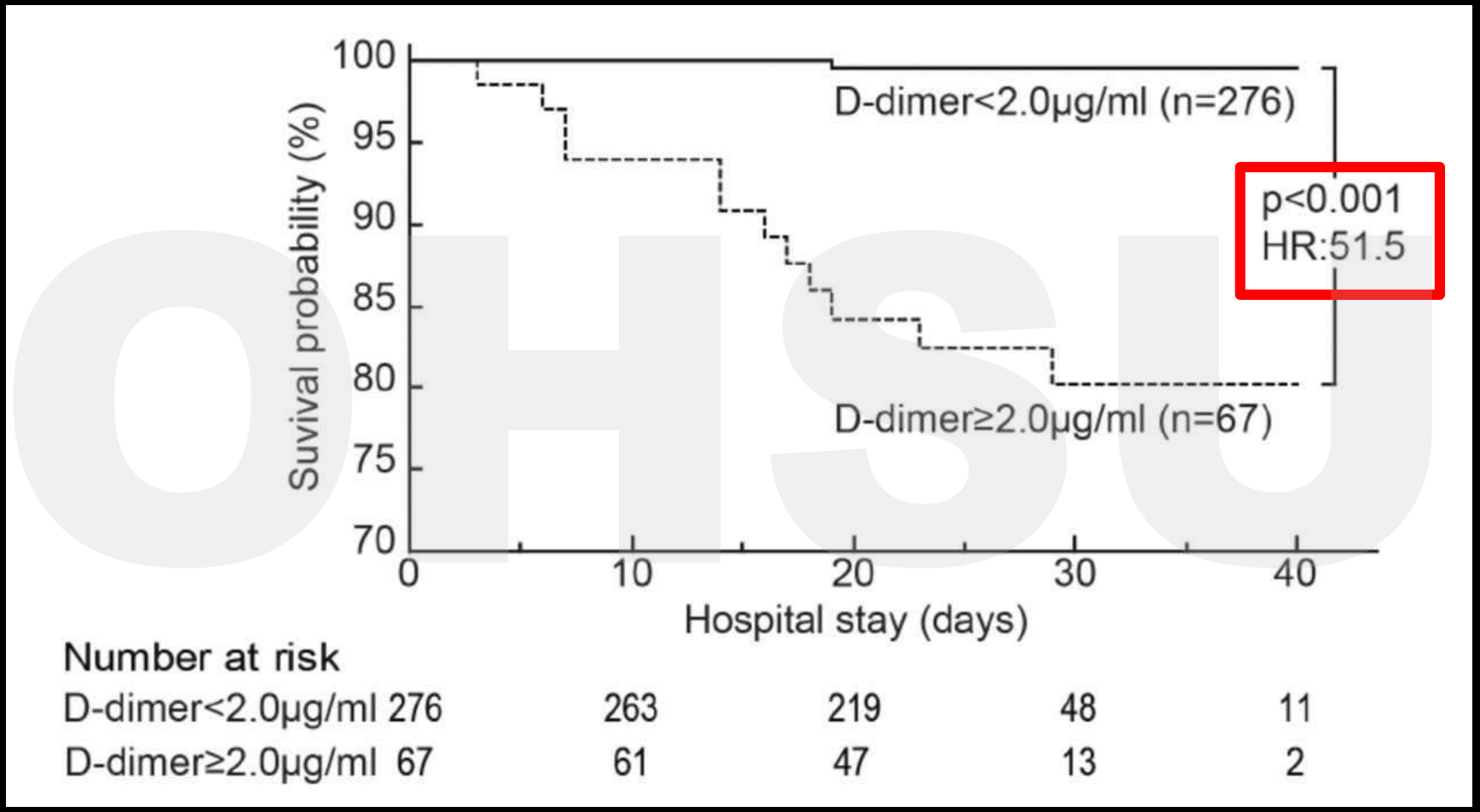

D
FPA
E
FPB
D
Thrombin
D
E
D
Fibrinogen
Fibrin
Monomer
D
E
D
D
E
D
X-Linked
Fibrin
E
D
D
D-Dimer

TABLE 1 Coagulation parameters of NCP patients 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

Abbreviations: APTT, activated partial thromboplastin time; AT, antithrombin activity; FDP, fibrin degradation product; NCP, novel coronavirus pneumonia; PT, prothrombin time (PT).

Zhang, J Throm Haemo 18:1324, 2020



Zhang, J Throm Haemo 18:1324, 2020

Thrombosis

- Rates of 17-69% reported even with prophylaxis
  - Much higher than literature
  - Venous thrombosis
  - Arterial thrombosis
  - Microthrombosis

Cui

- VTE = 25%
- Unknown prophylaxis
- D-Dimer predictive
- J Throm Hem 2020

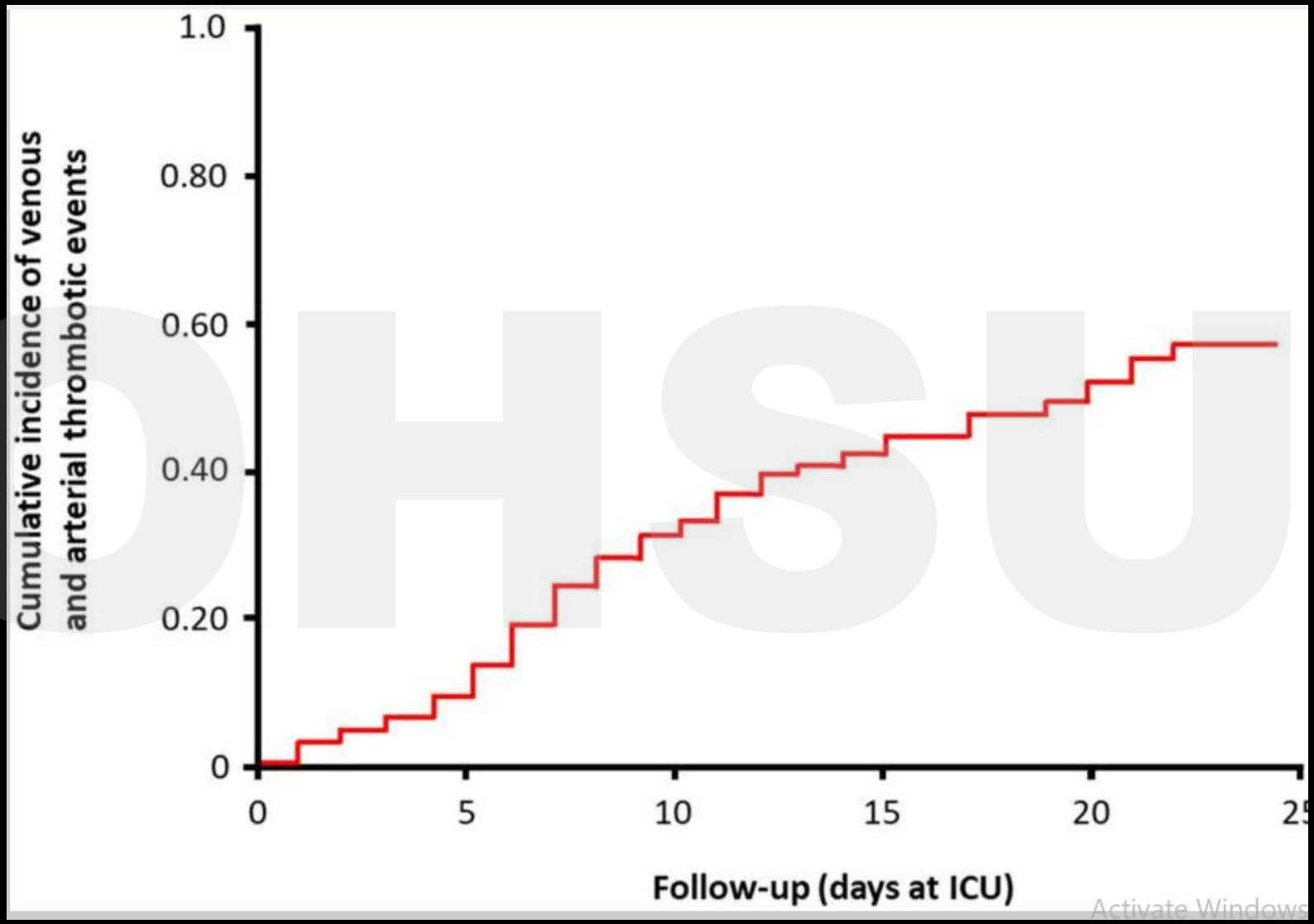
Table 3 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of different D-dimer cut-off levels for predicting VTE in NCP patients

Cut-off (μg/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1.0	85.0	77.0	54.8	94.0
1.5	85.0	88.5	70.8	94.7
2.0	80.0	90.2	72.7	93.2
2.5	70.0	93.4	77.8	90.5
3.0	70.0	96.7	87.5	90.8
3.5	65.0	96.7	86.7	89.4

Chu J Thromb Haemo 2020

Klok

- VTE = 27->49% (87% PE)
- Arterial = 3.7%
- All getting prophylaxis
- Coagulation abnormities predicted thrombosis
- Thrombosis HR 5.4 death
- Throm Research 2020



France

- 16.7% thrombosis rate
- 96% CRRT thrombosis rate
  - < 24 hours!
- All getting prophylaxes

- ICU medicine in press

France II

- 26 consecutive ICU patients
- 69% thrombosis
  - PE 23% patients
- No benefit of standard prophylaxs
- JTH in press

Middledorpf

- N = 199
- ICU: 26% @ 1wk, 47% @ 2 wks, and 59%@ 3 wks
  - ICU vs ward: 7.1
- 2.8%/day of ICU stay
- History of DVT not a risk factor

JTH

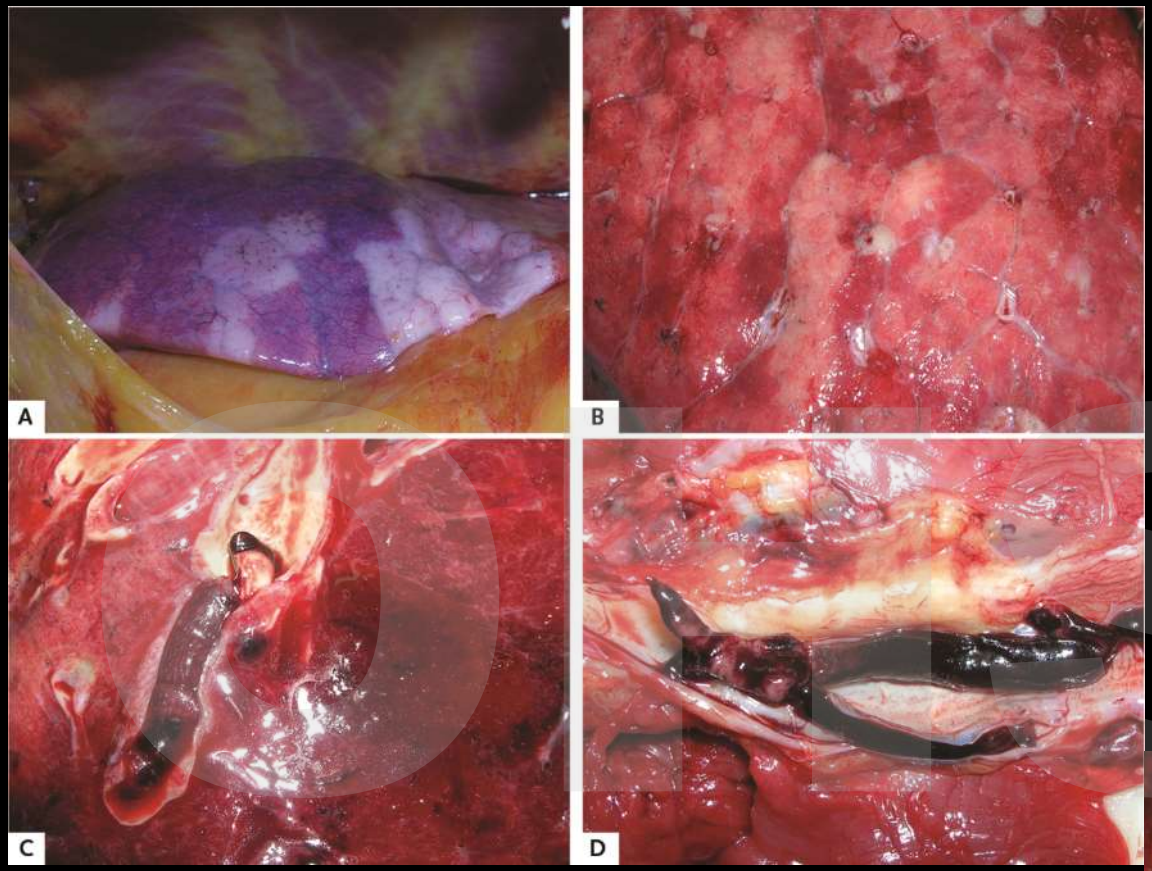
Venous Thrombosis Rates

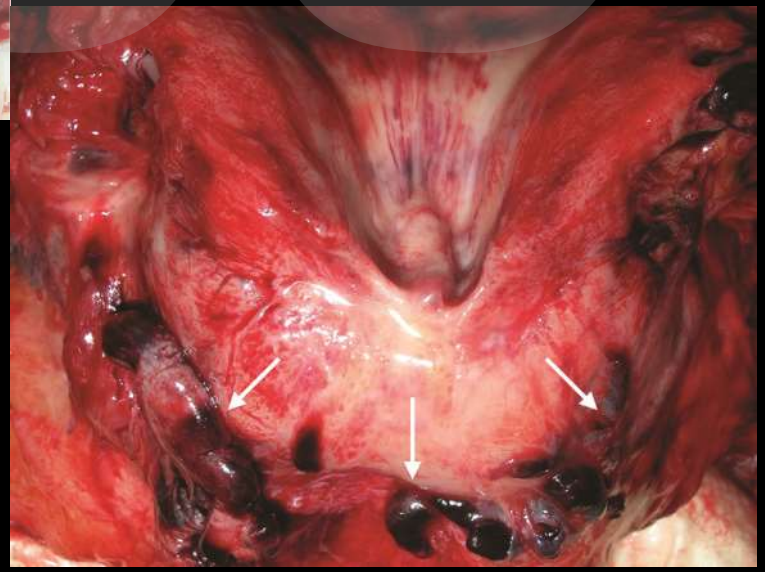
- COVID: 17-65%
  - Increases with duration of ICU stay
- Non-COVID ICU
  - 14.6% Controls (2% PE)
  - 7.5% Prophylaxis (1%)

Wichmann

- First 12 mandated COVID autopsy
- Consecutive series
- Age -73
- 75% male
- 4 (25%) die massive PE
- 3 more with DVT

Annals of Internal Medicine®

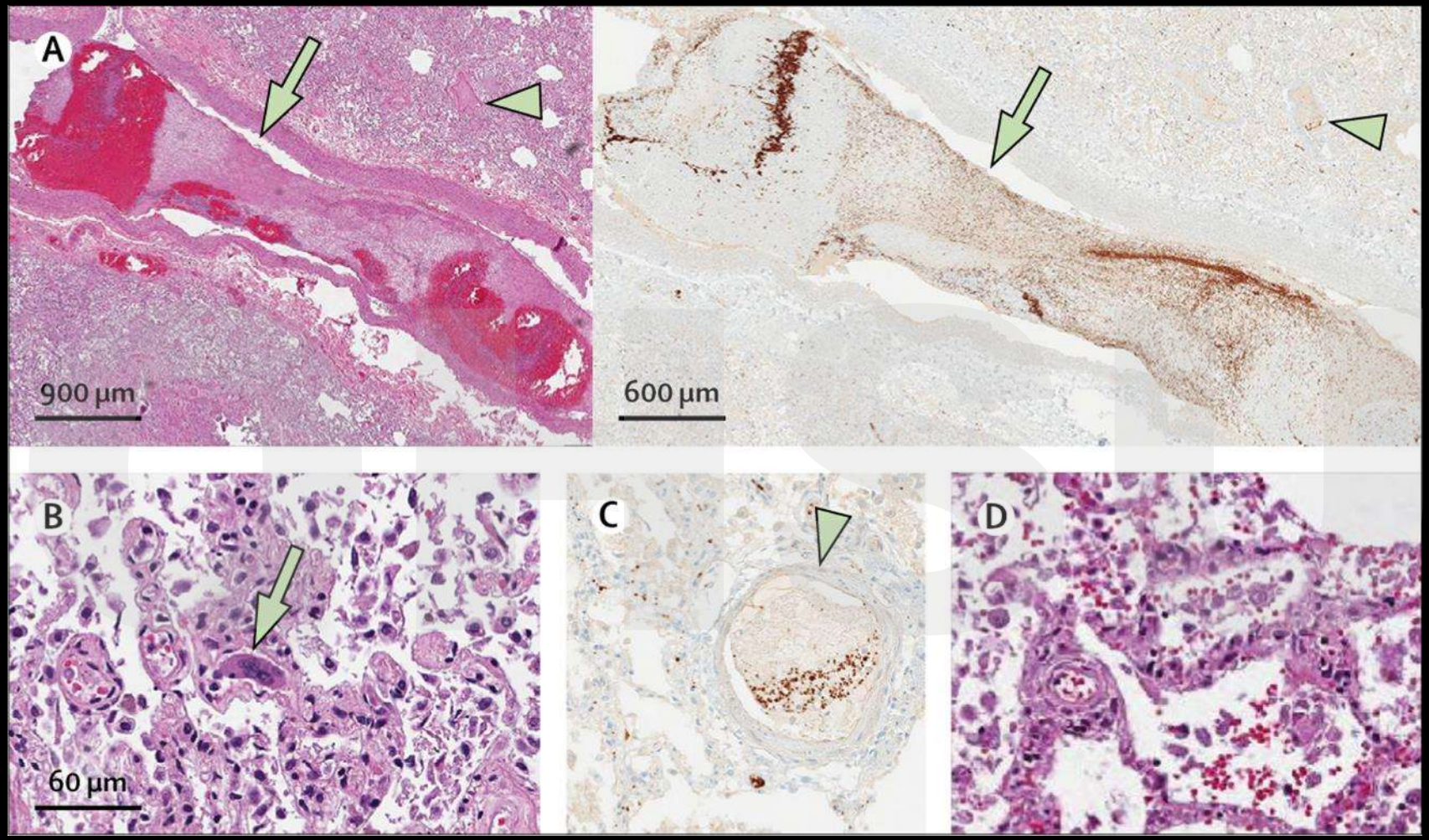




Ann Intern Med. Published online May 06, 2020. doi:10.7326/M20-2003

Autopsy/Pathology

- Uniformly show
  - Micro/macrovascular thrombosis in multiple organs
  - Minimal microangiopathy
  - Megakaryocytes in lungs



The Lancet Respiratory Medicine DOI: (10.1016/S2213-2600(20)30243-5)

Arterial Thrombosis

- Increasing reports in young patients without risk factors
- Stroke, MI, aortic or visceral arterial thrombosis


OHSU

Arterial Thrombosis

- Typical presentation – arterial event in young person
- Minimal to no respiratory symptoms
- Positive COVID testing

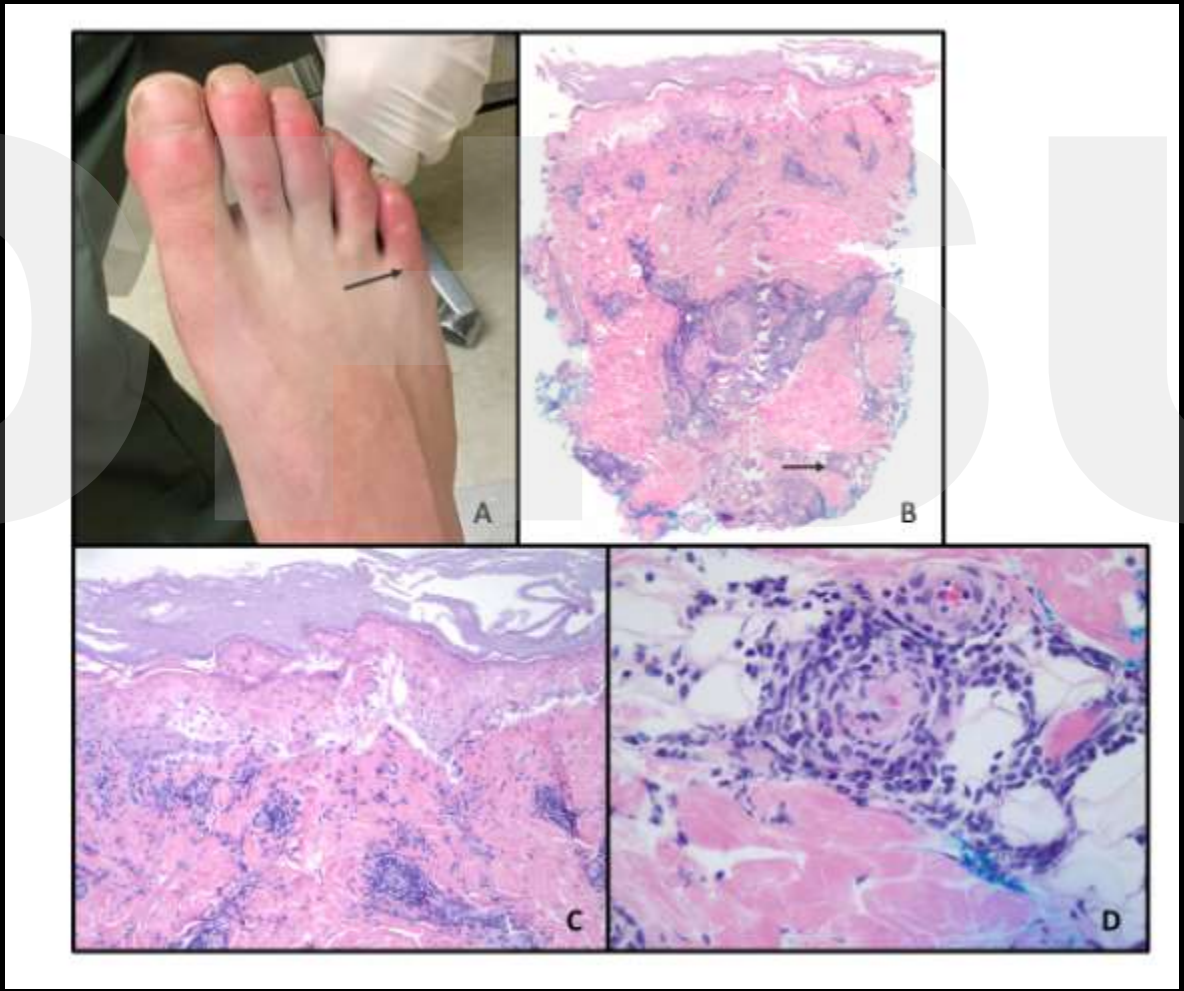
Stroke

- Increased incidence reported
- Rates of 1-2% in COVID patients
  - Higher on MRI??
- Unclear epidemiology

NYC Stroke

- 1.6% COVID patients with stroke
- 24% presented with stroke
- Mean age 69, 50% men
- OR 7.8 compared to flu patients
- Mortality 34% vs 14% no stroke
- JAMA Neurology 2020

COVID Toes



Heparin Resistance

- Increasing reports of high heparin requirements
  - > 4000u/hr
- Breakthrough thrombosis
- High rates of CRRT/dialysis thrombosis
  - > 90% in one study

Summary

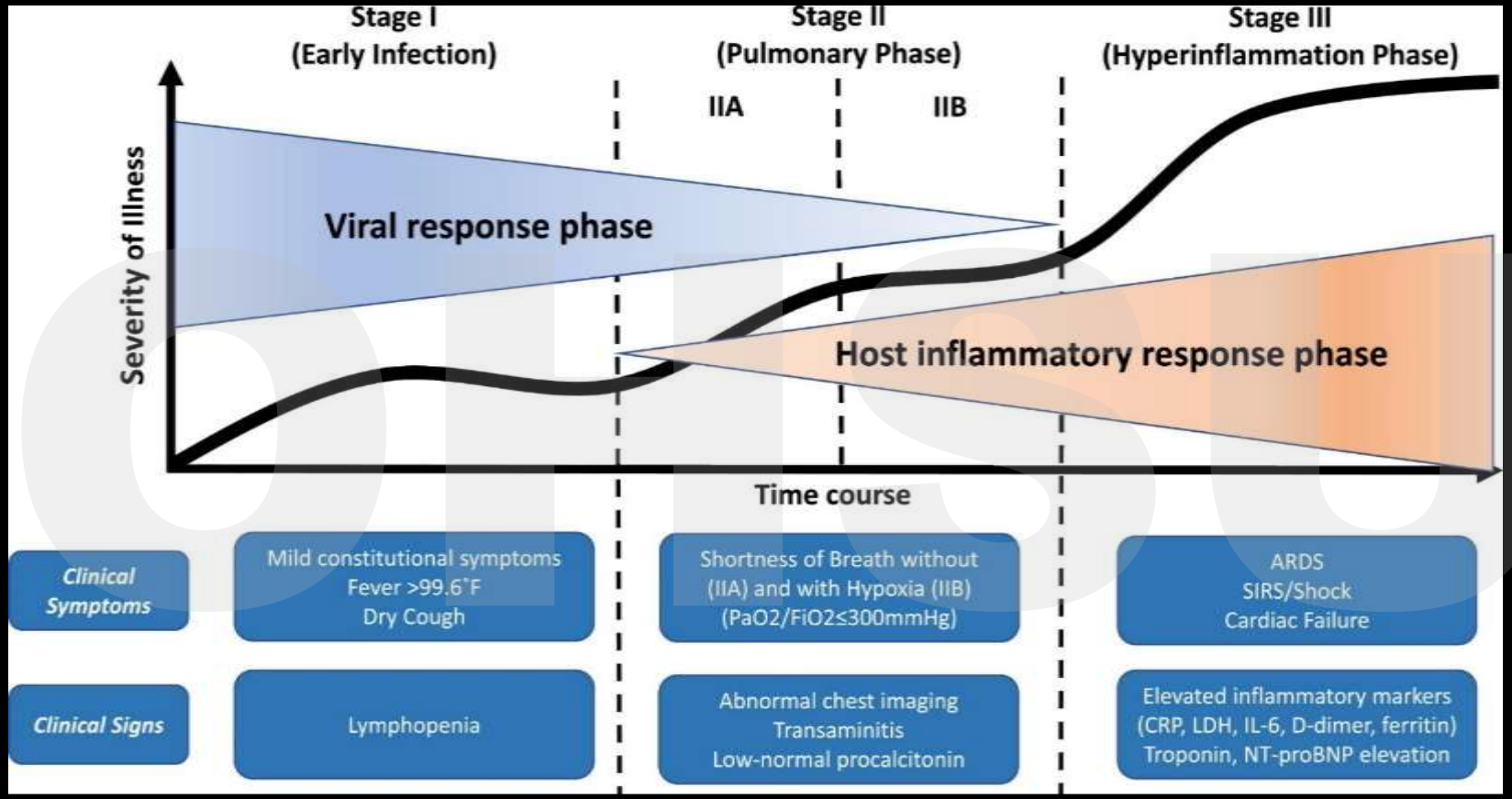
- Thrombosis
  - Much increased in ICU patients
    - 7x
  - Mainly venous but arterial reported
  - Occurs despite standard prophylaxis
  - Widespread

Etiology

- Intense inflammation
  - Raises procoagulants
  - Convert endothelium to prothrombotic state
- Pulmonary inflammation
- Viral attack on endothelial cells
- Platelets
- Other cascades

Inflammation

- IL-6 stimulates prothrombotic changes
  - Increased fibrinogen
  - Increased factor 8
  - Increased VWF
- TNF/IL-1 convert endothelium to prothrombotic state


Stage I
(Early Infection)
Stage II
(Pulmonary Phase)
IIA
IIB
Stage III
(Hyperinflammation Phase)
Severity of Illness
Viral response phase
Host inflammatory response phase
Time course
Clinical Symptoms
Mild constitutional symptoms
Fever >99.6˚F
Dry Cough
Shortness of Breath without (IIA) and with Hypoxia (IIB) (PaO2/FiO2≤300mmHg)
ARDS
SIRS/Shock
Cardiac Failure
Clinical Signs
Lymphopenia
Abnormal chest imaging
Transaminitis
Low-normal procalcitonin
Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
Troponin, NT-proBNP elevation

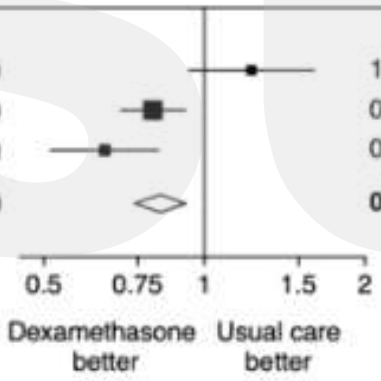
Evidence for Inflammation

- Antivirals +/- effectiveness
- Dexamethasone very effective
  - Only in patients requiring oxygen
- But maybe some inflammation good
  - Early dex harmful
  - Increasing reports of adverse outcomes with anti IL-6 therapy

Figure 2: Effect of allocation to dexamethasone on 28–day mortality by level of respiratory support received at randomization

Respiratory support at randomization	Dexamethasone	Usual care	RR (95% CI)
No oxygen received	85/501 (17.0%)	137/1034 (13.2%)	1.22 (0.93–1.61)
Oxygen only	275/1279 (21.5%)	650/2604 (25.0%)	0.80 (0.70–0.92)
Invasive mechanical ventilation	94/324 (29.0%)	278/683 (40.7%)	0.65 (0.51–0.82)
All participants	**454/2104 (21.6%)**	**1065/4321 (24.6%)**	**0.83 (0.74–0.92) p<0.001**

Trend across three categories: χ^2_1=11.49; p<0.001

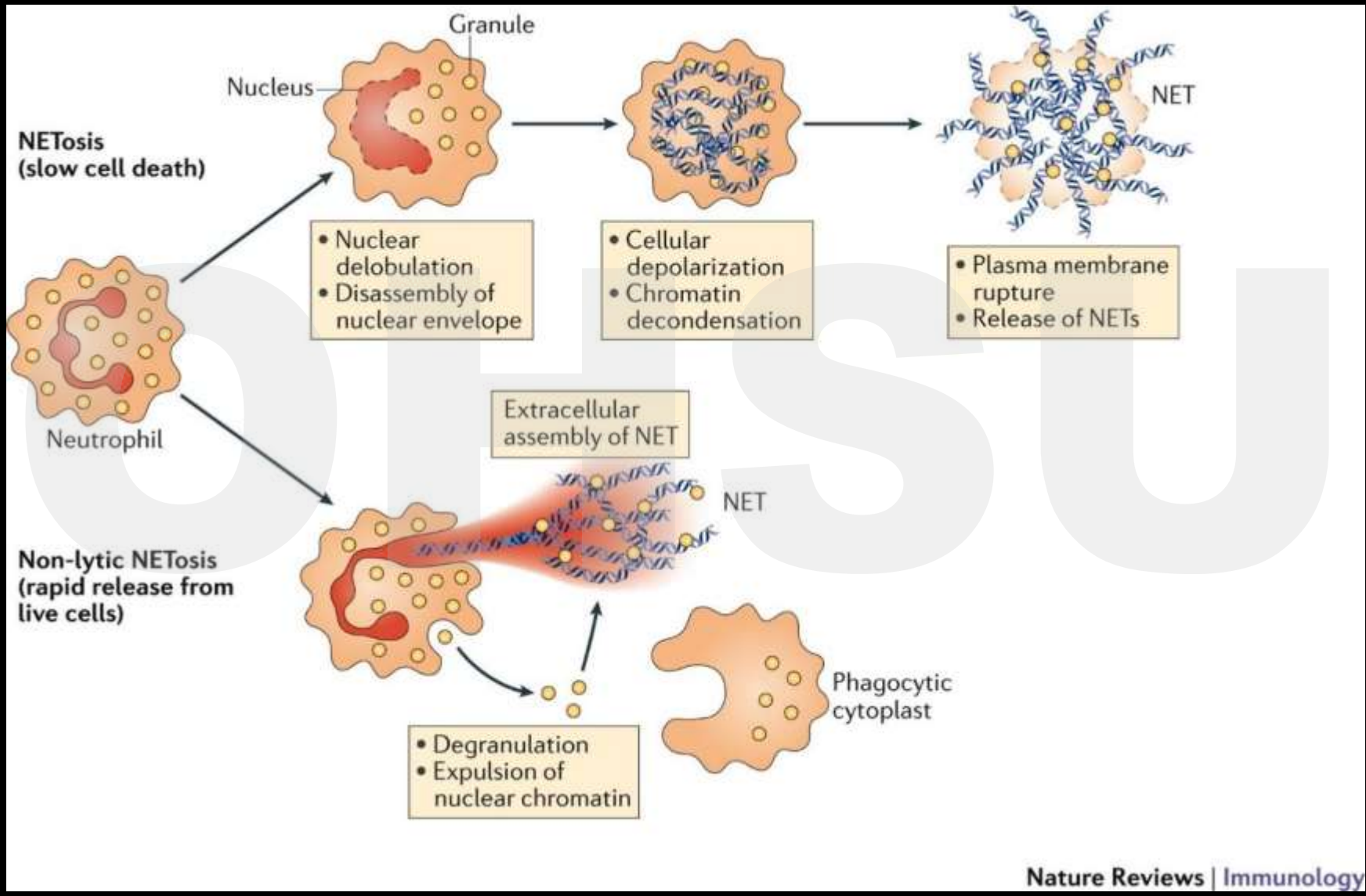


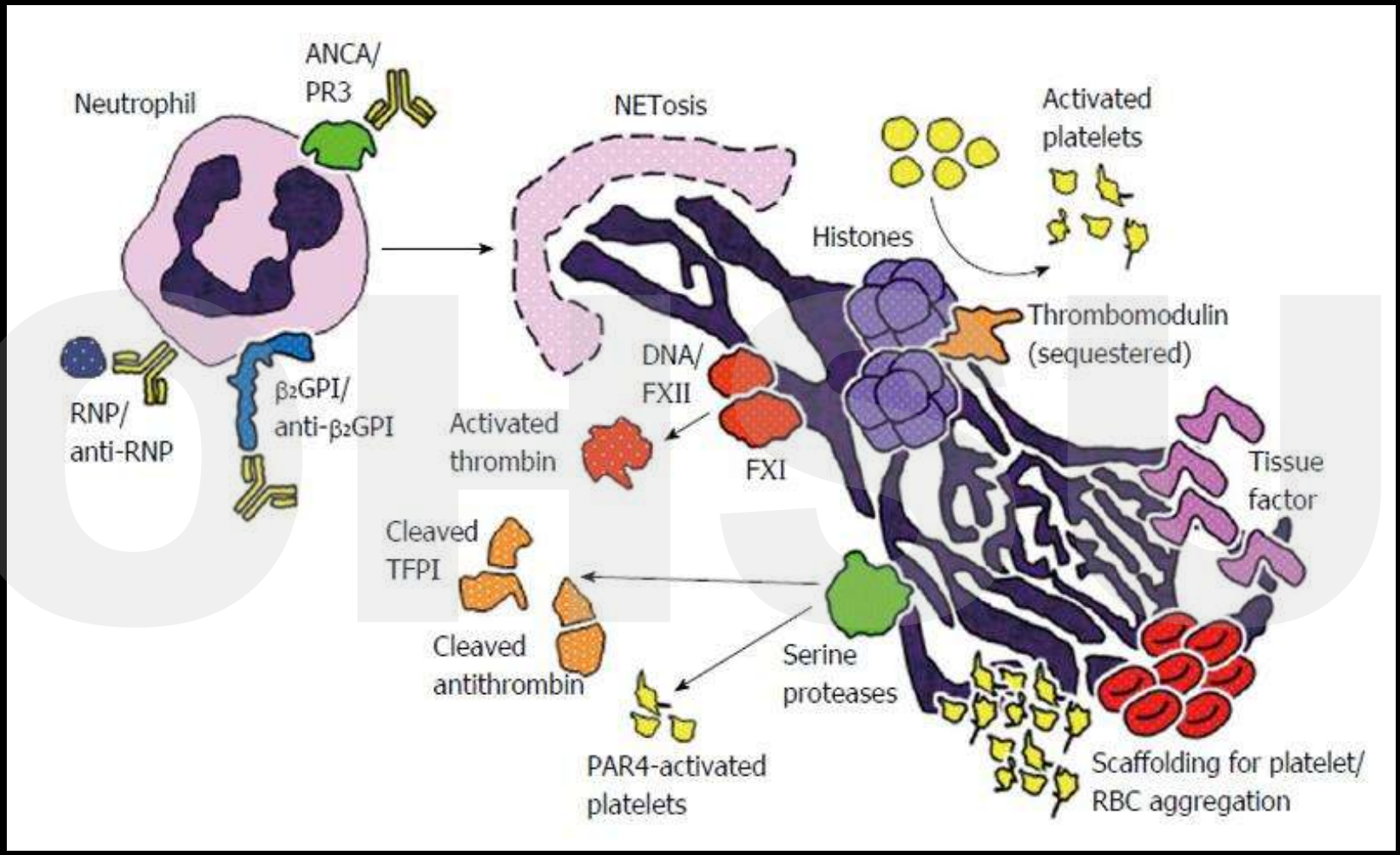
Potential Drivers

- Polyphosphates
  - Initiate contact pathway
- NETs
  - Powerful initiator of coagulation
- PAMP (Pathogen-associated molecular patterns)

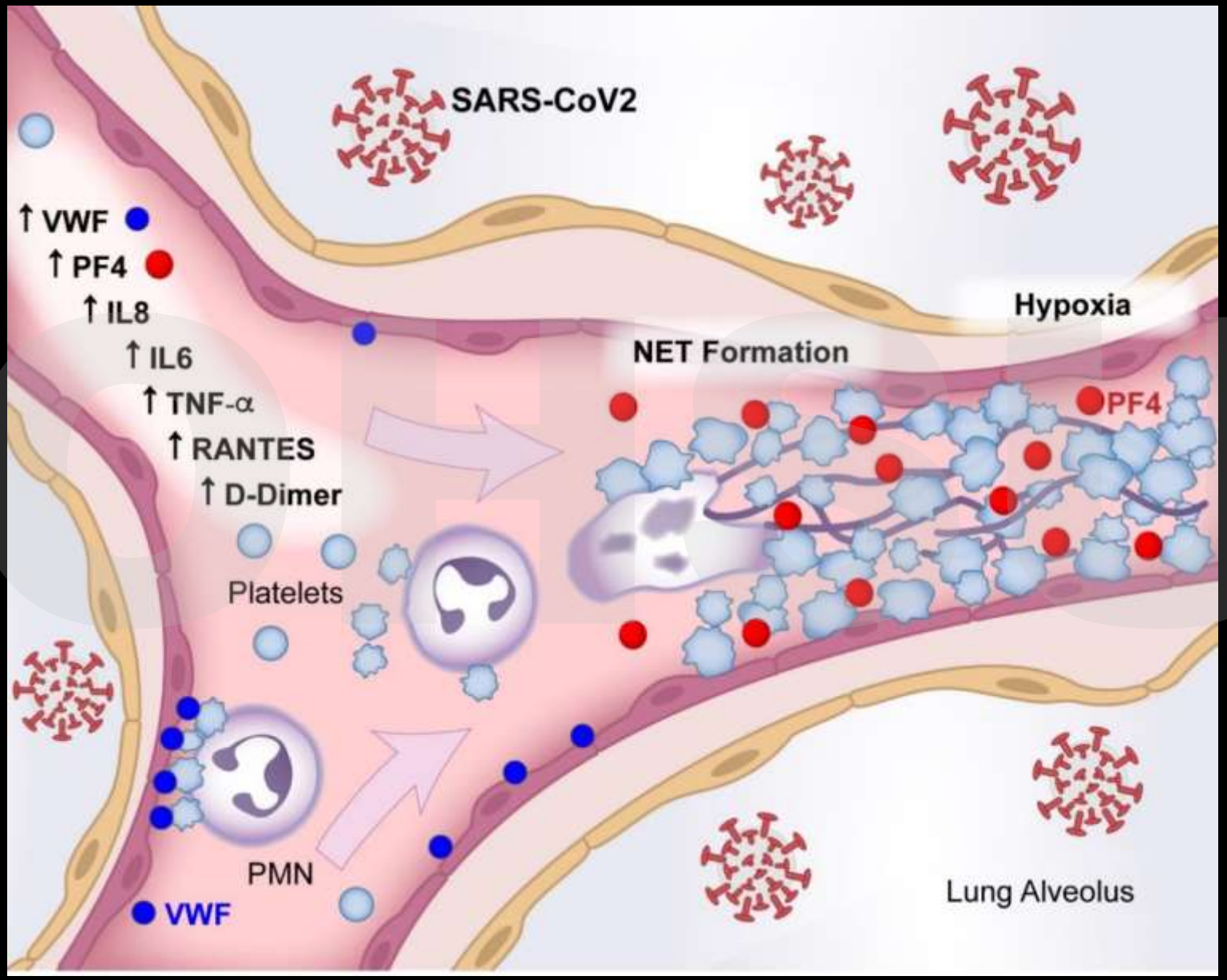
NET

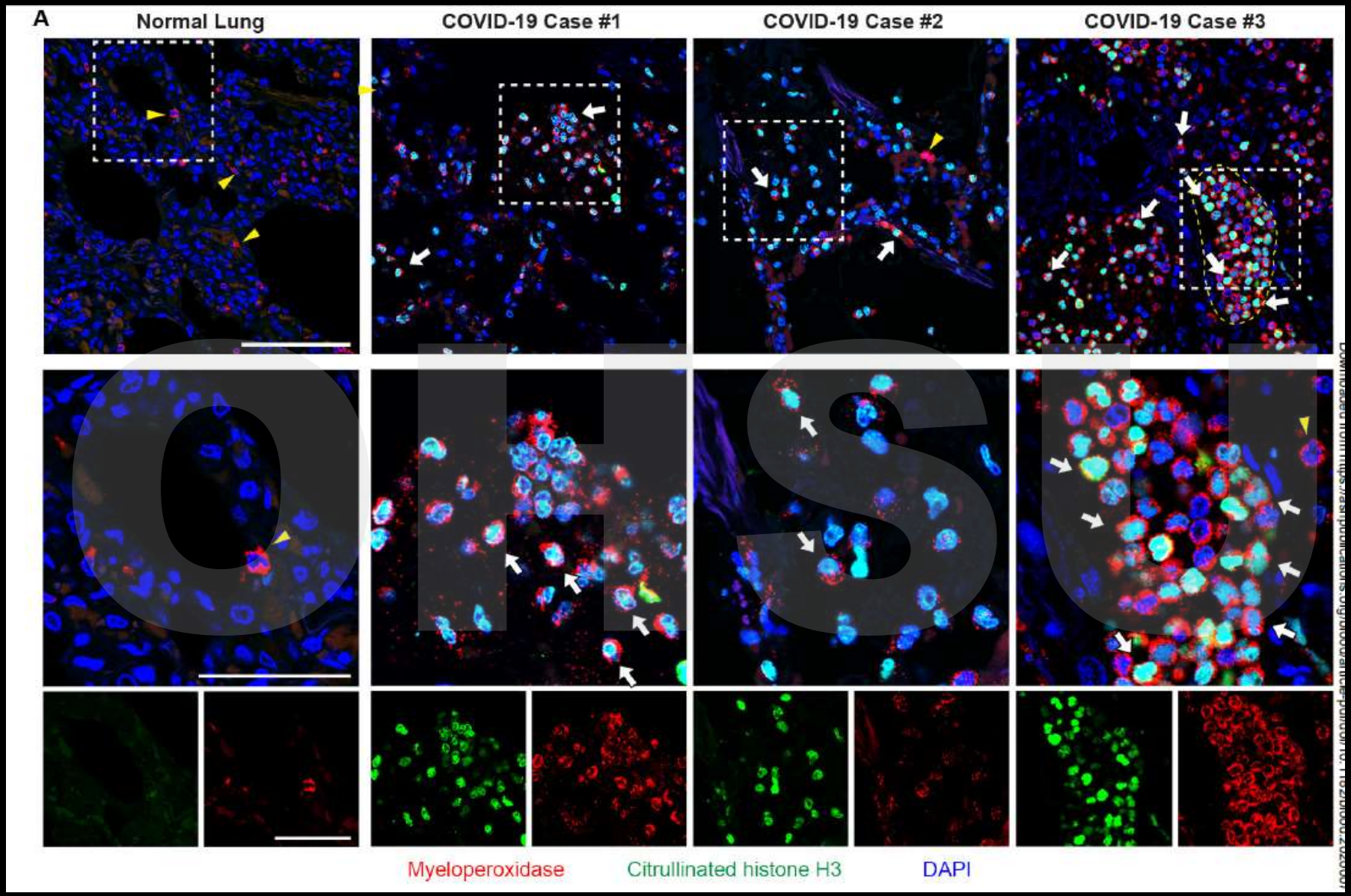
- Neutrophil extracellular traps
- DNA/Histones extruded from neutrophils
- Very prothrombotic
- Increased in sepsis, DIC, COVID


Granule
Nucleus
NETosis
(slow cell death)
• Nuclear delobulation
• Disassembly of nuclear envelope
• Cellular depolarization
• Chromatin decondensation
NET
• Plasma membrane rupture
• Release of NETs
Neutrophil
Extracellular assembly of NET
NET
Non-lytic NETosis
(rapid release from live cells)
Phagocytic cytoplast
• Degranulation
• Expulsion of nuclear chromatin
Nature Reviews | Immunology



Rao World J Cardiol. 7: 829-842, 2015


SARS-CoV2
↑ VWF
↑ PF4
↑ IL8
↑ IL6
↑ TNF-α
↑ RANTES
↑ D-Dimer
Platelets
PMN
VWF
Hypoxia
NET Formation
PF4
Lung Alveolus



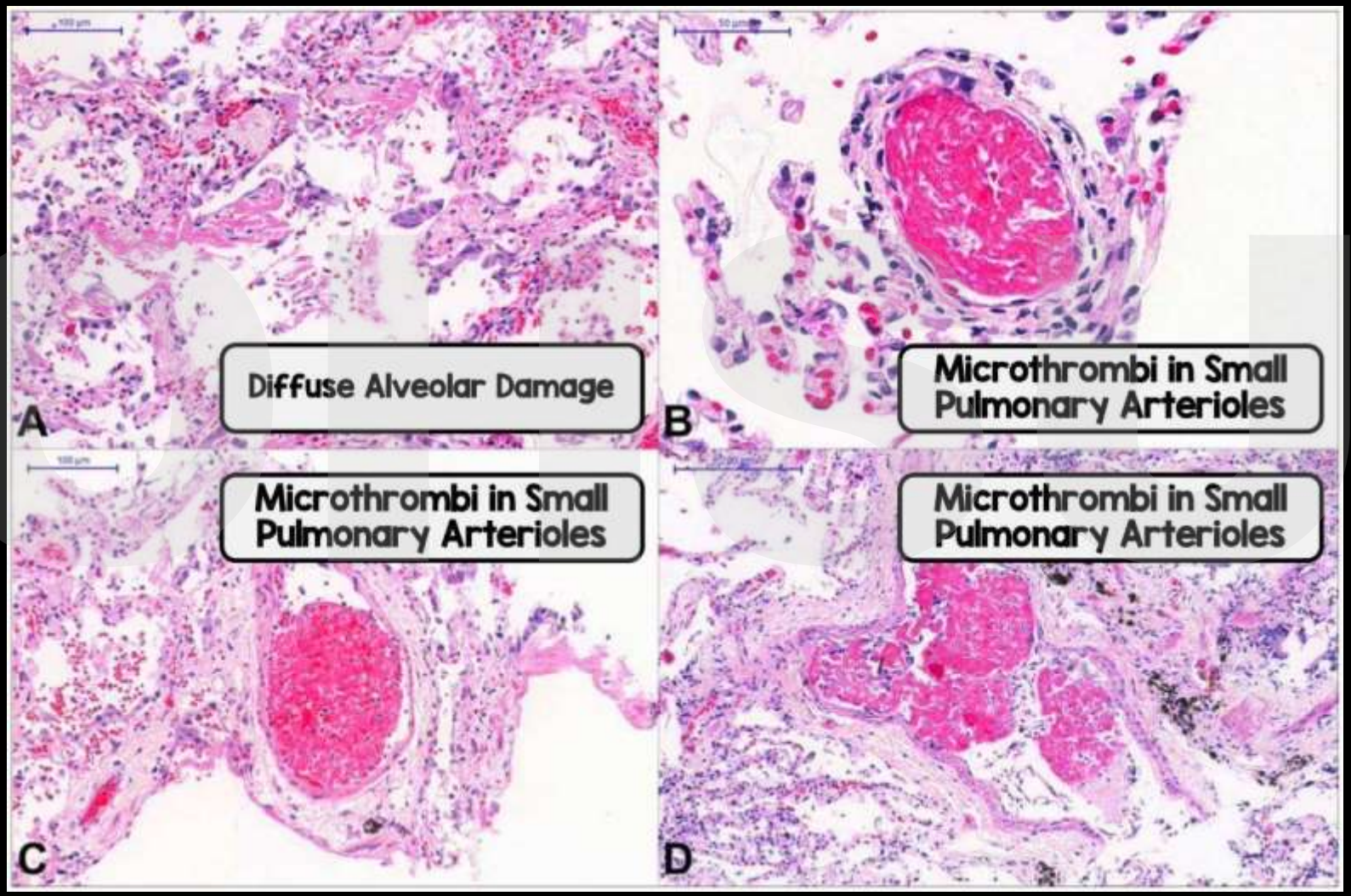
Middleton, Blood 2020

Antiphospholipid Antibodies

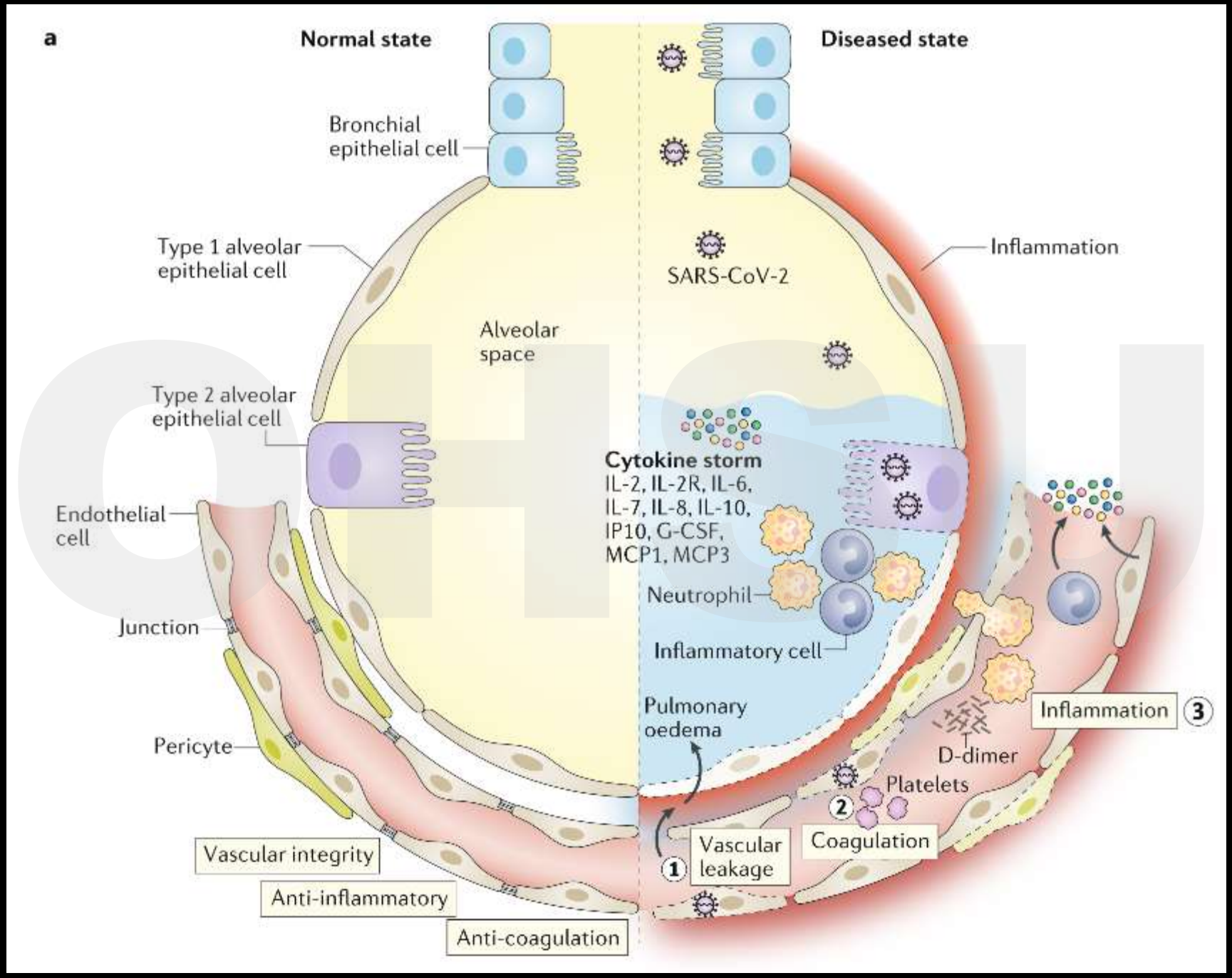
- Increased incidence in COVID patients
  - Up to 90% lupus inhibitors
- Pathogenic or false positives?
- Further muddies waters on PTT monitoring of heparin

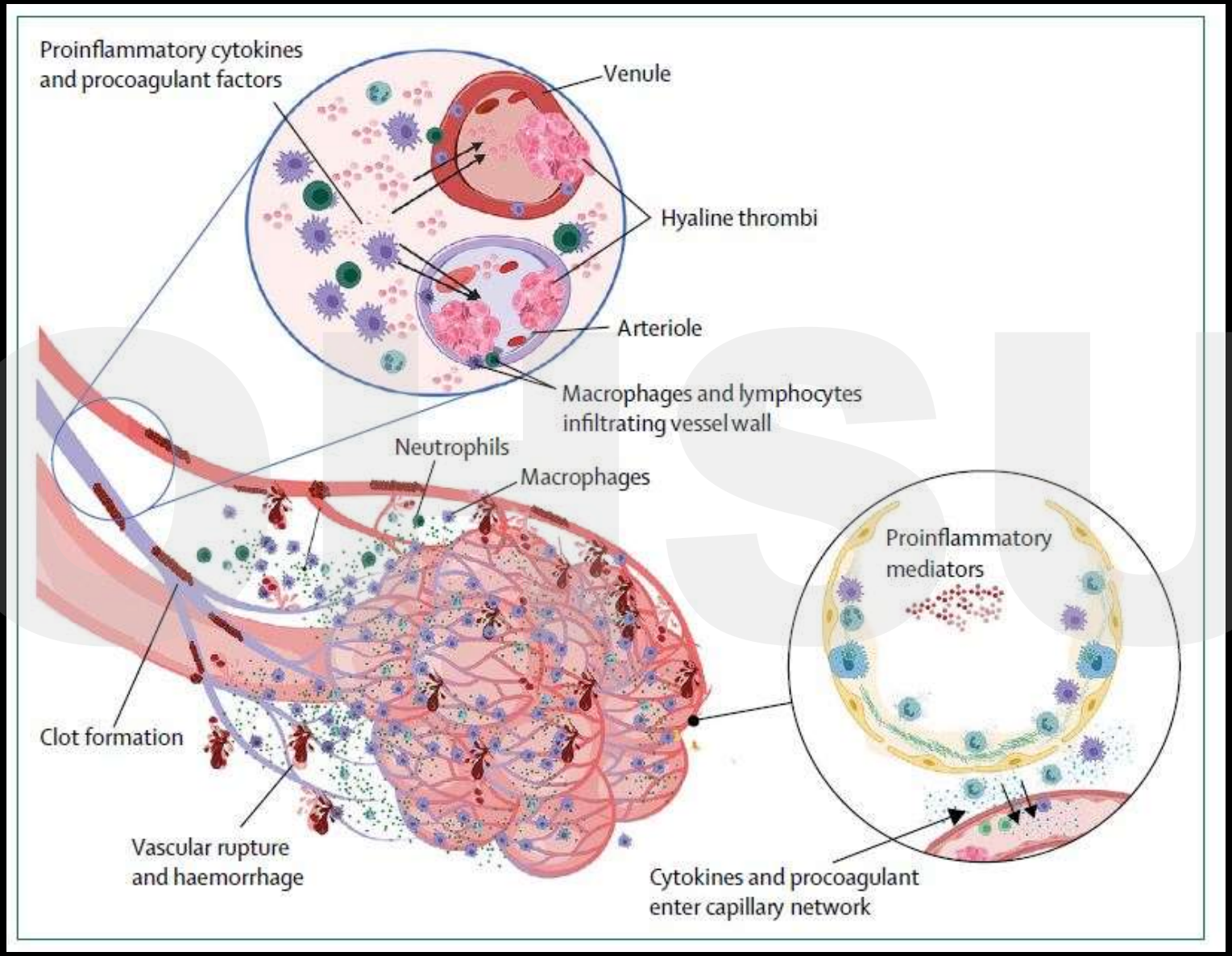
Pulmonary Inflammation

- Virus infection at alveolar level leads to local inflammation
- This spreads throughout the lung and system vasculature
- Path
  - Pulmonary inflammation with microthrombi


Diffuse Alveolar Damage
A
Microthrombi in Small Pulmonary Arterioles
B
Microthrombi in Small Pulmonary Arterioles
C
Microthrombi in Small Pulmonary Arterioles
D

Rebel EM


a
Normal state
Diseased state
Bronchial epithelial cell
Type 1 alveolar epithelial cell
SARS-CoV-2
Inflammation
Alveolar space
Type 2 alveolar epithelial cell
Cytokine storm
IL-2, IL-2R, IL-6, IL-7, IL-8, IL-10, IP10, G-CSF, MCP1, MCP3
Endothelial cell
Neutrophil
Junction
Inflammatory cell
Pulmonary oedema
Inflammation 3
Pericyte
D-dimer
Platelets
2
Coagulation
Vascular integrity
1
Vascular leakage
Anti-inflammatory
Anti-coagulation


Proinflammatory cytokines and procoagulant factors
Venule
Hyaline thrombi
Arteriole
Macrophages and lymphocytes infiltrating vessel wall
Neutrophils
Macrophages
Proinflammatory mediators
Clot formation
Vascular rupture and haemorrhage
Cytokines and procoagulant enter capillary network

Endothelial Infection

- Increasing evidence virus can attack vascular endothelium
- Converts antithrombotic surface to prothrombotic

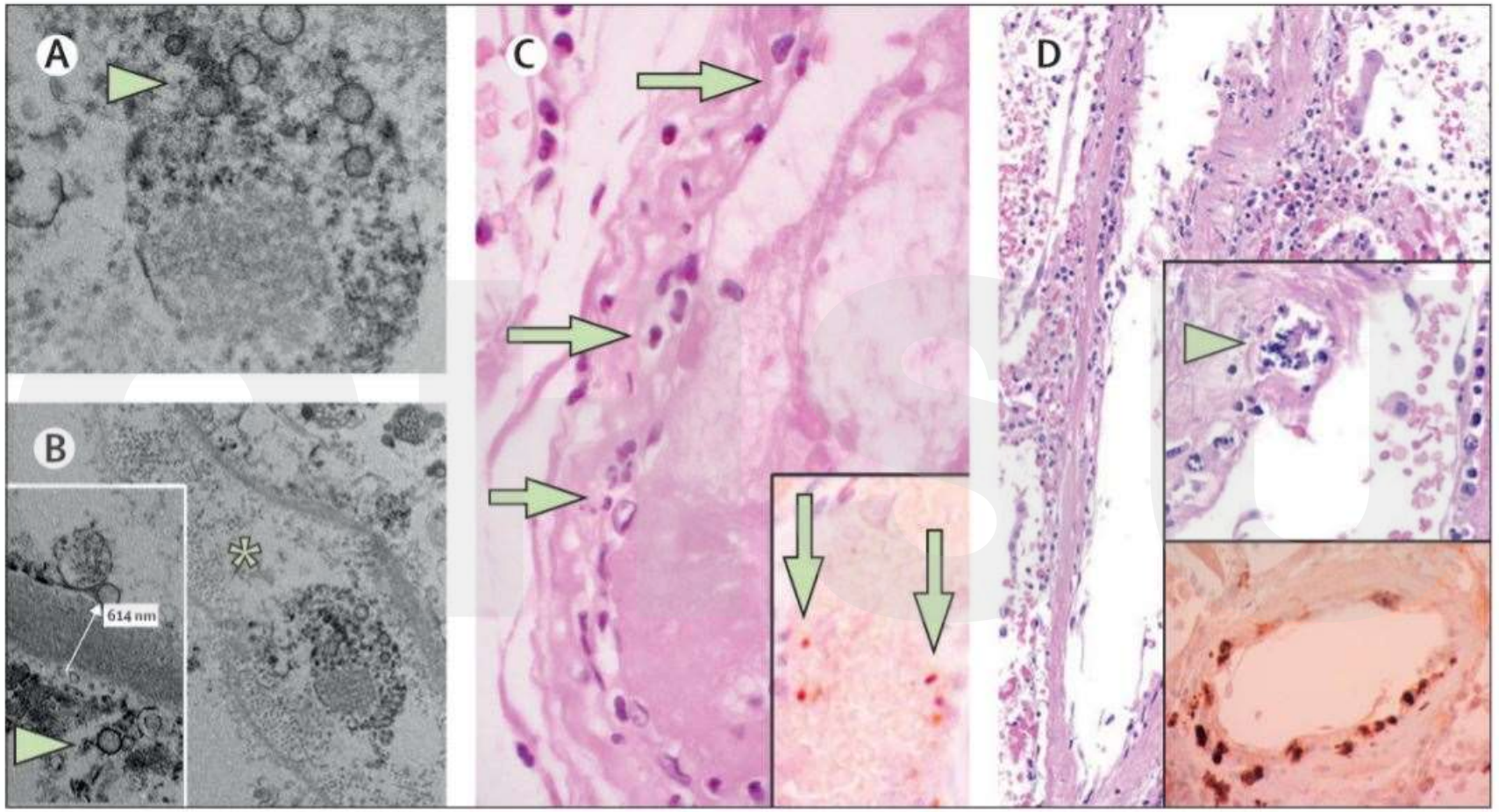
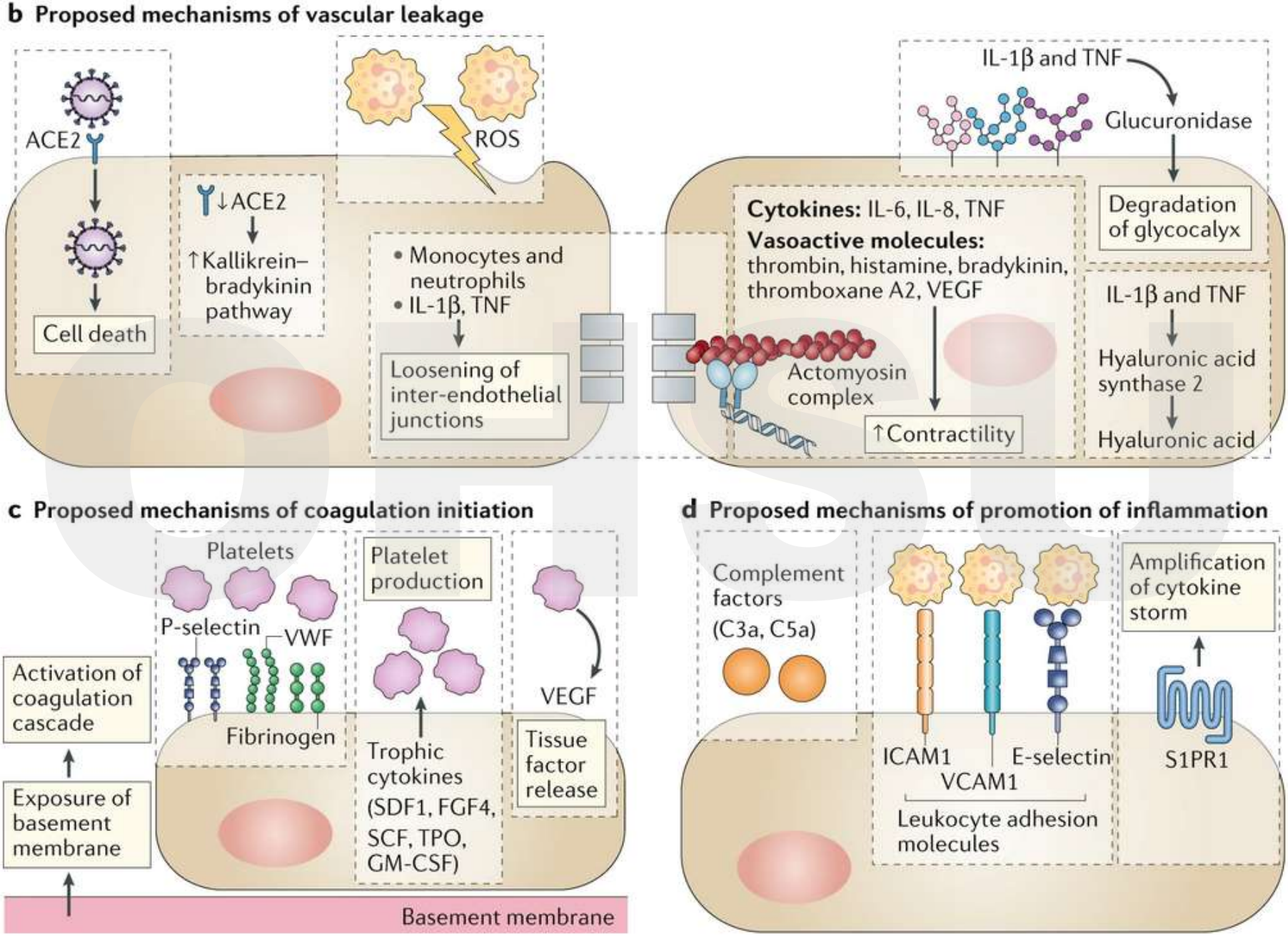
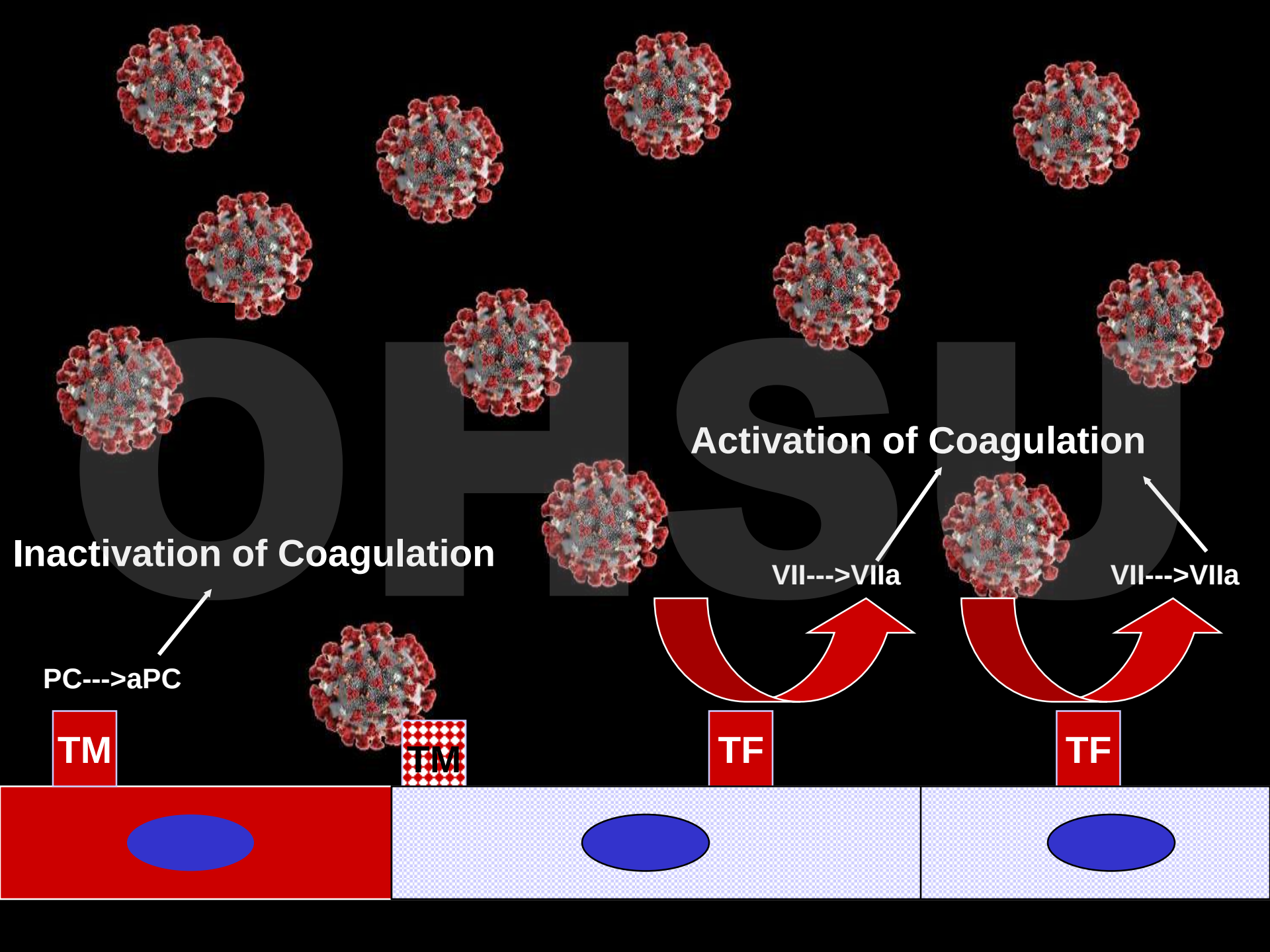
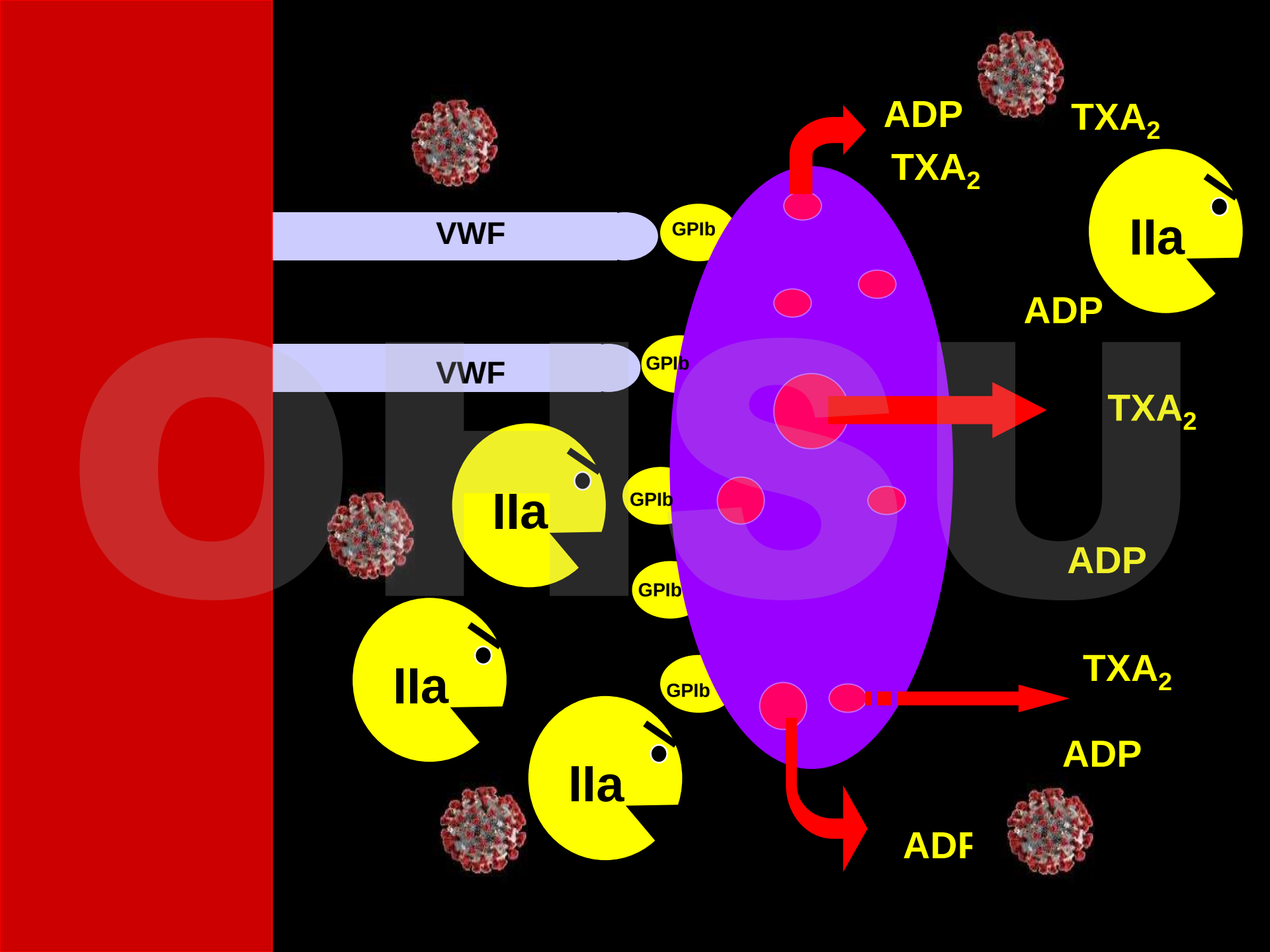


Figure: Pathology of endothelial cell dysfunction in COVID-19

Lancet: in press


b Proposed mechanisms of vascular leakage
ACE2
Cell death
ROS
↓ACE2
↑Kallikrein–bradykinin pathway
• Monocytes and neutrophils
• IL-1β, TNF
Loosening of inter-endothelial junctions
IL-1β and TNF
Glucuronidase
Degradation of glycocalyx
Cytokines: IL-6, IL-8, TNF
Vasoactive molecules: thrombin, histamine, bradykinin, thromboxane A2, VEGF
Actomyosin complex
↑Contractility
IL-1β and TNF
Hyaluronic acid synthase 2
Hyaluronic acid
c Proposed mechanisms of coagulation initiation
Platelets
P-selectin
VWF
Fibrinogen
Platelet production
Trophic cytokines (SDF1, FGF4, SCF, TPO, GM-CSF)
VEGF
Tissue factor release
Activation of coagulation cascade
Exposure of basement membrane
Basement membrane
d Proposed mechanisms of promotion of inflammation
Complement factors (C3a, C5a)
ICAM1
VCAM1
E-selectin
Leukocyte adhesion molecules
Amplification of cytokine storm
S1PR1

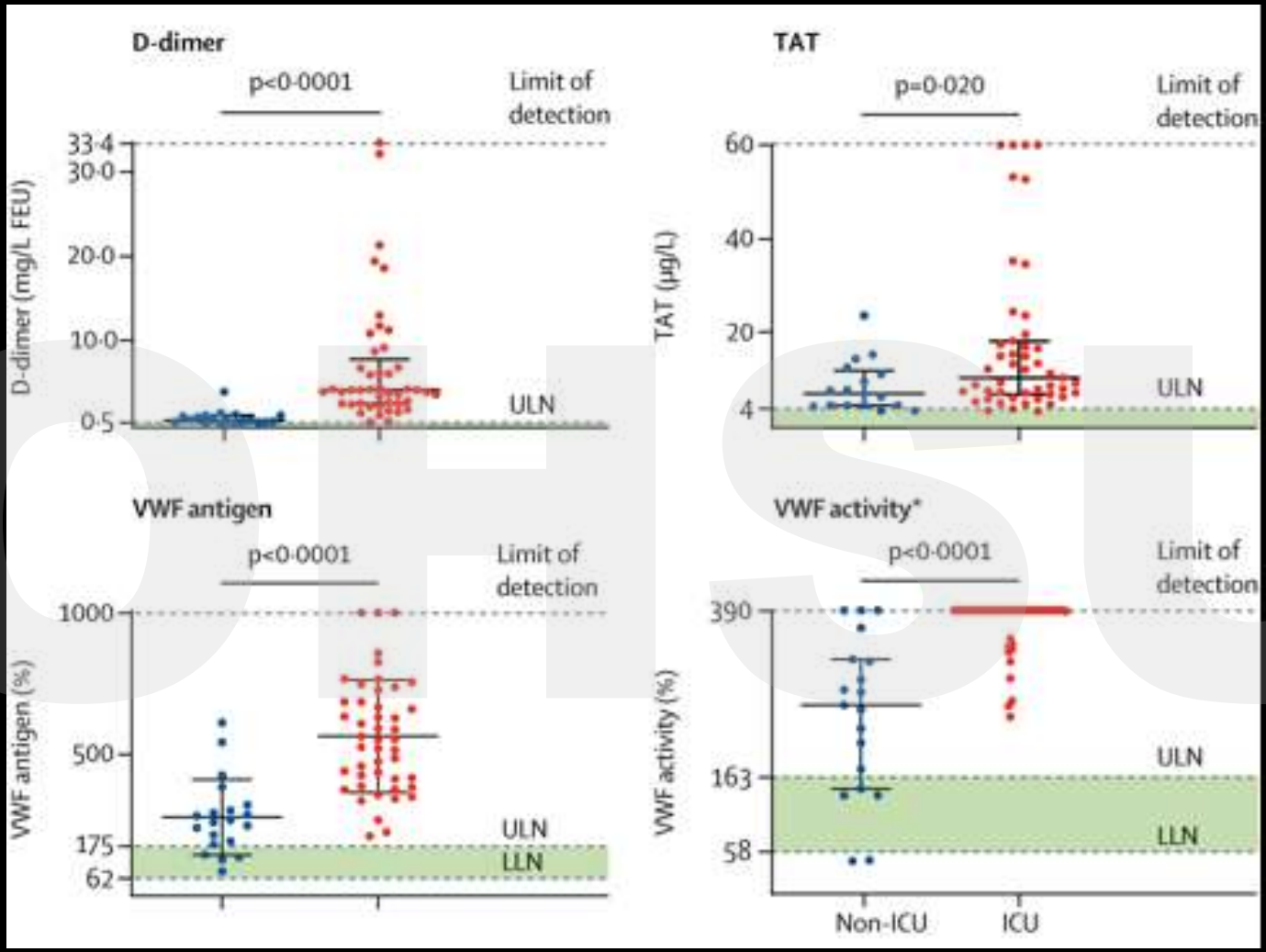

Activation of Coagulation
Inactivation of Coagulation
VII--->VIIa
VII--->VIIa
PC--->aPC
TM
TM
TF
TF


ADP
TXA2
TXA2
IIa
ADP
VWF
GPIb
VWF
GPIb
TXA2
IIa
GPIb
ADP
GPIb
IIa
TXA2
GPIb
ADP
IIa
ADP

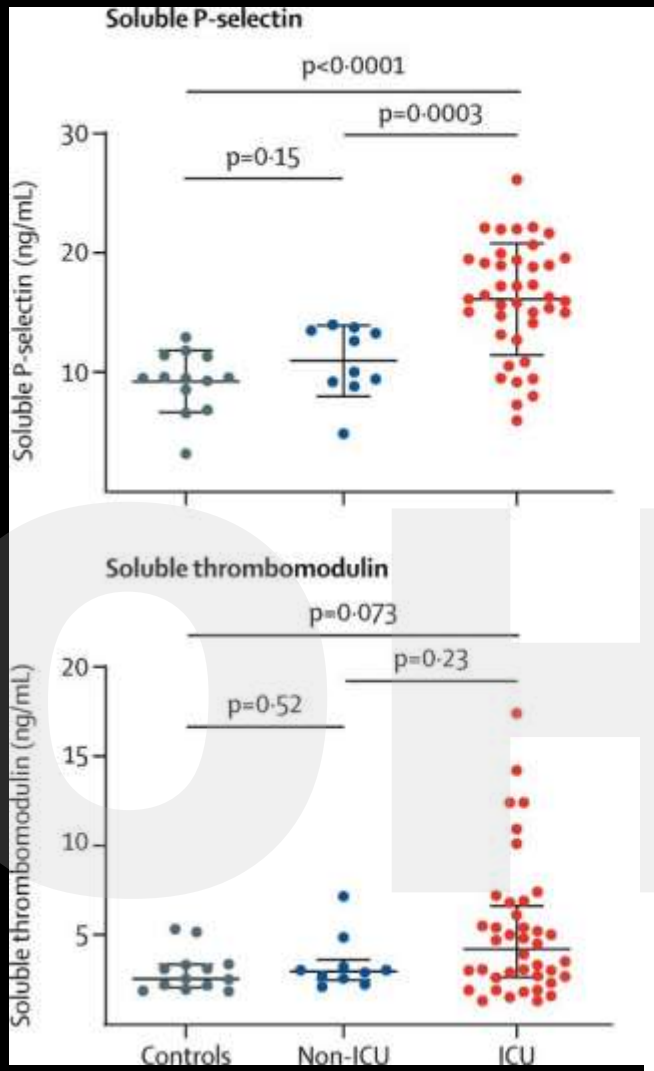
Endothelial Damage

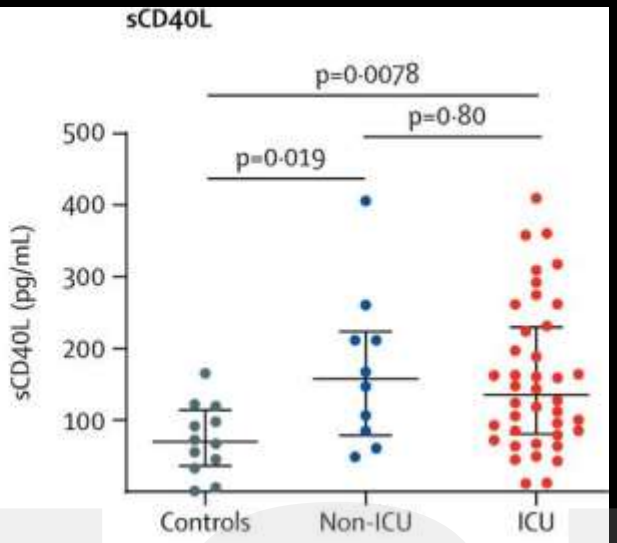
- ICU vs Ward patients
- vWF: 565% vs 278%
- P-selectin: 15.9 vs 11.2 ng/ml
- Mortality associated with increased thrombomodulin
- Goshua Lancet Haem 2020

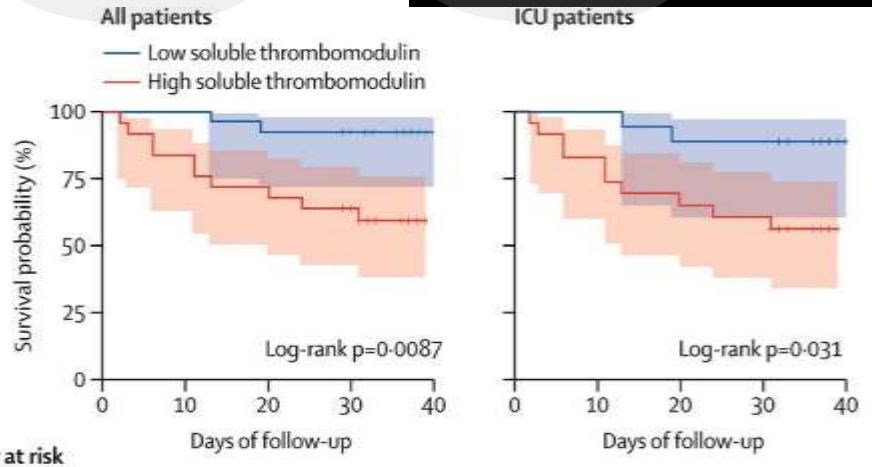
Figure 1



The Lancet Haematology DOI: (10.1016/S2352-3026(20)30216-7)







Number at risk (number censored)

Low soluble thrombomodulin	25 (0)	25 (0)	23 (0)	22 (8)	1 (23)	17 (0)	17 (0)	15 (0)	15 (0)	1 (15)
High soluble thrombomodulin	25 (0)	21 (0)	18 (0)	15 (2)	0 (15)	23 (0)	19 (0)	16 (0)	14 (0)	0 (13)

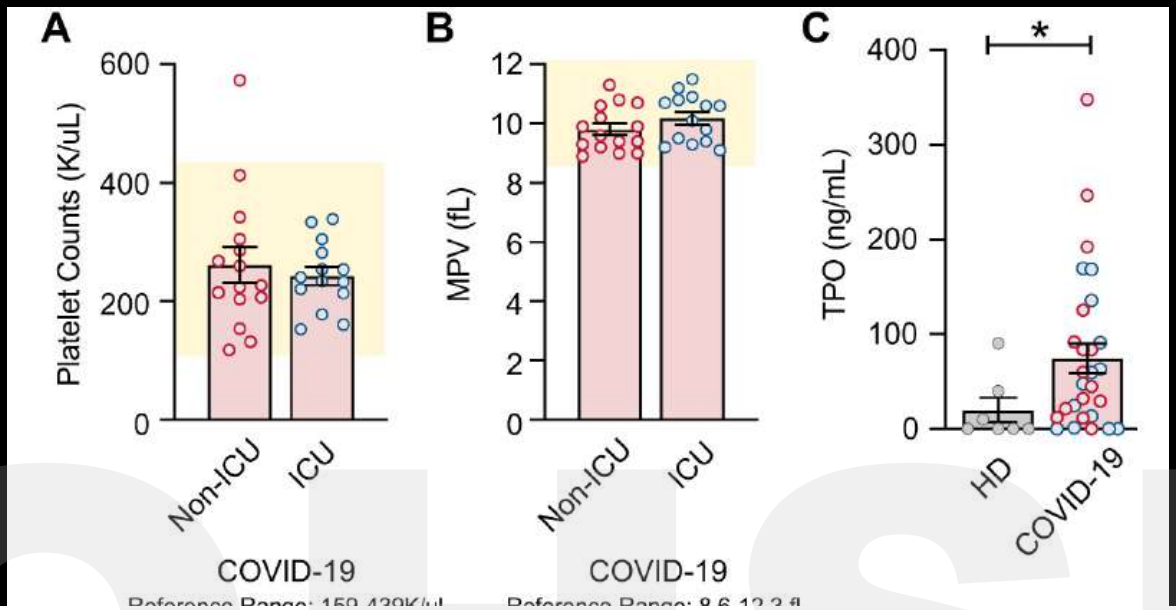
The Lancet Haematology DOI: (10.1016/S2352-3026(20)3

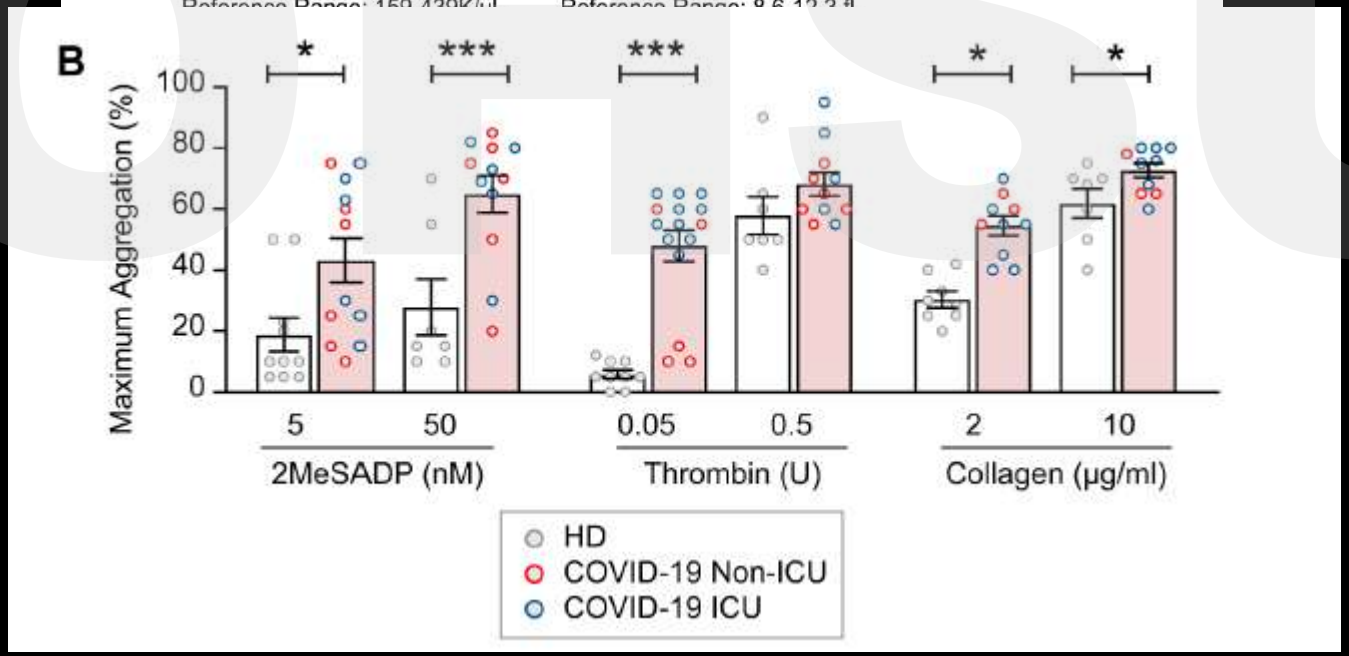
Platelets

- COVID platelets
  - Unique transcriptome
  - Increased P-selectin/PDGF
  - Increased aggregation
  - Increased thrombopoietin

Novel Findings

- Transcriptome changes same in all COVID patient but different than other viral infections
- Platelets not decreased
- Antiplatelet agents being studied

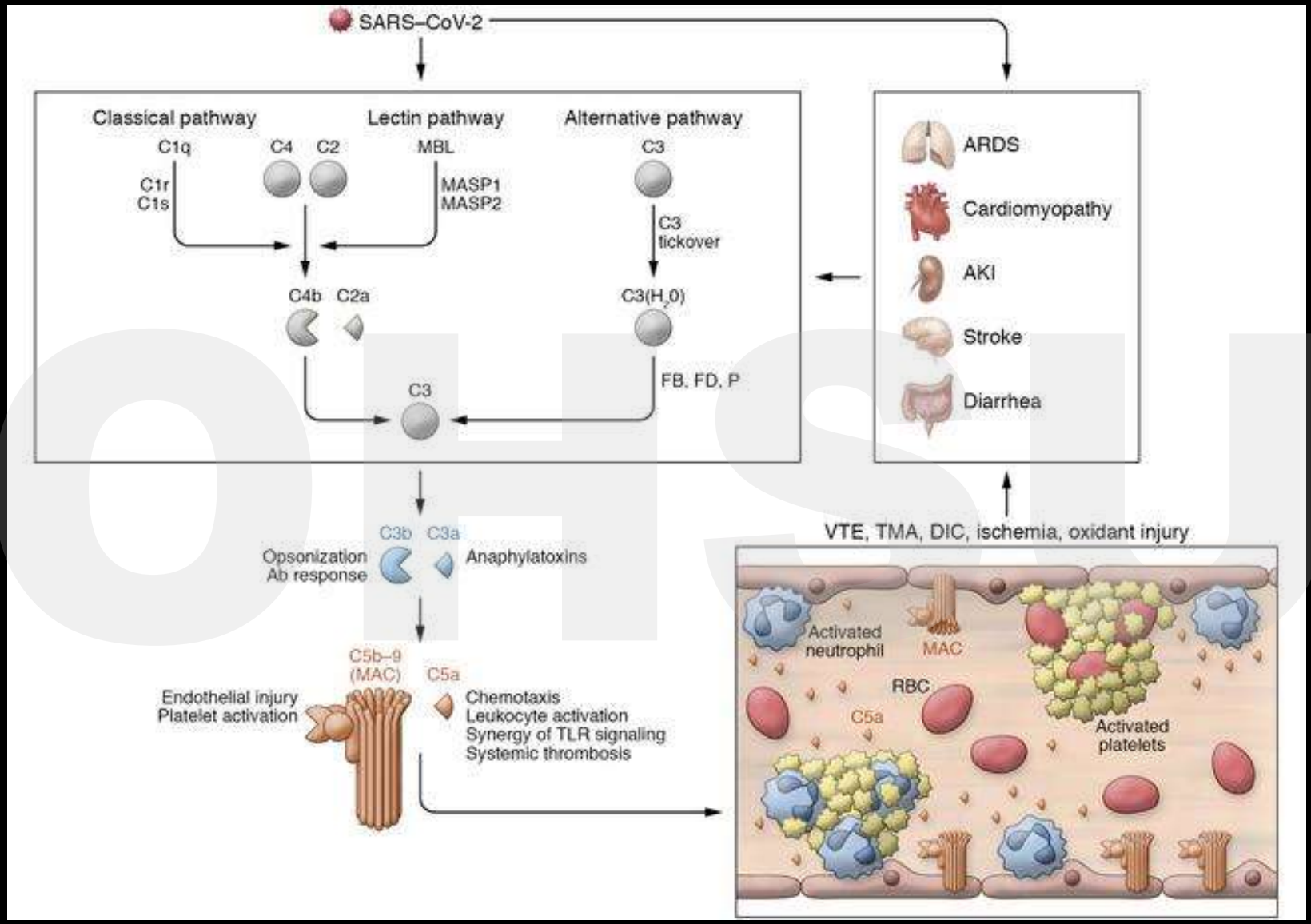




Manne Blood 2020

Complement

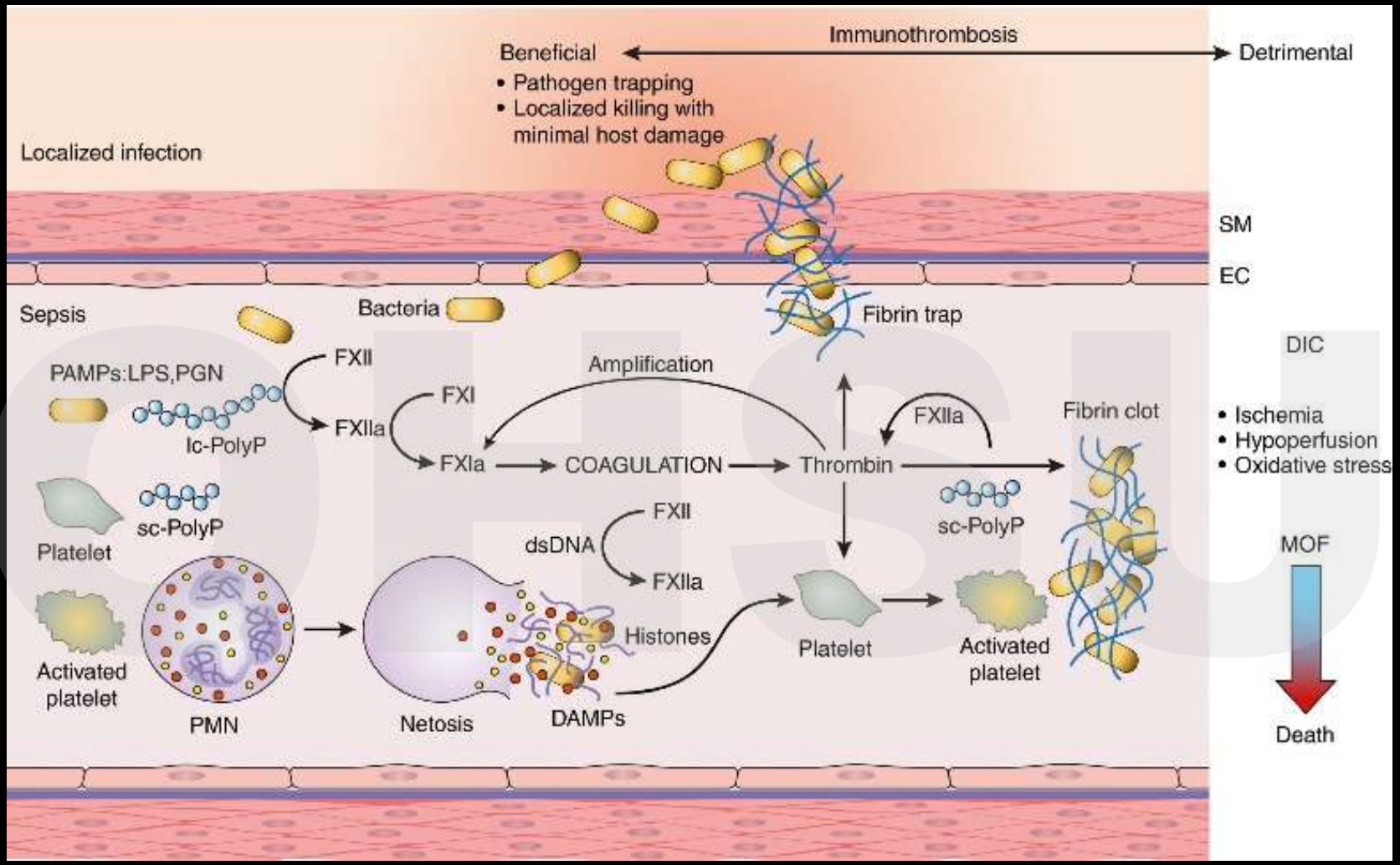
- Complicated inflammatory cascade
- Active proteins lead to tissue damage
  - Lung, microvascular
- Increase C5a seen in COVID
- Early work with complement blockers



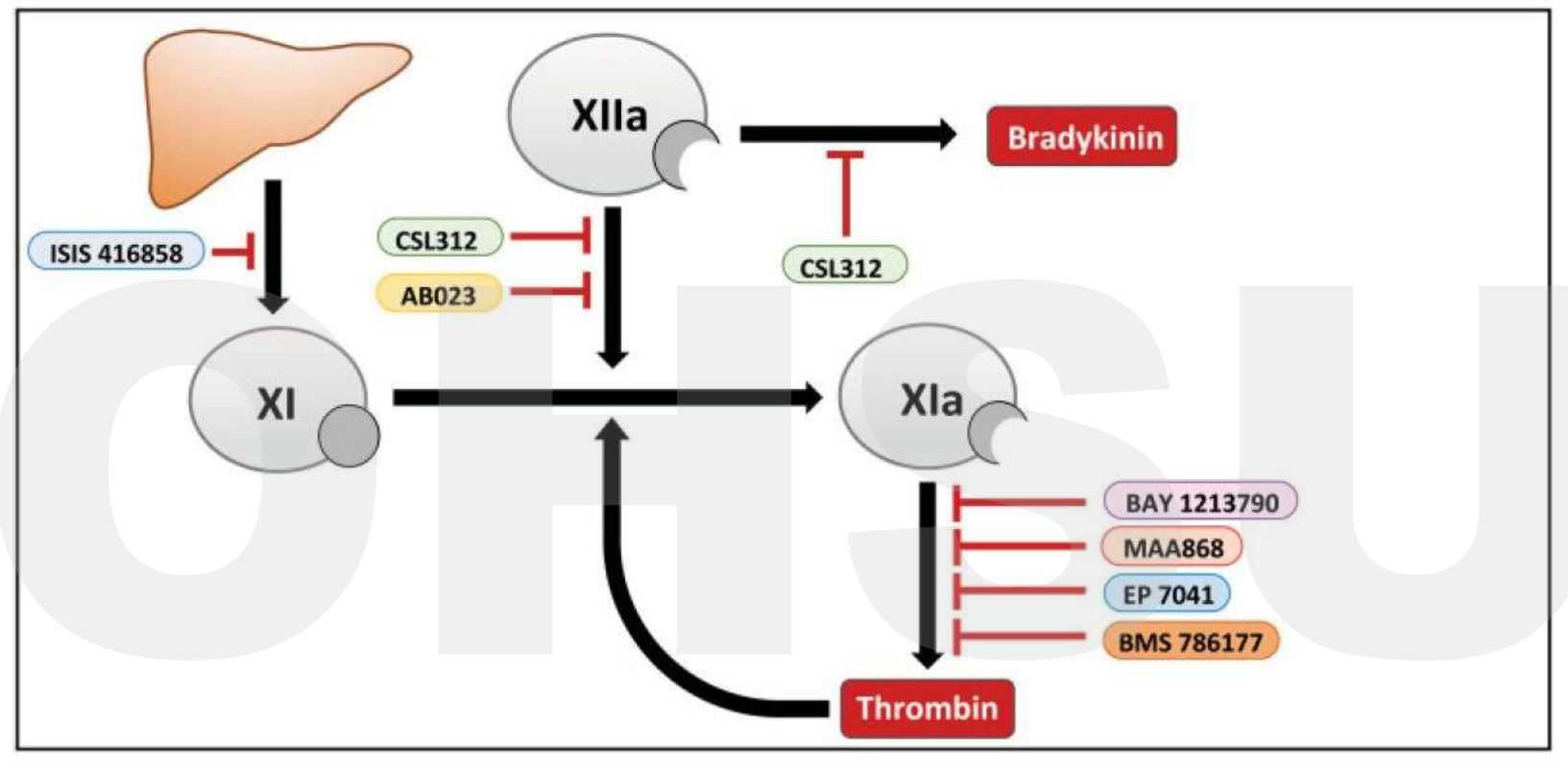
J Clin Invest DOI: 10.1172/JCI140183

Contact Pathway

- Coagulation/inflammation overlap
- Contact blocker effective in sepsis
- Low risk of side effects



Raghunathan Res Pract Thromb Haemost. 3:331, 2019



DeLoughery, EP Semin Thromb Hemost 45:502, 2019

Bottom Line

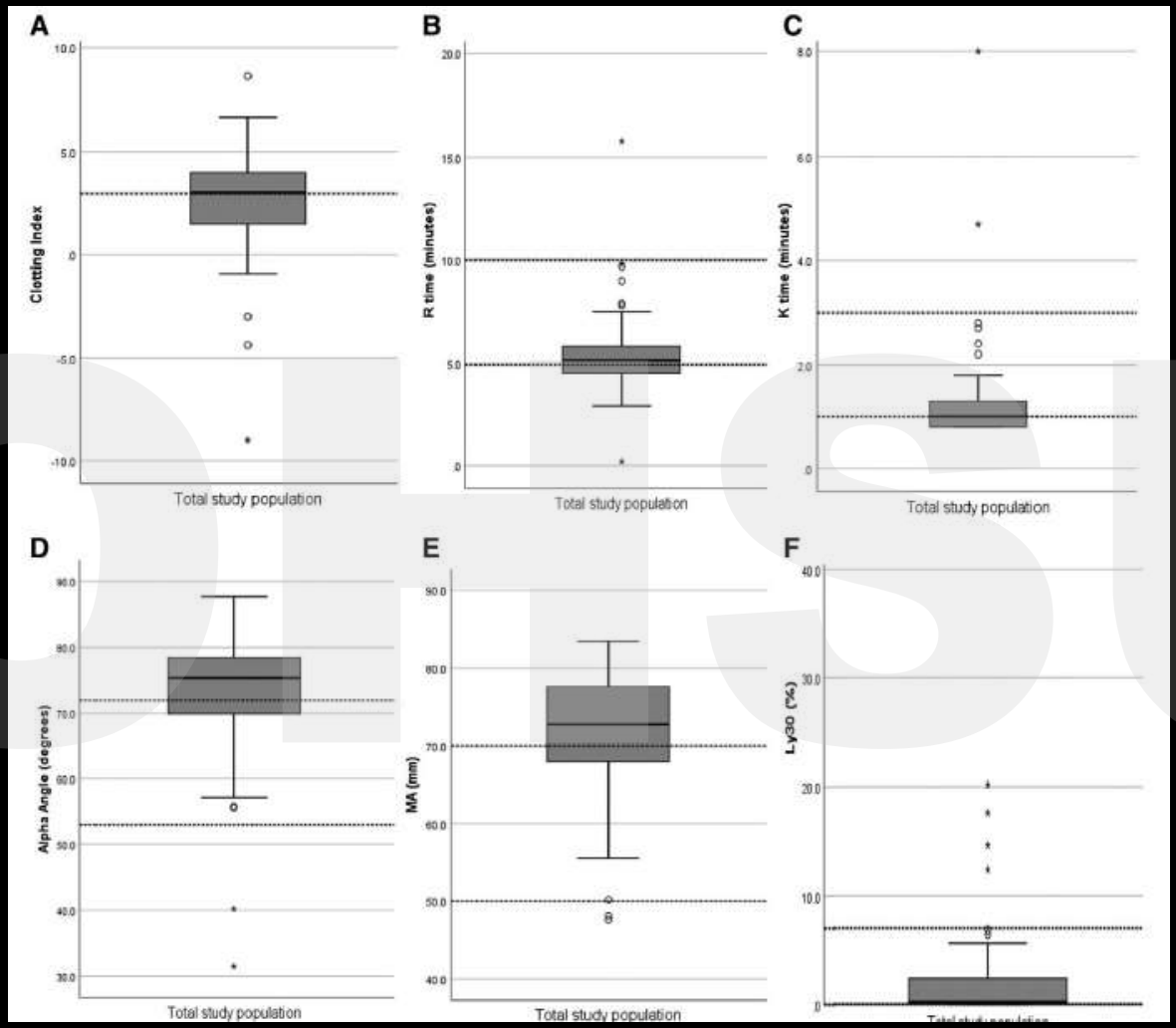
- COVID leads to a prothrombotic state via multiple mechanisms
- Unique compare to other infections

Testing

- Admit: INR, aPTT, platelets, D-dimer, fibrinogen,
- Daily platelets, D-dimers, fibrinogen

TEG

- Consistent findings
  - Shorten r time
  - Increase K time
  - Increased MA
  - Decreased lysis
- Hypercoagulability



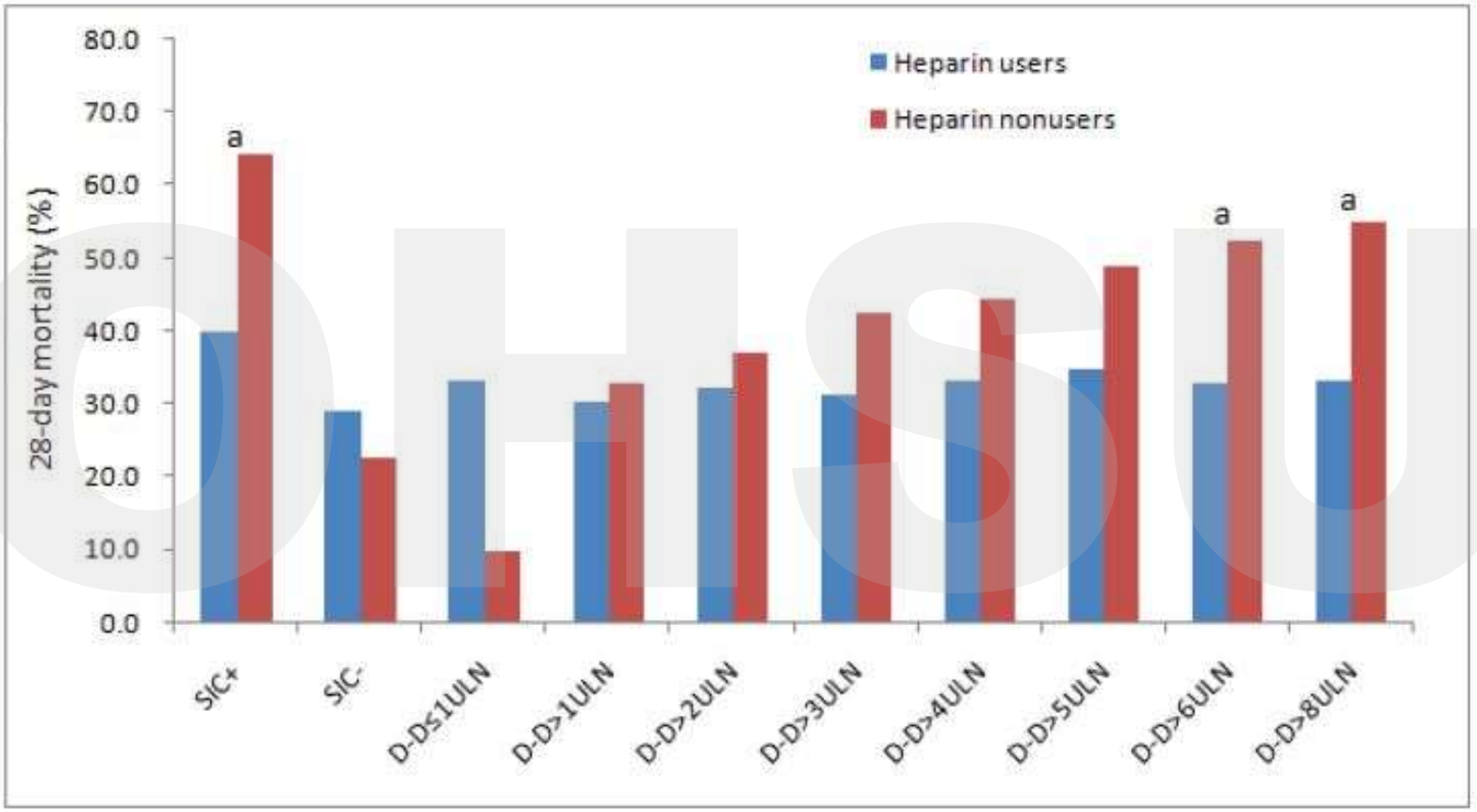
Yuriditsky CCM 2020

Anticoagulation

- Consensus
  - Everyone in hospital for COVID gets thromboprophylaxis with LMWH (UFH if renal failure)
- Controversy
  - Everything else

Is Heparin Beneficial?

- Teng study showed heparin associated with increase survival esp with high d-dimers
- Prophylaxis not standard in China
- Unclear doses used
- Ayerbe showed RR of 0.55



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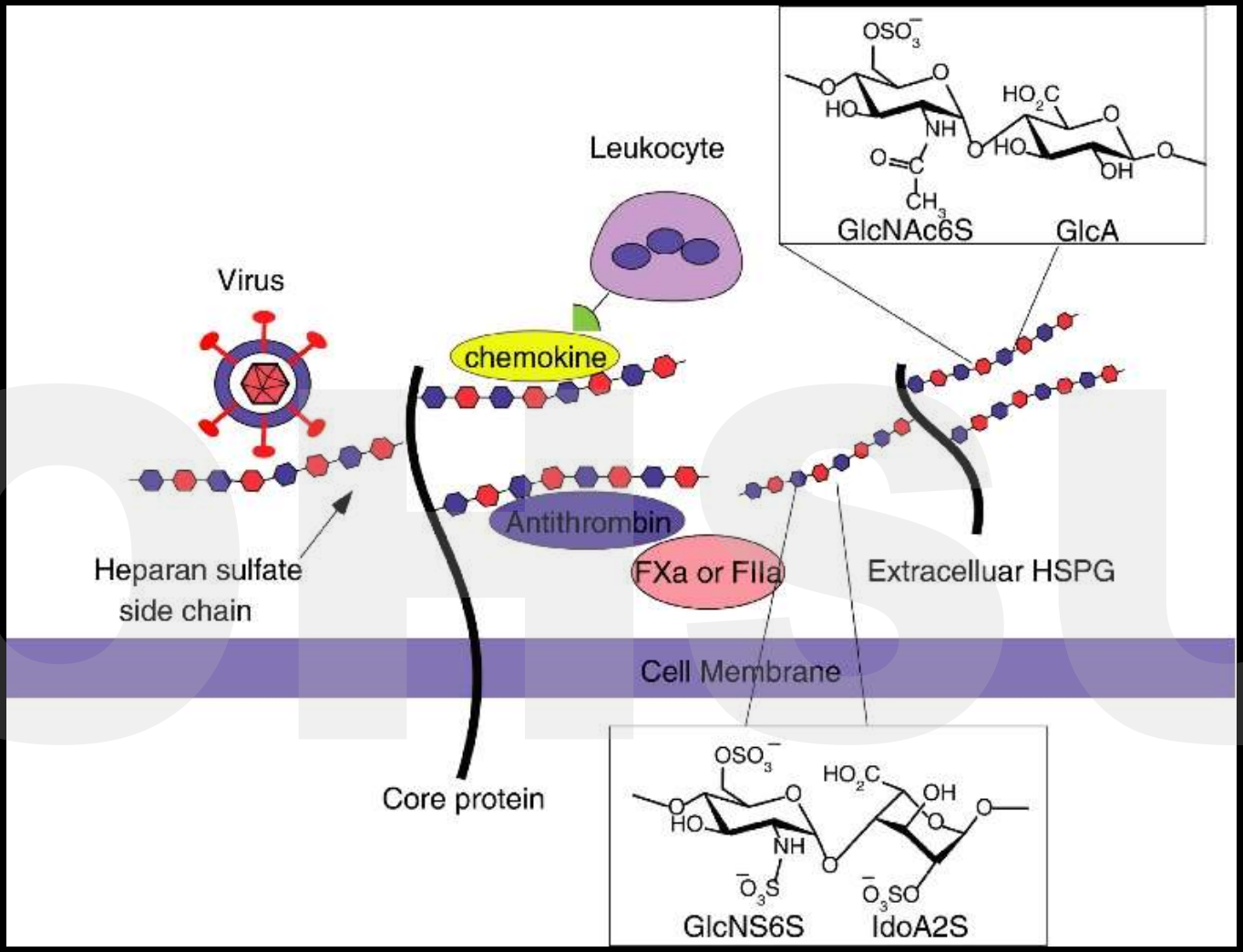
Heparin

- Observational data
- But
  - Antithrombotic?
  - Antiinflammatory?
  - Antiviral?
- Italian studies underway

Heparin as Antiviral

- Heparin can be a decoy for virus binding
- Heparin binds to spike protein
- Heparin has anti-inflammatory properties



Liu, RPTH 2020

Pre-Existing Anticoagulation

- Circulation study suggested being on anticoagulation at admission beneficial
- Studies controlling for baseline conditions no benefit

Increase Dosing?

- Many protocols increase heparin dosing for
  - ICU patients
  - D-Dimers 1.5- 3 x normal
- LMWH 40mg bid
- Multiple RCT in process

Therapeutic Dosing

- Some centers starting therapeutic dosing with D-Dimer 3-6x normal
  - High pretest probability of thrombosis

Thrombotic Risk

- Low – not in hospital
- Intermediate – in hospital but not requiring oxygen/vent
- High –obese or requires oxygen/vent
- Very high risk – obese + oxygen/vent, ECMO, high D-dimers or fibrinogen

- Susan, Crit Care 2020

Risk

- Low – nothing
- Intermediate – standard LMWH
- High – double LMWH
- Very high – therapeutic LMWH

- Susan, Crit Care 2020

Outpatient Prophylaxis

- Some advocate after discharge prophylaxis for 30-45 days due to perceived high risk of thrombosis
- 10% readmissions for thrombosis

Heparin Resistance

- Etiology
- Increased inflammatory proteins
  - Increased fibrinogen, etc absorb heparin
  - Interference with PTT
  - Heparinase?
- Prothrombotic drive

Heparin Resistance

- Solution
  - Use LMWH as much as possible
  - If using UFH, use heparin levels
  - Breakthrough: increase LMWH by 25% or use argatroban

Suggested Protocol

1. Prophylaxis for everyone with COVID admitted to hospital –
    - LMWH preferred
        - Enoxaparin 40mg daily is standard
        - BMI >40, enoxaparin 40mg BID
    - For renal failure
        - Unfractionated heparin 5000u BID or
        - Enoxaparin 30mg daily

Suggest Protocol

2. Screen for DVT at admit to ICU and every 4-5 days in ICU

- Low threshold for empiric treatment of thrombosis (sudden deterioration, D-Dimer > 3.0)
  - Enoxaparin 1mg/kg BID (preferred)
  - Renal failure: unfractionated heparin with goal 0.35-0.7

3. Double Prophylaxis for ICU patients
   – Enoxaparin 40mg bid

Suggested Protocol

4. Outpatient prophylaxis for patients who are likely to be immobile for a month either:

- **40mg enoxaparin or**
- **10mg rivaroxaban**

Guidelines

- Multiple ones!
  - ACCP, ISTH, AC Forum, BSH, etc
- Contentious issues:
  - Dosing of prophylaxis
  - Initiation of therapeutic dosing
  - Screening

Dosing of Prophylaxis

- Pro increase dosing:
  - High rates of thrombosis on standard dosing
  - Low risk of bleeding
- Con
  - No data
  - Is thrombosis driven by inflammation?
  - Not risk free

Initiation of Therapeutic Anticoagulation

- Pro
  - High rates of thrombosis
  - Difficult to get sick people to imaging
- Con
  - No data
  - Risk of bleeding
  - Can obtain testing if you try hard enough

Screening Dopplers

- Pro
  - High rates of thrombosis
  - Patients are unable to complain of symptoms
- Con
  - No data for screening
  - Exposes patients to risk of anticoagulation

Use of Convalescent Plasma

- Incredible hope and speculation about this
- Multiple trials/protocols in process

Convalescent Plasma

- Very old idea
- Antibodies in donor convalescent plasma can decrease infection in recipient
- Two types
  - Plasma
  - Hyperimmune globulin

Hyperimmune Globulin

- Long track records of effectiveness
- Process
  - Patients know to have high titers
  - Plasmapheresis
  - Fractionation to isolate IGG
  - Concentrate given to patient

Convalescent Plasma

- Patient documented to have infection
  - Ideally with high titers of ab
- Unit of whole blood drawn or plasmapheresis
- Plasma spun off and frozen

Issues

- Plasma raises IgG by ~5%
- Lack of antibody testing
  - Are high titers neutralizing?
- Many anecdotes but negative RCT studies in other disease
- One trial stopped because patients already had antibodies

Netherland Trial

- 86 patients (~ 10 days into illness, ~ 2 days in hospital)
  - 79% already had neutralizing antibodies
  - Titers same as plasma
  - Trial stopped

Plasma: Bottom Line

- ~ 10,000 received plasma outside of trials
- Many units no titer testing was done
- Need RCT data

Blood Groups

- Multiple (7) studies showing
  - Group O protective: 0.80
  - Group A risk factor: 1.20
  - Both serology and genetic studies

Blood Groups

- Type O protective?
  - Lower levels of von Willebrand factor
- Anti-A binds virus spike protein
  - Group A at risk

COVID Thrombosis

- Very high rate of thrombosis
  - ICU patients
    - Venous thrombosis
  - Arterial thrombosis
- Low suspicion for diagnosis and treatment
- Need RCT to report!