



UNIVERSITY of CALIFORNIA
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SCHOOL OF MEDICINE

COVID19 and Pulmonary Embolism

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COVID19

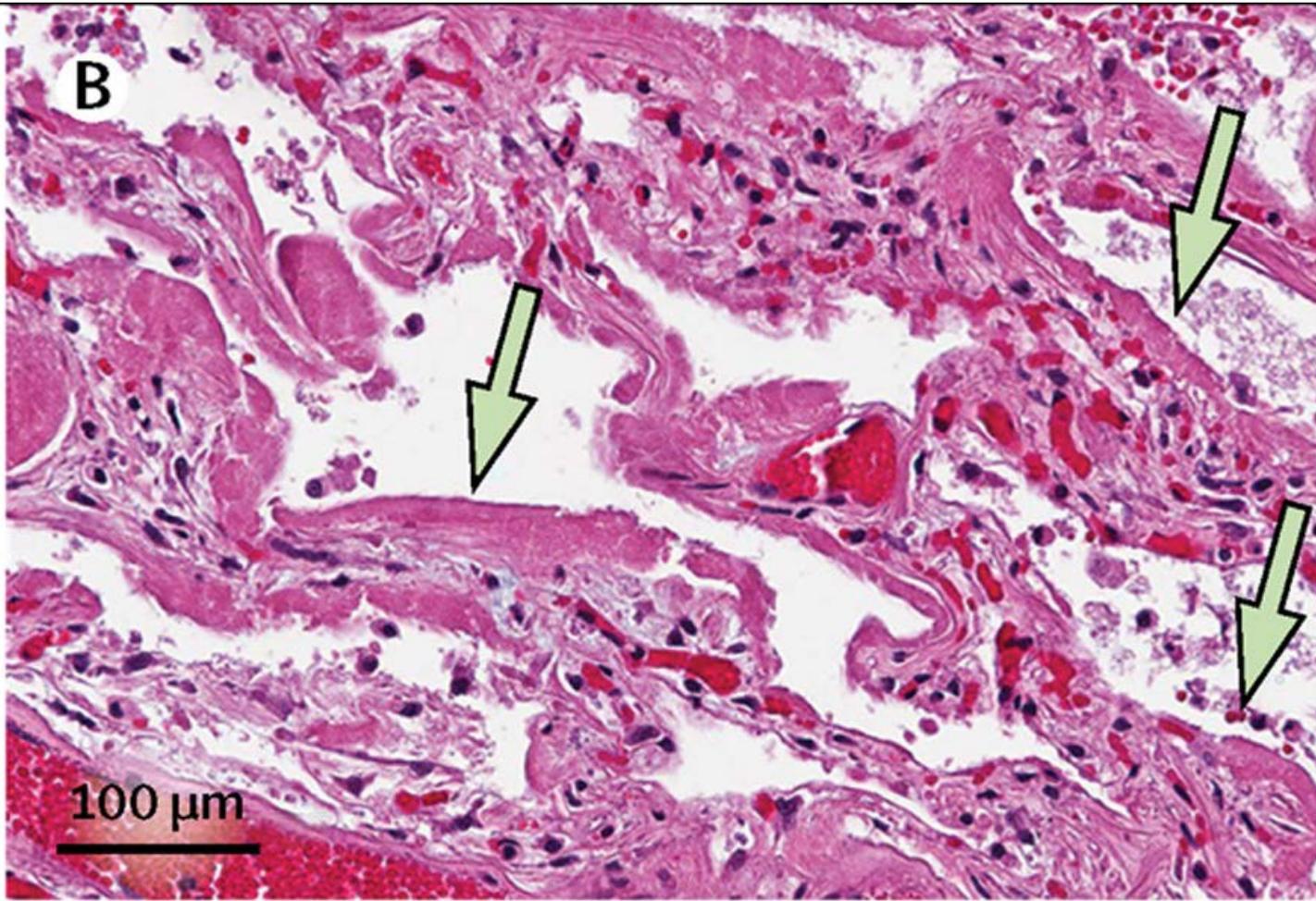
- Pathological features
- Macro vs Micro
- Serological markers
- Epidemiology
- Case presentations



COVID19

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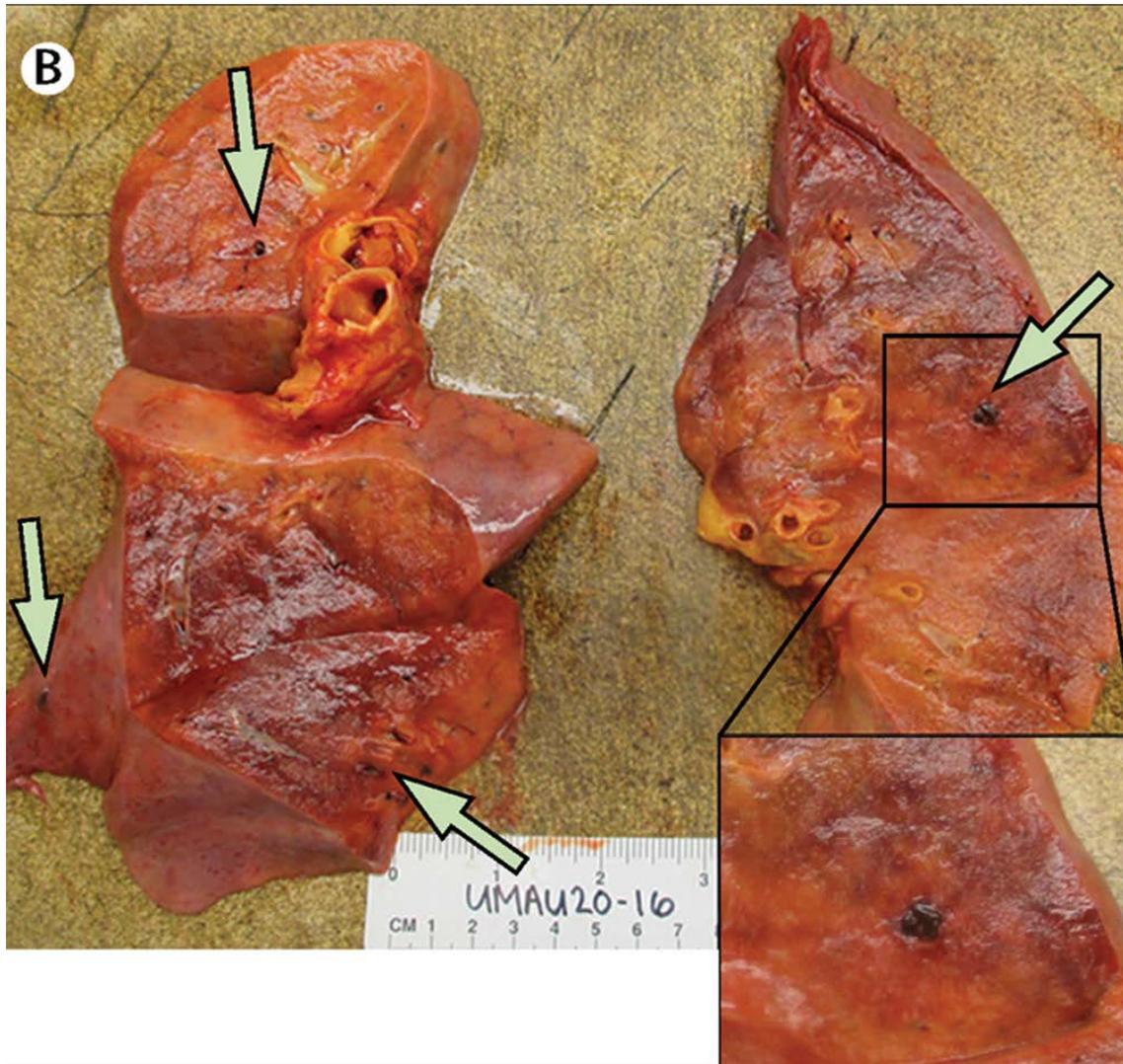
Alveolar fibrin in COVID19-ARDS (like most ARDS)



1. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med.* 2020;8(7):681-686.



Small *in situ* thrombosis in COVID19-ARDS



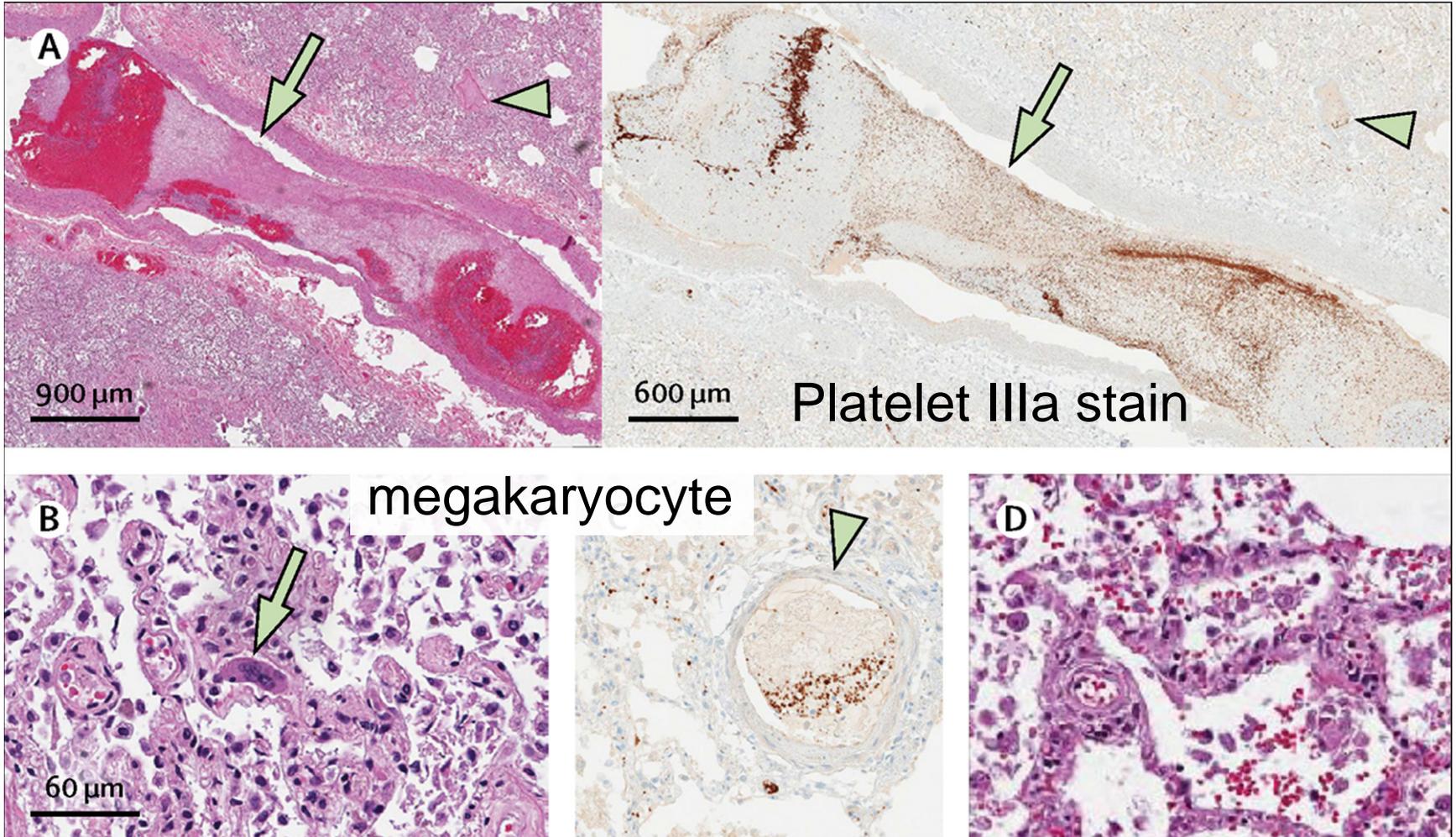
1. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med.* 2020;8(7):681-686.



Big RV dilatation in COVID19-ARDS

1. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med.* 2020;8(7):681-686.

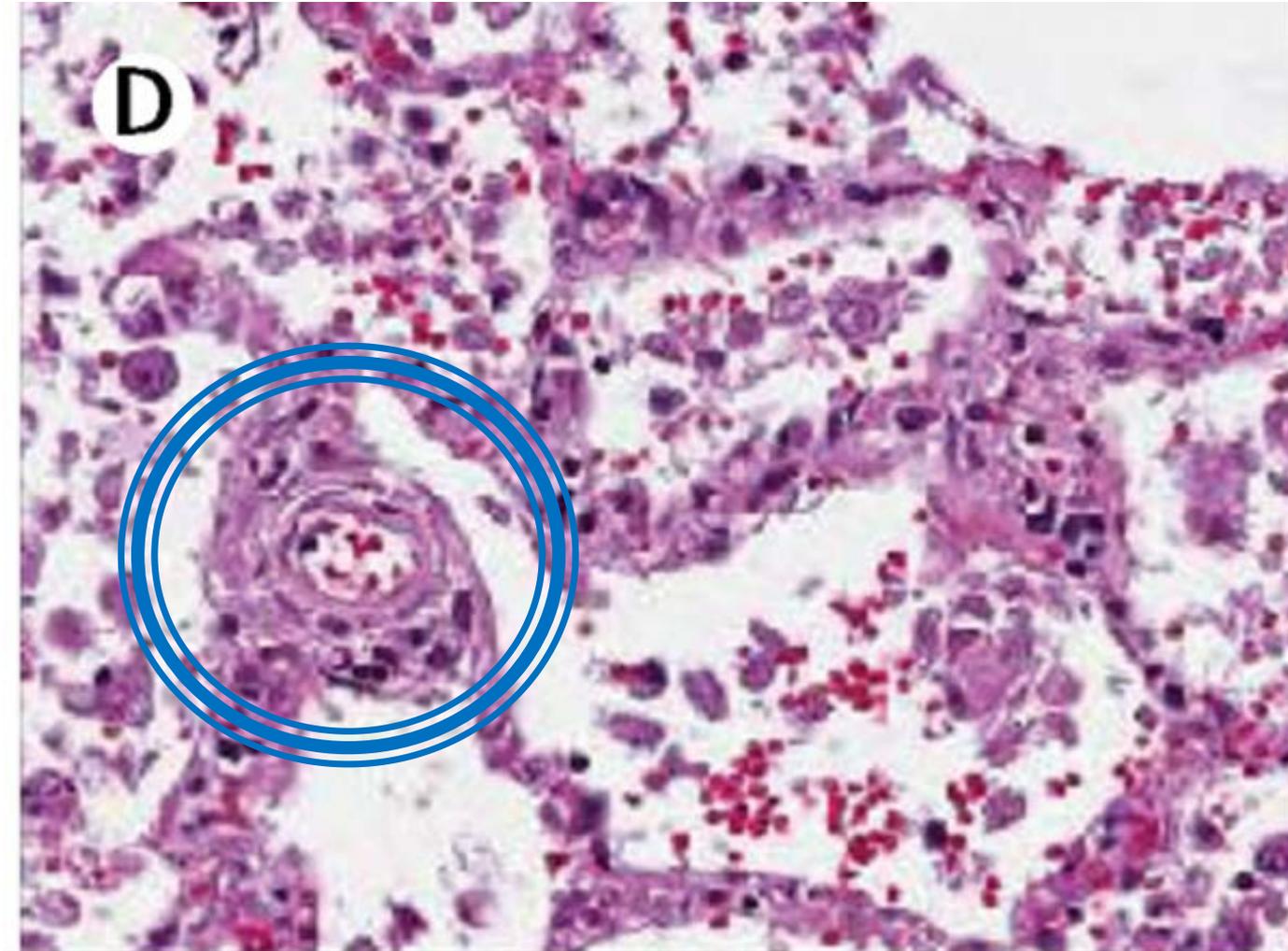
In situ arteriolar thrombosis in COVID19-ARDS



1. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med.* 2020;8(7):681-686.



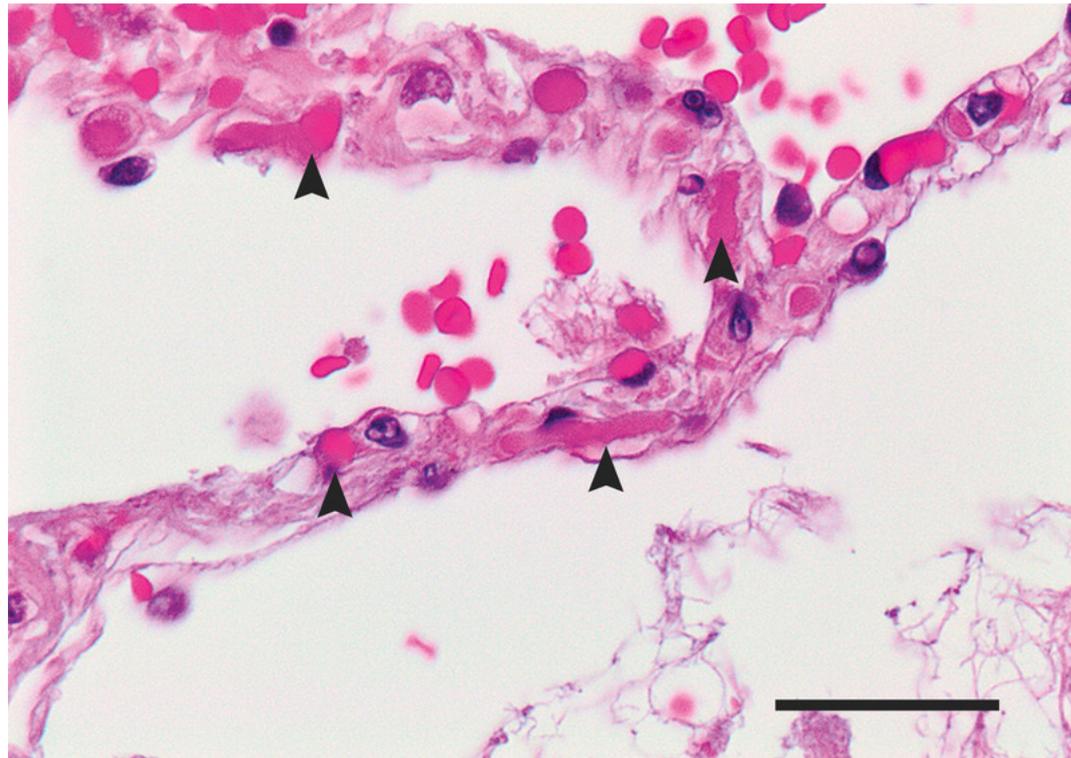
Angiitis in COVID19-ARDS



1. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med.* 2020;8(7):681-686.

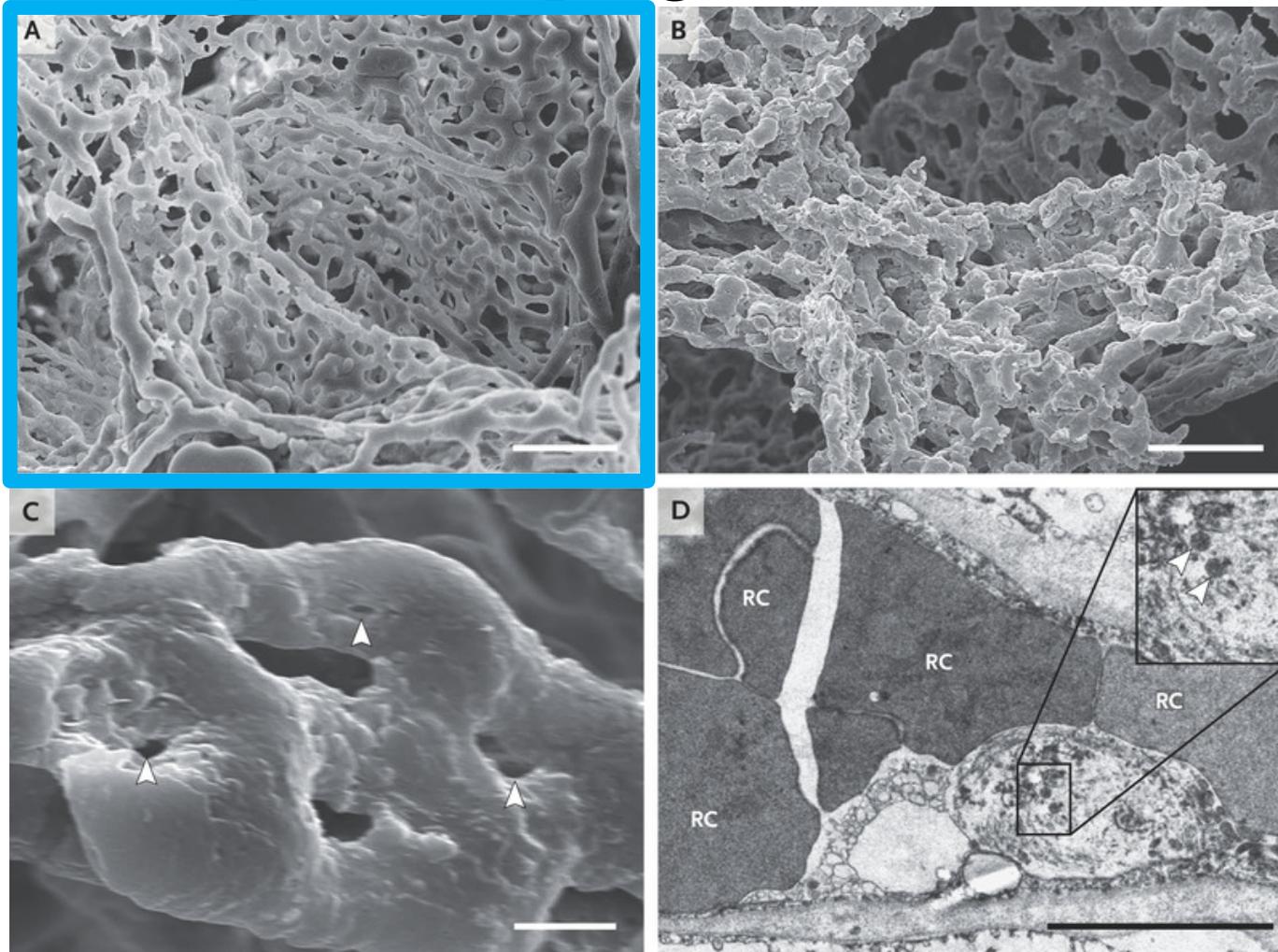


Capillary thrombi



1. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med.* 2020;383(2):120-128.

Angiitis/angiogenesis in COVID19



1. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med.* 2020;383(2):120-128.



COVID19

- Pathological features
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Macro vs Micro Thrombosis

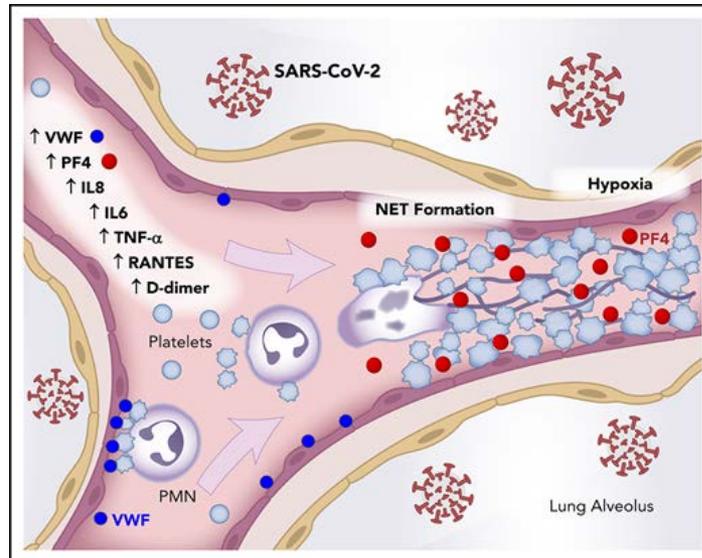
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Inflammation and Hypoxia lead to Thrombosis

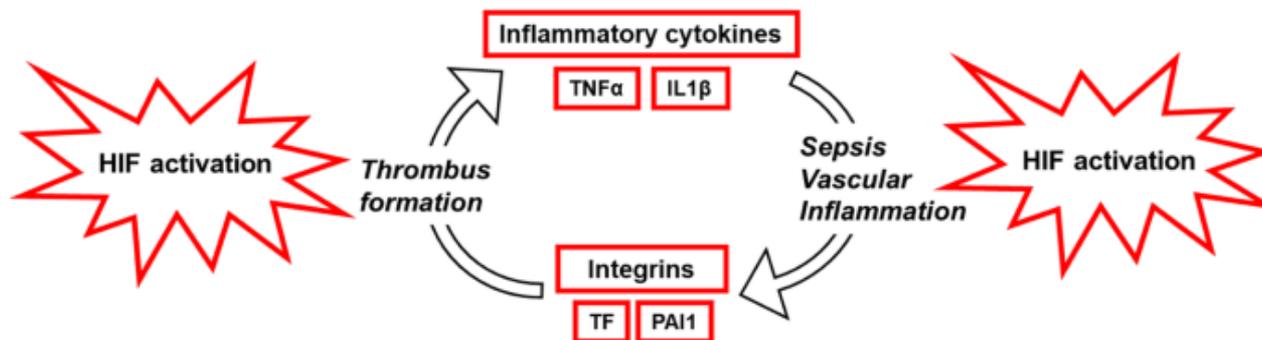
- The Coagulation system evolved as an effector pathway of the immune response
 - Neutrophils release NETs to trap bacteria but also lead to platelet aggregation
 - Fibrin is laid down to entrap infected cells/bacteria



Middleton EA, He X-Y, Denorme F. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome. *Blood*. 2020;136:1169–79.

Inflammation and Hypoxia lead to Thrombosis

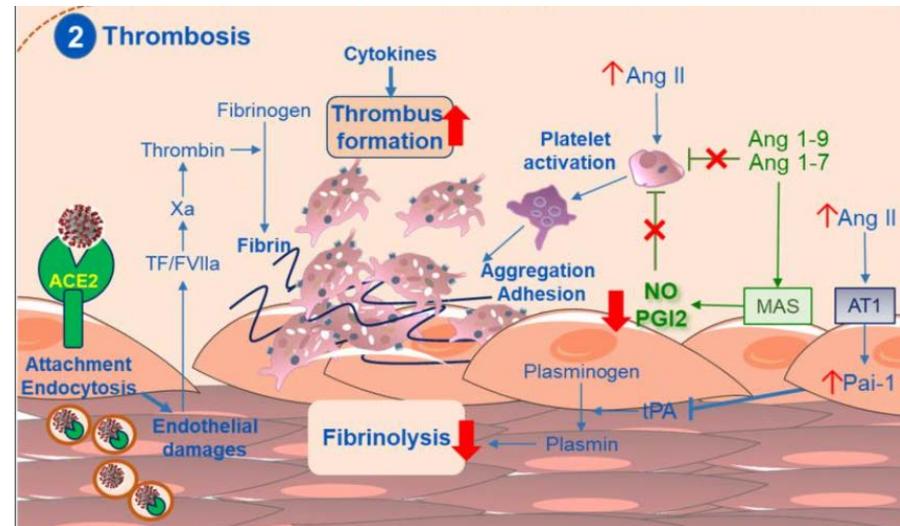
- The Coagulation system evolved as an effector pathway of the immune response
 - Neutrophils release NETs to trap bacteria but also lead to platelet aggregation
 - Fibrin is laid down to entrap infected cells/bacteria
- Hypoxia, via hypoxia-inducible transcription factors, lead to prothrombotic state



Evans CE. Hypoxia and HIF activation as a possible link between sepsis and thrombosis. *Thrombosis Journal*. 2019;17.

Inflammation and Hypoxia lead to Thrombosis

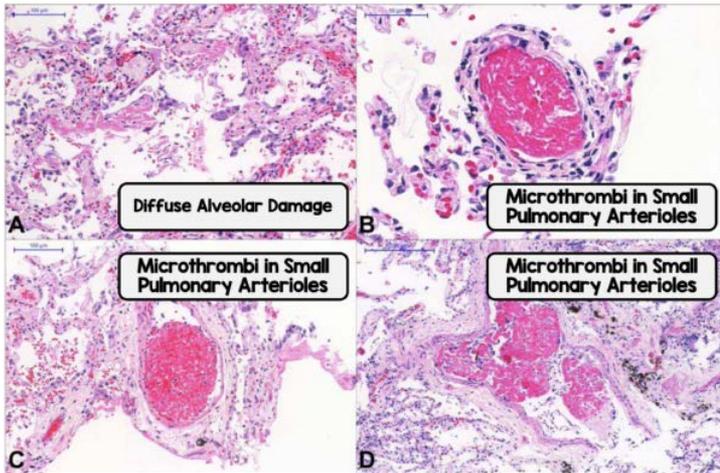
- Endothelial dysfunction can further impair vascular tone and drive more thrombosis
 - Endothelial injury releases tissue factor resulting in thrombin activation



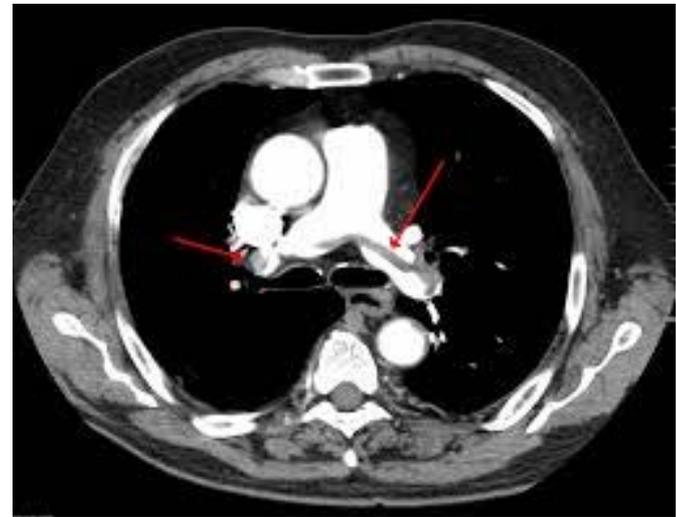
Huertas A, Montani D, Savale L. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)?. *European Respiratory Journal*. 2020;56:2001634.



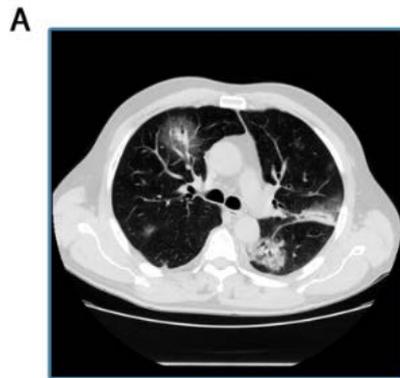
Microthrombosis vs. Macrothrombosis in COVID-19



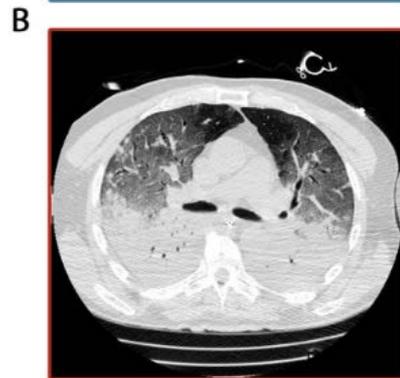
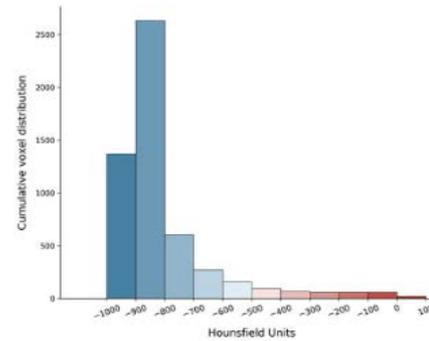
VS.



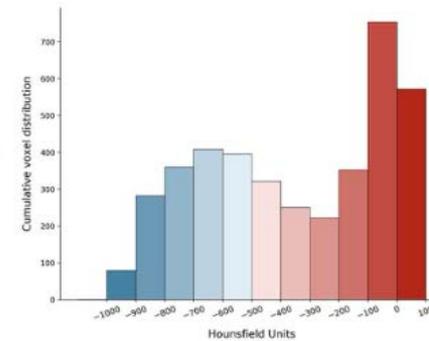
High Compliance, High Dead Space Phenotype of COVID-19 ARDS



$\text{PaO}_2/\text{FiO}_2$
95 mmHg



$\text{PaO}_2/\text{FiO}_2$
84 mmHg



Gattinoni L, Chiumello D, Caironi P. COVID-19 pneumonia: different respiratory treatments for different phenotypes?. Intensive Care Medicine. 2020;**46**:1099–102.

Is C-ARDS really that different from ARDS?

Viewpoint



COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted?

Eddy Fan, Jeremy R Beitler, Laurent Brochard, Carolyn S Calfee, Niall D Ferguson, Arthur S Slutsky, Daniel Brodie

Lancet Respir Med 2020;
8: 816–21

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The COVID-19 pandemic has seen a surge of patients with acute respiratory distress syndrome (ARDS) in intensive care units across the globe. As experience of managing patients with COVID-19-associated ARDS has grown, so too have efforts to classify patients according to respiratory system mechanics, with a view to optimising ventilatory management. Personalised lung-protective mechanical ventilation reduces mortality and has become the mainstay of treatment in ARDS. In this Viewpoint, we address ventilatory strategies in the context of recent discussions on phenotypic heterogeneity in patients with COVID-19-associated ARDS. Although early reports suggested that COVID-19-associated ARDS has distinctive features that set it apart from historical ARDS, emerging evidence indicates that the respiratory system mechanics of patients with ARDS, with or without COVID-19, are broadly similar. In the absence of evidence to support a shift away from the current paradigm of ventilatory management, we strongly

“Reports of phenotypic heterogeneity in patients with COVID-19-associated ARDS, although interesting, could easily be over-interpreted or inappropriately applied in the intensive care unit, potentially leading to detrimental ventilatory management strategies in these patients.”

Fan E, Beitler JR, Brochard L. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted?. *The Lancet Respiratory Medicine*. 2020;8:816–21.

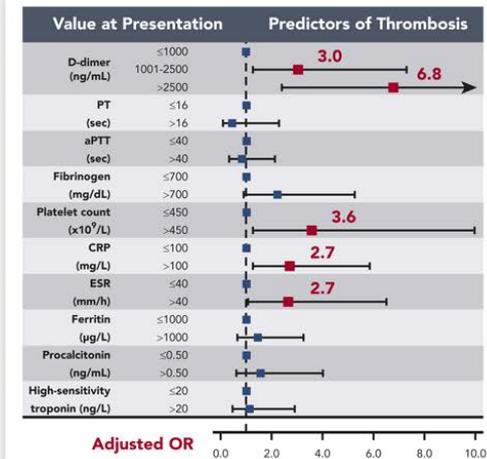
Bleeding and Clotting in COVID-19

400 hospital-admitted patients with COVID-19 (144 critically ill)

CLOTTING

4.8% **7.6%**
critically ill

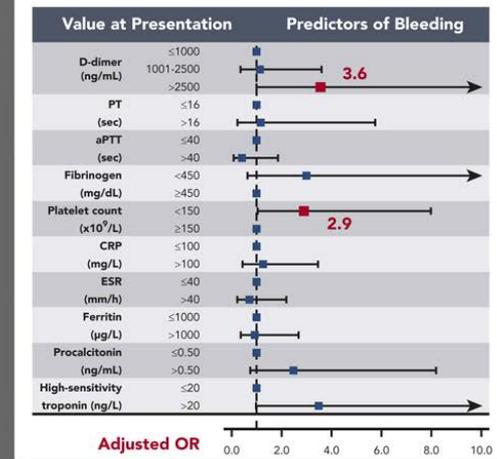
Confirmed VTE



Overall thrombotic complications **9.5%** **18.1%**
critically ill

COVID-19

Overall bleeding events **4.8%** **7.6%**
critically ill



Major Bleeding

5.6% **2.3%**
critically ill

BLEEDING



There are over 30 currently enrolling clinical trials for anticoagulation paradigms in COVID-19

TABLE 1 Registration details (as of June 17, 2020) and study characteristics of trials evaluating anticoagulant interventions in hospitalized patients with COVID-19

Study acronym or PI	Trial ID	Source registry	Countries	Date of registration	Estimated study completion date
COVID-HEP	NCT04345848	ClinicalTrials.gov	Switzerland	7 April 2020	March 2021
CORIMMUNO-COAG	NCT04344756	ClinicalTrials.gov	France	9 April 2020	September 2020
RAPID COVID COAG	NCT04362085	ClinicalTrials.gov	Canada, Ireland, Saudi Arabia, United States	20 April 2020	December 2020
HeSAcovid	RBR-949z6v	REBEC	Brazil	6 May 2020	July 2020
COALIZAO ACTION	NCT04394377	ClinicalTrials.gov	Brazil	8 May 2020	December 2020
COVID PACT	NCT04409834	ClinicalTrials.gov	United States	28 May 2020	May 2021
Berger et al.	NCT04359277	ClinicalTrials.gov	United States	20 April 2020	April 2021
REMAP-CAP	NCT02735707	ClinicalTrials.gov	Australia, Belgium, Canada, Croatia, France, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Saudi Arabia, Spain, United Kingdom, United States	20 April 2020 ^b	December 2021
ATTACC	NCT04372589	ClinicalTrials.gov	Brazil, Canada, Mexico, United States	24 April 2020	January 2021
Albaghdadi et al.	NCT04377997	ClinicalTrials.gov	United States	1 May 2020	January 2021
HEP-COVID	NCT04401293	ClinicalTrials.gov	United States	20 May 2020	April 2021
IMPACT	NCT04406389	ClinicalTrials.gov	United States	26 May 2020	June 2021
COVID-19 HD	NCT04408235	ClinicalTrials.gov	Italy	26 May 2020	June 2021
COVI-DOSE	NCT04373707	ClinicalTrials.gov	France	1 May 2020	October 2020 ^a
X-Covid 19	NCT04366960	ClinicalTrials.gov	Italy	24 April 2020	November 2020
Heparin-SARS-CoV2	EUCTR2020-001891-14-ES	EU Clinical Trials Register	Spain	5 May 2020	Not provided
Perepu et al	NCT04360824	ClinicalTrials.gov	United States	13 April 2020	April 2021
IMPROVE-COVID	NCT04367831	ClinicalTrials.gov	United States	27 April 2020	April 2021
COVID-PREVENT	NCT04416048	ClinicalTrials.gov	Germany	2 June 2020	May 2021
ACOVACT	NCT04351724	ClinicalTrials.gov	Austria	10 April 2020	December 2020

Tritschler T, Mathieu M, Skeith L. Anticoagulant interventions in hospitalized patients with COVID-19: A scoping review of randomized controlled trials and call for international collaboration. *Journal of Thrombosis and Haemostasis*. 2020;18:2958–67.



Operation Warp Speed: ACTIV-4 Anti-thrombotics

- ACTIV-4 Inpatient Protocol
 - Therapeutic vs. Prophylactic anticoagulation
 - 2000 Hospitalized patients
 - Primary Endpoint: 21 Day Organ Support (respiratory or vasopressor) Free Days
 - Secondary Endpoint: Composite endpoint of death, pulmonary embolism, systemic arterial thromboembolism, myocardial infarction, or ischemic stroke at hospital discharge or 28 days
 - Anticipated study completion by March 2021
- ACTIV-4 Inpatient Protocol (ASA/Apixiban/Placebo; 7000 patients)
- ACTIV-4 Convalescent Protocol



COVID19

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APL antibodies with COVID19

Table 1. Prevalence of antiphospholipid antibodies in serum from COVID-19 patients (n=172)

aPL antibody	Number positive (manufacturer's cut-off)	%	Number positive (titer ≥ 40 units)	%
aCL IgG	8	4.7%	2	1.2%
aCL IgM	39	23%	13	7.6%
aCL IgA	6	3.5%	1	0.58%
a β_2 GPI IgG	5	2.9%	3	1.7%
a β_2 GPI IgM	9	5.2%	7	4.1%
a β_2 GPI IgA	7	4.1%	3	1.7%
aPS/PT IgG	42	24%	21	12%
aPS/PT IgM	31	18%	21	12%
any positive aPL	89	52%	52	30%



But lots of viral infections have APL Ab

<i>Infection type</i>	<i>No. of positive patients/total (%)</i>
Anticardiolipin antibodies	
HIV + no OI ($n = 19$) ^{18,21,22,25,26,31,33,35,68–78}	840/1499 ^a (56)
HIV + all combined OI ($n = 6$) ^{28,31,43,45,76,79}	193/306 (63)
Hepatitis C virus ($n = 20$) ^{19,23,27,29,30,32,34,36,38,40,80–89}	368/1785 (21)
Hepatitis B virus ($n = 9$) ^{24,30,36,68,83,88–91}	93/483 (19)
Epstein-Barr virus ($n = 4$) ^{64,68,92,93}	68/137 (50)
Human T-lymphotropic virus type 1 ($n = 3$) ^{16,17,45}	31/191 (16)
Hepatitis A virus ($n = 1$) ⁶⁴	2/2 (100)
Human herpesvirus type 6 ($n = 1$) ³⁷	19/32 (59)
Lymphotropic viruses ($n = 1$) ⁷⁵	8/20 (40)
Parvovirus B19 ($n = 1$) ²⁰	8/60 (13)
Varicella zoster virus ($n = 1$) ⁶⁸	8/12 (67)

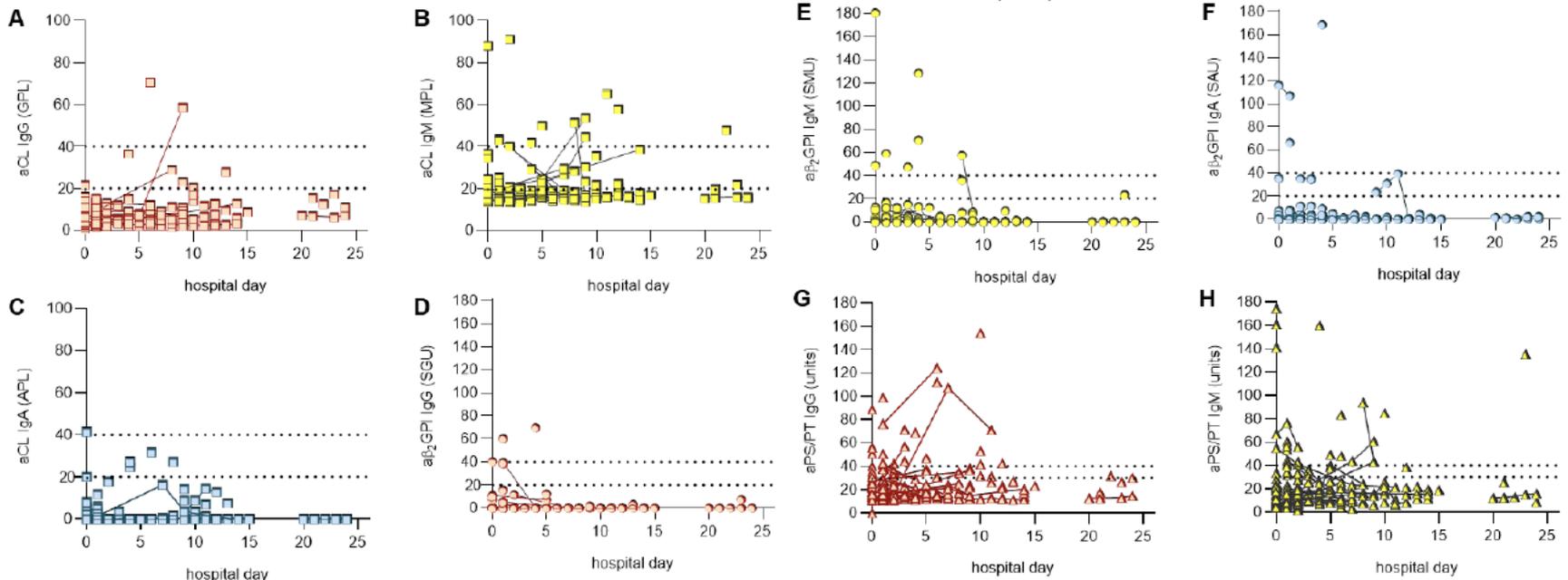
1. Abdel-Wahab N, Talathi S, Lopez-Olivo MA, Suarez-Almazor ME. Risk of developing antiphospholipid antibodies following viral infection: a systematic review and meta-analysis. *Lupus*. 2018;27(4):572-583.

Viral-associated APL Ab aren't necessarily associated with VTE

<i>Infection type (total number of studies)^a</i>	<i>Thromboembolic No. of positive/ Patients with infection and aPL antibodies (%)</i>
Hepatitis C virus (<i>n</i> = 9) ^{27,29,30,34,36,39,40,85,87}	20/178 (11.2)
HIV (<i>n</i> = 6) ^{18,21,26,41,46,71}	0/171
HIV + OI (<i>n</i> = 3) ^{43,45,79}	1/111 (<1)
Hepatitis B virus (<i>n</i> = 5) ^{24,30,39,90,91}	4/75 (5)
Epstein-Barr virus (<i>n</i> = 1) ⁴⁶	0/19
Human herpesvirus type 6 (<i>n</i> = 1) ³⁷	0/19
Human T-lymphotropic virus type 1 (<i>n</i> = 1) ¹⁶	0/23
Parvovirus B19 (<i>n</i> = 1) ²⁰	

1. Abdel-Wahab N, Talathi S, Lopez-Olivo MA, Suarez-Almazor ME. Risk of developing antiphospholipid antibodies following viral infection: a systematic review and meta-analysis. *Lupus*. 2018;27(4):572-583.

APL antibodies in COVID19 are mostly in the first week or two



Persistent ACL and A-PT Ab are associated with VTE

APLA subtype	Persistent		Persistent or transient	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
ACLA IgG	10.0 (1.8-56)	.013	2.8 (0.5-16)	.211
ACLA IgM	32.7 (4.2-256)	.001	10.0 (1.8-56)	.013
Anti- β_2 -GPI IgG	17.3 (2.6-116)	.005	10.6 (1.7-65)	.010
Anti- β_2 -GPI IgM	6.7 (1.2-37)	.036	9.2 (1.5-55)	.015
Anti-PT IgG	3.5 (0.7-19)	.155	3.1 (0.6-18)	.179
Anti-PT IgM	3.6 (0.3-46)	.358	2.6 (0.4-17)	.292

1. Male C, Foulon D, Hoogendoorn H, et al. Predictive value of persistent versus transient antiphospholipid antibody subtypes for the risk of thrombotic events in pediatric patients with systemic lupus erythematosus. *Blood*. 2005;106(13):4152-4158.

Laboratory criteria for antiphospholipid syndrome

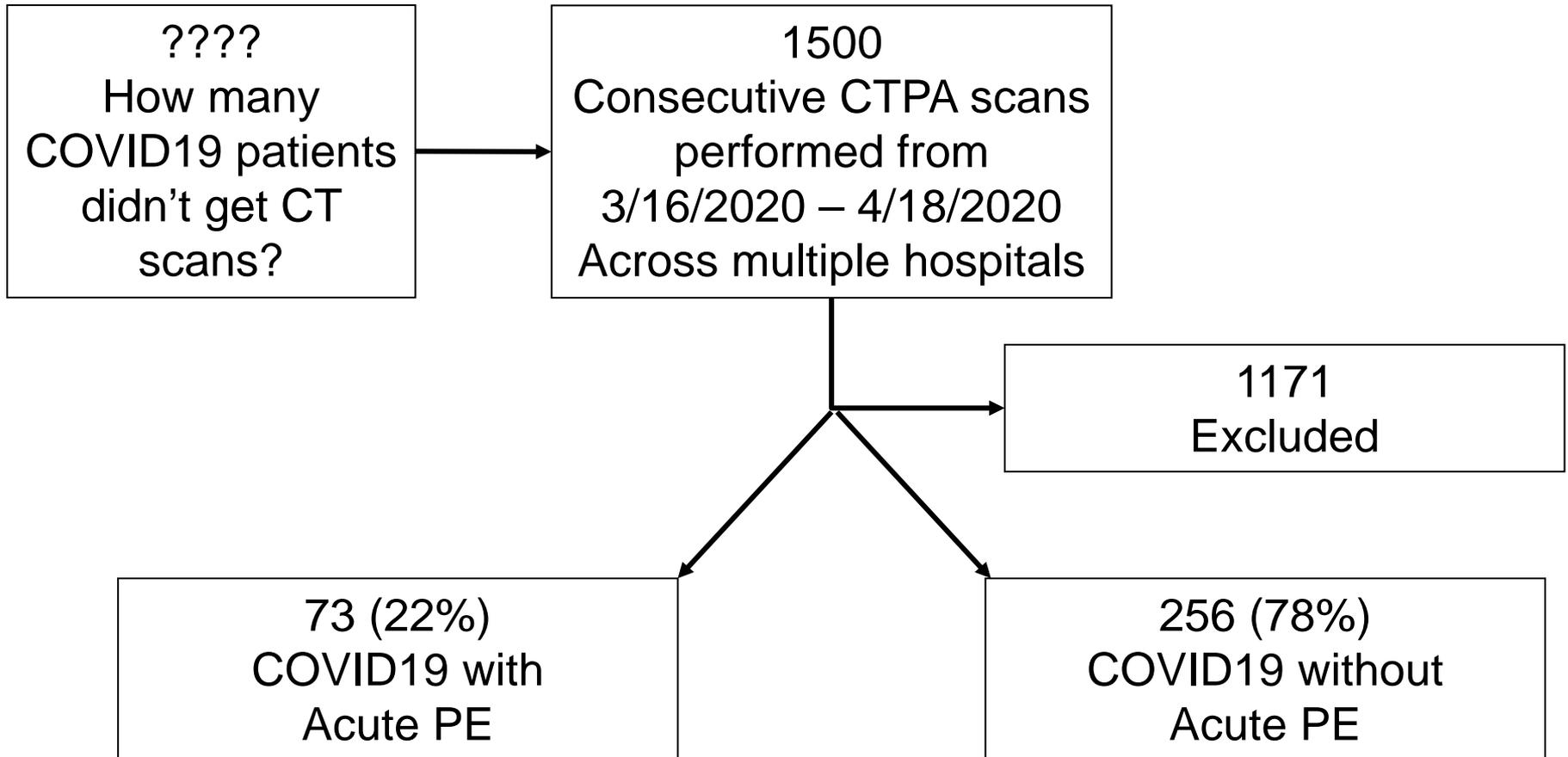
1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart.
2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype on two or more occasions, at least 12 weeks apart
3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype on two or more occasions at least 12 weeks apart



COVID19

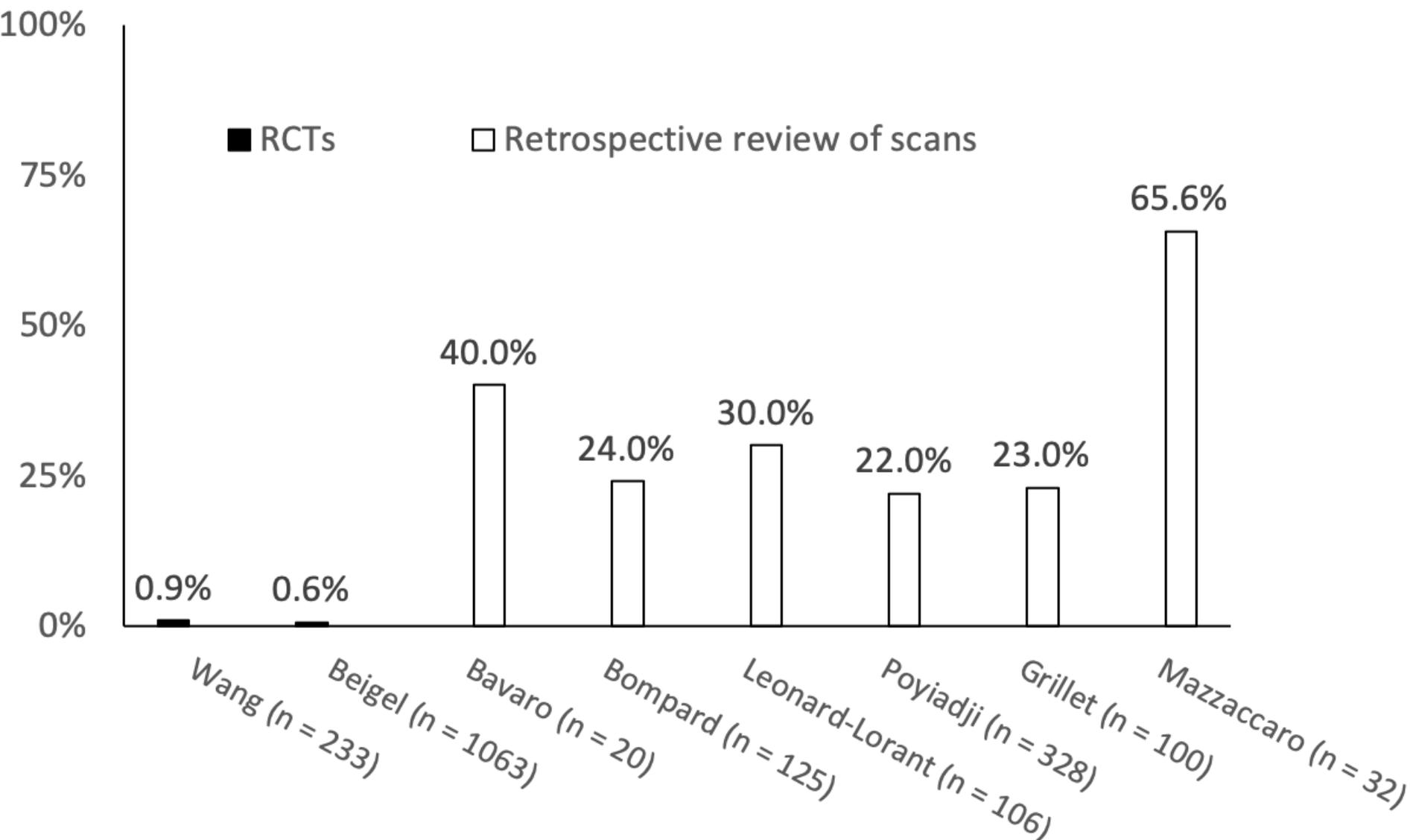
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High incidence of PE among COVID19 who get scanned





Incidence of PE among COVID19 patients





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Case presentations

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Fellow,

Division of Pulmonary and Critical Care Medicine

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Case #1



Case presentation #1

- 53 yo M with history of HTN and HLD who presented to the ED with progressive SOB following recent COVID-19 diagnosis 6 days prior to admission.



Admission vital signs

- T 100.9F
- HR 69
- BP 125/73
- RR 30
- SpO2 94% on RA

- BMI 31.6



Physical exam

- Gen: No acute distress, speaking complete sentences
- CV: Regular rate and rhythm, no murmur, rubs or gallops
- Lungs: Clear bilaterally
- GI: Abdomen soft and non-tender
- Ext: No swelling or erythema
- Skin: No rashes, wounds

Initial labs

- CBC
 - $6.1 > 15.1/45.6 < 158$
 - 71% segs, 21% lymph, 8% mono, 0% eos/basophils
- BMP – 136 / 4 / 96 / 26 / 13 / 1.0 < 113
- Liver enzymes – Normal except AST 49, ALT 52
- Pro-BNP – 67 pg/ml (normal 0-899)
- Troponin 5th Gen – 6ng/L (normal <22 ng/L)
- D-Dimer – 221 ng/mL (normal <241ng/mL)
- Rapid Covid-19 Assay - Positive



CXR

AP PORT SEMI ERECT

9/26/2020 12:30:40

L
ALW



Hospital course

- Admitted to Medicine and started on Remdesivir
 - initially saturating well on RA, overnight requiring 2-3L via NC to maintain sat >88%
- HD 4 – Increasing oxygen requirement overnight, now requiring NRB
 - Transferred to ICU and started on Dexamethasone 6mg daily
 - Over the next several days remains on NRB with intermittent self proning and occasional desaturations
- HD 9 – Increased WOB and significantly elevated D-dimer

D-Dimer (normal <241 ng/mL)

9/26/2020 1148	9/28/2020 0518	10/2/2020 0239	10/5/2020 0334	10/8/2020 0228
221 *	210 *	812 * ▲	6,232 * ▲	3,458 * ▲



Next step?

Dr. Timothy Fernandes, UCSD Pulmonary and Critical Care

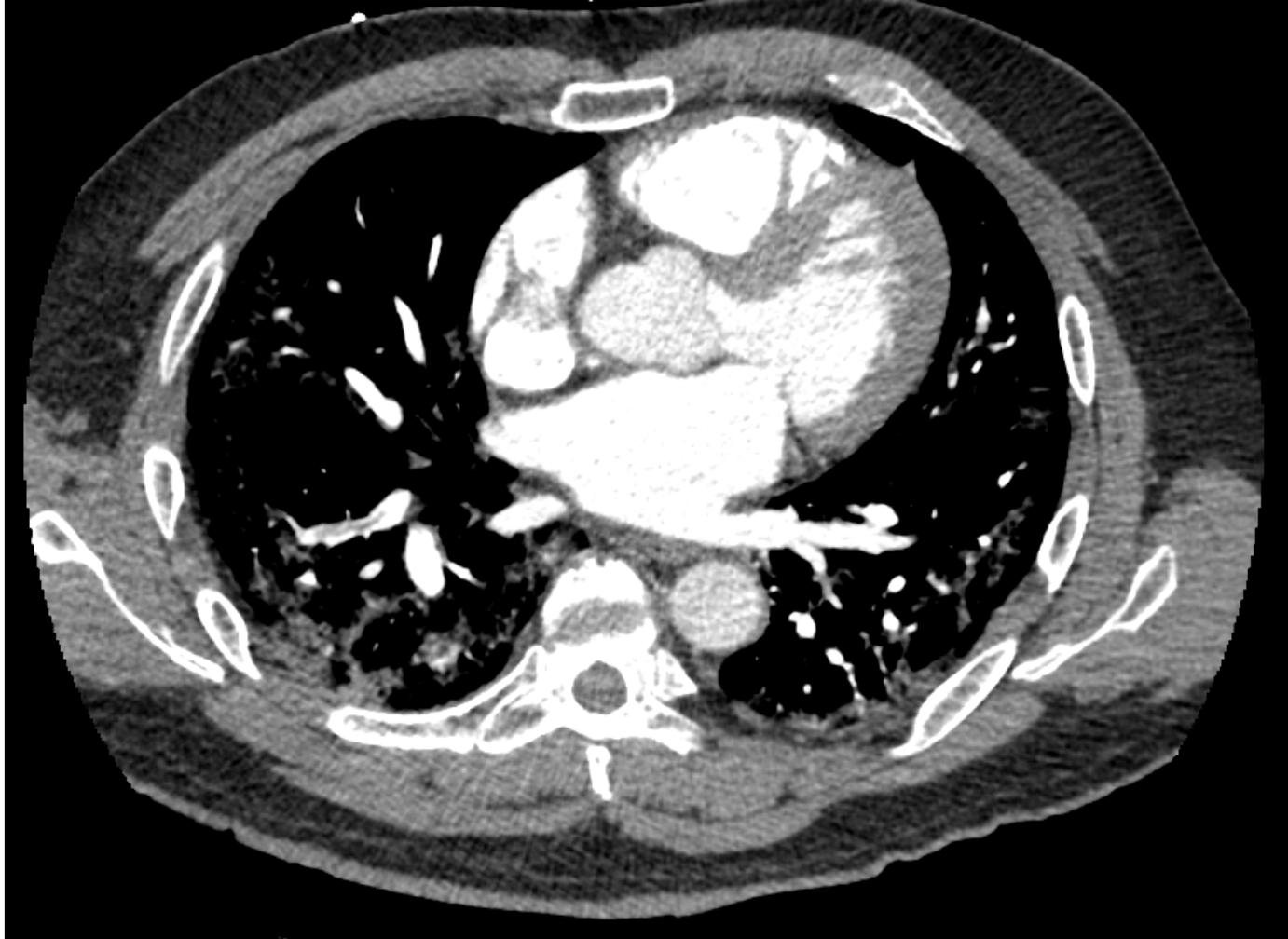
Dr. Richard Channick, UCLA Pulmonary and Critical Care

Dr. Victor Tapon, Cedars-Sinai Pulmonary and Critical Care

Dr. Nicolas Gallastegui Crestani, MD UCSD Hematology

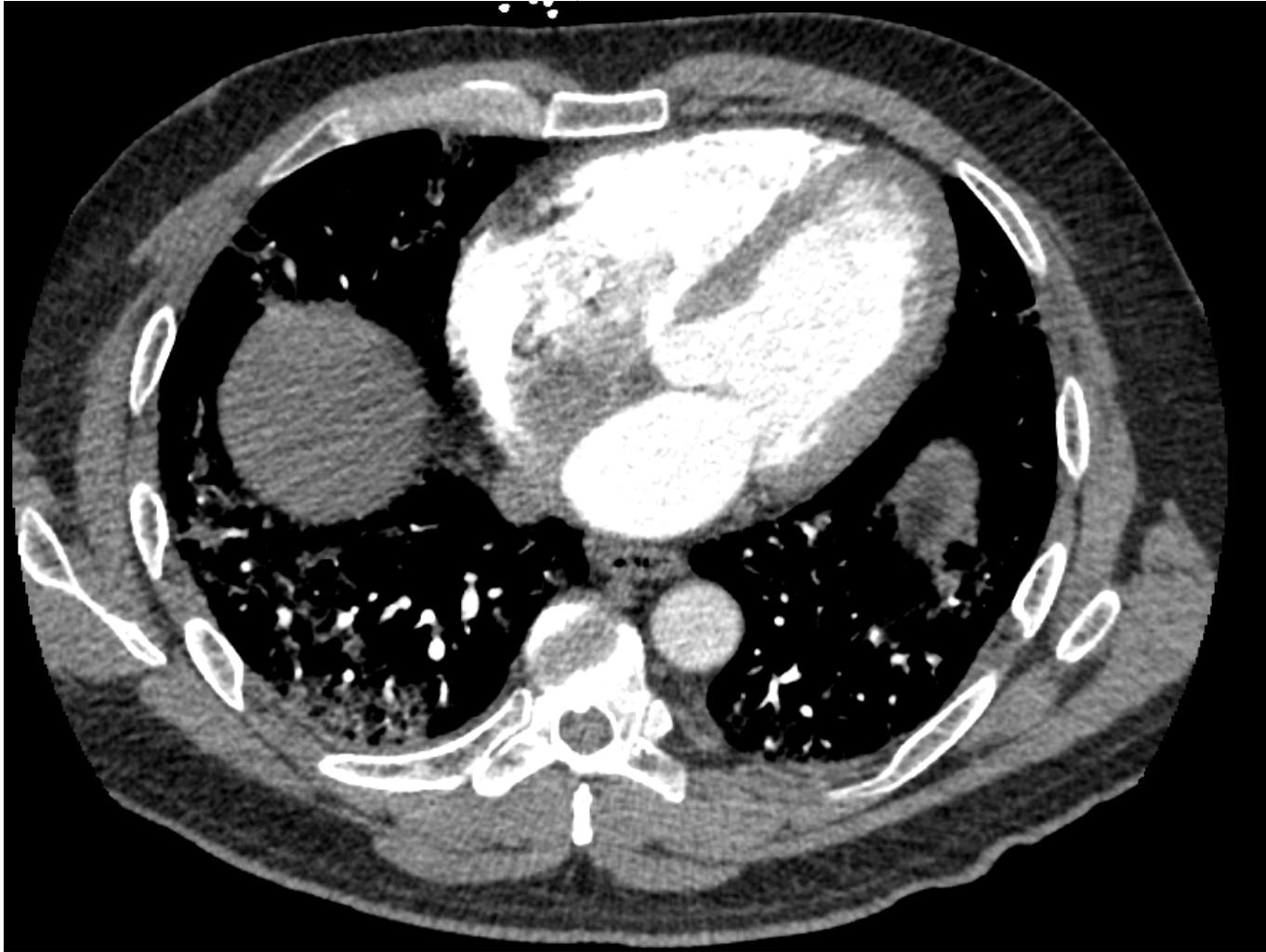


Case 1, CT slide 1





Case 1, CT slide 2





Case 1, CT slide 3





Hospital course

- Rx Heparin IV
- LE US: No evidence of DVT
- Oxygen gradually weaned down to NC
- HD 11 Transferred out of the ICU
- Transitioned from Heparin to Apixiban
- HD 15 Discharged home on RA



Comments

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Case #2



Case presentation #2

- 34 yo man
 - Poorly controlled non-insulin dependent T2DM
 - HTN
- Transferred from OSH with COVID-19 ARDS for consideration of VV-ECMO

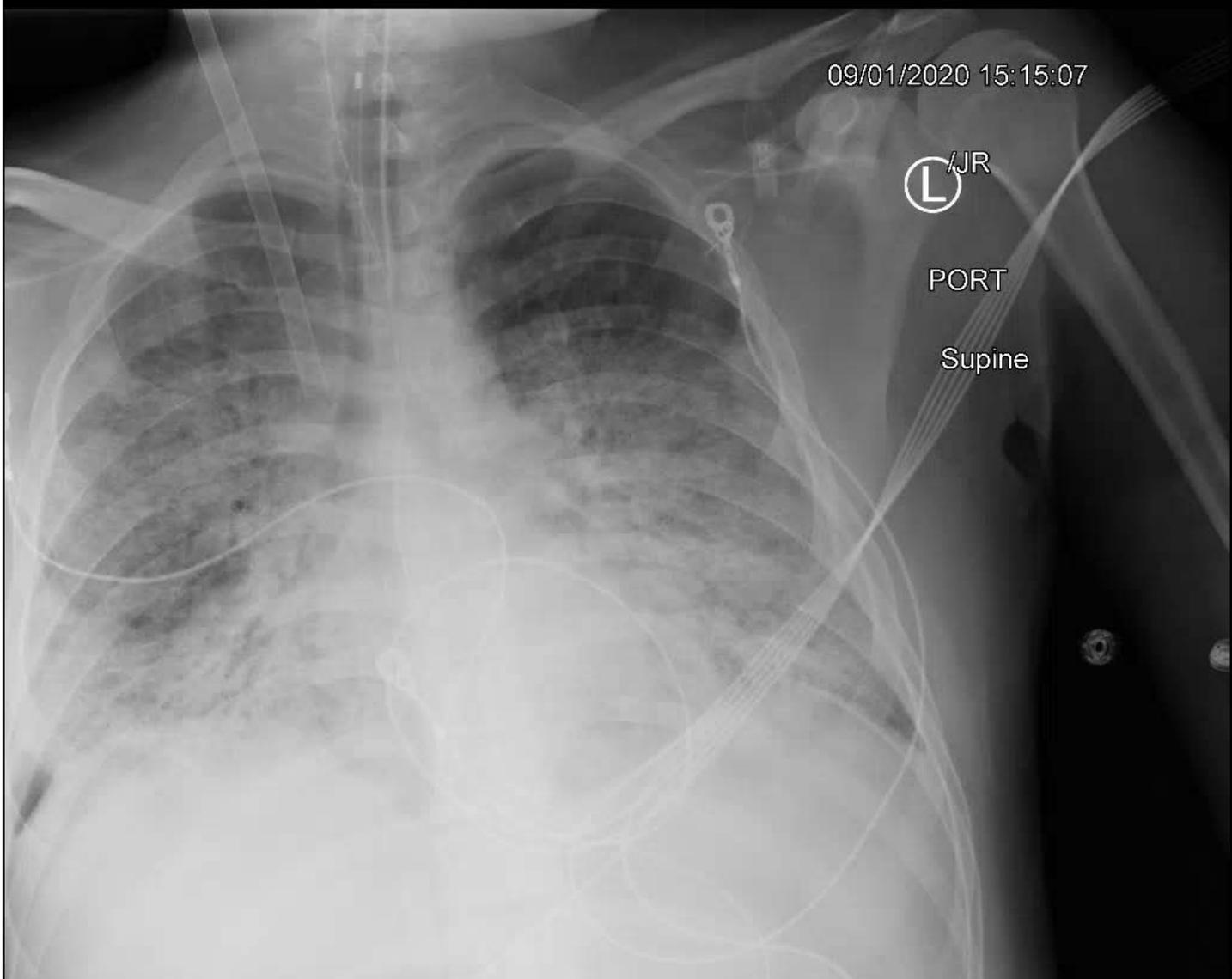


Hospital course

- Admitted to OSH after 1 week of dyspnea
- Received Remdesivir, Dexamethasone and convalescent plasma
- HD 12 Intubated
- HD 15 Transferred to UCSD



CXR





Continued

- HD 16 Cannulated for VV-ECMO (P/F = 55)
 - Started on Heparin gtt (goal Xa 0.11-0.3)

- HD 26 Percutaneous tracheostomy
 - HD 26-29 Heparin held due to oozing from trach site

- HD 30-60 Required ECMO flows of ~6L/min and Sweep 6-8 lpm,
 - pulmonary compliance ~10-20 ml/cmH₂O



Continued

- HD 57 acute episode of hypotension
 - Previously on no vasopressors now requiring norepinephrine 26mcg/min, epinephrine 0.06mcg/kg/min, and phenylephrine 200mcg/min despite IVF boluses
- Unstable for transport



Next step?

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Dr. Richard Channick, UCLA Pulmonary and Critical Care

Dr. Victor Tapon, Cedars-Sinai Pulmonary and Critical Care

Dr. Nicolas Gallastegui Crestani, MD UCSD Hematology

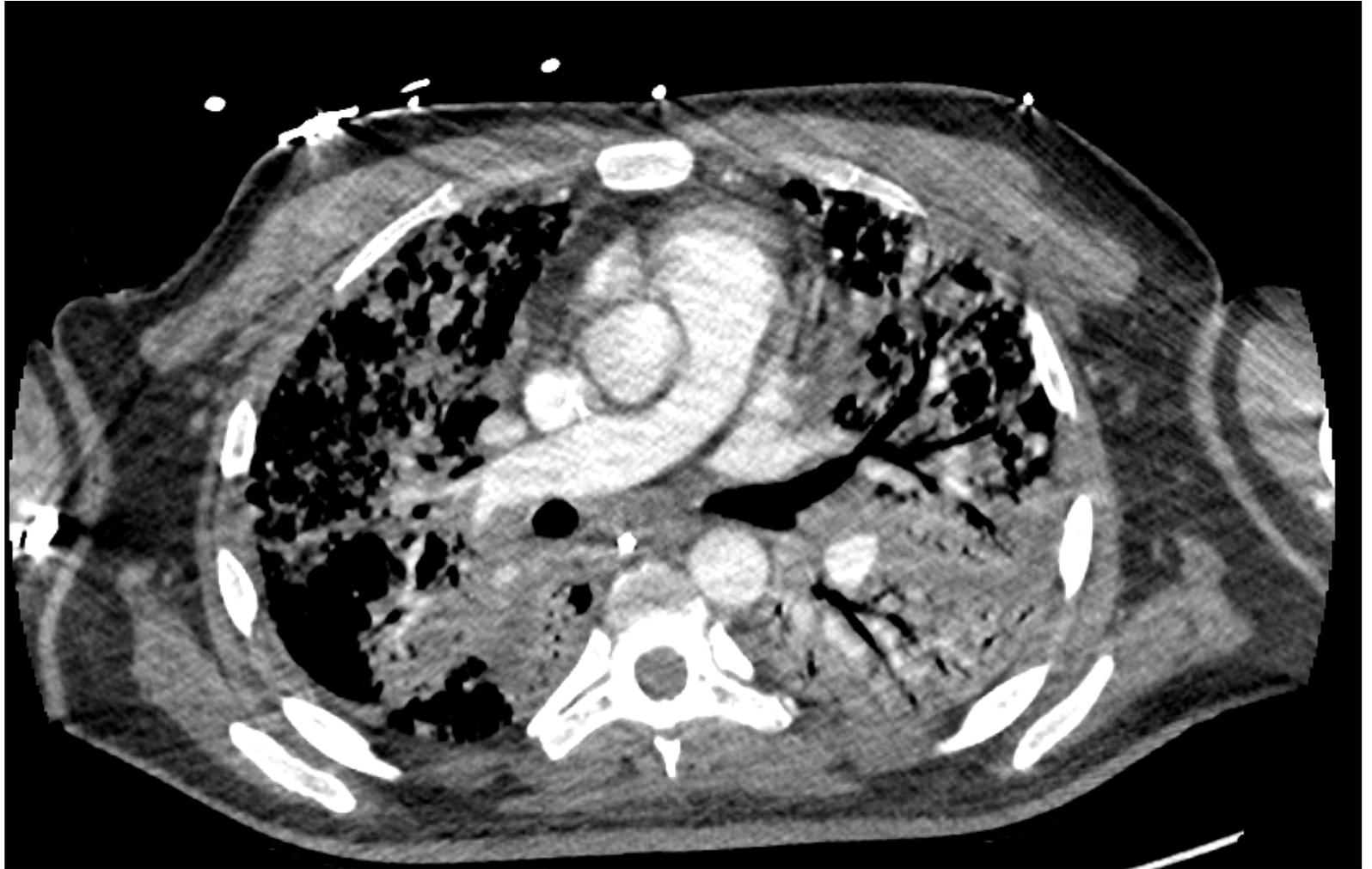


Continued

- Concern for possible PE
 - Empiric treatment with therapeutic heparin (Xa 0.2-0.45)

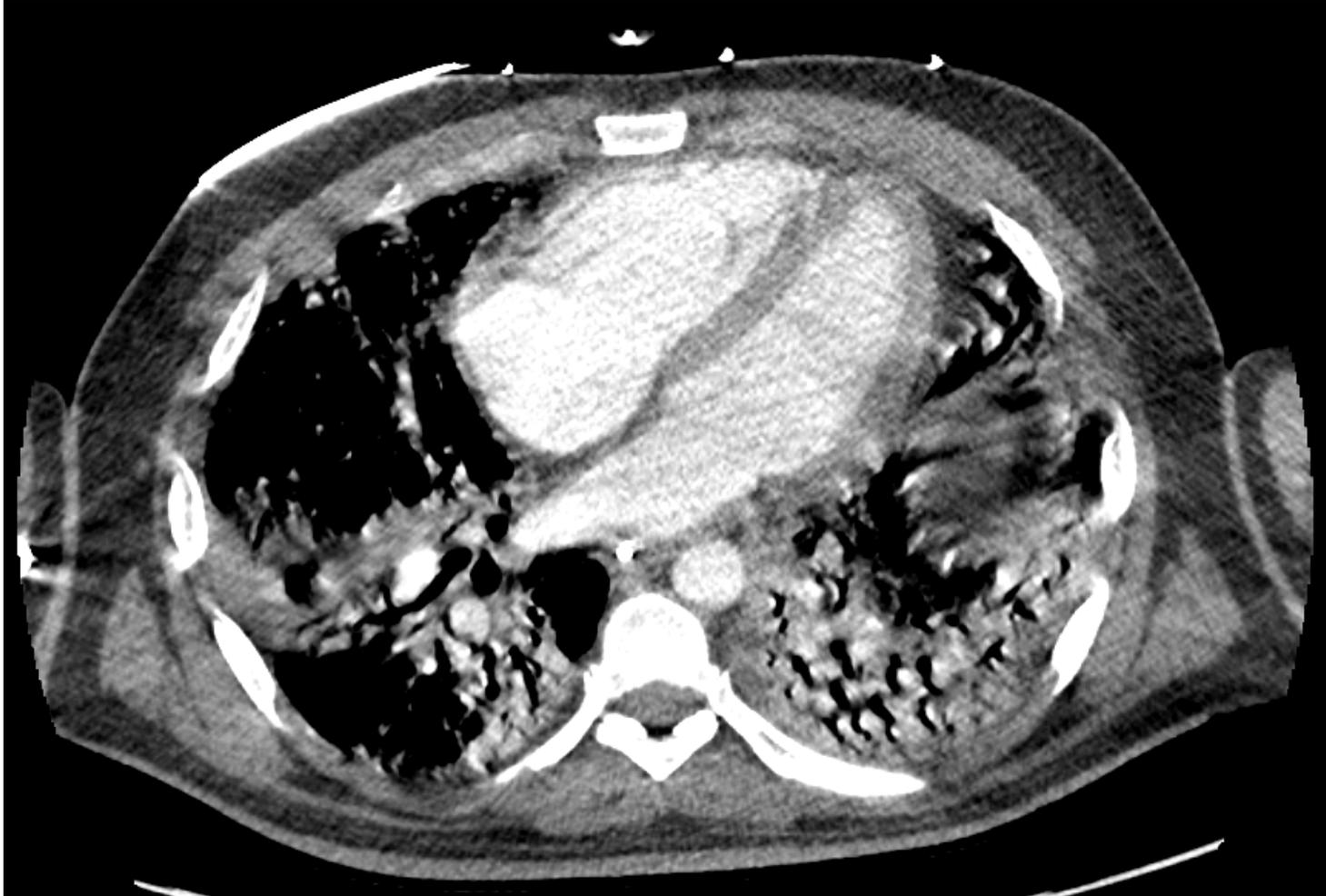


Case 2, CT slide 1





Case 2, CT slide 2



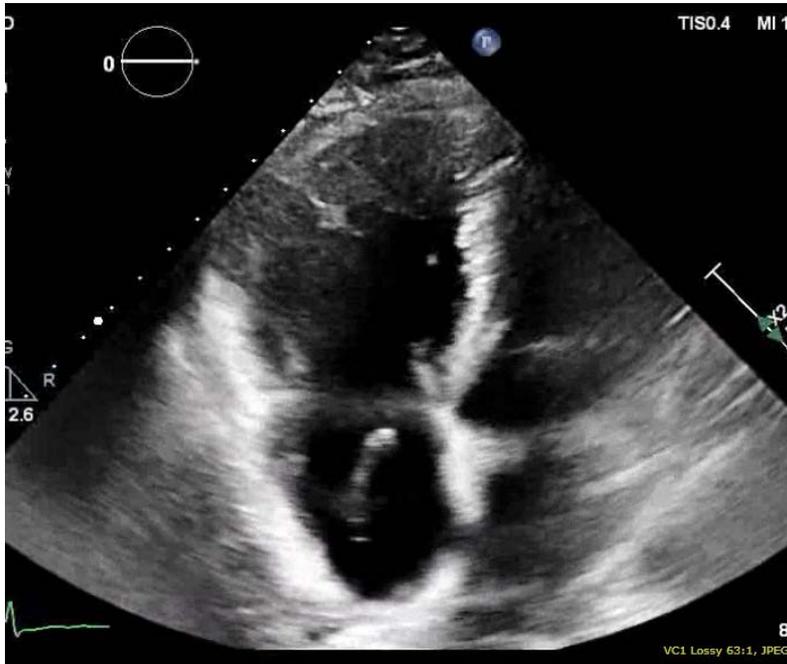


Case 2, CT slide 3





Echocardiogram





Hospital course

- Serial TTE with continued concern for RV thrombus
- Platelets drop from ~250 -> 120 over 4 days
 - PF4 0.446 (normal <0.400 OD) -> transitioned to bivalirudin gtt (Goal PTT 60 to 90 seconds)



Next step?

Dr. Timothy Fernandes, UCSD Pulmonary and Critical Care

Dr. Richard Channick, UCLA Pulmonary and Critical Care

Dr. Victor Tapon, Cedars-Sinai Pulmonary and Critical Care

Dr. Nicolas Gallastegui Crestani, MD UCSD Hematology



Hospital course

- HD 66 - Patient's left pupil is fixed and dilated



CT Head





Hospital course

- HD 71 – Transitioned to Comfort Care



Comments

Dr. Timothy Fernandes, UCSD Pulmonary and Critical Care

Dr. Richard Channick, UCLA Pulmonary and Critical Care

Dr. Victor Tapon, Cedars-Sinai Pulmonary and Critical Care

Dr. Nicolas Gallastegui Crestani, MD UCSD Hematology



Open discussion: COVID-19 and PE

