The Clinical Horizon of Coronavirus Treatment (Oct 12, 2020)

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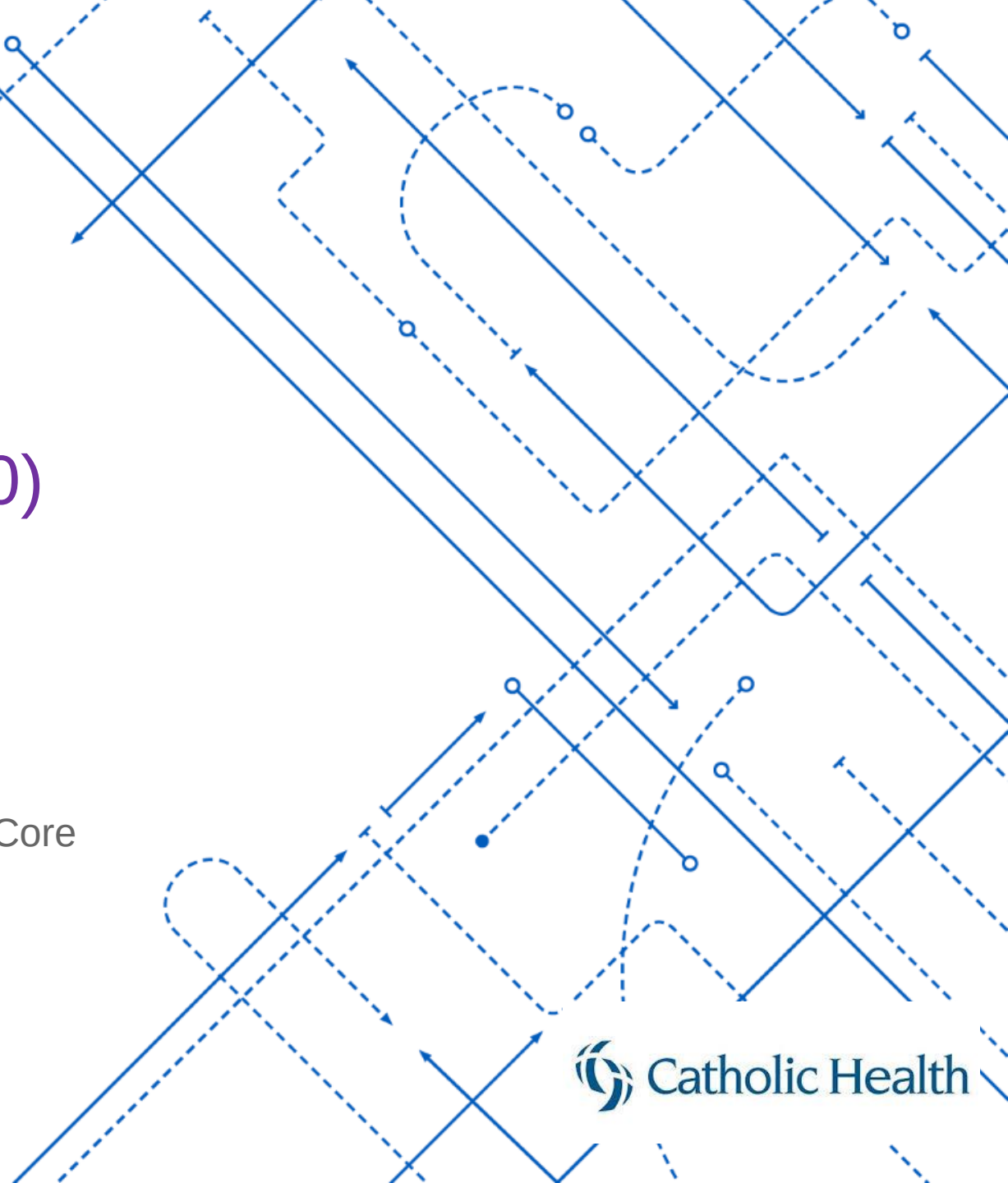


University at Buffalo The State University of New York

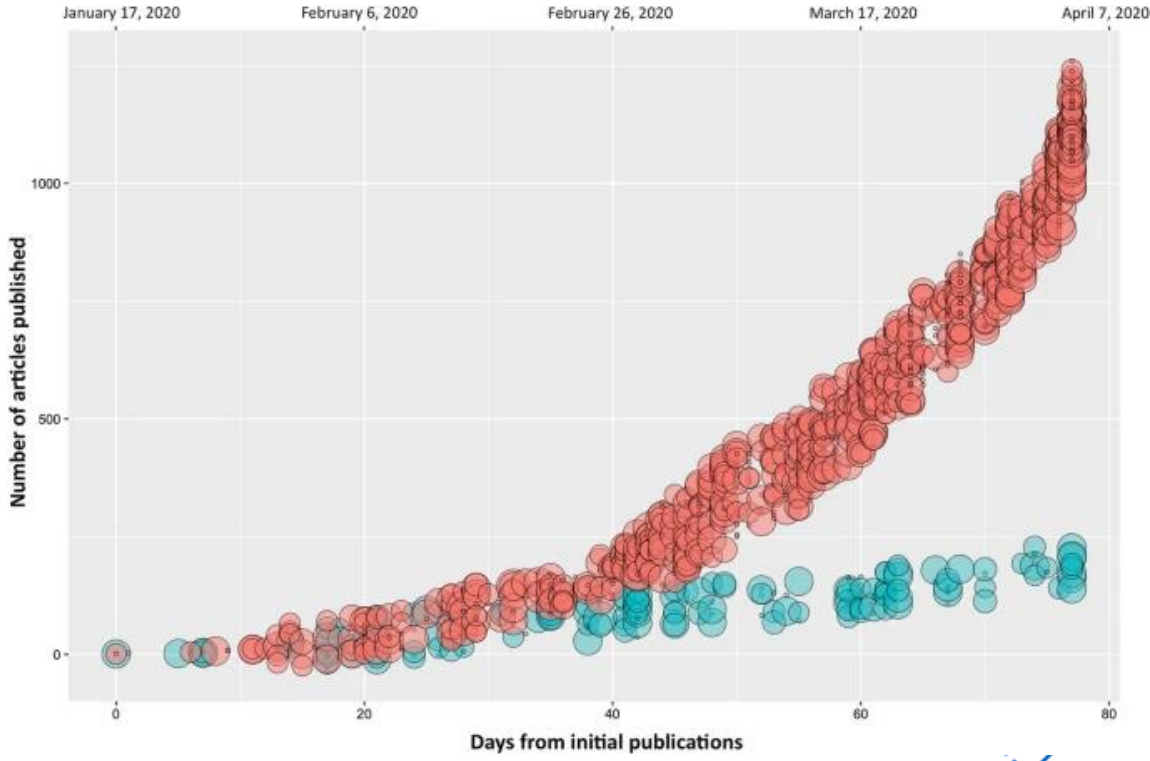
Catholic Health

Objectives

- Recognize the current magnitude of clinical complications of SARS-CoV 2
- Describe current treatment options for SARS CoV 2 infection

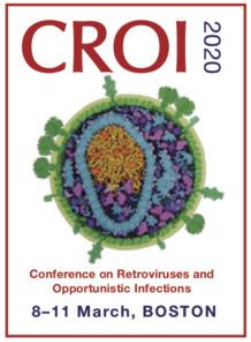
Conflicts of Interest/Research Support

- Research Funding: National Institutes of Health
  - (R01AI148560, UM1AI106701, UM1AI068636)
- Other: None



Di Girolamo, N., Meursinge Reynders, R. Characteristics of scientific articles on COVID-19 published during the initial 3 months of the pandemic. *Scientometrics* (2020).

The sun rises. Early December 2019 the first pneumonia cases of unknown origin were identified in Wuhan



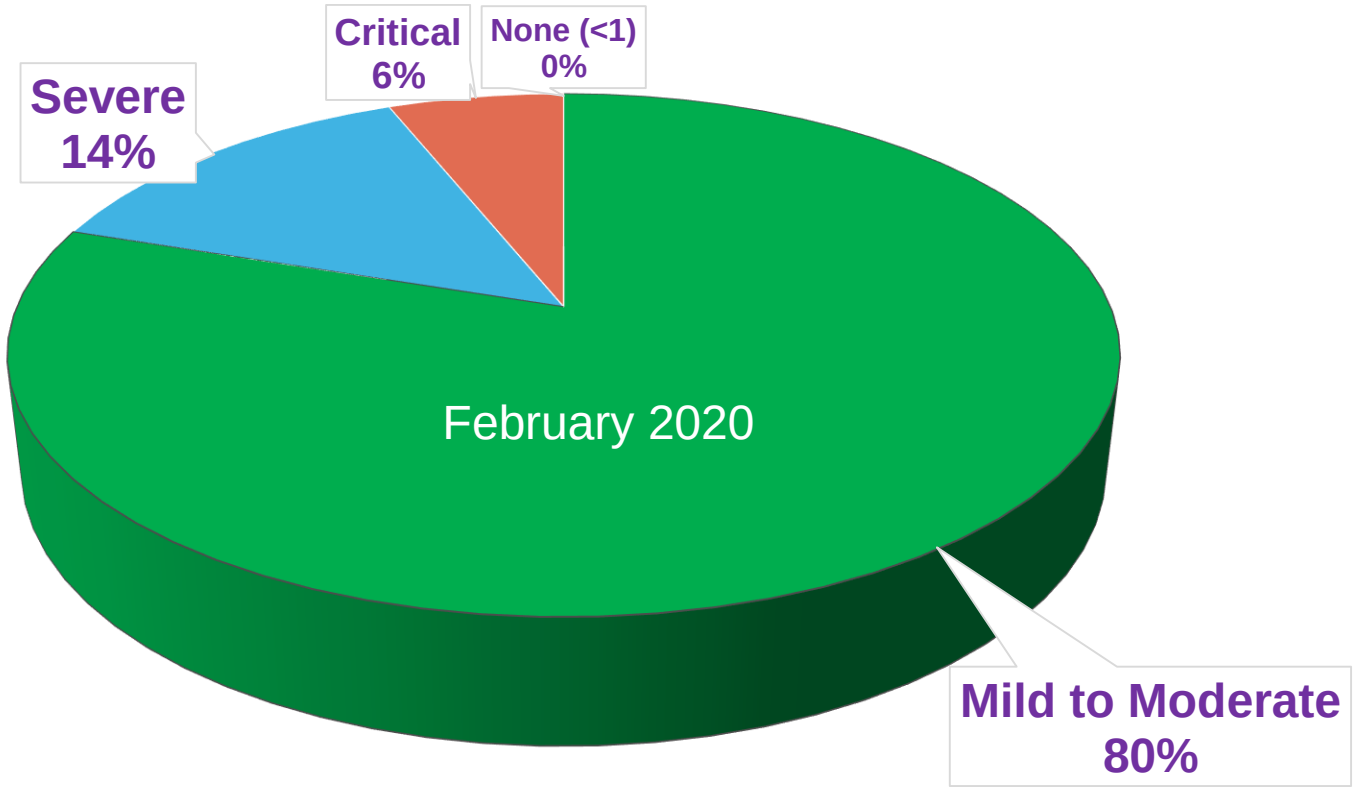
- Symptoms develop **5-6 days** (1-14) after infection
  - Fever = **43.8%** on admission and **88.7%** during hospitalization
  - Cough = **67.8%**
  - Fatigue = **38.1%**
  - SOB = **18.6%**
  - Myalgia/arthralgia = **14.8%**
  - Sore throat = **13.9%**
  - Headache = **13.6%**
  - Chills = **11.4%**
  - GI = **5%**

WHO-China Joint Mission on COVID-19 Report
Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020

Gulati A, Pomeranz C, Qamar Z, et al. A Comprehensive Review of Manifestations of Novel Coronaviruses in the Context of Deadly COVID-19 Global Pandemic. *Am J Med Sci*. 2020;360(1):5-34. doi:10.1016/j.amjms.2020.05.006

Initial symptom severity (n = 55,924)

CFR was only 3.8%



Severe = dyspnea, respiratory frequency ≥30/minute, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24-48 hours

Critical = respiratory failure, septic shock, and/or multiple organ dysfunction/failure

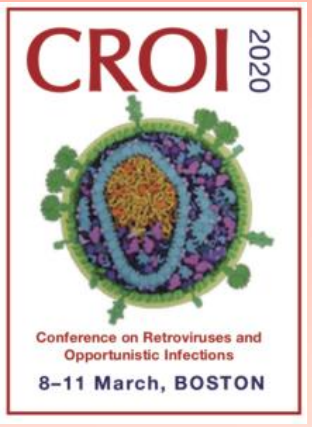
WHO-China Joint Mission on COVID-19 Report
Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020

UPDATE ON NEWLY DISCOVERED CORONAVIRUS

	SARS CoV	MERS CoV	SARS-CoV 2
Virion Structure	Enveloped RNA virus	Enveloped RNA virus	Enveloped RNA virus
Outbreak period	2003-2004	2012-present	Dec 2019-present
Initial site of isolation	Guangdong province, China	Saudi Arabia	Wuhan, China
No. of countries/cases	29	27	>70
No. of cases (mortality)	8,096 (9.6%)	2,494 (~34%)	~109,936 (N=3,806)(3.4%)* >6,129 critical (~14%)
No. of cases U.S.	8	2 (2014)	538 (WA, IL, CA, AZ, Mass, Wis)
Reservoir (intermediate host)	Bats (palm civet)	Bats (dromedary camels)	Bats (likely a zoonosis)
Incubation period	2-7 days (range, 2-21)	2-7 (range, 2-14 days)	2-14 days (mean 5-6)
Infectivity, rho	1.8-2.5	0.3-1.3	~3 (2.4-3.8)*
Super spreaders	Yes	Yes (common)	Yes (many examples)
Asymptomatic/mild Spread	No	Rare	Yes/Yes
Attack Rate	10.3% to 60%	4 to 20%	20-30%, 80% (early study)?
Transmission (including to HCP)	Droplet/Direct, Airborne/Indirect?	Droplet/Direct, Airborne/Indirect?	Droplet/Direct, Airborne/Indirect/Fecal
Treatment (PEP)	Supportive (none)	Supportive (none)	Supportive (drugs CU)
Infection Prevention	Airborne, contact, face shield	Airborne, contact, face shield	Airborne, contact, face shield

*About 83% of cases are mild or asymptomatic, Mortality Rates are age Stratified:

80+=14.8%, 70-79=8%; 60-69=3.6%, 50-59=1.3%, 40-49=0.4%, <40=0.2%, less than 15=0%.



University at Buffalo The State University of New York

6% of positively tested

Catholic Health

Department of Health Fatalities

Testing data as of: 10/12/2020 Midnight
Testing data last updated on: 10/13/2020
(Updated daily before 2 PM)

Fatalities by County

The increase in fatalities reflects new data reported Wednesday, May 6 in addition to confirmed fatalities within nursing homes and adult care facilities that were identified as part of a data reconciliation process earlier this week. Click here for additional detail.

County	Place of Fatality	Deaths by County of Residence
Grand Total	25,598	25,598
Albany	180	124
Allegany	0	4
Bronx	3,102	3,391
Broome	95	86
Cattaraugus	13	14
Cayuga	2	3
Chautauqua	5	4
Chemung	11	7
Chenango	3	6
Clinton	6	5
Columbia	43	47
Cortland	0	1
Delaware	0	5
Dutchess	166	163
Erie	668	639
Essex	12	14

Fatalities by Race/Ethnicity

Data is preliminary. With 99% reporting, below is the breakdown for NYS excluding NYC. With 63% reporting, below is the breakdown for NYC as provided by NYCDOHMH.

Click to see NYS excl. NYC age-adjusted rate

Race/Ethnicity	NYC	NYS Excl. NYC
Hispanic	34% (29% of population)	14% (12% of population)
Black	28% (22% of population)	17% (9% of population)
White	27% (32% of population)	61% (74% of population)
Asian	7% (14% of population)	4% (4% of population)
Other	4% (3% of population)	4% (1% of population)

Fatalities by Age Group

Age Group	%	Fatality Count
60 to 69	19.4%	4,968
70 to 79	26.0%	6,640
80 to 89	25.8%	6,598

Fatalities by Sex

Grand Total	25,598 (100.0%)
Female	10,912 (42.6%)
Male	14,677 (57.4%)
Unknown	9 (0.0%)

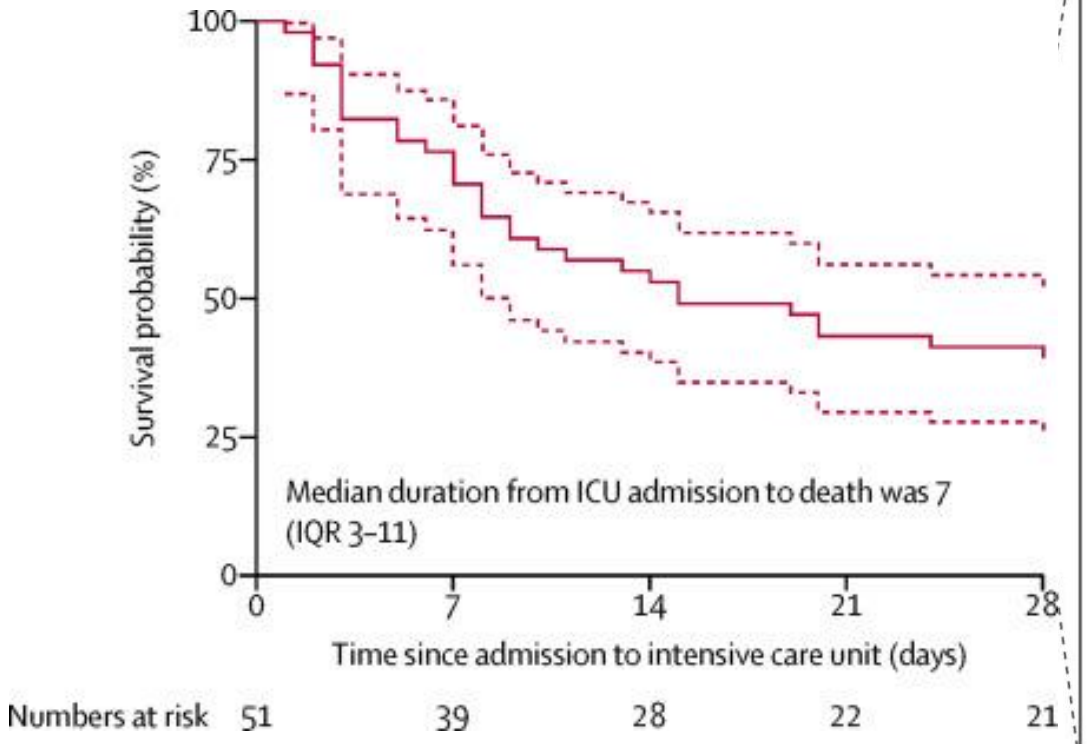
Top 10 Comorbidities by Age Group (23,072 out of 25,598 (90.1%) total fatalities have at least one comorbidity)

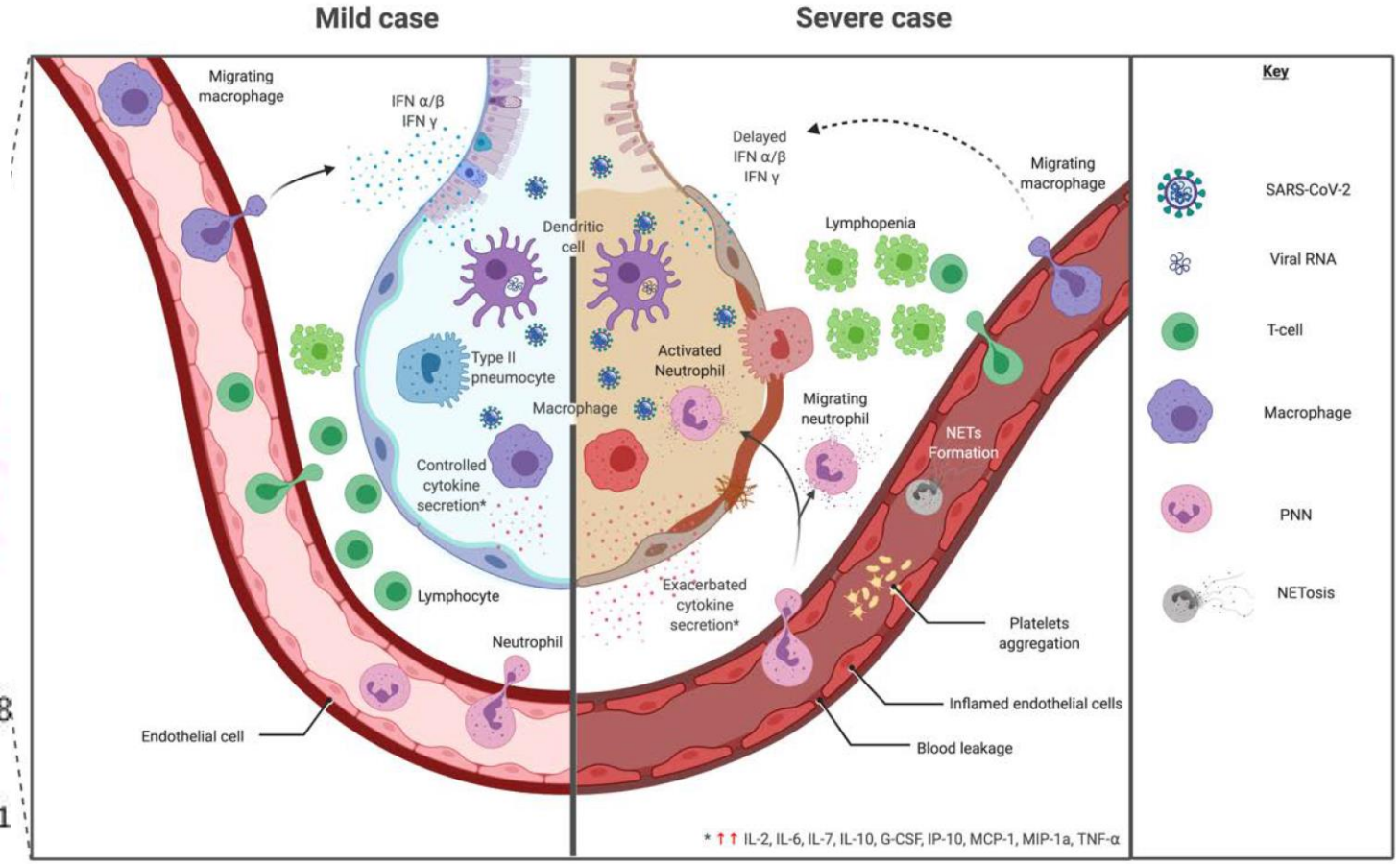
	Hypertension	Diabetes	Hyperlipidemia	Dementia	Coronary Artery Disease	Renal Disease	Copd	Atrial Fibrillation	Cancer	Stroke
Grand Total	13,632	8,991	5,321	3,479	3,006	2,683	2,420	2,024	1,957	1,679
0 to 9	1	0	0	0	0	0	0	0	0	0
10 to 19	1	2	0	0	0	0	0	0	0	1
20 to 29	14	22	4	0	0	4	0	0	7	3
30 to 39	75	85	19	0	1	21	2	2	10	4

Click for Map View | Click for Trend View | Click for Table View

1.4-60% CFR amongst ARDS

ARDS (ICU)





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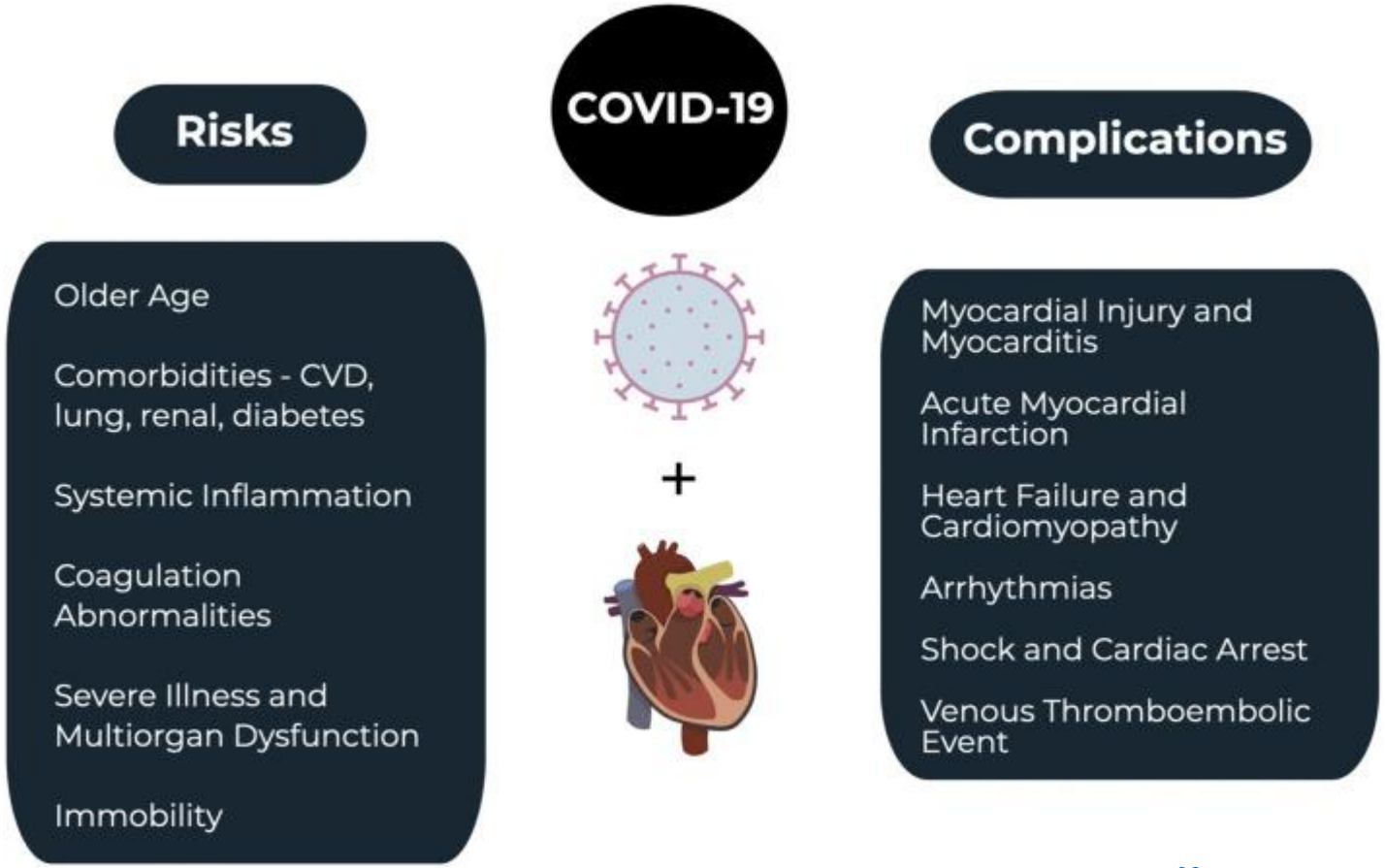
Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study [published correction appears in Lancet Respir Med. 2020 Apr;8(4):e26]. *Lancet Respir Med*. 2020;8(5):475-481. doi:10.1016/S2213-2600(20)30079-5
Gulati A, Pomeranz C, Qamar Z, et al. A Comprehensive Review of Manifestations of Novel Coronaviruses in the Context of Deadly COVID-19 Global Pandemic. *Am J Med Sci*. 2020;360(1):5-34. doi:10.1016/j.amjms.2020.05.006

Cardiovascular

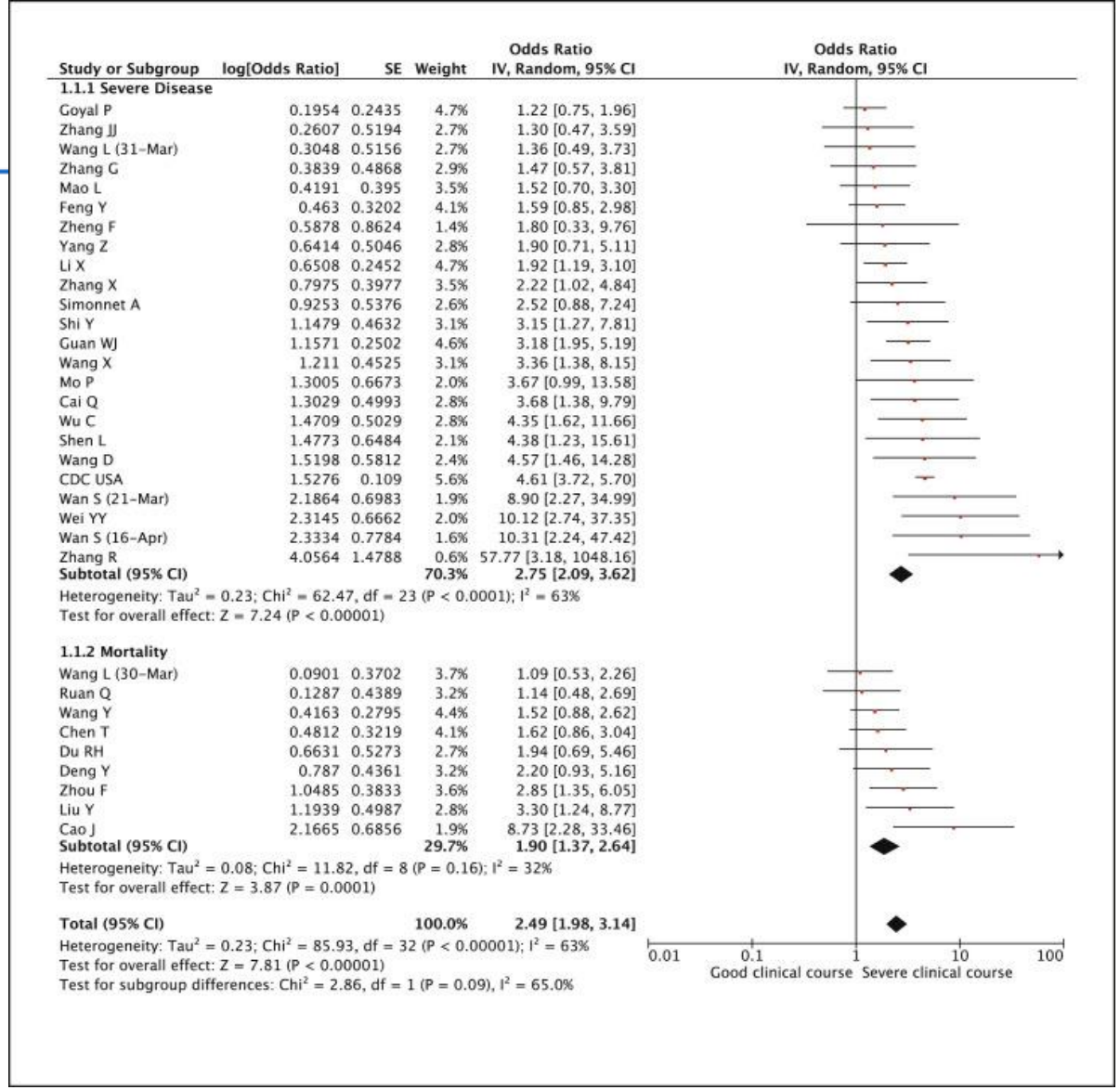
- Prevalence
  - Hypertension = **17%**
  - Cardiac disease =**16.4%**
  - Arrhythmia as high as **17%**
- Mortality
  - History of CVD = 5x mortality (**10.5%**)
  - **7%** of COVID-19 deaths attributed to MI



Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J Emerg Med*. 2020;38(7):1504-1507. doi:10.1016/j.ajem.2020.04.048
Zaki N, Alashwal H, Ibrahim S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: A systematic review [published online ahead of print, 2020 Jul 8]. *Diabetes Metab Syndr*. 2020;14(5):1133-1142.

Diabetes

- Prevalence
  - **5-11%** in 20k cases
  - **14-32%** in severe COVID-19
  - Case reports of DKA
- Mortality
  - **1-2.75x** likely lead to ARDS
  - **2.3%** among 44k cases



Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr*. 2020;14(4):535-545. doi:10.1016/j.dsx.2020.04.044
Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. *Diabetes Metab Syndr*. 2020;14(4):303-310. doi:10.1016/j.dsx.2020.04.004
Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. Diabetes Res Clin Pract 2020 April 24

Other complications

- Hepatobiliary (LFTs, Lactate, etc.) = **51%**
- GI (appetite, diarrhea, etc.) = up to **50%**
  - Abdominal pain associated with severity
- Renal
  - AKI up to **15%** (**60-90%** mortality)
  - Elevated SrCr (**20%**), low GFR (**13%**)
  - Proteinuria (**44-63%**), Hematuria (**27%**)
- Neurological = **36.4%**
- Thyrotoxicosis = **56%**
- Musculocutaneous
  - Myalgia (**36%**), Elevated CK (**33%**)
  - Rash (**20%**)
- Hematologic (coagulopathy)
  - Lymphopenia = **40-70%**, Thrombocytopenia = **40-69%**
- Other special population considerations

Fan Z, Chen L, Li J. Clinical features of COVID-19 related liver damage. Clin Gastroenterol Hepatol. 2020;18:1561–1566. doi: 10.1016/j.cgh.2020.04.002.
Pan L, Mu M, Yang P. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol. 2020;115(5):766–773.
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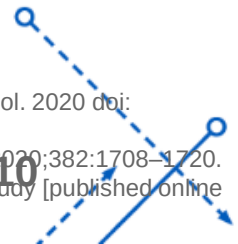
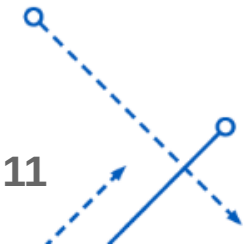


ClinicalTrials.gov = >3185 studies for COVID-19

- ACTT 2: remdesivir + baricitinib
- Vitamin C, D and Zinc
- Auxora
- Baricitinib + HQ
- Interferon Beta, Alpha
- Lopinavir/ritonavir + HQ
- Umifenovir
- Ribavirin
- Triiodothyronine
- Adjunctive IV IG
- Checkpoint inhibition and other immunomodulators: i.e. CD47, EDP1815
- Methylprednisolone
- Oseltamivir + Azithro
- acalabrutinib, a BTK inhibitor
- Melatonin
- Stromal Cell
- Triiodothyronine
- Various respiratory adjuvants
- And many more…

Saul S, Einav S. Old Drugs for a New Virus: Repurposed Approaches for Combating COVID-19 [published online ahead of print, 2020 Aug 10]. *ACS Infect Dis*. 2020;acsinfecdis.0c00343. doi:10.1021/acsinfecdis.0c00343



NIH guidelines: Remdesivir

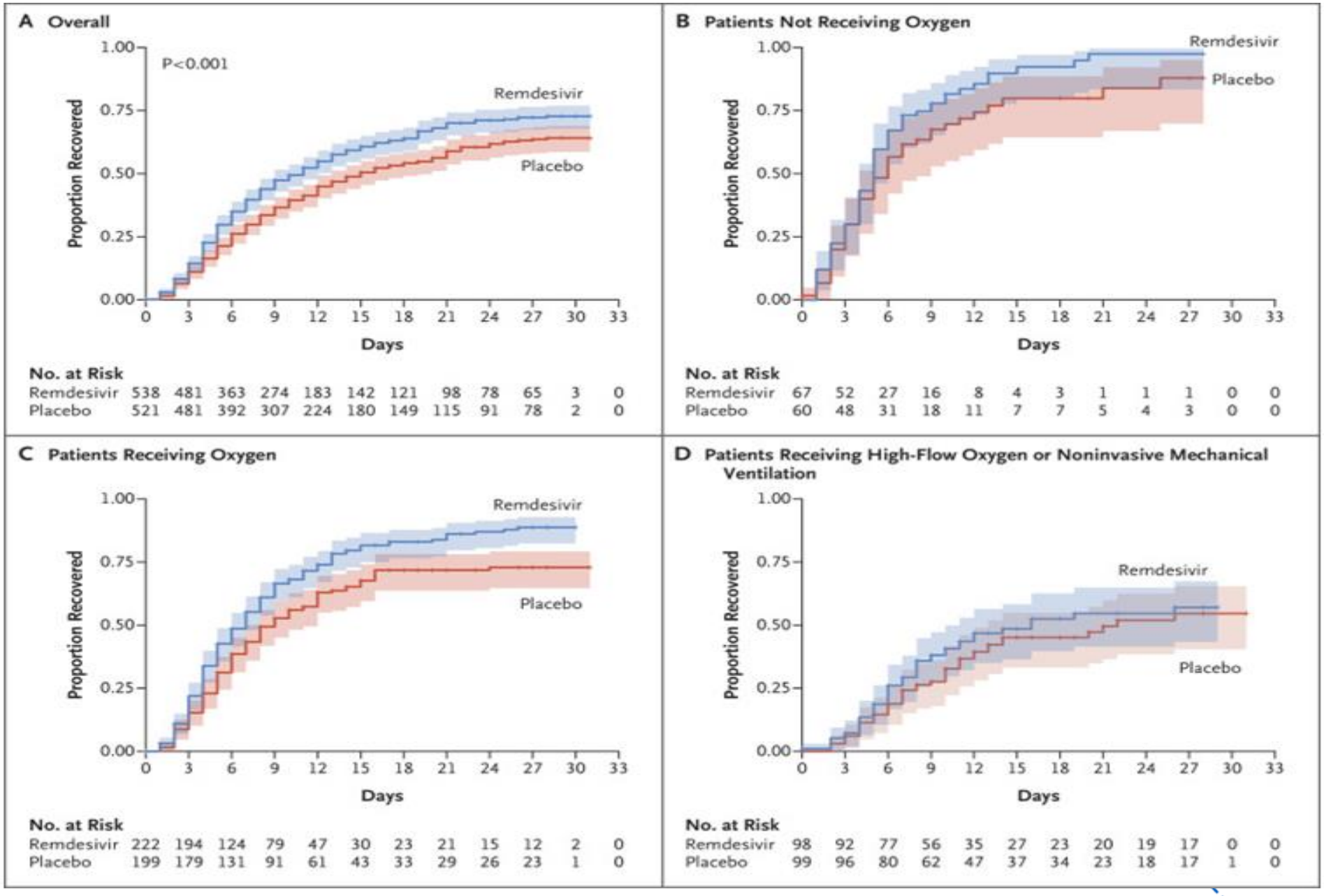
- Because remdesivir supplies are limited, prioritize remdesivir for recommended use in
  - hospitalized patients who require supplemental O2 but who do not require high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO **(BI)**.
  - Require Supplemental O2, duration = 5 days or until hospital discharge, whichever comes first **(AI)**.
  - Lack of improvement after 5 days, optimal duration is unknown though some experts extend up to 10 days **(CIII)**.
- Require *High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO*, = uncertainty

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 8/31/20.

University at Buffalo

ACTT-1

- 1059 prelim analysis
- 8 point ordinal scale
- ACTT-2 and -3 (combination with immunomodulators) are underway
- Moderate disease trial underway



Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report [published online ahead of print, 2020 May 22]. *N Engl J Med*. 2020;NEJMoa2007764. doi:10.1056/NEJMoa2007764

NIH guidelines : CQ/HCQ +/- Azithro

- **Against** the use of **chloroquine (including high dose)** or **hydroxychloroquine** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19, except in a clinical trial **(AI)**.
- The Panel **recommends against** using **hydroxychloroquine plus azithromycin** to treat COVID-19, except in a clinical trial **(AIII)**.
- QTc prolongation, Torsade de Pointes, ventricular arrythmia, and cardiac deaths.[15] If chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse events, especially prolonged QTc interval **(AIII)**.

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 8/31/20.

RECOVERY

- Ongoing, open-label national UK study across 176 hospitals
- 1561 randomized to HQ
- 17% high-flow, 60% O2
- Azithro and steroid use similar in both arms

Table 2: Effect of allocation to hydroxychloroquine on main study outcomes

	Hydroxychloroquine (n = 1561)	Usual care (n = 3155)	RR (95% CI)
Primary outcome:			
28-day all-cause mortality	418 (26.8%)	788 (25.0%)	1.09 (0.96 to 1.23)
Secondary outcomes:			
Discharged from hospital within 28 days	941 (60.3%)	1982 (62.8%)	0.92 (0.85 to 0.99)
Receipt of mechanical ventilation or death*	388/1300 (29.8%)	696/2623 (26.5%)	1.12 (1.01 to 1.25)
Death	308/1300 (23.7%)	572/2623 (21.8%)	1.09 (0.96 to 1.23)
Invasive mechanical ventilation	118/1300 (9.1%)	215/2623 (8.2%)	1.11 (0.89 to 1.37)

Peter Horby et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial.medRxiv 2020.07.15.20151852; doi: https://doi.org/10.1101/2020.07.15.20151852

HCQ, or Azithro, or HCQ+Azithro

- New York
- Observational
- Large sample (1438)
- No differences in ECG

Table 3. Model-Adjusted Risk of In-Hospital Death, Cardiac Arrest, and Arrhythmia

Outcome	Model type[a]	Estimate (95% CI)			
		Hydroxychloroquine + azithromycin vs neither drug	Hydroxychloroquine alone vs neither drug	Azithromycin alone vs neither drug	Hydroxychloroquine alone vs azithromycin alone
In-hospital death (hazard ratio)	Cox proportional hazards	1.35 (0.76-2.40)	1.08 (0.63-1.85)	0.56 (0.26-1.21)	1.92 (0.99-3.74)
Cardiac arrest (odds ratio)	GEE logistic regression	2.13 (1.12-4.05)	1.91 (0.96-3.81)	0.64 (0.27-1.56)	2.97 (1.56-5.64)
Abnormal ECG findings (odds ratio)[b]	GEE logistic regression	1.55 (0.89-2.67)	1.50 (0.88-2.58)	0.95 (0.47-1.94)	1.58 (0.77-3.24)

Abbreviations: ECG, electrocardiogram; GEE, generalized estimating equation.

[a] Models adjusted for sex, age category (<65 vs ≥65 years), diabetes, any chronic lung disease, cardiovascular disease, abnormal chest imaging, respiration rate >22/min, O_2 saturation <90%, elevated creatinine, and AST >40 U/L as fixed effects and repeated measures for hospital.

[b] Abnormal ECG included prolonged QT and arrhythmia.

Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. 2020.

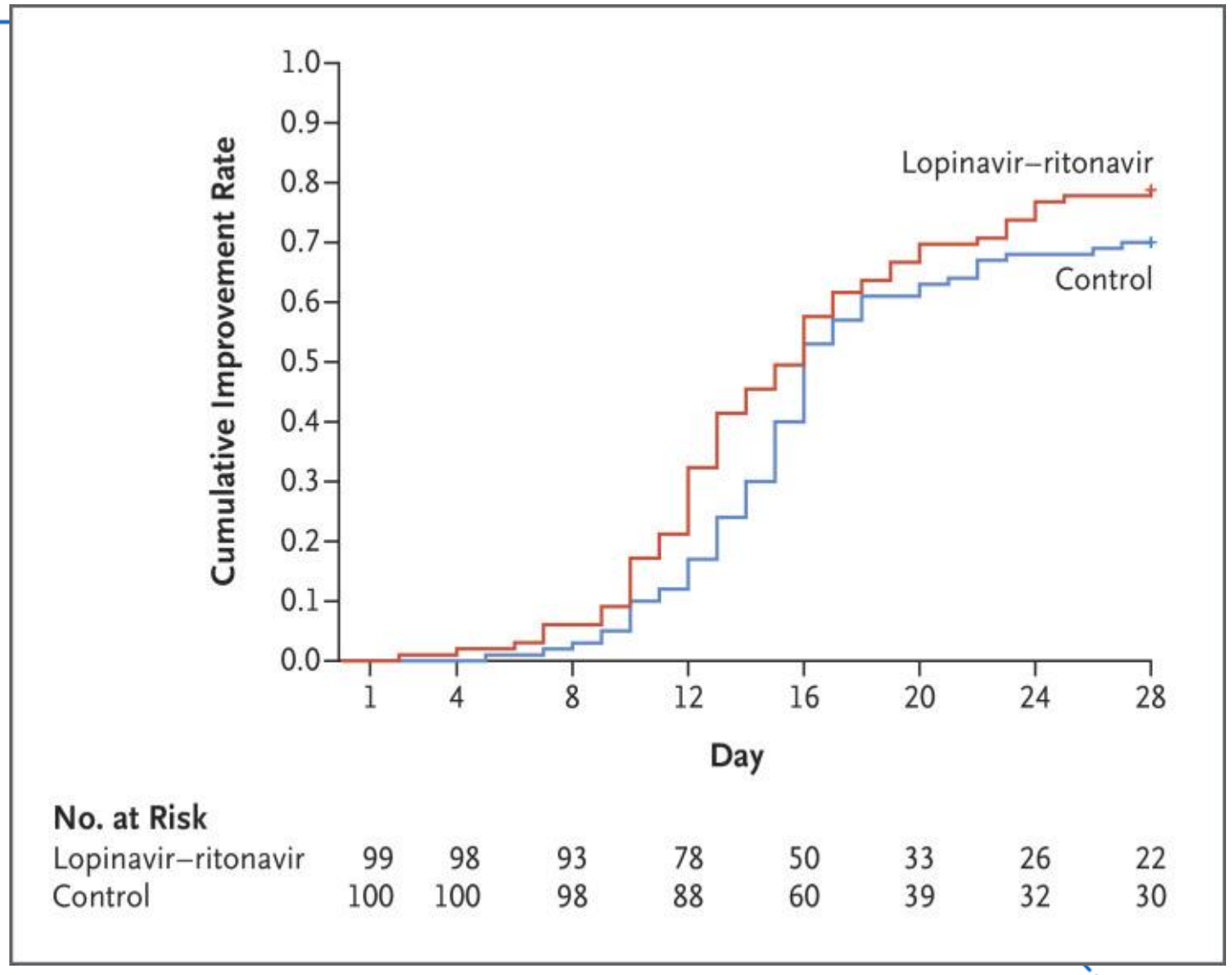
NIH guidelines : Lpv/Rit and other PIs

- The Panel **recommends against** using **lopinavir/ritonavir (AI)** or **other HIV protease inhibitors (AIII)** to treat COVID-19, except in a clinical trial.

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 8/31/20.

Lpv/Rit

- Randomized, open-labeled
- N = 199
- Not statistically different - underpowered
- No difference in LOS or viral clearance



Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med*. 2020.

PK/PD Lpv/Rit in COVID-19

- Brief report, case series
- Only trough
- 60-120 fold below potential threshold for SARS-CoV-2 EC50 (16.4)

Table. Lopinavir and Ritonavir Trough Concentrations in Patients Hospitalized With COVID-19

Patient	Lopinavir, μg/mL*	Ritonavir, μg/mL*	Age, y	Sex	Body Mass Index, kg/m²	C-reactive Protein Level, mg/L	Albumin Level, g/L	Treatment Day	Concomitant Medication
1	6.2	<0.19	72	Female	29	1.6	39.9	10	Oxazepam
2	19.9	0.56	21	Female	-	7.8	37.3	3	-
3	14.6	0.22	65	Female	24.5	19.3	37.4	10	Candesartan
4	24.3	0.67	26	Male	26.5	40.0	36.1	4	-
5	10.3	<0.19	52	Female	30	7.9	37.1	4	-
6	10.0	<0.19	79	Male	22	4.0	34.7	7	Atorvastatin, bisoprolol, edoxaban, and pantoprazole
7	12.6	0.20	67	Female	36	39.1	39.5	6	Metformin, ezetimibe, bisoprolol, valsartan, amlodipine, pantoprazole, and metamizole
8	23.0	<0.19	53	Male	29	184.7	32.6	4	Bisoprolol, triazolam, and budesonide/formoterol

COVID-19 = coronavirus disease 2019.
* Drug levels were quantified by liquid chromatography–tandem mass spectrometry.

Schoergenhofer C, Jilma B, Stimpfl T, Karolyi M, Zoufaly A. Pharmacokinetics of lopinavir and ritonavir in patients hospitalized with coronavirus disease 2019 (COVID-19). *Ann Intern Med*. 2020.

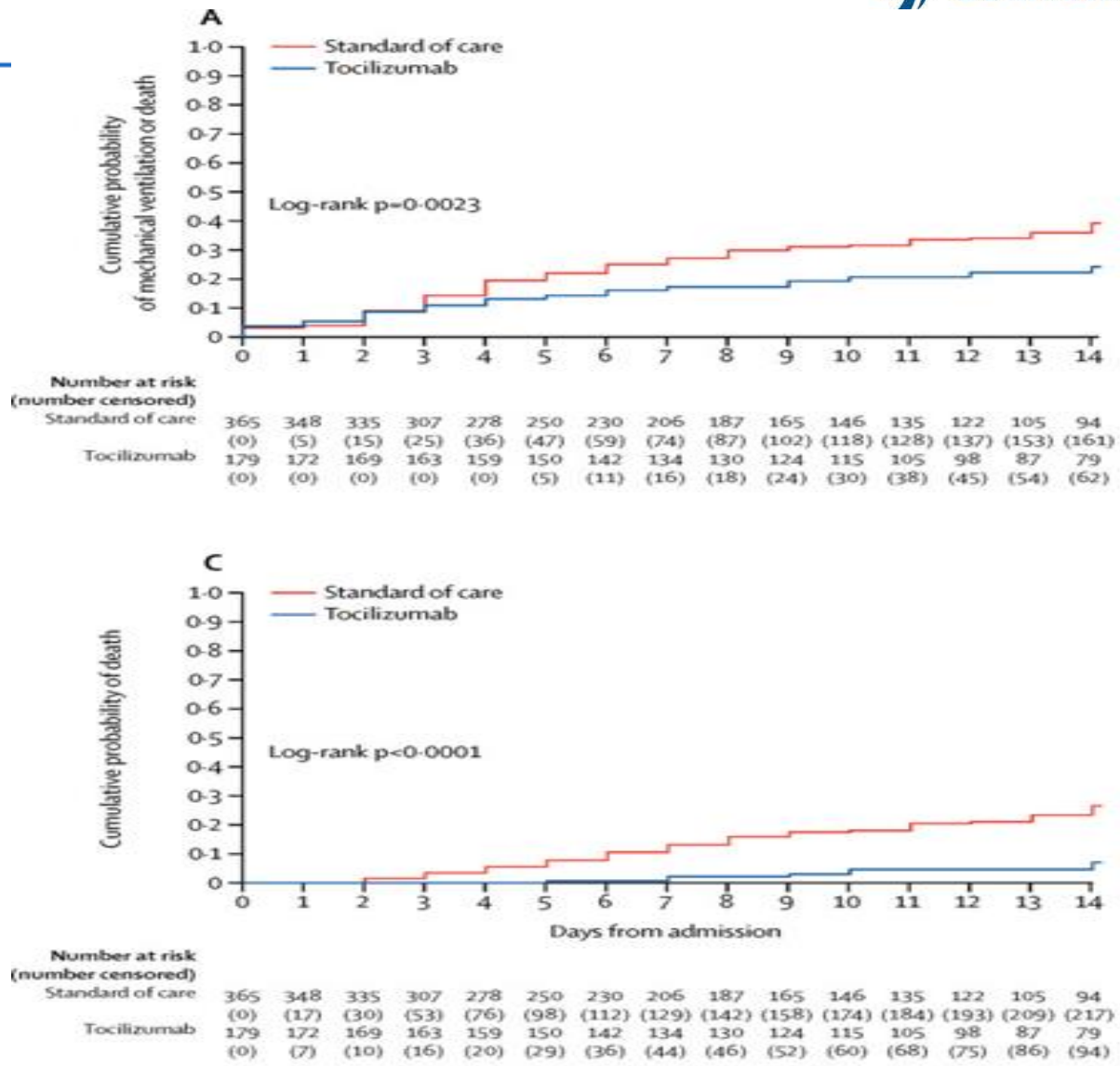
NIH guidelines : Immunomodulators

- There are insufficient data for the Panel to recommend either for or against the use of
  - Interleukin (IL)-1 inhibitors (e.g., **anakinra**)
  - **Interferon beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.
- The Panel **recommends against** the use of the following, except in a clinical trial:
  - Anti-IL-6 receptor monoclonal antibodies (e.g., **sarilumab**, **tocilizumab**) or anti-IL-6 monoclonal antibody (**siltuximab**) **(BI)**.
  - **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)**.
  - Bruton's tyrosine kinase inhibitors (e.g., **acalabrutinib**, **ibrutinib**, **zanubrutinib**) and Janus kinase inhibitors (e.g., **baricitinib**, **ruxolitinib**, **tofacitinib**) **(AIII)**.

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 8/31/20.

Early experience with TOC

- Italian tertiary centers
- N = 1351 (179 with TOC)
- Pneumonia
- Primary outcome = respiratory recovery score (Brescia COVID respiratory severity score)
- >50% not in ICU
- 77% improved



Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(8):e474-e484. doi:10.1016/S2665-9913(20)30173-9

Press releases, Sep.

- COVACTA
  - Phase 3, Randomized placebo controlled, in 450 adults
  - Primary outcome = improved clinical status over 4 weeks
  - Failed to meet primary or several key secondary endpoints (4 week mortality)
  - No statistical difference in primary (OR 1.19; 95% CI, 0.81–1.76; *P* = 0.36) or in mortality (19.7% vs. 19.4%; difference of 0.3%; 95% CI, -7.6% to 8.2%; *P* = 0.94)

- CORIMUNO-TOCI
  - Open label, randomized trial with/without SOC in 129 adults across France
  - Mortality and proportion requiring ventilation lower in TOC group, details forthcoming

HQ+/-Azithro+/-Toc

- Retrospective, observational cohort, Hospital network in NJ
- Among 547 ICU patients, 134 receiving TOC
- 30 day unadjusted mortality with and without tocilizumab of 46% versus 56%.

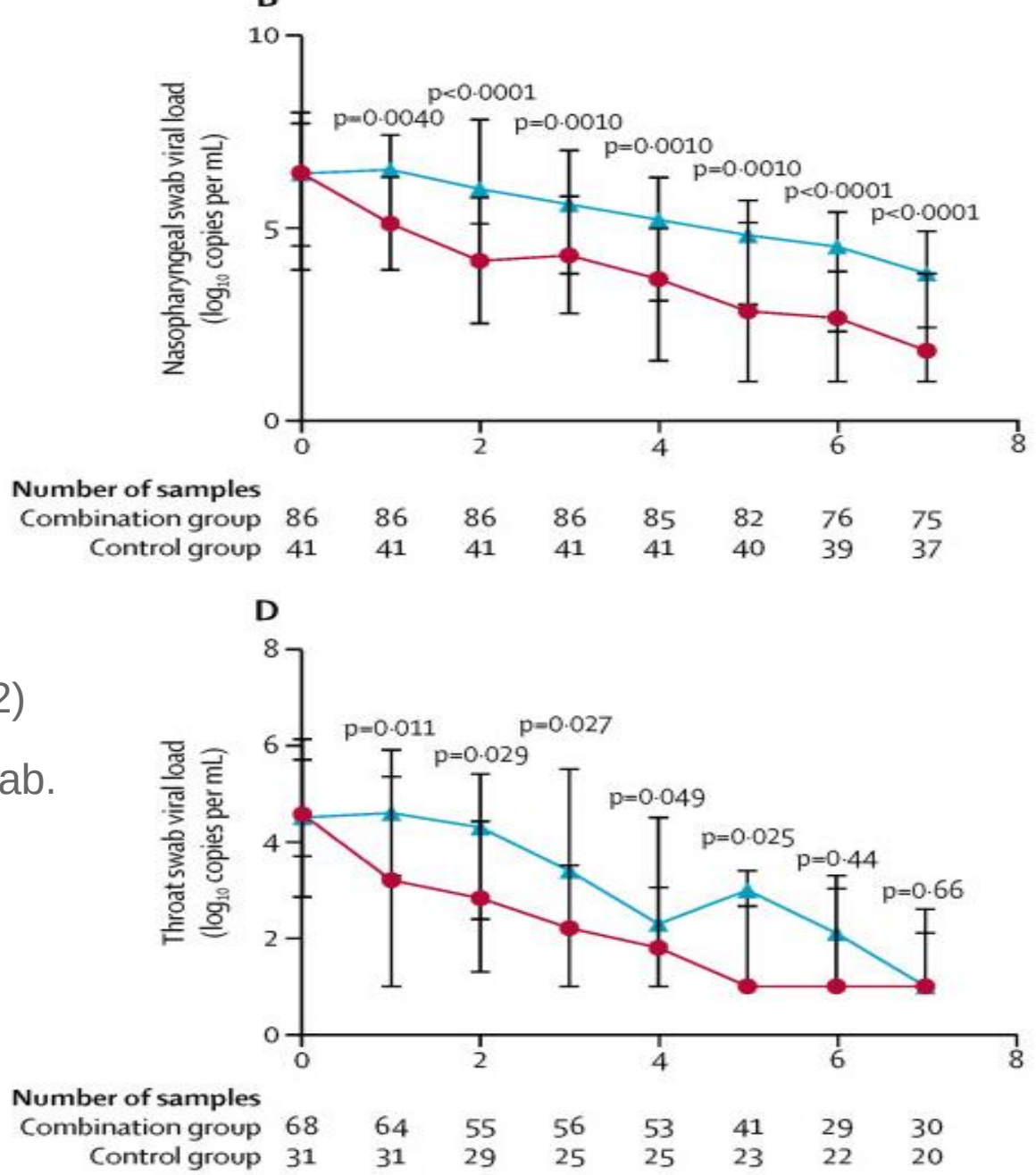
	HR	95% conf. interval		P-value	30-day mortality rate	
		Lower	Upper		Experimental	Control
Any HCQ in hospital	0.99	0.80	1.22	0.92	0.20	0.20
HCQ+AZI in hospital	0.98	0.75	1.28	0.89	0.18	0.20
Factorial main effects and interaction of HCQ and AZI						
HCQ main effect	1.02	0.83	1.27	0.83	0.25 (HCQ only)	0.20 (Neither)
AZI main effect	0.89	0.72	1.10	0.28	0.20 (AZI only)	0.20 (Neither)
Interaction				0.091	0.18 (Both)	0.20 (Neither)
Tocilizumab therapy in the Intensive Care Unit						
Toci in ICU	0.76	0.57	1.00	0.053	0.46	0.56

https://doi.org/10.1371/journal.pone.0237693.t002

Ip A, Berry DA, Hansen E, et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients-An observational study. *PLoS One*. 2020;15(8):e0237693. Published 2020 Aug 13. doi:10.1371/journal.pone.0237693

Lpv/Rit+Interferon+Ribavirin

- Open label, randomized
- N = 127
- Both arms had Lpv/Rit
- Lopinavir/Ritonavir + Ribavirin + Interferon beta-1b (n=52)
- Significantly shorter time to negative nasopharyngeal swab.
- Mostly mild illness



Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet*. 2020;395(10238):1695-1704. doi:10.1016/S0140-6736(20)31042-4

NIH guidelines : Convalescent Plasma

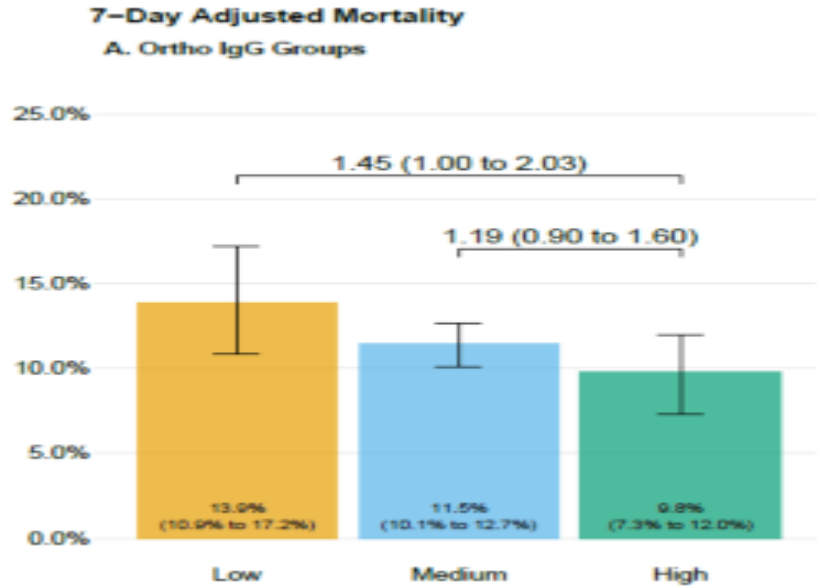
- There are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.
- Convalescent plasma should not be considered the standard of care for the treatment of patients with COVID-19.

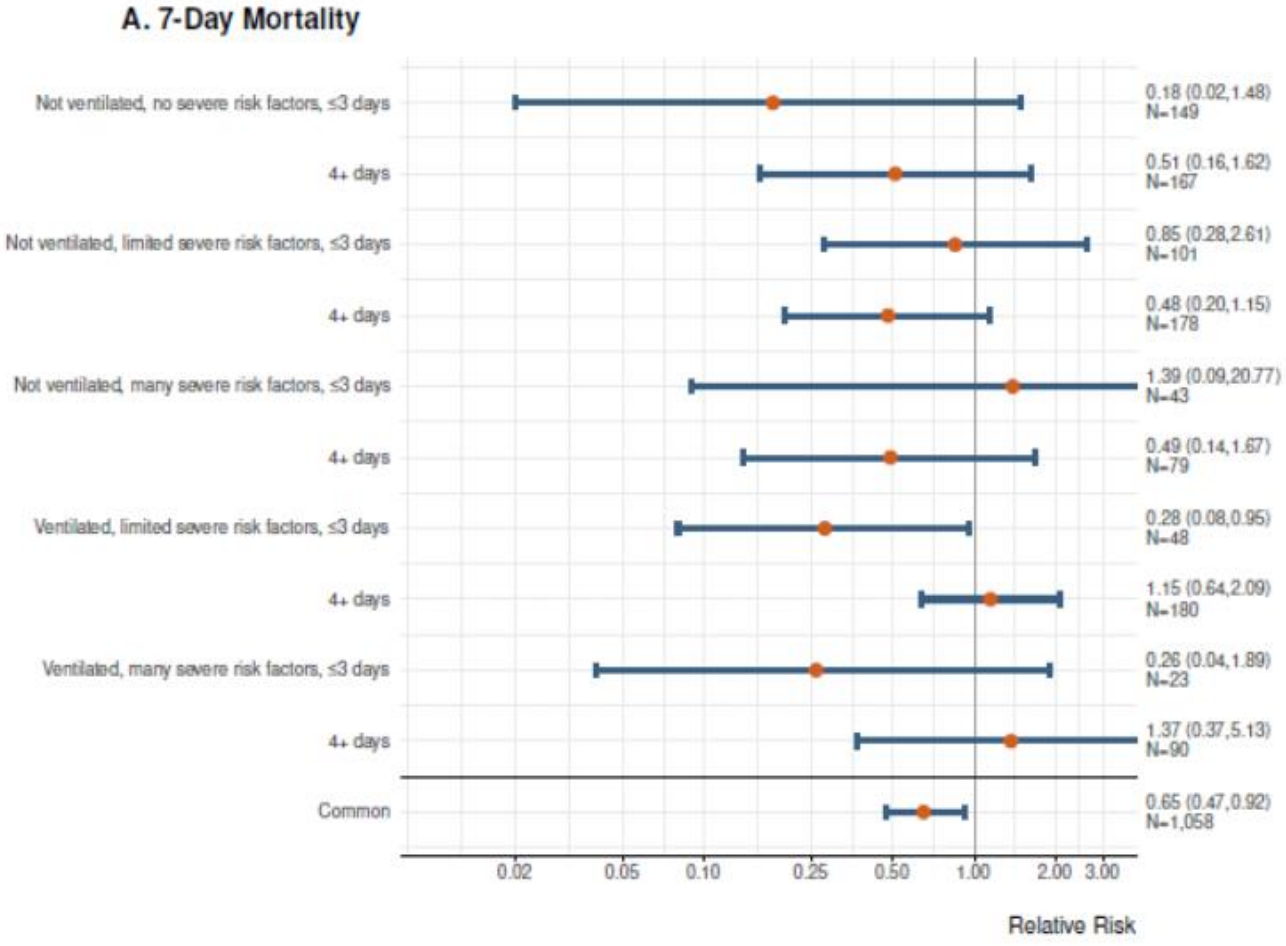
- **08/26/20: FDA assigns EUA status**

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 8/31/20.

U.S. Convalescent Plasma Expanded Access Program (EAP)

- Cohort with N = 35k, mostly critically ill
- In 3500, reduced mortality with higher AB and earlier administration





Michael J Joyner et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. medRxiv 2020.08.12.20169359; doi: https://doi.org/10.1101/2020.08.12.20169359

NIH guidelines: Dexamethasone

- The Panel **recommends** using **dexamethasone** 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated **(AI)** and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**.
- If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** (see Additional Considerations in the Corticosteroids section for dosing recommendations) **(AIII)**.

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 8/31/20.

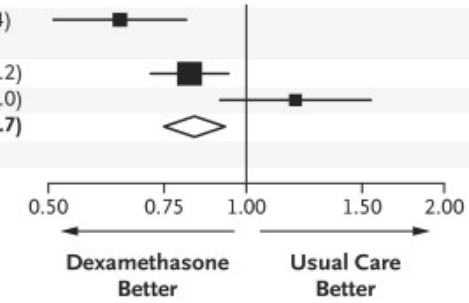
University at Buffalo The State University of New York

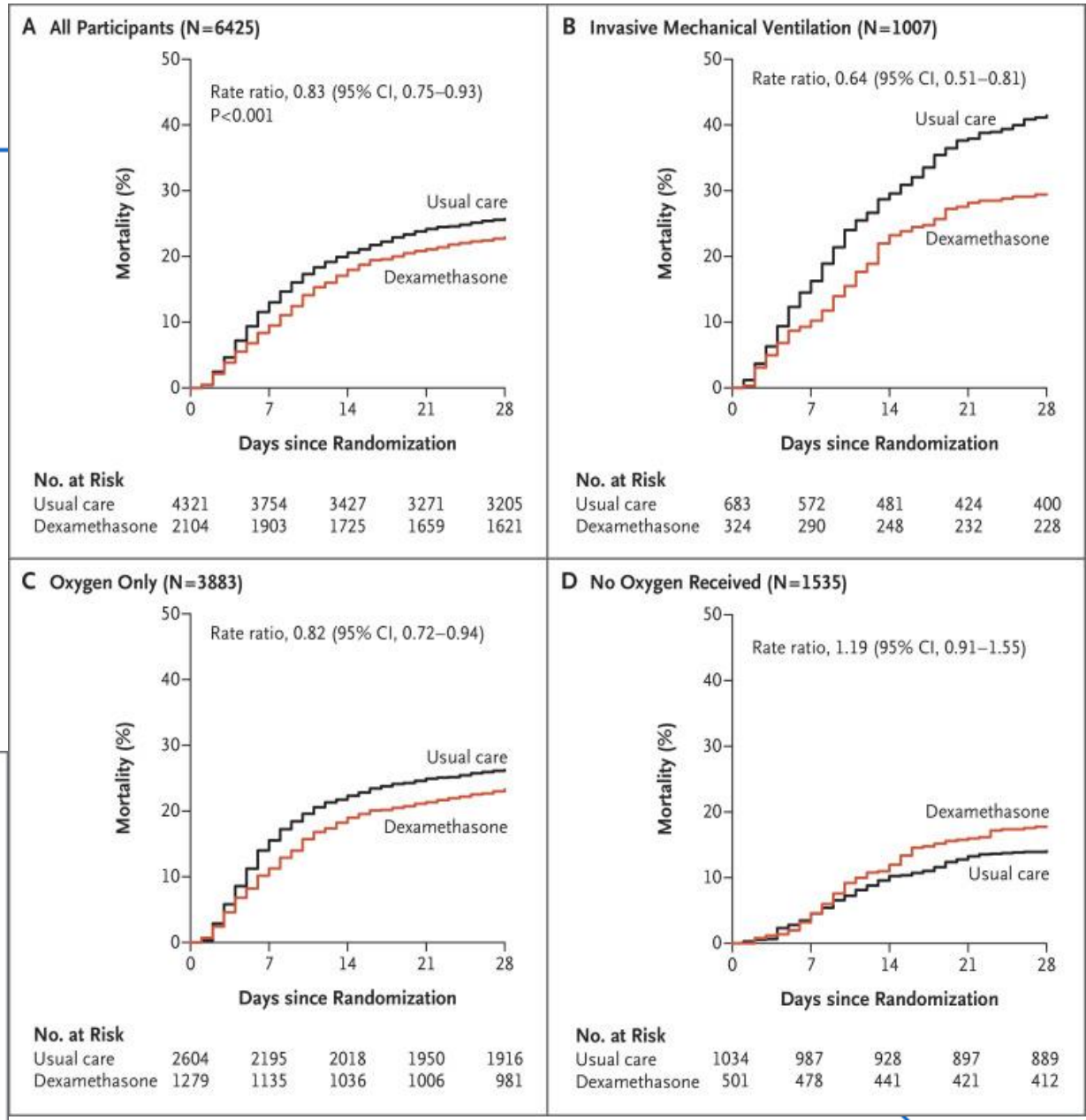
RECOVERY

- N = 11.5k across the UK
- 2k on dexamethasone (6mg QD po or iv) vs. 4k SOC
- Halted due to sufficient data
- lower 28-day mortality among on mechanical ventilation or oxygen alone at randomization but not among without respiratory support

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5



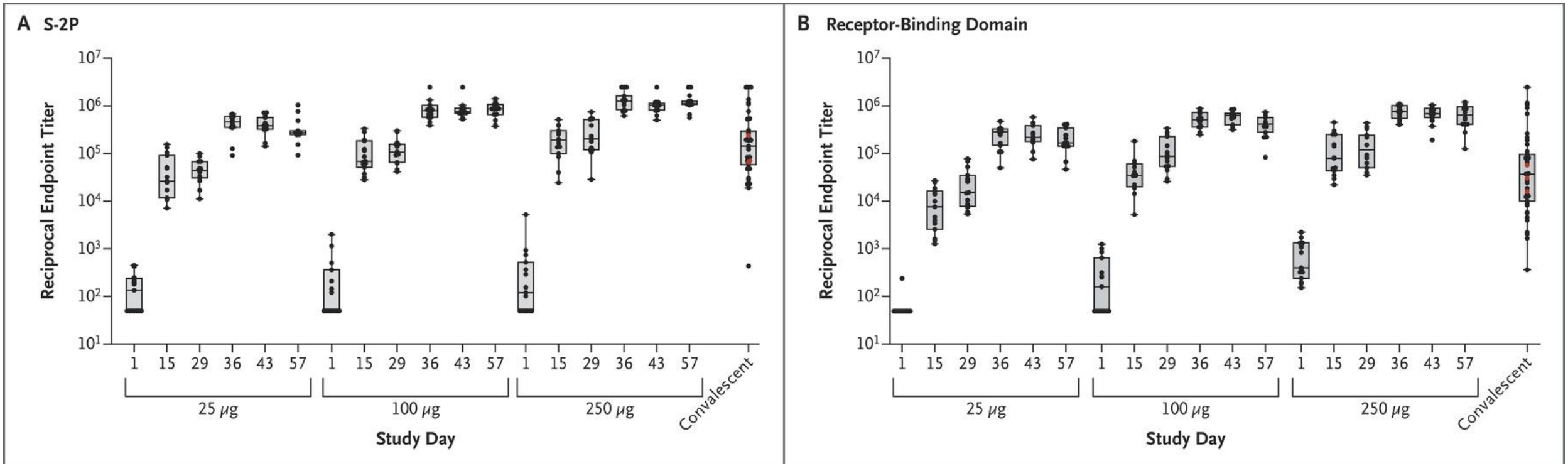


RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report [published online ahead of print, 2020 Jul 17]. *N Engl J Med*. 2020;NEJMoa2021436. doi:10.1056/NEJMoa2021436

Vaccine Development – targeting 50%

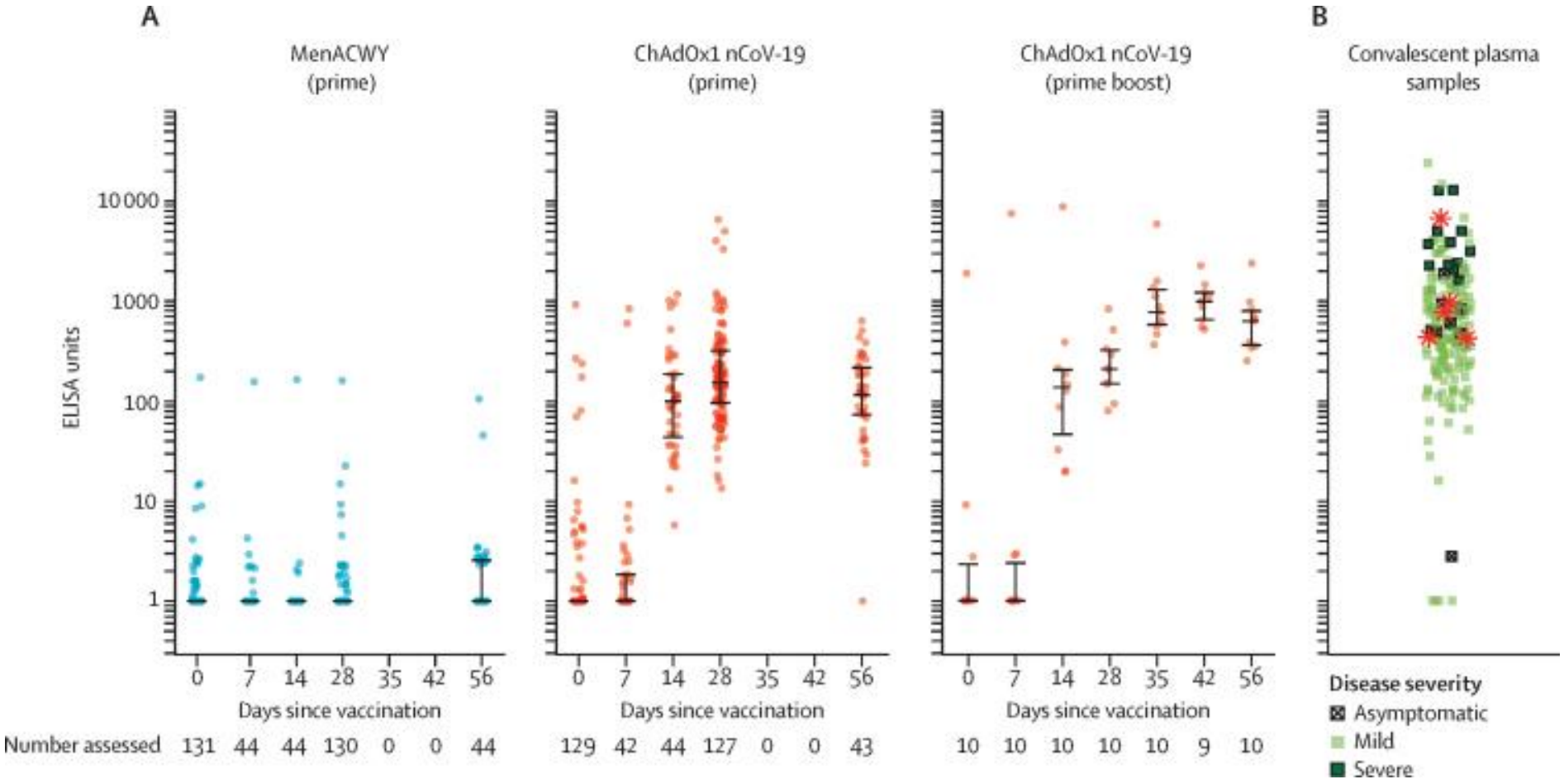
- 8/11/20 Russia approves the first SARS CoV2 vaccine w/o PIII trials
- 10/6/20 FDA announces EUA criteria
- WHO reports over 143 vaccines in preclinical and 33 candidates in clinical trials (+60 in the month of august)
- U.S has invested in more than five candidates through “Operation Warp Speed,” a partnership between the government, scientific community, and drug companies
- Several platforms based on major technical advancements: recombinant adenovirus vector, mRNA, whole-inactivated
- Currently 11 candidates in PIII trials, 19 in PII, 35 in PI.

mRNA-1273



Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report . *N Engl J Med*. 2020.
Anderson *et al.* Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med*. 2020

Adenovirus-vectored = ChAdOx1 nCov-19

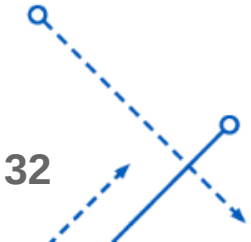


Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial [published correction appears in Lancet. 2020 Aug 15;396(10249):466]. *Lancet*. 2020;396(10249):467-478. doi:10.1016/S0140-6736(20)31604-4

Audience Poll

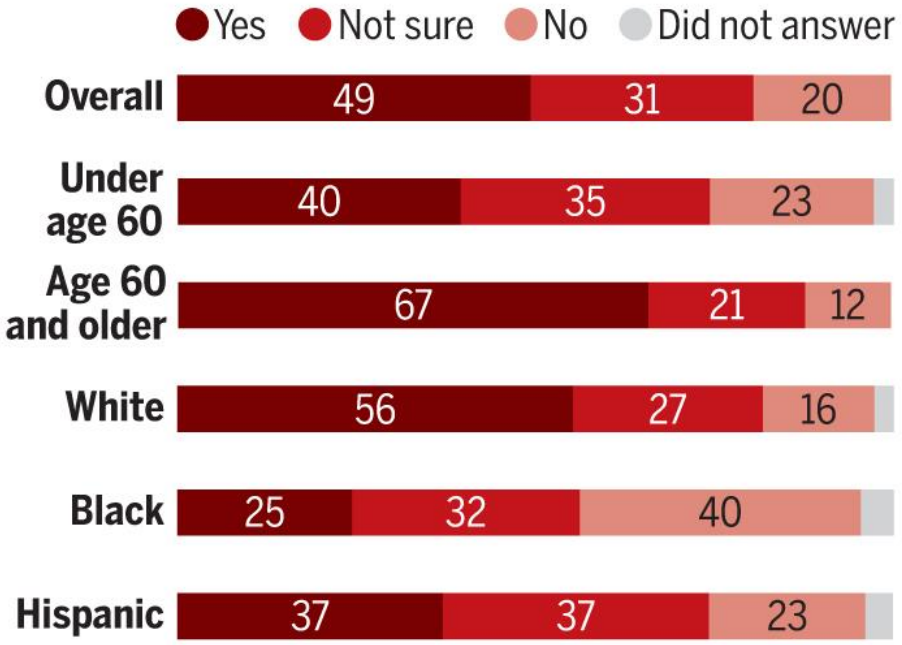
Do you plan on getting the coronavirus vaccine when one is available?

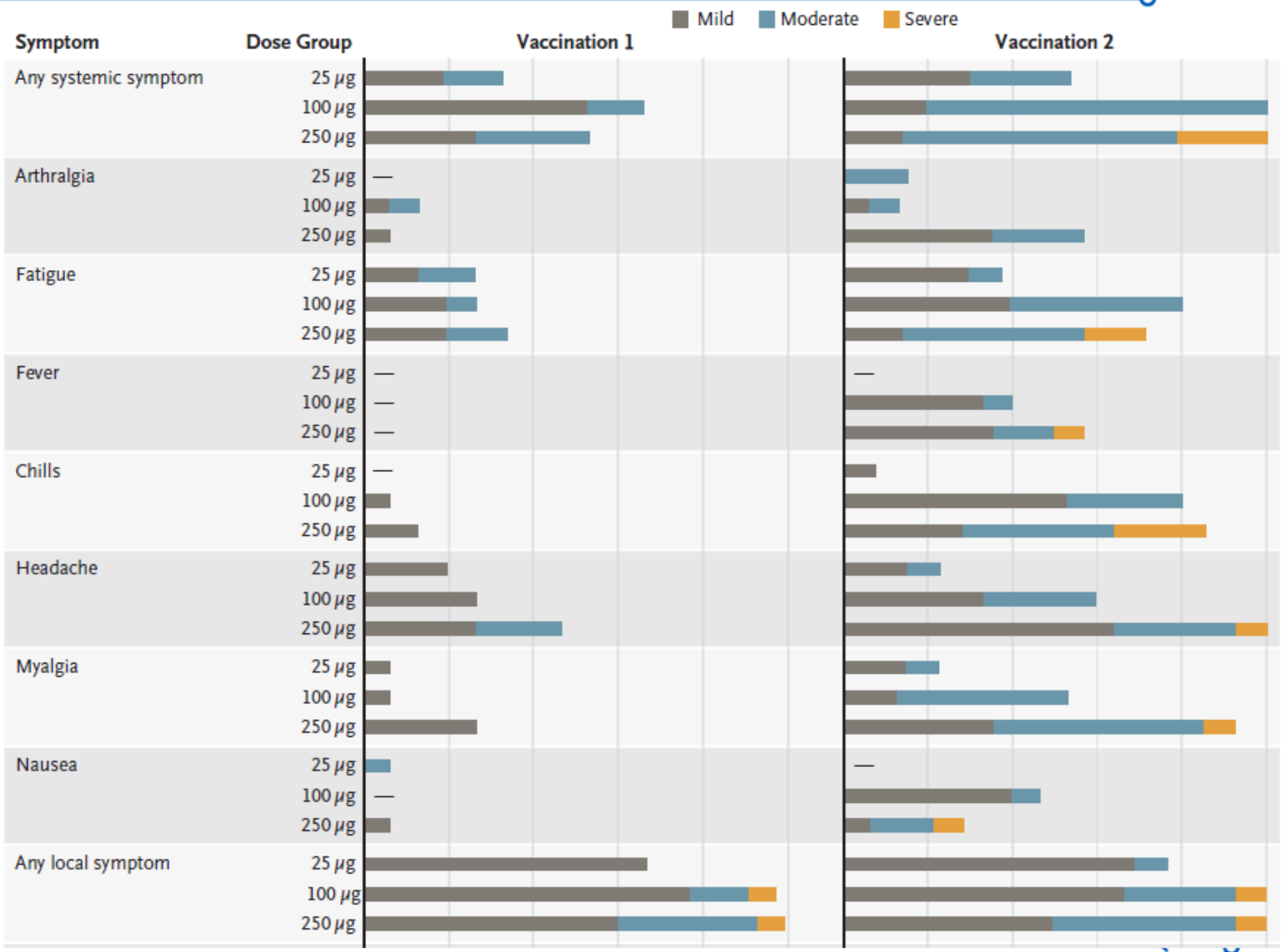
- Yes
- Not sure
- No



Do you plan to get a coronavirus vaccine when one is available?

For some in the United States, the answer is no, according to a survey of 1056 people in mid-May.

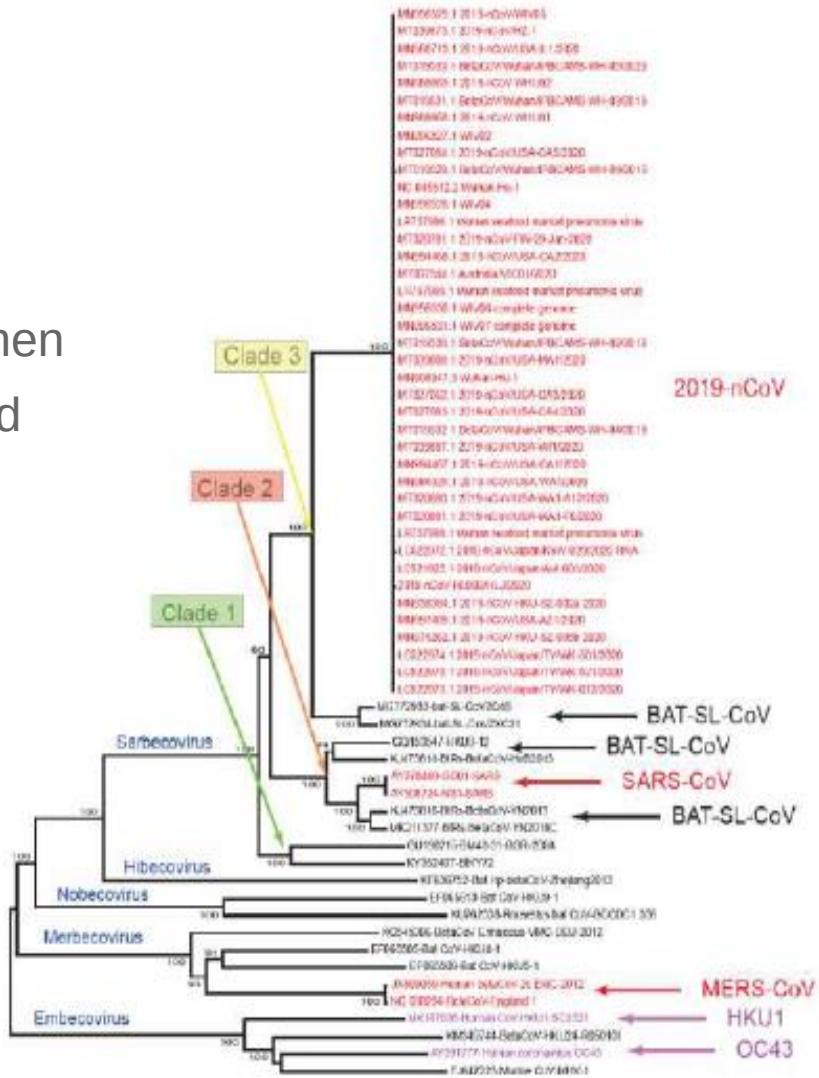




Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report [published online ahead of print, 2020 Jul 14]. *N Engl J Med*. 2020;NEJMoa2022483. doi:10.1056/NEJMoa2022483
ASSOCIATED PRESS–NORC CENTER FOR PUBLIC AFFAIRS RESEARCH AT THE UNIVERSITY OF CHICAGO, Accessed 8/31/2020

Genomic evidence for a case of reinfection with SARS-CoV-2

- Posted: 27 Aug 2020
  - 33yo man was diagnosed with COVID-19 on March 26, hospitalized, then recovered. He tested positive for SARS-CoV-2 again on August 15, and whole genome sequencing indicated they were from different clades
- Posted: 2 Oct 2020
  - 60 yo care-home resident re-infected with different strains and with different immunologic responses
- Additional considerations for CoV evolution:
  - 120Kb, 10^{-6} mutation rate, 25% recombination (modular), plastic glycoproteins



Preprints with THE LANCET

medRxiv, WHO-China Joint Mission on COVID-19 Report

Into the unknown…

- Complications
  - Metrics for clinical outcome, treatment
  - Re-infection
  - Chronic conditions
  - Steroids in early disease
  - Alkalosis, Hyperkalemia, AKI, Hepatic encephalopathy
  - Biomarkers
- Treatment
  - Confounding variables induce headaches
  - Pharmacogenomics (D614G)
  - Special populations: racial, pregnancy, cancer, etc.
  - Timing (initiation, duration)
  - Combinations – PK/PD conundrum
  - Supportive: ACE-2/ARB inhibitors, Vitamins, Herbals, NO2, etc.

Meng J, et. al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect. 2020 Dec;9(1):757-760.

Chen T, et. al. . Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020 Mar 26;368:m1091.

Little P. Non-steroidal anti-inflammatory drugs and covid-19. BMJ. 2020 Mar 27;368:m1185.

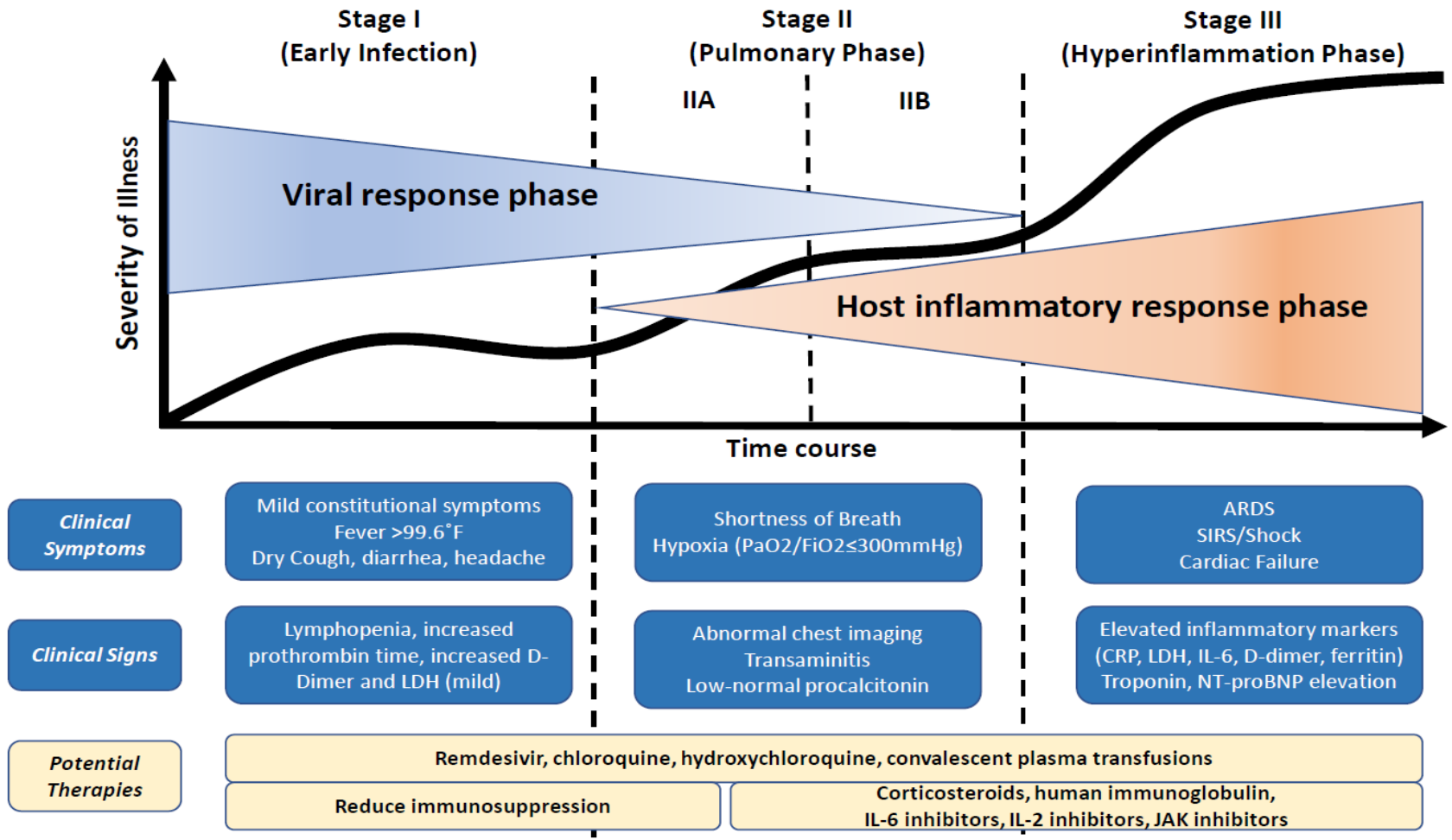
Thank You!

EXTRA SLIDES FOR QUESTIONS

University at Buffalo The State University of New York

Catholic Health

Disease Course



Siddiqi, H. K., & Mehra, M. R. (2020). COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. The Journal of Heart and Lung Transplantation. doi: 10.1016/j.healun.2020.03.012

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Catholic Health

New York State Department of Health COVID-19 Tracker

Testing data as of: 10/12/2020 Midnight
Testing data last updated on: 10/13/2020
(Updated daily before 2 PM)

Statewide

Total Persons Tested
12,230,436

Total Tested 10/12
99,070

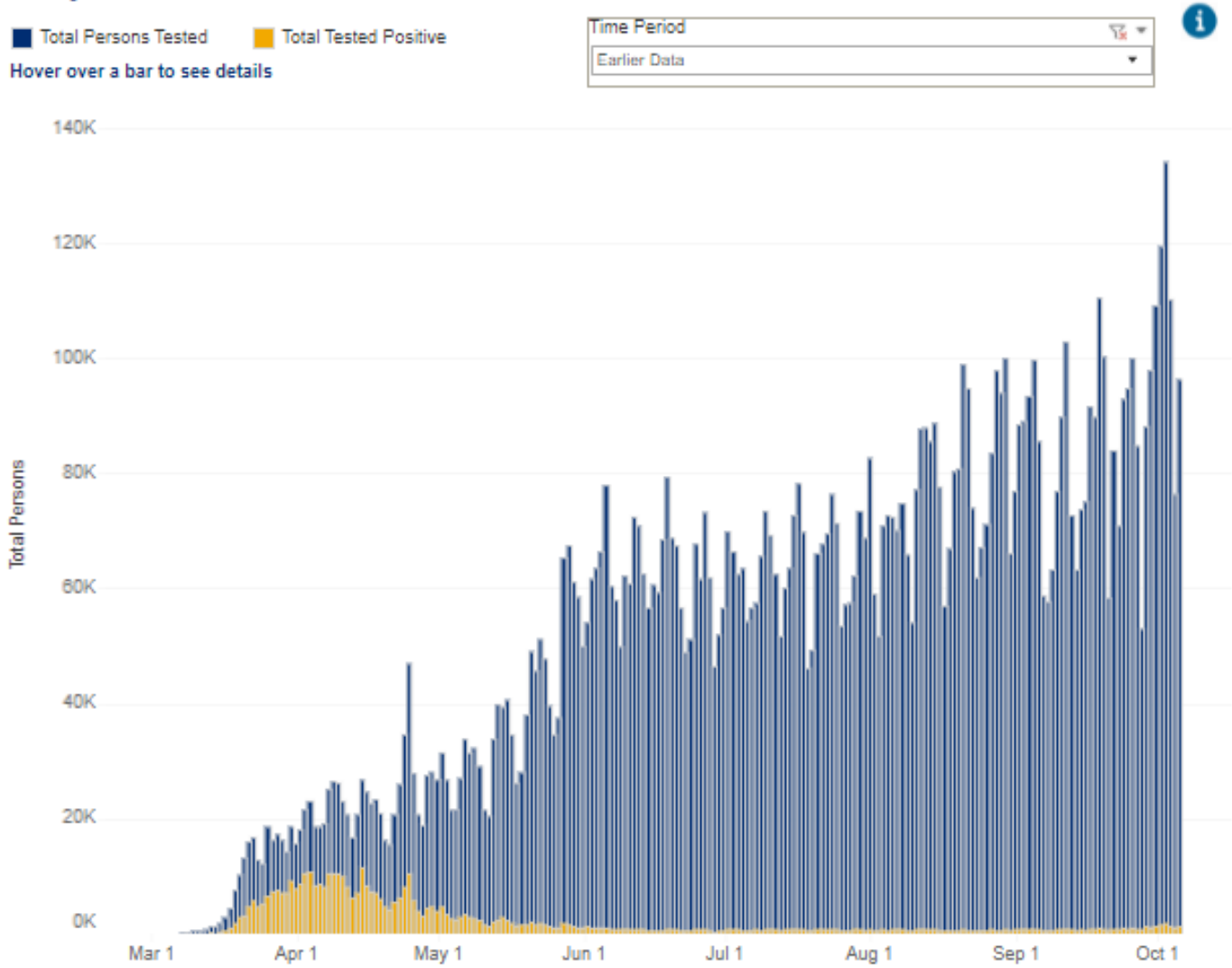
Total Tested Positive
476,708

Sex Distribution of Positive Cases

Female	Male	Unknown
49.0%	50.2%	0.9%

New Positives 10/12
1,393

Daily Totals: Persons Tested and Persons Tested Positive



Click County to See Detai
Click Again for Statewide

Albany	3,32
Allegany	15
Bronx	53,96
Broome	2,53
Cattaraugus	36
Cayuga	25
Chautauqua	73
Chemung	1,01
Chenango	28
Clinton	18
Columbia	62
Cortland	33
Delaware	15
Dutchess	5,27
Erie	12,18
Essex	18
Franklin	7
Fulton	35
Genesee	36
Greene	42
Hamilton	1

Click for Map View

Click for Table View

Click for Fatality Data

	Gautret et al (6)	Gautret et al (7)	Chen et al (8)	Chen et al (9)	Molina et al (10)
Study Type	Prospective open-label, Nonrandomized (n=42)	Prospective observational study (n=80)	RCT (n=30)	RCT (n=62)	Prospective observational study (n=11)
Treatment	HCQ 200mg TID x 10 days +/- Z-pak vs no treatment	HCQ 200mg PO TID + Z-pak (No control patients)	HCQ 400mg per day x 5 days vs conventional treatment	HCQ 200mg BID vs control	HCQ 200mg TID + Z-pak (No control patients)
Primary Outcome	Virological clearance at day-6 post-inclusion	Disease progression: Need for oxygen or ICU Admission, viral load	Negative conversion rate of nucleic acid in pharyngeal swab on day 7	Time to clinical recovery	Viral load (nasopharyngeal swab): On days 5–6
Results	HCQ: 70% HCQ + Z-pak: 100% Control: 12.5%	Day 7: 83% negative VL Day 8: 93% negative VL 3 transferred to ICU ICU mean LOS 5 days	HCQ: 86.7% Control: 93.3% (P > 0.05)	Fever resolution: 2.2 days HCQ vs 3.2 days Improved pneumonia day 6: HCQ 80.6% control group 54.8%	80% positive on days 5-6 of treatment
Safety	Not documented	N/V: 2.5% Diarrhea: 5% Blurred Vision: 1.2% Death: 1 patient	26.7% of the HCQ group and 20% of the control group had diarrhea and abnormal LFTs	HCQ group: 1 rash and 1 headache occurred	In 1 patient, treatment was stopped after 4 days due to QTc prolongation Death: 1 patient

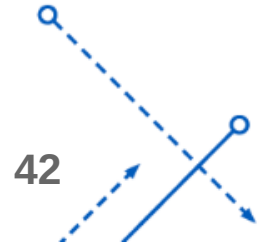
Chief Complaint and HPI

- CC: Shortness of breath and cough

- HPI: 48 year old African American Male
  - A “few days ago” he drank some water and felt like it “went down the wrong tube”
  - Almost immediately afterwards shortness of breath and cough developed
  - Spiked fever of 101 F and contacted PCP who instructed him to manage his symptoms at home (Rest + acetaminophen as needed)
  - Cough has been mostly productive consisting of clear-colored sputum
  - Developed body aches effecting his entire body
  - Symptoms continued to worsen and patient decided to go to the emergency department

Patient History

- Past Medical Hx: Diabetes, dyslipidemia, hypertension, GERD, obesity, OSA on CPAP
- Surgical Hx: Cholecystectomy, Tonsillectomy
- Social Hx: Denies drug use, alcohol use, or illicit drug use
- Family Hx: Not available
- Home medications: Atorvastatin 40mg PO QD, Gabapentin 400mg PO TID, Jardiance 10mg PO QD, Metformin 1,000mg PO BID, Omeprazole DR 20mg PO QD, Amlodipine 10mg PO QD
- Allergies: Penicillin's (Hives)



Physical Exam

- Vitals: BP 144/76, RR 24, **spO2 73% on RA,** HR 108, Temp 99.4 F
- General: Alert and oriented x3
- HEENT: Atraumatic, normocephalic. EOMI, moist mucous membranes.
- CV: Tachycardic, regular rhythm, normal heart sounds, normal S1 and S2
- **Respiratory: Tachypnea, essentially clear, but few rare scattered crackles at bases posteriorly**
- Abdomen: Soft, non-tender, normal bowel sounds
- Extremities: Normal, no evidence for cellulitis, full range of motion
- Psych: Pleasant and cooperative

Emergency Department Workup

- Lab work
  - CBC: WBC: 7.0, Hgb: 15.0, Plts: 166**, Neutrophil: 86%, Lymphocytes: 9%, Bands: 0%**
  - CMP: Na: 140, K: 3.8, Cl: 101, CO2: 27, BUN: 12, SCr: 1.0, Glucose: 138
  - APTT: 31.3, **PT: 18.8(H), INR: 1.6(H), D-dimer: 792 (H)**
  - **Blood gas on 100% NRB**: pH: 7.46, pCO2: 39, p02: 78, HCO3: 27, oxygen sat: 97%
  - HS troponin: 6, lactic acid: 1.5, influenza A/B negative, **LDH: 411 (H), CRP: 50.9 (H), Ferritin: 688.8(H), Procalcitonin: 0.09**
  - Blood cultures, urine antigens, nasal cultures, tox screen, **COVID-19 testing ordered**
  - **BMI: 54.39**
- Imaging/EKG:
  - CXR: **Extensive bilateral infiltrates consistent with bilateral pneumonia**
  - EKG: Sinus tachycardia, moderate intraventricular conduction delay + nonspecific T-wave abnormality. QTc: 418
- Given NS 500ml IV @ 150ml/hr, Ceftriaxone 1g IV, Azithromycin 500mg IV, Acetaminophen 975mg PO

Diagnostic Lab Findings

- CBC with differential
  - WBC is usually normal (4-11): 7.0
  - Lymphopenia is common (20-40%): 9%
  - Mild thrombocytopenia is common (145-450): 166
- CMP with magnesium and phosphorus
  - LFTs commonly elevated AST/ALT WNL
- Coagulation studies with D-dimer
  - PT/PTT/INR usually normal
  - D-dimer commonly elevated (0-500): 792
- Procalcitonin
  - Usually not elevated* (0-0.10): 0.09

CRP (0-5): 50.9

- Usually elevated and increases with progression

- Other Labs:
  - LDH (105-210): 411
  - Ferritin (23.9 – 336.2): 688.8
  - Urine legionella antigens (Negative)
  - Blood cultures (Negative)
  - Troponin (0-20): 6
  - ABG 7.46/39/78/27.7
  - Lactate Not ordered on admission
  - CPK Not ordered on admission
  - *G6PD Not ordered on admission*
- EKG: Qtc: 418

Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020

Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020

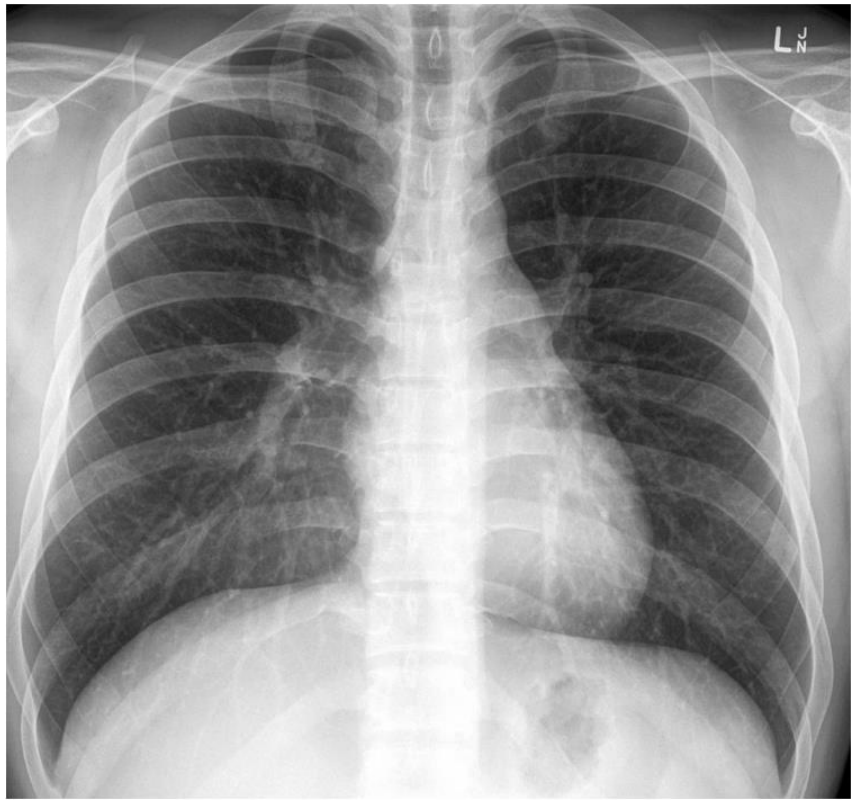
Diagnostic Imaging: Chest X-Ray

- Patchy ground glass opacities
  - Present bilaterally and predominantly peripherally
- Clear lungs**
  - Seen early in course of disease in many mildly symptomatic patients → Quickly progresses to ground class opacities
- Pleural effusions are uncommon

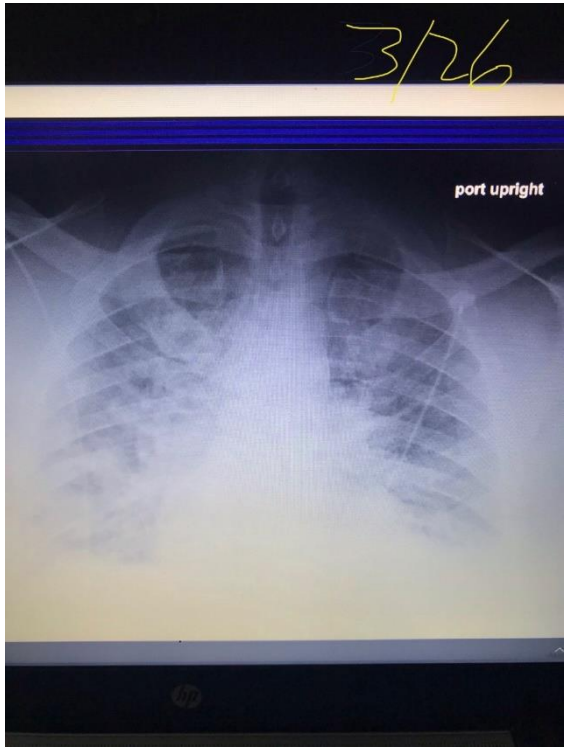
Shi, H., Han, X., Jiang, N., Cao, Y., Alwalid, O., Gu, J., … Zheng, C. (2020). Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases, 20(4), 425–434. doi: 10.1016/s1473-3099(20)30086-4

Patient's Initial Chest X-Ray

NORMAL CHEST X-RAY

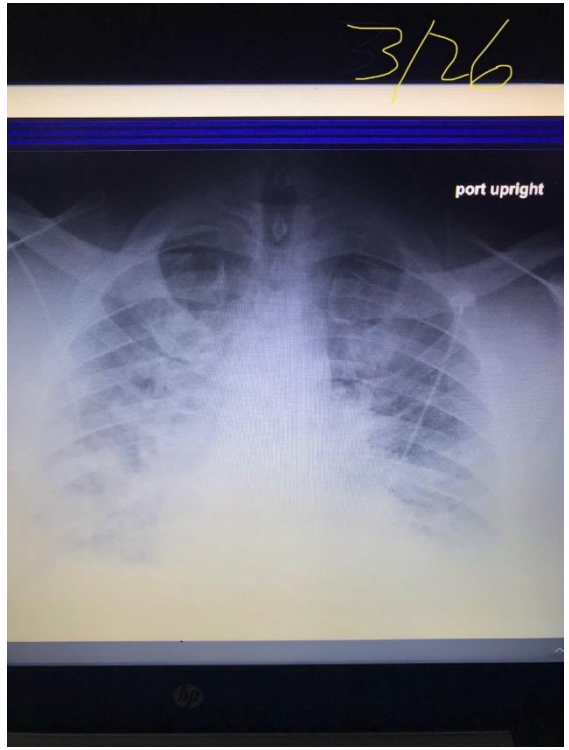


ADMISSION CHEST X-RAY

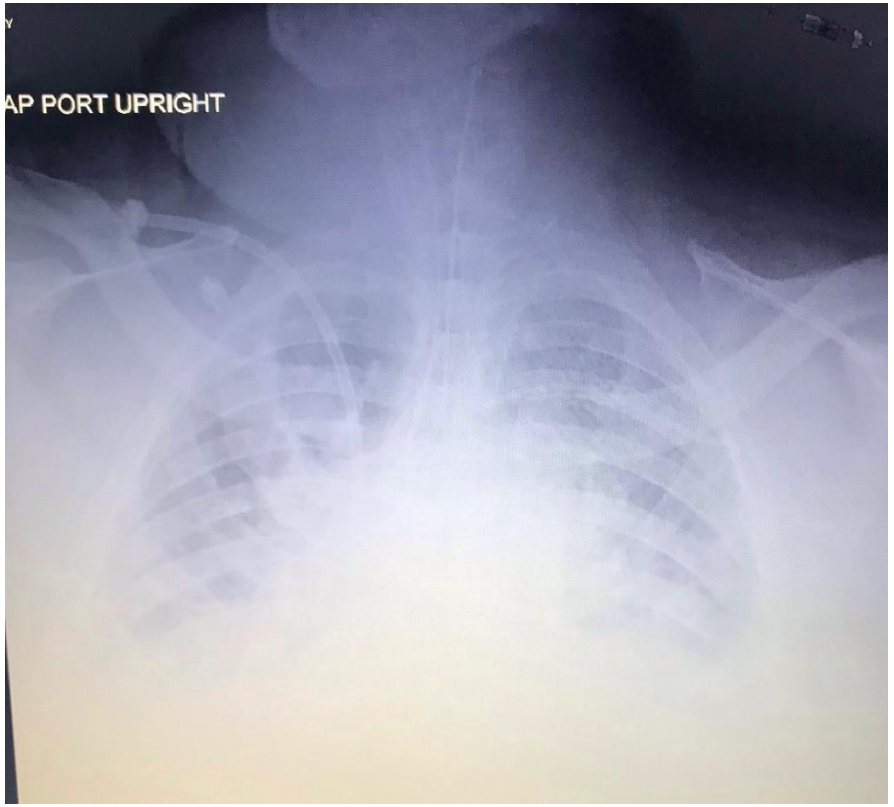


Imaging Progression

ADMISSION CHEST X-RAY



X-RAY HOSPITAL DAY 4



HCQ+ azithro + cefriaxone

HCQ + ABX Complete dNimbex started

Vanco + Cefepime

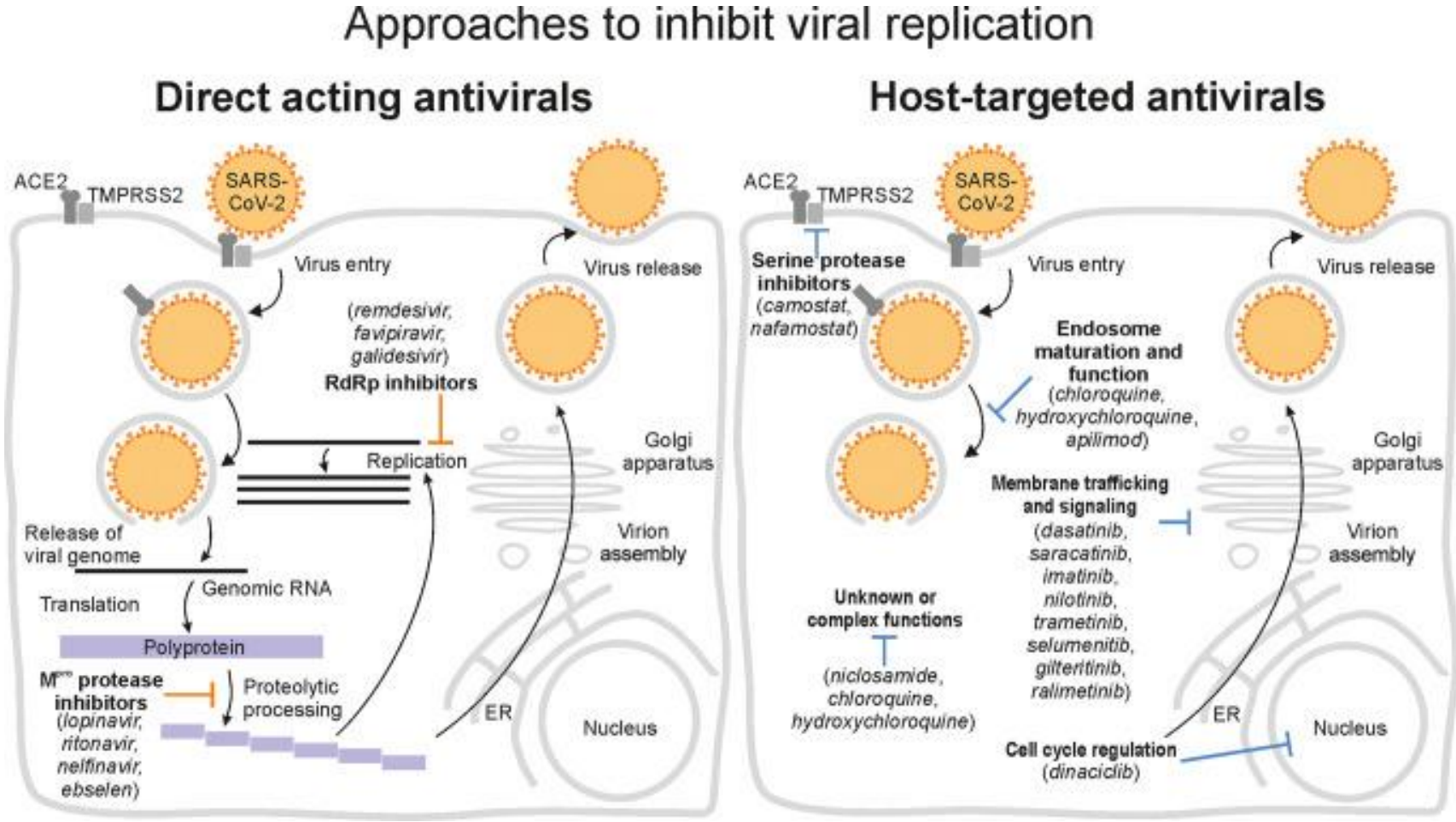
	D-Dimer (0-500ng/mL)	Serum Creatinine (0.9-1.3 mg/dL)	CRP (0.0-5.0mg/L)	Ferritin (23.9 – 336.2 ng/mL)	WBC (4.0-11.0)
Day 1	792	1.0	50.9	688.8	7.0
Day 2	-	2.37	-	-	5.2
Day 3	-	5.73	-	-	5.3
Day 4	-	7.45	116.4	-	6.1
Day 5	-	7.74	-	-	8.6
Day 6	18,129	7.63	176.9	-	9.1
Day 7	15,919	7.79	152.6	1,814.0	10.2
Day 8	23,560	7.42	118.6	1,487.3	13.6
Day 9	-	7.49	-	-	15.6
Day 10	-	7.49	-	-	19.6
Day 11	-	7.92	-	-	18.1
Day 12	-	8.06	-	-	20.7

Coagulopathy

- Common: fibrin-platelet micro-thrombi in the pulmonary vasculature
- 183 patients admitted to the Tongji Hospital in Wuhan
  - DIC in **71.4%** of non-survivors and **0.6%** of survivors
- High fibrinogen levels reduce efficacy of prophylactic dose heparin agents
  - Whole-blood samples obtained from healthy volunteers (n = 10)
  - Results: Hyperfibrinogenemia negated the effect of heparin and was noted in all TEG parameters

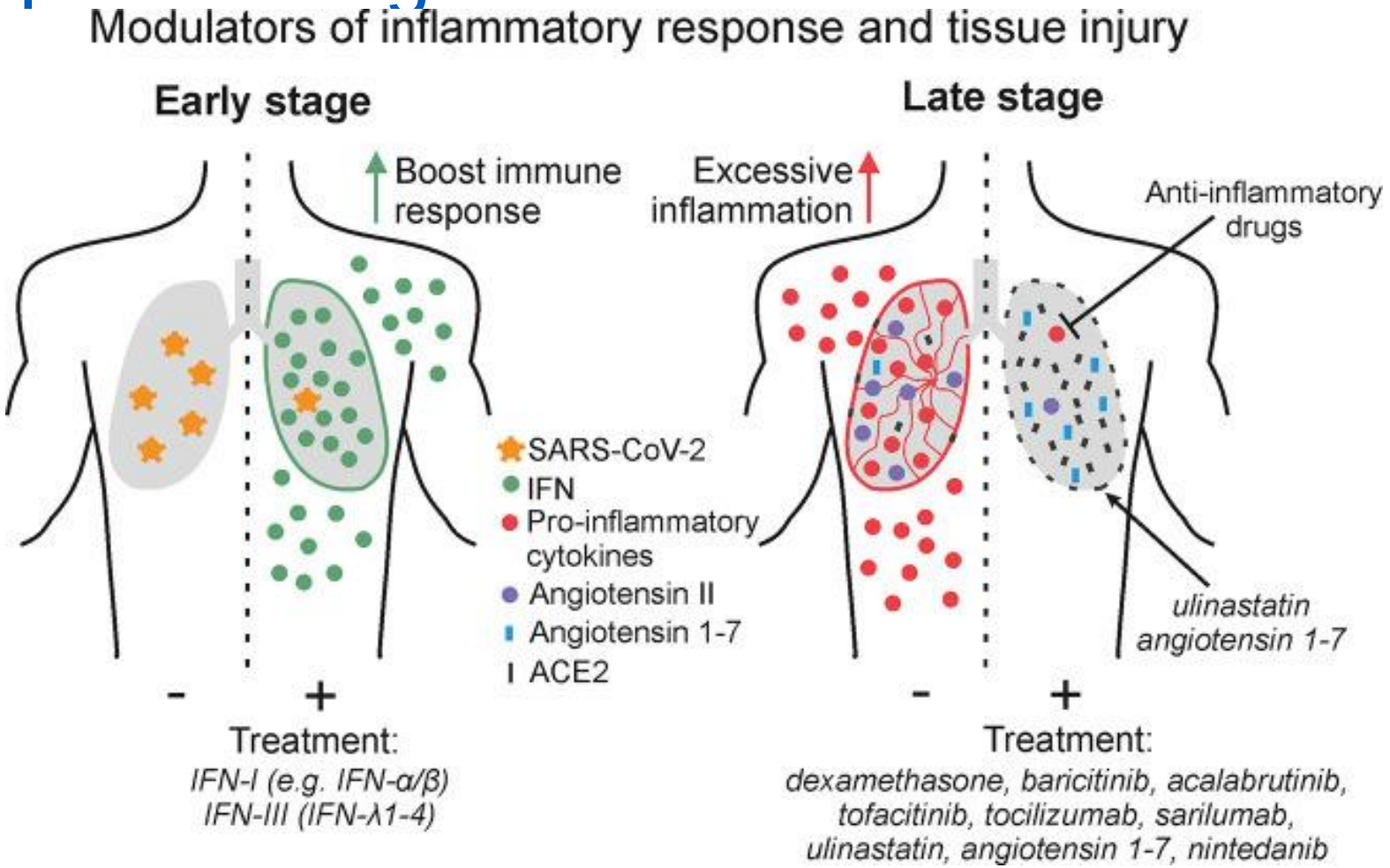
Bikdeli, B., Madhavan, M. V., Jimenez, D., Chuich, T., Dreyfus, I., Driggin, E., … Lip, G. Y. (2020). COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. Journal of the American College of Cardiology. doi: 10.1016/j.jacc.2020.04.031
Harr JN, Moore EE, Chin TL, et al. Postinjury hyperfibrinogenemia compromises efficacy of heparin-based venous thromboembolism prophylaxis. Shock. 2014;41(1):33-9.
Barrett CD, Moore HB, Yaffe MB, Moore EE. ISTH interim guidance on recognition and management of coagulopathy in COVID-19: A Comment. J Thromb Haemost. 2020;

Therapeutic Targets



Saul S, Einav S. Old Drugs for a New Virus: Repurposed Approaches for Combating COVID-19 [published online ahead of print, 2020 Aug 10]. *ACS Infect Dis*. 2020;acsinfecdis.0c00343. doi:10.1021/acsinfecdis.0c00343

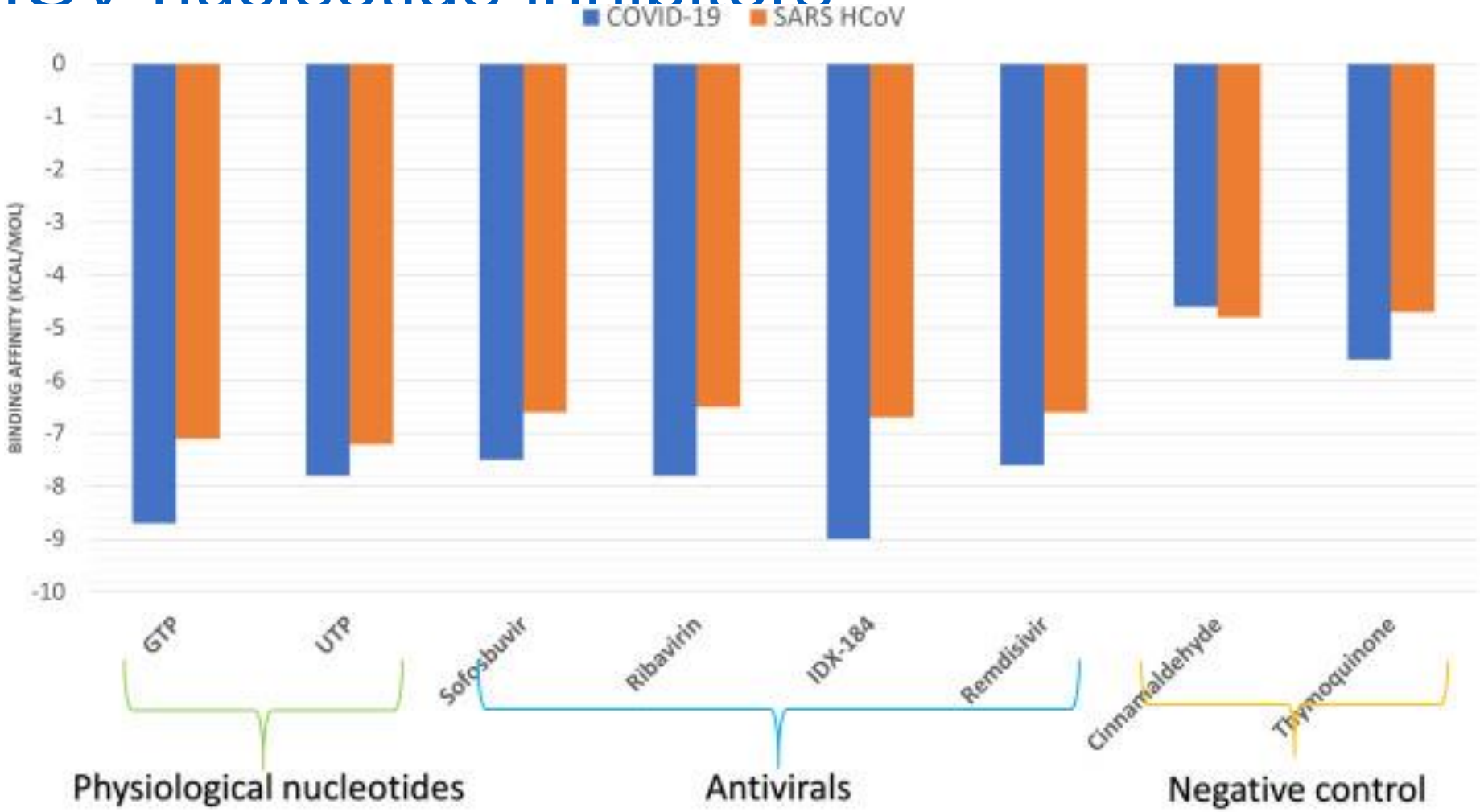
Therapeutic Targets



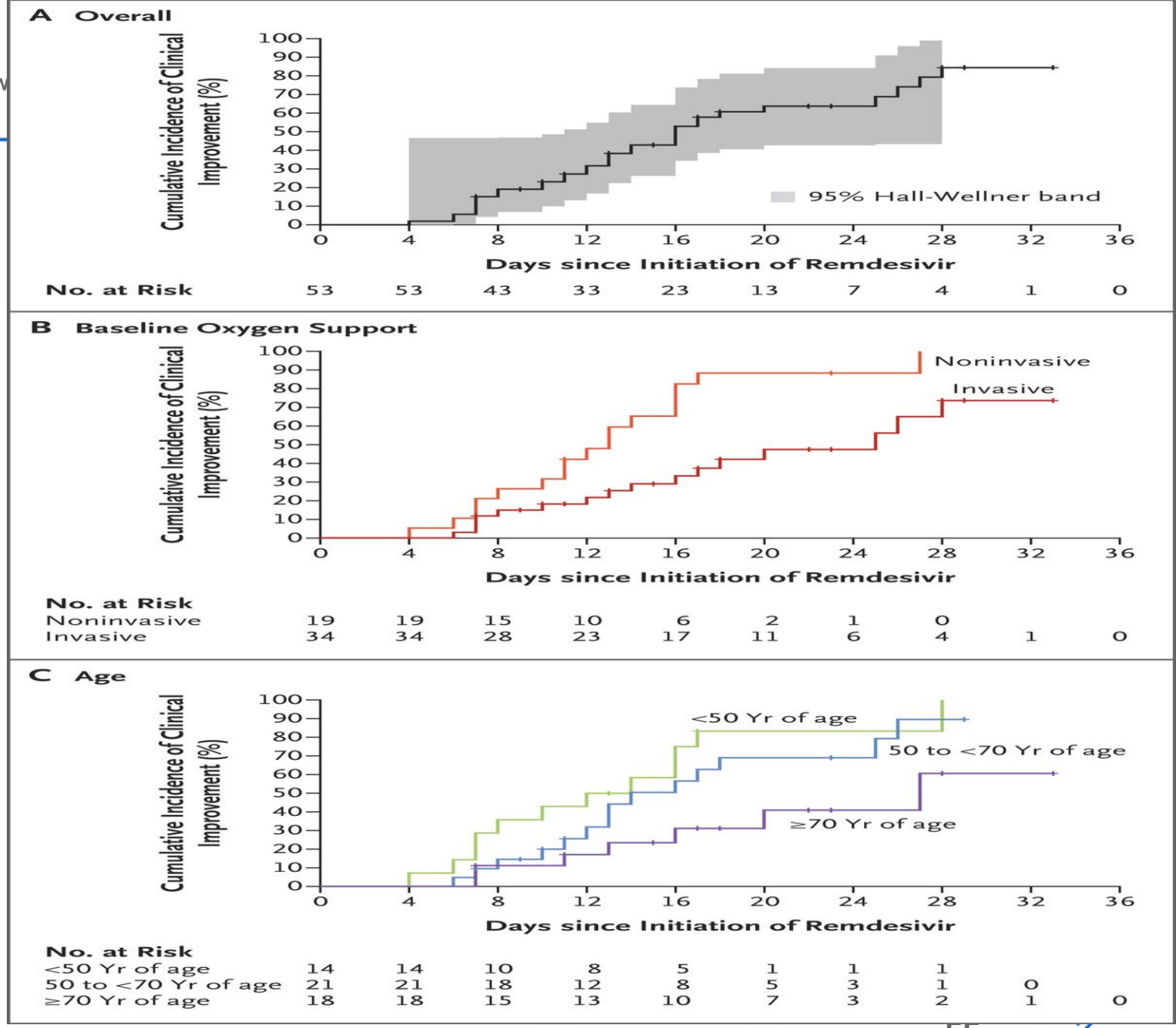
Saul S, Einav S. Old Drugs for a New Virus: Repurposed Approaches for Combating COVID-19 [published online ahead of print, 2020 Aug 10]. *ACS Infect Dis*. 2020;acsinfecdis.0c00343. doi:10.1021/acsinfecdis.0c00343

Therapeutic target	Drug and article reference	Drugs related studies
Receptor recognition (ACE2, CD147 receptors)	Human recombinant soluble form of ACE2 (Khan et al., 2017; Monteil et al., 2020; Monteil et al., 2020).	NCT04335136, NCT04375046 NCT04287686 (withdrawn)
	Meplazumab (mAb antiCD147 receptor) (Wang K. et al., 2020)	NCT04275245
Clathrin-mediated endocytosis	Hydroxychloroquine (Hq) sulphate (Picot et al., 1993; Jang et al., 2006; Bender et al., 2020) and Chloroquine phosphate (Savarino et al., 2003; Vincent et al., 2005) *multiple targets: clathrin-mediated endocytosis, endosomal Ph, TLR7/8, IFN response, and proinflammatory cytokines release) Controversial results: (Borba et al., 2020; Lane et al., 2020; Shamshirian et al., 2020; Tu et al., 2020)	-ongoing studies NCT04315948, DisCoVeRy trial, NCT04304053 ChiCTR2000029803, NCT04334148, ChiCTR2000029609 -discontinued study: Hq arm of Solidarity trial -withdrawn: NCT04347512, NCT04371926
	Baricitinib (Richardson et al., 2020; Stebbing et al., 2020)	NCT04320277, NCT04401579 NCT04362137
	Ruxolitinib (Gaspari et al., 2020; Yeleswaram et al., 2020)	
Endosomal fusion	Umifenovir (Deng et al., 2020; Lian et al., 2020)	IRCT20151227025726N15
	Camostat mesylate (Kawase et al., 2012; Yamamoto et al., 2016; Hoffmann et al., 2020b) * multiple targets: TMPRSS2, endosomal fusion	NCT04321096
Viral synthesis	Protease inhibitors: lopinavir/darunavir/ritonavir (3CLpro, PLpro)	RECOVERY trial, NCT04251871, NCT04255017, ChiCTR2000029539 NCT04252274, NCT04295551, ChiCTR2000029308, NCT04252274
	Remdesivir * (Sheahan et al., 2017; Agostini et al., 2018; Beigel et al., 2020; Goldman et al., 2020; Grein et al., 2020; Wang M. et al., 2020; Wu et al., 2020a; Wang Y. et al., 2020) *multiple targets: viral autophagy, mTORC1, Nsp12-RdRp, replicase/ transcription complex –RTC	Trial ACTT-NCT04280705 si ACTT-II, NCT04292899 NCT04257656, SIMPLE trial, WHO Solidarity trial, DisCoVeRy trial
	Favipiravir/target: Nsp12-RdRp) (Coomes and Haghbayan, 2020)	ChiCTR2000030254, ChiCTR2000029544 ChiCTR2000029600
Cytokine response, Th1 response	IFN administration (Hung et al., 2020)	See **Table 1**
	Controversial results (Gandhi, 2020)	
	Ruxolitinib (anti-Janus kinase inhibitor) (Gaspari et al., 2020; Yeleswaram et al., 2020)	NCT04362137
IL-6 production	Tocilizumab (Xu et al., 2020). (Anti IL-6 mAb)	NCT04317092, NCT04315480 COVACTA, NCT04320615
	Sarilumab and siltuximab (Anti IL-6 mAb)	NCT04324073, NCT04315298, NCT04329650
VEGFA	Bevacizumab (anti-VEGFA mAb)	NCT04275414
GM-CSF	Gimsilumab (Zhou Y. et al., 2020) (anti GM-CSF mAb)	BREATH clinical trial
Inflammatory response	Corticosteroids (Horby et al., 2020; Wu et al., 2020b).	UK RECOVERY trial NCT04381936
Immuno-modulatoy activity	Mesenchymal stem cells (Shi et al., 2018; Leng et al., 2020)/ *multiple targets:inflammatory cytokines, Th2 response, regeneration of damaged cell	See **Table 2**
	Thalidomide	NCT04273529, NCT04273581
	Fingolimod	NCT04280588
Neutralizing antibodies	Convalescent plasma (Rogers et al., 2020; Zhou and Zhao, 2020)	NCT04381936, NCT04373460, ISRCTN50189673, NCT04348656
	mAb (Sui et al., 2004; Elshabrawy et al., 2012); neutralizing IgG1 monoclonal antibody (mAb) directed against the spike protein of SARS-CoV-2 (LY-CoV555) JS016	NCT04427501, NCT04441918
	-cross-reactive neutralizing antibodies against SARS-CoV-2 RBD specific epitopes (Lan et al., 2020; Wang C. et al., 2020; Yuan et al., 2020)	See **Table 3**

Anti-HCV nucleotide inhibitors



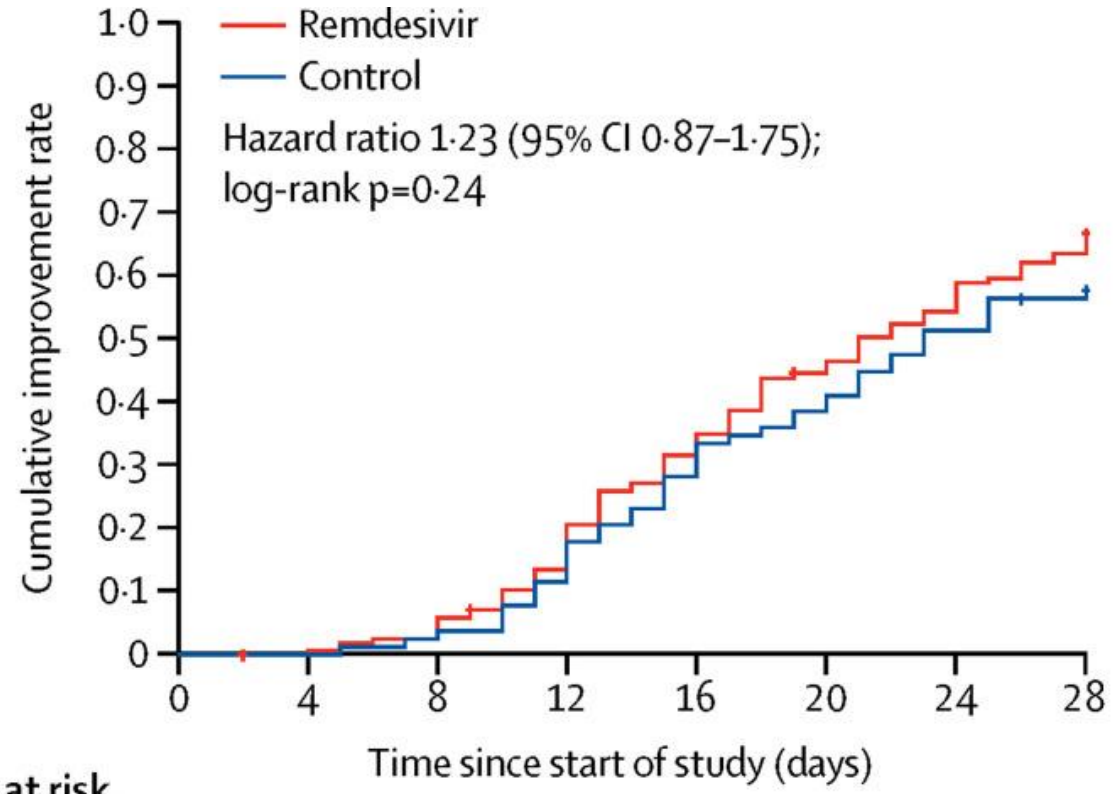
Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci. 2020 May 1;248:117477.



J Grein et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2007016

Modest beginnings

- Randomized, placebo
- N=237
- Concomitant treatments allowed
- Onset of symptoms <12 days
- Participants had SpO2 <94 and pneumonia
- Terminated early

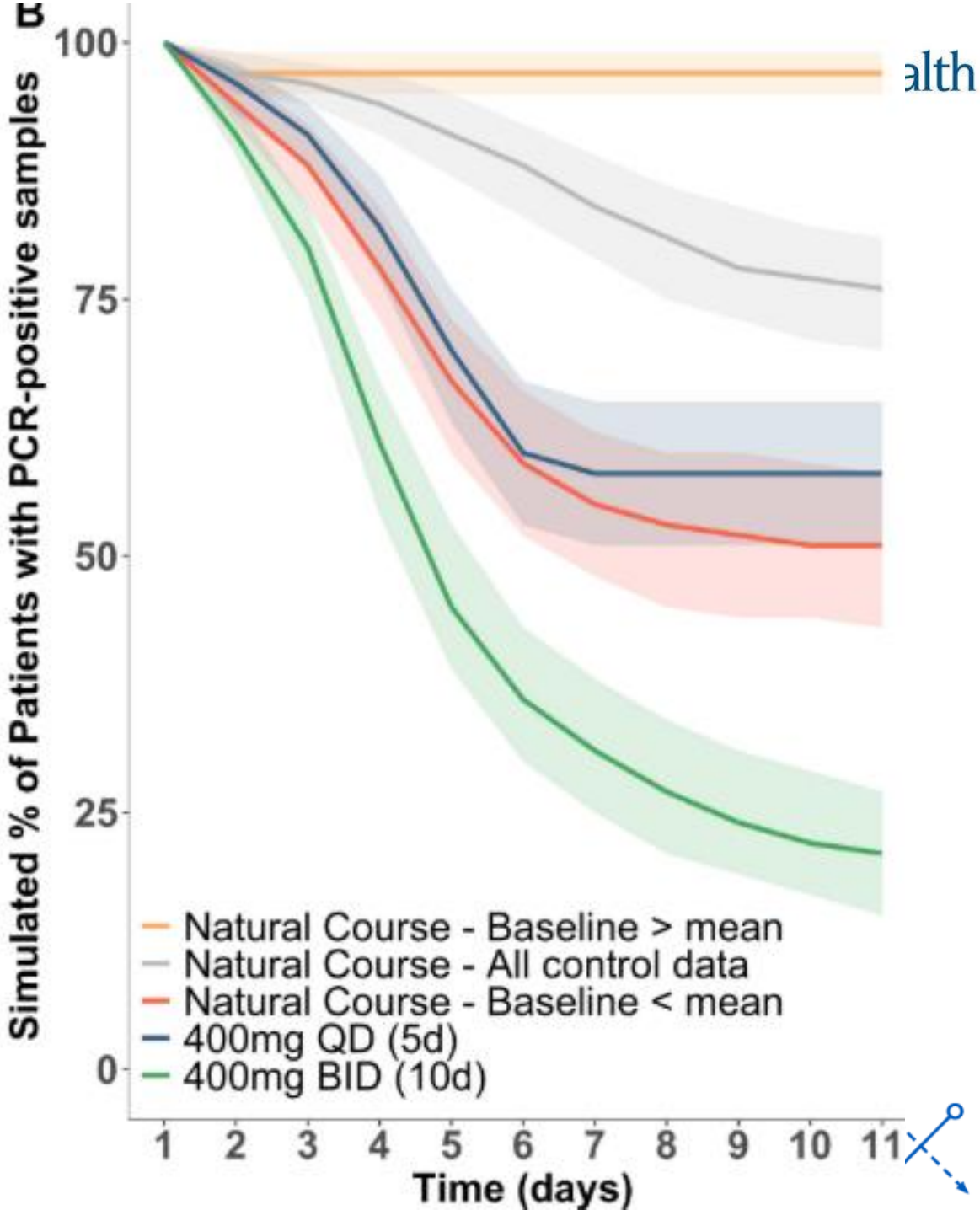


Number at risk (number censored)								
Remdesivir	158	155	147	123	101	82	63	25
	(0)	(2)	(0)	(1)	(0)	(1)	(0)	(26*)
Control	78	78	75	64	52	46	38	17
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(16*)

Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569-1578.

University at Buffalo The State University of New York

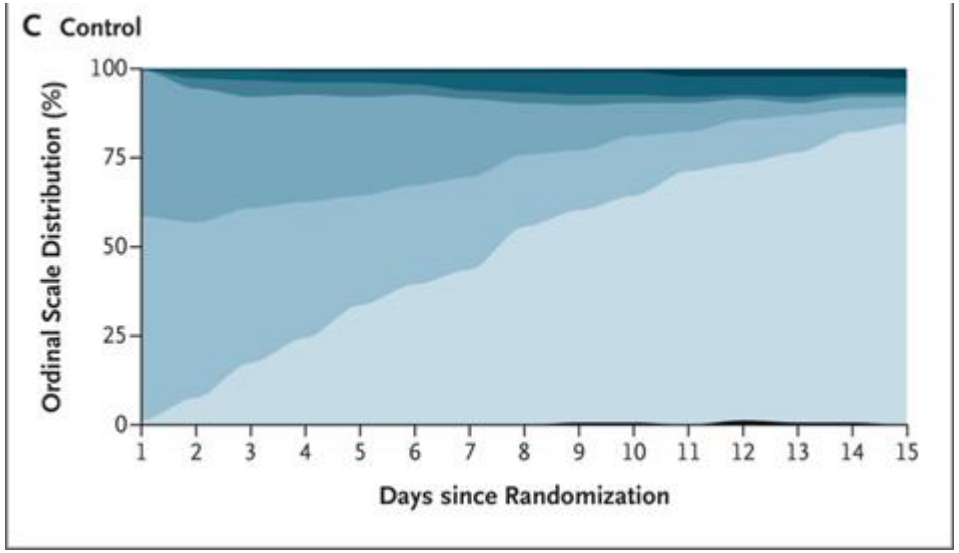
Mechanistic PK/PD model - HCQ

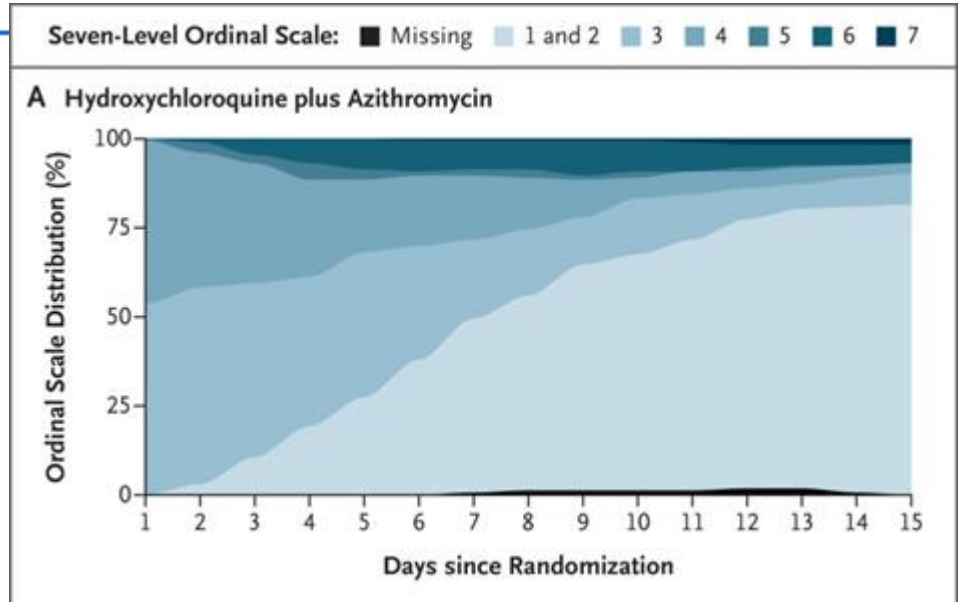


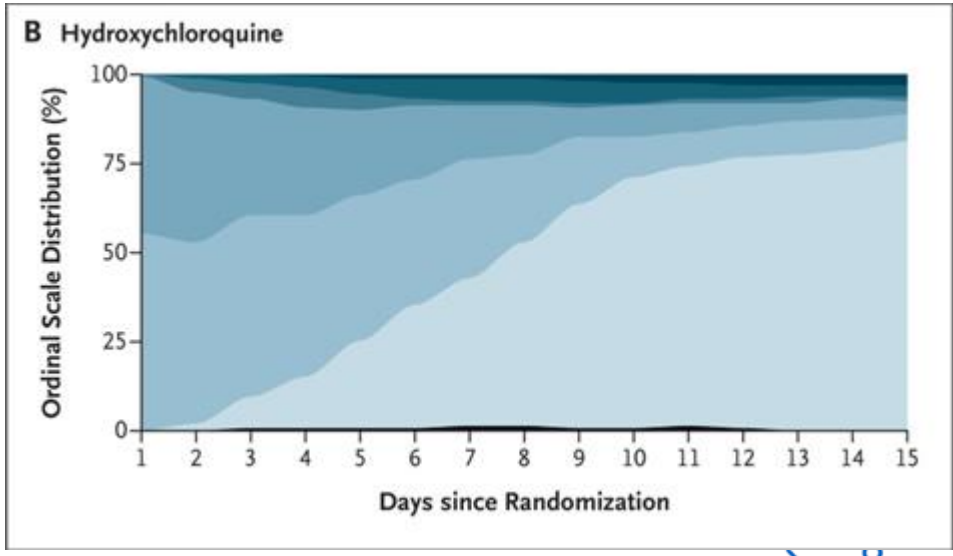
Garcia-Cremades M, et al. Optimizing hydroxychloroquine dosing for patients with COVID-19: An integrative modeling approach for effective drug repurposing. Clin Pharmacol Ther. 2020 Apr 14. doi: 10.1002/cpt.1856.

HCQ or HCQ+Azithro

- Brazil
- Unblinded
- N = 504
- 15d follow-up
- Differences in AE







Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. *N Engl J Med*. 2020.

Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with COVID-19

- Retrospective analysis of data from patients hospitalized with confirmed SARS-CoV- 2 infection in all United States Veterans Health Administration medical centers

- The two primary outcomes were death and the need for mechanical ventilation

Treatment	Number of Patients	Death Rate (%)	Ventilation Rate (%)
HCQ	97	**27.8**	13.3
HCQ + AZ	113	**22.1**	6.9
No HCQ	158	**11.4**	14.1

Shi, H., Han, X., Jiang, N., Cao, Y., Alwalid, O., Gu, J., … Zheng, C. (2020). Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. The Lancet Infectious Diseases, 20(4), 425–434. doi: 10.1016/s1473-3099(20)30086-4

LPV/RIT (n=42)

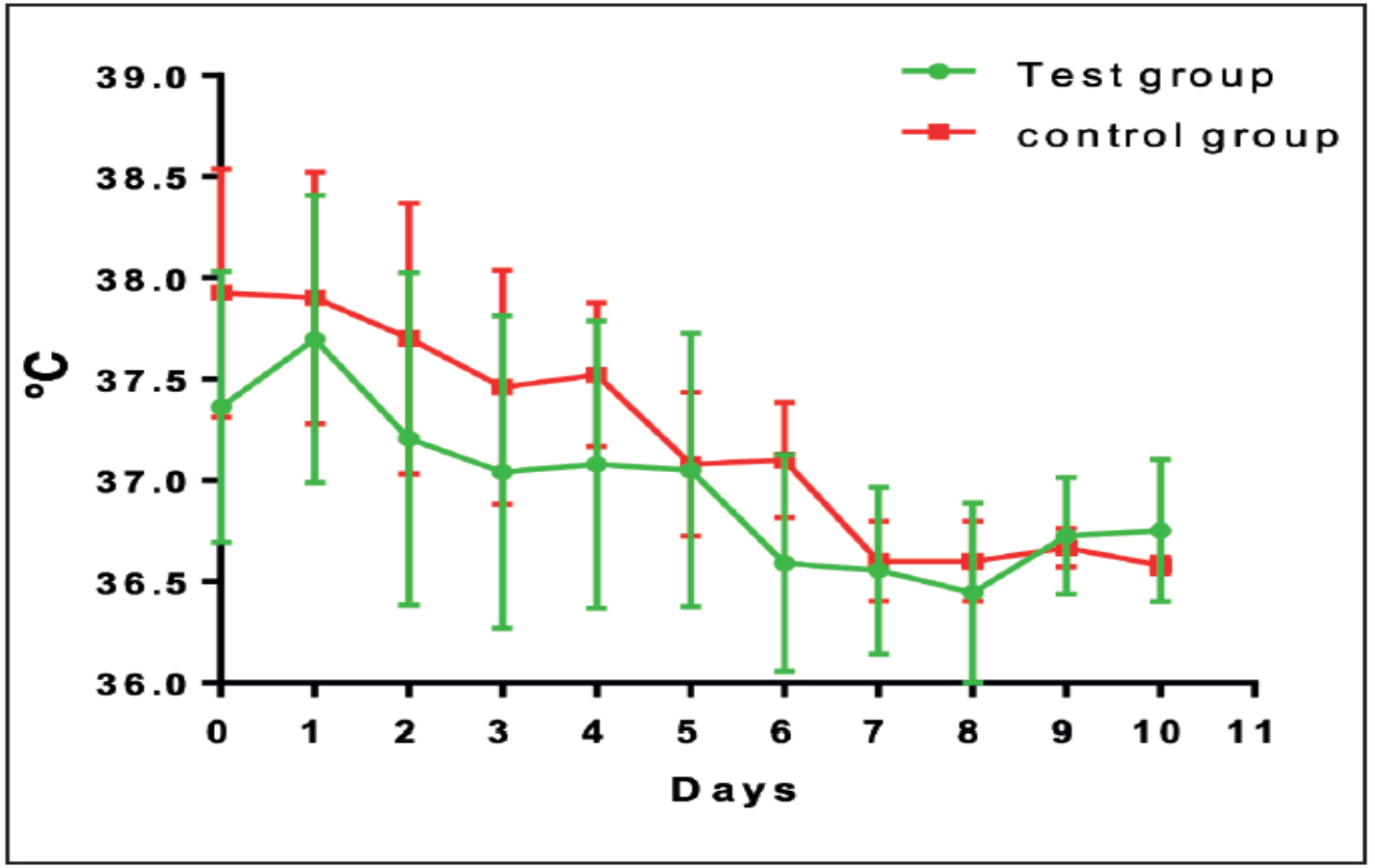
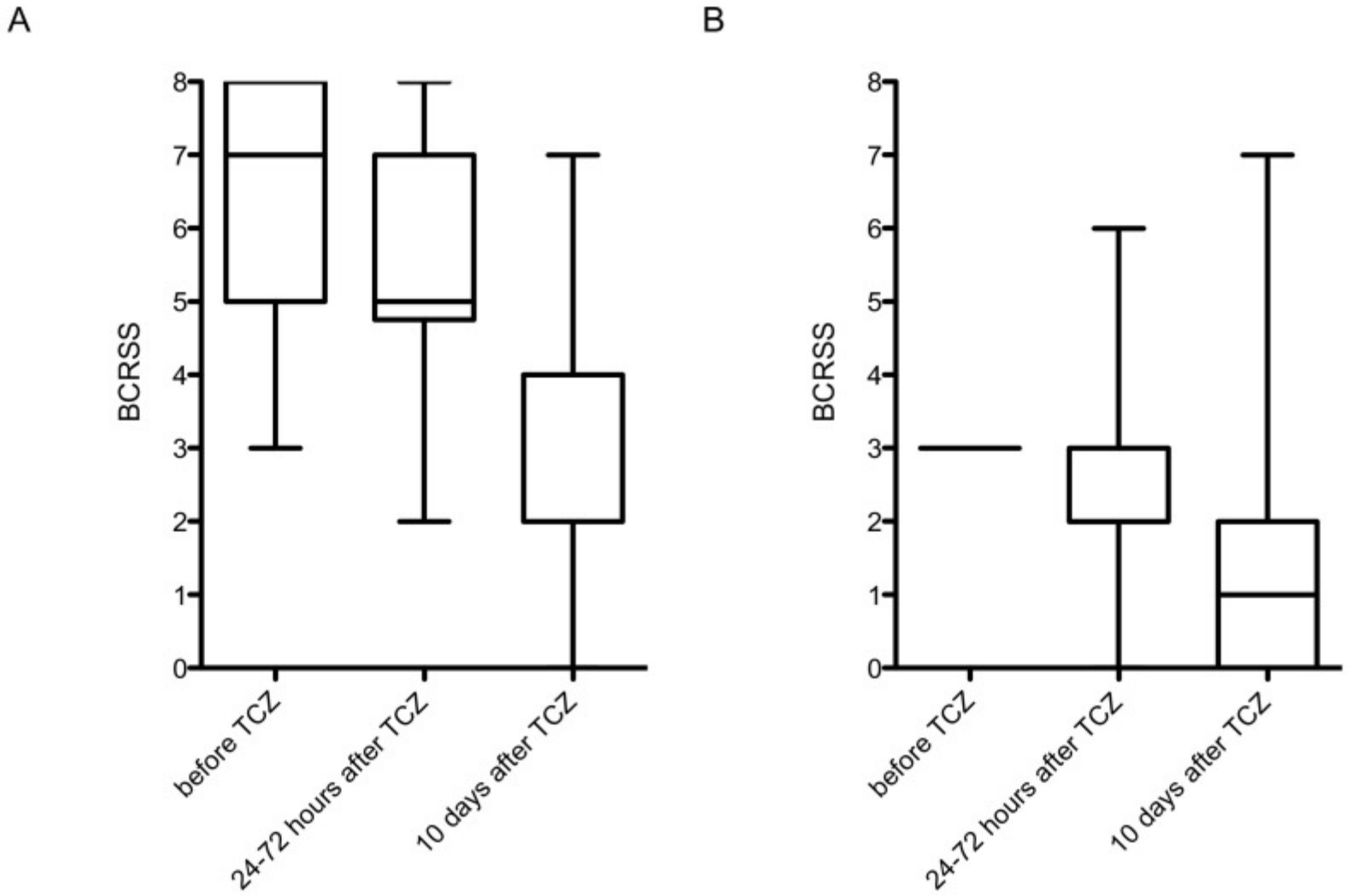


Figure 1. Daily temperature variations of patients in the two groups during 10-day hospitalization period.

Ye XT, et al. Clinical efficacy of lopinavir/ritonavir in the treatment of Coronavirus disease 2019. Eur Rev Med Pharmacol Sci. 2020 Mar;24(6):3390-3396.



Toniati P, Piva S, Cattalini M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. *Autoimmun Rev*. 2020;19(7):102568. doi:10.1016/j.autrev.2020.102568

Steroids: Conflicting Recommendations

SURVIVING SEPSIS CAMPAIGN

- Recommendation 22:
  - For adults with COVID-19 and refractory shock, we suggest using low-dose corticosteroid therapy over no corticoid therapy
- Recommendation 41:
  - In mechanically ventilated patients with COVID-19 and respiratory failure **(without ARDS),** we suggest **against the routine use** of systemic corticosteroids
- Recommendation 42:
  - In mechanically vented patients with COVID-19 and **ARDS** we **suggest using** systemic corticosteroids, over not using corticosteroids

INFECTIOUS DISEASE SOCIETY

- Recommendation 4:
  - Among patients who have been admitted to the hospital with COVID-19 pneumonia, the IDSA guideline panel suggests **against the use of corticosteroids**
- Recommendation 5:
  - Among patients who have been admitted to the hospital with ARDS due to COVID-19, the IDSA guideline panel recommends the use of corticosteroids **in the context of a clinical trial** (Knowledge gap)

Retrieved from https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
Alhazzani, W., Møller, M. H., Arabi, Y. M., Loeb, M., Gong, M. N., Fan, E., … Rhodes, A. (2020). Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Medicine. doi: 10.1007/s00134-020-06022-5

2004: Effects of early corticosteroid treatment on plasma SARS-associated *Coronavirus* RNA concentrations in adult patients

- Ribavirin-treated patients who received early hydrocortisone therapy vs those who received placebo (n = 16 non-ICU)
- Plasma SARS-CoV RNA concentrations in the 2nd/3rd week of illness were significantly higher in patients who received tx
- Pts tx with early steroid were less likely to deteriorate clinically

2006: Treatment of Severe Acute Respiratory Syndrome With Glucocorticoids

(Correlative study)

- Review: 401/1,278 SARS cases treated in Guangzhou China
- Use of corticosteroid in confirmed critical SARS resulted in lowered mortality and shorter hospitalization stay, and was not associated with significant secondary lower respiratory infection and other complications

2016: Clinical recommendations from an observational study on MERS: glucocorticoids was benefit in treating SARS patients

- Non-severe disease, steroid use was generally non-beneficial. Use of >160 mg/day methylprednisone correlated with *increased* risk of death
- More severe disease, steroid correlated with improved survival (even at relatively high doses and extended courses)

Lee N, Allen C, Hui D, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol. 2004;31(4):304-309. doi:10.1016/j.jcv.2004.07.006
Chen R, Tang X, Tan S, et al. Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. Chest. 2006;129(6):1441-1452. doi:10.1378/chest.129.6.1441
Int J Clin Exp Med 2016;9(5):8865-8873

Corticosteroid Therapy for Critically ill Patients with the Middle East Respiratory Syndrome

- Analyzed data from a multicenter, retrospective cohort study from 14 participating Saudi Arabian tertiary care hospitals
- Hydrocortisone was the most frequently administered corticosteroid followed by methylprednisolone
- The use of corticosteroid therapy was not associated 90-day mortality but was associated with delayed MERS-CoV RNA clearance

Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19

- 25/78 received corticosteroids, divided into general/severe
- General (9): Oral methylprednisolone hydrocortisone-equivalent dose, 237.5 mg/day x 9 days
- Severe (16) : IV methylprednisolone hydrocortisone-equivalent dose, 250.0 mg/day x 4.5 days
- RT-PCR to assess viral clearance: No significant difference identified in both general group + severe group vs no steroid

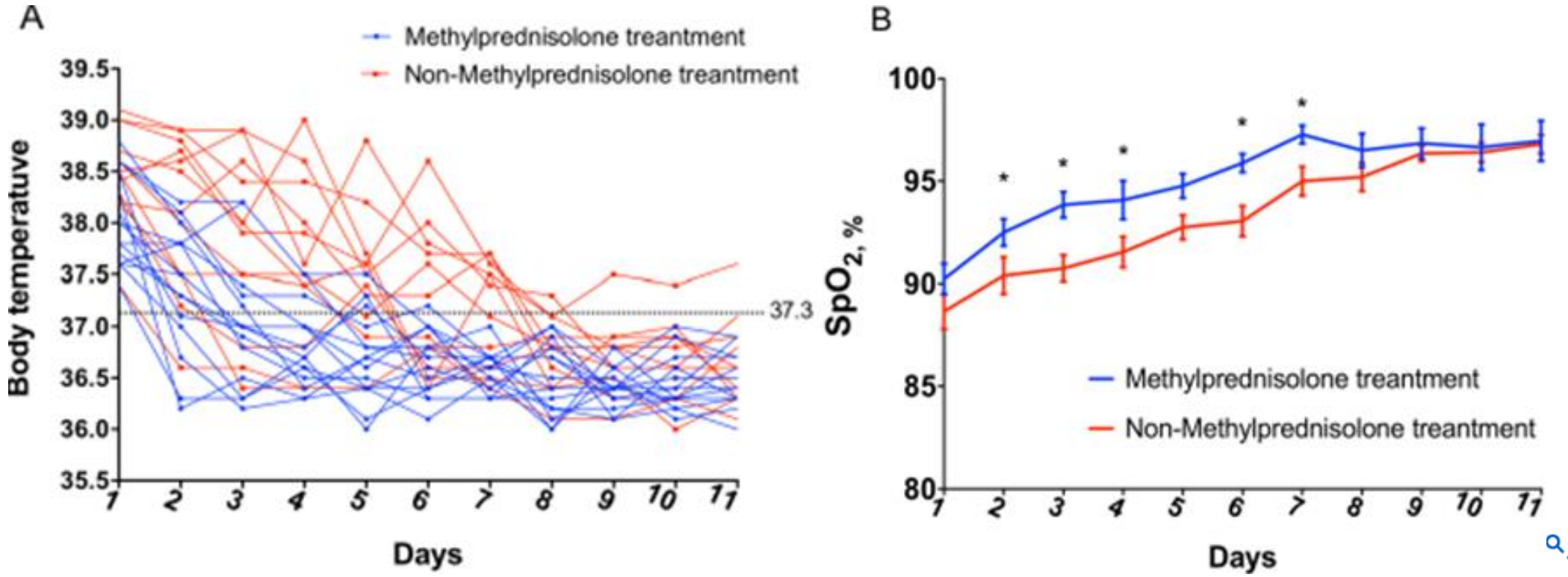
Arabi YM, Mandourah Y, Al-hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. Am J Respir Crit Care Med. 2018;197(6):757-767.

Application of Corticosteroid Treatment in Patients with Severe COVID-19 Pneumonia

- 46 hospitalized patients with severe COVID-19 pneumonia hospitalized at Wuhan Union Hospital from January 20 to February 25, 2020, were retrospectively reviewed
  - The patients were divided into two groups based on whether they received corticosteroid treatment
- 26 patients received IV administration of methylprednisolone with a dosage of 1-2mg/kg/d for 5-7 days, while the remaining patients not
- The average number of days for body temperature back to the normal range was significantly shorter in patients with administration of methylprednisolone.
- Methylprednisolone group had a faster improvement of SpO2, while patients without administration had a significantly longer interval of using supplemental oxygen therapy

Wang Y , Jiang W , He Q , et al Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv. Preprint posted March 12, 2020. doi:10.1101/2020.03.06.20032342v1

Early, Low-Dose and Short-Term Application of Corticosteroid Treatment in Patients with Severe COVID-19 Pneumonia

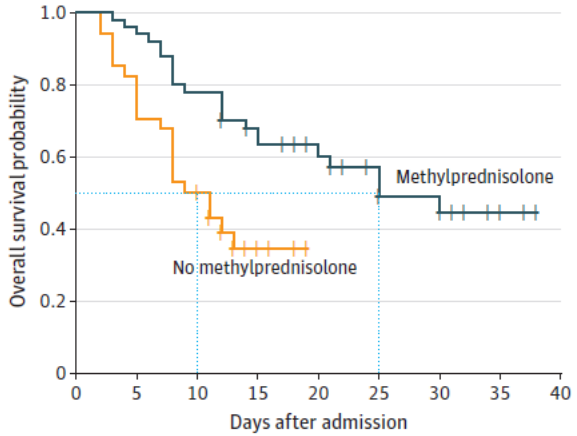


Wang Y , Jiang W , He Q , et al Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv. Preprint posted March 12, 2020. doi:10.1101/2020.03.06.20032342v1

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

- Retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia admitted to Wuhan Jinyintan Hospital in China
  - Methylprednisolone was given to 62 (30.8%) patients
- Patients who developed ARDS were more likely to be treated with methylprednisolone
- A higher proportion of patients who received methylprednisolone were classified into a higher grade on the Pneumonia Severity Index

Figure. Survival Curve in Patients With Acute Respiratory Distress Syndrome Who Did and Did Not Receive Methylprednisolone Treatment

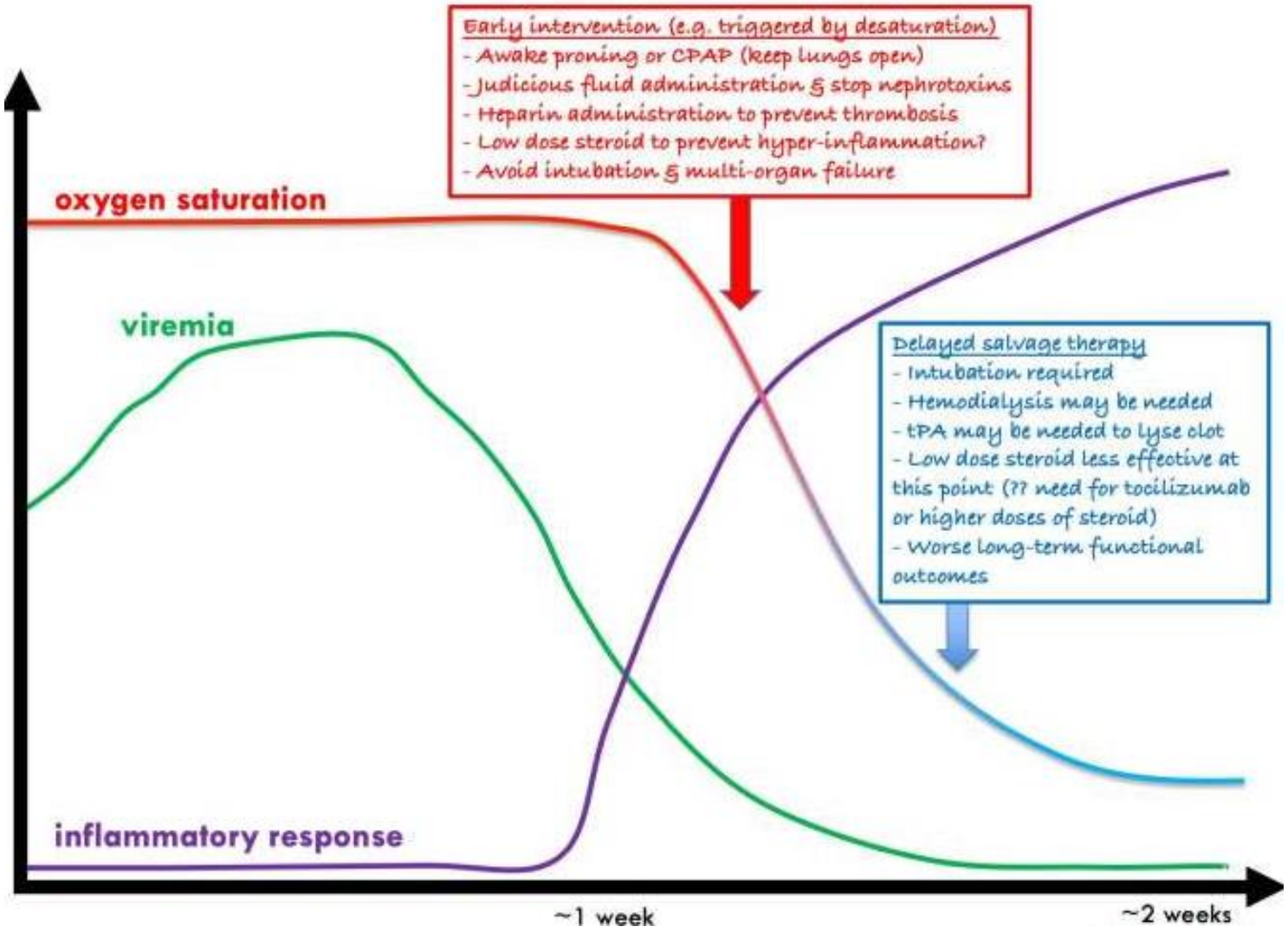


No. at risk									
No methylprednisolone	34	28	17	4	0	0	0	0	0
Methylprednisolone	50	48	39	29	20	14	11	4	0

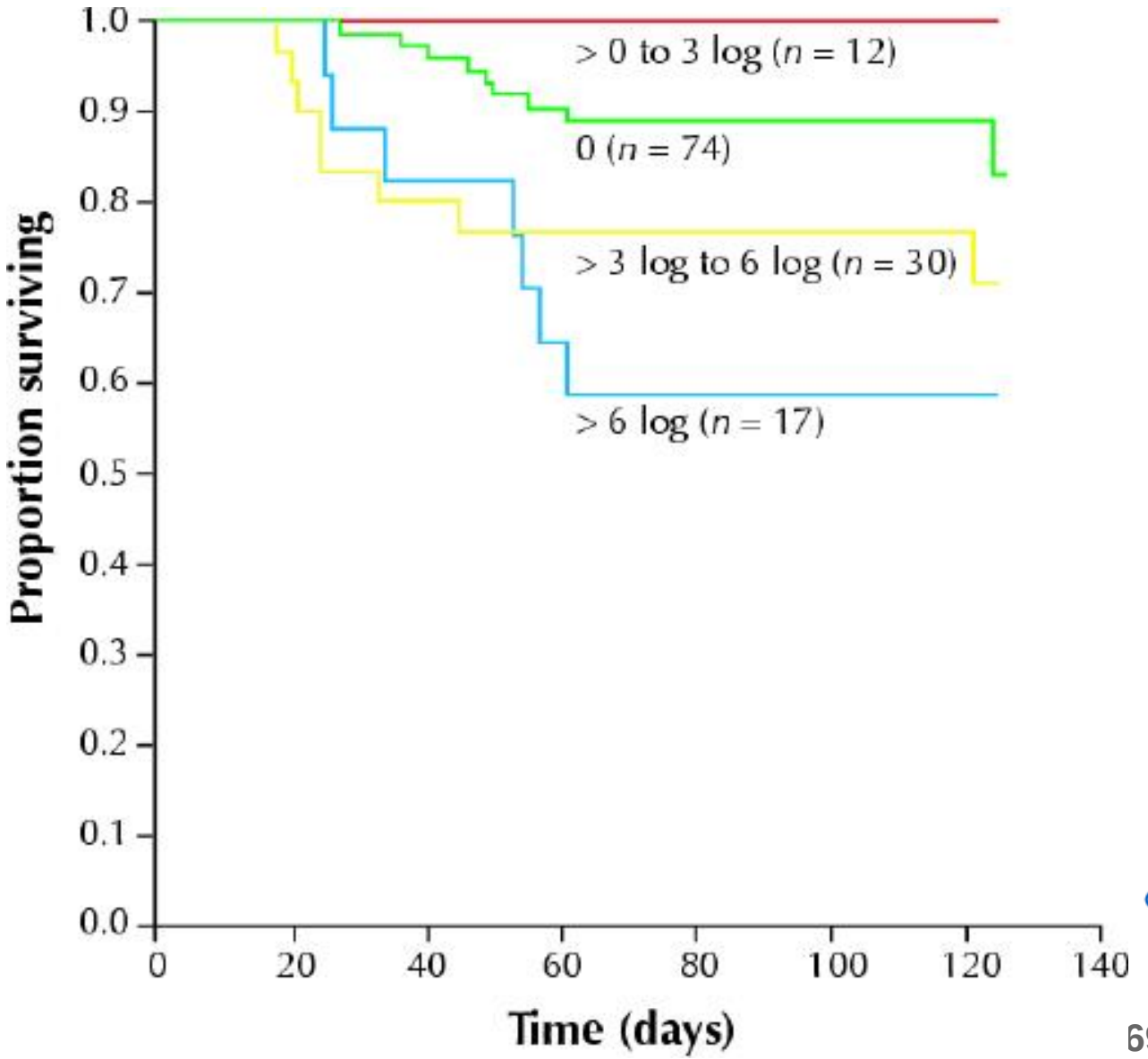
Administration of methylprednisolone reduced the risk of death (hazard ratio, 0.38; 95% CI, 0.20-0.72; P = .003).

Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. March 2020. doi:10.1001/jamainternmed.2020.0994

Steroids: Optimal Treatment Window



Viral Load predicts severity



D-Dimer Levels on Admission to Predict In-Hospital Mortality in Patients With COVID-19

- laboratory confirmed Covid-19 were retrospectively enrolled in Wuhan Asia General Hospital from January 12, 2020 to March 15, 2020
  - A total of 343 eligible patients were enrolled in the study
  - D-dimer levels on admission, and death events were collected

- The optimum cutoff value of D-dimer to predict in-hospital mortality was 2.0 μg/ml with a sensitivity of 92.3% and a specificity of 83.3%

- Patients with D-dimer levels ≥2.0 μg/ml had a higher incidence of mortality when comparing to those who with D-dimer levels < 2.0 μg/ml (P <0.001)

Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020

Virchow's Triad

Hypercoagulability:

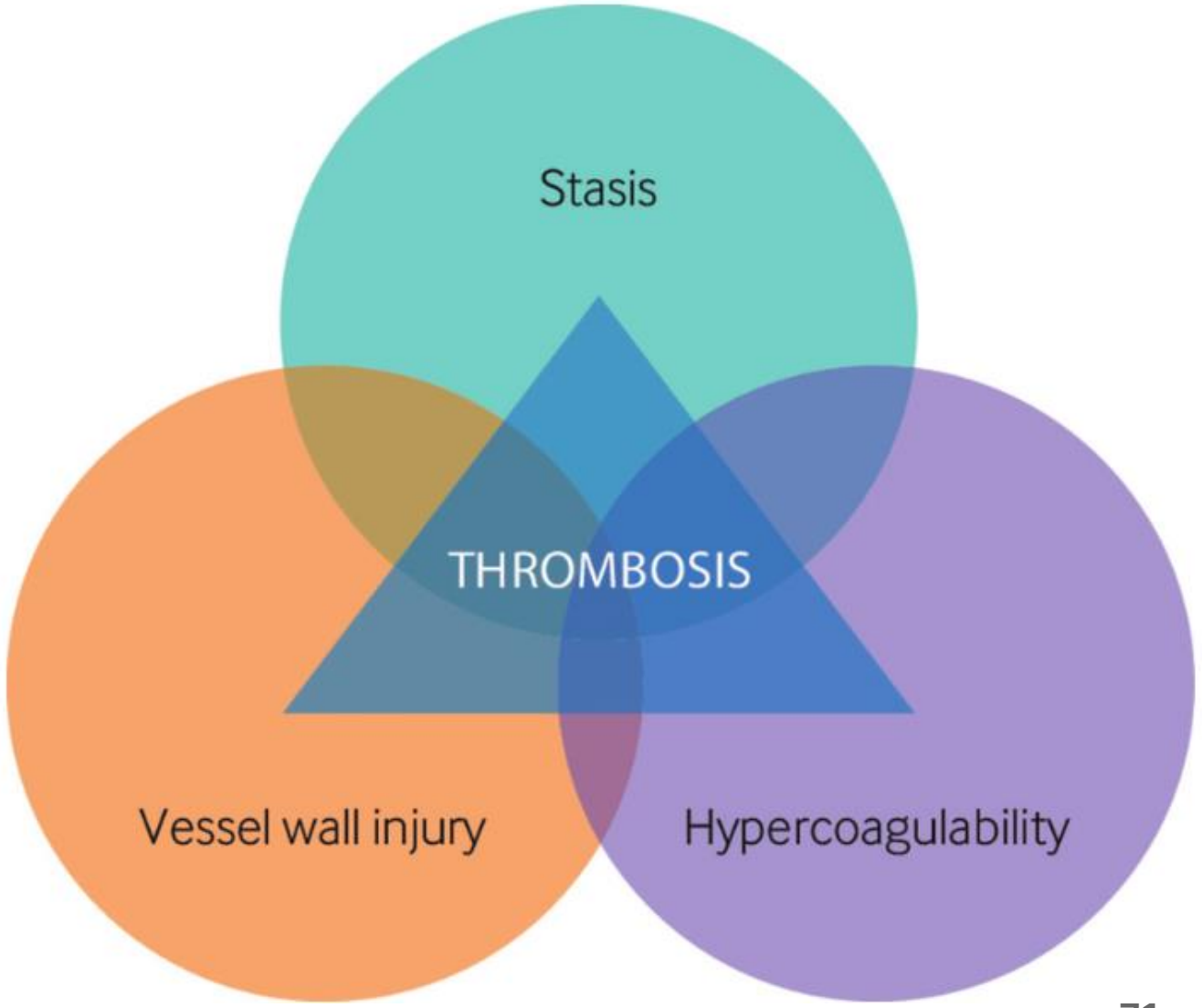
- ❑ High fibrinogen
- ❑ High D-dimer

Vessel wall injury:

- ❑ ARDS

Venous stasis :

- ❑ Immobile/paralyzed



Anticoagulation

- D-Dimer < 3,000 and not high ARITA score
  - CrCl ≥ 30 mL/min: Enoxaparin 40mg SQ Q12H
  - CrCl < 30 mL/min: Heparin 7,500 units SQ Q8H
- D-Dimer ≥ 3,000 and not high ARITA score
  - CrCl ≥ 30 mL/min: Enoxaparin 1mg/kg Q12H
  - CrCl < 30 mL/min: High dose IV heparin protocol
- High risk ATRIA score and/or fibrinogen ≤ 100, platelets ≤ 50,000, INR ≥ 1.5 (Regardless of D-Dimer)
  - CrCl ≥ 30 mL/min: Enoxaparin 40mg SQ daily
  - CrCl < 30 mL/min: Heparin 5,000 units SQ Q8H
- De-escalate patients being transferred from ICU to floor
  - CrCl ≥ 30 mL/min: Enoxaparin 40mg SQ daily
  - CrCl < 30 mL/min: Heparin 5,000 units SQ Q8H

Day	PLTS	INR	D-Dimer
1	166	1.6	792
2	146	-	-
3	139	1.5	-
4	145	-	-
5	149	-	-
6	175	-	18,129
7	202	-	15,919
8	224	1.4	23,560

Anticoagulation: Guideline Recommendations

- Journal of Thrombosis and Haemostasis:
  - Recommend: Measure D-dimers, prothrombin time and platelet count (decreasing order of importance) in all patients
  - If there is worsening, more aggressive support and consideration for more 'experimental' therapies

- American College of Cardiology:
  - Consider prophylactic anticoagulation, although a minority consider intermediate-dose or therapeutic dose to be reasonable
  - It is reasonable to employ individualized risk stratification for thrombotic and hemorrhagic risk, followed by consideration of extended prophylaxis (for up to 45 days) for patients with elevated risk of VTE

- American Society of Hematology:
  - Whether critically ill should receive therapeutic-intensity anticoagulation in the absence of confirmed or suspected VTE is currently unknown
  - It is reasonable to consider extended thromboprophylaxis after discharge using a regulatory-approved regimen

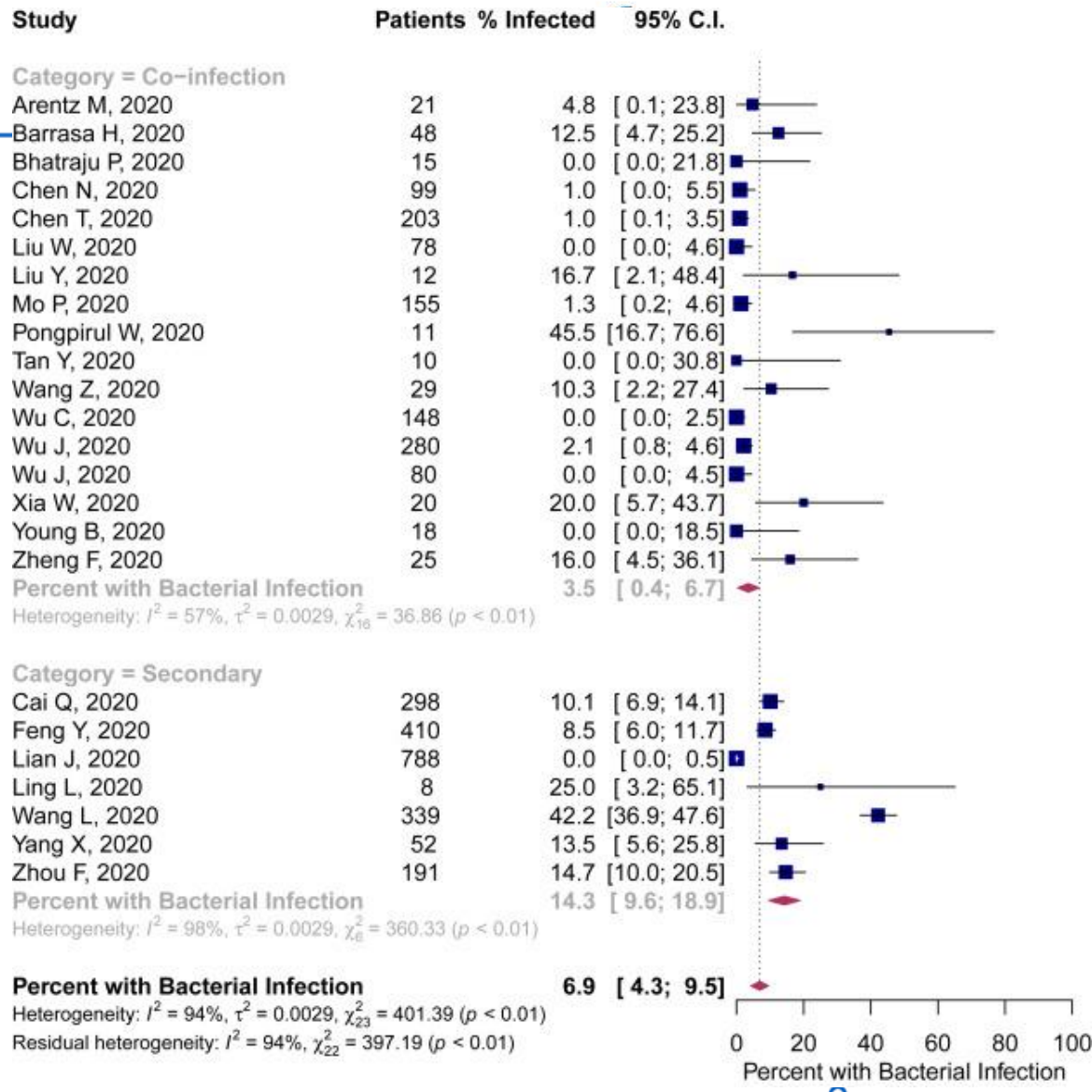
Thachil, J., Tang, N., Gando, S., Falanga, A., Cattaneo, M., Levi, M., … Iba, T. (2020). ISTH interim guidance on recognition and management of coagulopathy in COVID-19. Journal of Thrombosis and Haemostasis. doi: 10.1111/jth.14810
Bikdeli, B., Madhavan, M. V., Jimenez, D., Chuich, T., Dreyfus, I., Driggin, E., … Lip, G. Y. (2020). COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-up. Journal of the American College of Cardiology. doi: 10.1016/j.jacc.2020.04.031
COVID-19 and VTE/Anticoagulation: Frequently Asked Questions. (n.d.). Retrieved from https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation

University at Buffalo The State University of New York

Accompanying Bacterial Infection

- Stats:
  - Co-infection = **3.5%**
  - Secondary infection = **14.3%**
  - **>70%** received antibiotics (empiric, varied)

- Surviving Sepsis Campaign
  - Recommendation: In mechanically ventilated patients with COVID-19 and respiratory failure, we suggest using empiric antimicrobials/antibacterial agents, over no antimicrobials. **(Weak recommendation, low-quality evidence)**

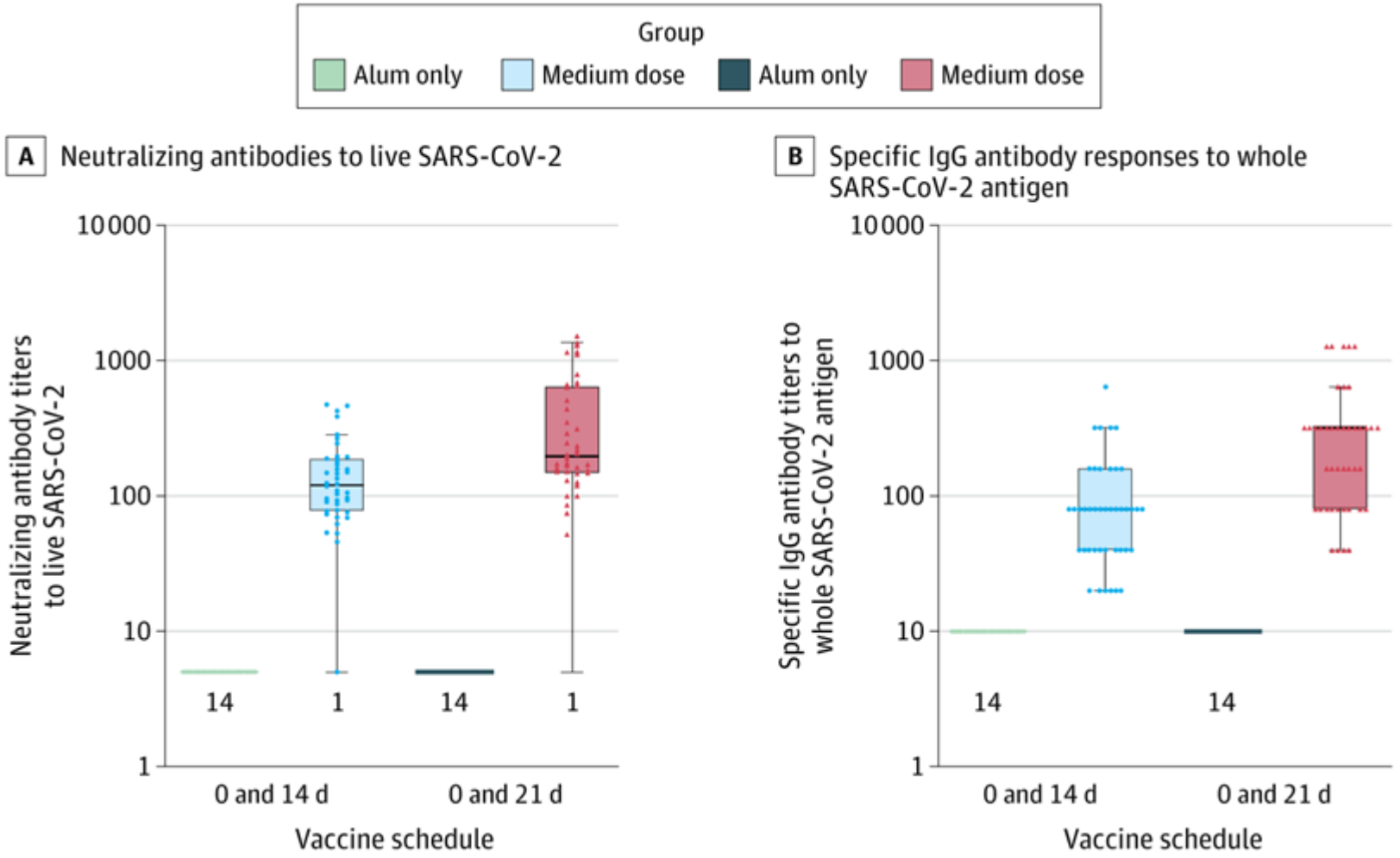


Alhazzani, W., Møller, M. H., Arabi, Y. M., Loeb, M., Gong, M. N., Fan, E., … Rhodes, A. (2020). Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Medicine. doi: 10.1007/s00134-020-06022-5

Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis [published online ahead of print, 2020 Jul 22]. *Clin Microbiol Infect*. 2020;S1198-743X(20)30423-7. doi:10.1016/j.cmi.2020.07.016

Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing [published online ahead of print, 2020 May 2]. *Clin Infect Dis*. 2020;ciaa530. doi:10.1093/cid/ciaa530

Whole inactivated



Xia S, Duan K, Zhang Y, et al. Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials [published online ahead of print, 2020 Aug 13]. *JAMA*. 2020;e2015543. doi:10.1001/jama.2020.15543

The impending Flu season…

- To reduce the pressure, drugmakers including AstraZeneca PLC, GlaxoSmithKline PLC and Sanofi SA are making about 200 million flu shots this year for shipment to doctors, hospitals and pharmacies, up 13% from last year and a record, according to the U.S. Centers for Disease Control and Prevention.

Table 1. Patient Characteristics and Sites of Specimen Collection, by SARS-CoV-2 and Non-SARS-CoV-2 Pathogen Status

Characteristic	SARS-CoV-2 status, No. (%)			
	Negative (n = 1101)		Positive (n = 116)	
	Positive for other respiratory pathogen	Negative for other respiratory pathogen	Positive for other respiratory pathogen	Negative for other respiratory pathogen
No. of samples	294	807	24	92
No. of patients[a]	292	800	23	92
Age, mean (range), y[b]	35.7 (1-95)	45.7 (1-100)	46.9 (14-74)	51.1 (7-83)
Female, No./total (%)[b]	160/292 (54.8)	439/800 (54.9)	12/23 (52.2)	52/92 (56.5)
Site of specimen collection, No./total (%)[c]				
Outpatient clinic	115/294 (39.1)	347/807 (43.0)	11/24 (45.8)	39/92 (42.4)
Emergency department				
Discharged	122/294 (41.5)	301/807 (37.3)	12/24 (50.0)	38/92 (41.3)
Admitted[d]	28/294 (9.5)	109/807 (13.5)	1/24 (4.2)	15/92 (16.3)
Inpatient	29/294 (9.9)	50/807 (6.2)	0/24	0/92

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Row sum (1207) is greater than the total number of unique patients (1206) because 1 patient was tested twice, 11 days apart, with different results for non-SARS-CoV-2 pathogens, and so appears in the first 2 columns.

[b] Mean age and proportion female are calculated with respect to unique patients.

[c] Proportions of samples collected at different sites are calculated with respect to numbers of samples.

[d] Denotes patients tested in the emergency department and admitted to an inpatient ward from the emergency department.

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