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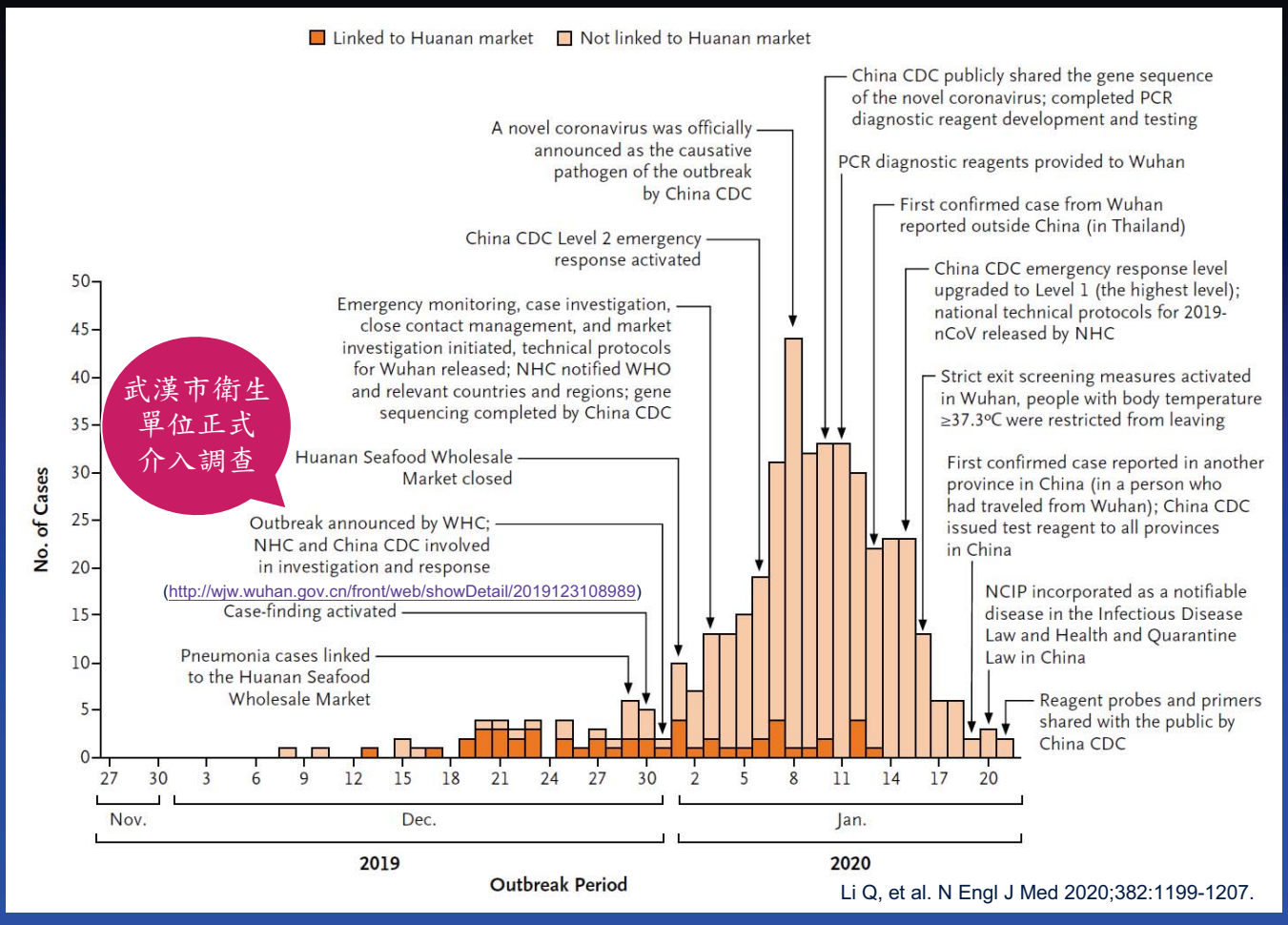
SPECIFIC TREATMENT FOR COVID-19

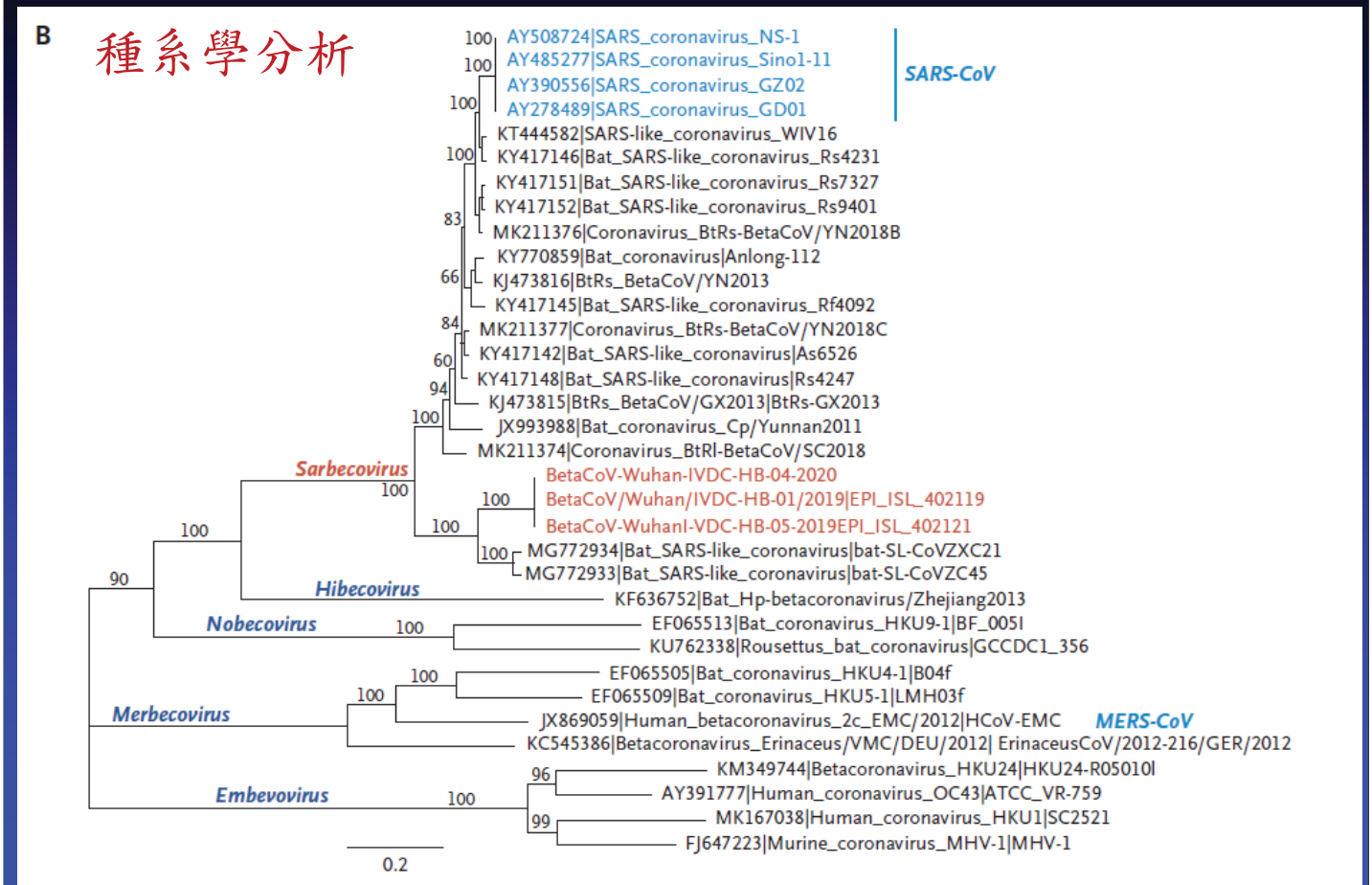


Li Q, et al. N Engl J Med 2020;382:1199-1207.

Identification of the Pathogen

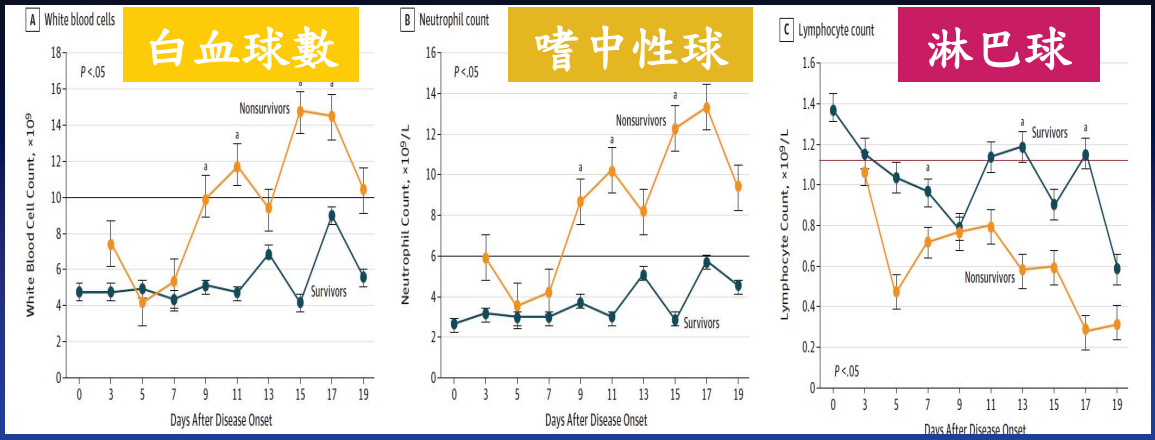
- Belonging to β Coronavirus：
  - There are four groups: α, β, γ, δ
  - In the same group of SARS-CoV, MRSA-CoV
    - Initially, named as 2019-nCoV, now as SARS-CoV-2

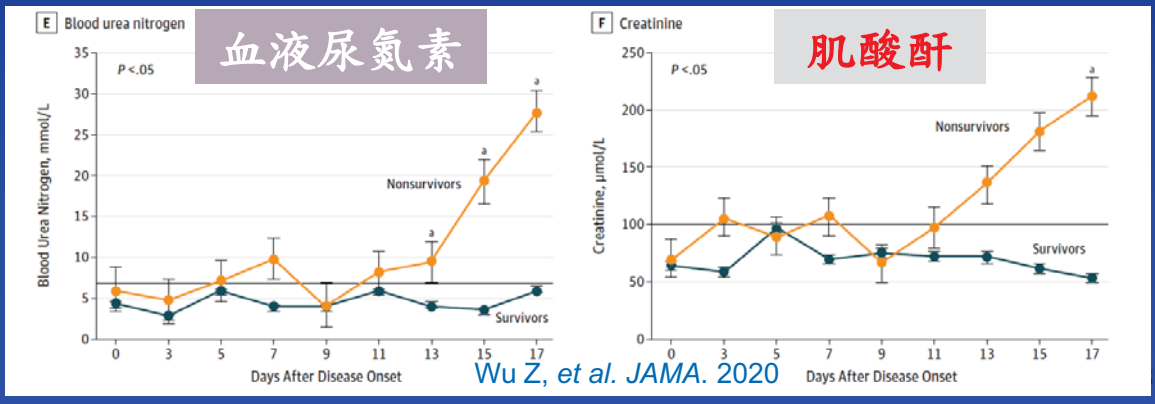
Zhu N, et al. N Engl J Med 2020;382:727–33.



Zhu N, et al. N Engl J Med 2020;382:727–33.

檢驗數據的動態變化狀





Wu Z, *et al. JAMA*. 2020

Characteristics & Management of COVID-19

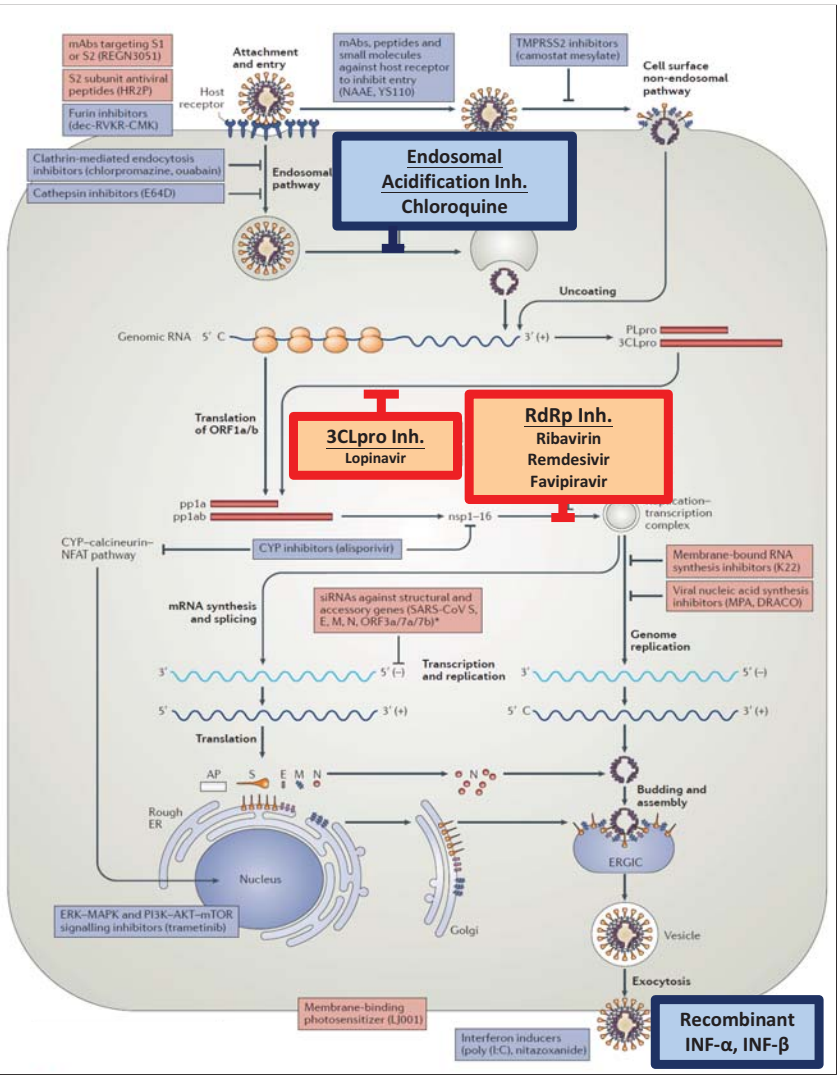
	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94%; respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed Disease Pathogenesis		Viral replication	Viral replication / Inflammation	Inflammation	Inflammation
Potential Treatment		Antiviral therapy	Antiviral therapy / Antibody therapy	Antibody therapy / Antiinflammatory therapy	Antiinflammatory therapy
Management Considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

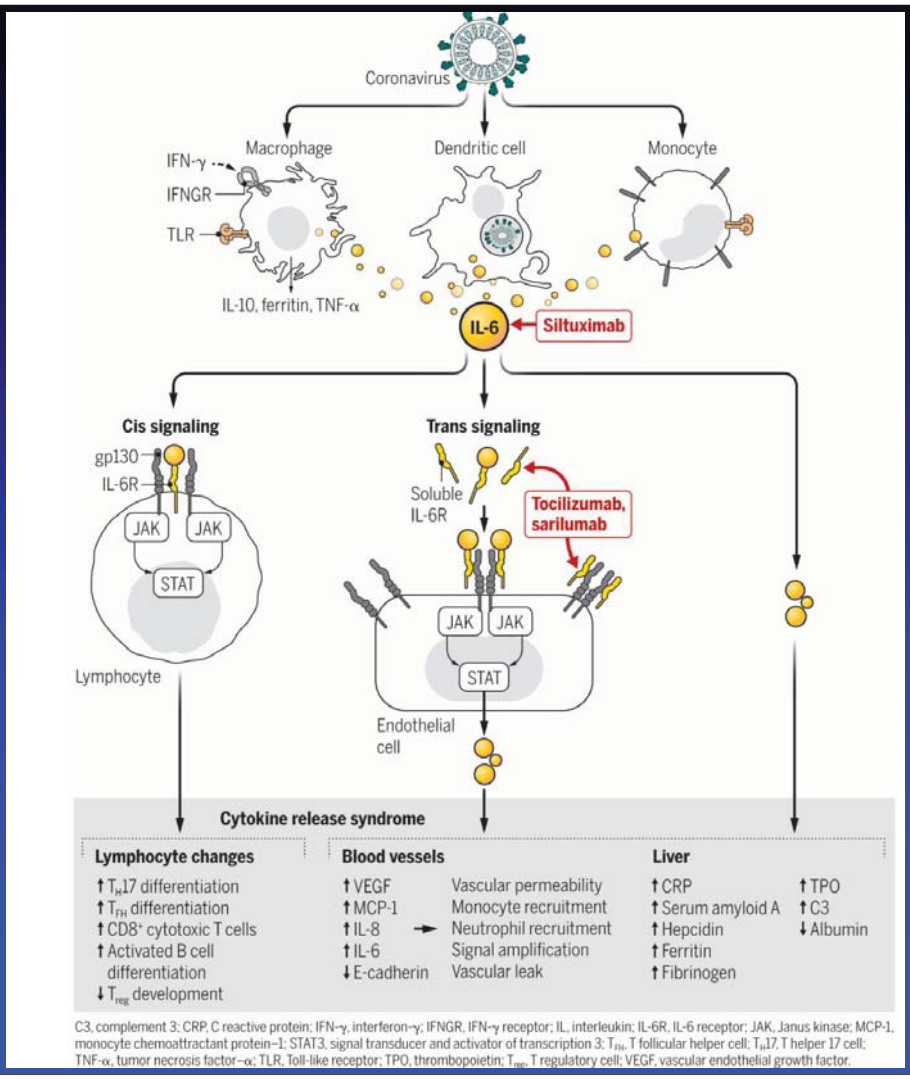
Gandhi RT *et al. N Engl J Med* 2020;383:1757 – 66.

Probable targets

Zumla A, et al. Nat Rev Drug Discov 2016;15:327–47.

Host-based treatment options
Virus-based treatment options





C3, complement 3; CRP, C reactive protein; IFN-γ, interferon-γ; IFNGR, IFN-γ receptor; IL, interleukin; IL-6R, IL-6 receptor; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein-1; STAT3, signal transducer and activator of transcription 3; T_{FH}, T follicular helper cell; T_H17, T helper 17 cell; TNF-α, tumor necrosis factor-α; TLR, Toll-like receptor; TPO, thrombopoietin; T_{reg}, T regulatory cell; VEGF, vascular endothelial growth factor.

Coronavirus infection:

- Monocyte, macrophage, dendritic cells activation
- IL-6 release
  - Lymphocyte: cis signaling
  - Endothelial cells: trans signaling
- CRS:
  - Hypotension
  - ARDS
- IL-6 antagonists?
  - Tocilizumab
  - Siltuximab
  - Sarilumab
  - Or just steroid

Moore JB, et al. Science 2020:368;473–4.

ACTT-1 Final Report

- Double-blind, placebo control RCT
- Feb. 21 ~ Apr.19, 2020
- Totally 1062 were analyzed
  - RDV group: 541 (10 did not receive RDV)
    - 200 mg on Day 1, then 100 mg Day 2 – 10
    - 75, 232, 95, 131 in category 4, 5, 6, 7 (8 missing
  - Placebo group: 521
    - 63, 203, 98, 154 in category 4, 5, 6, 7 (3 missing)
- Primary outcome:
  - Time to recovery: 1st day met criteria of category 1 – 3

Beigel JH, et al. N Engl J Med 2020;383:1813–26.

Eight Ordinary Categories

Category	Hospitalized	Activities	Oxygen	On-going Medical care
1	No	Not limited	No	No
2	No	Limited	Home oxygen	No
3	Yes	Limited	No	No
4	Yes	Limited	No	Yes
5	Yes	Limited	Yes	Yes
6	Yes	Limited	Non-invasive ventilation / high-flow oxygen device	Yes
7	Yes	Limited	Invasive mechanical ventilation, ECMO	Yes
8	Death			

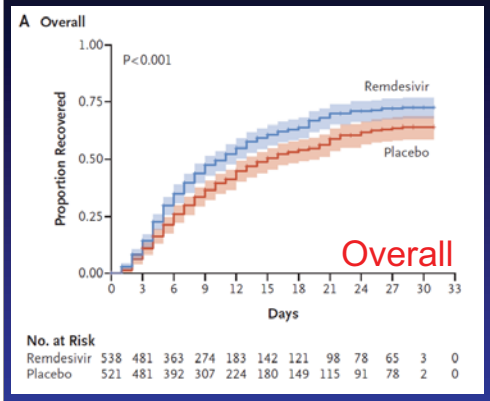
Beigel JH, et al. N Engl J Med 2020;383:1813–26.

NIAID Study Design: Adaptive COVID-19 Treatment Trial (ACTT-1)

	RDV (n=541)	Placebo (n=521)	RR (95% CI)
Time to recovery Median days (95% CI)	**10 (9–11)**	**15 (13–18)**	**1.29 (1.12-1.49)**
1 point improvement, median days (95% CI)	7 (6.0-8.0)	9 (8.0-11.0)	1.23 (1.08-1.41)
2 point improvement, median days (95% CI)	11 (10.0, 13.0)	14 (13.0-15.0)	1.29 (1.12-1.48)
Mortality at day 29, KM estimate (%)	11.4 (9.0-14.5)	15.2 (12.3-18.6)	0.73 (0.52-1.03)
Discharge or NEWS* ≤2, median days (95% CI)	8 (7.0-9.0)	12 (10.0-15,0)	1.27 (1.10-1.46)
Hospitalization, median days (95% CI)	12 (6-28)	17 (8-28)	--

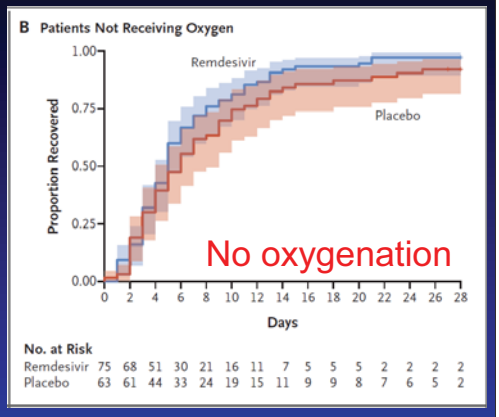
*The National Early Warning Score includes six physiological measures; total scores range from 0 to 20, with higher scores indicating greater clinical risk.

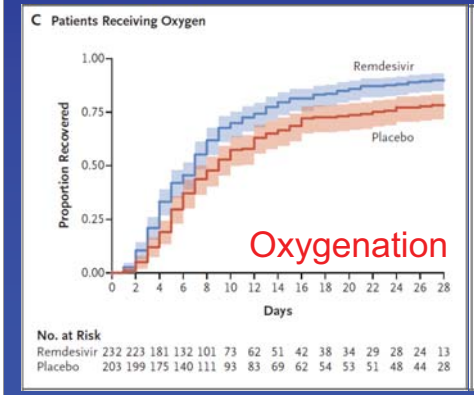
Beigel JH, et al. N Engl J Med 2020;383:1813–26.

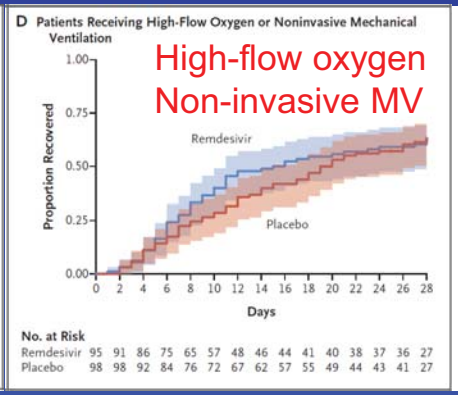


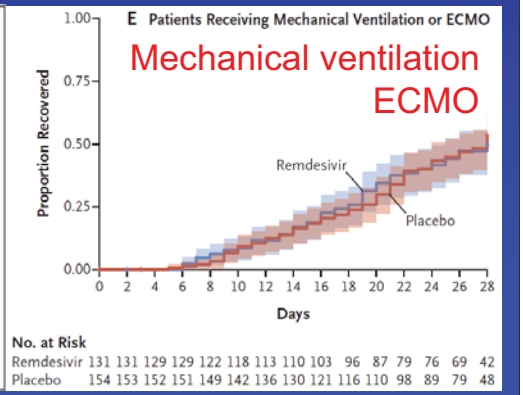
Remdesivir for COVID-19 ACTT I – Final Report

1062 patients



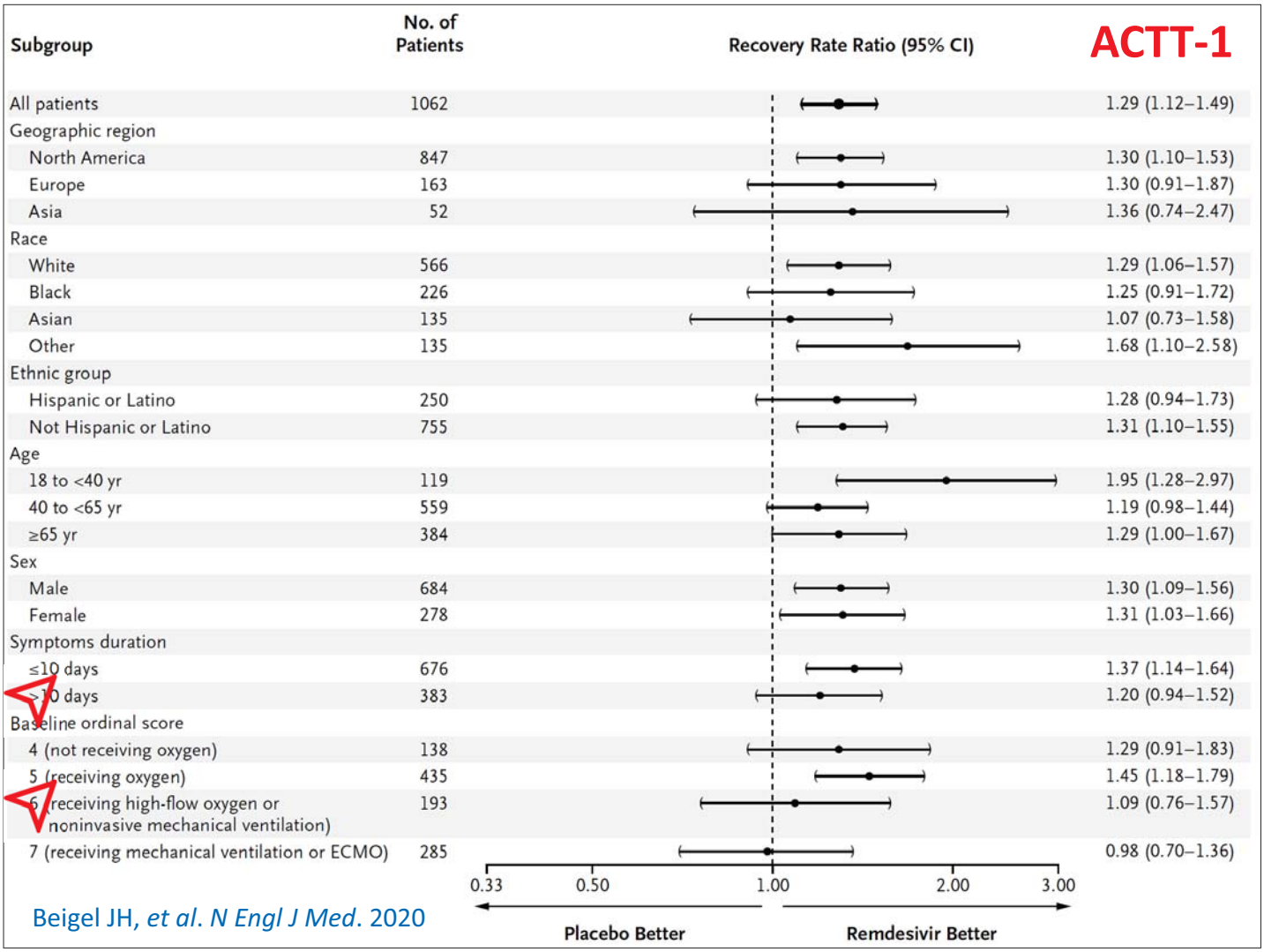






Beigel JH, et al. N Engl J Med 2020;383:1813–26.

ACTT-1



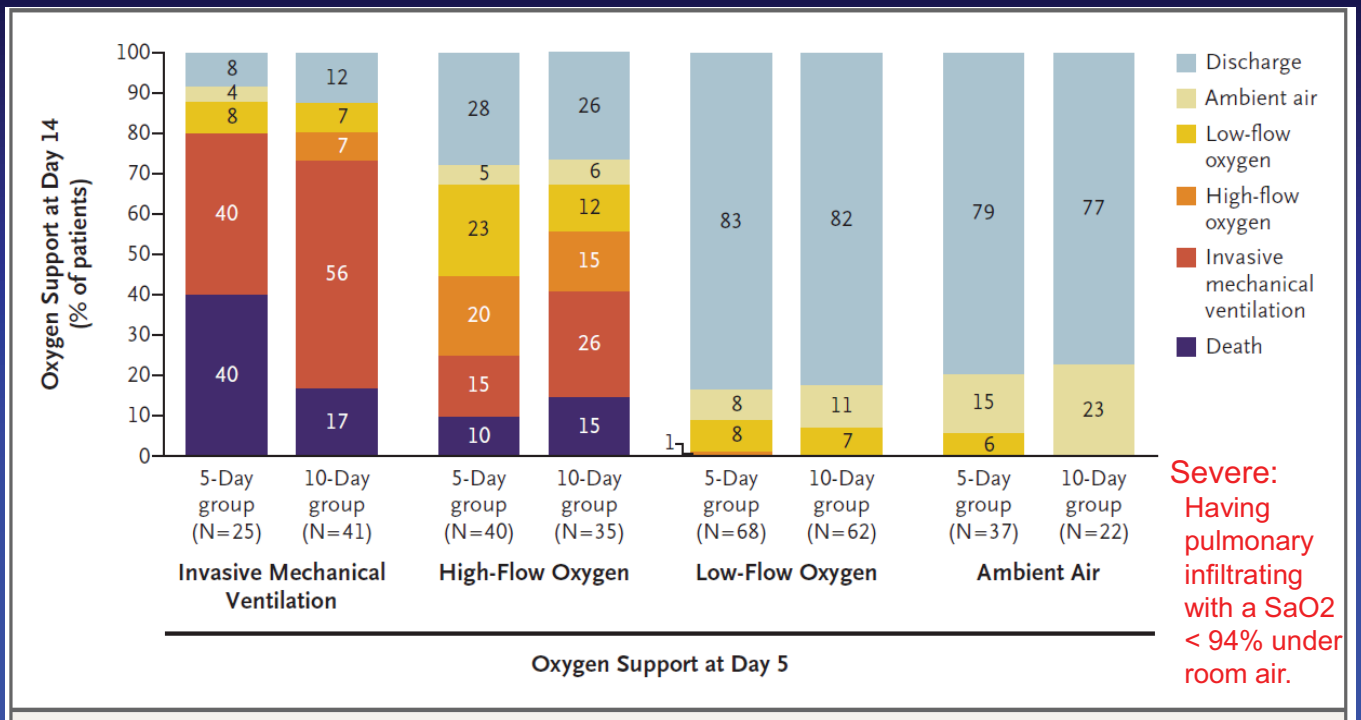
Beigel JH, *et al*. *N Engl J Med*. 2020

ACTT-1: Safety

Safety event outcomes	RDV (N=532)	Placebo (N=516)	P
Grade 3 or 4 AE	273 (51%)	295 (57%)	0.058
SAE	131 (24.6%)	163 (31.6%)	0.010
Renal failure	2 (0.4%)	5 (1.0%)	-
Acute kidney injury	7 (1.3%)	12 (2.3%)	-
Septic shock	8 (1.5%)	15 (2.9%)	-
Respiratory failure	39 (7.3%)	66 (12.8%)	-
Acute respiratory failure	8 (1.5%)	14 (2.7%)	-
Hypotension	4 (0.8%)	7 (1.4%)	-
Shock	5 (0.9%)	4 (0.8%)	-
AE leading to discontinuation	57 (11%)	77 (15%)	-
Non-serious AE	276 (51.9%)	295 (57.2%)	-

Beigel JH, et al. N Engl J Med 2020;383:1813–26.

Remdesivir in Severe COVID-19: 5 vs 10 days

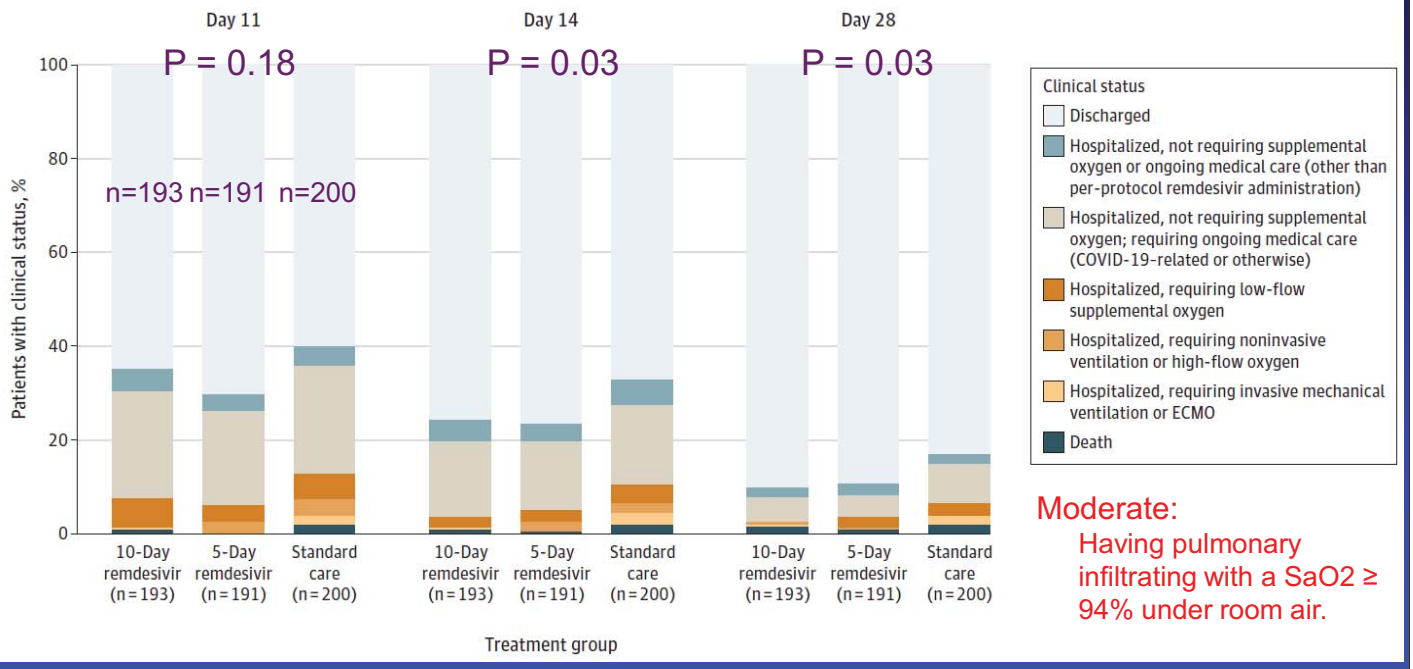


Severe: Having pulmonary infiltrating with a SaO2 < 94% under room air.

Figure 2. Oxygen Support on Day 14 According to Oxygen Support on Day 5.

Goldman JD, et al. N Engl J Med 2020;383:1827 – 37.

Remdesivir in Moderate COVID-19



Moderate: Having pulmonary infiltrating with a SaO2 ≥ 94% under room air.

Spinner CD, et al. JAMA 2020;324:1048 – 57.

Visual summary of recommendation

Population

This recommendation applies only to people with these characteristics:

Adults with confirmed covid-19

Disease severity

Mild | Moderate | Severe

Does not apply to:

- ✖ Patients with mild or moderate covid-19
- ✖ Pediatric patients

Applies to people with at least one of:

- ✔ Respiratory rate >30
- ✔ Respiratory distress
- ✔ SpO_2 <94% on room air
- ✔ Requires intensive care admission

⚠ Resource limited settings

Remdesivir is a new drug with uncertain benefits and undetermined cost-effectiveness, not yet approved for marketing or reimbursed for use in many countries. The significant opportunity costs and potential to exacerbate existing health inequities in resource-limited settings may well justify policy decisions not to offer remdesivir to patients until more conclusive evidence is available

Recommendation 1

Usual supportive care		Remdesivir
No remdesivir	or	100 mg intravenously daily for 5-10 days
Strong / Weak		**Weak** / Strong

"We suggest remdesivir rather than no remdesivir in patients with severe covid-19"

Rochwerg B, et al. BMJ 2020;370:m2924

Evidence profile

Usual supportive care | No important difference | Remdesivir

	Events per 1000 people			Evidence quality
Mortality	330	85 fewer	245	★★☆☆ Low
Mechanical ventilation risk	116	No important difference	119	★★☆☆ Low
Serious adverse events	80	19 fewer	99	★★☆☆ Low
	Median days			**Evidence quality**
Hospitalisation duration	24	No important difference	25	★★☆☆ Low
Mechanical ventilation duration	16	4 lower	7	★★☆☆ Low
	Mean days			**Evidence quality**
Time to clinical improvement	19	3 lower	16	★★☆☆ Low
Length of stay in intensive care		**Not measured**		

Individual considerations

Key practical issues

Usual supportive care

No additional practical issues

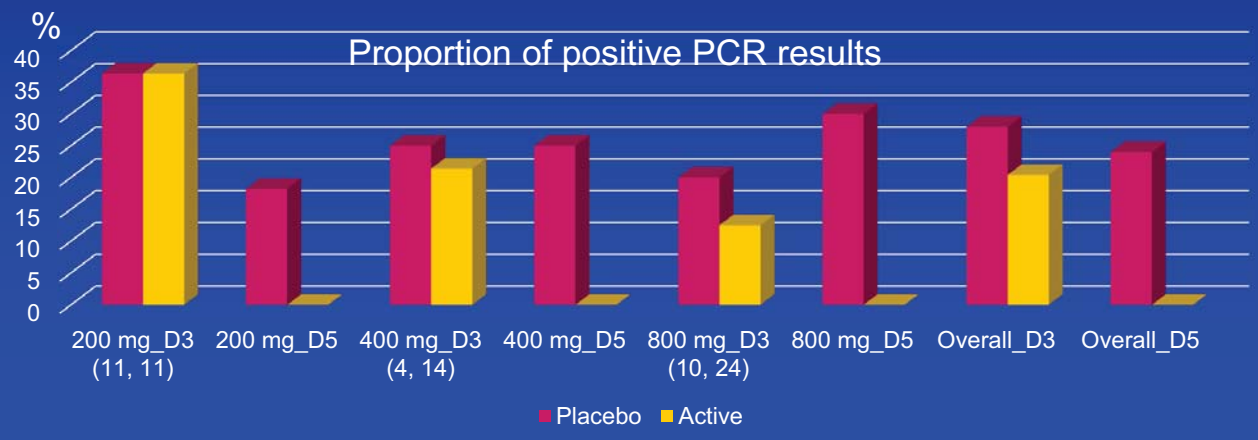
Remdesivir

- May increase adverse events leading to discontinuation of medication
- Administration via intravenous infusion
- Optimal timing, duration and dosing remain unclear
- Not a significant inducer or inhibitor of CYP enzymes but should be monitored when co-administrated with strong inducers or inhibitors
- May be relatively costly, and there may be limited availability

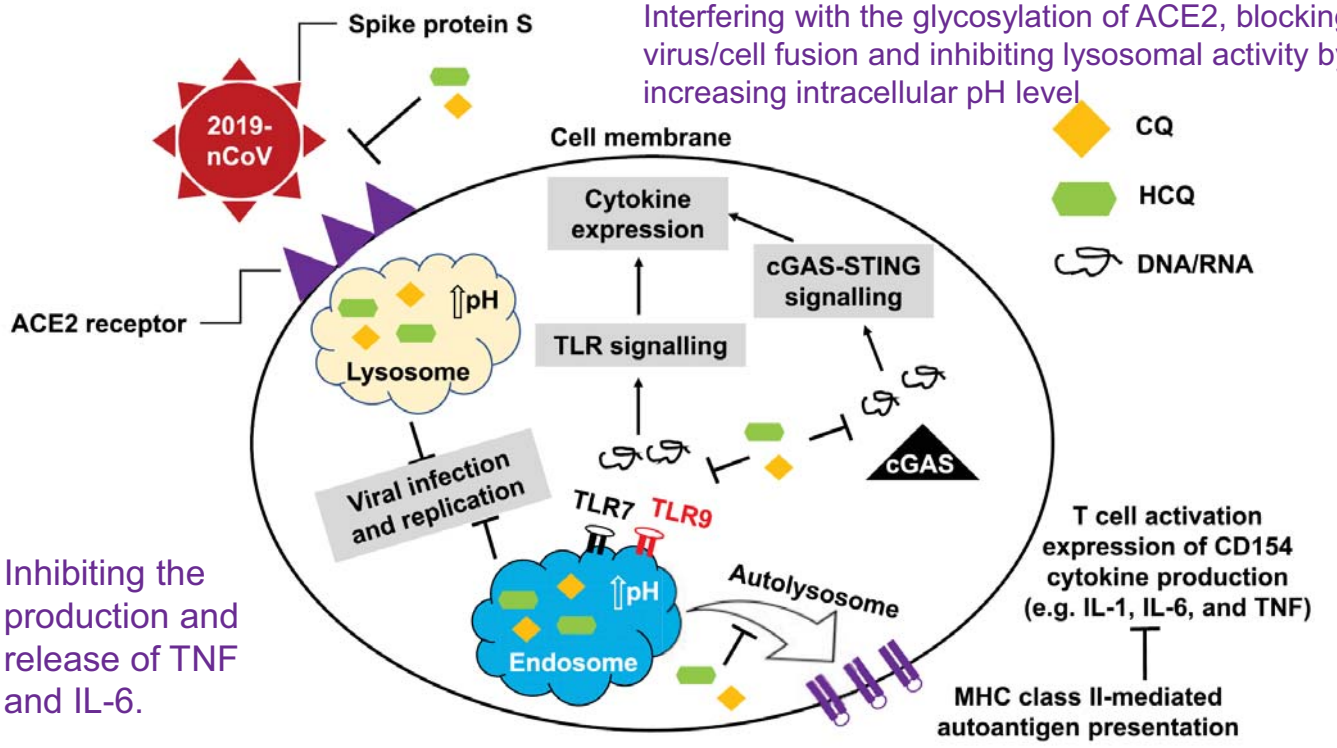
Rochwerg B, et al. BMJ 2020;370:m2924

Molnupiravir

- A developing anti-viral agent:
  - Nucleoside derivative, leading to copying errors during RNA synthesis
  - Anti-influenza and SARS-CoV2



Chemical Structure



Zhou D, et al. J Antimicrob Chemother. 2020;75:1667 – 70.

The Role of Hydroxychloroquine

Pre-exposure prophylaxis	Post-exposure prophylaxis	Non-hospitalized	Hospitalized
Abella BS, *et al. JAMA Intern Med*. 2020	Mitjà O, *et al. N Engl J Med*. 2020	Mitjà O, *et al. Clin Infect Dis*. 2020	RECOVERY *N Engl J Med*. 2020
		Skipper CP, *et al. Ann Intern Med*. 2020	Tang W, *et al. BMJ*. 2020
			High vs. low HCQ Borba MGS, *et al. JAMA Netw Open*. 2020
			± Azithromycin Cavalcanti AB, *et al. N Engl J Med*. 2020

All RCTs don't show clinical benefits for therapeutic or prophylactic effect of HCQ on COVID-19.

No role of Lopinavir/ritonavir

- Basically, the amino acids at the activity center of protease are different.

Young BE, et al. JAMA 2020;323:1488 – 94.

- There at least a small early series and three later large scale studies demonstrated that Lop/rit was not effective.

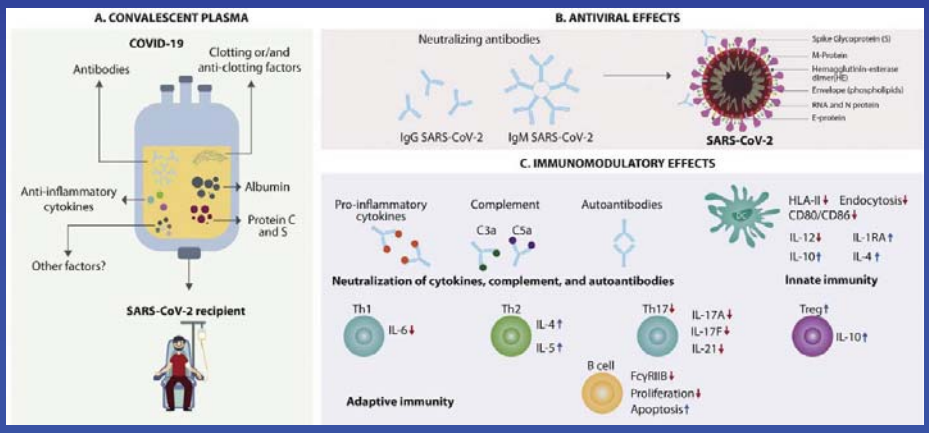
Cao B, et al. N Engl J Med 2020;382:1787 – 99.

RECOVERY Collaborative Group. Lancet 2020;ahead of print.

Pan H, et al. https://doi.org/10.1101/2020.10.15.20209817 doi: medRxiv preprint

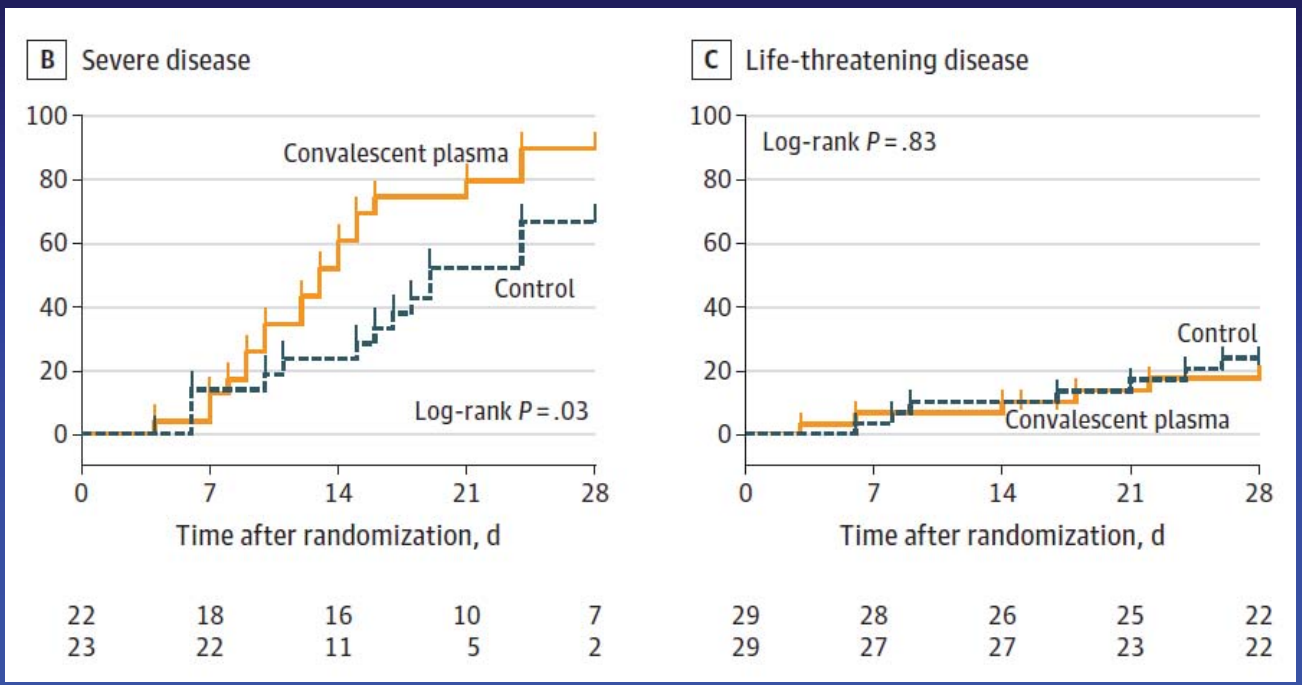
Convalescent Plasma

- Possible mechanisms：
  - Neutralizing virus
  - Inhibiting overwhelm immune response
  - Immunomodulation for over coagulation



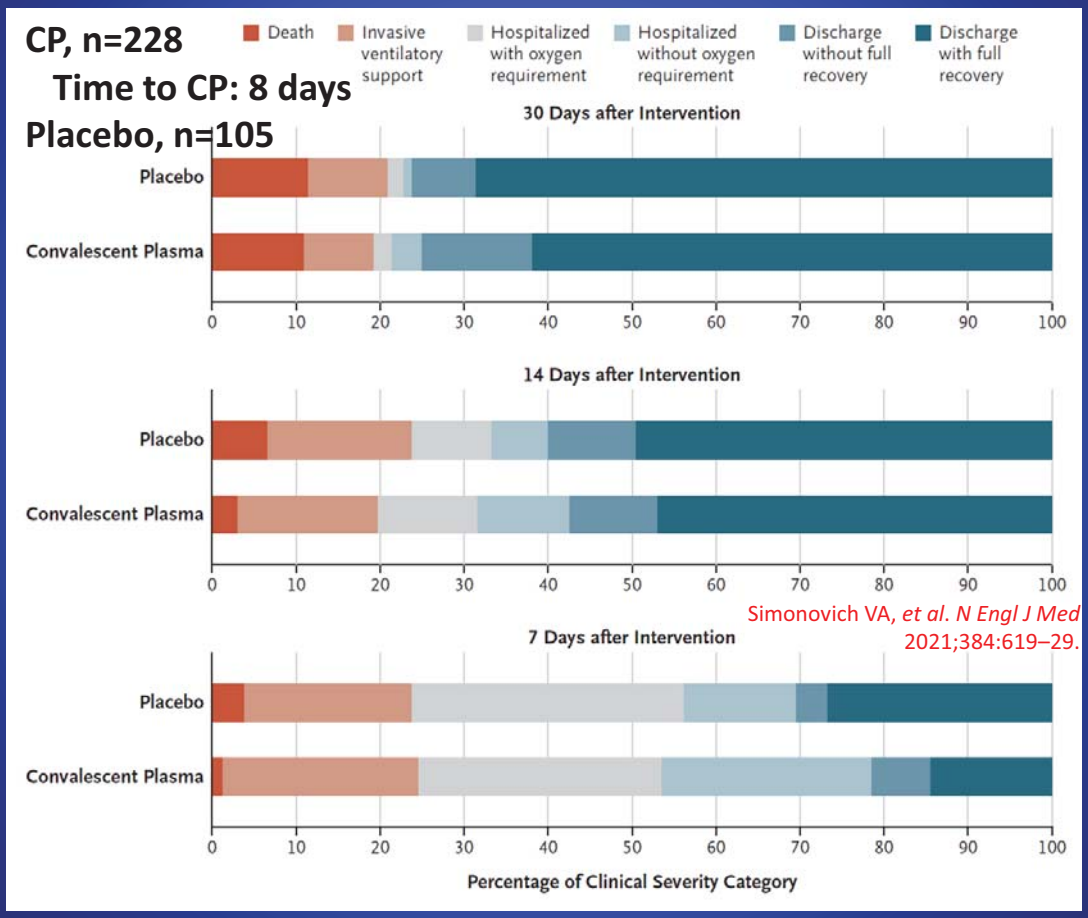
Rojas M, et al. Autoimmun Rev 2020;19:102554

Convalescent Plasma: a RCT



Li L, et al. JAMA 2020;324:460–70.

PlasmaAr: Severe COVID-19



Simonovich VA, *et al. N Engl J Med* 2021;384:619–29.

Lessons from CP Trials

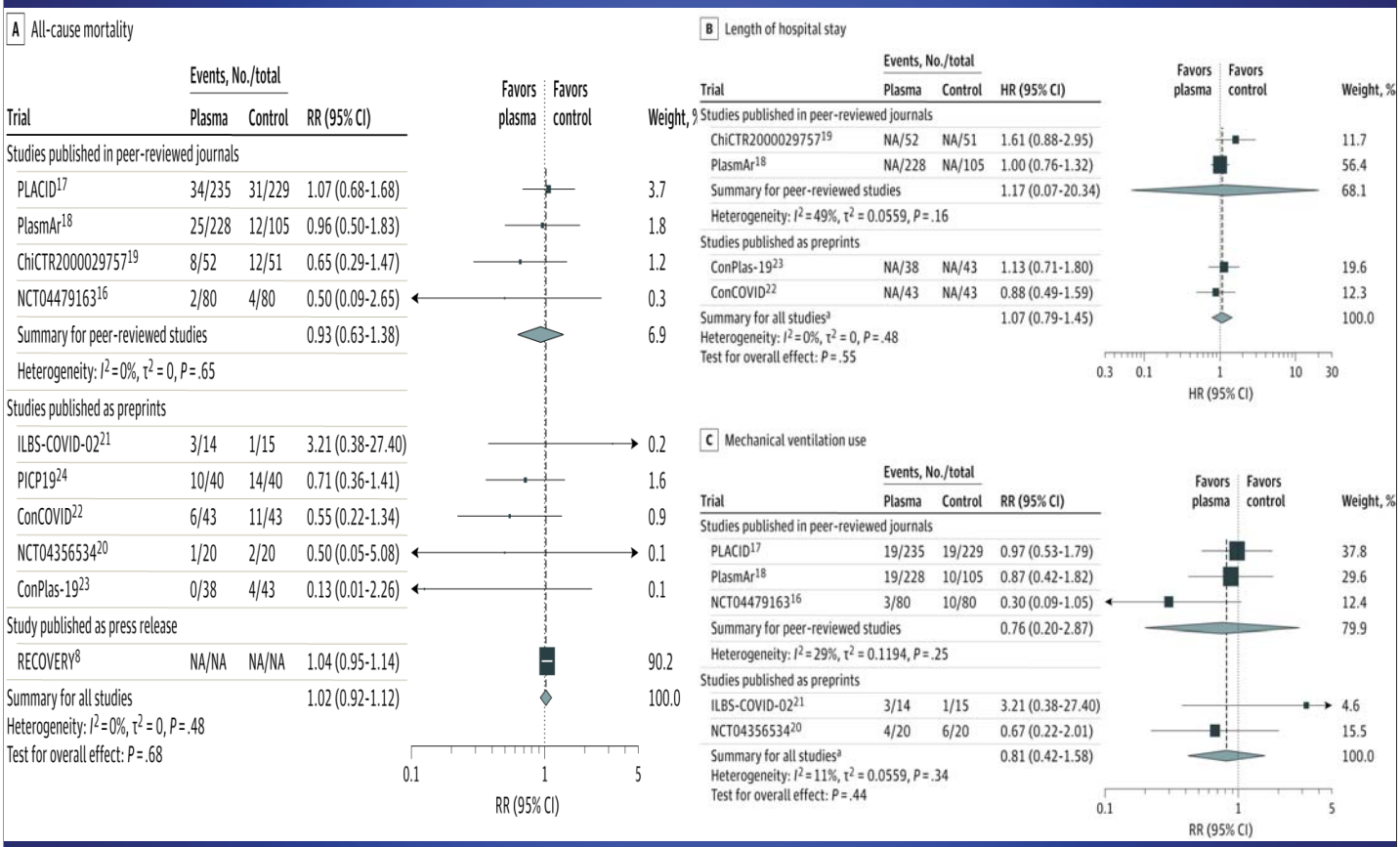
SARS-CoV2 total antibodies titers	Baseline	day 2	day 7	day 14
Convalescent plasma group, *median (IQR)*	1:50 (0-1:800)	1:400 (1:200-1:1600)	1:3200 (1:1600-1:6400)	1:6400 (1:3200-1:12800)
Placebo group, *median (IQR)*	1:50 (0-1:1600)	1:400 (1:50-1:3200)	1:3200 (1:1600-1:6400)	1:12800 (1:3200-1:12800)
N	215	298	240	165
p value	0.955	0.044	0.806	0.449

- Administration of antibody-rich therapy earlier
- Targeting patients with high-risk progression to severe COVID-19
- Concomitant therapeutics:

  steroid, 90%; RDV, 0% in PlasmAr

Simonovich VA, *et al. N Engl J Med* 2021;384:619–29.

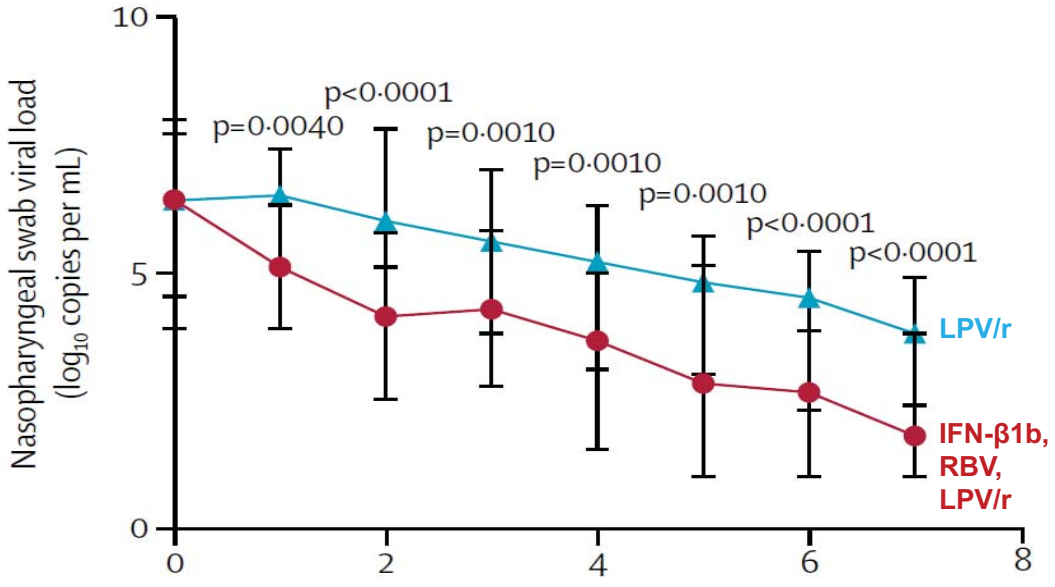
CP: Systemic review and meta-analysis



Janiaud P, *et al*. *JAMA*. 2021

Early Supplement of INF-β1b as a Key to Assist Host Eradicating SARS-CoV-2

Time to negative RT-PCR, **6.5d (Triple)** vs. **12.5d (Mono)**, among TTA<7d

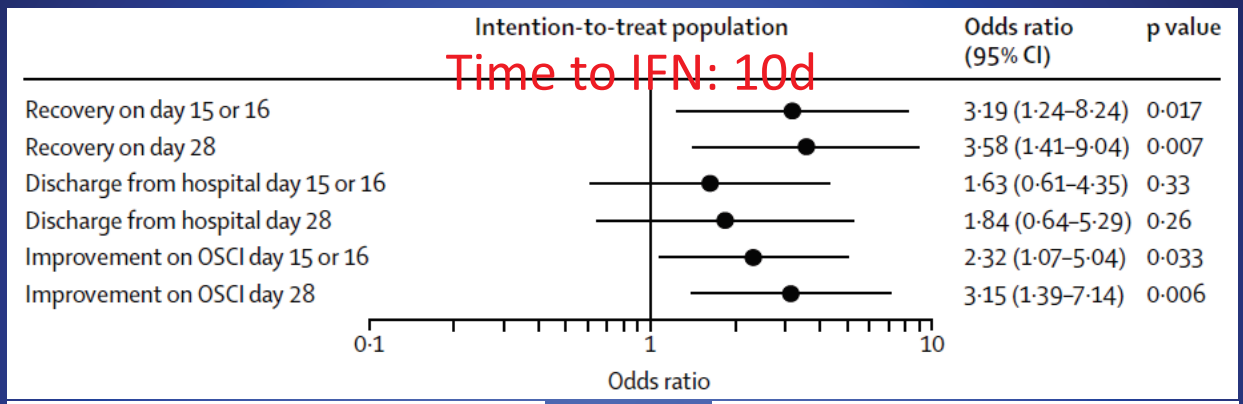


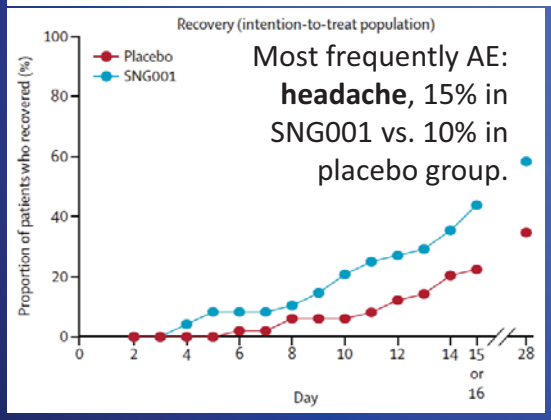
Number of samples

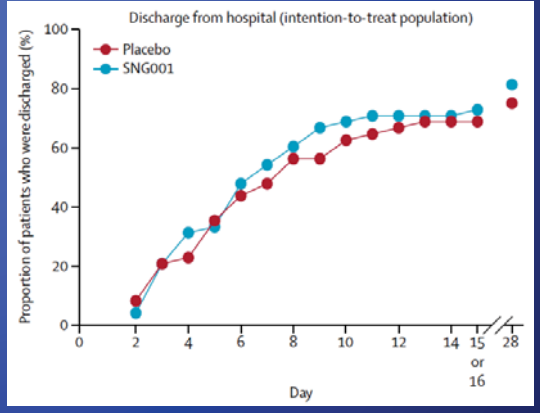
Combination group	86	86	86	86	85	82	76	75
Control group	41	41	41	41	41	40	39	37

Hung IF, et al. Lancet 2020;395:1695–704.

Inhaled IFN-β1a for Moderate/Severe COVID-19







Monk PD, *et al. Lancet Respir Med.* 2021;9:196 – 206.

Monoclonal Ab for Outpatients with COVID-19

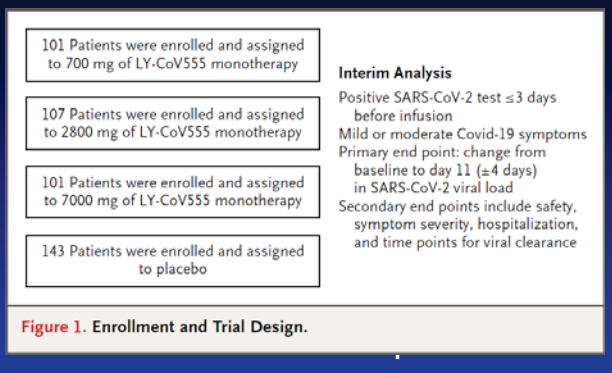
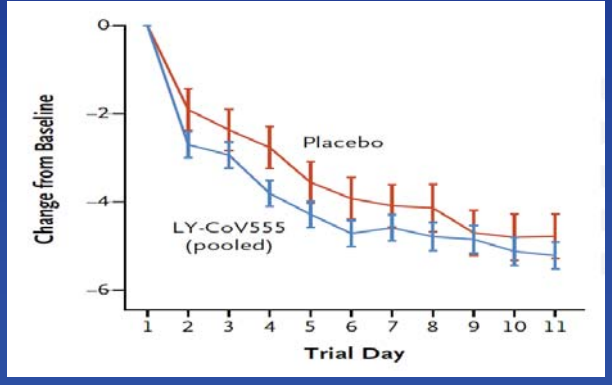
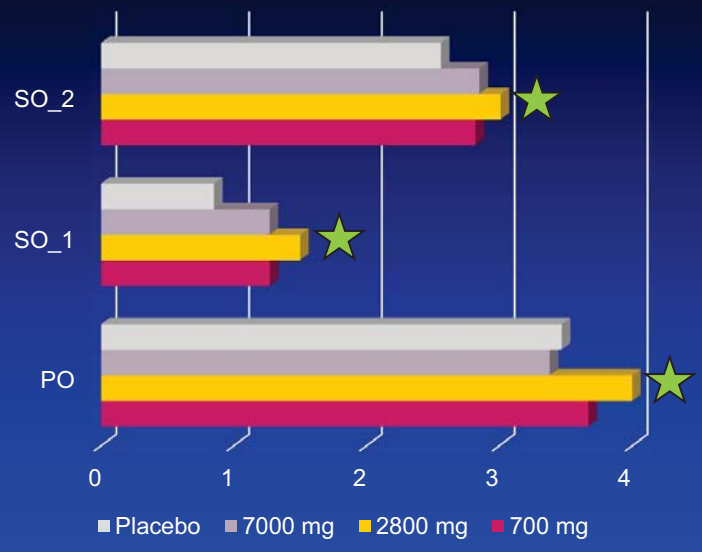


Figure 1. Enrollment and Trial Design.

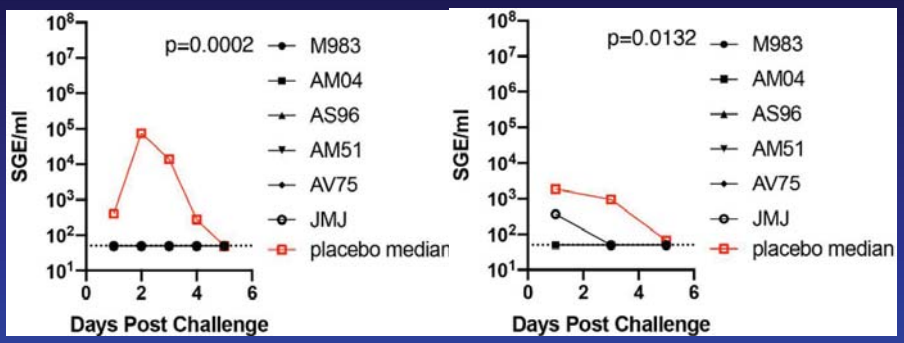




PO: primary outcome, [- change from baseline in viral load at day 11]
SO_1 / SO_2: secondary outcomes, [- change from baseline in viral load at day 3 & 7]

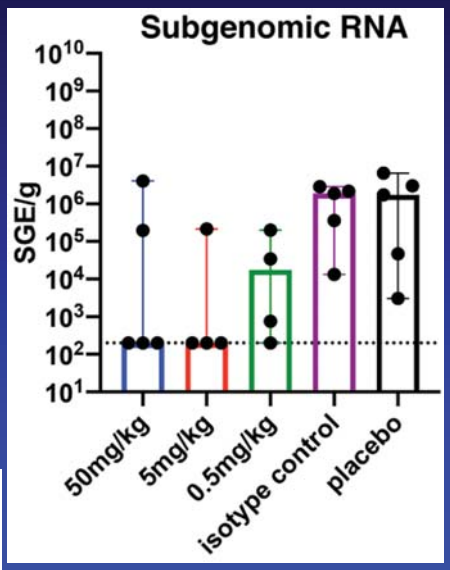
Chen P, *et al. N Engl J Med.* 2021;384:229 – 37.

REGN-CoV2 for Rhesus Macaques and Hamsters



1X10^5 PFU, NP sgRNA

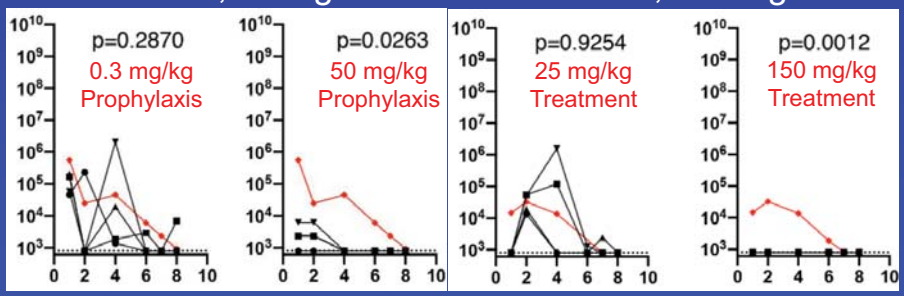
1X10^5 PFU, BAL sgRNA



Hamsters

1X10^6 PFU, NP sgRNA

1X10^6 PFU, Oral sgRNA



Rhesus Macaques

Baum A, et al. Science 2020;370:1110 – 15.

mAbs (REN10987+REGN10933)

- REGN-COV2—consists of two Abs simultaneously binding to two independent epitopes on the RBD—retained its ability to neutralize all identified mutants.

  Baum A, *et al. Science.* 2020

- REGN-COV-2 can greatly reduce virus load in lower and upper airways and decrease virus induced pathological sequelae in rhesus macaques.

  Baum A, *et al. Science.* 2020

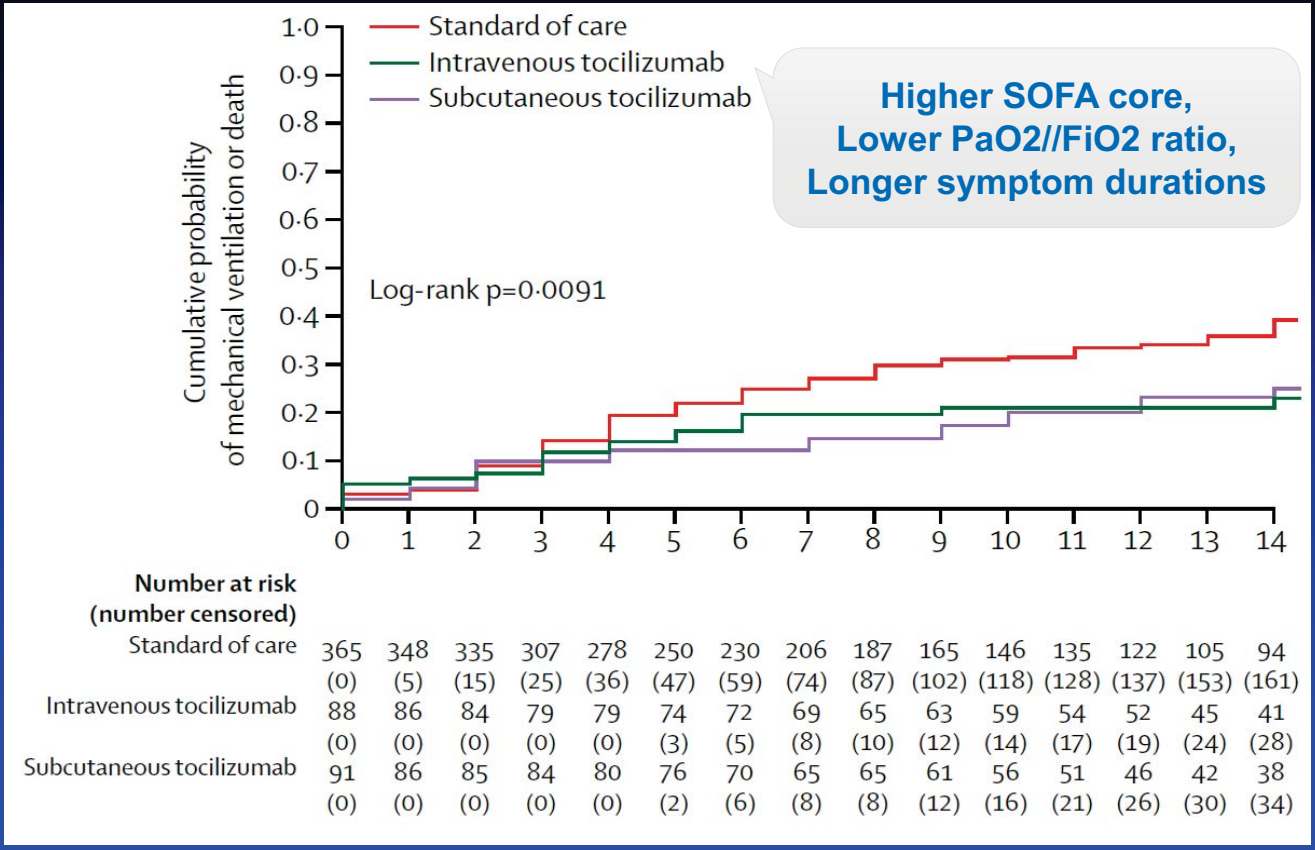
- **FDA EUA** Nov. 21, 2020

  Co-administration of casirivimab and imdevimab is authorized for patients with COVID-19 ≥12 years and with high risk for progressing to severe COVID-19 and/or hospitalization.

RECOVERY
Randomised Evaluation of COVID-19 Therapy

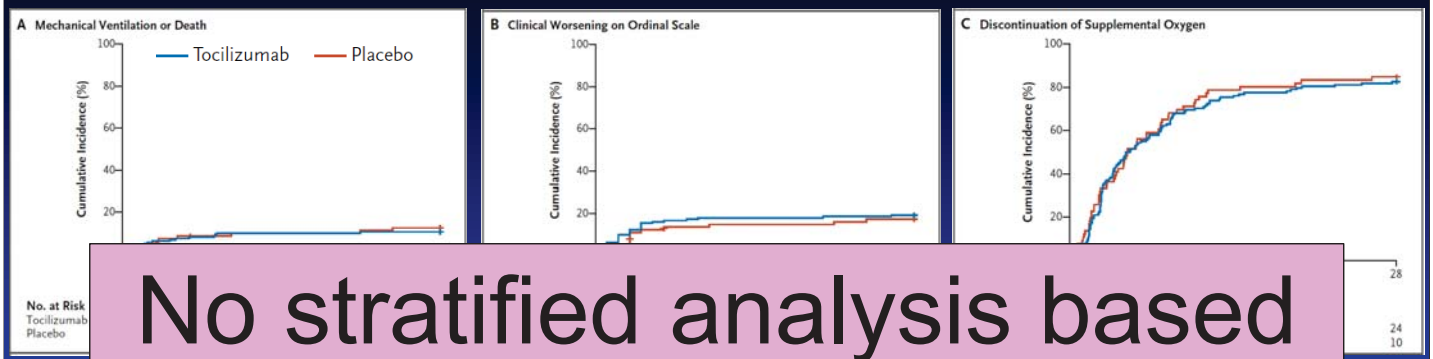
https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19 [Accessed Nov. 28, 2020]

Tocilizumab In Severe COVID-19



Guaraldi G, *et al. Lancet Rheumarol* 2020;2:e474–84.

No Significant Efficacy Noted



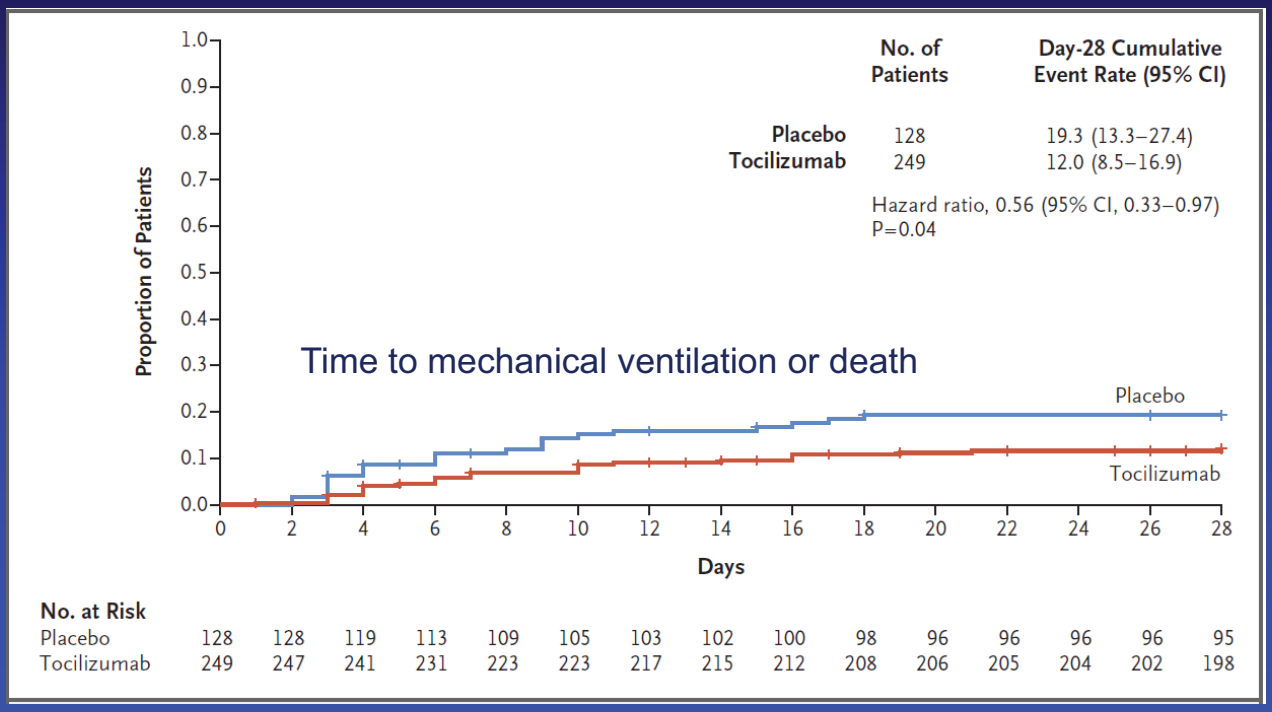
No stratified analysis based CRP level

Tabl

Outcome	(N=161)	(N=81)	Relative Risk
Median duration of receipt of supplemental oxygen (IQR) — days*	4.0 (1.8–11.6)	3.9 (1.1–9.2)	—
Median duration of mechanical ventilation (IQR) — days†	15.0 (12.6–NR)	27.9 (16.3–NR)	—
Admission to ICU or death — %	15.9	15.8	0.97 (0.50–1.88)

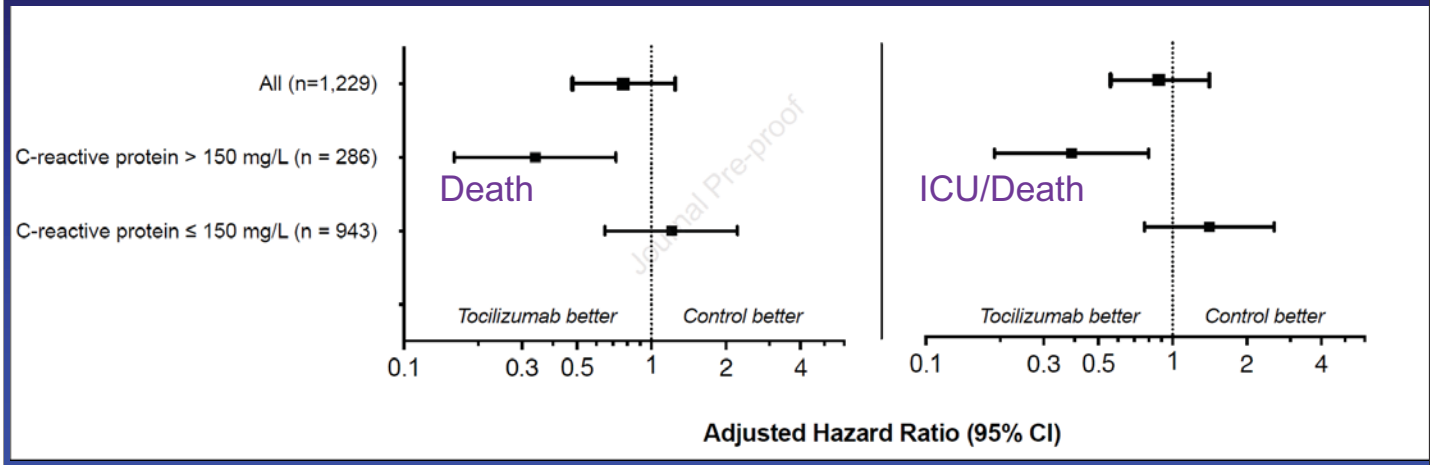
Stone JH, et al. N Engl J Med 2020;383:2333–44.

Tocilizumab for Pneumonia without Mechanical Ventilation

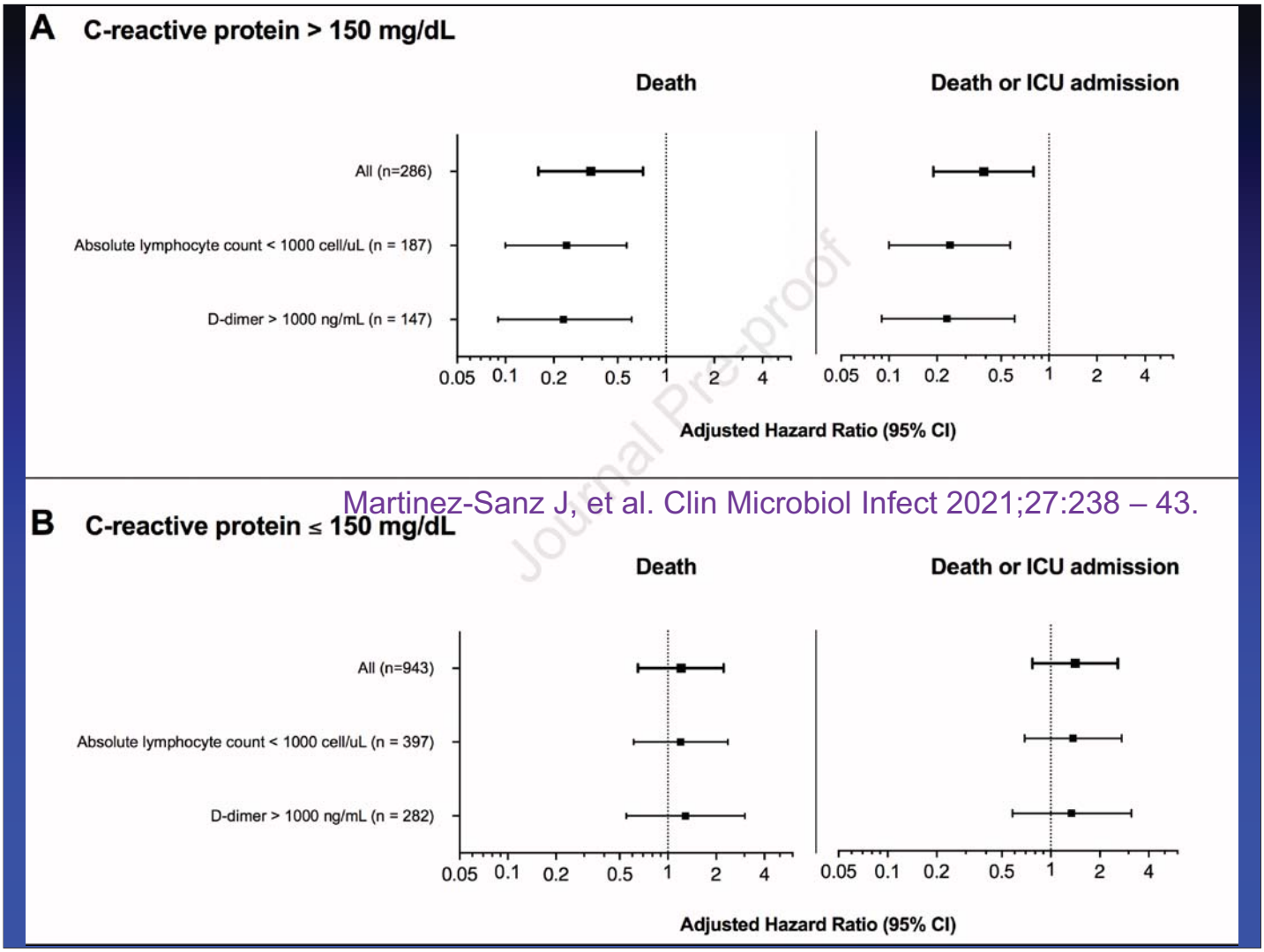


Salama C, et al. N Engl J Med 2021;384:20–30.

Tocilizumab, a Retrospective Cohort 17 Hospitals in Spain



Martinez-Sanz J, et al. Clin Microbiol Infect 2021;27:238 – 43.



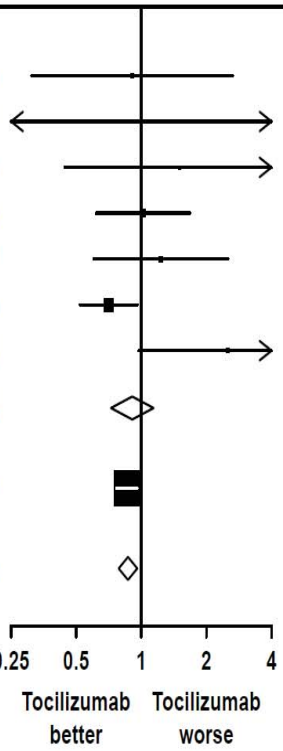
Martinez-Sanz J, et al. Clin Microbiol Infect 2021;27:238 – 43.

Figure 4: Tocilizumab vs usual care in patients hospitalised with COVID – Meta-analysis of mortality in RECOVERY and other trials

C-reactive protein >7.5mg/dl

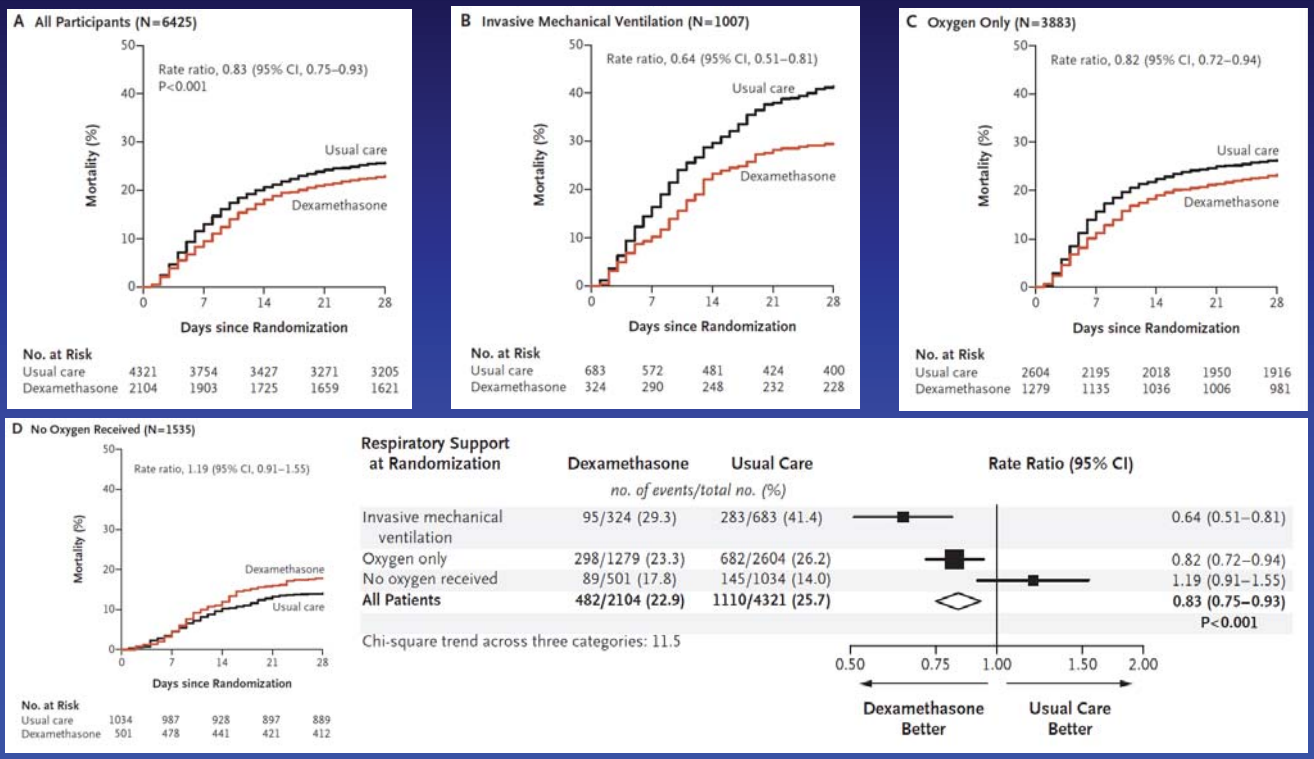
	Deaths / Patients randomised (%)		Observed-Expected		Ratio of death rates, RR (95% CI)
	Tocilizumab	Usual care	(O-E)*	Var(O-E)	
COR-IMUNO TOCI	7/64 (10.9)	8/67 (11.9)	-0.3	3.3	0.91 (0.31-2.65)
RCT-TCZ-COVID-19	2/60 (3.3)	1/66 (1.5)	0.6	0.7	2.17 (0.22-21.3)
BACC Bay	9/161 (5.6)	(3/82) x2† (3.7)	1.0	2.6	1.51 (0.44-5.13)
COVACTA	58/294 (19.7)	(28/144) x2† (19.4)	0.3	15.3	1.02 (0.62-1.68)
EMPACTA	26/249 (10.4)	(11/128) x2† (8.6)	1.6	7.5	1.23 (0.60-2.52)
REMAP-CAP	98/353 (27.8)	142/402 (35.3)	-14.2	40.8	0.71 (0.52-0.96)
TOCIBRAS	14/65 (21.5)	6/64 (9.4)	3.9	4.3	2.51 (0.97-6.50)
Subtotal: 7 trials	**214/1246 (17.2)**	**241/1307 (18.4)**	**-7.2**	**74.5**	**0.91 (0.72-1.14)**
RECOVERY	596/2022 (29.5)	694/2094 (33.1)	-48.2	316.0	0.86 (0.77-0.96)
All trials	**810/3268 (24.8)**	**935/3401 (27.5)**	**-55.4**	**390.5**	**0.87 (0.79-0.96) p=0.005**

Heterogeneity between RECOVERY and previous trials: χ^2_1=0.2



Horby P, *et al. medRxiv* 2021

Dexamethasone for Hospitalized COVID-19: RECOVERY Study



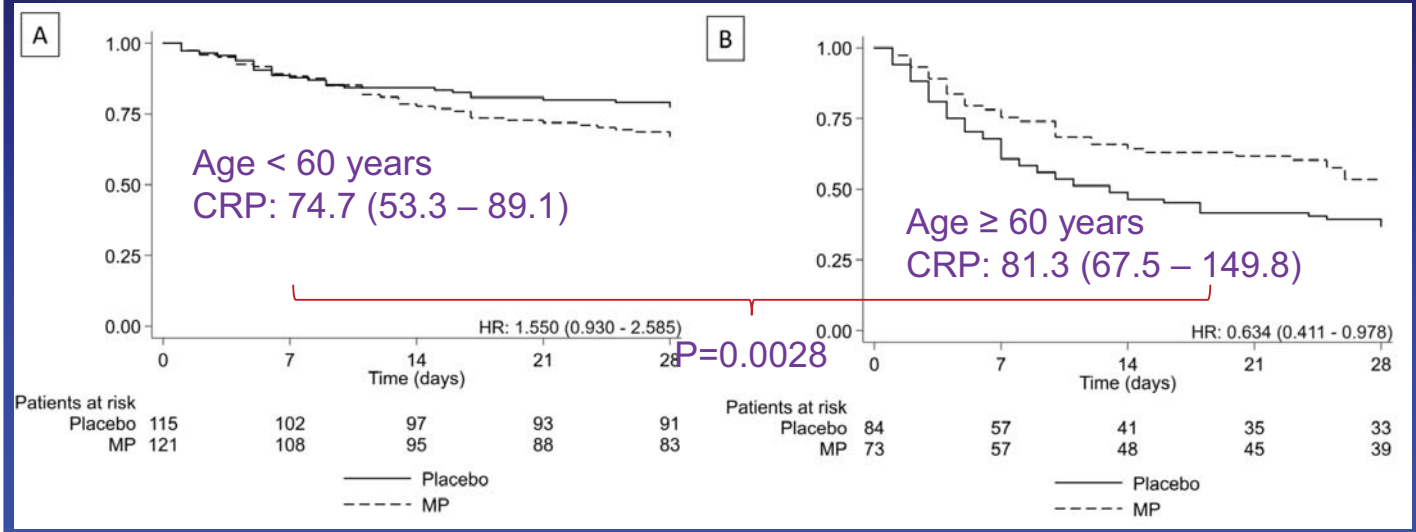
The RECOVERY Collaborative Group. N Engl J Med 2021:384:693 – 704.

Methylprednisolone for Day 28 in-hospital Mortality

- A RCT, Apr. 18 ~ Jun. 16 2020
- ≥ 18 years, COVID-19, needing oxygen
- 194 using MP 0.5 mg/kg, twice daily, 5 days
- 199 using placebo control
- Overall mortality:
  - 38.2% in control vs. 37.1% in MP group

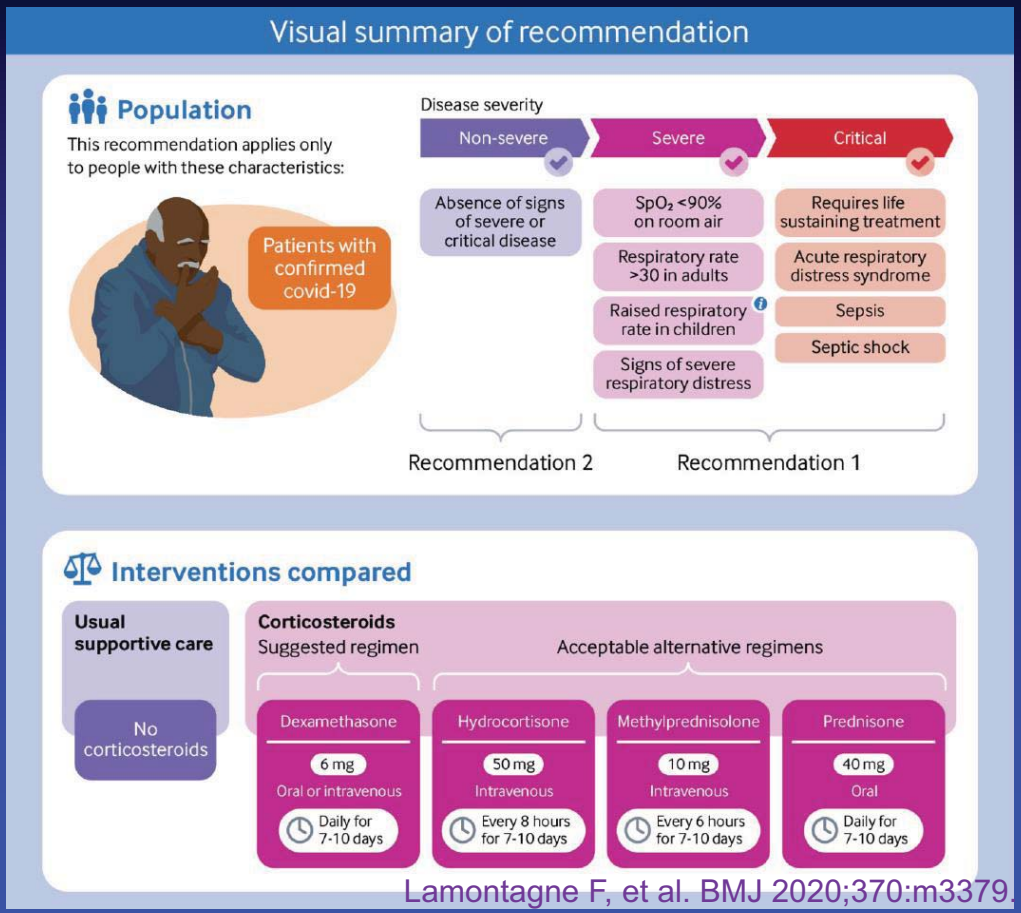
Jeronimo CMP, et al. Clin Infect Dis 2020;ahead of print.

Methylprednisolone for Day 28 in-hospital Mortality



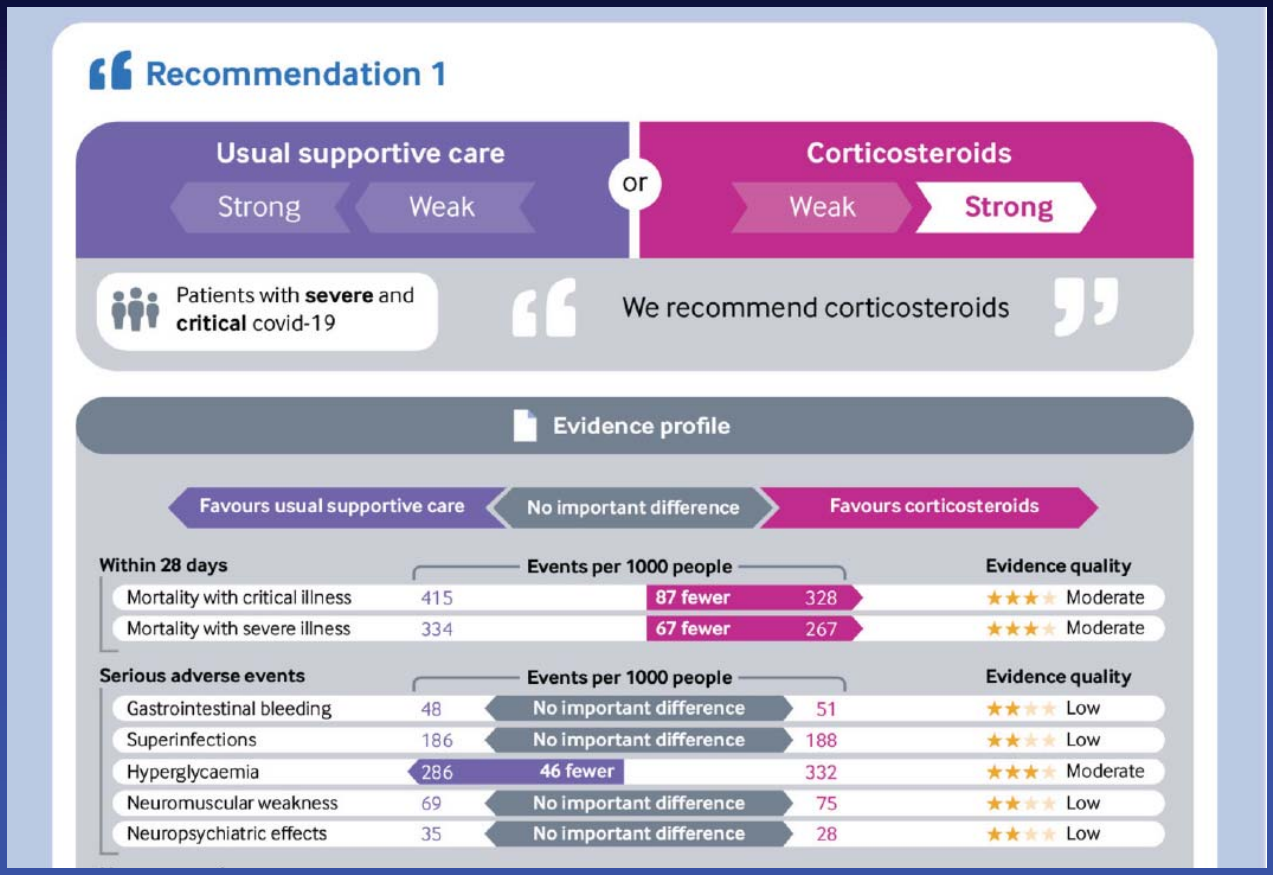
Jeronimo CMP, et al. Clin Infect Dis 2020;ahead of print.

Recommendations for Steroid

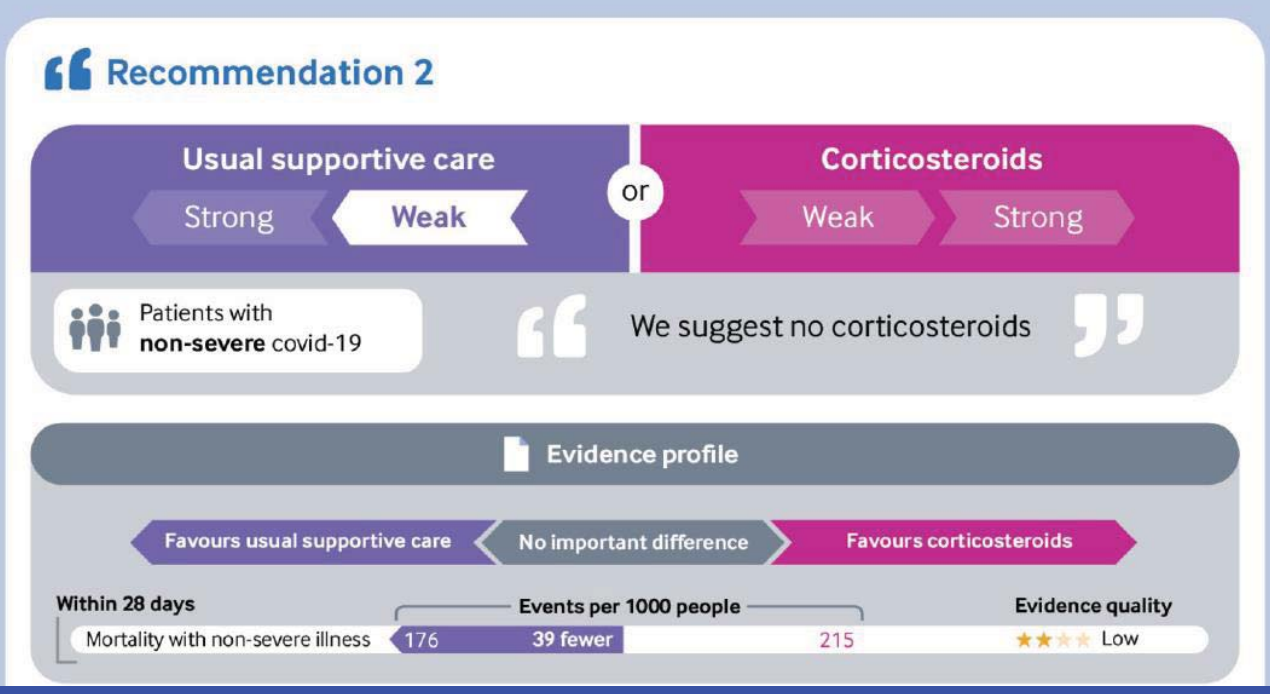


Lamontagne F, et al. BMJ 2020;370:m3379.

Recommendations for Steroid



Recommendations for Steroid



Risk Factor for Poor Prognosis

Variables	Deterioration	Discharge	OR	95% C.I.	P
	n=18	N=93			
Male sex	14	32	24.8	1.8 – 342.1	0.016
Comorbidity	15	18	52.6	3.6 – 776.4	0.004
Lymphopenia	16	30	17.3	1.1 – 261.8	0.039
↑ CRP	17	13	96.5	4.6 – 2017.6	0.003

Zhang J, et al. J Clin Virol 2020;127:104392.

Specific Treatment in Listing TCDC Guideline

- Remdesivir
  - Adults: 200 mg D1, 100 mg D2-D5 / D2-D10
  - Pediatrics: 5 mg/kg D1, 2.5 mg/kg D2-D5 / D2-D10
  - 5 days for those without ventilator or ECMO
- Dexmethasone:
  - 6 mg/day, less than 10 days
  - Pregnant women: prednisolone 40 mg/day, less than 10 days
  - Those who need oxygen supplement

亢龍有悔　盈不可久

易經　乾卦

THANKS FOR YOUR ATTENTION!