Icahn School of Medicine at Mount Sinai

Management of COVID-19: Anticoagulation IL-6 Inhibitors

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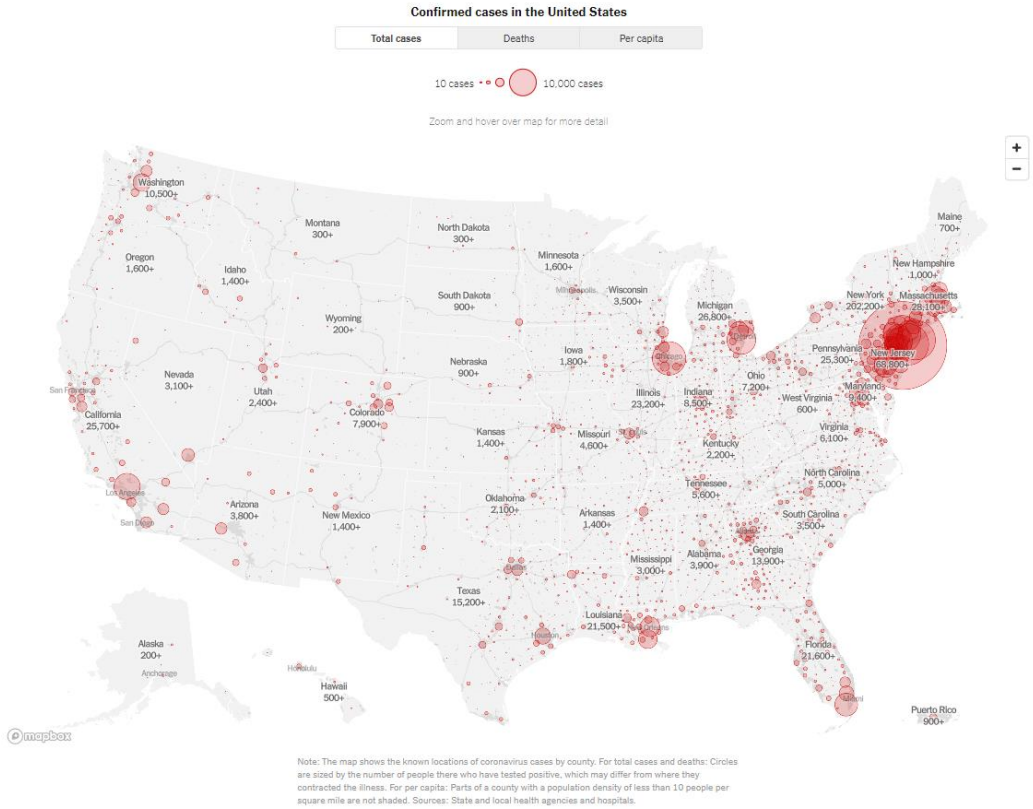
Mount Sinai West

Objectives

- Describe the pathophysiology of COVID-19 infection
- Appraise evidence for use of anticoagulation in patients with COVID-19
- Discuss potential algorithm for use of anticoagulation
- Describe early experience with IL-6 inhibitors and steroid

SBAR: SITUATION

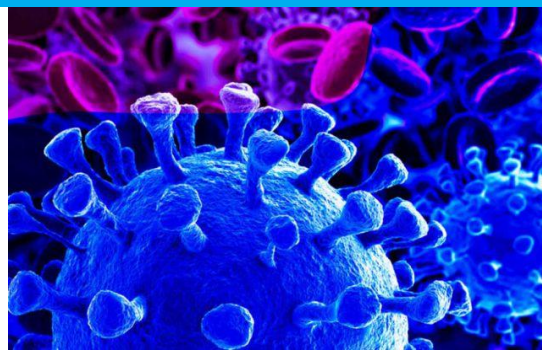


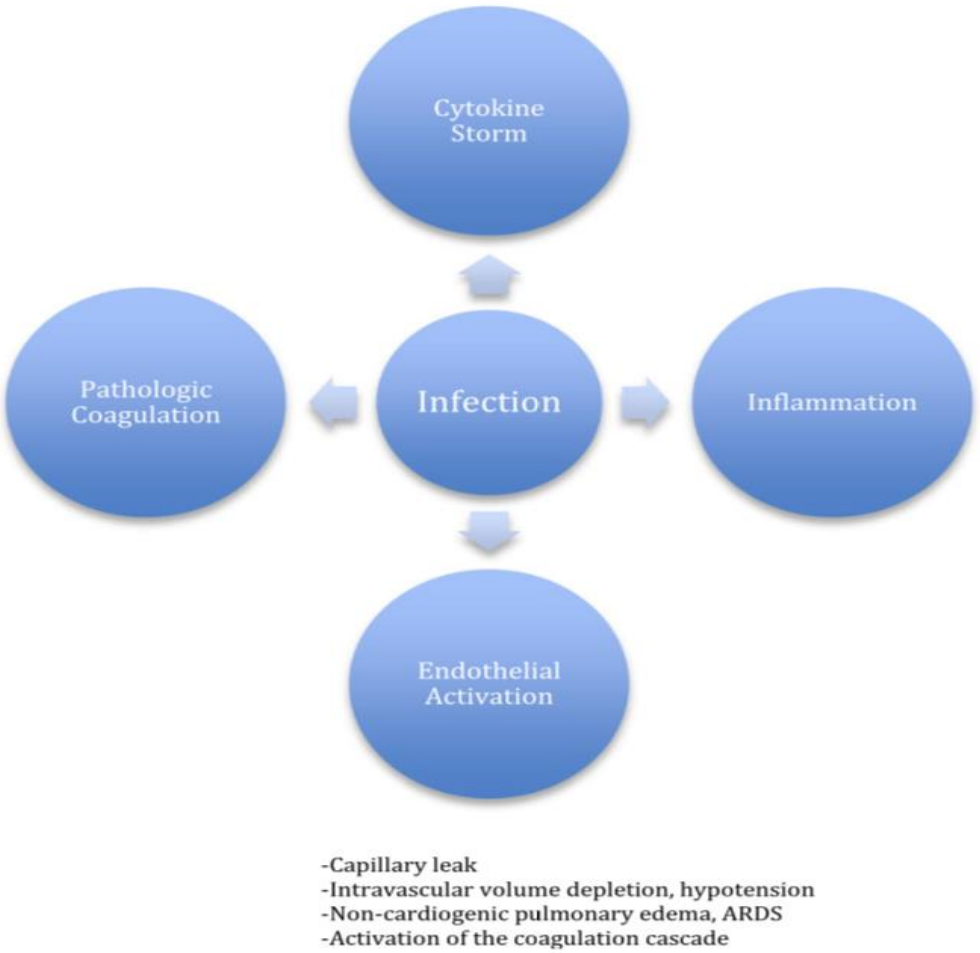
	Total Cases	Deaths
USA	606,800	25,922
NYS	202,208	10,834
NYC	110,465	7,690
Nassau	25,250	1,217
Suffolk	22,462	617
Westchester	20,191	654
Rockland	8,335	192
Orange	5,578	129
Dutchess	1,934	41
Erie	1,668	99

NY Times Interactive Map. Accessed 4/14/2020

Background

-Vasodilation
-Hypotension
-Capillary leak
-Non-cardiogenic pulmonary edema, ARDS





-Microcirculatory clot
-Tisssue hypoperfusion
-Organ failure

-Capillary leak
-Non-cardiogenic pulmonary edema, ARDS

-Capillary leak
-Intravascular volume depletion, hypotension
-Non-cardiogenic pulmonary edema, ARDS
-Activation of the coagulation cascade

ICU Management:
Supportive care, ARDS management, acetaminophen, hydroxychloroquine

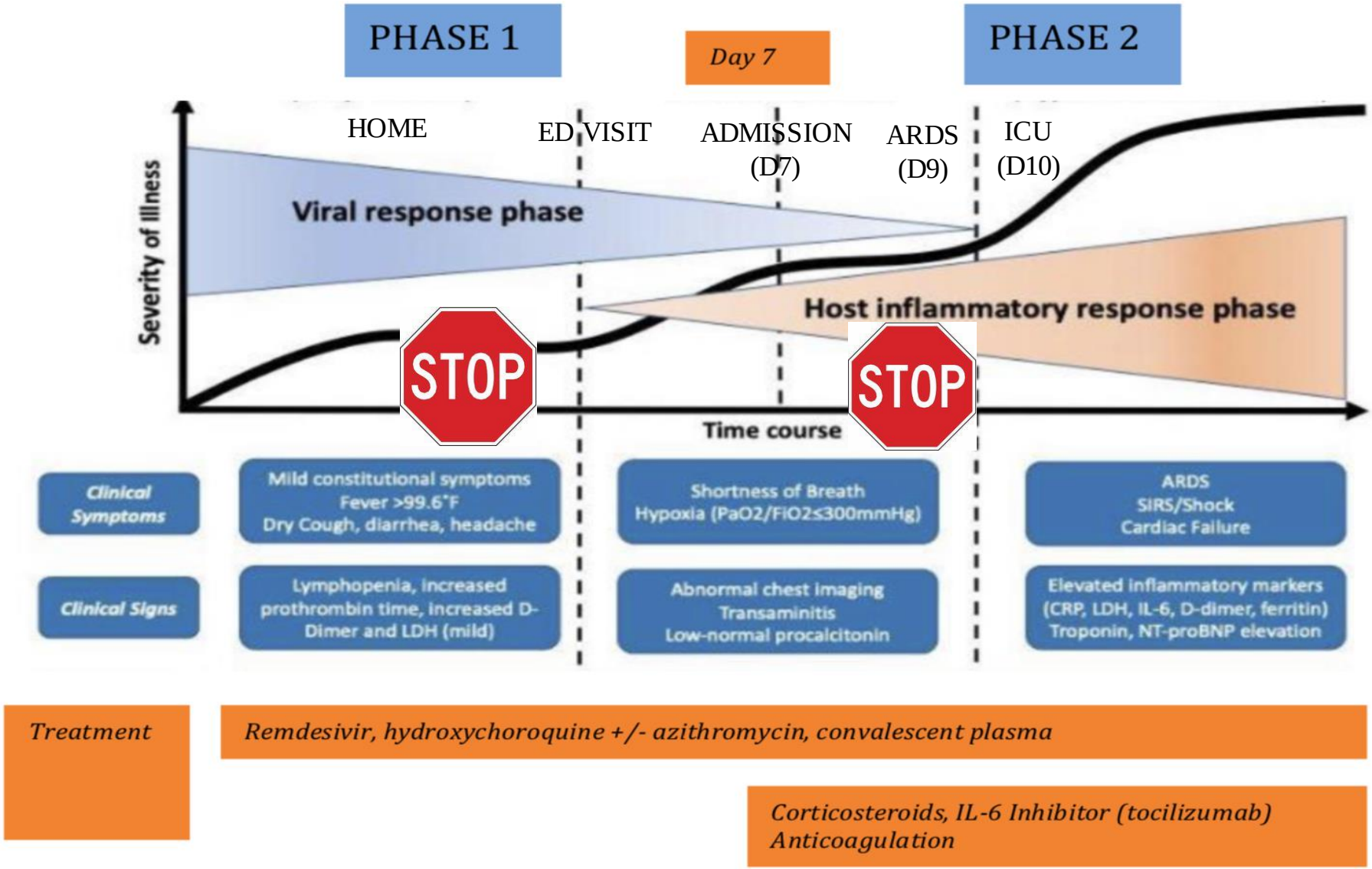
Keith et al. Critical Care (2020) 24:128

Assessment: Think Outside the Box

Figure 1. Fluorescent Dye Expelled from a Simulated Patient Cough That Ended Up on the Laryngoscopist.

Canelli R & Connor C. NEJM 2020

BACKGROUND: ICU JOURNEY



Huang C. Lancet 2020;395:497-506

Early Observations

- High incidence of acute kidney injury
- Hemodialysis catheters clotting constantly
  - Multiple catheters
  - Blood and supplies wasted
- DVTs despite standard VTE prophylaxis
- Elevated D-dimers - >20 µg/mL [normal <0.5 µg/mL]
- Elevated fibrinogen, normal platelets

- First death: sudden cardiac arrest in patient whose respiratory status was improving
- Autopsy: Saddle PE

Data from Wuhan

Table 2. Radiographic and Laboratory Findings.*

Variable	All Patients (N=1099)	Disease Severity		Presence of Composite Primary End Point	
		Nonsevere (N=926)	Severe (N=173)	Yes (N=67)	No (N=1032)
Platelet count					
Median (IQR) — per mm^3	168,000 (132,000–207,000)	172,000 (139,000–212,000)	137,500 (99,000–179,500)	156,500 (114,200–195,000)	169,000 (133,000–207,000)
Distribution — no./total no. (%)					
<150,000 per mm^3	315/869 (36.2)	225/713 (31.6)	90/156 (57.7)	27/58 (46.6)	288/811 (35.5)
Median hemoglobin (IQR) — g/dl‡	13.4 (11.9–14.8)	13.5 (12.0–14.8)	12.8 (11.2–14.1)	12.5 (10.5–14.0)	13.4 (12.0–14.8)
Distribution of other findings — no./total no. (%)					
C-reactive protein ≥10 mg/liter	481/793 (60.7)	371/658 (56.4)	110/135 (81.5)	41/45 (91.1)	440/748 (58.8)
Procalcitonin ≥0.5 ng/ml	35/633 (5.5)	19/516 (3.7)	16/117 (13.7)	12/50 (24.0)	23/583 (3.9)
Lactate dehydrogenase ≥250 U/liter	277/675 (41.0)	205/551 (37.2)	72/124 (58.1)	31/44 (70.5)	246/631 (39.0)
Aspartate aminotransferase >40 U/liter	168/757 (22.2)	112/615 (18.2)	56/142 (39.4)	26/52 (50.0)	142/705 (20.1)
Alanine aminotransferase >40 U/liter	158/741 (21.3)	120/606 (19.8)	38/135 (28.1)	20/49 (40.8)	138/692 (19.9)
Total bilirubin >17.1 μmol/liter	76/722 (10.5)	59/594 (9.9)	17/128 (13.3)	10/48 (20.8)	66/674 (9.8)
Creatine kinase ≥200 U/liter	90/657 (13.7)	67/536 (12.5)	23/121 (19.0)	12/46 (26.1)	78/611 (12.8)
Creatinine ≥133 μmol/liter	12/752 (1.6)	6/614 (1.0)	6/138 (4.3)	5/52 (9.6)	7/700 (1.0)
D-dimer ≥0.5 mg/liter	260/560 (46.4)	195/451 (43.2)	65/109 (59.6)	34/49 (69.4)	226/511 (44.2)

Data from Wuhan

D-Dimer		ICU	Non-ICU
Huang, Lancet 2020 (n=41)	D-dimer	2.4 µg/ml	0.5 µg/ml
Wang, JAMA 2020 (n=138)	D-dimer	414 mg/l	166 mg/L

D-Dimer		Non-survivor	Survivor
Tang, JTH 2020 (n=183)	D-dimer	2.12 µg/ml	0.66 µg/ml
	PT	15.5 sec	13.6 sec
	FDP	7.6 µg/ml	4.0 ug/ml

- Cui S. Brief report. JTH 2020 (n=81)
- 25% of patients (20/81) had VTE; 8 out of 20 patients died
- D-dimer 1.5 µg/ml – sensititivy 85% and specificity 85%
- Higher D-dimer in non-survivors (5.2 vs. 0.8)

Anticoagulation in COVID-19

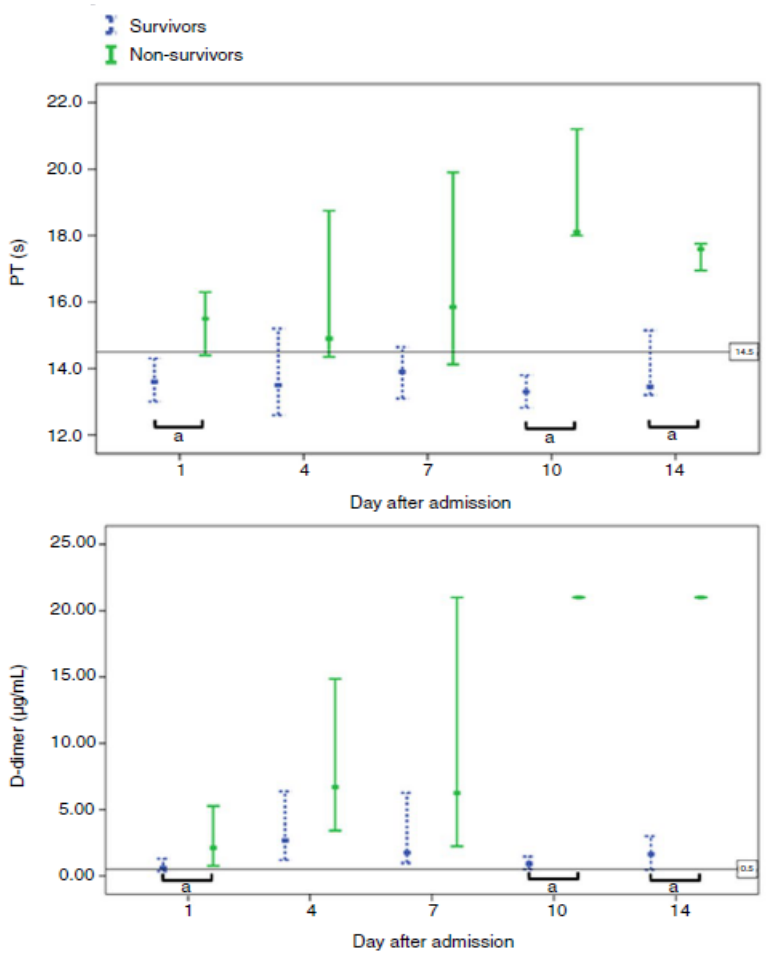
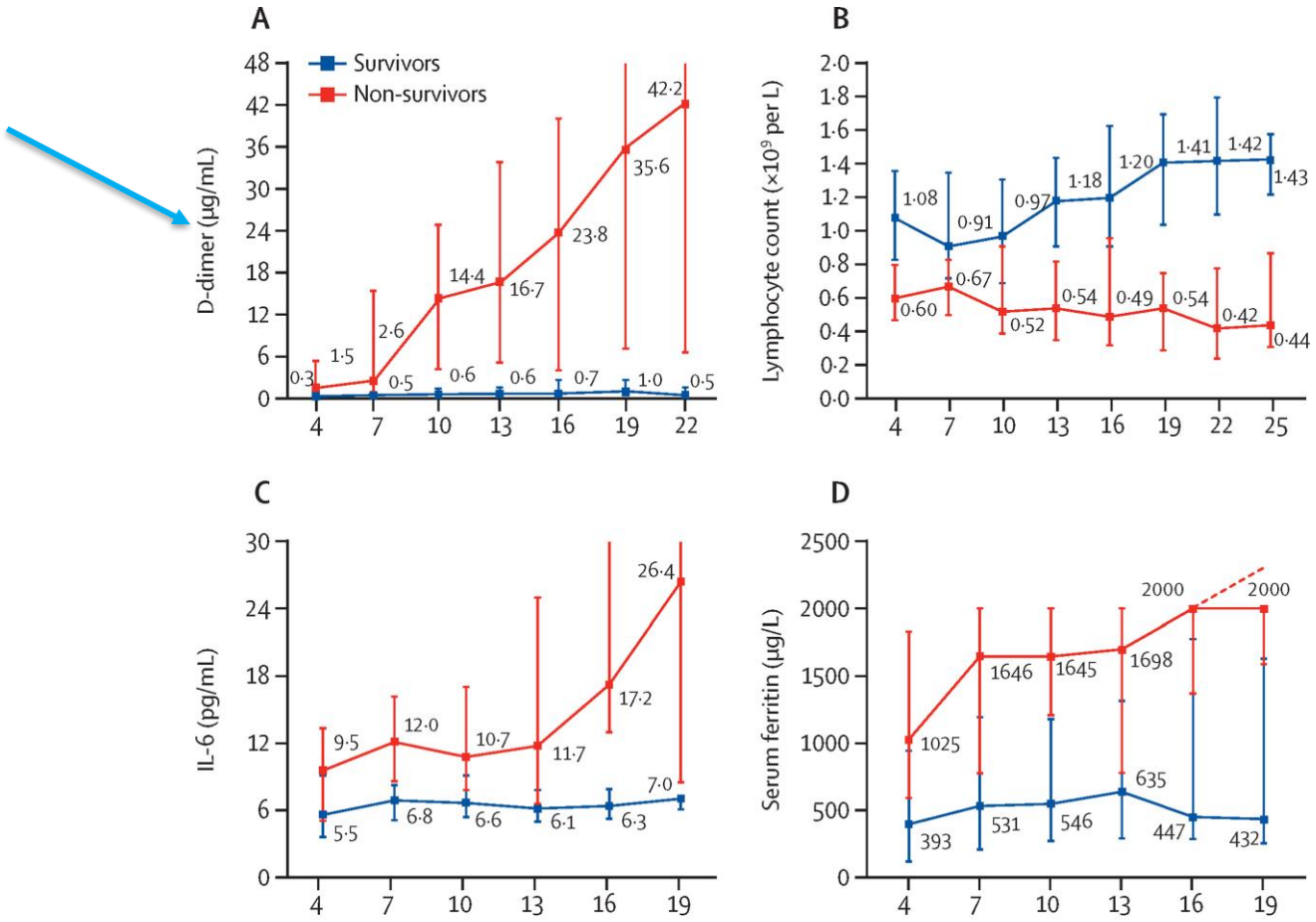


TABLE 2 The grade of DIC in non-survivors with NCP (n = 21)

	Number of patients (%)
Platelet counts (×10⁹/L)	
50-100 (1 point)	7 (33.3)
<50 (2 points)	5 (23.8)
D-dimer (μg/mL)	
1.0-3.0 (2 points)	3 (14.3)
>3.0 (3 points)	18 (85.7)
Fibrinogen (g/L)	
<1.0 (1 point)	6 (28.6)
Prolongation of PT (sec)	
3-6 (1 point)	5 (23.8)
>6 (2 points)	10 (47.6)
Meeting the ISTH criteria of DIC (Total points ≥5)	15 (71.4)

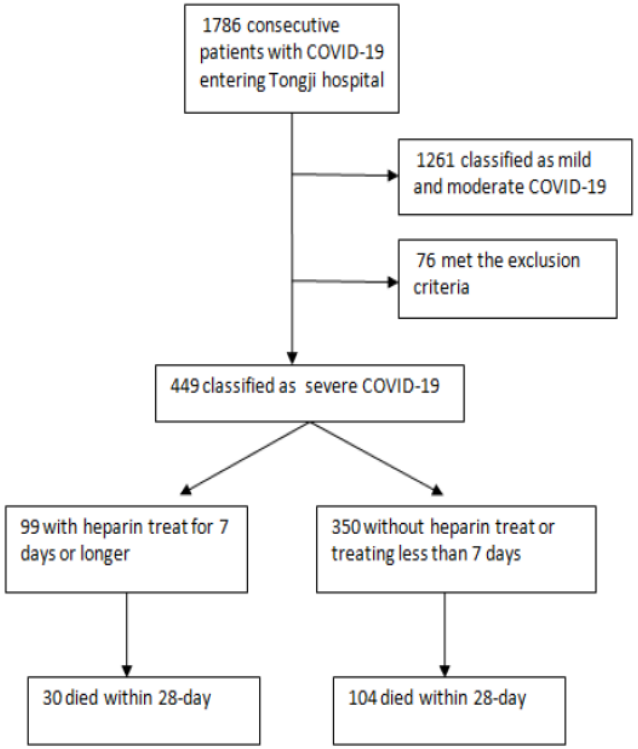
Tang N. J Thromb Haemost 2020;18:844-847

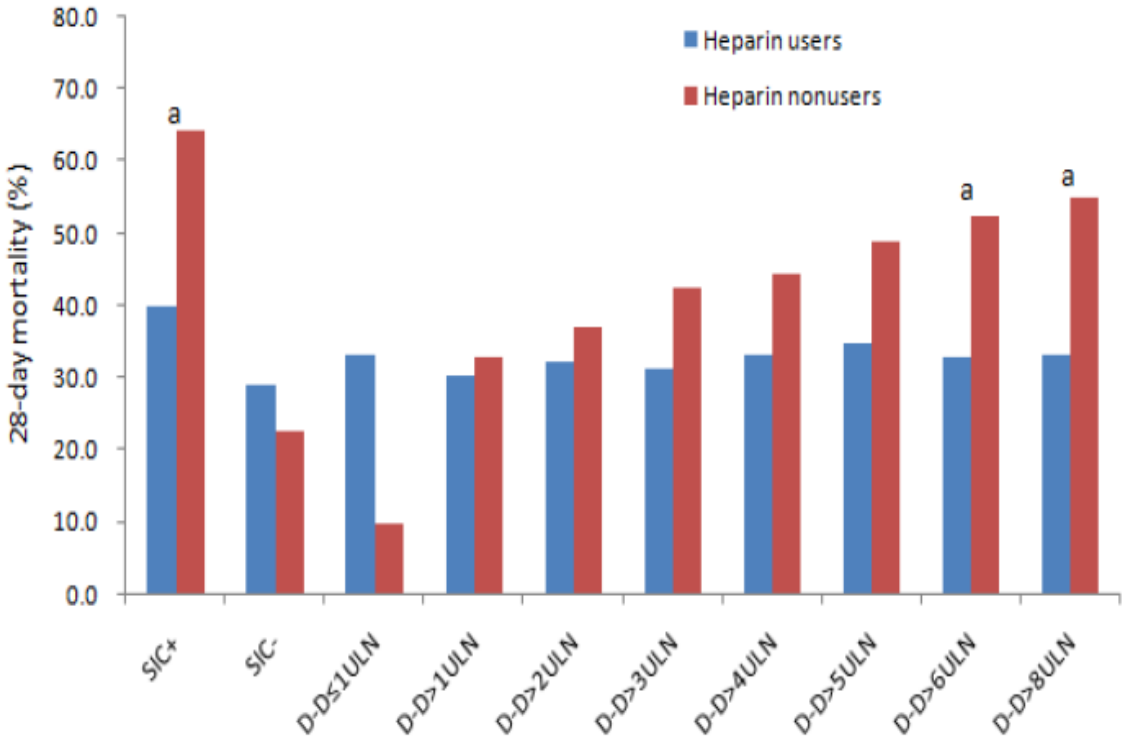


	Total	Non-survivor	Survivor
D-dimer > 1 ug/ml	72/172 (42%)	44/54 (81%)	28/118 (24%
Platelet count	206	165	220
IL-6 pg/ml	7.4	11	6.3

Zhou. The Lancet 2020 3951054-1062

Anticoagulation Associated with Decreased Mortality in COVID-19





- 28-day mortality of heparin users lower than non-users in patients with sepsis induced coagulopathy (SIC) score ≥4 or D-dimer >3μg/ml
- SIC score: PT, platelet, SOFA score
- Heparin treatment (>7d) associated with better prognosis in severe COVID-19 patients with coagulopathy
- Criticisms: Retrospective, other Tx, dose, ?no heparin

Tang N. JTH 202. doi:10.1111?JTH.14817

Autopsy Series

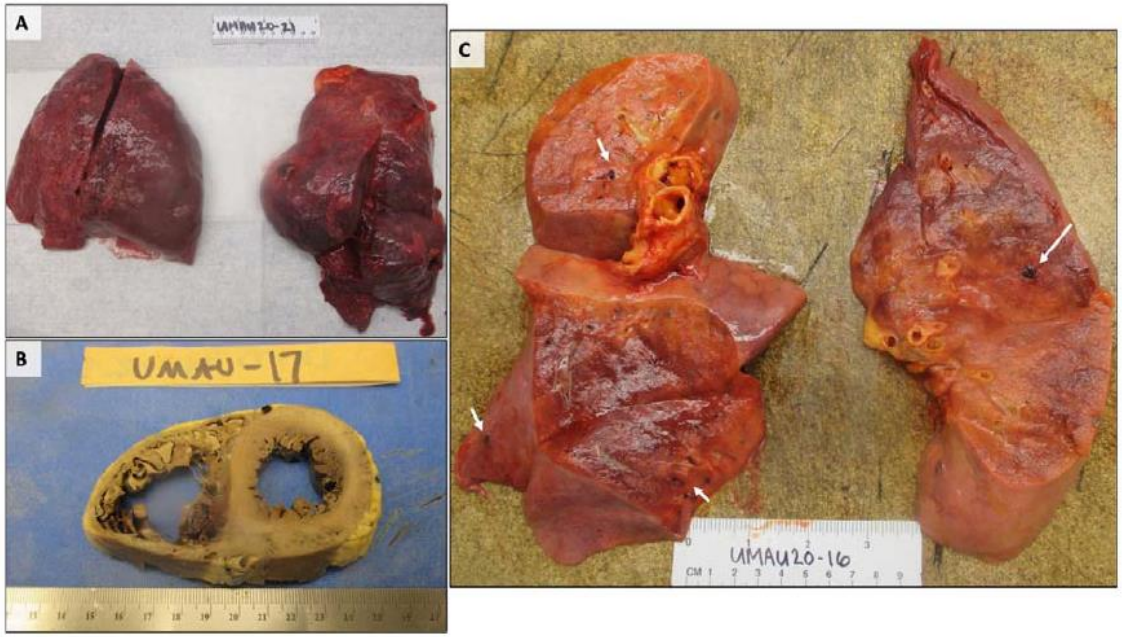
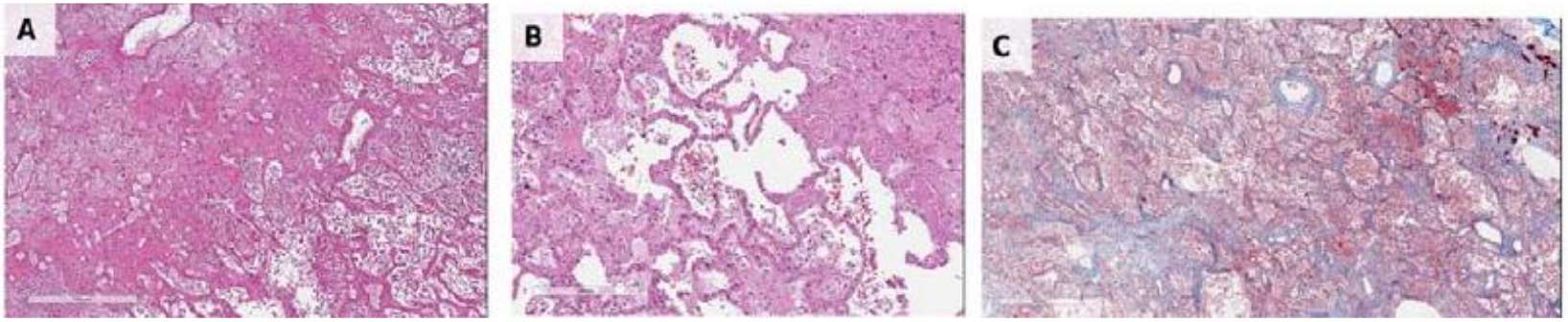


FIGURE 1: Gross Findings of the Lungs and Heart. A) Lungs with bilateral pulmonary edema and patches of dark hemorrhage, and **B)** A heart showing extreme right ventricular dilatation, with straightening of the interventricular septum. **C)** Cut sections of lung showing thrombi present within peripheral small vessels (white arrows).



Thrombotic microangiopathy restricted to lungs. Small vessel thrombus formation in lung periphery with associated foci of alveolar hemorrhage

Fox S. MedRxiv preprint.

Response: Mount Sinai COVID-19 Anticoagulation Algorithm

Rationale for early anticoagulation

- Pathophysiology of COVID-19 associated respiratory disease is consistent with pulmonary vascular thromboemboli with increased dead space ventilation
- Autopsy studies have demonstrated venous thromboembolism in deceased coronavirus patients[1]
- Early anticoagulation is necessary to prevent propagation of microthrombi at disease presentation
- Anticoagulation may be associated with decreased mortality[2]

Rationale for choice of anticoagulant

- Heparins bind tightly to COVID-19 spike proteins[3,4]
- Heparins also downregulate IL-6 and directly dampen immune activation[5]
- DOACs do not appear to have these anti-inflammatory properties
- Rivaroxaban can be used in place of Apixaban in this algorithm

Definition of high risk for progression to ICU

- There is insufficient evidence to precisely define “high-risk” or provide specific cut-off values for individual factors
- Clinicians should consider a combination of exam findings (e.g, labored breathing, RR >24, decreased O_2 sat<90%), increased O_2 requirement (eg, ≥4L NC), and lab biomarkers (eg, elevated CRP, elevated creatinine, rising d-dimer >1.0).

References

1. Xiang-Hua et al. Am J Respir Crit Care Med, 182 (3), 436-7. PMID: 20675682
2. Tang et al. J Thromb Haemost 2020 Mar 27. PMID: 32220112
3. Belouzard et al. Proc Natl Acad Sci, 2009 106 (14), 5871-6. PMID: 19321428
4. de Haan et al. J Virol. 2005 Nov; 79(22): 14451–14456. PMID: 16254381
5. Mummery et al. J Immunol, 2000. 165 (10), 5671-9. PMID: 1106792

Mount Sinai COVID-19 Anticoagulation Algorithm

Version: April 8, 2020

Admitted patients with moderate or severe COVID-19

High Risk#
↑ O_2 requirement
↑ D-dimers
↑ creatinine
↑ CRP

No → **Apixaban 2.5-5mg PO BID^ or Enoxaparin SC 40mg QD**

Yes → Admitted to an ICU?

Yes → **Heparin drip per PE protocol (goal PTT 70 - 110) or Enoxaparin SC 1mg/kg BID. Consider clinical trial of tPA.**

No → CrCl >50

Yes → **Enoxaparin SC 1mg/kg BID**

No → On RRT†

Yes → **Apixaban 5mg PO BID (or heparin drip per PE protocol)‡**

No → **Apixaban 5mg BID‡ or Adjusted Dose Enoxaparin***

Inclusion: All admitted patients with moderate or severe COVID-19
Exclusion: High risk of bleeding as judged by treating physician

Obtain at baseline and daily:
- CBC, PT/PTT, D-dimer

Hold anticoagulation if:
- Platelet count <50,000; INR>1.5
- Evidence of current or recent bleeding

If patients take AC at home:
- May switch to therapeutic enoxaparin or heparin (as per algorithm) for the duration of hospitalization, unless contraindicated

Rivaroxaban may be used in place of Apixaban at any indication

Discharged COVID-19 patient on therapeutic anticoagulation while hospitalized

Consider Prophylactic AC for 2 weeks post discharge (Apixaban 5mg PO BID for 2 wks)

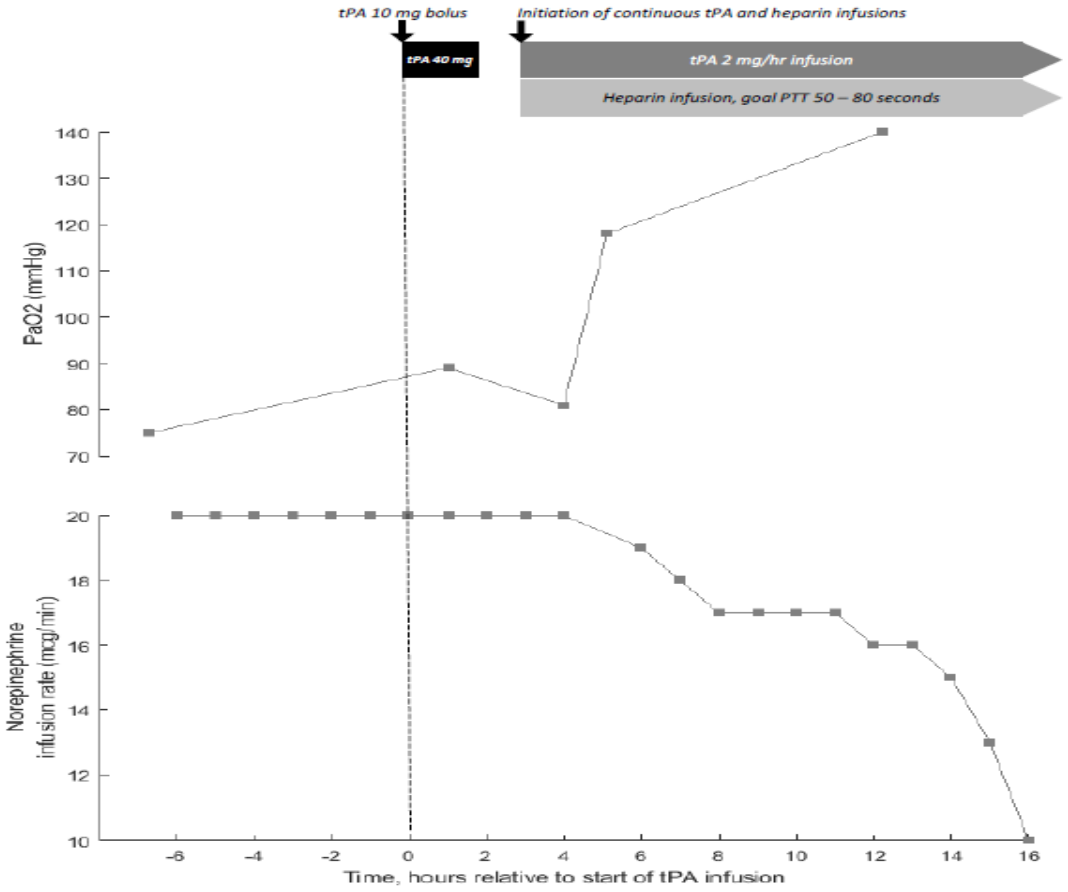
#High Risk: No precise metrics exist. Consider exam (eg O_2 sat<90%, RR >24), ↑O_2 requirement (eg, ≥4L NC), labs (eg, ↑d-dimers, C-reactive protein)
^Efficacy and dose not established; prophylactic or treatment doses acceptable

†RRT – Renal Replacement Therapy
‡ If ≥80 years of age or weight ≤60 kg, reduce apixaban to 2.5 mg BID
* If CrCl <30: enoxaparin 0.5mg/kg BID with anti-Xa level after 3rd dose

Observations Post-Anticoagulation Protocol

- Heparin infusion or enoxaparin in ICU patients
- Renal function improved in some
- CVVH much smoother process
- Aggressive VTE prophylaxis
- Monitor PTTs very closely – avoid supratherapeutic PTT
- Monitor closely for bleeding – examine patients
- Need RCTs

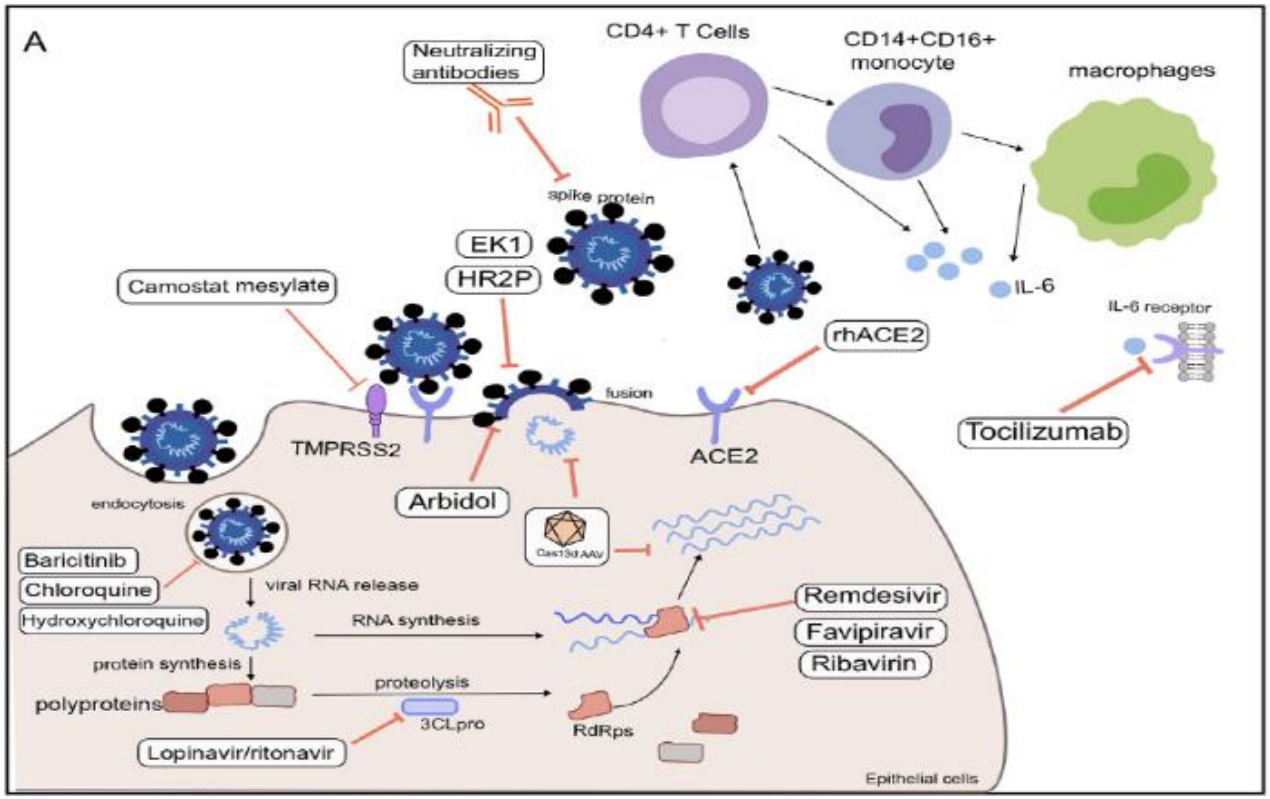
Role of Thrombolysis?



Tenecteplase randomized control trial under way at MSHS

Poor H et al. COVID-19 Critical Illness Pathophysiology Driven by Diffuse Pulmonary Thrombi and Pulmonary Endothelial Dysfunction Responsive to Thrombolysis. Pre-print.

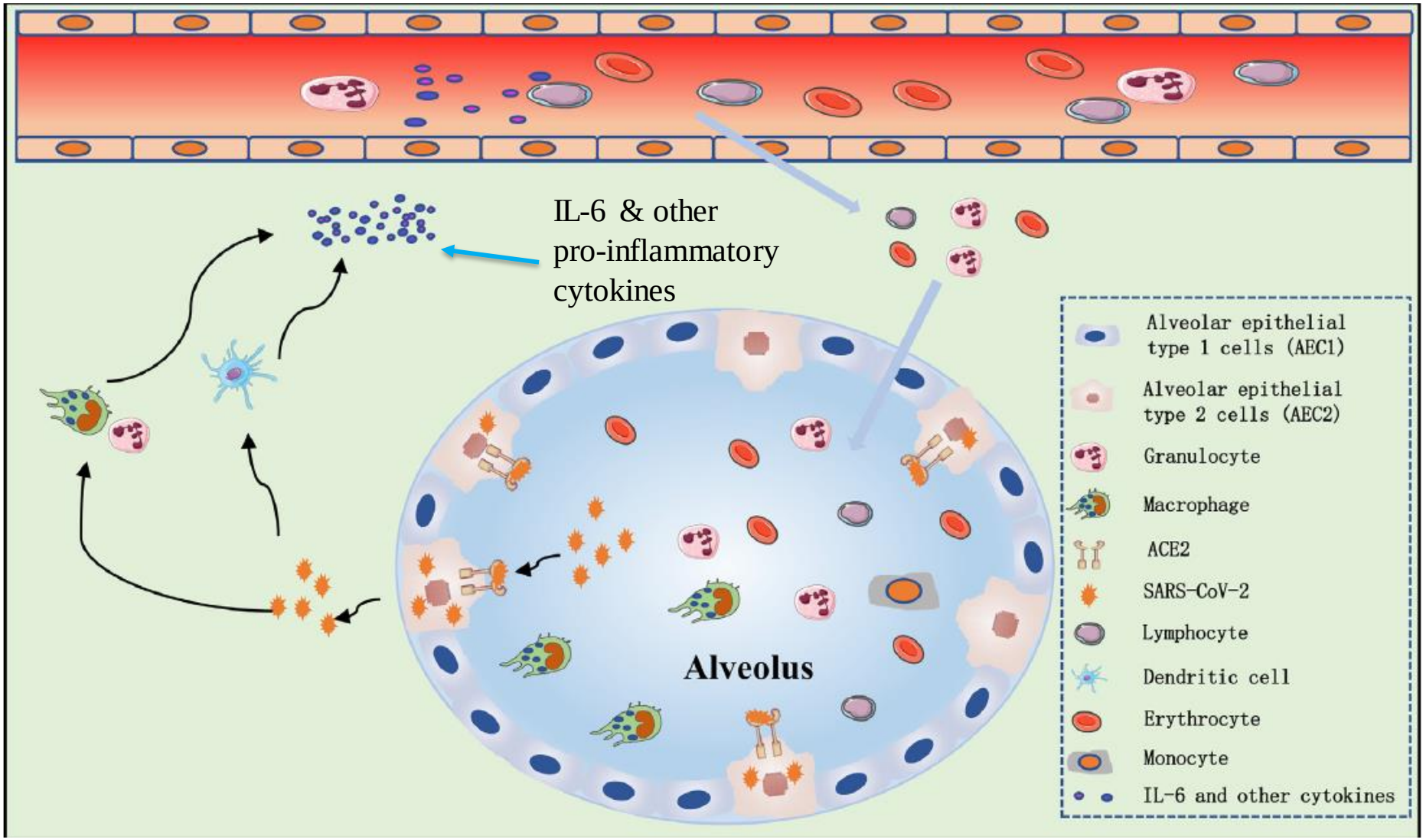
Potential Treatments for SARS-CoV-2: IL-6 Inhibitors



Haiou Li et al. Antimicrob Agents Chemother. 2020.

- Multicenter, single-arm, open-label, phase 2 study in Italy (NCT04317092)
  - 330 participants; primary outcome: 30-day mortality
- Multicenter, randomized controlled trial in China (ChiCTR2000029765)
  - Tocilizumab + standard care vs standard care, 98 participants; primary outcome: clinical cure rate
- Three arms, multi-center, randomized and controlled study for COVIA-19 patients with increased IL-6 in China (NCT04310228) - Favipiravir vs Tocilizumab vs Favipiravir Combined With Tocilizumab; 50 participants
- Sarilumab and Situximab RCTs

Cytokine Release Syndrome



Cytokine Release Syndrome

- CRS is a systemic inflammatory response, which can be caused by infection, some drugs
- Sharp increase in the level of a large number of pro-inflammatory cytokines
- More common in immune system-related diseases or immune-related therapy, such as CAR-T cell therapy, organ transplantation sepsis and viral infection
- SARS-CoV-2 bind to alveolar epithelial cells, then the virus activates innate immune system and adaptive immune system, resulting in the release of a large number of cytokines, including IL-6
- Increased vascular permeability leading to fluid and blood cells into the alveoli, resulting in dyspnea and respiratory failure
- Early stage of infectious inflammation, IL-6 is produced by monocytes and macrophages stimulated by Toll-like receptors
- IL-6 plays a central role in CRS

Zhang C. Int J of Antimicrobial Agents 2020
Stephan A. NEJM 2013;368:1509-1518

Cytokine Release Syndrome

- 2018 : FDA approved tocilizumab for severe or life-threatening CRS from chimeric antigen receptor therapy (CAR) T-cell therapy
- CRS is a medical emergency, fatal
- Retrospective analysis of trials
  - Tocilizumab, steroids
  - Patients 2 yrs to >18
  - ALL, DLBCL
  - 31/45(69% success)
  - No reports of adverse effects

Table 3. Resolution of cytokine release syndrome in the efficacy populations

Analyses	CTL019 series ($n = 45$) responders n (%, 95% CI)	KTE-C19 series ($n = 15$) responders n (%, 95% CI)
Primary analysis:		
Response by day 14	31 (68.9, 53.4–81.8)	8 (53.3, 26.6–78.7)
Additional analyses		
Response by day 2	9 (20.0, 9.6–34.6)	3 (20.0, 4.3–48.1)
Response by day 7	26 (57.8, 42.2–72.3)	8 (53.3, 26.6–78.7)
Response by day 21	31 (68.9, 53.4–81.8)	8 (53.3, 26.6–78.7)

Abbreviation: CI, confidence interval.

Li R. The Oncologist 943-947

The Holy Grail?

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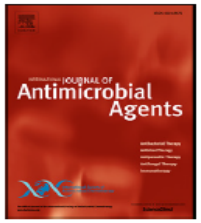

The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality ☆,☆☆

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ABSTRACT

Since December 2019, a viral pneumonia (COVID-19) from Wuhan, China has swept the world. Although the case fatality rate is not high, the number of people infected is large, and there are still a large number of patients dying. With the collation and publication of more and more clinical data, a large number of data suggest that there are mild or severe cytokine storms in severe patients, which is also an important cause of death. Therefore, the treatment of cytokine storm has become an important part of rescuing severe patients. Interleukin-6 (IL-6) plays an important role in cytokine release syndrome (CRS). If it can block the signal transduction pathway of IL-6, it is expected to become a new method for the treatment of severe patients. Tocilizumab is a blocker of IL-6R, which can effectively block IL-6 signal transduction pathway. So, tocilizumab is likely to become an effective drug for patients with severe COVID-19.

Early Experience with Tocilizumab

Baseline Characteristics	All Patients (N=24)
Mount Sinai West ICU patients non-ICU	27 24 3
Mean age (range) — yr	59.3 ± 15.8
Sex — no. (%) Male Female	 21 6
Race White African American Hispanics Asians Others	 13 4 2 5 3
Body mass index	32.8 ± 9.32
Comorbidities Hypertension Hyperlipidemia Diabetes Asthma COPD Heart failure Coronary artery disease (past NSTEMI/STEMI) Atrial fibrillation Chronic kidney disease	 15 12 8 4 2 2 2 1 1
Charlson Comorbidity Index 0 1 2 3+	 5 2 7 13
Concurrent methylprednisolone	27 (100%)
Clinical Outcomes Discharged Expired Transfer out of ICU Remain in ICU (critically ill)	 11 (40.7%) 5 (18.5%) 3 (2 HFNC, 1 NRB) 8 (6 intubated, 1 trach collar, 1 HFNC)

Early Experience with Tocilizumab

Characteristics	Before Tocilizumab (N=27)	After Tocilizumab (N=27)
Clinical Response		
O2 Support		
Nasal cannula	3	4
HFNC	6	6
BiPAP	5	4
Invasive MV	13	13
FiO2 (%, S.D)	83.8 ± 19.8	67.6 ± 18.6
Non-invasive	91.1 ± 10.9	76.8 ± 16.7
Invasive	80.5 ± 23.3	62.2 ± 19.2
Paralytics		
Yes	7	7
No	20	20
Sepsis / Organ Dysfunction Markers		
WBC	15.5 ± 7.2	10.4 ± 4.6
Renal	2.91 ± 3.3	2.6 ± 2.5
Cr		
Liver		
AST	94.1 ± 45.2	61.3 ± 27.3
ALT	73.2 ± 41.6	59.4 ± 29.2
Inflammatory Markers		
C Reactive Protein	212..9 ± 80.1	69.6 ± 44.1
Interleukin-6	463 ± 811	261 ± 323
Ferritin	2314 ± 2121	1844 ± 1518
D-dimer	4.84 ± 5.42	3.95 ± 3.23
Procalcitonin	1.88 ± 2.43	0.96 ± 0.93

Adverse Effects:
Risk of infection
GI perforation

Thank you