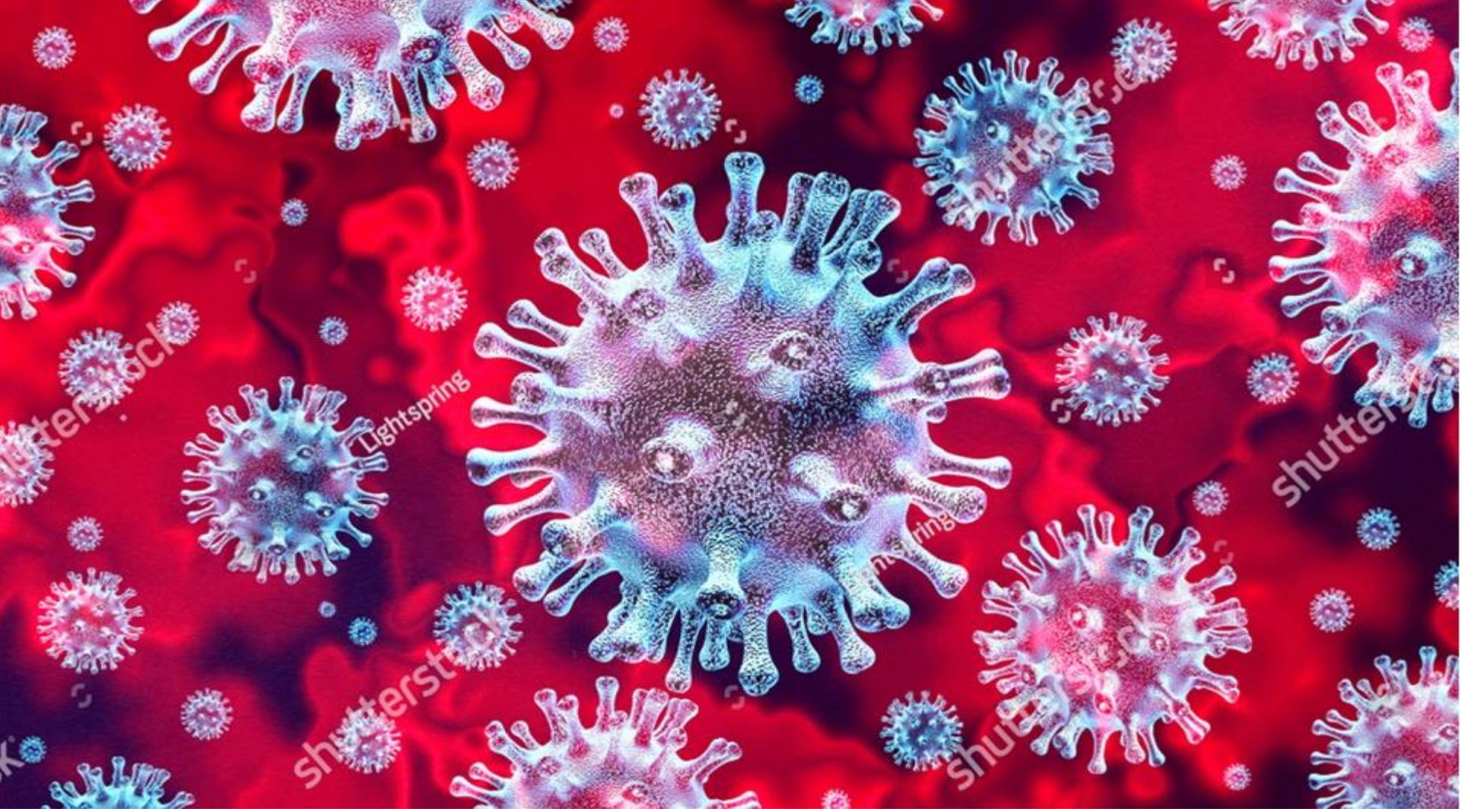
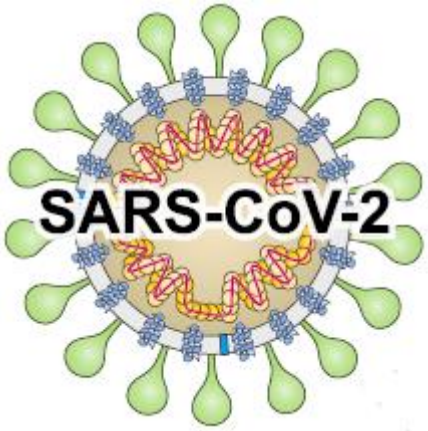


COVID-19

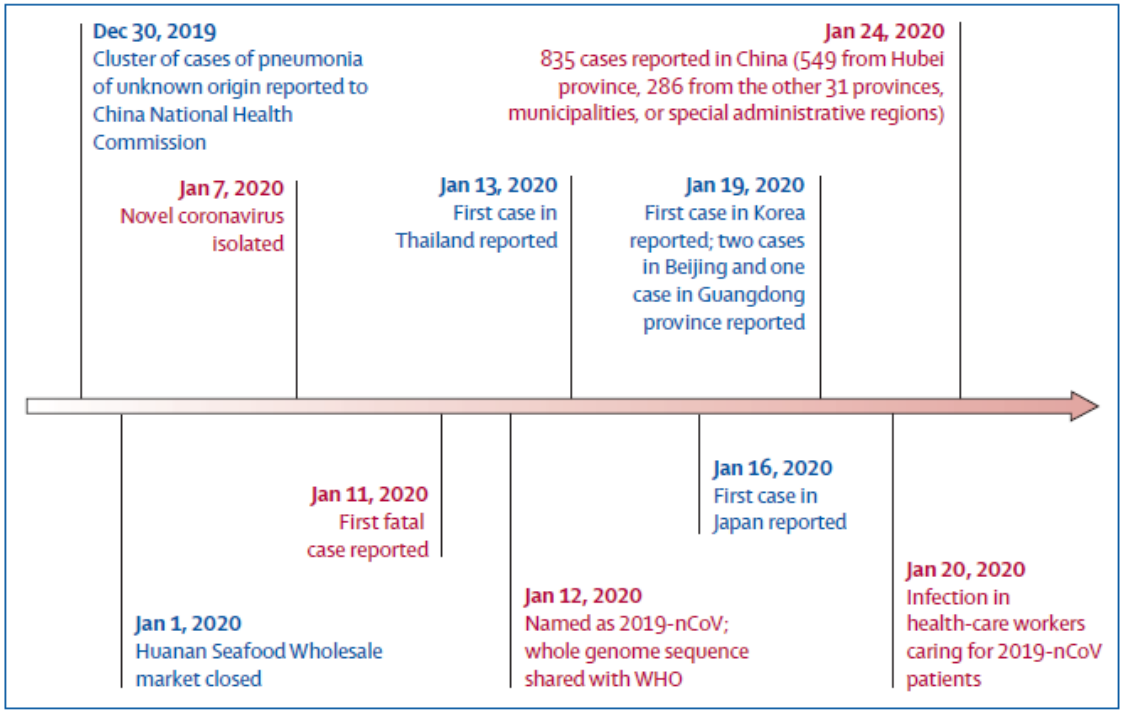
한림대학교 춘천성심병원 홍지영

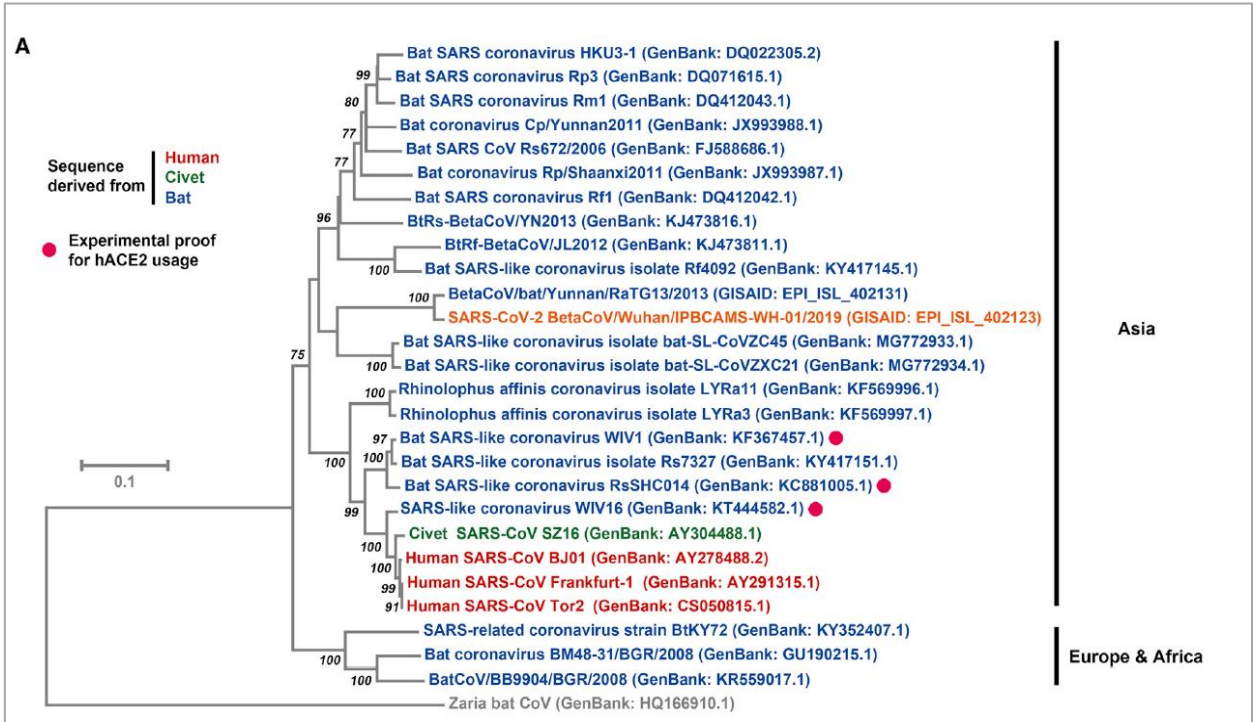
Agenda

- Pathogenesis and Viral mechanism
- Epidemiology and risk factor
- Transmission
- COVID-19 ARDS/ NIV-prone/ ECMO
- Treatment



SARS-CoV2 Outbreak



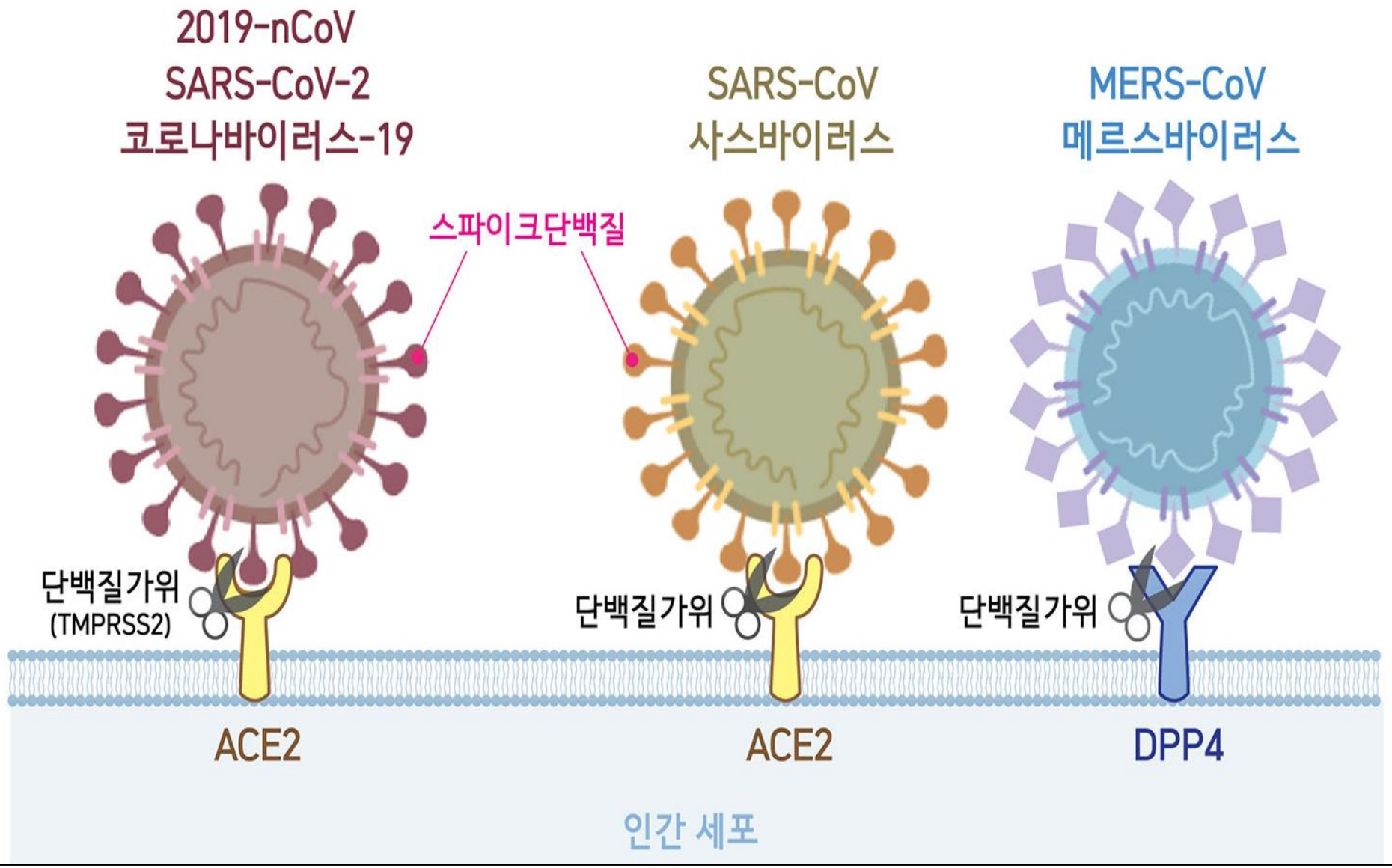


	2019-nCoV*	MERS-CoV	SARS-CoV
Demographic			
Date	December, 2019	June, 2012	November, 2002
Location of first detection	Wuhan, China	Jeddah, Saudi Arabia	Guangdong, China
Age, years (range)	49 (21–76)	56 (14–94)	39·9 (1–91)
Male:female sex ratio	2·7:1	3·3:1	1:1·25
Confirmed cases	835†	2494	8096
Mortality	25† (2·9%)	858 (37%)	744 (10%)
Health-care workers	16‡	9·8%	23·1%
Symptoms			
Fever	40 (98%)	98%	99–100%
Dry cough	31 (76%)	47%	29–75%
Dyspnoea	22 (55%)	72%	40–42%
Diarrhoea	1 (3%)	26%	20–25%
Sore throat	0	21%	13–25%
Ventilatory support	9·8%	80%	14–20%

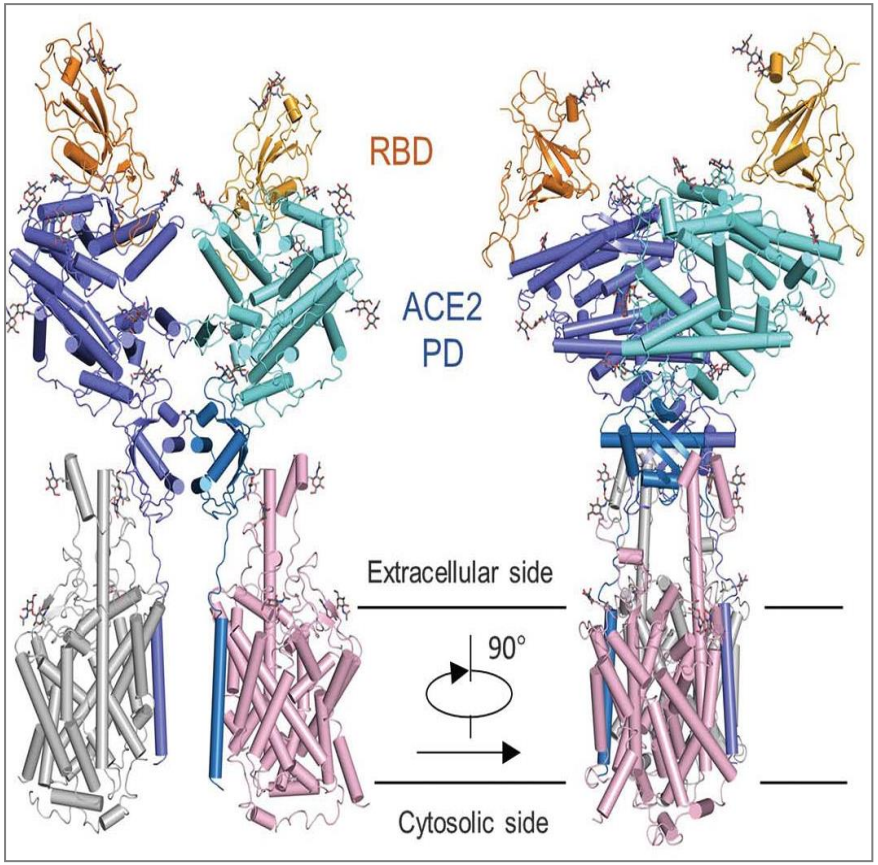
Data are n, age (range), or n (%) unless otherwise stated. 2019-nCoV=2019 novel coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus. *Demographics and symptoms for 2019-nCoV infection are based on data from the first 41 patients reported by Chaolin Huang and colleagues (admitted before Jan 2, 2020).[8] Case numbers and mortalities are updated up to Jan 21, 2020) as disclosed by the Chinese Health Commission. †Data as of Jan 23, 2020. ‡Data as of Jan 21, 2020.[9]

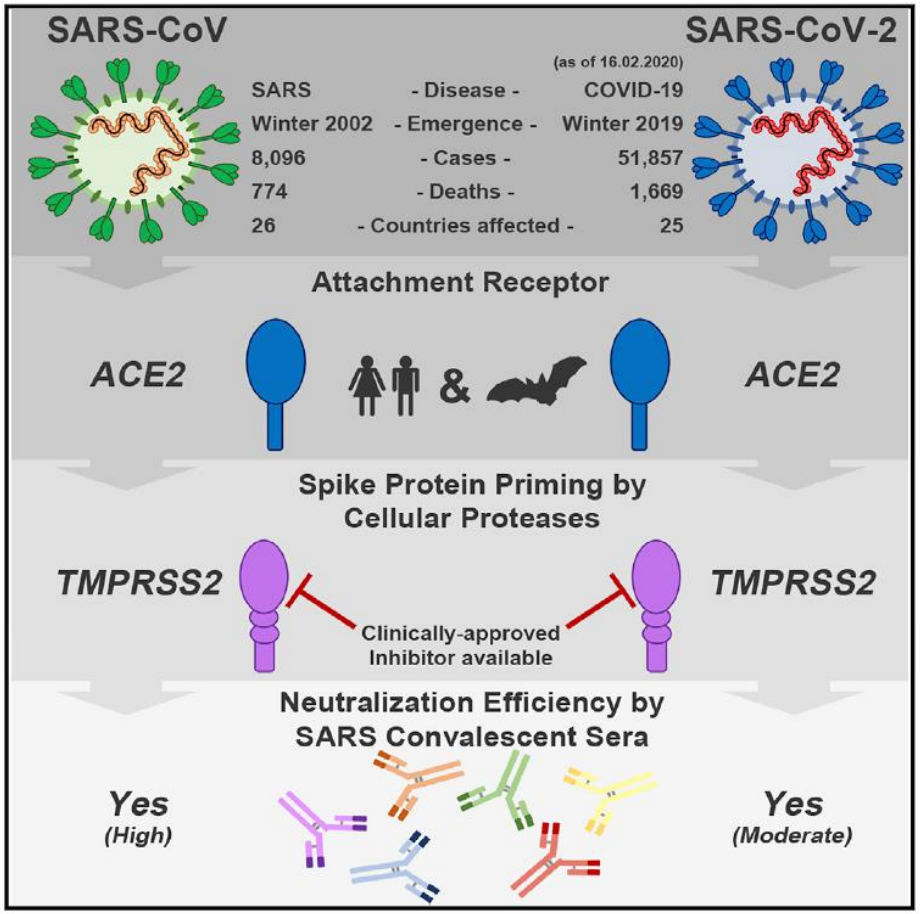
Table: **Characteristics of patients who have been infected with 2019-nCoV, MERS-CoV, and SARS-CoV**[7,8,10-12]

Virus	Location of Origin	Phylogenetic origin	Source/ Intermediate source	Receptor	Mortality Rate	R_0
SARS-CoV-2	Wuhan, China	Class I, Cluster IIa	Bats/unknown	ACE-2	2.3%	2-2.5
SARS-CoV	Guangdong, China, 2002-2003	Class I, Cluster IIb	Bats/palm civets or Dromedary camels	ACE-2	9.5%	1.7-1.9
MERS-CoV	Saudi Arabia	Class II	Bats/palm civets or Dromedary camels	DDP4	34.4%	0.7



IBS 과학리포토 인용 Cui et al., 2019, Yan et al., 2020

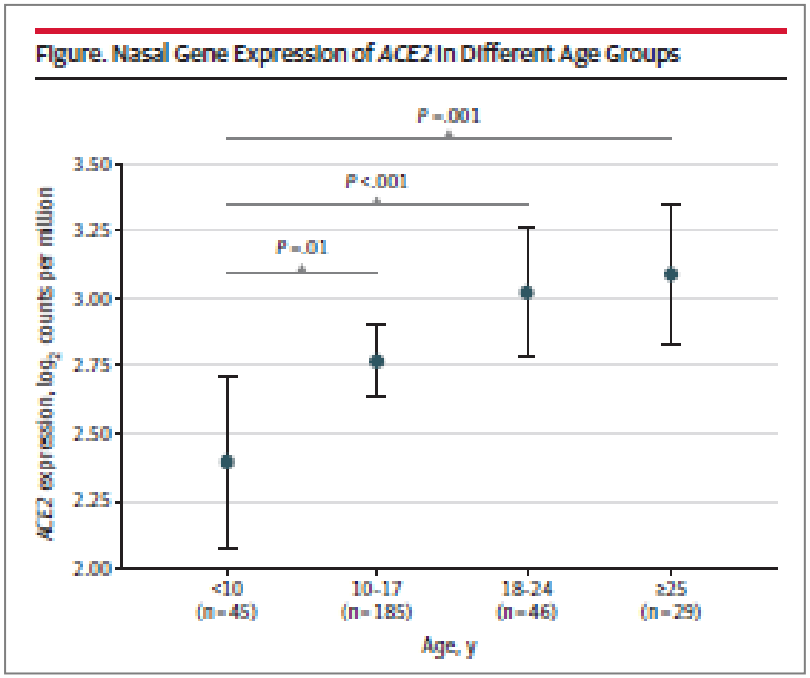




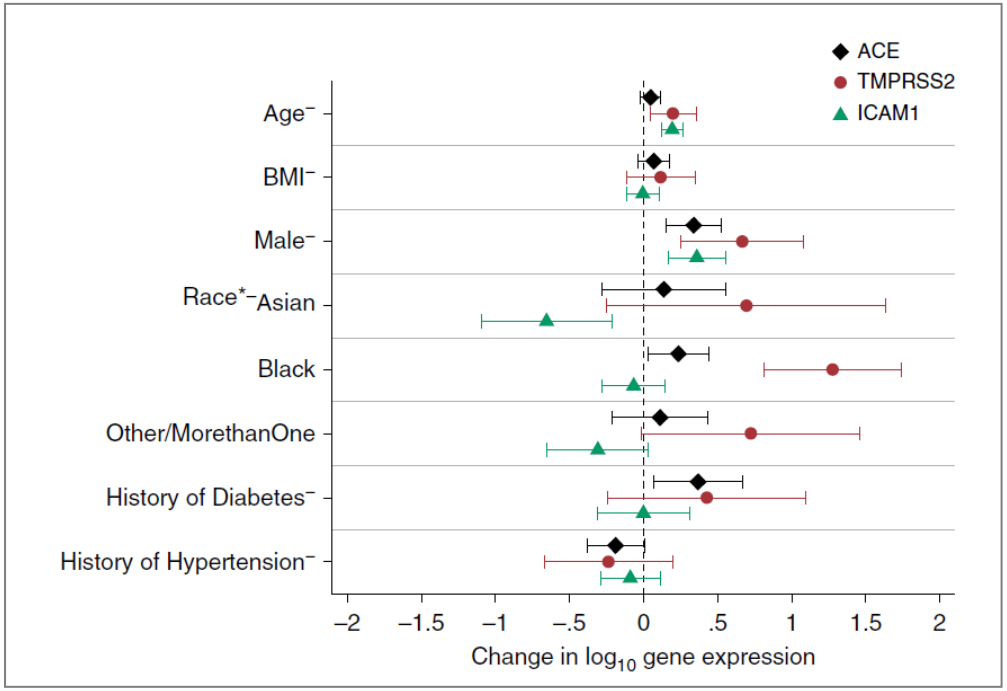
Yan et al., Science 367, 1444–1448 (2020)

Cell 181, 271–280, April 16, 2020

ACE2 gene expression



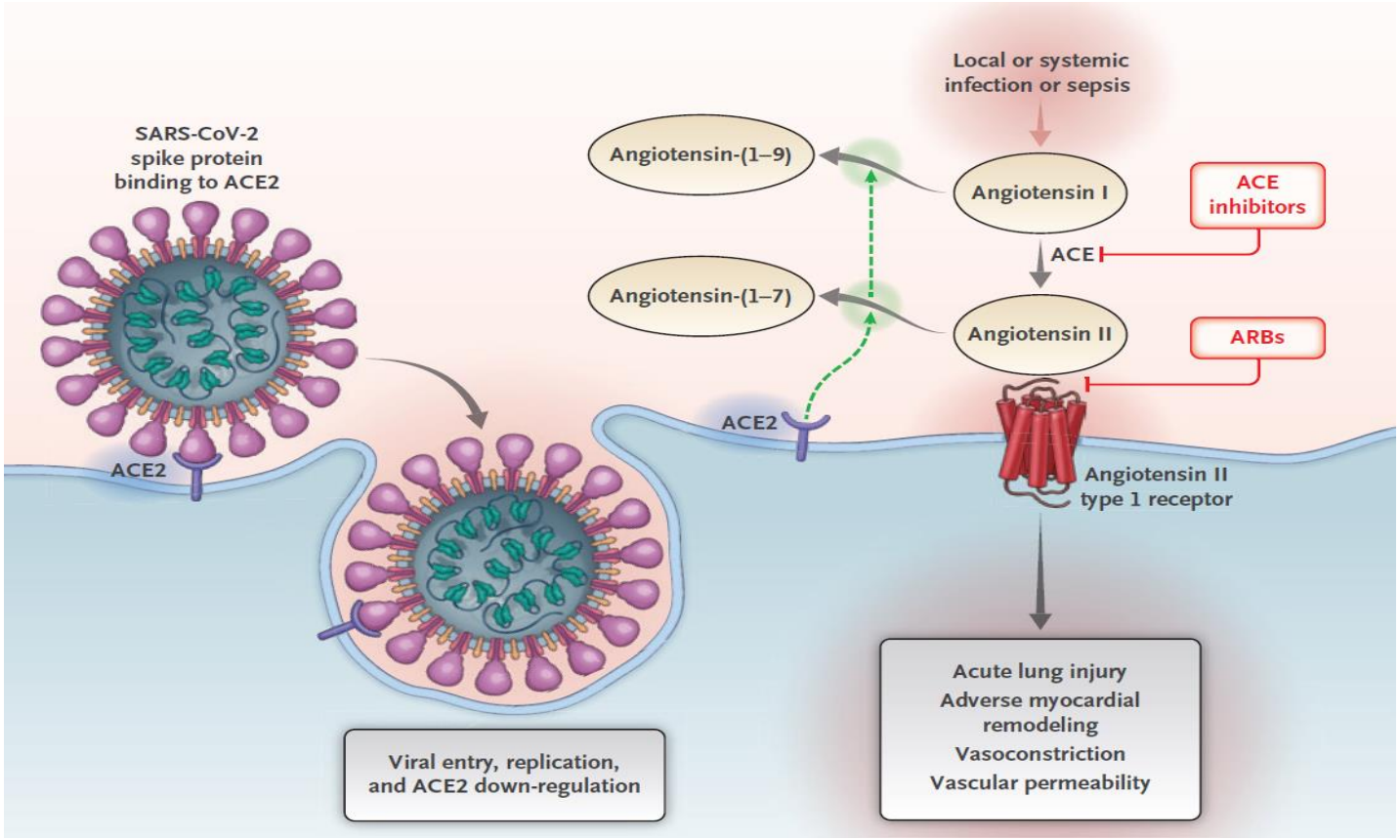
JAMA 323(23):2427-2429



AJRCCM 202(1) 98-90

- The positive association between *ACE2* gene expression and age was independent of sex and asthma.

- Higher expression of ACE2 and TMPRSS2 in males, African Americans, and patients with DM
- The lower expression of ACE2 and TMPRSS2 with ICS use



- Hypothesis:

  -The use of ARB or ACE inhibitor may modify susceptibility to infection with SARS-CoV2 in human.

  -RASS modulator may be effective in COVID-19.

Variable	Odds Ratio for Covid-19 (95% CI)†	
	Unadjusted	Adjusted
Drugs‡		
Antihypertensive drugs overall	1.53 (1.43–1.63)	
ACE inhibitors	1.16 (1.08–1.24)	0.96 (0.87–1.07)
ARBs	1.20 (1.12–1.29)	0.95 (0.86–1.05)
Calcium-channel blockers	1.28 (1.18–1.38)	1.03 (0.95–1.12)
Beta-blockers	1.42 (1.33–1.51)	0.99 (0.91–1.08)

NEJM 2020;382:2431-40.

Table 2. Likelihood of Positive Test for Covid-19, According to Treatment with Various Antihypertensive Agents, among Propensity-Score–Matched Patients, with Hypertension and Overall.*

Medication	Matched Patients with Hypertension			All Matched Patients		
	Covid-19 in Patients Treated with Medication	Covid-19 in Patients Not Treated with Medication	Median Difference (95% CI)	Covid-19 in Patients Treated with Medication	Covid-19 in Patients Not Treated with Medication	Median Difference (95% CI)
	no./total no. (%)		*percentage points*	*no./total no. (%)*		*percentage points*
ACE inhibitor	584/954 (61.2)	583/954 (61.1)	0.1 (–4.3 to 4.5)	627/1044 (60.1)	653/1044 (62.5)	–2.5 (–6.7 to 1.6)
ARB	629/1057 (59.5)	612/1057 (57.9)	1.6 (–2.6 to 5.8)	664/1137 (58.4)	639/1137 (56.2)	2.2 (–1.9 to 6.3)
ACE inhibitor or ARB	1019/1692 (60.2)	986/1692 (58.3)	2.0 (–1.4 to 5.3)	1110/1909 (58.1)	1101/1909 (57.7)	0.5 (–2.6 to 3.6)
Beta-blocker	792/1381 (57.3)	829/1381 (60.0)	–2.7 (–6.3 to 1.0)	912/1686 (54.1)	976/1686 (57.9)	–3.8 (–7.1 to –0.4)
Calcium-channel blocker	950/1577 (60.2)	930/1577 (59.0)	1.3 (–2.2 to 4.7)	992/1672 (59.3)	976/1672 (58.4)	0.9 (–2.3 to 4.3)
Thiazide diuretic	515/903 (57.0)	520/903 (57.6)	–0.6 (–5.1 to 3.9)	549/986 (55.7)	590/986 (59.8)	–4.2 (–8.5 to 0.2)

* Patients were propensity-score matched for age; sex; race; ethnic group; body-mass index; smoking history; history of hypertension, myocardial infarction, heart failure, diabetes, chronic kidney disease, and obstructive lung disease (e.g., asthma and obstructive pulmonary diseases); and other classes of medication. CI denotes credible interval.

NEJM 2020;382:2441-8.

	Cases (n=1139)	Matched controls (n=11 390)	Crude odds ratio*	Adjusted odds ratio†
Current use of other antihypertensive drugs	155 (13·6%)	1129 (9·9%)	1 (ref)	1 (ref)
Current use of RAAS inhibitors	497 (43·6%)	3822 (33·6%)	0·94 (0·77–1·14)	0·94 (0·77–1·15)
ACE inhibitors	240 (21·1%)	2192 (19·2%)	0·78 (0·63–0·97)	0·80 (0·64–1·00)
Monotherapy	82 (7·2%)	757 (6·7%)	0·75 (0·57–1·00)	0·83 (0·62–1·12)
Combinations	158 (13·9%)	1435 (12·6%)	0·80 (0·63–1·01)	0·78 (0·62–0·99)
Angiotensin-receptor blockers	237 (20·8%)	1552 (13·6%)	1·11 (0·89–1·38)	1·10 (0·88–1·37)
Monotherapy	38 (3·3%)	328 (2·9%)	0·82 (0·56–1·20)	0·87 (0·60–1·28)
Combinations	199 (17·5%)	1224 (10·8%)	1·18 (0·94–1·48)	1·15 (0·92–1·45)
Aldosterone antagonists	19 (1·7%)	71 (0·6%)	2·05 (1·20–3·49)	1·68 (0·97–2·91)
Renin inhibitors	1 (0·1%)	7 (0·1%)	1·08 (0·13–8·86)	1·04 (0·13–8·62)
Non-use	487 (42·8%)	6439 (56·5%)	0·47 (0·38–0·58)	0·55 (0·44–0·68)

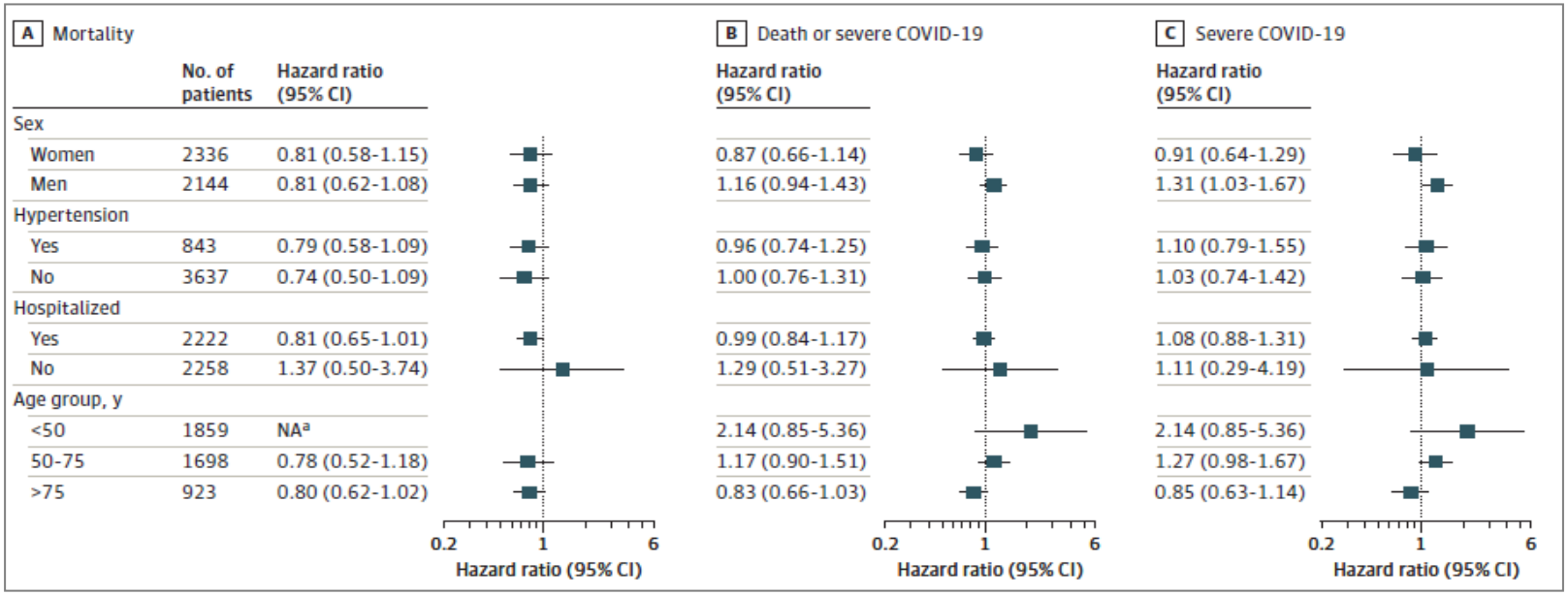
Lancet 2020; 395: 1705–14

(matched on sex and age)

RAAS inhibitors do not increase the risk of COVID-19 requiring admission to hospital.

Fully Adjusted Hazard Ratios for Angiotensin-Converting Enzyme Inhibitor (ACEI)/ Angiotensin Receptor Blocker (ARB) Use and Death

JAMA 2020 Jun 19;e2011301

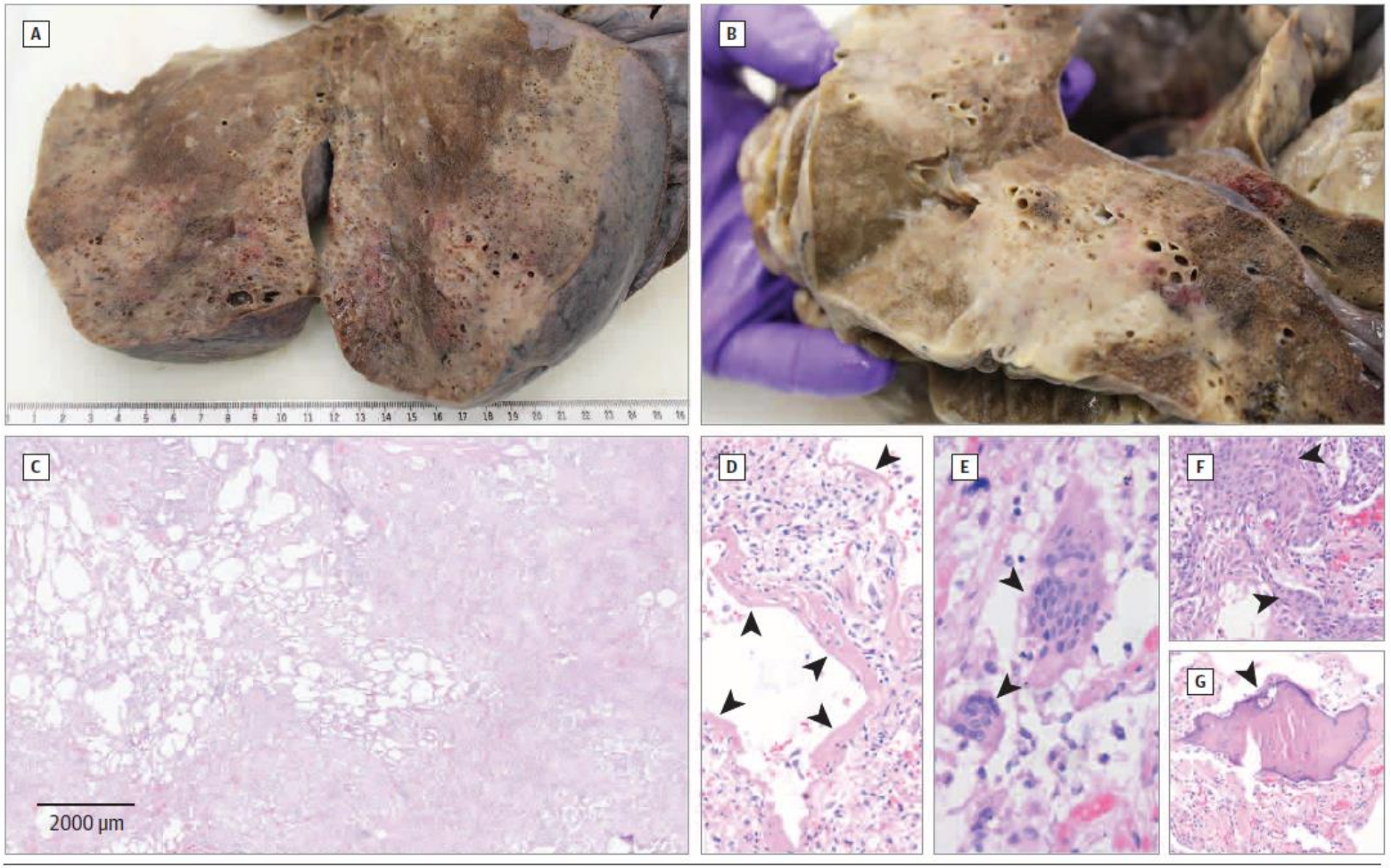


Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Recommendations:

- Persons with COVID-19 who are prescribed angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for cardiovascular disease (or other indications) should continue these medications **(AIII)**.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of ACE inhibitors or ARBs for the treatment of COVID-19 outside the setting of a clinical trial **(AIII)**.

Postmortem Examination of Patients With COVID-19



- Diffuse alveolar damage
- Hyaline membrane formation and pneumocyte atypical hyperplasia
- Platelet–fibrin thrombi in small arterial vessels

JAMA. 2020;323(24):2518-20

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

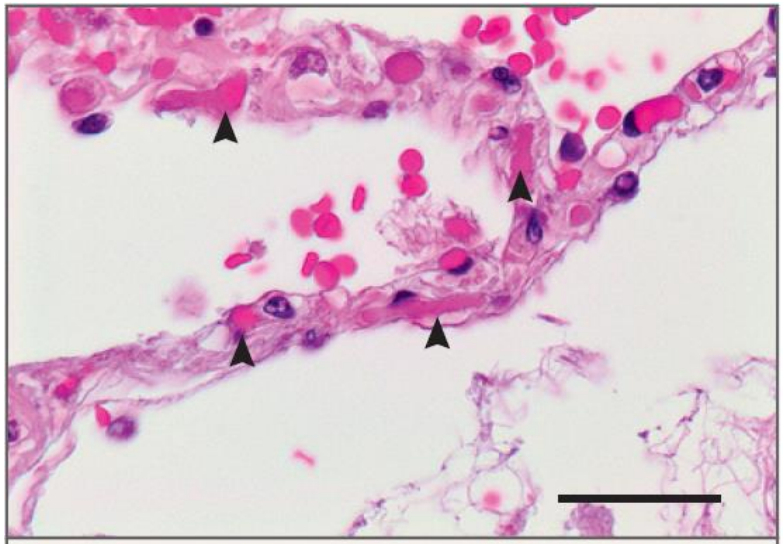
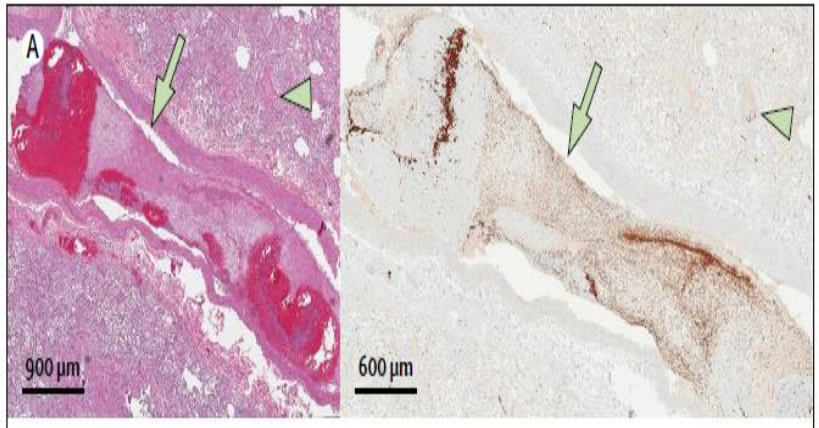
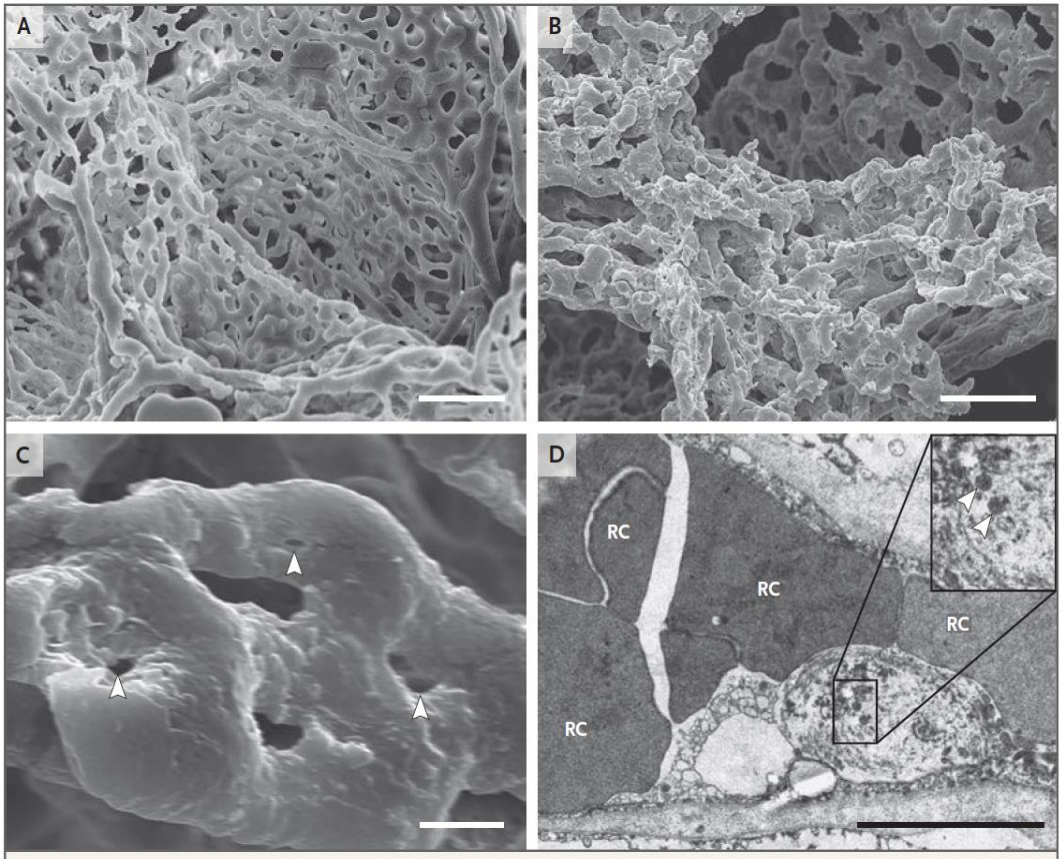


Figure 2. Microthrombi in the Interalveolar Septa of a Lung from a Patient Who Died from Covid-19.





thrombotic and microangiopathic pathology in the lungs

JAMA Internal Medicine | Original Investigation

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

JAMA | Orig

Baselin
With SA

Characte
Patients

Epidem
adults with COVID-19 in New York City: a prospective cohort study

Lancet 2020; 395: 1763–70

Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study

Lancet Respir Med 2020; 8: 475–81

Older age/Comorbidity/Obesity

Age, Neutrophilia, organ dysfunction, D-dimer, fever : ARDS development

High rate of ARDS/ICU admission/Death

High frequency of invasive mechanical ventilation, extrapulmonary organ dysfunction

JAMA Internal Medicine | Original Investigation

Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset

Figure 2. Number of Contacts, Secondary Cases, and Secondary Clinical Attack Rate by the Time of First Exposure

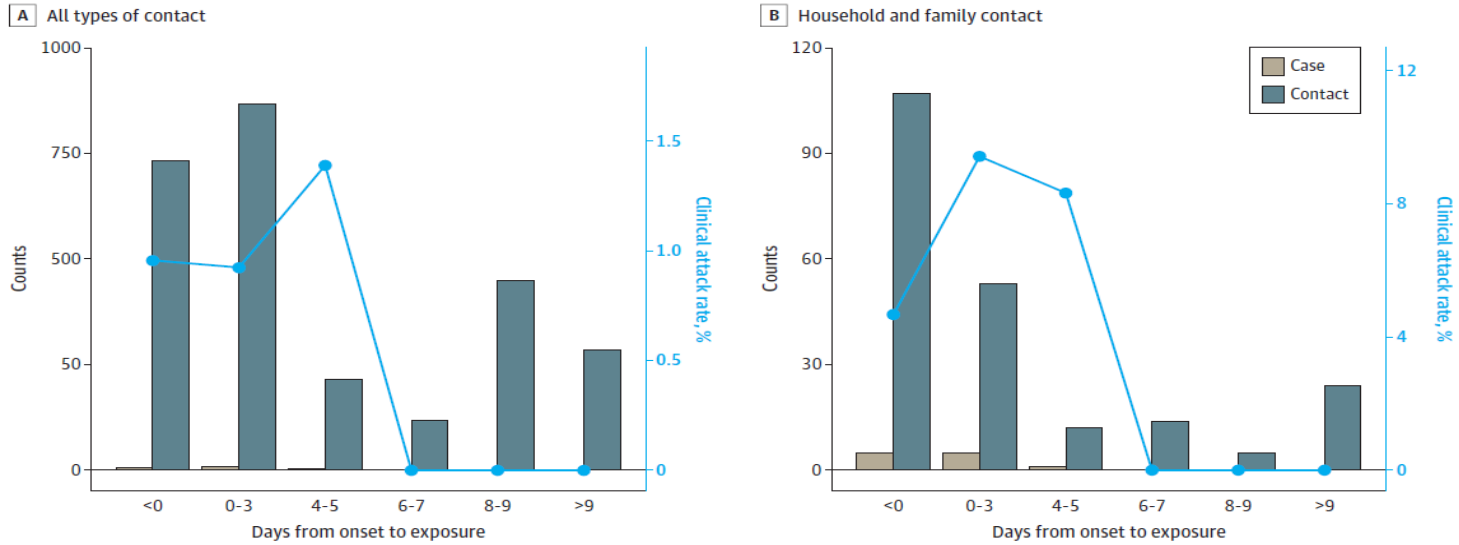
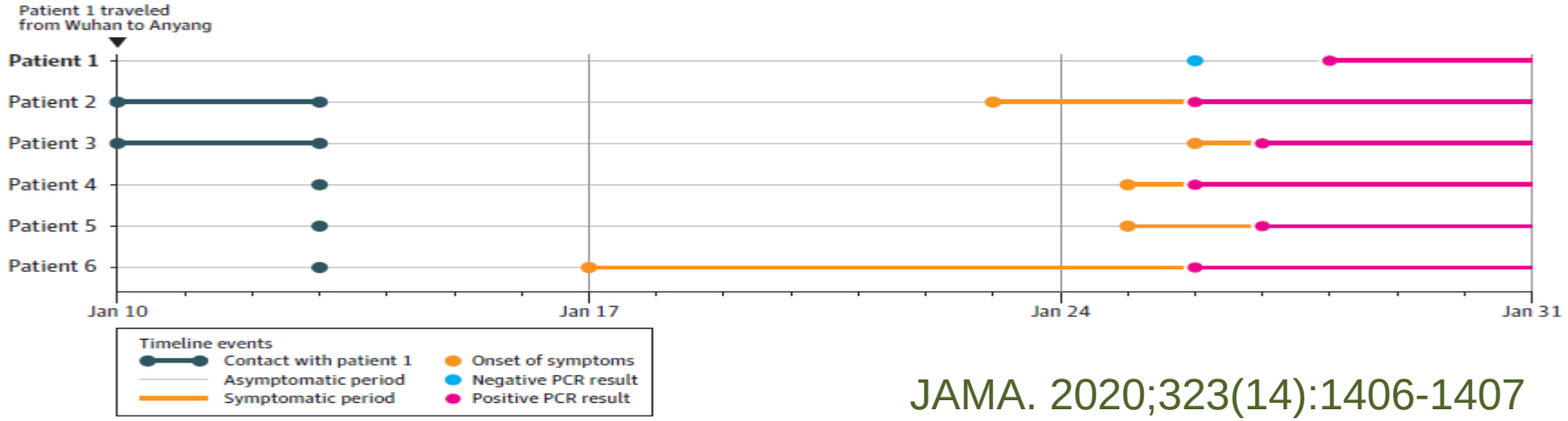


Figure. Timeline of Exposure to the Asymptomatic Carrier of the Novel Coronavirus That Causes COVID-19 in a Familial Cluster



JAMA. 2020;323(14):1406-1407

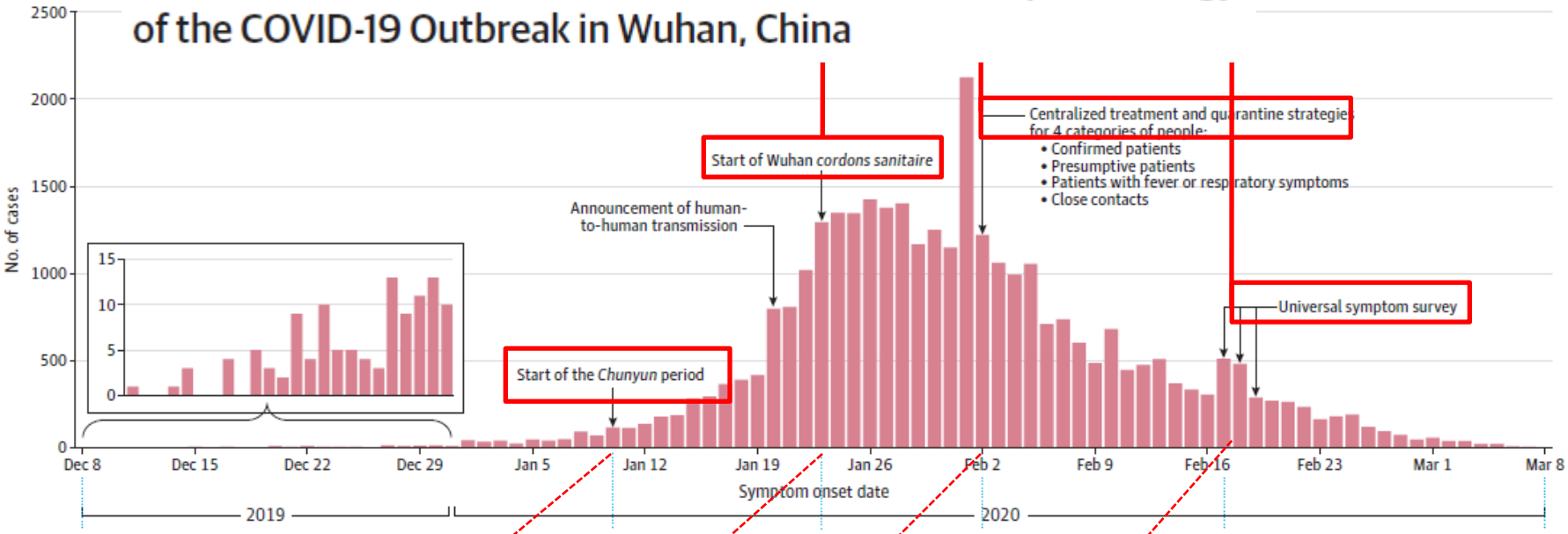
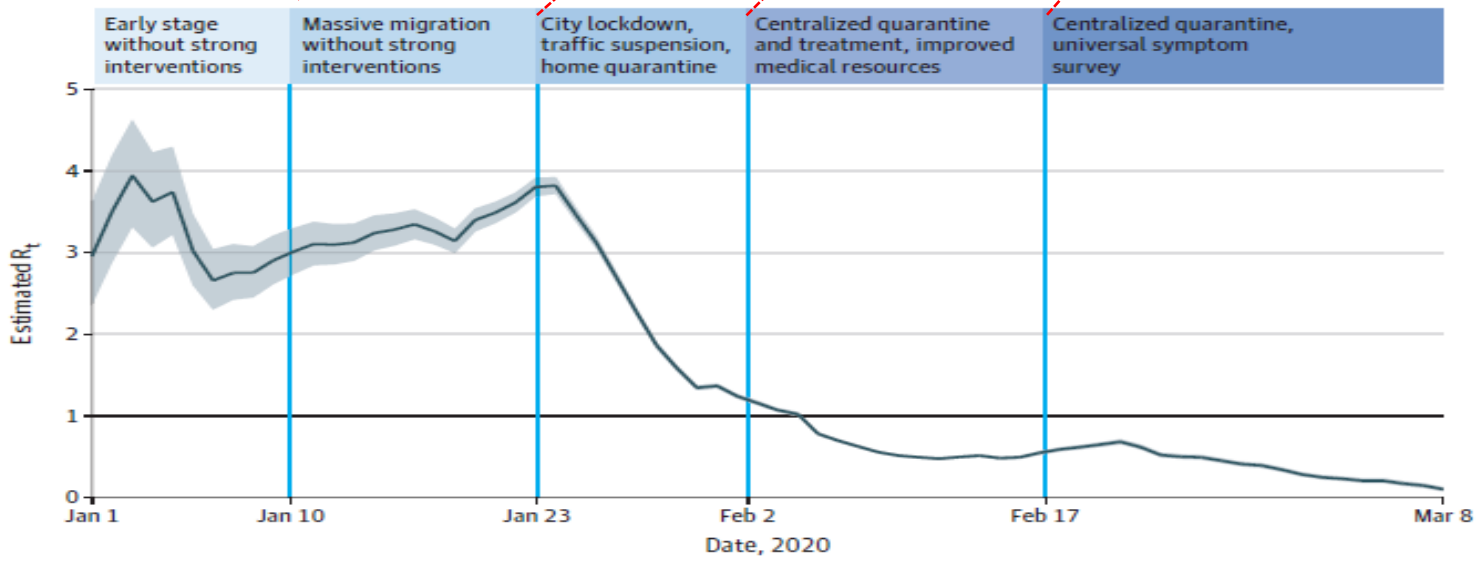


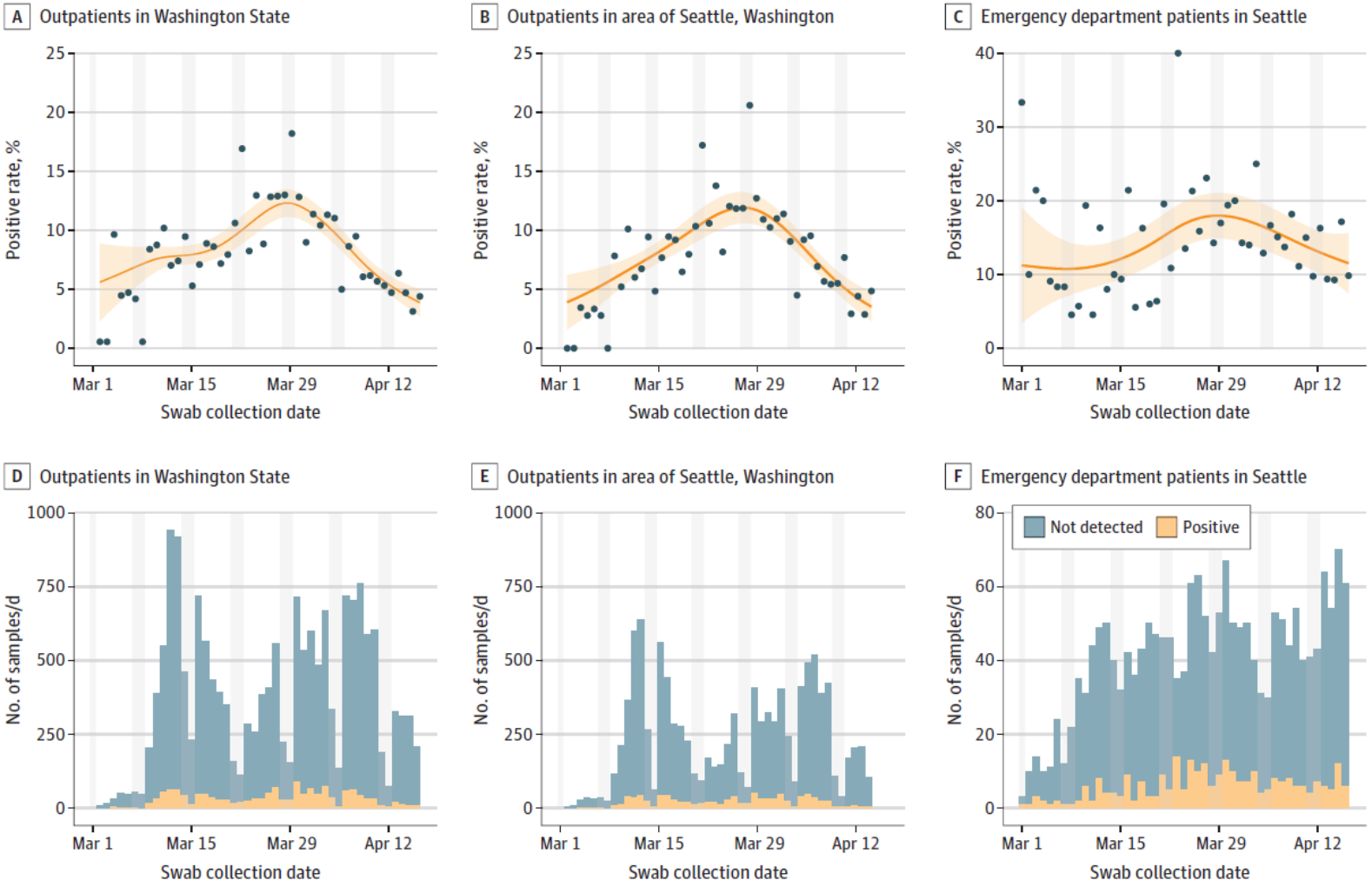
Figure 4. The Effective Reproduction Number (R_t) Estimates Based on Laboratory-Confirmed Coronavirus Disease 2019 (COVID-19) Cases in Wuhan, China



JAMA. 2020;323(19):1915-1923

This trajectory is aligned with local physical distancing guidelines "Stay Home, Stay Healthy" March 16 2020

Figure. SARS-CoV-2 Positivity Rates and Amount of Samples Tested at Outpatient and Emergency Department Settings in Washington State



JAMA. 2020;323(22):2334-2336

Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

Lancet 2020; 395: 1973–87

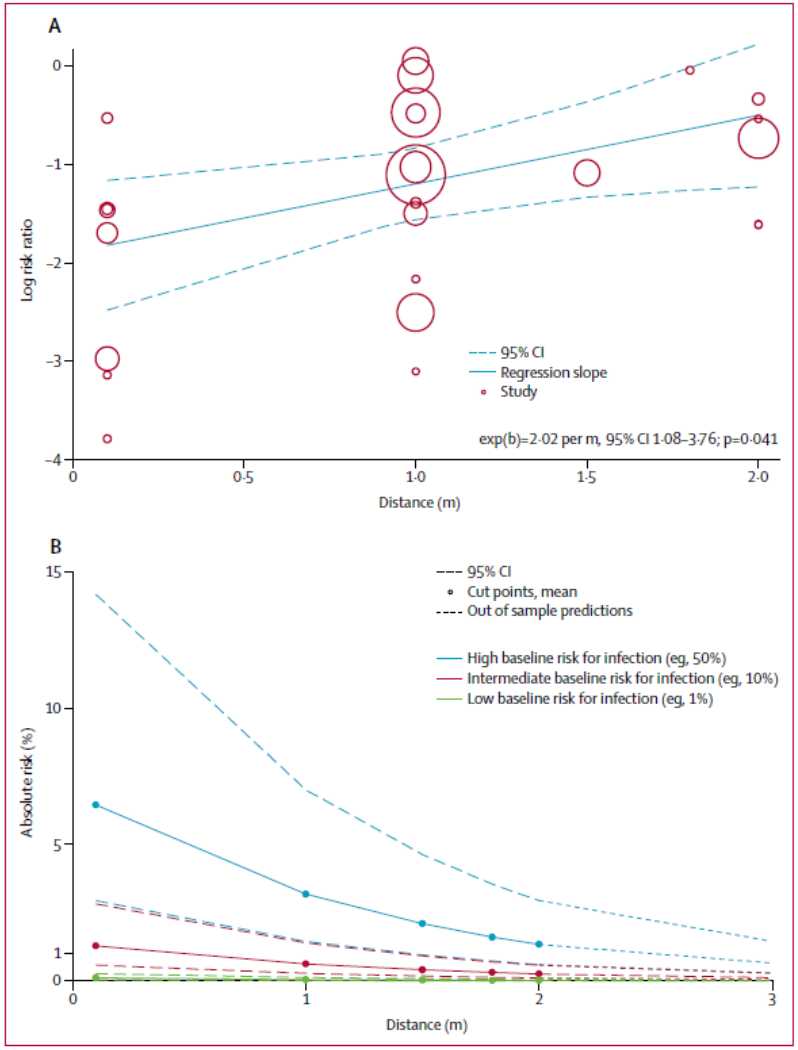
- **Lower transmission of viruses**
- **Physical distancing of 1 m or more**

  RD -10.2% (95% CI -11.5%,-7.5%)
- **Face mask**

  RD -14.3% (95% CI -15.9%,-10.7%)

  N95 respiratory support a stronger assocation of protection than other face masks.
- **Eye protection**

  RD -10.6% (95% CI -12.5%,-7.7%)



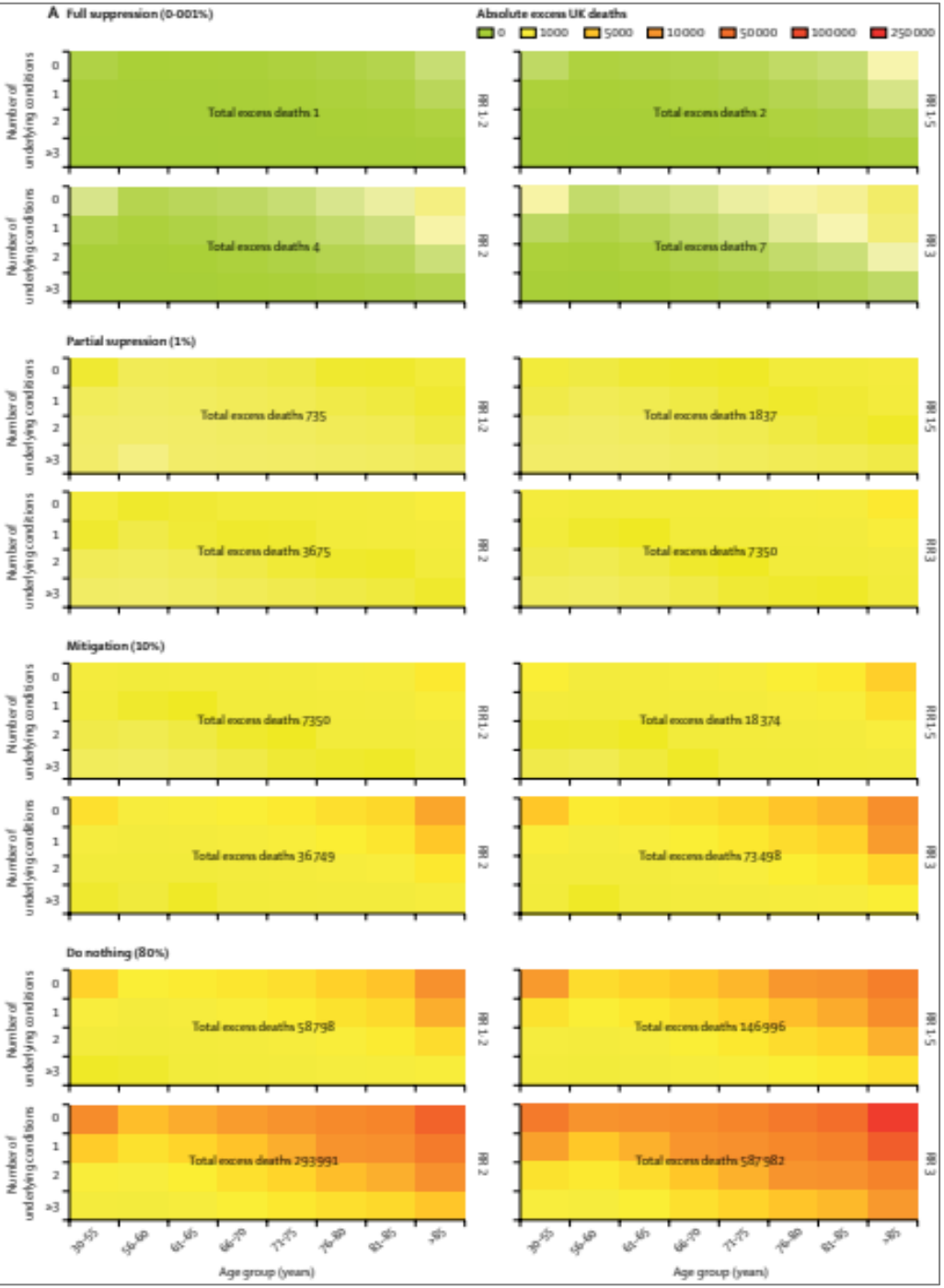
Effectiveness of isolation, testing, contact tracing, and physical distancing on reducing transmission of SARS-CoV-2 in different settings: a mathematical modelling study

	Self-Isolation	Contact tracing	Non-HH contacts who are potentially traceable (%)	Cases who have R>1 (%)	R_{eff}	Mean reduction in R_{eff}
No control	No	No	NA	50%	2·6	0%
Self-isolation within home	Yes	No	NA	40%	1·8	29%
Self-isolation outside home	Yes	NA	NA	37%	1·7	35%
Self-isolation plus HHQ	Yes	HH	NA	35%	1·6	37%
Self-isolation plus HHQ plus work or school contact tracing	Yes	HH and work or school	100%	27%	1·2	53%
Self-isolation plus HHQ plus manual contact tracing of acquaintances	Yes	All	90% school, 79% work, and 52% other	26%	1·1	57%
Self-isolation plus HHQ plus manual contact tracing of all contacts	Yes	All	100%	21%	0·94	64%
Self-isolation plus HHQ plus app-based tracing	Yes	All	53%	30%	1·4	47%
Self-isolation plus HHQ plus manual contact tracing of acquaintances plus app-based tracing	Yes	All	90% school, 79% work, and 52% other with manual tracing; 53% with app tracing	23%	1	61%
Self-isolation plus HHQ plus manual contact tracing of acquaintances plus limit to four daily contacts with other individuals	Yes	All	90% school, 79% work, and 52% other	21%	0·93	64%
Self-isolation plus HHQ plus manual contact tracing of acquaintances plus app-based tracing plus limit to four daily contacts with other individuals	Yes	All	90% school, 79% work, and 52% other with manual tracing; 53% with app tracing	20%	0·87	66%
Mass testing of 5% of population per week	No	NA	NA	49%	2·5	2%

Results from 20 000 simulated setting-specific secondary transmissions, assuming a secondary attack rate of 20% among household contacts and 6% among other contacts. Results under the assumption of some workplace restrictions remaining in place are shown in table 4. Estimates are shown to two significant figures. HH=household. HHQ=household quarantine. NA=not applicable. R_{eff}=effective reproduction number.

***Table 3*: Mean reduction in R_{eff} under different control measures**

Lancet Infect Dis. 2020 Jun 15:S1473-3099(20)30457-



Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study

Lancet 2020; 395: 1715–25

Electronic health records from England (Health Data Research UK–CALIBER)

Underlying conditions

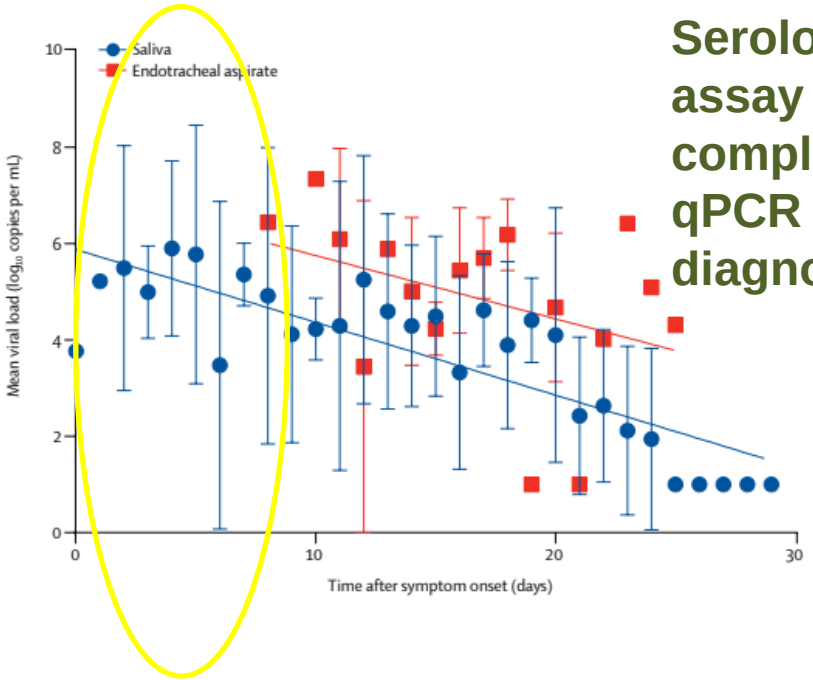
Age

Suppression strategies

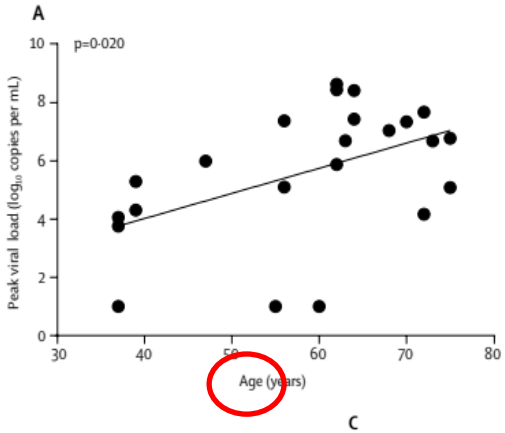
- full suppression
- Partial suppression
- mitigation
- do nothing

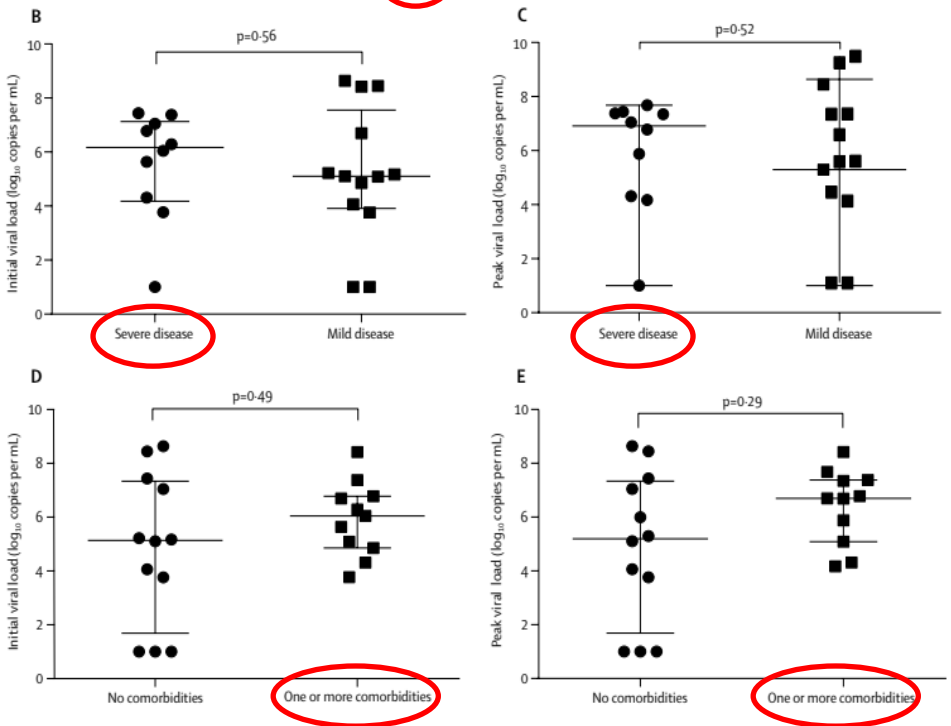
Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study

Lancet Infect Dis 2020; 20: 565–74



Serological assay can complement RT-qPCR for diagnosis.





14 days or longer after symptom onset, rates of seropositivity were

- 94% for anti-NP IgG (n=15)
- 88% for anti-NP IgM (n=14),
- 100% for anti-RBD IgG (n=16)
- 94% for anti-RBD IgM (n=15)

Virus neutralisation titre (R^2>0·9)

Seroprevalence of anti-SARS-CoV-2 IgG SEROCoV-POP study

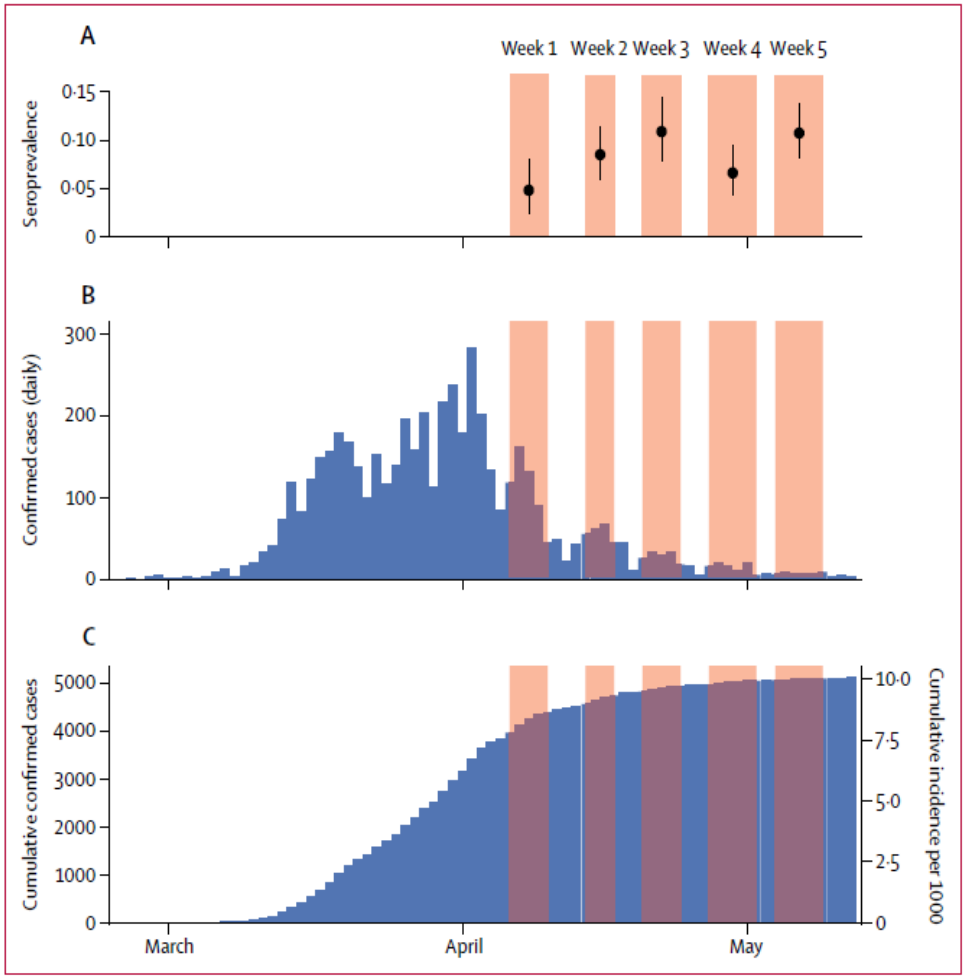


Figure: Seroprevalence estimates and 95% CIs for each week of the survey (A), daily confirmed COVID-19 cases reported in Geneva (B), and cumulative case counts per day and cumulative incidence rate of confirmed COVID-19 (C)

The immunological landscape has not changed **despite the high prevalence of COVID-19 in the region**

Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study

The Lancet 2020

	Point-of-care test		Immunoassay	
	Number of participants	Seroprevalence (95% CI)	Number of participants	Seroprevalence (95% CI)
Symptoms compatible with COVID-19*				
Asymptomatic	40325	2·5% (2·3–2·8)	34016	2·0% (1·8–2·3)
Paucisymptomatic	12399	4·5% (4·0–5·0)	10669	3·9% (3·4–4·4)
Symptomatic	8351	16·9% (15·5–18·4)	7273	16·9% (15·4–18·5)
≤14 days before study visit	2397	13·9% (11·8–16·4)	2155	14·0% (11·8–16·5)
>14 days before study visit	5954	18·0% (16·4–19·8)	5118	18·0% (16·3–19·9)
PCR status				
Never done	59568	4·6% (4·3–4·9)	50594	4·2% (3·8–4·5)
Negative	1249	7·9% (6·0–10·3)	1134	8·0% (6·0–10·6)
Positive (≤14 days before study visit)	35	45·6% (25·0–67·8)	31	65·8% (41·5–83·9)
Positive (>14 days before study visit)	213	88·6% (82·3–92·8)	195	90·1% (84·3–93·9)
Contact with confirmed case				
No contact	55989	3·9% (3·6–4·2)	47385	3·4% (3·1–3·7)
Household member	1011	31·4% (26·5–36·8)	860	37·4% (31·8–43·3)
Non-cohabitating family member or friend	1467	13·2% (11·0–15·8)	1284	13·7% (11·2–16·7)
Co-worker	1579	10·6% (8·5–13·1)	1461	9·9% (8·0–12·2)
Cleaning staff, housemaid, or caregiver	83	13·5% (6·3–26·5)	78	12·4% (7·0–21·0)
Client†	940	11·7% (9·1–14·9)	888	11·2% (8·6–14·4)
Contact with symptomatic person				
No contact	50691	3·2% (3·0–3·5)	42894	2·7% (2·4–3·0)
Household member	4503	15·1% (13·3–17·0)	3728	15·6% (13·6–17·9)
Non-cohabitating family member or friend	2351	12·7% (10·7–14·9)	2037	12·2% (10·0–14·7)
Co-worker	2382	10·7% (9·0–12·6)	2221	10·1% (8·4–12·1)
Cleaning staff, housemaid, or caregiver	109	8·8% (3·9–18·8)	96	6·1% (2·9–12·3)
Client†	1033	10·0% (7·8–12·8)	980	10·2% (7·8–13·1)

Despite the high impact of COVID-19 in Spain,

prevalence estimates remain low (5%) and are clearly insufficient to provide herd immunity.

Positive PCR more than 14 days before the study visit

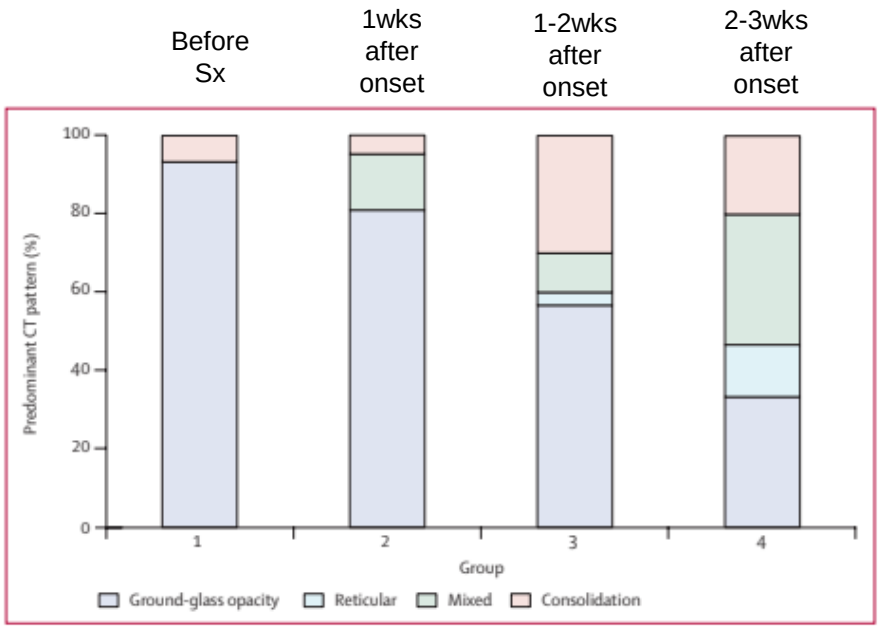
87.6(Both), 91.8% (either)

Seropositive participants

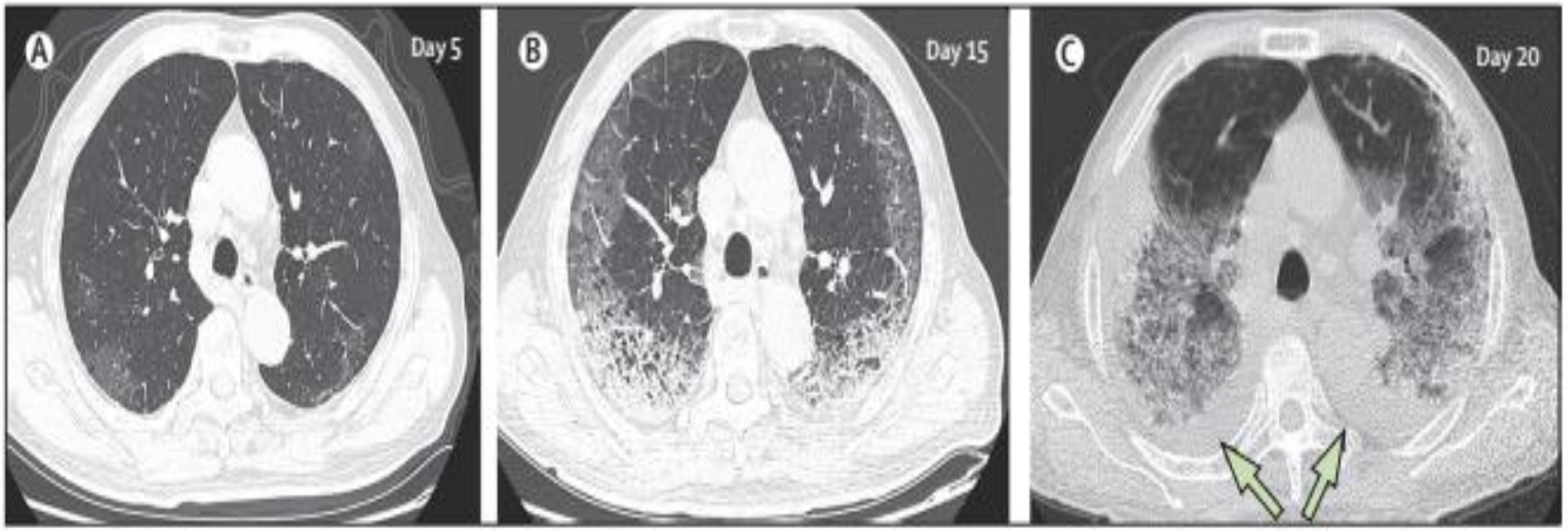
- asymptomatic was 32·7%/28·5%
- Anosomia, three or more symptoms 49·1% /54·2%

Radiological finding

Lancet Infect Dis 2020; 20: 425-34



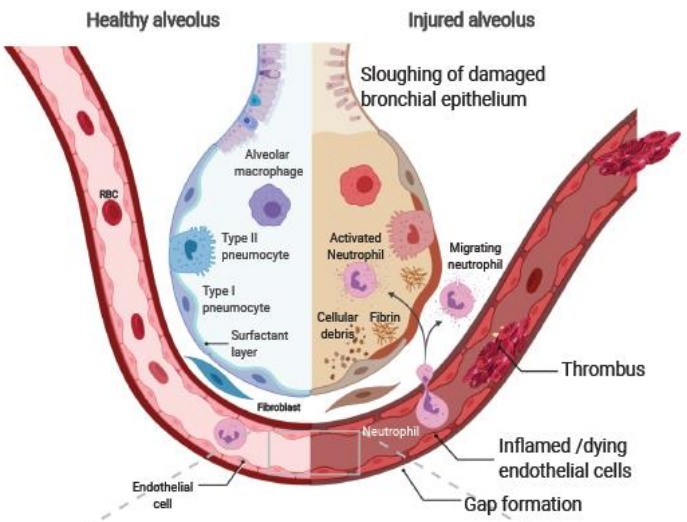
- Abnormal finding even in asymptomatic patients
- GGO and consolidation within 1–3 weeks after onset of symptoms, peaking at around 2 weeks after onset

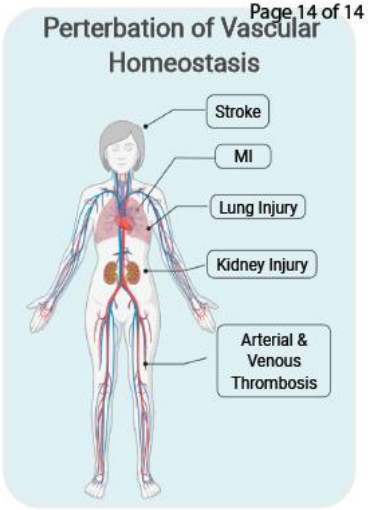


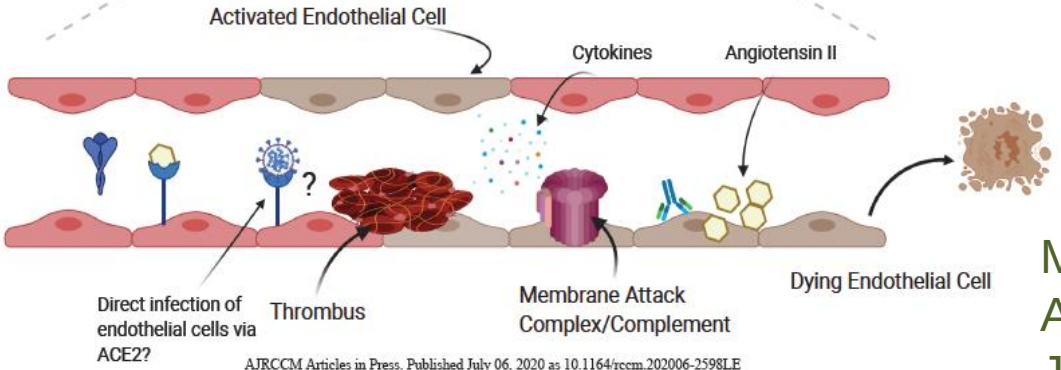
COVID-19 ARDS: A Vascular Endotype?

Relatively well preserved lung mechanics
The severity of hypoxemia

Risk Factors
Age
Diabetes
HTN
CV disease
Obesity
ABO



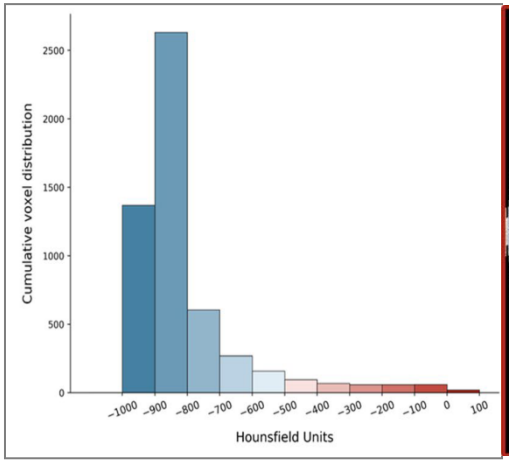


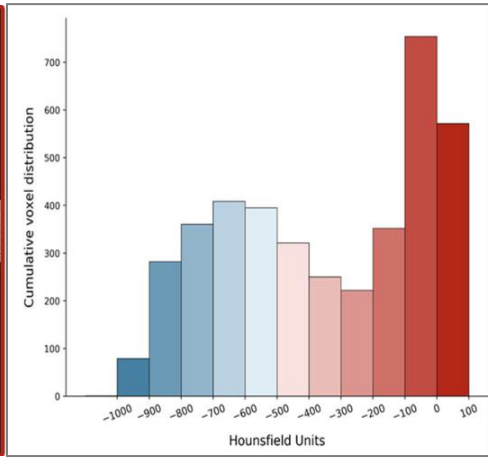


Mangalmurti et al AJRCCM 2020, June

COVID-19 pneumonia: different respiratory treatments for different phenotypes?

TYPE L	TYPE H
Low elastance Low ventilation to perfusion ratio Low lung weight Low recruitability	High elastance High right-to-left shunt High lung weight High recruitability
Response to hypoxemia Minute ventilation↑,PaCO2 ↓ HFNC/NIV, avoid high PEEP	Treatment as severe ARDS Higher PEEP, Prone position, ECMO





Intensive Care Med (2020) 46:1099–1102

Care of Critically Ill Patients with COVID-19

COVID-19 Treatment Guidelines

Surviving sepsis campaign COVID-2019

Ventilatory Support:

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) **(BI)**.
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure for whom HFNC is not available **(BIII)**.
- For adults with COVID-19 who are receiving supplemental oxygen, the Panel recommends close monitoring for worsening respiratory status and that intubation, if it becomes necessary, be performed by an experienced practitioner in a controlled setting **(AII)**.
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation **(CIII)**.
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise require intubation and mechanical ventilation **(AIII)**.
- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS), the Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher tidal volumes (VT >8 mL/kg) **(AI)**.
- For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation **(BII)**.
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies, the Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off **(CIII)**.
- There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation (ECMO) for patients with COVID-19 and refractory hypoxemia.

Noninvasive Ventilation in the Prone Position

Study population	Primary endpoint	Results	
25 Awake, Nonintubated Patients With COVID-19 (SaO2<93% with 6L nasal/ 15L/min face mask) New York	Change in SpO2 before and 1 hr after Intubation rates	Improved oxygenation 7% [1.2%]; 95% CI,4.6%-9.4%) 7/19 with ≥95% SPO2 intubated (37%) 5/6 with <95% SpO2 intubated (83%)	JAMA internal medicine
24 patients with Nonintubated COVID-19 who required O2 and had pneumonia at CT France	Proportion of responders (20% increase between before and during PP) PaO2, PaCO2,variation	6/24(25%) responders 3 persistent responders 6/15 (40%) among sustaining PP >3hrs 15 sustaining PP>3hrs PaO2 73.6 vs 94.9 (P=0.006)	JAMA 323(22) 2337
15 patients who had poor response to NIV outside the ICU Italy	Respiratory parameters at : before NIV, during NIV in pronation and 60min after NIV	During pronation All had improvement in SpO2, PaO2/FiO2 After pronation 12(80%) improved 2 same, 1 worsed 9 discharge, 1 improved, 3 continued pronation, 1 admitted to ICU 1 death	JAMA 2020;323(22):2338-2340
10 patients with supplementary oxygen in GW Singapore	Intubation rates	1/10 (10%) If hemodyanamic unstability or FiO2>0.5, trasferred to the ICU (3/10, 30%)	ERJ 2020 Jul 16;200 2571

Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study

Lancet Respir Med 2020

SP1(supine) - PP (prone at least 3 hours)- SP2 (supine)

	SP1	PP1	SP2	SP1 vs PP1		SP1 vs SP2	
				Difference (95% CI)	p value	Difference (95% CI)	p value
FiO_2, %	68·9 (19·8)	68·9 (19·8)	65·9 (20·2)	0·0 (0·0 to 0·0)	1·0	3·0 (−0·7 to 6·8)	0·11
PEEP, cm H_2O	8·3 (2·3)	8·3 (2·3)	8·3 (2·3)	0·1 (−0·1 to 0·2)	1·0	0·2 (−0·1 to 0·2)	0·32
Arterial blood gas							
pH	7·46 (0·03)	7·46 (0·04)	7·46 (0·03)	0·0 (0·0 to 0·0)	0·50	0·0 (0·0 to 0·0)	0·08
PaO_2, mm Hg	117·1 (47·4)	200·4 (110·9)	121·4 (69·6)	83·3 (56·1 to 110·4)	<0·0001	4·3 (−13·2 to 21·6)	0·60
PaO_2/FiO_2 ratio, mm Hg	180·5 (76·6)	285·5 (112·9)	192·9 (100·9)	104·9 (70·9 to 134·0)	<0·0001	12·3 (−10·9 to 35·5)	0·29
$PaCO_2$, mm Hg	35·3 (4·9)	35·6 (4·5)	35·5 (4·4)	0·4 (−1·3 to 0·6)	0·48	0·3 (−0·9 to 1·4)	0·64
SaO_2, %	97·2 (2·0)	98·4 (1·3)	97·1 (2·0)	1·2 (0·8 to 1·7)	<0·0001	0·1 (−1·0 to 0·4)	0·35
SpO_2, %	97·2 (2·8)	98·2 (2·2)	97·1 (1·9)	1·0 (0·3 to 2·0)	0·01	0·1 (−0·8 to 1·0)	0·87
Respiratory rate, breaths per min	24·5 (5·5)	24·5 (6·9)	23·9 (6·3)	0·1 (−1·0 to 1·5)	0·71	−0·6 (−2·0 to 0·8)	0·40
Use of accessory respiratory muscles	9 (20%)	7 (15%)	5 (11%)	−4·4% (−15·0 to 6·2)	0·32	−8·7% (−22·7 to 5·3)	0·16
Dyspnoea	7 (15%)	4 (9%)	2 (4%)	−6·5% (−19·8 to 6·8)	0·26	−10·9% (−23·8 to 2·1)	0·06

Responder 23
Non-responder 23

Extracorporeal Membrane Oxygenation for Critically Ill Patients with COVID-19 Related Acute Respiratory Distress Syndrome: Worth the Effort?

- 17 patients
- At 60days: death (6/35.5%) ICU (1/5.9%), discharge from hospital (7/41%)
- Increased risk of thrombotic and hemorrhagic complications
- Switch of the circuit: 12% vs 7% (EOLIA study)

	Adverse effect under ECMO	
	Hemorrhagic shock – no. – (%)	1 (5.9)
	Bleeding leading to transfusion – no. – (%)	6 (35.3)
	Transfusion of packed red blood cells – units	4 [0;26]
	Thrombopenia leading transfusion – no. – (%)	1 (5.9)
	Cardiac tamponade – no. – (%)	1 (5.9)
	Stroke – no. – (%)	1 (5.9)
	Thrombophlebitis or pulmonary embolism – no. – (%)	3 (17.6)
	Oxygenator thrombosis – no. – (%)	2 (11.8)
	Ventilator-associated pneumonia treated with antibiotics – no. – (%)	10 (58.8)
	Renal replacement therapy – no. – (%)	12 (70)

Falcoz et al AJRCCM 2020 June

High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study

Table 3 Outcomes of COVID-19 ARDS and non-COVID-19 ARDS

	Population before matching ($n=383$)				Population after matching ($n=222$)			
	Non-COVID-19-ARDS ($n=233$)	COVID-19-ARDS ($n=150$)	OR [95% IC]	*p*-value	Non-COVID-19-ARDS ($n=145$)	COVID-19-ARDS ($n=77$)	OR [95% IC]	*p*-value
Thrombo-embolic complications—*n* (%)	14 (6)	27 (18)	3.4 [1.7–7.3]	< 0.001	7 (4.8)	9 (11.7)	2.6 [1.1–6.1]	0.04
Pulmonary embolisms—*n* (%)	3 (1.3)	25 (16.7)	15.2 [4.5–80.4]	< 0.001	3 (2.1)	9 (11.7)	6.2 [1.6–23.4]	0.01
Deep vein thrombosis—*n* (%)	3 (1.3)	3 (2)	1 [0.1–9.2]	1	2 (1.4)	0 (0)	–	–
Myocardial infarction—*n* (%)	6 (2.6)	0 (0)	0 [0–1.3]	0.09	2 (1.4)	0 (0)	–	–
Cerebral ischemic attack—*n* (%)	1 (0.4)	2 (1.3)	3.1 [0.2– 185.5]	0.68	0 (0.0)	0 (0)	–	–
Limb ischemia—*n* (%)	0 (0)	1 (0.7)	Inf [0.0–Inf]	0.78	0 (0.0)	0 (0)	–	–
Mesenteric ischemia—*n* (%)	3 (1.3)	1 (0.7)	0.5 [0.0–6.5]	0.98	2 (1.4)	1 (1.3)	0.96 [0.09–9.8]	0.97
Nb of RRT filter per dialyzed patient—median, IQR	1 [2–1]	3 [2–7]	–	< 0.001	2.0 [1.0–2.5]	3.0 [2.0–6]	–	0.03
Nb of RRT filter per day of RRT—median, IQR	0.3 [0.3; 0.5]	0.7 [0.5; 1]	–	< 0.001	0.3 [0.3; 0.4]	0.7 [0.5; 1]	–	< 0.001
ECMO oxygenator thrombosis—*n* (%)	1/10 (10)	2/12 (16.7)	–	0.59	1/7 (14.3)	0/4 (0)	–	–
Hemorrhagic complications—*n* (%)	1 (1.8)	4 (2.7)	2.4 [0.27–28.5]	0.6	2 (1.4)	0 (0)	–	–

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy

https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation

- **What is the recommended VTE prophylaxis in patients with COVID-19?**

  All hospitalized adults with COVID-19 should receive pharmacologic thromboprophylaxis with LMWH over unfractionated heparin to reduce contact, unless the risk of bleeding outweighs the risk of thrombosis.

  Whether critically ill COVID-19 patients should receive therapeutic-intensity anticoagulation in the absence of confirmed or suspected VTE is currently unknown.

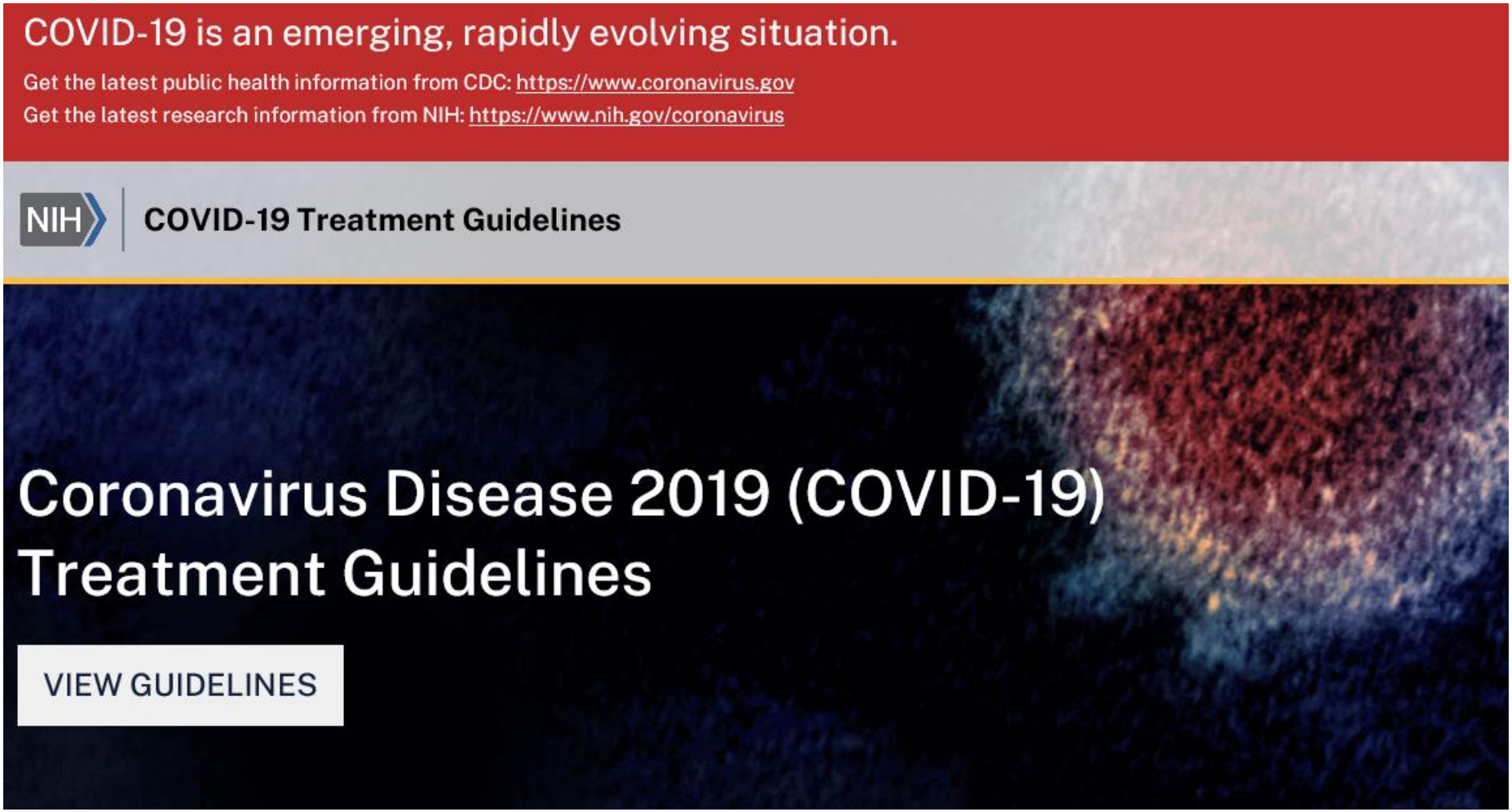
- **How should we manage COVID-19 patients who experience recurrent clotting of access devices (e.g., central venous catheters, arterial lines) or extracorporeal circuits (e.g., CRRT, ECMO) despite prophylactic anticoagulation?**

  Although of unproven benefit, it may be reasonable to increase the intensity of anticoagulation (i.e., from standard-intensity prophylaxis to intermediate-intensity prophylaxis or from intermediate-intensity prophylaxis to therapeutic-intensity)

- **If a patient with COVID-19 requires therapeutic anticoagulation for VTE or AFIB stroke prevention, are there any special considerations?**

  Drug-drug interactions (dexamethasone, tocilizumab, lopinavir/ritonavir)

Last Updated: July 17, 2020



Corticosteroids (Including Dexamethasone)

Last Updated: July 17, 2020

Recommendation for Patients with COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** (at a
n
n

THERAPY		
41	In mechanically ventilated adults with COVID-19 and respiratory failure (**without ARDS**), we ***suggest against*** the routine use of systemic corticosteroids	Weak
42	In mechanically ventilated adults with COVID-19 **and ARDS**, we ***suggest*** using systemic corticosteroids, over not using corticosteroids	Weak

- The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**.

- The potent anti-inflammatory effects of corticosteroid
- MERS, SARS- delayed virus clearance
- It is not known whether other corticosteroids have a similar benefit as dexamethasone

COVID-19 Treatment Guidelines NIH recommendation

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

DOI: 10.1056/NEJMoa2021436

	Treatment allocation	
	Dexamethasone (n=2104)	Usual care (n=4321)
Follow-up forms received	2079	4278
Treatments given		
Dexamethasone	1975 (95%)	336 (8%)
Lopinavir/ritonavir	2 (<0.5%)	4 (<0.5%)
Hydroxychloroquine	17 (1%)	22 (1%)
Azithromycin	499 (24%)	1082 (25%)
Tocilizumab or sarilumab	43 (2%)	128 (3%)
Not recorded	7 (<0.5%)	12 (<0.5%)

Percentages are of those with a completed follow-up form. Among patients allocated dexamethasone, it was taken for a median of 7 days [IQR 3-10 days].

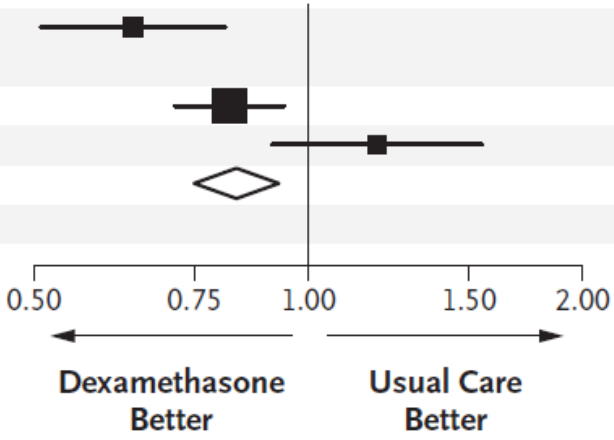
Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

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

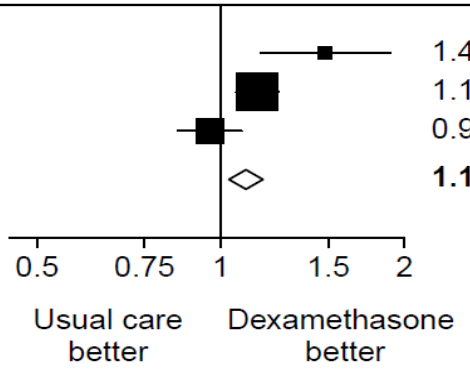
Chi-square trend across three categories: 11.5



a) Discharge from hospital alive within 28 days

Respiratory support at randomization	Dexamethasone	Usual care	RR (95% CI)
Invasive mechanical ventilation	107/324 (33.0%)	159/683 (23.3%)	1.48 (1.16–1.90)
Oxygen only	921/1279 (72.0%)	1755/2604 (67.4%)	1.15 (1.06–1.24)
No oxygen received	385/501 (76.8%)	831/1034 (80.4%)	0.96 (0.85–1.08)
All participants	**1413/2104 (67.2%)**	**2745/4321 (63.5%)**	**1.10 (1.03–1.17)**

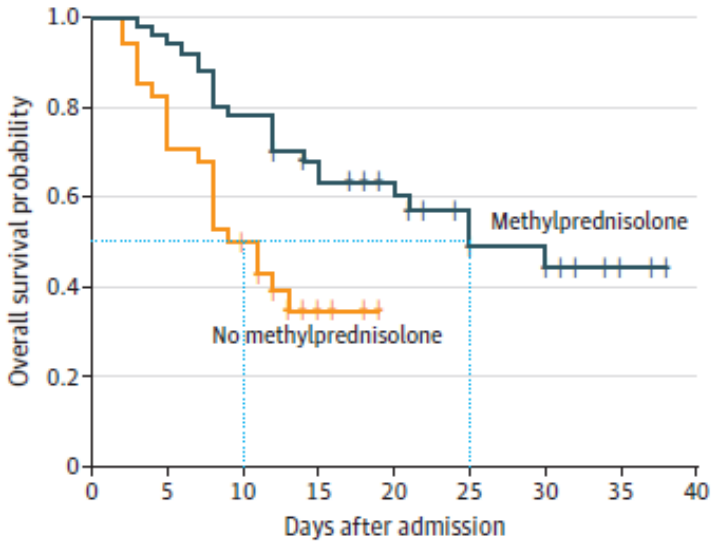
Trend across three categories: χ^2_1=11.5; p<0.001



JAMA Internal Medicine | Original Investigation

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

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

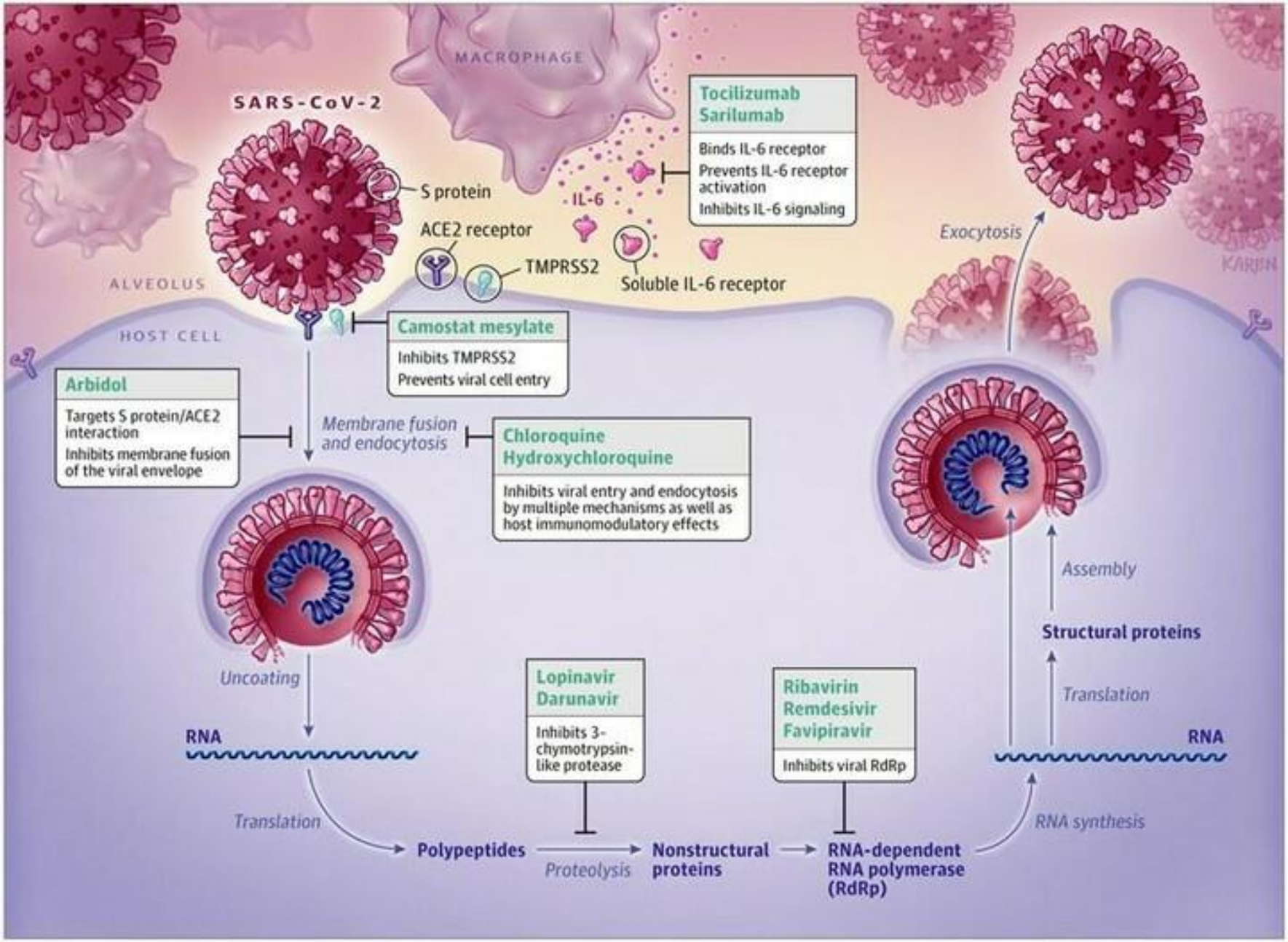
Administration of methylprednisolone reduced the risk of death (hazard ratio, 0.38; 95% CI, 0.20-0.72; *P* = .003).

Early Short Course Corticosteroids in Hospitalized Patients with COVID-19

Clin Infect Dis. 2020

Patients with moderate/severe COVID19
a single pre-test, single post-test quasi-experiment
Methylprednisolone 0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days

Outcomes	Standard of Care (n=81)	Early CP (n=132)	Odds Ratio (CI)	p-value
Primary Outcome				
Primary composite outcome – no. (%)	44 (54.3)	46 (34.9)	0.45 (0.26 – 0.79)	0.005
Death – no. (%)	21 (26.3)	18 (13.6)	0.45 (0.22 – 0.91)	0.024
Respiratory failure requiring mechanical ventilation – no. (%)*	26 (36.6)	26 (21.7)	0.47 (0.25-0.92)	0.025
Escalation from GMU to ICU – no. (%)†	31 (44.3)	32 (27.3)	0.47 (0.25 – 0.88)	0.017


MACROPHAGE
SARS-CoV-2
S protein
ACE2 receptor
TMPRSS2
IL-6
Soluble IL-6 receptor
Tocilizumab
Sarilumab
Binds IL-6 receptor
Prevents IL-6 receptor activation
Inhibits IL-6 signaling
Exocytosis
ALVEOLUS
HOST CELL
KARIN
Camostat mesylate
Inhibits TMPRSS2
Prevents viral cell entry
Arbidol
Targets S protein/ACE2 interaction
Inhibits membrane fusion of the viral envelope
Membrane fusion and endocytosis
Chloroquine
Hydroxychloroquine
Inhibits viral entry and endocytosis by multiple mechanisms as well as host immunomodulatory effects
Assembly
Structural proteins
Translation
Uncoating
RNA
Lopinavir
Darunavir
Inhibits 3-chymotrypsin-like protease
Ribavirin
Remdesivir
Favipiravir
Inhibits viral RdRp
RNA
Translation
Polypeptides
Proteolysis
Nonstructural proteins
RNA-dependent RNA polymerase (RdRp)
RNA synthesis

Remdesivir

Inhibits viral RNA-dependent RNA polymerase

Recommendation for Prioritizing Limited Supplies of Remdesivir

- **Because remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO (BI).**

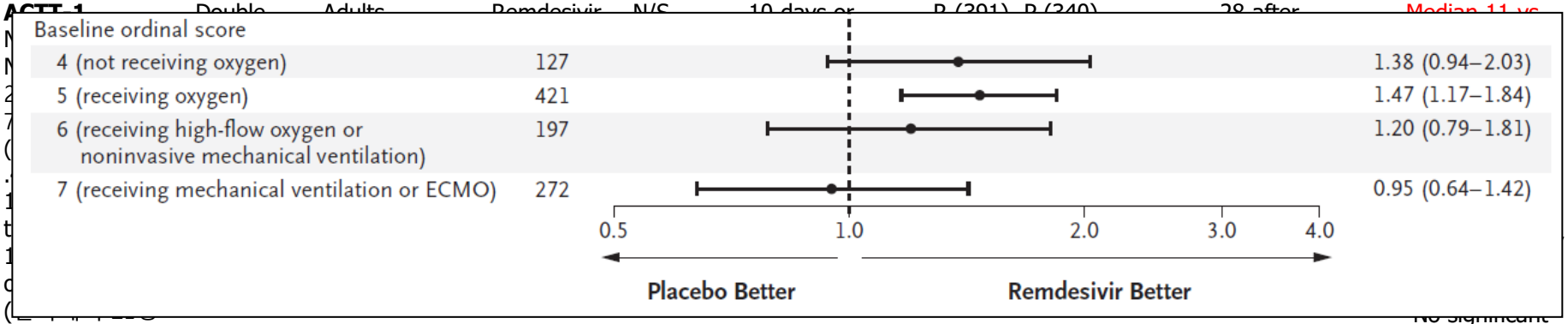
Recommendation for Patients with COVID-19 Who Are on Supplemental Oxygen but Who Do Not Require High-Flow Oxygen, Noninvasive or Invasive Mechanical Ventilation, or ECMO

- The Panel recommends using **remdesivir** for 5 days or until hospital discharge, whichever comes first **(AI)**.
- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

Recommendation for Patients with COVID-19 Who Require High-Flow Oxygen, Noninvasive Ventilation, Mechanical Ventilation, or ECMO

- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.

Study	Design	Indication	Drug	Comparator	Duration of therapy	Results	Time end point assessed	Outcome Drug versus comparator
ACTT-1 (2020.2.21~2020.4.19) 1,062pts. at 60 centers in 10 countries (+Korea) [*NEJM* 2020 NIAID 주도 임상 참여)	Double	Adults	Remdesivir	N/S	10 days or	P (391) P (340)	28 after	Median 11 vs. No significant difference
SIMPLE trial (1st) (2020.3.6~2020.3.26) 397pts. at 55 centers in 8 countries (+Korea) [*NEJM* 2020 Gilead 주도 임상	Randomized, open label, phase III trial	- 12 years of age who had SARS-CoV-2 hospitalized pts. confirmed by PCR **within 4 days** before randomization. - **O_2 94% or less** while they were breathing ambient air, and radiologic evidence of pneumonia. (MV, ECMO, MOF excluded)	Remdesivir 200mg IV loading -> 100mg IV	none	5d vs. 10d	- 5d (200) vs. 10d (197) - At baseline, patients randomly assigned to the 10-day group had significantly worse clinical status than those assigned to the 5-day group (P=0.02). - After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was **similar** to that among patients in the 5-day group (P=0.14). - Adverse events 10-day group (35%) 5-days (21%)	- Clinical status at 14d	- In patients with severe Covid-19 not requiring mechanical ventilation, our trial **did not show a significant difference** between a 5-day course and a 10-day course of remdesivir. .



Study	Design	Indication	Drug	Comparator	Duration of therapy	Results	Time end point assessed	Outcome Drug versus comparator
NEJM2020;382:2327-36 (2020.1.25~2020.3.7) 53 pts. (USA : 22, Italy : 12, Japan : 9, France : 4, Germany : 2, Austria /Spain/Canada/Netherland : 1)	Open label, Compassionate use	Hospitalized pts. for **severe** Covid-19	Remdesivir 200mg IV loading -> 100mg IV	none	10 days	- At baseline, 30/53 (57%) : mechanical ventilation, 4/53 (8%) : ECMO - During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. : clinical improvement was less frequent among ventilator (HR 0.33, 95% CI, 0.16-0.68)	Mortality rate at least 28 days after the beginning of treatment with remdesivir or until discharge or death.	(1) A total of 25 patients (47%) were discharged, and 7 patients (13%) died; (2) Mortality was 18% (6 of 34) among ventilator and 5% (1 of 19) among those not ventilator
Lancet 2020; 395: 1569–78 (2020.2.6~2020.3.12) 237 pts. at 10 centers in Hubei, China	Double-blind, randomized, Placebo-controlled	-≥18 ages hospitalized with Covid-19 an interval from symptom onset to enrollment of 12 days or less, O2 **of 94% or less** on room air or radiologically confirmed pneumonia.	Remdesivir (200mg loading dose on day 1 -> 100mg daily up to 9 additional days concomitant Lopinavir, IFN, steroid permitted	N/S placebo for up to 10days	10 days or until hospital or death	- R (158), P (79) - Median time from sx. onset to start trial : 10 (IQR 9-12d) - Time to clinical improvement within 28days after enrollment	Clinical improvement (1) two-points reduction in patients' admission status on a six-point ordinal scale, or (2) live discharge from the hospital	- Remdesivir use **was not associated with a difference** in time to clinical improvement (21 vs. 23d) (HR 1·23 [95% CI 0·87–1·75]) - Faster time to CI than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1·52 [0·95–2·43]) : no signifant difference.

Chloroquine or Hydroxychloroquine

- Both increase the endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membranes
- Both block the transport of SARS-CoV-2 from early endosomes to endolysosomes for release of the viral

Overall Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19, except in a clinical trial **(AII)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Recommendation:

- The Panel recommends against the use of **hydroxychloroquine plus azithromycin** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**.

Study	Design	Indication	Drug	Comparator	Duration of therapy	Results	Time end point assessed	Outcome Drug versus comparator
CloroCOVID-19 [*JAMA Netw Open*. 2020; 3(4):e208857.] (2020.3.23~2020.4.5) 81 pts. at 1 center in Manuas, Brazil	Double-blind, randomized, Phase IIb	-≥18 ages hospitalized with Covid-19, RR> 24 and/or PR > 125 and/ or **O2 <90%** in ambient air and/or shock	High dose CQ (600mg = 150*4 bid for 10days, total 12g Ceftriaxone 1g bid for 7d, AZM 500mg for 5d, Oseltamivir 75mg bid (flu suspected)	Low dose CQ (450mg = 150*3 + placebo bid) : D_0 450mg bid, D_{1-4} 450mg qd, D_{5-9} placebo : total 2.7g	10 days	- High dose (41) vs. low (40) - Median time from sx. onset to start trial : 10 (IQR 9-12d) - Older age (mean [SD] age, 54.7 [13.7] years vs 47.4 [13.3] years), more heart disease (5 of 28 [17.9%] vs 0) were seen in the high-dose group. - All of the participants received AZM, 89% oseltamivir - Time to clinical improvement within 28days after enrollment	-Primary outcome : reduction in mortality by at least 50% in the high-dosage group compared with the low-dosage group on 13d - Clinical status, EGC on 28d	-Lethality until day 13 was 39.0% in the high-dosage group (16 of 41) and 15.0% in the low-dosage group (6 of 40). -QTcF>500ms high dose arm(7 of 37 [18.9%]) compared with low dose arm(4 of 36 [11.1%]). : **early discontinued**
NEJM 1376 patients with COVID-19	Observation study Open label, non-randomized	COVID-19 who were admitted to a large New York City hospital	HCQ 600mg-400mg for 4days concomitant azithromycin and/or other antibiotics	No HCQ	5days	- 811 (H) vs. 565 (N) -The difference of concomitant drug between two groups. HCQ group: a lower PaO2/FiO2 ratio at baseline (median of 233 mm Hg vs. 360 mm Hg).	the time from study baseline to intubation or death	hydroxychloroquine use was not associated with intubation or death (hazard ratio [HR] 1.04; 95% CI, 0.82–1.32)

Study	Design	Indication	Drug	Comparator	Duration of therapy	Results	Time end point assessed	Outcome Drug versus Comparator
[*Med* 2020 June 5] (2020.3.9~2020.4.11) 368 male pts. at all veteran hospitals in USA	Retrospective	- Hospitalized adults pts. with Covid-19	-HCQ mono	- HCQ + AZM - Those who didn't receive HCQ	Not refered	- HCQ mono 26.4% (97), HCQ+ AZM 30.7% (113), non-HCQ 42.9% (158) - Deaths : 27.8% (27/97) in HCQ mono, 22.1% (25/113) in HCQ+ AZM, 11.4% (18/158) in non-HCQ - Mechanical ventilation: 13.3% in HCQ mono, 6.9% in HCQ+ AZM, 14.1% in non-HCQ (p=0.547)	Death and the need for mechanical ventilation - Death among patients who required mechanical ventilation	- **Higher risk** of death from any cause in the **HCQ mono** (aHR, 2.61; 95% CI, 1.1 to 6.17, p=0.03) but not in HCQ + AZM (aHR, 1.14, 95% CI, 0.56 to 2.32; p= 0.72) - No significant difference between three groups in the risk of ventilation and death after ventilation
[*BMJ* 2020; 369 2020 May 14] (2020.2.11~2020.2.29) 150 pts. at 16 centers in China	Open label, - randomized controlled	- Hospitalized adults pts. with Laboratory confirmed Mild/moderate dird COVID-19	-HCQ 1200mg qd loading for 3days → 800mg qd main tenance dose for total 2 or 3weeks Concomitant drugs were permitted	No HCQ group	2 or 3 weeks for pts. with mild to moderate or severe dz.	- 148 for mild to moderate - 2 for severe - Median duration of HCQ treatment : 14 d (range, 1-22) - Median duration of f/u: 20 d in HCQ vs. 21 d in non-HCQ	- Viral negative conversion by 28d - Alleviation of sx. - Adverse events	-No difference 85.4% in HCQ vs. 81.3% in non-HCQ -No difference - 21 (30%) in HCQ vs. 7 (9%)
[*BMJ* 2020; 369 : m1844] (2020.3.12~2020.3.31) 181 pts. at 4 centers in France	Comparative observational	-181 patients aged 18-80 yrs. with SARS-CoV-2 pneumonia **who required O_2 but not intensive care**	- HCQ 600mg 18% HQQ group concomitant azithromycin 52% amoxicillin/clavulanic acid	No HCQ group		- 84 (HCQ) vs. 89 (non-HCQ) : within 48hrs of admission - 8 (HCQ) over 48 hrs of admission	- Survival without transfer to ICU at 21d -Survival without ARDS at 21d	-No difference 76% in HCQ vs. 75% in non-HCQ -No difference 69% in HCQ vs. 74% in non-HCQ

ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

- High-risk exposure: a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield
- Moderate-risk exposure: a distance of less than 6 ft for more than 10 minutes while a face mask but no eye shield
- Treatment: either placebo or hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days)
- The incidence of either laboratory-confirmed Covid-19 or illness compatible with Covid-19 within 14 days

Table 2. Outcomes of Hydroxychloroquine Therapy for Postexposure Prophylaxis against Covid-19.*

Outcome	Hydroxychloroquine (N=414)	Placebo (N=407)	P Value
	number (percent)		
Confirmed or probable Covid-19	49 (11.8)	58 (14.3)	0.35
Laboratory-confirmed diagnosis	11 (2.7)	9 (2.2)	0.82
Symptoms compatible with Covid-19	48 (11.6)	55 (13.5)	0.46
All new symptoms	57 (13.8)	59 (14.5)	0.84
Any hospitalization	1 (0.2)	1 (0.2)	0.99
Death	0	0	—

Hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure

JAMA | Original Investigation

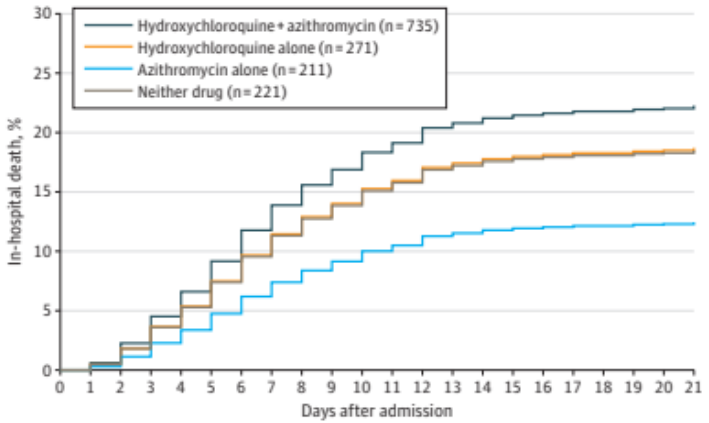
Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State

A retrospective cohort study of 1438 patients hospitalized in NYS

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)

Figure 2. Model-Adjusted Estimated In-Hospital Mortality, by Treatment Group



No. at risk (in hospital)

	Admission	Day 7	Day 14	Day 21
Hydroxychloroquine + azithromycin	735	653 (384)	568 (106)	557 (47)
Hydroxychloroquine alone	271	245 (136)	226 (59)	220 (28)
Azithromycin alone	211	191 (33)	190 (4)	190 (2)
Neither drug	221	206 (63)	197 (19)	195 (13)

Table 4. Adverse Events Reported During Hospitalization

	No./total No. (%)				
	Hydroxychloroquine + azithromycin (n = 735)	Hydroxychloroquine alone (n = 271)	Azithromycin alone (n = 211)	Neither drug (n = 221)	*P* value
Diarrhea	85 (11.6)	22 (17.0)	16 (8.5)	16 (7.2)	.003
Hypoglycemia	25 (3.4)	9 (3.3)	1 (0.5)	6 (2.7)	.15
Cardiac arrest	114 (15.5)	37 (13.7)	13 (6.2)	15 (6.8)	<.001
Abnormal ECG[a]					
Total sample	199 (27.1)	74 (27.3)	34 (16.1)	31 (14.0)	<.001
Among ECG screened	192/634 (30.3)	73/233 (31.3)	34/180 (18.9)	31/155 (20.2)	.002
Arrhythmia					
Overall	150 (20.4)	44 (16.2)	23 (10.9)	23 (10.4)	<.001
Among ECG screened	144/634 (22.7)	43/233 (18.5)	23/180 (12.8)	23/155 (14.8)	<.001
QT prolongation					
Overall	81 (11.0)	39 (14.4)	15 (7.1)	13 (5.9)	.006
Among ECG screened	80/634 (12.6)	39/233 (16.7)	15/180 (8.3)	3/155 (8.4)	.03

hydroxychloroquine +azithromycin, P = .31; hydroxychloroquine alone, P = .79; and azithromycin alone, P = .14

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

- Lopinavir/ritonavir is an inhibitor of SARS-CoV 3CLpro in vitro.
- The enzymes responsible for this cleavage are two proteases, 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro).
- Adverse Effects : Nausea, vomiting, diarrhea, QTc prolongation, Hepatotoxicity

Recommendation:

- The Panel **recommends against** the use of **lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII)** for the treatment of COVID-19, except in the context of a clinical trial.

Study	Design	Indication	Drug	Comparator	Duration of therapy	Results	Time end point assessed	Outcome Drug versus comparator
LOTUS China trial [*NEJM* 2020 May 7;382(19) (2020.1.18~2020.2.3) 86 pts. in Wuhan in China	randomized, controlled	-Male and nonpregnant female patients 18 years of age or older who had a positive RT-PCR, had pneumonia confirmed by chest imaging, and had **SaO_2 of 94% or less** while they were breathing ambient air or Pao_2:Fio_2 at or below 300 mg Hg. (SEVERE)	- LPV/r (400mg/100mg bid)	standard care	14d	- 99 (L) vs. 100 (S) - The median interval time between symptom onset and randomization was 13 days (IQR, 11 to 16 days)	- Time to clinical improvement - Mortality at 28d -viral RNA loads or duration of viral RNA detectability	- The median time to clinical improvement 15 days (L) vs. 16 days (S) (HR, 1.39; 95% CI, 1.00 to 1.91) : no difference - L (19.2%) vs S (25%) No difference - no difference
[*J Mol Cell Biol*. 2020] (2020.1.27~2020.2.15) 22 pts. at 1 center in China	-Small randomized, controlled	Hospitalized adults pts. with Covid-19	- CQ 500mg bid	LPV/r 400/100mg bid	10 d		- Rate of negative PCR conversion at day 10,14 - improvement of lung computed tomography (CT) scan - clinical recovery	-D10: C (90%)-L(75%) D14: C (100%)-L(91.2%) -D10: C (20%)-L(8.3%) -D14: C (100%)-L(75%) - CQ were discharged from hospital in a much quicker pace than LPV/r

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19:
  - **COVID-19 convalescent plasma**
  - **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins**
- The Panel **recommends against** the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial:
  - **Mesenchymal stem cells (AII)**
  - **Non-SARS-CoV-2-specific intravenous immunoglobulins (IVIG) (AIII)**. This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Other Immunomodulators

There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19:

- **Interleukin-1 inhibitors** (e.g., **anakinra**)
- **Interleukin-6 inhibitors** (e.g., **sarilumab**, **siltuximab**, **tocilizumab**)
- **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 immunomodulators for the treatment of COVID-19, except in a clinical trial:

- **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)**.

'렘데시비르' 애매해지자 '혈장치료제'에 쏠리는 눈..이번주 생산·임상

이영성 기자,이형진 기자 입력 2020.07.13. 07:05 수정 2020.07.13. 09:30 댓글 202개

국내 '코로나19' 완치자 혈장 171건 확보 완료..앞서 치료 성공사례도
혈장 구하기 수월하지 않지만 가장 빠른 치료대안 기대

12일 중앙방역대책본부에 따르면, 방역당국은 임상에 필요한 혈장 확보를 완료한 상태로 이번 주부터 혈장제제를 생산하고 임상에 들어간다.

임상에 필요한 혈장은 최소 130명분 이상이다. 당국은 지난 11일 기준으로 혈장을 공여하기로 한 완치자 375명 중 171명의 혈장을 받아놨다. 대구와 경북지역 신천지 교회 신도 완치자 500명의 혈장도 추가로 제공받을 예정이다.

혈장치료제는 '코로나19' 회복기 환자의 혈장(혈액의 액체 성분)에서 여러 유효 면역 항체(중화항체)를 추출해 만드는 전문의약품이다. 신종 감염병이 유행하면 가장 빠르게 투약할 수 있는 의약품으로 꼽힌다. 이미 다른 질환에는 처방되고 있는 혈장치료제가 있어 안전성에 대한 신뢰도는 높은 편이다. 이미 형성된 항체를 체내 주입한다는 개념인 만큼 백신의 역할도 기대할 수 있다.

혈장치료제는 이론상 완벽한 약이지만 사실 여러 한계가 있어 전세계가 개발에 뛰어들었음에도 아직 성공한 나라가 없다. 개발을 위해선 혈장을 매번 공급받아야 하고 이렇게 받은 혈장에는 바이러스를 무력화하는 '중화항체'가 감염 후 3개월 정도면 급격히 감소한다는 연구결과도 있다. 혈장치료제를 만들 수 있더라도 치료에 타이밍이 중요하다는 지적이다.

Convalescent Plasma

- Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARSCoV-2
- help suppress the virus and modify the inflammatory response
- Neutralising immunoglobulin (Ig) G or M is to decrease the viral load and to control viraemia symptoms.

- Clinical Data for Other Viral Infections
  - SARS: Ribavirin plus prednisolone+ Methylprednisolone 500mg bid+ 200 mL of plasma donated by SARS patients

Hong Kong Med J 2003;9:199-201

  - A higher day 22 discharge rate: The time of convalescent plasma ther apy(before day 14) and coronavirus PCR positivity

Eur J Clin Microbiol Infect Dis (2005) 24: 44–46

Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients

Mayo Clinic Proceedings

Table 2. SAE Characteristics in Patients Transfused with COVID-19 Convalescent Plasma. (*n* = 20,000)

Serious Adverse Events (SAE): Transfusion Reactions	Reported	Related	Estimate[a] (95% CI)
Mortality within four hours of transfusion	63	13	0.06% (0.04%, 0.11%)
Transfusion-Associated Circulatory Overload (TACO)	37	37	0.18% (0.13%, 0.25%)
Transfusion-Related Acute Lung Injury (TRALI)	20	20	0.10% (0.06%, 0.15%)
Severe allergic transfusion reaction	26	26	0.13% (0.09%, 0.19%)
Seven-day SAE Reports			
Thrombolic or thromboembolic complication	87	32	0.16% (0.11%, 0.23%)
Sustained Hypotension[b]	406	54	0.27% (0.21%, 0.35%)
Cardiac Events[c]	643	74	0.37% (0.29%, 0.46%)
Seven Day Mortality	**Reported**		**Estimate (95% CI)**
Overall (5,000)[a]	602		12.04% (11.17%, 12.97%)
Overall (20,000)	1,711		8.56% (8.18%, 8.95%)
Clinical Status			
No ICU admission (*n* = 8,323)	501		6.02% (5.53%, 6.55%)
ICU admission (*n* = 11,468)	1,202		10.48% (9.93%, 11.06%)
No Mechanical Ventilation (*n* = 12,147)	749		6.17% (5.75%, 6.61%)
Mechanical Ventilation (*n* = 6,337)	767		12.10% (11.32%, 12.93%)
Clinical Symptoms			
No MOF or Septic Shock (*n* = 17,081)	1,302		7.62% (7.23%, 8.03%)
MOF or Septic Shock (*n* = 2,919)	409		14.01% (12.80%, 15.32%)

JOURNAL OF MEDICAL VIROLOGY WILEY

Convalescent plasma transfusion for the treatment of COVID-19: Systematic review

Author	Country	Study period	Study population	CPT dosage	Antiviral (antimicrobial drugs)	Administrated day	Status during CPT	Outcome	Viral load	Severe adverse events & treatment complications
Duan et al[6]	China	23 January 2020 to 19 February 2020	10, 6 M:4 F, Age (x̄-52.5 y), Cardiovascular and/or cerebrovascular diseases and HTN (n = 4)	200 mL within 4 h, antibody titer >1:640	arbidol or/and remdesivir/ ribavirin/ peramivir (n = 9) ribavirin (n = 1) Antibacterial/ antifungal for coninfecion (n = 8)	Onset to CPT (x̄ -16.5 d)	All at ICU, Mechanical ventilation (n = 3), HFNO (n = 3), Conventional LFNO (n = 2)	Clinical symptoms, paraclinical improved, Increase of oxyhemoglobin saturation within 3 d CP well tolerated, increase/ maintain the neutralizing antibodies, Varying degrees of absorption of lung lesions within 7 d	Viral load undetectable (n = 7), Neutralizing antibody increased rapidly up to 1:640 (n = 5), maintained at a high level (1:640) (n = 4)	No severe adverse effects, Evanescent facial red spot (n = 1)
Jin Young Ahn et al[9]	South Korea	22 February 2020 to 6 March 2020	71 y/M	500 mL in 2 doses at 12 h interval	hydroxychloroquine, lopinavir/ritonavir	After admission 10th d	Severe ARDS, mechanical ventilation	Weaned from the mechanical ventilator, underwent a tracheostomy	Ct changed 24.98 (10th d) - 33.96 (20th d), Negative (after 26th d)	No adverse reaction
			67 y/F, HTN			After admission 6th d		Extubated and discharged on 24th d	Negative (after 20th d). Ct changed 20.51 (5th d) - 36.33 (9th d)	
Mingxiang Ye et al[10]	China	11 February 2020 to 18 March 2020	69/M	600 mL in 3 doses	arbidol, levofloxacin	After symptom 33th d	Myalgia, Chest CT-patchy areas of GGOs	Symptoms improved, GGOs resolved 37th d, Cured and ready to discharge.	Negative	No adverse reaction
			75/F	400 mL in 2 doses	arbidol		Fatigue, shortness of breath, oxygen therapy through nasal catheter, respiratory distress, Multiple consolidation	Symptoms improved, alleviation of respiratory distress, two-fold increase in IgM and IgG titers, consolidation gradually reduced, turned into scattered GGOs, Cured and under further clinical monitoring	Negative	
Chenguang Shen et al[7]	China	20 January 2020 to 25 March 2020	5, Age (range, 36-73 y), 3M:2F, HTN; mitral insufficiency (n=1)	400 mL of CP in 2 doses on the same day, antibody titer >1:1000	interferon alfa-1b + Lopinavir/ritonavir (n = 4) + favipiravir (n = 1), arbidol + darunavir + Lopinavir/ ritonavir (n=1)	After admission between 10 and 22 d	All 5 critical severe ARDS on mechanical ventilation, ECMO (n = 1)	Temp normalized within 3 d (n = 4), SOFA score decreased, and PAO2/FIO2 increased within 12 d (range, 172	Decreased and became negative within 12 d	No severe adverse effects

JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19

A Randomized Clinical Trial

- Open-label, multicenter, randomized clinical trial, Wuhan
- Convalescent plasma +standard care vs standard care
- S-RBD specific IgG >1:640, 4 to 13 mL/kg of BW

Table 3. Primary and Secondary Clinical Outcomes at Day 28[a]

	Convalescent plasma group (n = 52)	Control group (n = 51)	Absolute difference (95% CI)[b]	Effect estimate (95% CI)	*P* value[c]
All patients					
Primary clinical outcome					
Time to clinical improvement, median (IQR),d[d]	28.00 (13.00-Indeterminate)	Indeterminate (18.00-Indeterminate)	−2.15 (−5.28 to 0.99)	HR, 1.40 (0.79-2.49)	.26
Clinical improvement rate, No./total (%)[e]					
At day 7	5/52 (9.6)	5/51 (9.8)	−0.2% (−11.6% to 11.2%)	OR, 0.98 (0.30-3.19)	.97
At day 14	17/52 (32.7)	9/51 (17.6)	15.0% (−1.4% to 31.5%)	OR, 1.85 (0.91-3.77)	.08
At day 28	27/52 (51.9)	22/51 (43.1)	8.8% (−10.4% to 28.0%)	OR, 1.20 (0.80-1.81)	.37
Secondary clinical outcomes					
Discharge rate at 28 d, No./total (%)	26/51 (51.0)	18/50 (36.0)	15.0% (−4.1% to 34.1%)	OR, 1.42 (0.90-2.24)	.13
Time from randomization to discharge, median (IQR), d[d]	28.00 (13.00-Indeterminate)	Indeterminate (19.00-Indeterminate)	−2.43 (−5.56 to 0.69)	HR, 1.61 (0.88-2.93)	.12
Time from hospitalization to discharge, median (IQR),d[d]	41.00 (31.00-Indeterminate)	53.00 (35.00-Indeterminate)	−11.95 (−26.33 to 2.43)	HR, 1.68 (0.92-3.08)	.09
Mortality at 28 d, No./total (%)	8/51 (15.7)	12/50 (24.0)	−8.3% (−23.8% to 7.2%)	OR, 0.65 (0.29-1.46)	.30
Time from randomization to death, median (IQR), d[d]	Indeterminate	Indeterminate (26.00-Indeterminate)	0.52 (−2.10 to 3.14)	HR, 0.74 (0.30-1.82)	.52
Viral nucleic acid negative rate, No./total (%)					
At 24 h	21/47 (44.7)	6/40 (15.0)	29.7% (11.7% to 47.7%)	OR, 4.58 (1.62-12.96)	.003
At 48 h	32/47 (68.1)	13/40 (32.5)	35.6% (15.9% to 55.3%)	OR, 4.43 (1.80-10.92)	.001
At 72 h	41/47 (87.2)	15/40 (37.5)	49.7% (32.0% to 67.5%)	OR, 11.39 (3.91-33.18)	<.001

Interleukin-1 Inhibitors/Interleukin-6 Inhibitors

- There are insufficient data to recommend either for or against the use of **interleukin-1 (IL-1) and interleukin-6 (IL-6).**

- It is associated with response with cytokine release syndrome
- There are insufficient data.

- Clinical trials are currently underway
  - Anakinra (a recombinant human IL-1 receptor antagonist)
  - Sarilumab (a recombinant humanized (IL-6R) monoclonal Ab)
  - Siltuximab (a recombinant human-mouse chimeric monoclonal antibody for IL-6)

PARIS and TARRYTOWN, N.Y. - July 2, 2020 – Sanofi and Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that the U.S. Phase 3 trial of Kevzara® (sarilumab) 400 mg in COVID-19 patients requiring mechanical ventilation did not meet its primary and key secondary endpoints when Kevzara was added to best supportive care compared to best supportive care alone (placebo).
Based on the results, the U.S.-based trial has been stopped,

  - **Tocilizumab**

(a recombinant humanized anti-IL-6R monoclonal Ab)

Study	Design	Indication	Drug	Comparator	Duration of therapy	Results	Time end point assessed	Outcome Drug versus comparator
[*PNAS* 2020 May 19, 117 (20) 10970-10975 (2020.2.5~2020.2.14) 21 pts. at 2 centers of Anhui in China	Retrospective	-Hospitalized adults (>18yrs) pts. with **severe and critical** Covid-19	-Toclizumab	- None	Once or two doses	- Severe (81%, 17/21) - Critical (19%, 4/21) - High-flow O_2, 45.0% (9/21), nasal cannula, 35.0%(7/21), mask O_2, 5.0% (1/21), NIV 5.0% (1/21), MV, 10.0% (2/21). - 85.7% (18/21) received tocilizumab once, 14.3% (3/21) had another one at the same dose due to fever within 12 h.	- Clinical improvement - Changes on Chest CT	- Within 5 d after tocilizumab, 75.0% (15/20) had lowered their oxygen intake, and 1 patient needed no oxygen therapy. - CT scans manifested that the lung lesion opacity absorbed in 90.5% (19/21).
(CORIMUNO-TOCI trial) (2020.3-27~) 129 pts. at 7 centers I France [Press release]	Prospective, randomized, controlled	-Hospitalized with **moderate or severe** COVID-19 pneumonia **not requiring ICU upon admission.**	- Toclizumab 8 mg/kg on Day 1. If there was no response to the treatment (i.e., no decrease in oxygen requirement), a second infusion of tocilizumab was administered on Day 3.	Standard care		T (65) vs S only (64)	- Need for ventilation (non-invasive or mechanical) or death at day 14.	- A significantly lower proportion of patients reached the primary outcome in the tocilizumab arm.

Study	Design	Indication	Drug	Comparator	Duration of therapy	Results	Time end point assessed	Outcome Drug versus comparator
(2020.2.21~2020.4.30) 544pts. in Italy [*Lancet Rheumatol* 2020 June 24. 52665-9913 (20) 30173-9]	Retrospective	Hospitalized adults (>18yrs) pts. with **severe and critical** Covid-19	Toclizumab IV 8mg/kg bid (maximum 800mg) or SC 162mg in each thigh (total 324mg) plus standard care	-standard care (1) HCQ (2) AZM (3) LPV/r or Darunavir/cobistat (4) Unfractionated heparin	Up to 14d	- 66% (366/544) were male, with a median age of 67 years (56-77) - 179 in T vs. 365 in S - a median SOFA score of 2 (1–4) - 13% (24/179) in T diagnosed with new infections, vs. 4% (14/365) in S (p<0.0001). : BSI (3 vs. 4), bacterial pn. (8 vs. 6), IA (4 vs. 0), Candidemia (2 vs.2)	composite of death or MV	- MV was started in 17% (90/544) : 16% (57/365) in S vs. 18% (33/179) in T (p =0.41) -Death S: 20% (73/544) vs. T: 7% (13/544) p=0.0007) - T was associated with a reduced risk of MV or death (a HR 0.61, 95% CI 0.40–0.92; p=0.020).
[*Clinical and experimental rheumatology* 2020; 38: 529-532] (2020.3.19~2020.6.8) 63 pts. at 4 centers of Torino in Italy	Pilot, prospective, single-arm	Hospitalized adults with **severe** COVID-19 pneumonia by oxygen saturation (Sa02) <93% on room air or PaO2/FiO2 ratio <300 mm Hg	Toclizumab IV 8mg/kg or SC 324mg + anti-virals : LPV/r 71.4% (45/63) : Darunavir/ Cobistat 28.6% (18/63)	None	1-2 doses	- 34 in IV T vs. 29 in SC T : 91% (31/34) : second dose in IV : 72% (21/29) : second dose in SC - Overall mortality at 14d : 11% (7/63)	-Safety at 14d Improvement of respiratory and laboratory parameters at 14d	- No severe to moderate adverse events - The PaO_2/FiO_2 improved (at admission : 152 ± 53 vs. at 7d : 283.73 ± 115.9 vs. at 14d : 302.2 ± 126, p <0.05)

Interferon

- Interferon-beta used alone and in combination with ribavirin in patients with SARS and MERS has failed to show a significant positive effect on clinical outcomes

Int J Infect Dis. 2014;20:42-46.
Lancet Infect Dis. 2014;14(11):1090-1095

- Mortality rates were higher among MERS patients who received ribavirin and interferon (beta-1a, alfa-2a, or alfa-2b) than among those who did not receive either drug

Clin Infect Dis 2020 Apr 15;70(9):1837-1844

Interferons (Alfa, Beta)

Recommendation:

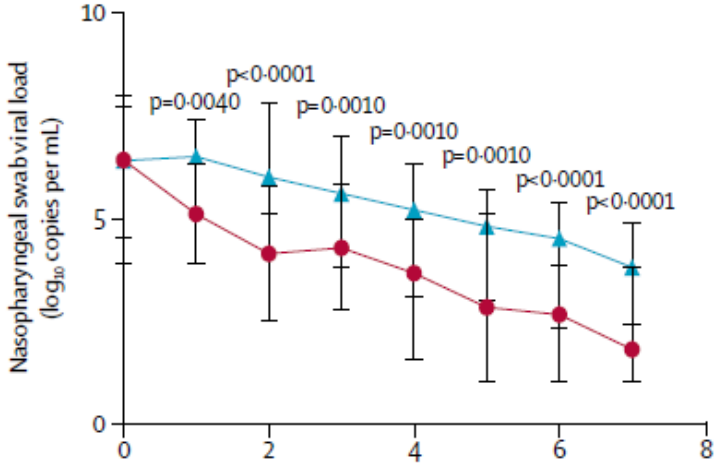
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **interferons** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**.

Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin

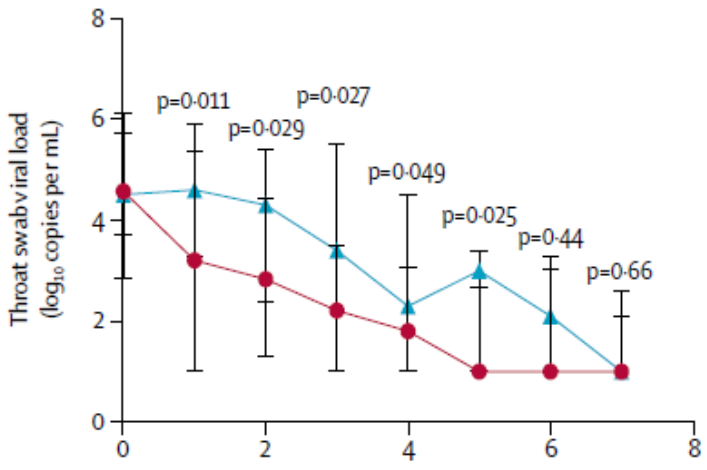
multicentre, prospective, open-label, randomised, phase 2 trial

Combination group: 14days lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million IU of interferon beta-1b
Control group: 14 days of lopinavir 400 mg and ritonavir100 mg every 12 h
Primary end point : the time to negative nasopharyngeal swab for SARS-COV2 RT-PCR

Interpretation Early triple antiviral therapy was safe and superior to lopinavir–ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19. Future clinical study of a double antiviral therapy with interferon beta-1b as a backbone is warranted.

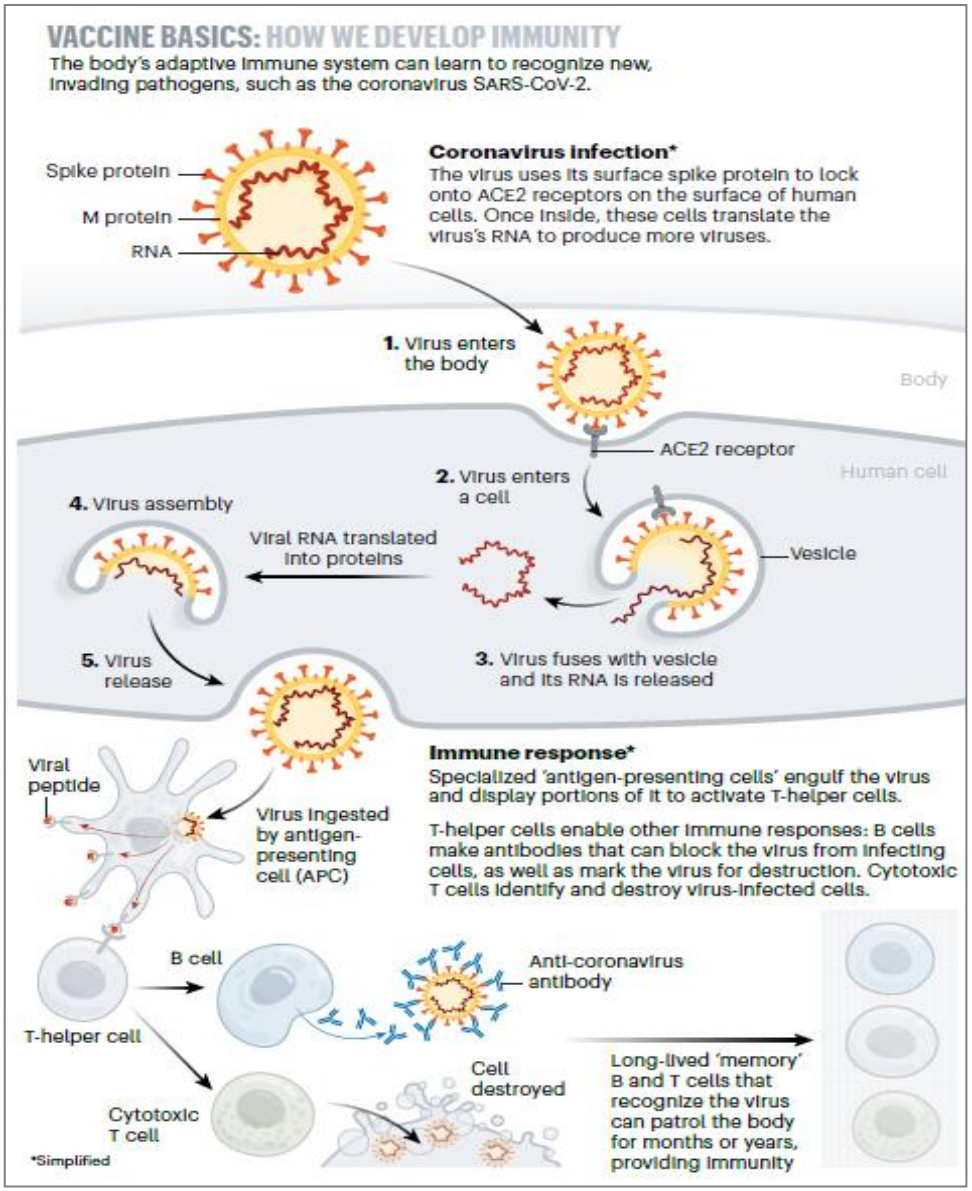


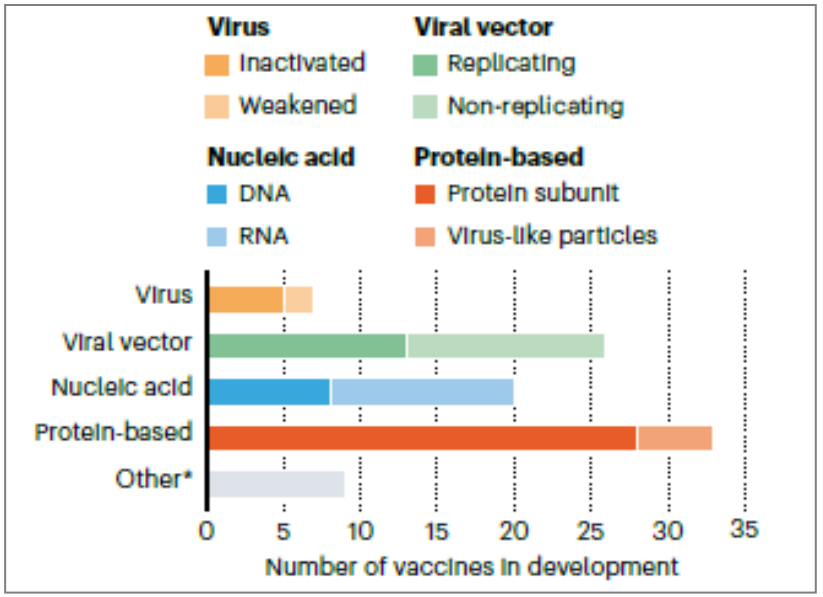
Number of samples								
Combination group	86	86	86	86	85	82	76	75
Control group	41	41	41	41	41	40	39	37



Number of samples								
Combination group	68	64	55	56	53	41	29	30
Control group	31	31	29	25	25	23	22	20

More than 90 COVID-19 vaccines are being developed against SARS-CoV2.





- 4 candidates

Viral rector vaccine

ChAdOx1 nCoV-19 vaccine (AZD1222)

Ad5-vectored COVID-19 vaccine

RNA vaccine

mRNA-1273

BNT162b1

CAVID-19 Vaccine

Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial

Lancet 2020; 395: 1845–54

- Ad5 vectored vaccine expressing the spike glycoprotein of SARS-CoV-2
- A dose-escalation, single-centre, open-label, non-randomised, phase 1 trial
- No serious adverse event within 28 days post-vaccination
- Specific T-cell response peaked at day 14 post-vaccination.

	Day 14				Day 28			
	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	p value	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	p value
ELISA antibodies to the receptor binding domain								
GMT	76·5 (44·3–132·0)	91·2 (55·9–148·7)	132·6 (80·7–218·0)	0·29	615·8 (405·4–935·5)	806·0 (528·2–1229·9)	1445·8 (935·5–2234·5)	0·016
≥4-fold increase	16 (44%)	18 (50%)	22 (61%)	0·35	35 (97%)	34 (94%)	36 (100%)	0·77
Neutralising antibodies to live SARS-CoV-2								
GMT	8·2 (5·8–11·5)	9·6 (6·6–14·1)	12·7 (8·5–19·0)	0·24	14·5 (9·6–21·8)	16·2 (10·4–25·2)	34·0 (22·6–50·1)	0·0082
≥4-fold increase	10 (28%)	11 (31%)	15 (42%)	0·42	18 (50%)	18 (50%)	27 (75%)	0·046

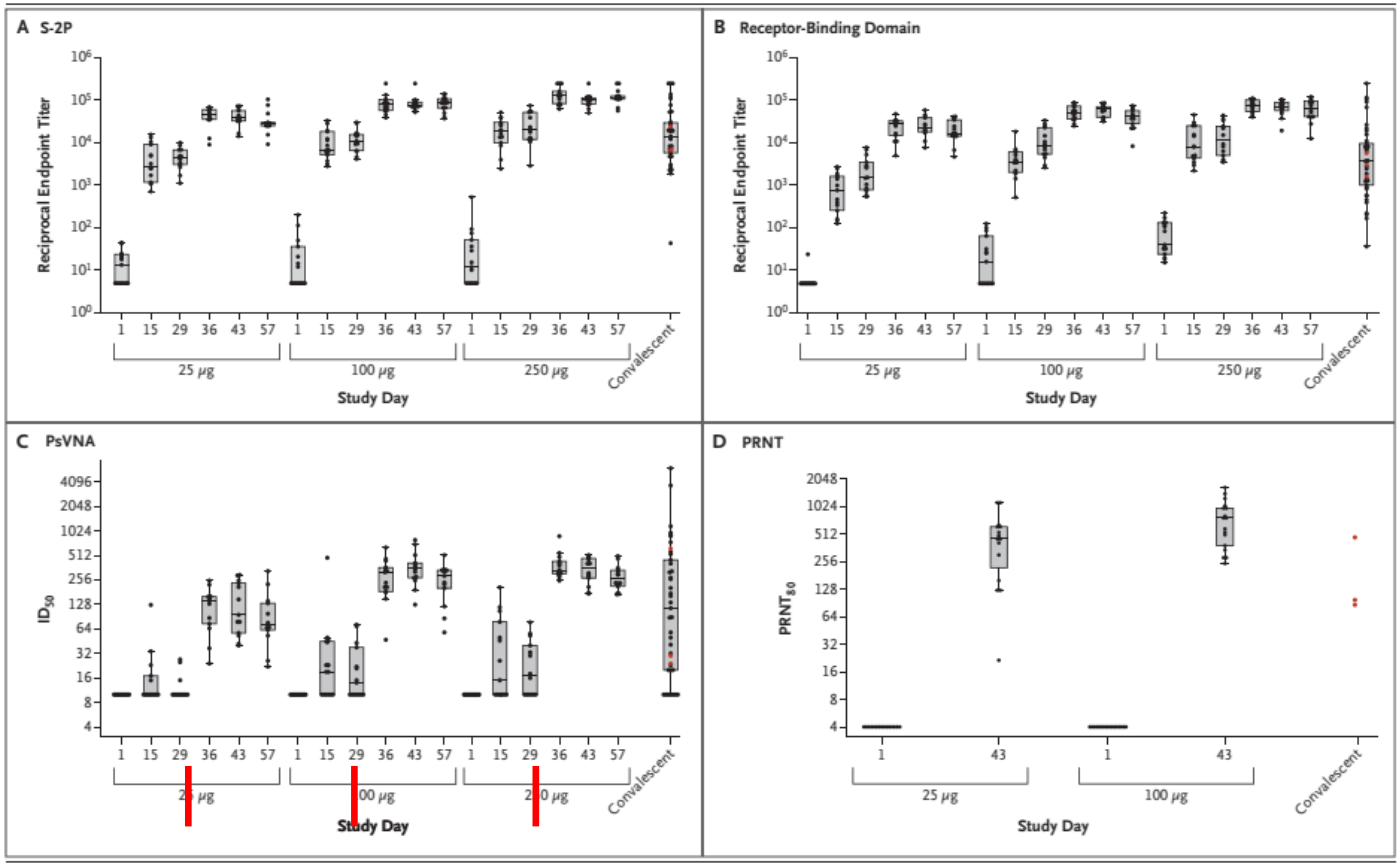
Data are mean (95% CI) or n (%). The p values are the result of comparison across the three dose groups. If the difference was significant across the three groups, the differences between groups were estimated with 95% CIs. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. GMT=geometric mean titre.

Table 3: Specific antibody responses to the receptor binding domain, and neutralising antibodies to live SARS-CoV-2

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

DOI: 10.1056/NEJMoa2022483

- The mRNA-1273 vaccine by Moderna
  - encodes the S-2P antigen
- Two vaccinations(D1,D29), Dose :25 μg, 100 μg, or 250 μg



SARS-CoV-2 Binding Antibody Responses

SARS-CoV-2 Neutralization Responses

Dose dependent reponse

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