Latest Research of Drug Trial and Recommended Treatment for Covid-19

CHP COVID-19 Symposium: From Prevention to Control

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Disclosure

- Received honoraria from Pfizer, Roche, MSD, Abbvie, Ferring, Gilead and Chong Lap

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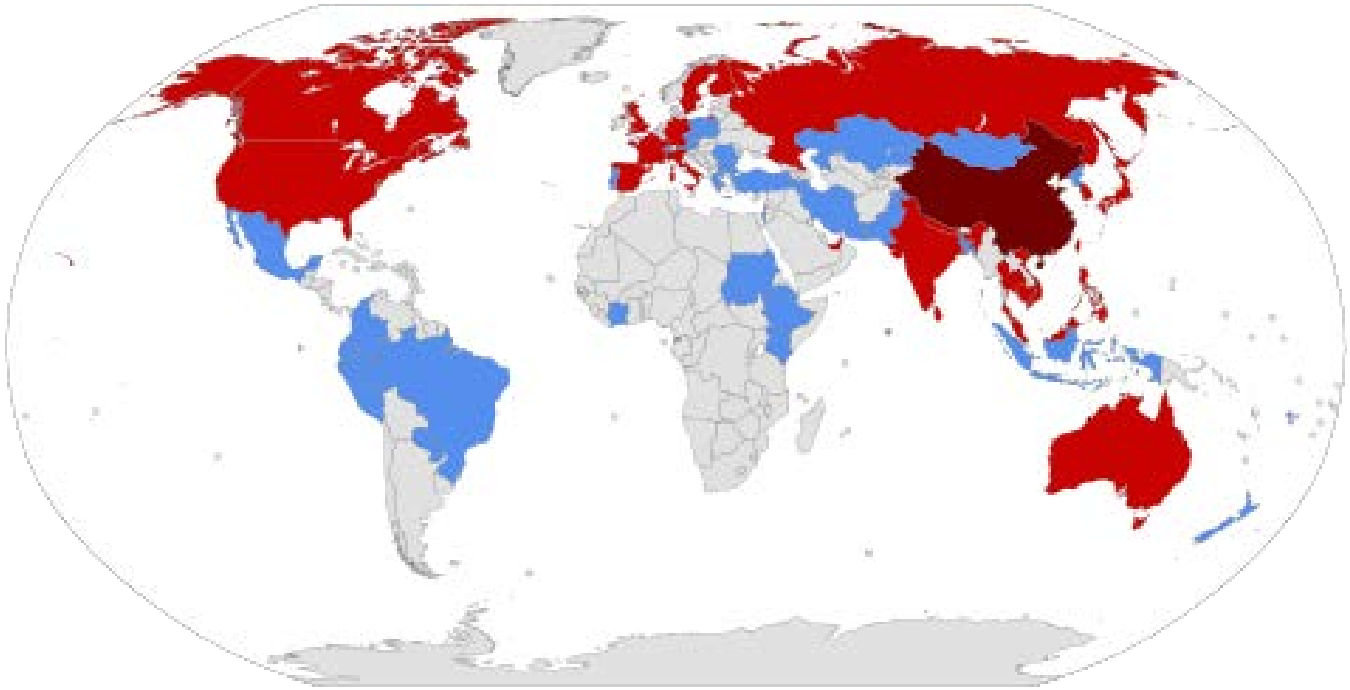
1 Introduction

COVID-19 Pandemic: 19 March 2020



COVID-19: 218,584 cases; 8938 mortality; 157 countries worldwide; mortality rate: 4.1% 19 March 2020)

https://en.wikipedia.org/wiki/2019_novel_coronavirus_(2019-nCoV)
https://www.chp.gov.hk/files/pdf/statistics_of_the_cases_novel_coronavirus_infection_en.pdf

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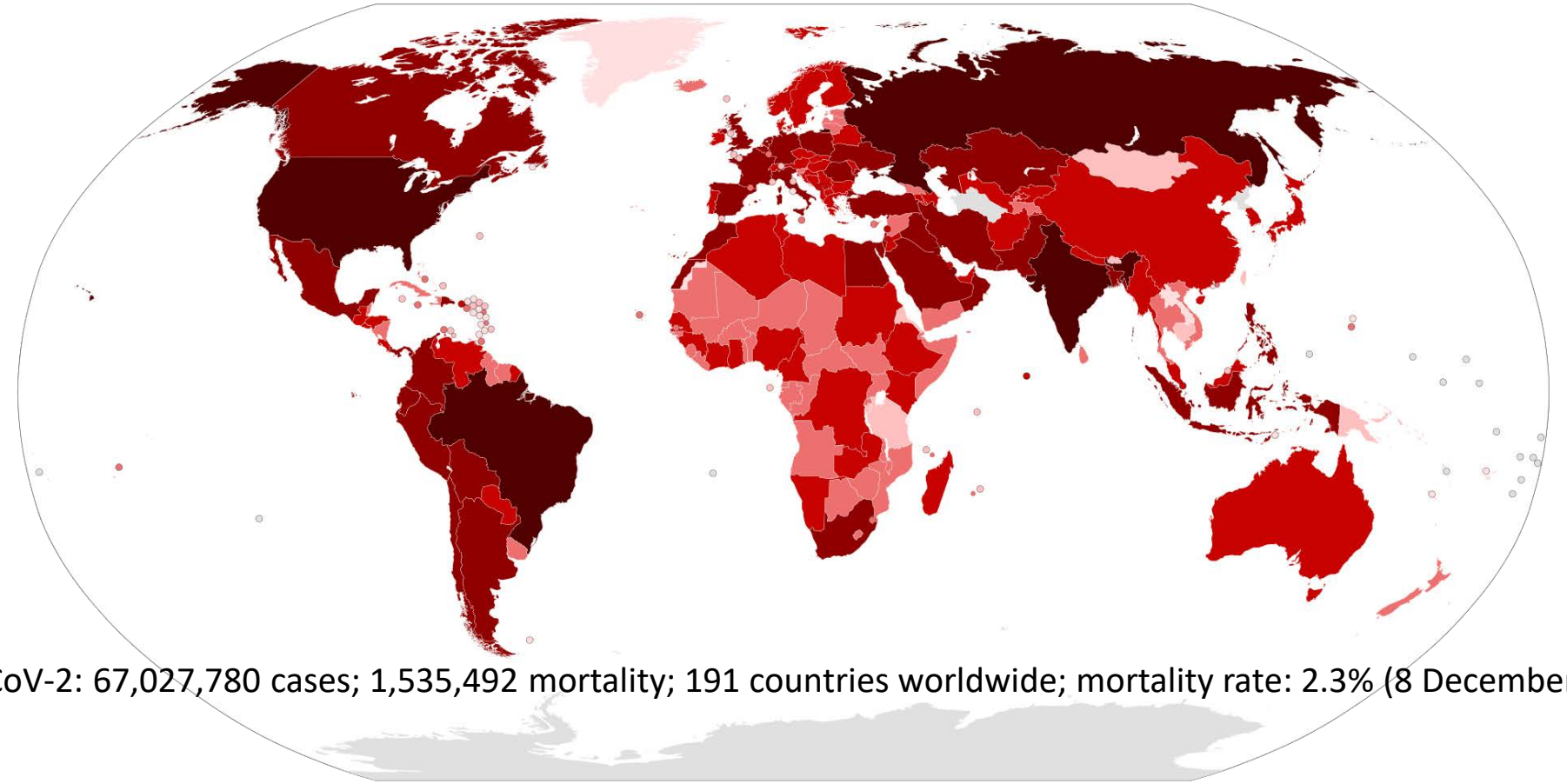
COVID-19 Epidemic: 8 December 2020



SARS-CoV-2: 67,027,780 cases; 1,535,492 mortality; 191 countries worldwide; mortality rate: 2.3% (8 December 2020)

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https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200507covid-19-sitrep-128.pdf?sfvrsn=44cc8ed8_2
https://en.wikipedia.org/wiki/2019_novel_coronavirus_(2019-nCoV)
https://www.chp.gov.hk/files/pdf/statistics_of_the_cases_novel_coronavirus_infection_en.pdf

COVID-19 Pandemic: Changes

19 March 2020

2019–20 coronavirus pandemic by country and territory [show all]

Location[a]	Cases[b]	Deaths	Deaths per 10 million capita	Recoveries[c]	Ref.
157	218,584	8,938		85,711	
China (mainland)[d]	80,928	3,245	23	70,420	[33]
Italy[e]	35,713	2,978	492	4,025	[36]
Iran	17,361	1,135	140	5,710	[33]
Spain	14,769	638	137	1,081	[37]
Germany	12,327	28	3	105	[38]
United States[f]	9,452	150	5	106	[33][39]
France[g]	9,134	264	39	602	[40]
South Korea	8,565	91	18	1,947	[41]
Switzerland[h]	2,772	21		15	[42]
United Kingdom[i]	2,626	104	16	65	[43][44]
Netherlands[j][k]	2,059	58		–	[33][46]
Austria	1,646	4		9	[33][47]
Norway[l]	1,590	6		1	[33][48]
Belgium	1,486	14		31	[33]
Sweden[m]	1,231	10		15	[33][49]
Denmark[n]	1,117	4		–	[50][51]
Japan	899	29	2	191	[33][52]
Malaysia	790	2		60	[53][54]
Canada	727	9	3	11	[55]
Diamond Princess[o]	712	7		527	[52]
Portugal	642	2		3	[33][56]
Australia	596	6	2	43	[33]
Brazil	529	4		2	[33][57]
Czech Republic	522	0		3	[33][58]
Qatar	452	0		4	[33][59]
Israel	433	0	0	11	[33][60]
Greece	418	5		14	[61][33]
Ireland	366	2		5	[33][62]
Finland	359	0	0	10	[33][63]
Singapore	313	0	0	117	[64][65]
Pakistan	307	1		2	[33][66]
Poland	287	5		1	[67]

8 December 2020

COVID-19 pandemic by location [show all]

Location[a]	Cases[b]	Deaths[c]	Recov.[d]	Ref.
World[e]	67,027,780	1,535,492	43,062,006	[4]
United States[f]	14,879,831	285,564	6,971,281	[13]
India	9,677,203	140,573	9,139,901	[14]
Brazil	6,603,540	176,962	5,776,182	[15][16]
Russia[g]	2,488,912	43,597	1,956,588	[17]
France[h]	2,292,497	55,155	169,586	[18][19]
Italy	1,728,878	60,078	913,494	[20]
United Kingdom[i]	1,737,960	61,434	No data	[22]
Spain[j]	1,684,647	46,252	No data	[23]
Argentina[k]	1,463,097	39,770	1,294,679	[25]
Colombia	1,371,103	37,808	1,257,410	[26]
Germany[l]	1,184,845	18,864	846,273	[28][27]
Mexico	1,175,850	109,717	866,186	[29]
Poland	1,067,870	20,181	722,446	[30]
Iran	1,051,374	50,594	742,955	[31]
Peru	973,912	36,274	907,654	[32][33]
Turkey[m]	828,295	14,900	431,253	[38]
Ukraine[n]	821,947	13,733	423,704	[39][40]
South Africa	814,565	22,206	744,780	[41][42]
Belgium[o]	589,942	17,254	No data	[44][45]
Indonesia	581,550	17,867	479,202	[46]
Iraq	564,200	12,432	493,567	[47]
Chile[p]	562,142	15,663	536,267	[51]
Netherlands[q]	557,224	9,687	No data	[53][54]
Czech Republic	546,833	8,902	478,094	[55]
Romania	517,236	12,447	409,121	[56][57]
Bangladesh	479,743	6,874	398,623	[58][59]

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200507covid-19-sitrep-128.pdf?sfvrsn=44cc8ed8_2
https://en.wikipedia.org/wiki/2019_novel_coronavirus_(2019-nCoV)

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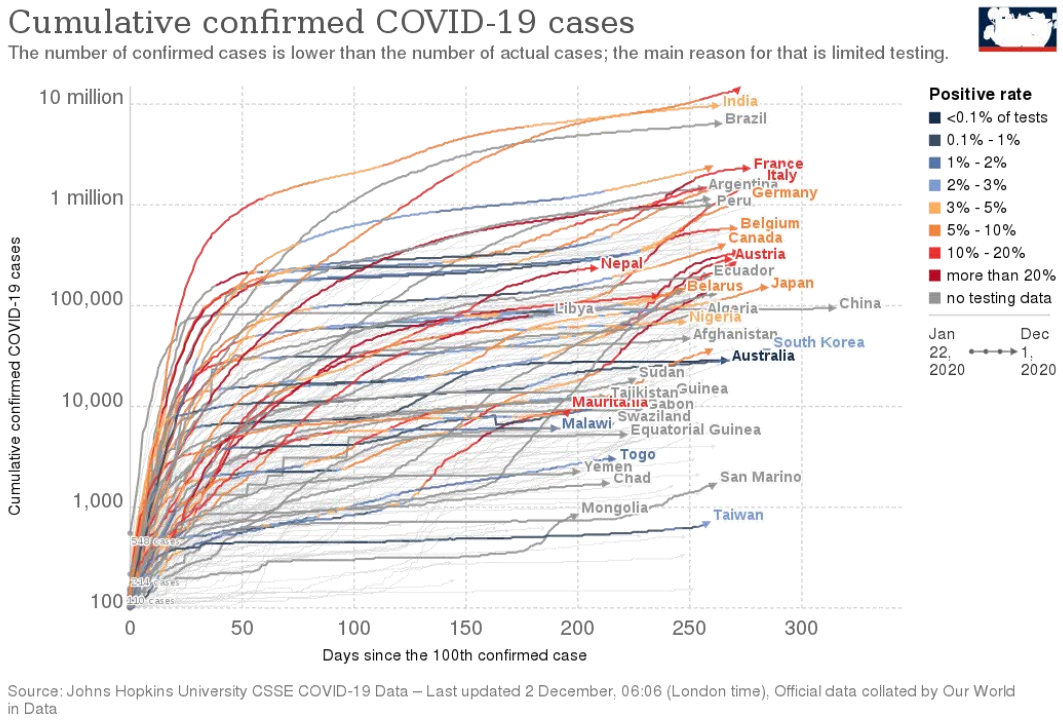
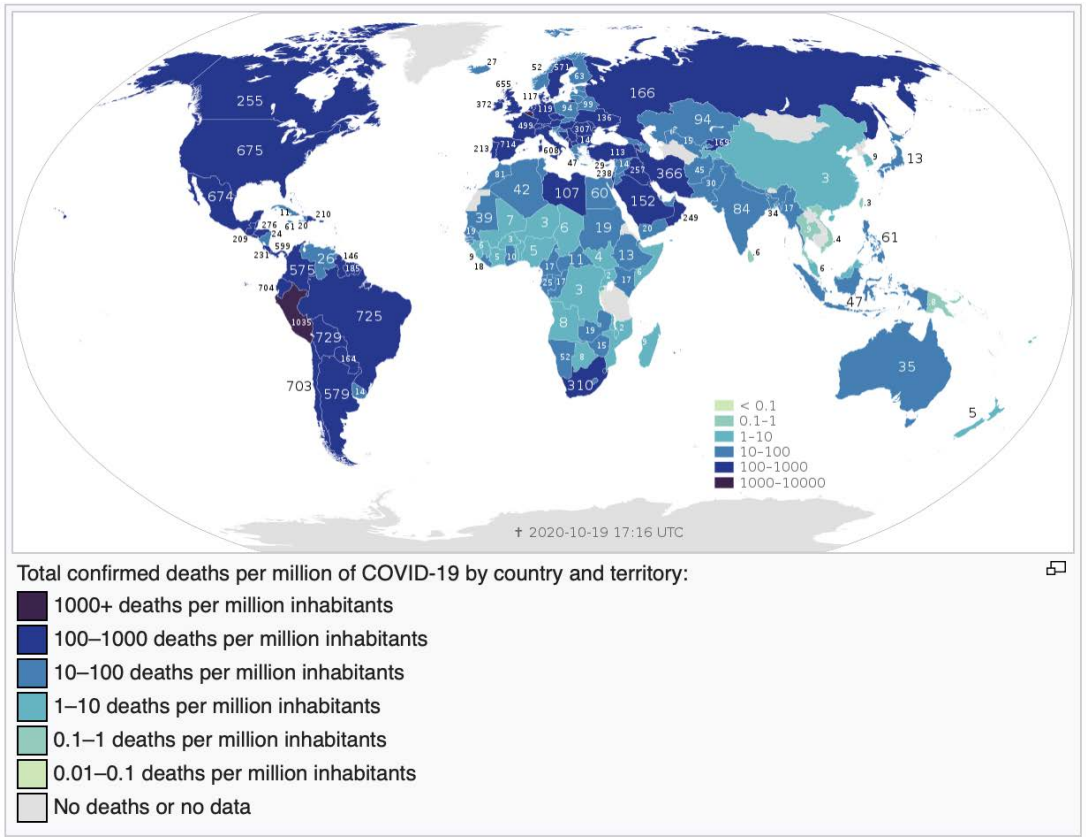
COVID-19 Epidemic: 1 December 2020

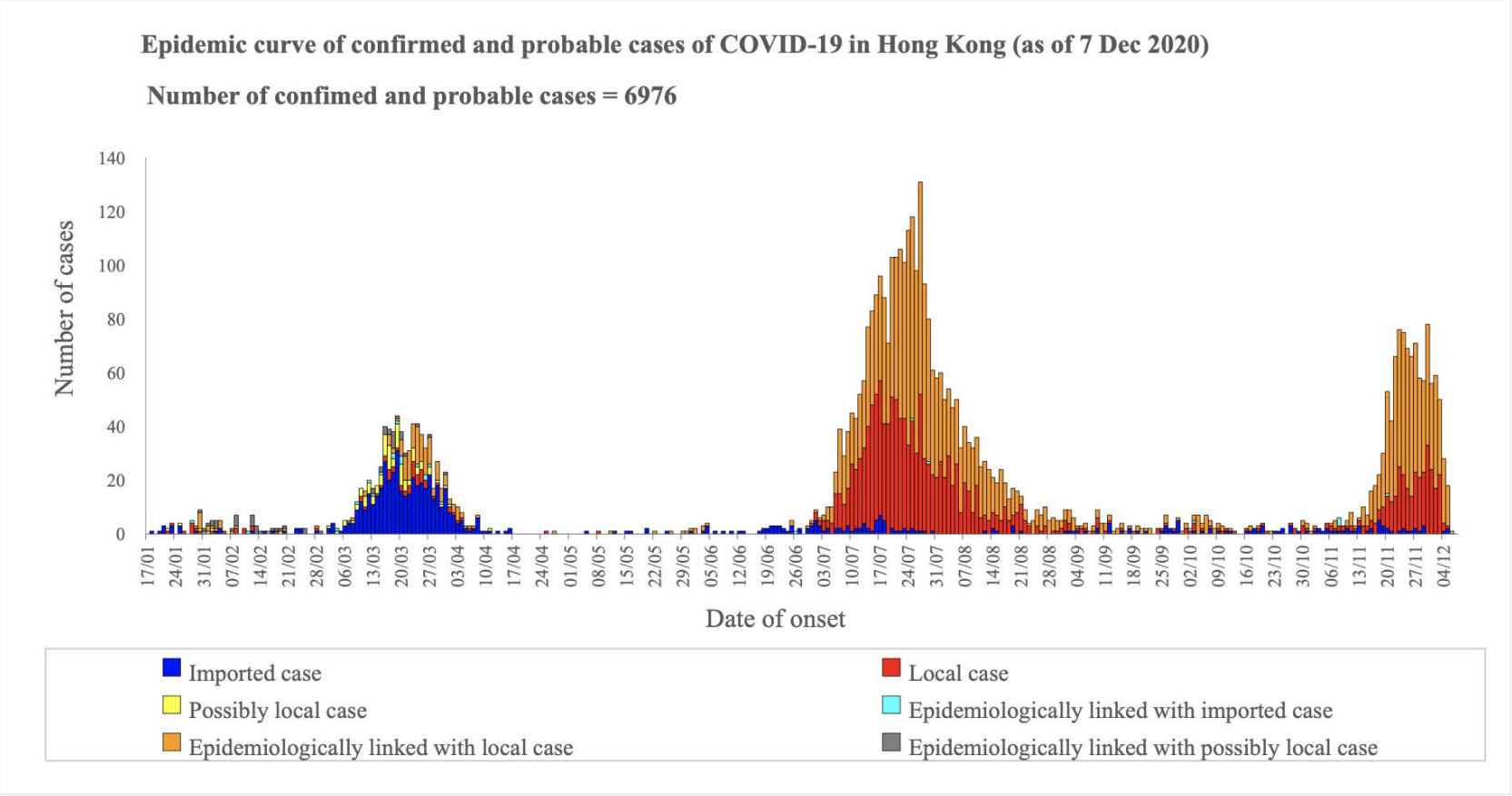


Source: Johns Hopkins University CSSE COVID-19 Data – Last updated 2 December, 06:06 (London time), Official data collated by Our World in Data



https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200507covid-19-sitrep-128.pdf?sfvrsn=44cc8ed8_2
https://en.wikipedia.org/wiki/2019_novel_coronavirus_(2019-nCoV)

Latest Situation in Hong Kong



D614G mutation
Spike protein
More transmissible

3rd wave: elderly

4th wave commenced
Latin dancing cluster
Nepalese clade
Community clusters

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https://chp-dashboard.geodata.gov.hk/covid-19/en.html

Hong Kong vs. NYC

- Hong Kong population: 7.5 million in 1104 km^2; 3rd densely populated in the world
- NYC population: 8.3 million in 784 km^2

- Hong Kong Covid-19: 6976 cases; 112 deaths (mortality rate 1.6%); ICU occupancy <50%
- NYC Covid-19: 711000 cases; 34,552 deaths; (mortality rate 4.9%); ICU occupancy 100%

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https://www1.nyc.gov/site/doh/covid/covid-19-data.page
https://chp-dashboard.geodata.gov.hk/covid-19/en.html
Celum C et al. NEJM 2020; DOI:10.1056

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Dying in a Leadership Vacuum

The Editors

Covid-19 has created a crisis throughout the world. This crisis has produced a test of leadership. With no good options to combat a novel pathogen, countries were forced to make hard choices about how to respond. Here in the United States, our leaders have failed that test. They have taken a crisis and turned it into a tragedy.

The magnitude of this failure is astonishing. According to the Johns Hopkins Center for Systems Science and Engineering,[1] the United States leads the world in Covid-19 cases and in deaths due to the disease, far exceeding the numbers in much larger countries, such as China. The death rate in this country is more than double that of Canada, exceeds that of Japan, a country with a vulnerable and elderly population, by a factor of almost 50, and even dwarfs the rates in lower-middle-income countries, such as Vietnam, by a factor of almost 2000. Covid-19 is an overwhelming challenge, and many factors contribute to its severity. But the one we can control is how we behave. And in the United States we have consistently behaved poorly.

We know that we could have done better. China, faced with the first outbreak, chose strict quarantine and isolation after an initial delay. These measures were severe but effective, essentially eliminating transmission at the point where the outbreak began and reducing the death rate to a reported 3 per million, as compared with more than 500 per million in the United States. Countries that had far more exchange with China, such as Singapore and South Korea, began intensive testing early, along with aggressive contact tracing and appropriate isolation, and have had relatively small outbreaks. And New Zealand has used these same measures, together with its geographic advantages, to come close to eliminating the disease, something that has allowed that country to limit the time of closure and to largely reopen society to a prepandemic level. In general, not only have many democracies done better than the United States, but they have also outperformed us by orders of magnitude.

Why has the United States handled this pandemic so badly? We have failed at almost every step. We had ample warning, but when the disease first arrived, we were incapable of testing effectively and couldn't provide even the most basic personal protective equipment to health care workers and the general public. And we continue to be way behind the curve in testing. While the absolute numbers of tests have increased substantially, the more useful metric is the number of tests performed per infected person, a rate that puts us far down the international list, below such places as Kazakhstan, Zimbabwe, and Ethiopia, countries that cannot boast the biomedical infrastructure or the manufacturing capacity that we have.[2] Moreover, a lack of emphasis on developing capacity has meant that U.S. test results are often long delayed, rendering the results useless for disease control.

Although we tend to focus on technology, most of the interventions that have large effects are not complicated. The United States instituted quarantine and isolation measures late and inconsistently, often without any effort to enforce them, after the disease had spread substantially in many communities. Our rules on social distancing have in many places been lackadaisical

2

Lessons Learnt from the Past

From SARS to SARS-CoV-2

From SARS to Influenza, What Have We Learnt?

HKU Medical Summer Broadening Programme
18 July 2016

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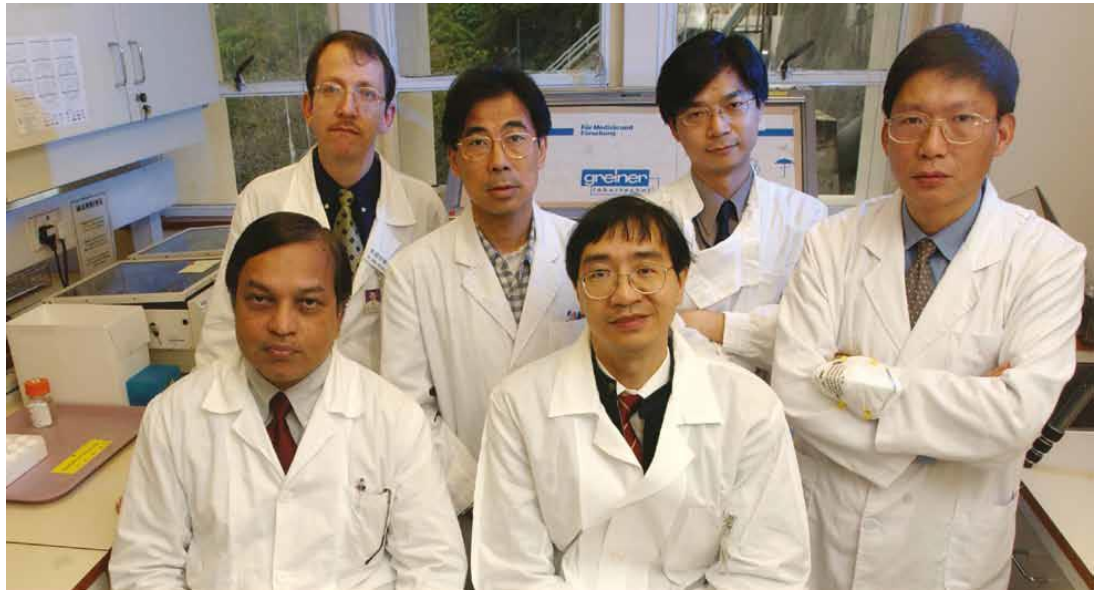

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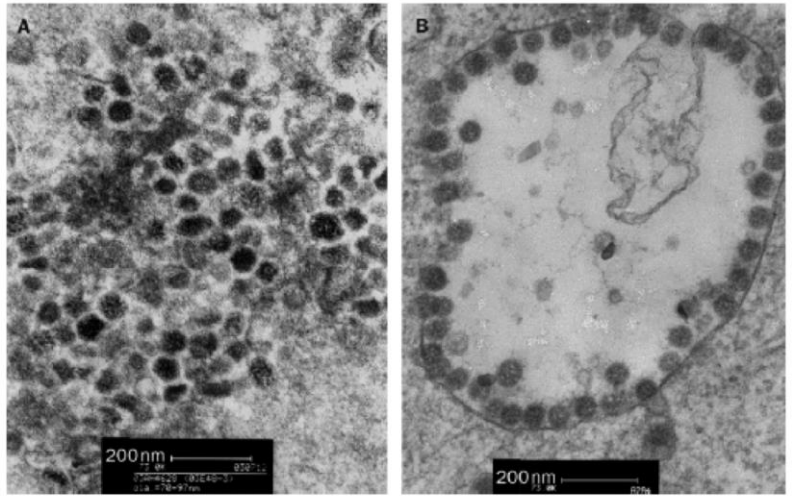
SARS 2003

Articles

Coronavirus as a possible cause of severe acute respiratory syndrome

J S M Peiris, S T Lai, L L M Poon, Y Guan, L Y C Yam, W Lim, J Nicholls, W K S Yee, W W Yan, M T Cheung, V C C Cheng, K H Chan, D N C Tsang, R W H Yung, T K Ng, K Y Yuen, and members of the SARS study group*



Lung biopsy, TEM

Cell culture, TEM

Lancet 2003; 361: 1319-25

ARTICLES

Articles

Coronavirus as a possible cause of severe acute respiratory syndrome

J S M Peiris, S T Lai, L L M Poon, Y Guan, L Y C Yam, W Lim, J Nicholls, W K S Yee, W W Yan, M T Cheung, V C C Cheng, K H Chan, D N C Tsang, R W H Yung, T K Ng, K Y Yuen, and members of the SARS study group*

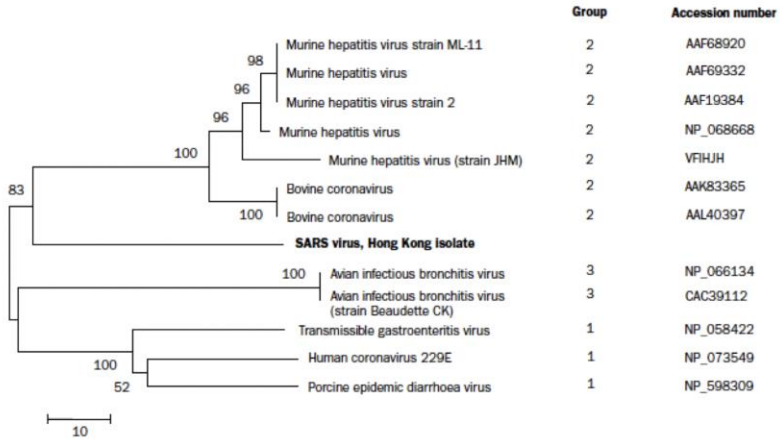


Figure 3: **Phylogenetic analysis of the partial protein sequence (215 aminoacids) of the coronavirus (SARS)**
GenBank accession number AY268070. Tree is constructed by neighbour-jointing method. Horizontal-line distance represents number of sites at which the two sequences compared are different. Bootstrap values deducted from 500 replicates.

Lancet 2003; 361: 1319-25

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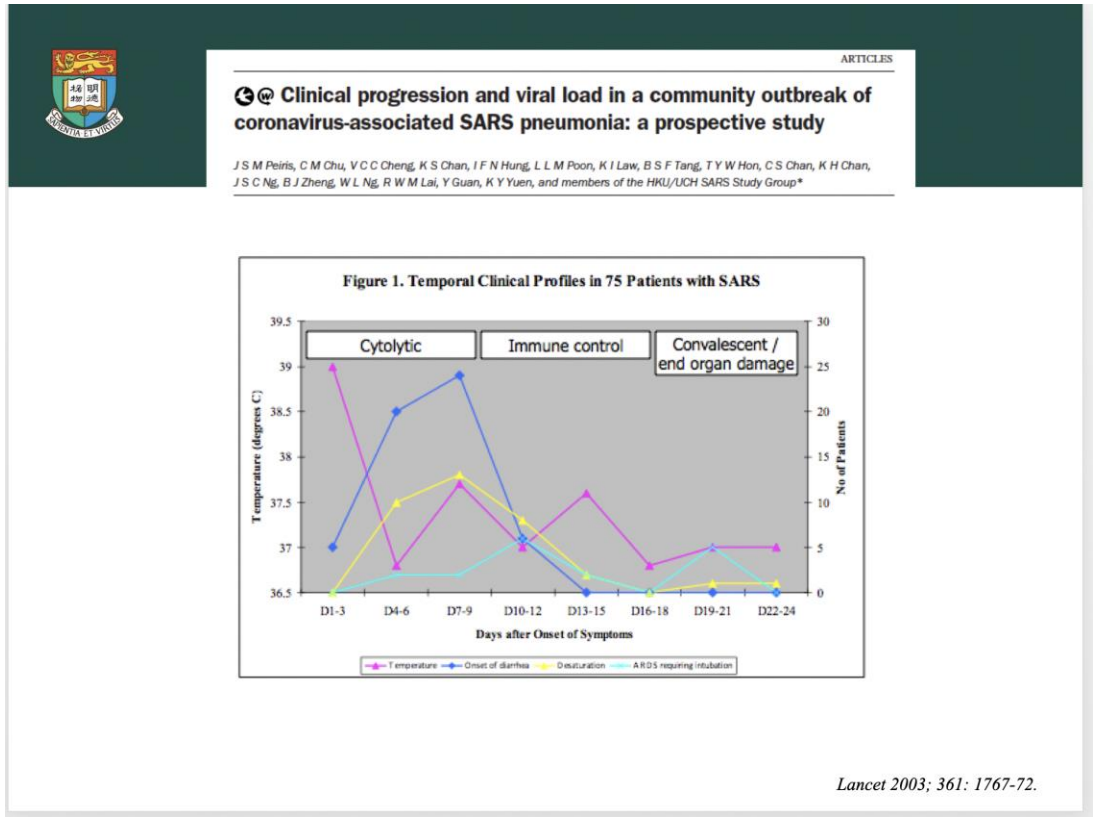
SARS 2003



ARTICLES

Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study

J S M Peiris, C M Chu, V C C Cheng, K S Chan, I F N Hung, L L M Poon, K I Law, B S F Tang, T Y W Hon, C S Chan, K H Chan, J S C Ng, B J Zheng, W L Ng, R W M Lai, Y Guan, K Y Yuen, and members of the HKU/UCH SARS Study Group*

Figure 1. Temporal Clinical Profiles in 75 Patients with SARS

Lancet 2003; 361: 1767-72.

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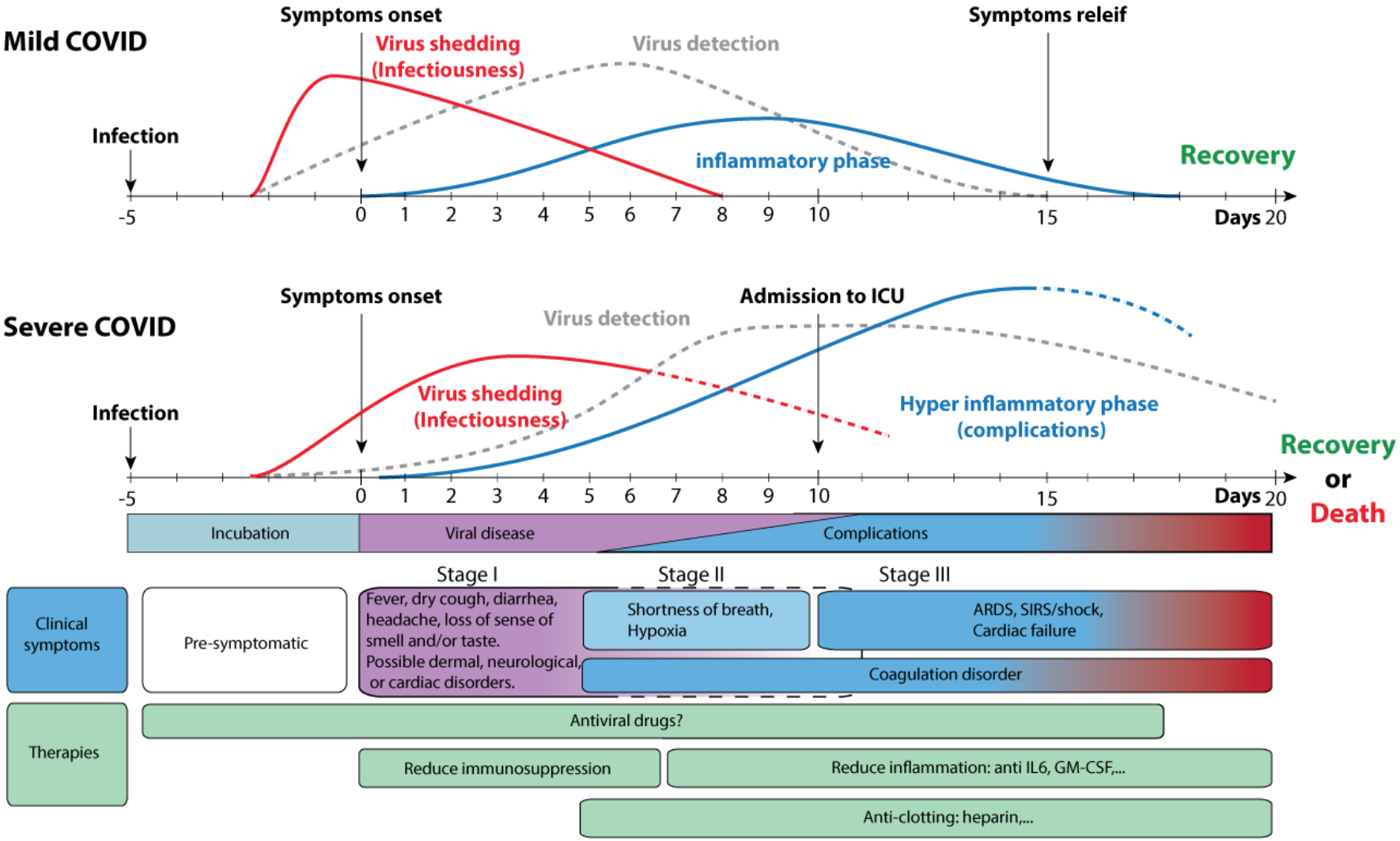
3

Clinical Characteristics

Covid-19 Disease Pathogenesis Models



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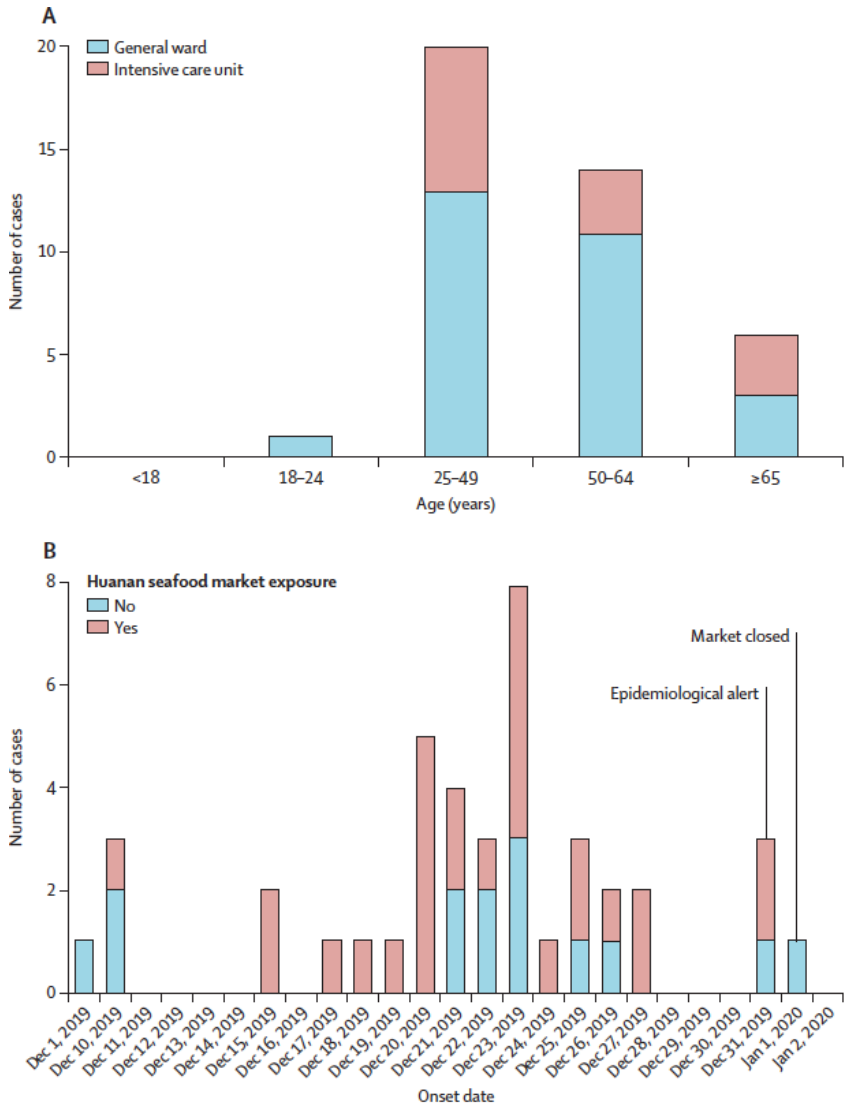
https://viralzone.expasy.org/9116

High Risk Populations



	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
Characteristics				
Age, years	49·0 (41·0–58·0)	49·0 (41·0–61·0)	49·0 (41·0–57·5)	0·60
Sex	..	..	..	0·24
Men	30 (73%)	11 (85%)	19 (68%)	..
Women	11 (27%)	2 (15%)	9 (32%)	..
Huanan seafood market exposure	27 (66%)	9 (69%)	18 (64%)	0·75
Current smoking	3 (7%)	0	3 (11%)	0·31
Any comorbidity	13 (32%)	5 (38%)	8 (29%)	0·53
Diabetes	8 (20%)	1 (8%)	7 (25%)	0·16
Hypertension	6 (15%)	2 (15%)	4 (14%)	0·93
Cardiovascular disease	6 (15%)	3 (23%)	3 (11%)	0·32
Chronic obstructive pulmonary disease	1 (2%)	1 (8%)	0	0·14
Malignancy	1 (2%)	0	1 (4%)	0·49
Chronic liver disease	1 (2%)	0	1 (4%)	0·68
Signs and symptoms				
Fever	40 (98%)	13 (100%)	27 (96%)	0·68
Highest temperature, °C	..	..	..	0·037
<37·3	1 (2%)	0	1 (4%)	..
37·3–38·0	8 (20%)	3 (23%)	5 (18%)	..
38·1–39·0	18 (44%)	7 (54%)	11 (39%)	..
>39·0	14 (34%)	3 (23%)	11 (39%)	..
Cough	31 (76%)	11 (85%)	20 (71%)	0·35
Myalgia or fatigue	18 (44%)	7 (54%)	11 (39%)	0·38
Sputum production	11/39 (28%)	5 (38%)	6/26 (23%)	0·32
Headache	3/38 (8%)	0	3/25 (12%)	0·10
Haemoptysis	2/39 (5%)	1 (8%)	1/26 (4%)	0·46
Diarrhoea	1/38 (3%)	0	1/25 (4%)	0·66
Dyspnoea	22/40 (55%)	12 (92%)	10/27 (37%)	0·0010
Days from illness onset to dyspnoea	8·0 (5·0–13·0)	8·0 (6·0–17·0)	6·5 (2·0–10·0)	0·22
Days from first admission to transfer	5·0 (1·0–8·0)	8·0 (5·0–14·0)	1·0 (1·0–6·5)	0·0023
Systolic pressure, mm Hg	125·0 (119·0–135·0)	145·0 (123·0–167·0)	122·0 (118·5–129·5)	0·018
Respiratory rate >24 breaths per min	12 (29%)	8 (62%)	4 (14%)	0·0023

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Guan W, N Zhong et al. NEJM DOI:10.1056

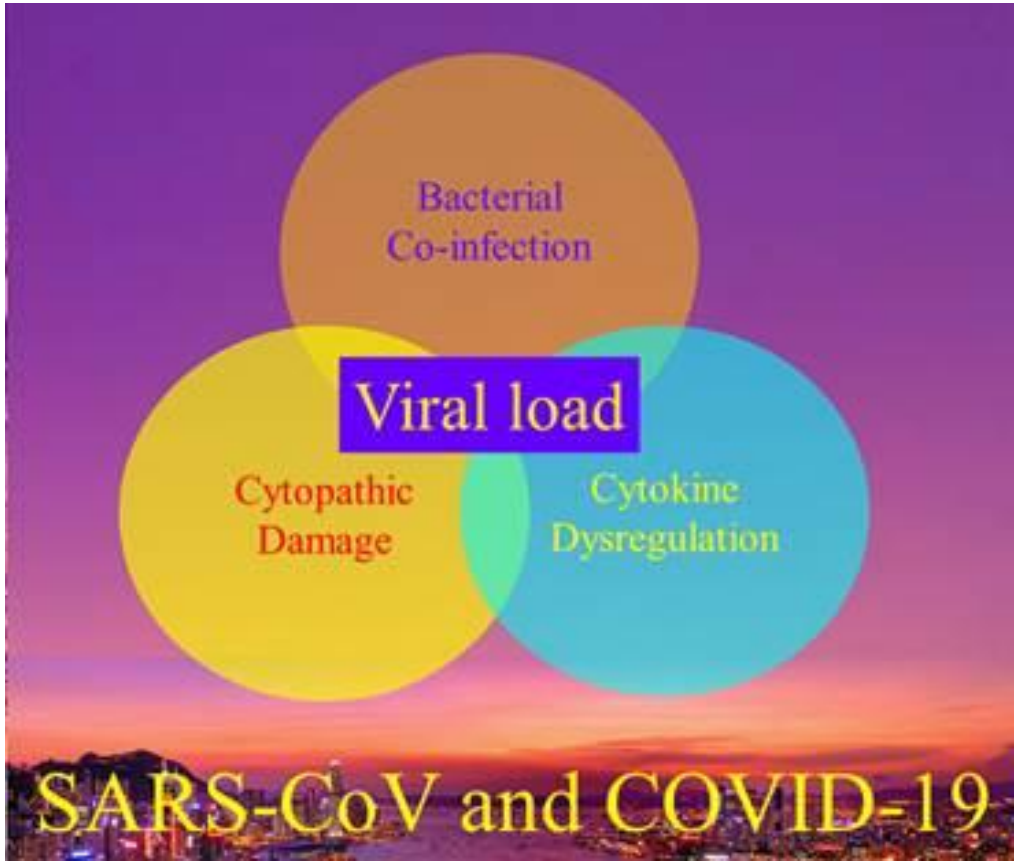
Huang C et al. Lancet 2020; S0140-6736

4

Antiviral Treatments

Principles of Antiviral Treatments

- Early commencement of antiviral Combination therapy
  - Increase spectrum of activity
  - Increase potency
  - Reduce resistance emergence
- Rapid suppression of viral load
- Prevent subsequent complications
- Reduce viral shedding



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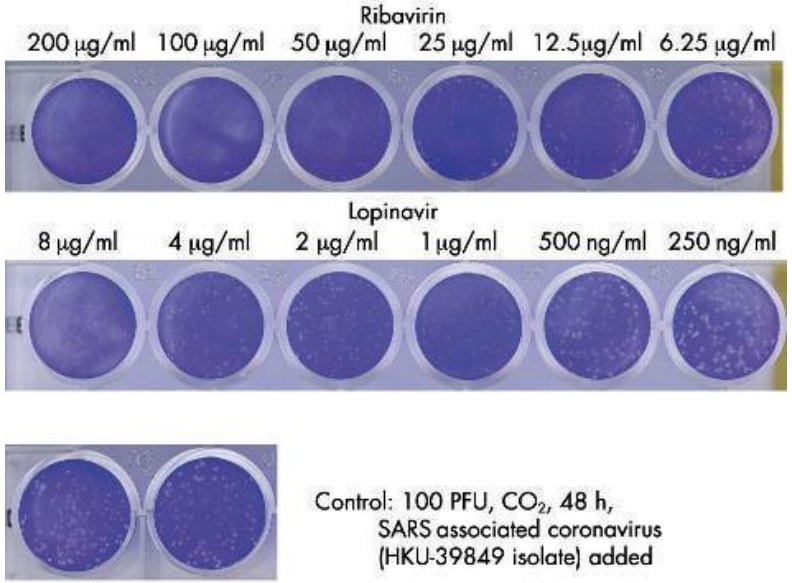
Courtesy of Dr. KY Lai

In Vitro Screening of Repurposed Drugs



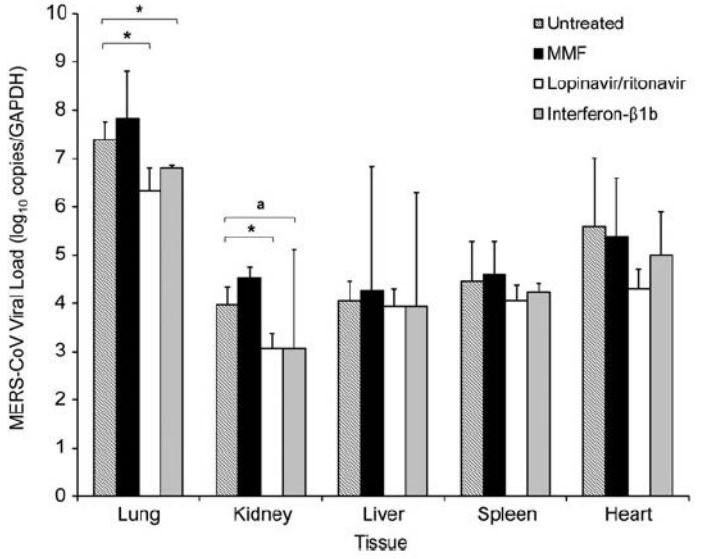


Figure 6. Mean viral loads with standard deviation values in different tissues of MERS-CoV-infected common marmosets collected at the time of necropsy. *P<.05. [a]Two of the 3 interferon-β1b-treated animals had undetected viral loads in necropsied kidney tissues, which accounted for a large standard deviation value and apparent lack of statistically significant difference from the mean viral load of the untreated animals. Abbreviations: GAPDH, glyceraldehyde 3-phosphate dehydrogenase; MERS-CoV, Middle East respiratory syndrome coronavirus; MMF, mycophenolate mofetil.

1. VL of COVID-19 peaks at presentation like influenza
2. Combination of multiple antiviral drugs is more effective
3. Three modestly active drugs against SARS-CoV-2

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Chu CM et al. Thorax 2004;59:252:256
Chan JF et al. J Infect Dis 2015;212:1904-13

In Vitro Screening of Repurposed Drugs

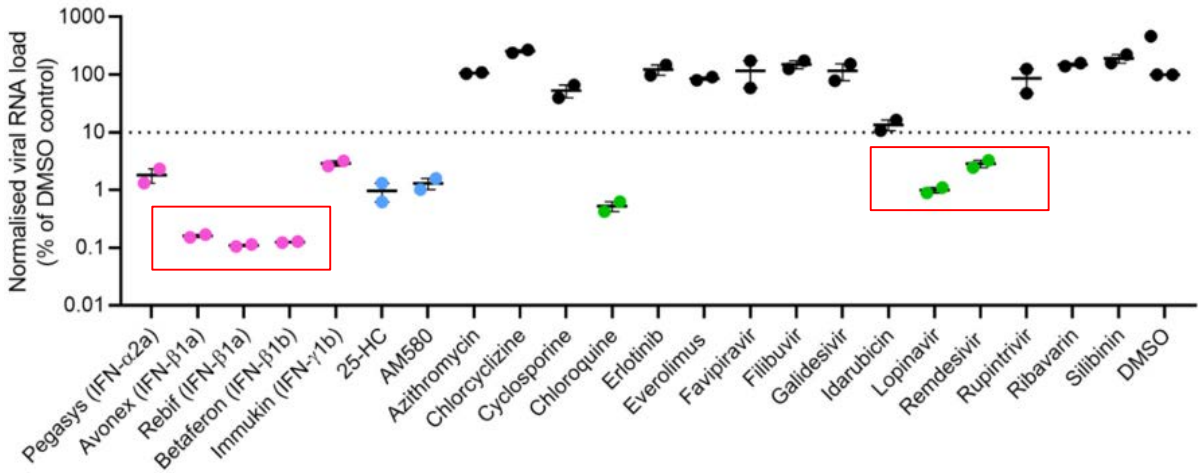
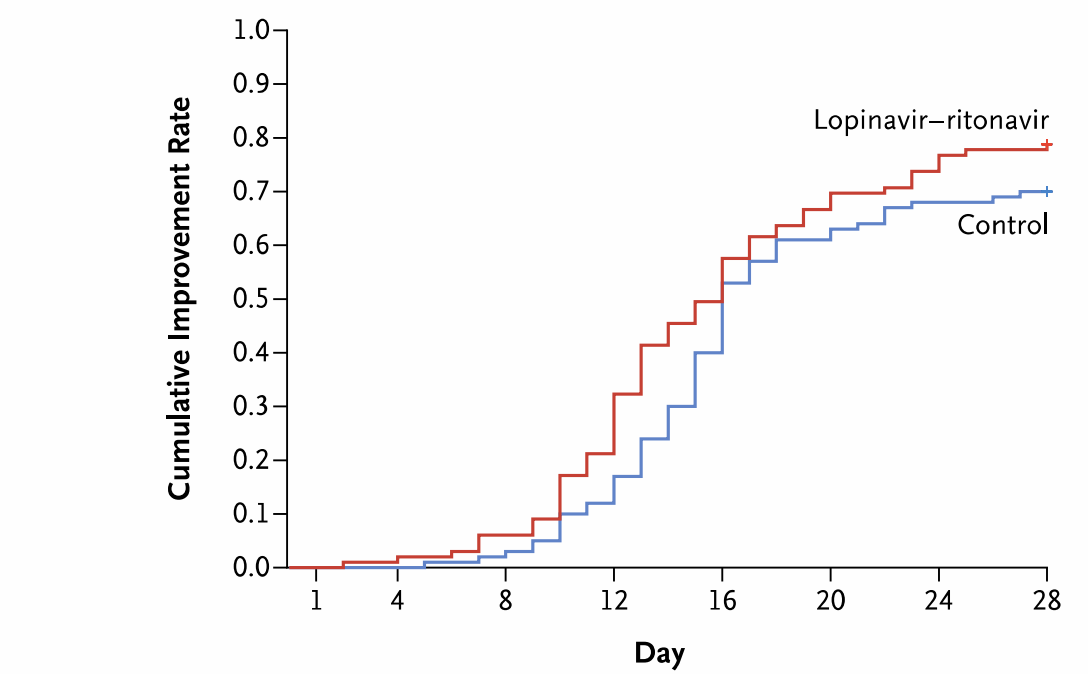


Table 2. Antiviral activities and cytotoxicities of the anti-SARS-CoV-2 antiviral agents identified in the primary screening.

Antiviral Agent	CC_{50} (CellTiterGlo®) [a]	EC_{50} (Plaque Reduction Assay)	Select Index (CC_{50}/EC_{50})
Pegasys (pegylated IFN-α2a)	>50,000 IU/mL	1068.0 IU/mL	>46.8
Avonex (IFN-β1a)	>50,000 IU/mL	109.6 IU/mL	>456.2
Rebif (IFN-β1a)	>50,000 IU/mL	70.8 IU/mL	>706.2
Betaferon (IFN-β1b)	>50,000 IU/mL	31.2 IU/mL	>1602.6
Immukin (IFN-γ1b)	>50,000 IU/mL	142.2 IU/mL	>351.6
25-hydroxycholesterol	>50 μM	4.2 μM	>11.9
AM580	126 μM	7.6 μM	16.6
Lopinavir	102 μM	11.6 μM	8.8
Remdesivir	>100 μM	1.04 μM	96.2

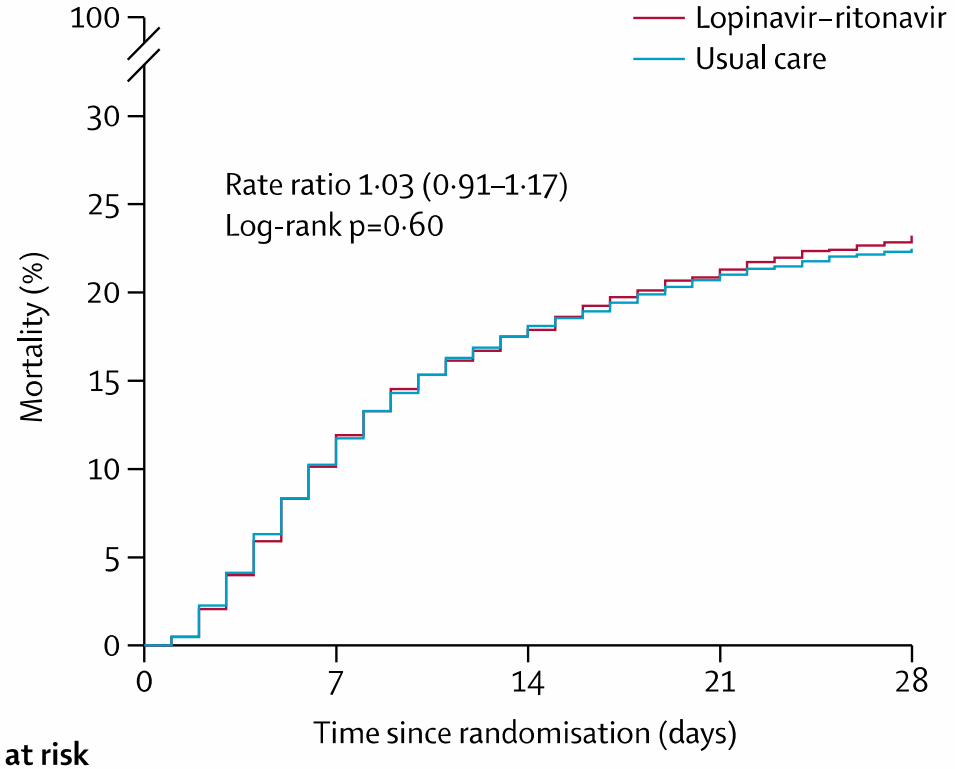
Yuan S et al. Viruses 2020;628;doi:10.3390

Lopinavir-Ritonavir (protease inhibitor)



No. at Risk

Lopinavir–ritonavir	99	98	93	78	50	33	26	22
Control	100	100	98	88	60	39	32	30



Number at risk

Active	1616	1422	1325	1269	1238
Control	3424	3018	2799	2700	2650

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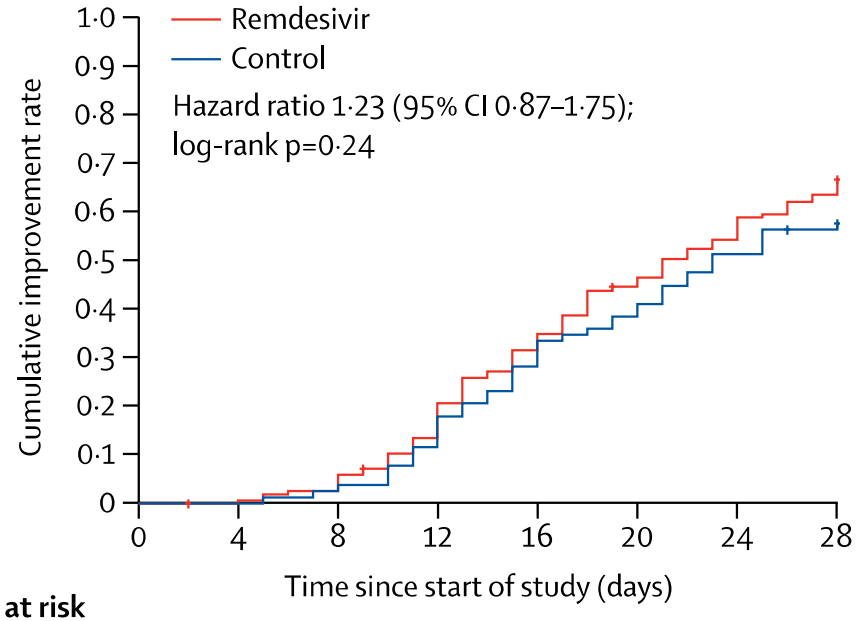
Cao B et al. NEJM 2020;382:1787-1799
Horby PW et al. Lancet 2020; S1040-6736

Remdesivir

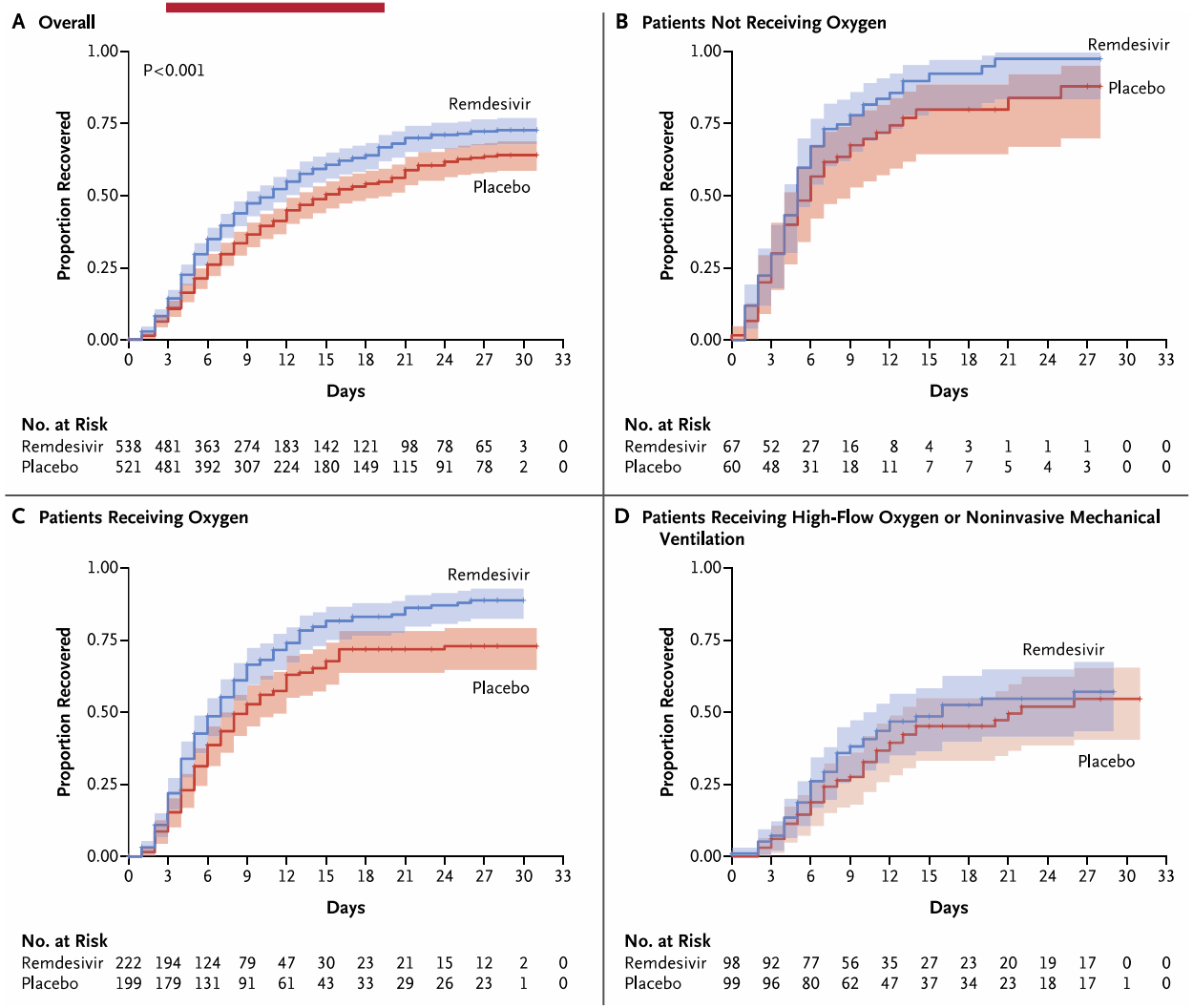
(adenosine nucleoside analogue)

vs.



Number at risk (number censored)

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



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No difference in time to clinical improvement
(HR 1.23; 95% CI 0.87-1.75)

Clinical recovery: 11 days vs 15 days
HR 1.32; 95% CI 1.12-1.55; p<0.001

Wang Y et al. Lancet 2020
http://doi.org/10.1016
Beigel JH, et al NEJM 2020; doi;10.1056

Dexamethasone in Hospitalized Patients With Covid-19

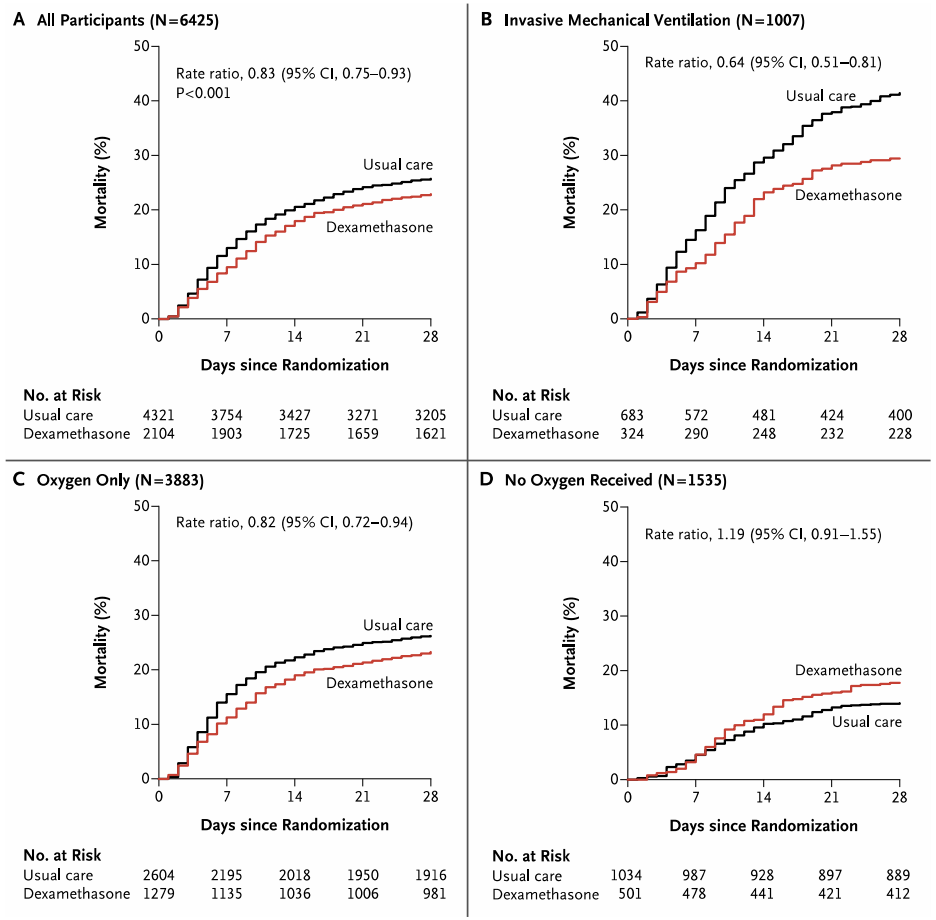

Table 2. Primary and Secondary Outcomes.

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)

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The RECOVERY Collaborative Group NEJM 2020; DOI:10.1056

Repurposed Antiviral Drugs for Covid-19 – Interim WHO Solidarity Trial Results

Table 1. Entry Characteristics According to Random Assignment, and Adherence to That Assignment.*

Variable	Any Intention-to-Treat Analysis (N=11,266)			Remdesivir vs. Its Control		Hydroxychloroquine vs. Its Control		Lopinavir vs. Its Control		Interferon vs. Its Control†	
	Entered Trial	Died in Hospital‡	28-Day Mortality§	Active (N=2743)	Control (N=2708)	Active (N=947)	Control (N=906)	Active (N=1399)	Control (N=1372)	Active (N=2050)	Control (N=2050)
	no. (%)	*no.*	*%*	*no. of patients*							
Entry characteristics											
Age											
<50 yr	3995 (35)	237	6.2	961	952	335	317	511	501	720	697
50–69 yr	5125 (45)	618	12.8	1282	1287	410	396	597	596	934	973
≥70 yr	2146 (19)	398	20.4	500	469	202	193	291	275	396	380
Respiratory support											
No supplemental oxygen at entry	3204 (28)	78	2.5	661	664	345	341	528	539	482	490
Supplemental oxygen at entry	7146 (63)	844	12.8	1828	1811	517	483	759	719	1429	1430
Already receiving ventilation	916 (8)	331	39.0	254	233	85	82	112	114	139	130
Lesions in both lungs											
No	1266 (11)	49	3.7	287	259	154	170	235	256	162	155
Yes	8832 (78)	1043	12.7	2175	2153	656	618	985	945	1723	1718
Not imaged at entry	1168 (10)	161	14.9	281	296	137	118	179	171	165	177
Previous days in the hospital											
0	3289 (29)	319	9.8	724	712	296	281	423	403	678	677
1	3713 (33)	384	10.8	917	938	317	312	442	445	681	662
≥2	4264 (38)	550	14.6	1102	1058	334	313	534	524	691	711
Geographic region											
Europe and Canada¶	2488 (22)	188	7.8	715	698	286	267	349	350	254	244
Latin America‖	1941 (17)	400	22.7	470	514	97	96	145	148	474	478
Asia and Africa**	6837 (61)	665	10.3	1558	1496	564	543	905	874	1322	1328
Other characteristics											
Male sex	6985 (62)	852	13.0	1706	1725	574	535	851	802	1303	1278
Current smoker	830 (7)	93	11.8	178	161	92	82	141	124	136	138
Coexisting conditions											
Diabetes	2768 (25)	379	14.7	707	666	199	205	341	324	489	537
Heart disease	2337 (21)	319	14.7	571	567	193	194	289	290	427	456
Chronic lung disease	635 (6)	102	17.2	151	145	62	66	95	87	114	109
Asthma	529 (5)	56	11.5	139	139	41	46	65	56	75	97
Chronic liver disease	135 (1)	21	17.2	36	41	15	14	15	23	11	22
Adherence to assigned treatment											
Percent taking trial drug midway through scheduled duration††‡‡				96	2	95	6	94	2	94	2
Percent ever reported as discharged who were still in the hospital at various times††											
On day 7				69	59	64	54	68	59	55	51
On day 14				22	19	23	20	31	22	19	18
On day 21				9	8	11	10	12	11	8	7

405 hospitals in 30 countries
11,330 adults
Remdesivir: 2750
HCQ: 954
Lopinavir: 1411
IFN beta-1a: 2063 (651 with lopinavir)
No drug: 4088
28-day mortality: 11.8%

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WHO Solidarity Trial Consortium NEJM 2020; DOI:10.1056

Repurposed Antiviral Drugs for Covid-19 – Interim WHO Solidarity Trial Results

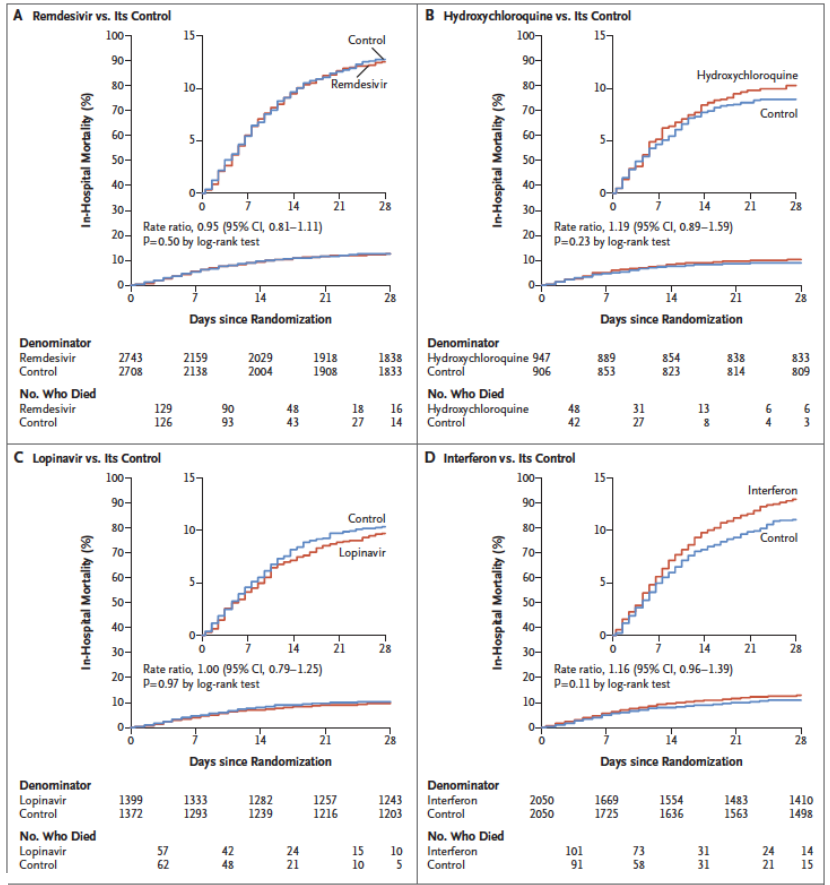
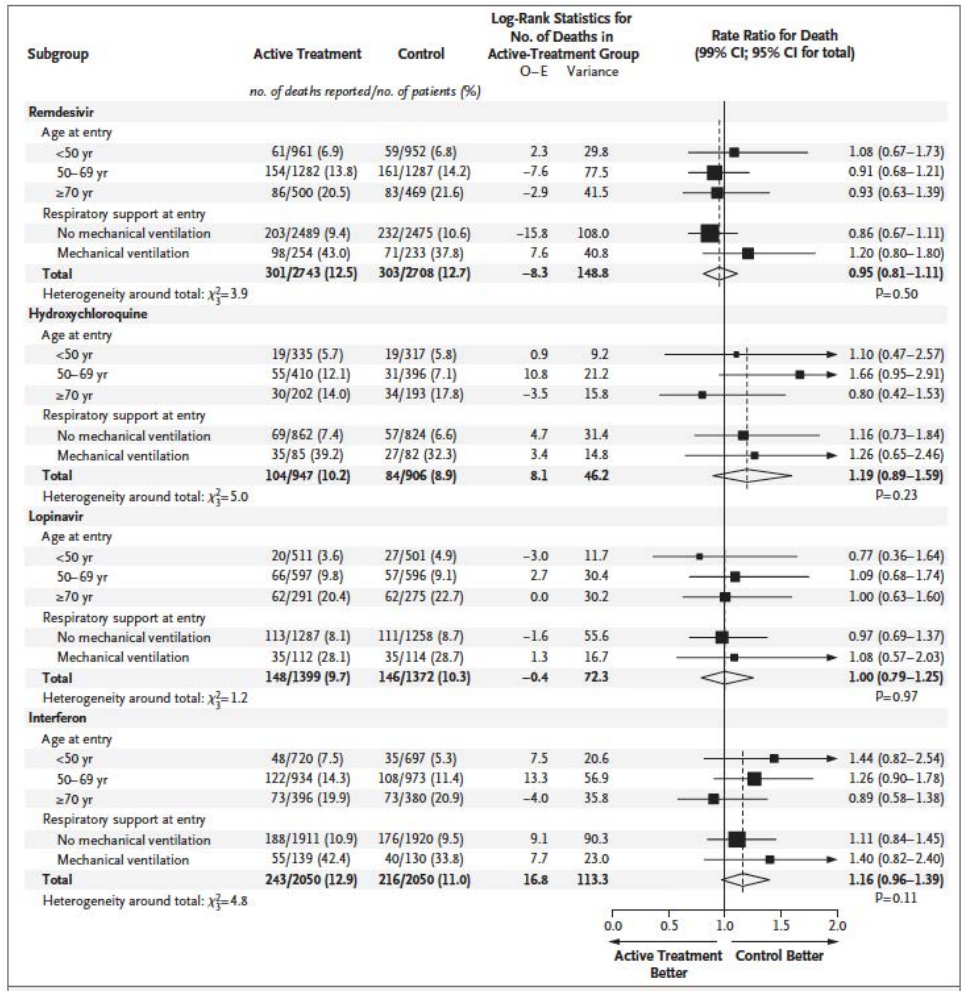


Figure 2. Effects of Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon on In-Hospital Mortality.

Shown are Kaplan–Meier graphs of in-hospital mortality at any time (the primary outcome), comparing each treatment with its control without standardization for any initial patient characteristics. Insets show the same data on an expanded y axis. The rate ratios for death were standardized for age and for ventilation status at entry. Denominators for the few events on day 0, but not thereafter, include patients with no follow-up. Numbers of deaths are by week, and then deaths after day 28. CI denotes confidence interval.



Subgroup	Active Treatment	Control	Log-Rank Statistics for No. of Deaths in Active-Treatment Group O–E	Variance	Rate Ratio for Death (99% CI; 95% CI for total)
	no. of deaths reported/no. of patients (%)				
Remdesivir					
Age at entry					
<50 yr	61/961 (6.9)	59/952 (6.8)	2.3	29.8	1.08 (0.67–1.73)
50–69 yr	154/1282 (13.8)	161/1287 (14.2)	−7.6	77.5	0.91 (0.68–1.21)
≥70 yr	86/500 (20.5)	83/469 (21.6)	−2.9	41.5	0.93 (0.63–1.39)
Respiratory support at entry					
No mechanical ventilation	203/2489 (9.4)	232/2475 (10.6)	−15.8	108.0	0.86 (0.67–1.11)
Mechanical ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Total	**301/2743 (12.5)**	**303/2708 (12.7)**	**−8.3**	**148.8**	**0.95 (0.81–1.11)**
Heterogeneity around total: χ^2_3=3.9					P=0.50
Hydroxychloroquine					
Age at entry					
<50 yr	19/335 (5.7)	19/317 (5.8)	0.9	9.2	1.10 (0.47–2.57)
50–69 yr	55/410 (12.1)	31/396 (7.1)	10.8	21.2	1.66 (0.95–2.91)
≥70 yr	30/202 (14.0)	34/193 (17.8)	−3.5	15.8	0.80 (0.42–1.53)
Respiratory support at entry					
No mechanical ventilation	69/862 (7.4)	57/824 (6.6)	4.7	31.4	1.16 (0.73–1.84)
Mechanical ventilation	35/85 (39.2)	27/82 (32.3)	3.4	14.8	1.26 (0.65–2.46)
Total	**104/947 (10.2)**	**84/906 (8.9)**	**8.1**	**46.2**	**1.19 (0.89–1.59)**
Heterogeneity around total: χ^2_3=5.0					P=0.23
Lopinavir					
Age at entry					
<50 yr	20/511 (3.6)	27/501 (4.9)	−3.0	11.7	0.77 (0.36–1.64)
50–69 yr	66/597 (9.8)	57/596 (9.1)	2.7	30.4	1.09 (0.68–1.74)
≥70 yr	62/291 (20.4)	62/275 (22.7)	0.0	30.2	1.00 (0.63–1.60)
Respiratory support at entry					
No mechanical ventilation	113/1287 (8.1)	111/1258 (8.7)	−1.6	55.6	0.97 (0.69–1.37)
Mechanical ventilation	35/112 (28.1)	35/114 (28.7)	1.3	16.7	1.08 (0.57–2.03)
Total	**148/1399 (9.7)**	**146/1372 (10.3)**	**−0.4**	**72.3**	**1.00 (0.79–1.25)**
Heterogeneity around total: χ^2_3=1.2					P=0.97
Interferon					
Age at entry					
<50 yr	48/720 (7.5)	35/697 (5.3)	7.5	20.6	1.44 (0.82–2.54)
50–69 yr	122/934 (14.3)	108/973 (11.4)	13.3	56.9	1.26 (0.90–1.78)
≥70 yr	73/396 (19.9)	73/380 (20.9)	−4.0	35.8	0.89 (0.58–1.38)
Respiratory support at entry					
No mechanical ventilation	188/1911 (10.9)	176/1920 (9.5)	9.1	90.3	1.11 (0.84–1.45)
Mechanical ventilation	55/139 (42.4)	40/130 (33.8)	7.7	23.0	1.40 (0.82–2.40)
Total	**243/2050 (12.9)**	**216/2050 (11.0)**	**16.8**	**113.3**	**1.16 (0.96–1.39)**
Heterogeneity around total: χ^2_3=4.8					P=0.11

Limitations:
1. Heterogeneity of each countries (ICU support)
2. No data on symptoms onset days (late presenters)
3. No virological data, biochemical and inflammatory markers

WHO Solidarity Trial Consortium NEJM 2020; DOI:10.1056

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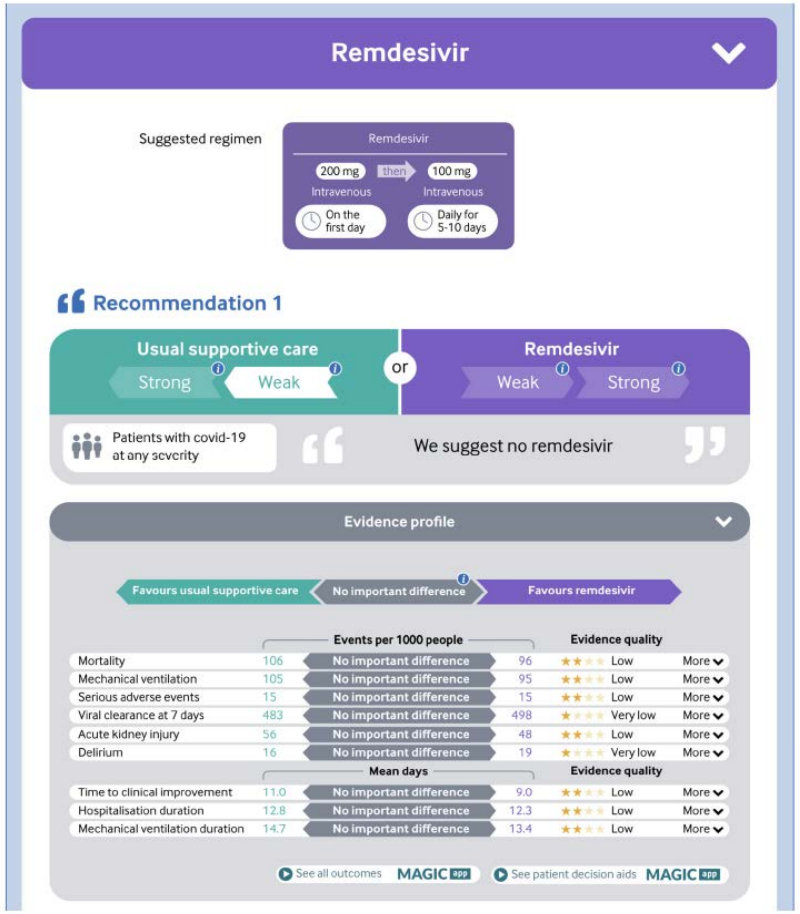
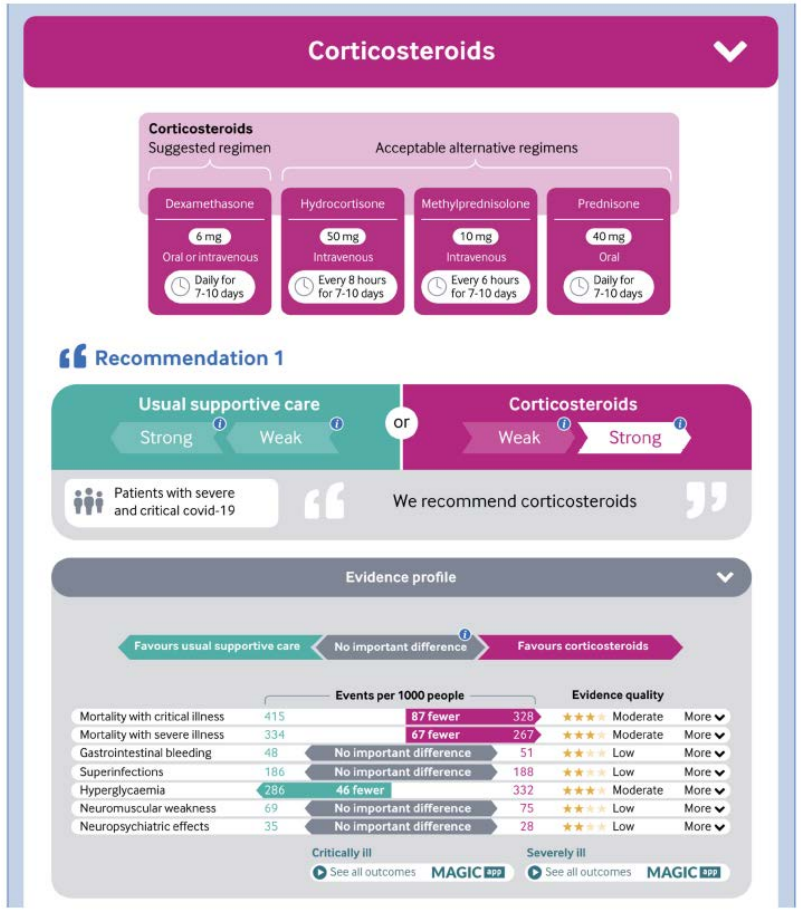
A Living WHO Guideline on Drugs for COVID-19

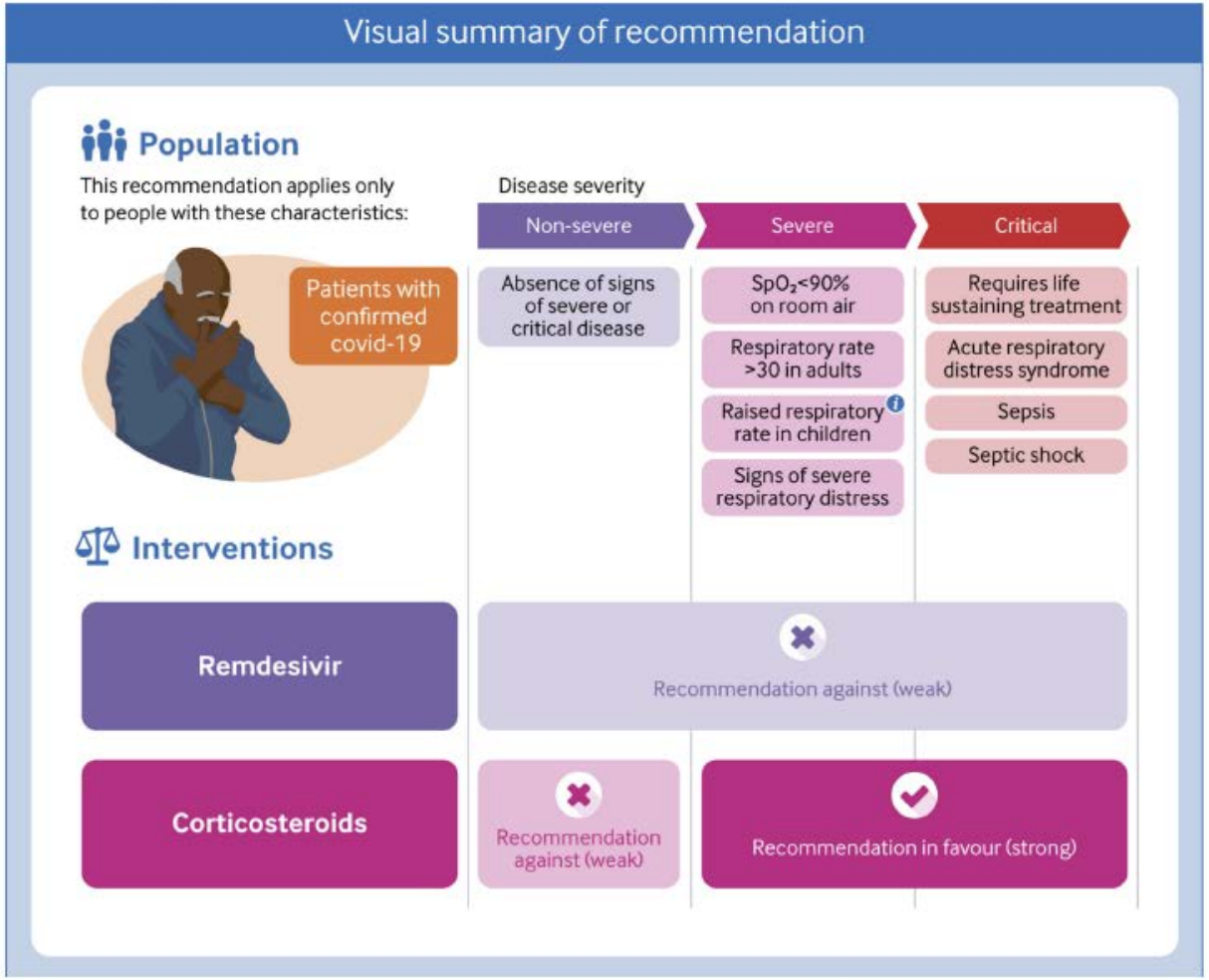




HKU Med

Rochwerg B et al. BMJ 2020;370:m3379

A Living WHO Guideline on Drugs for COVID-19



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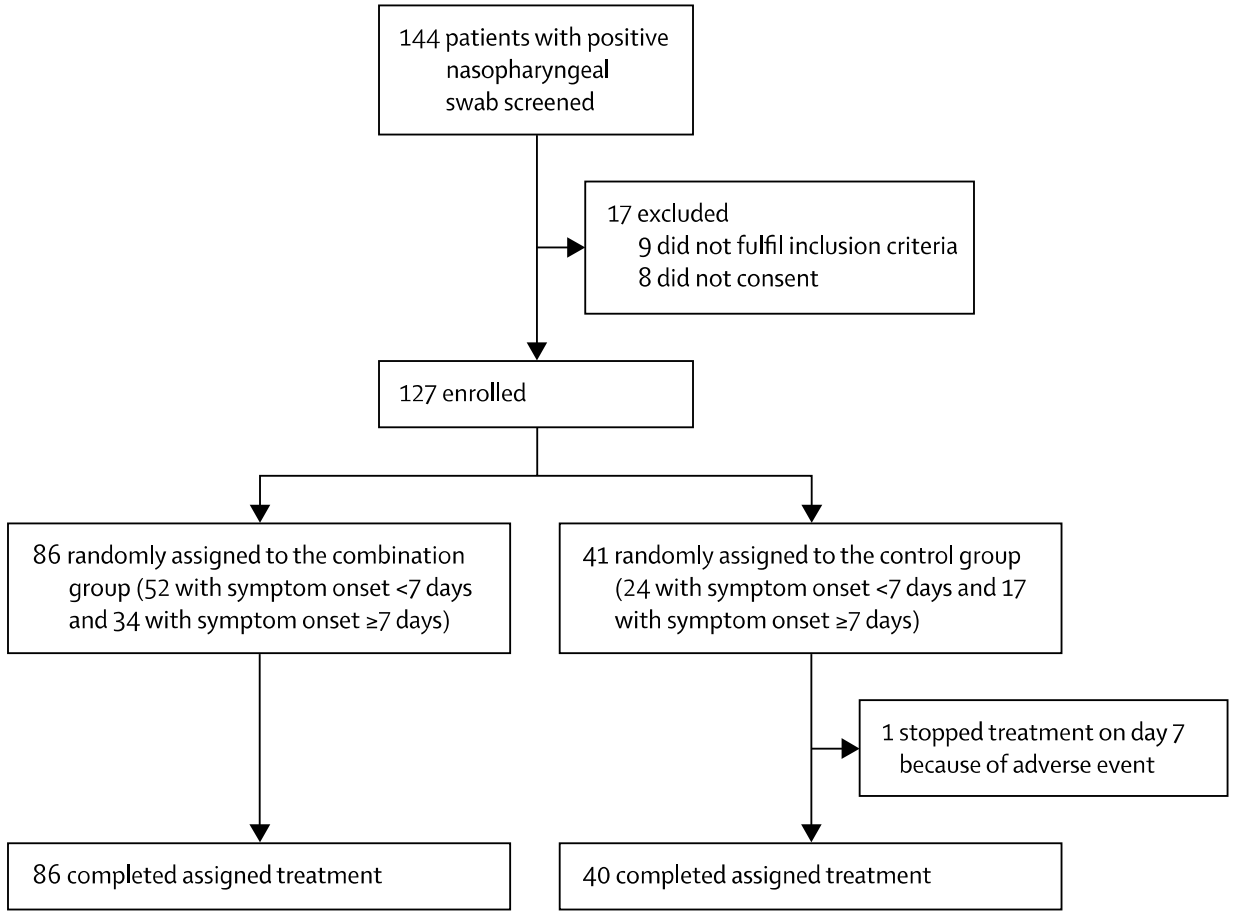
Rochwerg B et al. BMJ 2020;370:m3379

IFN beta-1b + lopinavir-ritonavir + ribavirin

Time from symptom onset to treatment
for triple therapy within combo group:
Median 4 days (3-6)

Median number of IFN beta-1b received: 2 doses



HKU Med

Hung IF et al. Lancet 2020:doi.org/10.1016/PII

IFN beta-1b + lopinavir-ritonavir + ribavirin

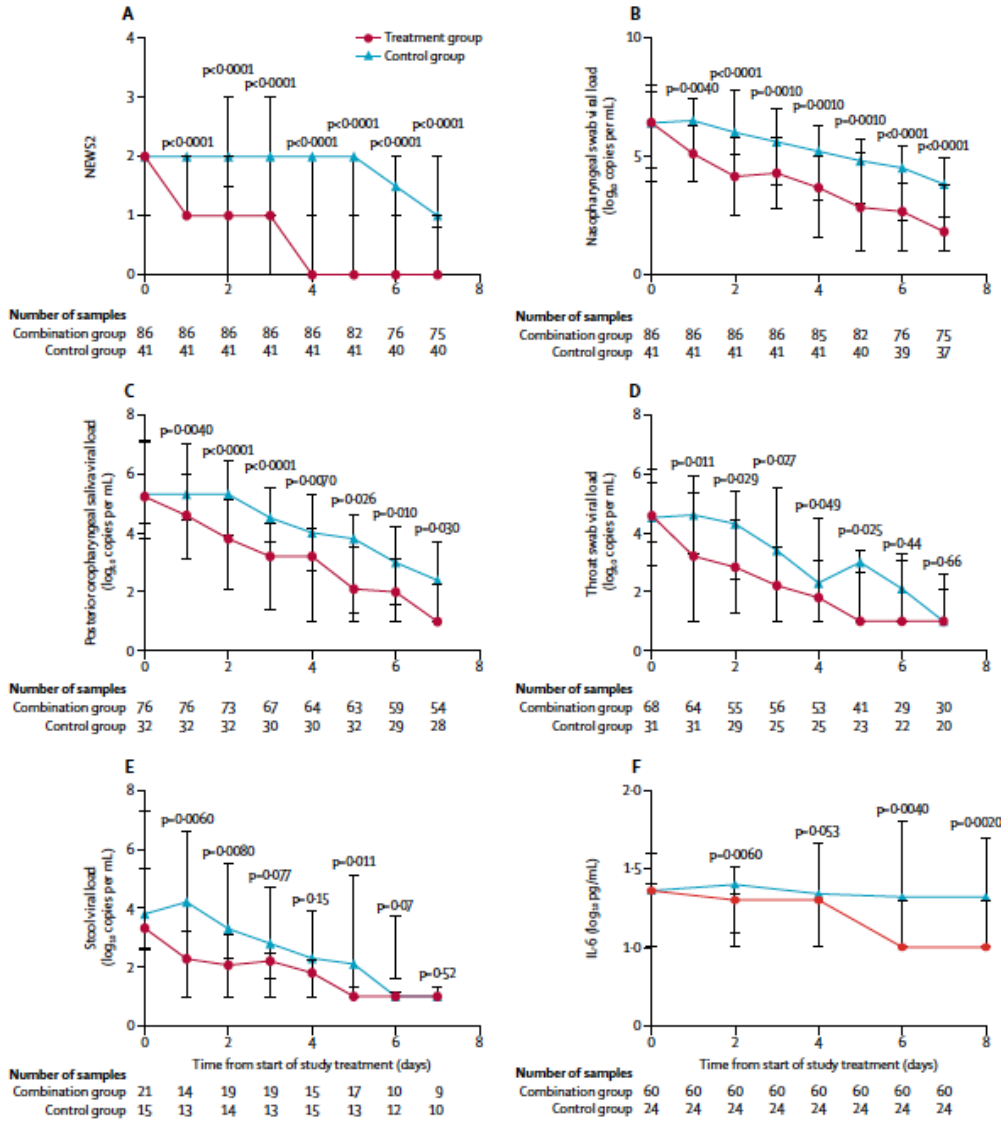
Primary outcome:
Combo group significantly shorter median time from start of treatment to negative NPS: 7 (5-11) vs. 12 (8-15) days

HR: 4.37 [95% CI 1.86-10.24} p=0.0010

No significant nsp5 mutations were identified in serial NPS

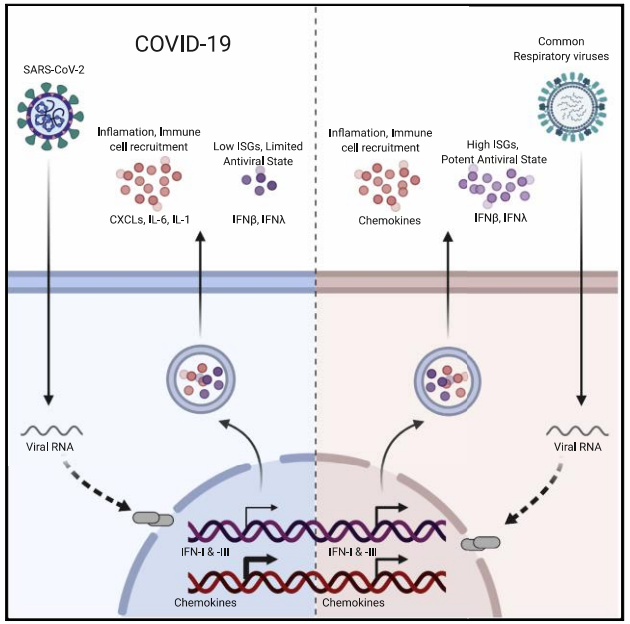
Few GI side effects and self-limiting

Conclusion:
IFN beta-1b based triple therapy is safe and superior to lopinavir-ritonavir alone



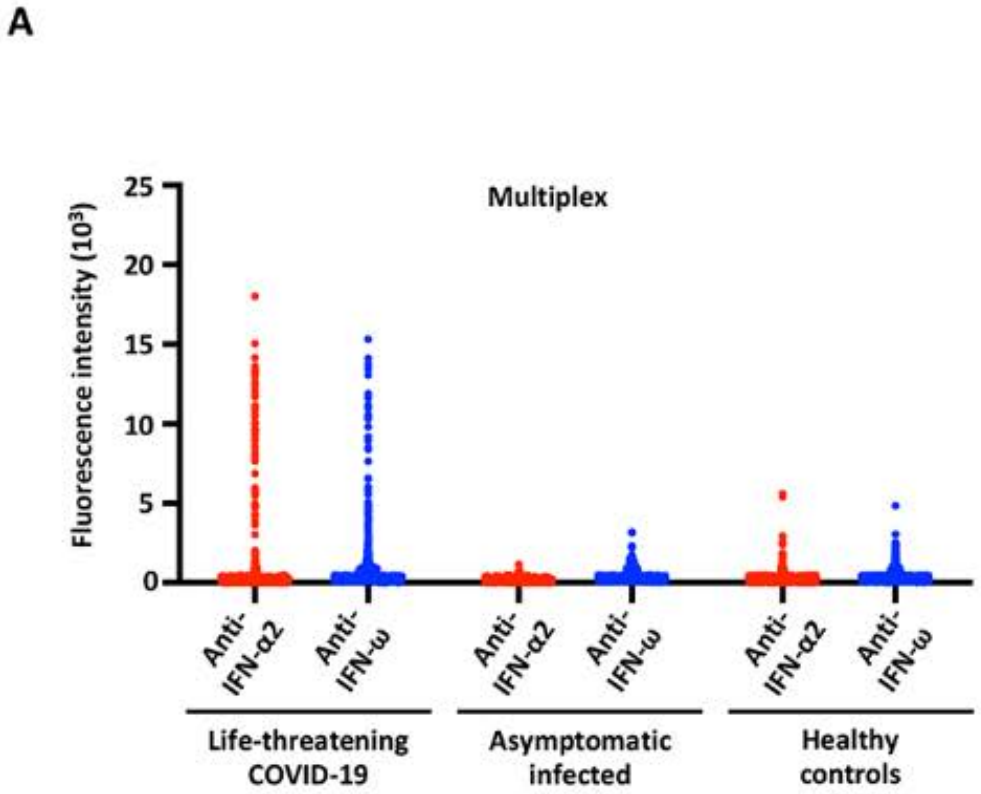
Hung IF et al. Lancet 2020:doi.org/10.1016/PII

Intrinsic Interferon in Covid-19



Highlights

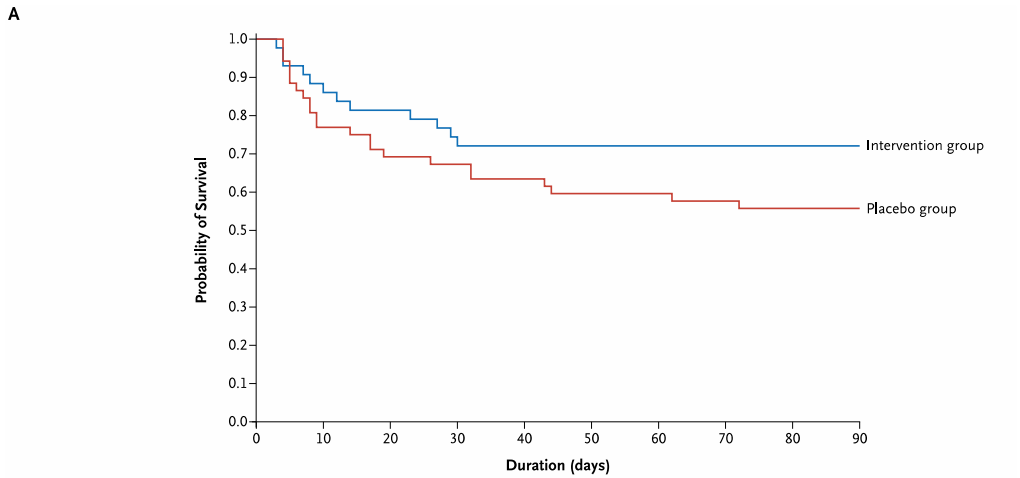
- SARS-CoV-2 infection induces low IFN-I and -III levels with a moderate ISG response
- Strong chemokine expression is consistent across *in vitro*, *ex vivo*, and *in vivo* models
- Low innate antiviral defenses and high pro-inflammatory cues contribute to COVID-19

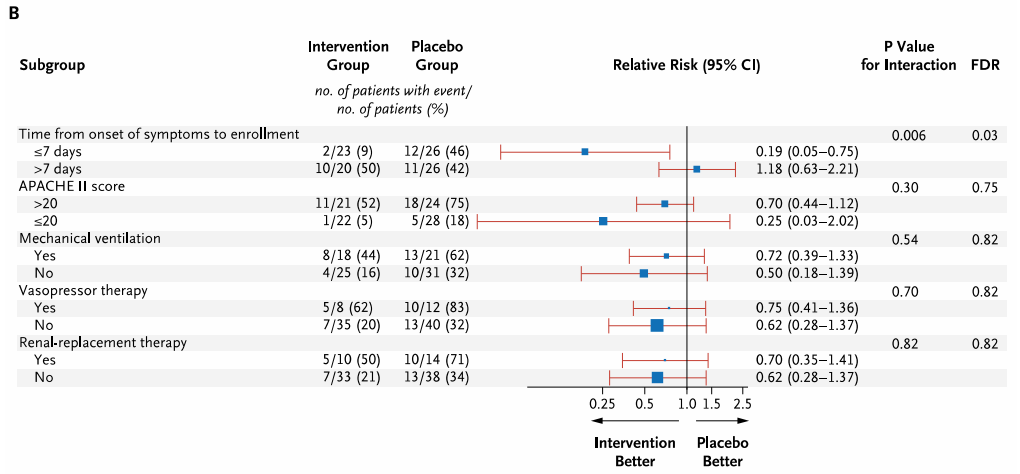


HKU Med

Blanco-Melo D, et al. Cell 2020;181:1036-45
Bastard P et al. Science 2020;eabd4585

IFN Beta-1b and Lopinavir-Ritonavir for MERS





HKU Med

Arabi YM et al. NEJM 2020;DOI:10.1056

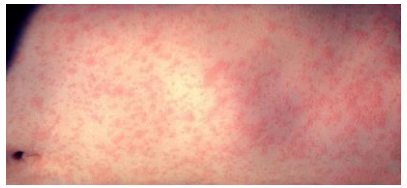
CONVALESCENT PLASMA/DERIVED PRODUCTS HAS BEEN USED IN THE TREATMENT OF PATHOGENS IN HUMANS FOR >100 YEARS

PLASMA THERAPY

Early 1890s Convalescent plasma protect against bacteria & toxin

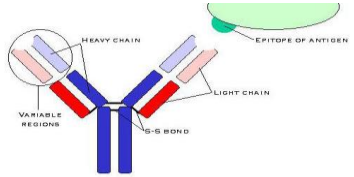
Pre-antibiotic Era

Introduction of antibiotics
1940 Penicillin



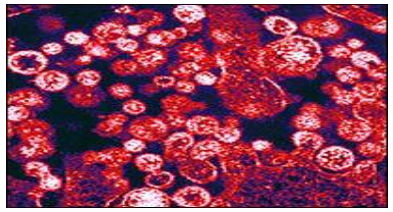
Post-antibiotic Era

1960-1990 Development of immune globulin



Emerging Viral Infection Era

Renewed interest in plasma therapy since 1980s



- **1890 – Diphtheria/ Mumps**
- **1910s - Epidemic meningitis**
- **1918 - Spanish flu (8 studies, 1703 patients)**
- **1924 - Chickenpox**
- **1935 - Measles**
- **1944 – Whooping cough**
- **WWII – Measles/Hepatitis outbreaks**
- **1961 - Smallpox**
- **1966 - Bolivian hemorrhagic fever**
- **1984 - Lassa fever (Nigeria)**
- **1986 – Junin virus (Argentina) 4433 cases**
- **1999 - Ebola (reduce mortality 80% to 13%)**
- **2003 - SARS**
- **2007 - H5N1**
- **2009/10 – Human Swine Flu H1N1**

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Annals of Internal Medicine | Review

Meta-Analysis: Convalescent Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?

Thomas C. Luke, MD, MTMH; Edward M. Kilbane, MD, MPH; Jeffrey L. Jackson, MD, MPH; and Stephen L. Hoffman, MD, DTMH

Background: Studies from the Spanish influenza era reported that transfusion of influenza-convalescent human blood products reduced mortality in patients with influenza complicated by pneumonia. Treatments for H5N1 influenza are unsatisfactory, and convalescent human plasma containing H5N1 antibodies could be an effective therapy during outbreaks and pandemics.

Purpose: To determine whether transfusion with influenza-convalescent human blood products reduced the risk for death in patients with Spanish influenza pneumonia.

Data Sources: Manual search of English-language journals from 1918 to 1925. Citations from retrieved studies were also searched.

Study Selection: Published English-language studies that had at least 10 patients in the treatment group, used convalescent blood products to treat Spanish influenza pneumonia in a hospital setting, and reported on a control or comparison group.

Data Extraction: Two investigators independently extracted data on study characteristics, outcomes, adverse events, and quality.

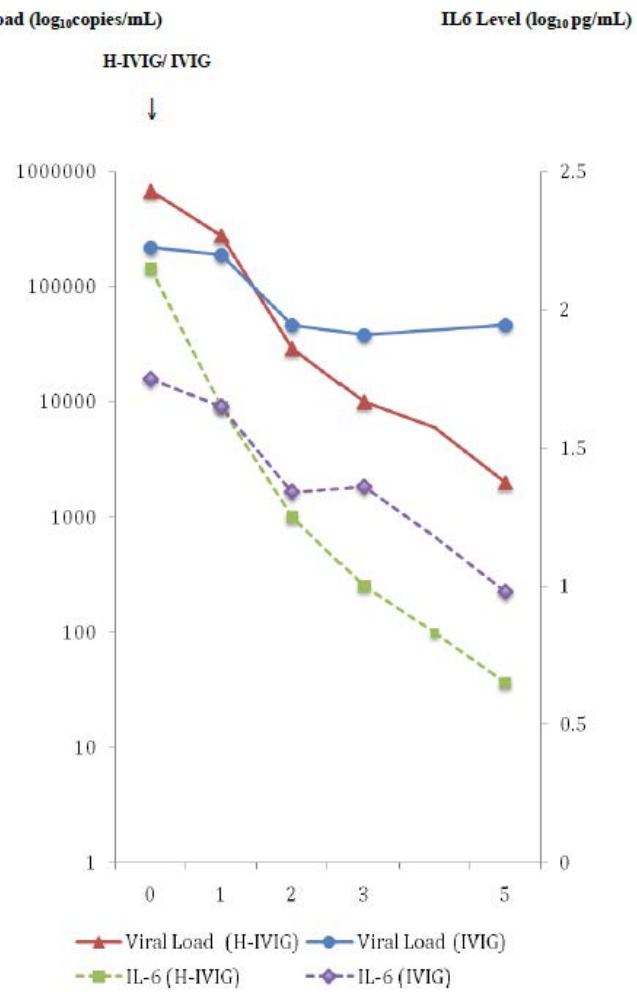
Data Synthesis: Eight relevant studies involving 1703 patients were found. Treated patients, who were often selected because of more severe illness, were compared with untreated controls with influenza pneumonia in the same hospital or ward. The overall crude case-fatality rate was 16% (54 of 336) among treated patients and 37% (452 of 1219) among controls. The range of absolute risk differences in mortality between the treatment and control groups was 8% to 26% (pooled risk difference, 21% [95% CI, 15% to 27%]). The overall crude case-fatality rate was 19% (28 of 148) among patients who received early treatment (after <4 days of pneumonia complications) and 59% (49 of 83) among patients who received late treatment (after ≥4 days of pneumonia complications). The range of absolute risk differences in mortality between the early treatment group and the late treatment group was 26% to 50% (pooled risk difference, 41% [CI, 29% to 54%]). Adverse effects included chill reactions and possible exacerbations of symptoms in a few patients.

Limitations: Studies were few and had many methodologic limitations. No study was a blinded, randomized, or placebo-controlled trial. Some pertinent studies may have been missed.

Conclusions: Patients with Spanish influenza pneumonia who received influenza-convalescent human blood products may have experienced a clinically important reduction in the risk for death. Convalescent human H5N1 plasma could be an effective, timely, and widely available treatment that should be studied in clinical trials.

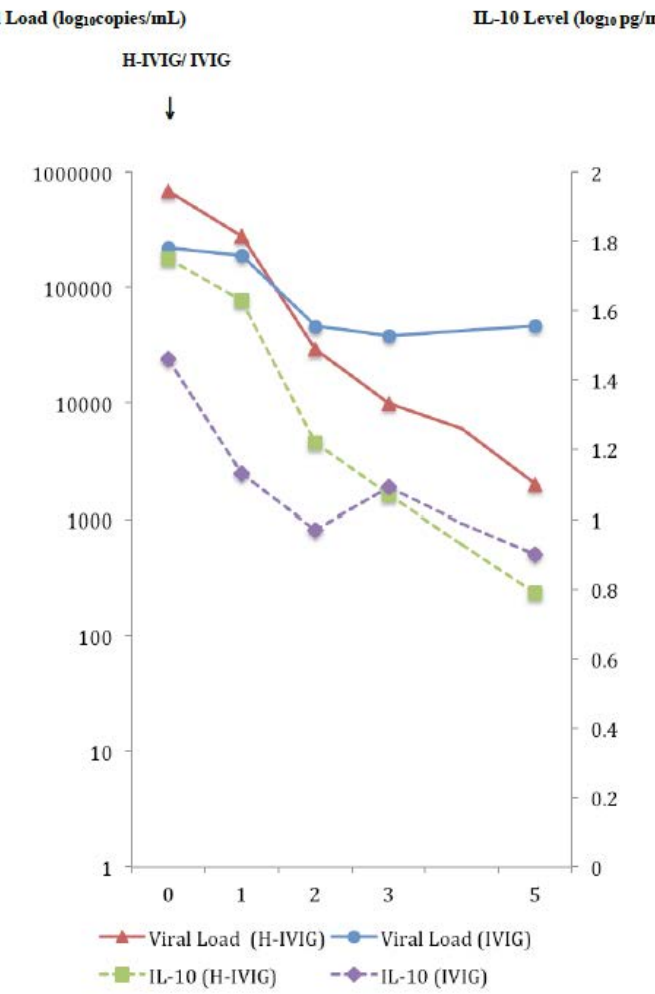
Ann Intern Med. 2006;145:599-609. www.annals.org
For author affiliations, see end of text.

Figure 3. Temporal changes of Viral Load and IL-6 Level in Treatment and Control Groups



Days after ICU admission
Treatment: H-IVIG; Control: IVIG
H-IVIG/ IVIG infused on day 0 of ICU admission.
Viral load: lowest detection limit 2.95 $\log_{10}$copies/mL; IL-6 lowest detection limit 0.2 $\log_{10}$pg/mL

Figure 4. Temporal changes of Viral Load and IL-10 Level in Treatment and Control Groups



Days after ICU admission
Treatment: H-IVIG; Control: IVIG
H-IVIG/ IVIG infused on day 0 of ICU admission.
Viral load: lowest detection limit 2.95 $\log_{10}$copies/mL; IL-10 lowest detection limit 0.2 $\log_{10}$pg/mL

HKU Med

Hung IF et al. Chest 2013;12-2907

The Effectiveness of Convalescent Plasma and H-IVIG for the Treatment of Severe Acute Respiratory Infections of Viral Aetiology: a Systematic Review and Exploratory Meta-analysis

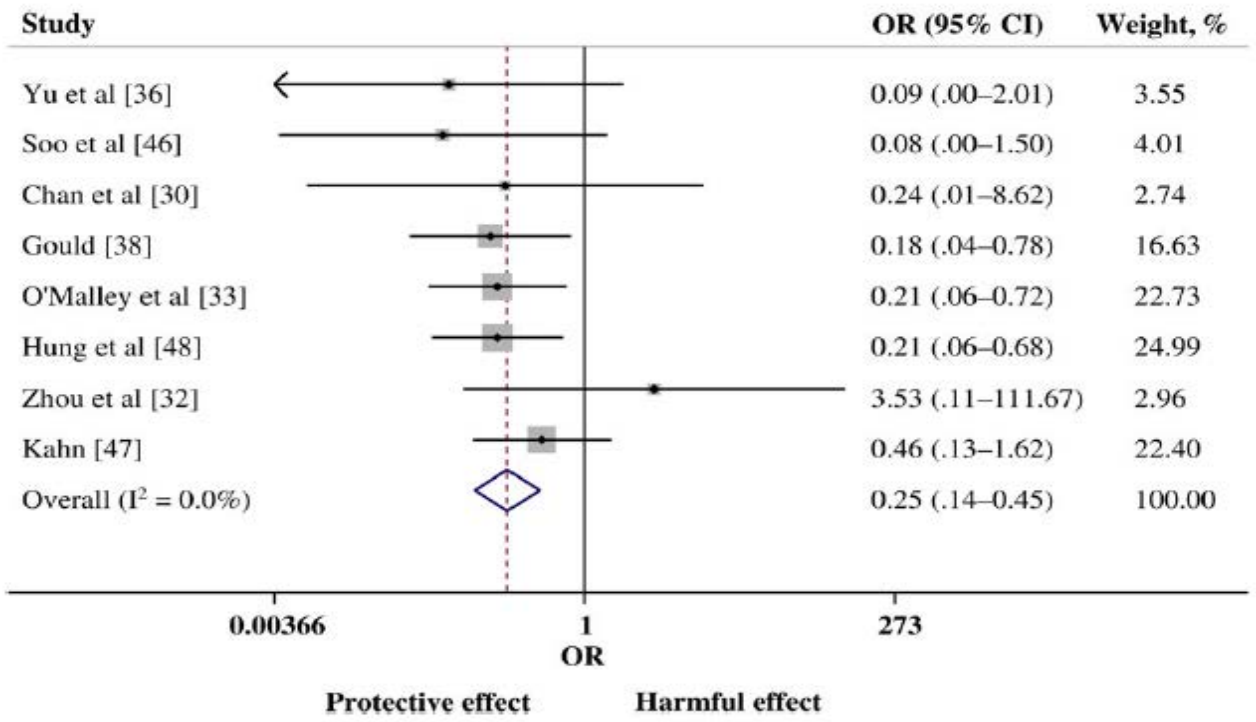


Figure 3. Forest plot of pooled odds ratios (ORs) of mortality following treatment with convalescent plasma or convalescent serum (n = 8 studies). Weights are from random-effects analysis. Abbreviation: CI, confidence interval.

HKU Med

Mair-Jenkins J. JID 2014

Immune plasma for the treatment of severe influenza: an open-label, multicentre, phase 2 randomised study

John H Beigel, Pablo Tebas, Marie-Carmelle Elie-Turenne, Ednan Bajwa, Todd E Bell, Charles B Cairns, Shmuel Shoham, Jaime G Deville, Eric Feucht, Judith Feinberg, Thomas Luke, Kanakatte Raviprakash, Janine Danko, Dorothy O'Neil, Julia A Metcalf, Karen King, Timothy H Burgess, Evgenia Aga, H Clifford Lane, Michael D Hughes, Richard T Davey, on behalf of the IRC002 Study Team*

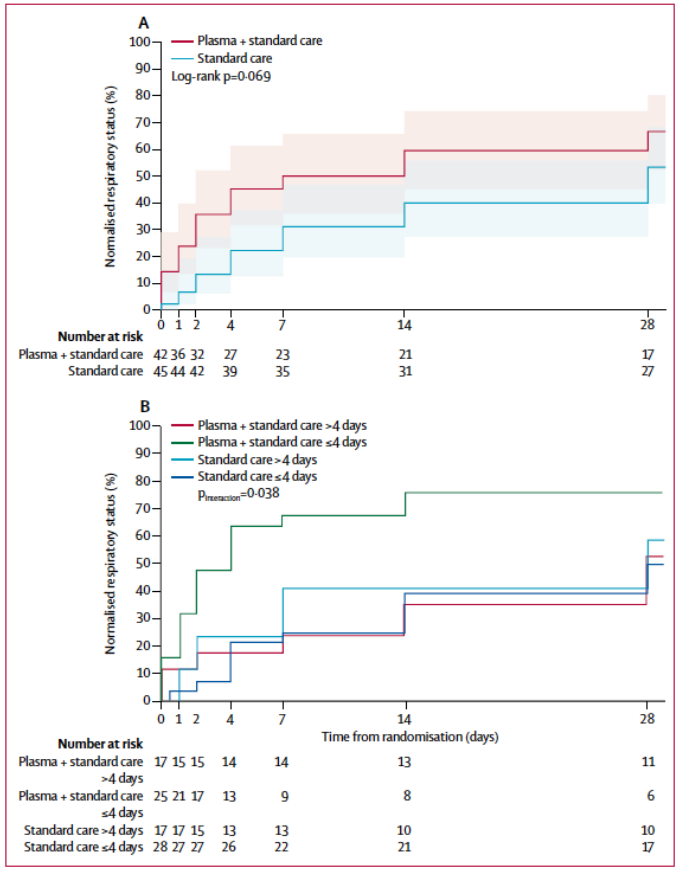


***Figure 2*: Kaplan-Meier curves of normalised respiratory status over time with intention-to-treat analyses in the primary efficacy population**
Shaded areas denote 95% CIs. Normalised respiratory status over time, by randomised treatment (A) and by randomised treatment and days from symptoms onset to randomisation. .

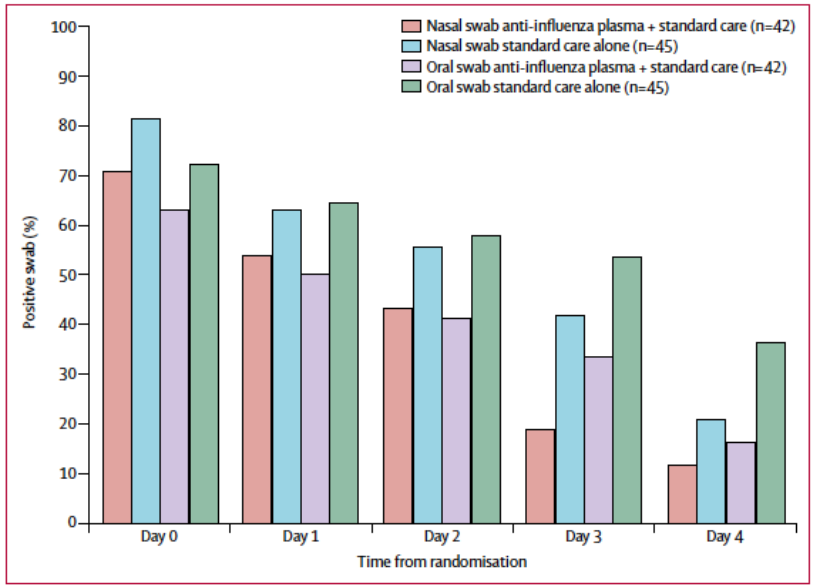


***Figure 3*: Percentage of participants with influenza virus detectable by PCR, by sample type and treatment group, by study day (intention-to-treat analysis in the primary efficacy population)**

98 subjects recruited; 2011-2015; 29 academic centres
Mortality 2% vs. 10%; (HR 0.19; p=0.093)

HKU Med

Beigel JH et al. Lancet Respir Med 2017;5:500-11

COVID-19 Convalescent Plasma

EAP to EUA transition

All program forms must be completed and submitted by November 30, 11:59 CST. Any uncompleted work will be submitted to the central IRB as a potential non-compliance.

Due to the overwhelming volume of program inquiries, it may take longer to receive a response. We appreciate your patience as we work through our communications backlog.

The US COVID Plasma Team is currently focused on collecting missing information and verifying the accuracy of information for each patient enrolled in the EAP.

Top priorities

1. Ensuring information on the patient is accurate
2. Ensuring physician information is accurate

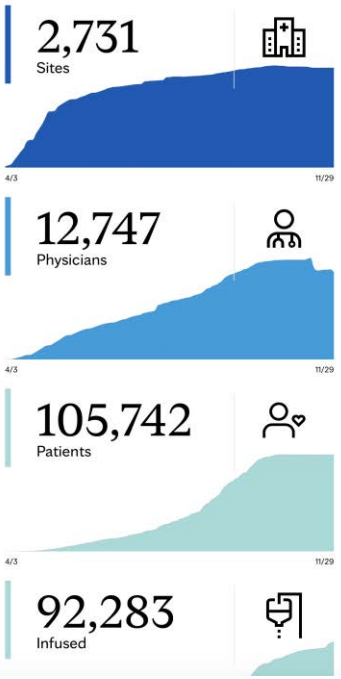
Complete data is vital

We will improve the accuracy of patient data by:

- Pursuing delinquent reporting by physicians
- Obtaining missing medical history information

Historical EAP program participation

November 29, 2020



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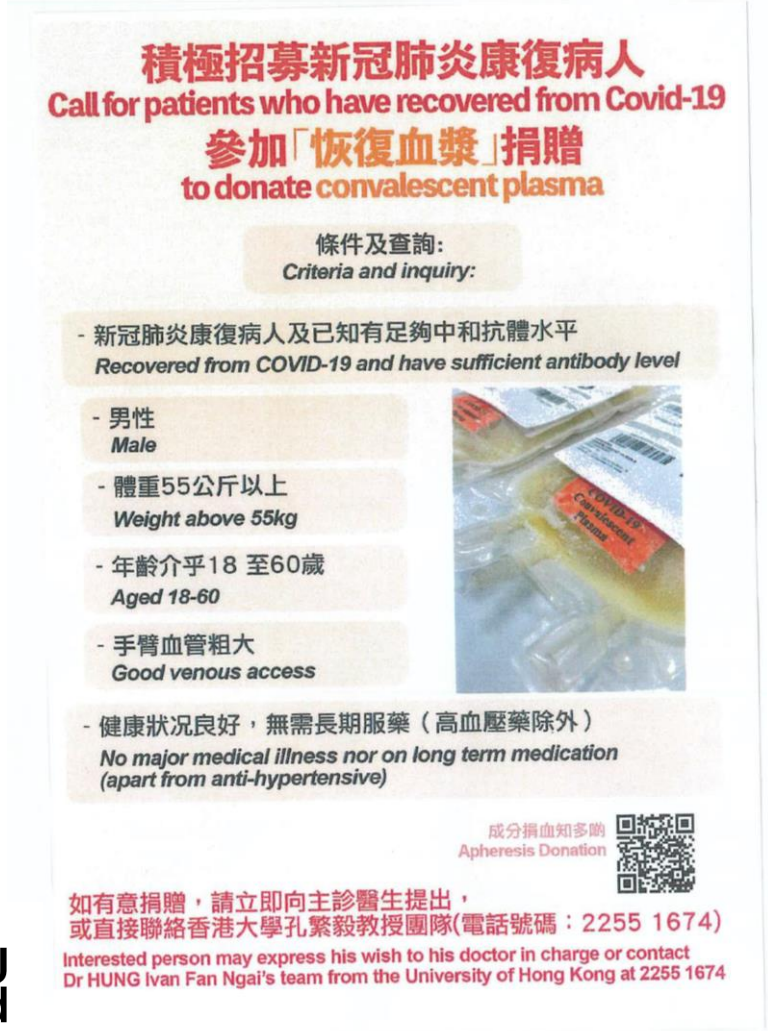
Convalescent Plasma Donation in HK



豬流感康復者血漿 提煉高免疫球蛋白

豬流感康復者血漿 提煉高免疫球蛋白

港大聯同多個醫療機構，研究提煉高免疫球蛋白，治療嚴重豬流感患者。 (蔡雄賢攝)

為了應付人類豬流感第二波的爆發，香港大學聯同多個醫療機構，收集人類豬流感康復者的血漿，提煉出高免疫球蛋白，用來醫治嚴重人類豬流感患者。

現時治療人類豬流感主要是用抗病毒藥物特敏福等，香港大學醫學院內科學系臨床助理教授孔繁毅表示，最近有研究顯示人類豬流感病人對抗流感藥物特敏福出現抗藥性，另一種吸入式的藥物樂感清，較難用於有肺部實質化的嚴重患者身上。

香港大學會聯同醫管局、紅十字會和衞生防護中心將展開以高免疫球蛋白的研究計劃，研究需收集人類豬流感康復者的血漿，製成可透過靜脈注射的高免疫球蛋白，用來醫治嚴重人類豬流感患者。

蛋白可在明年一月完成

高免疫球蛋白需 8 周製造，儲存期為兩年，希望可在明年 1 月前，製造出有關的蛋白。提煉血漿治病已有超過 100 年的歷史，在 1918 年西班牙 H1N1 流感大爆發時亦是提煉血漿治病。這是全球首次使用抗人類豬流感免疫球蛋白治療嚴重人類豬流感患者。

是項研究計劃將分兩個階段進行。第一階段主要是招募已康復之病人、篩選和收集血漿，並提煉成高免疫球蛋白。預計找出有 640 名捐贈者，收集 420 升的血漿。

紅十字會會主動聯絡人類豬流感的康復者，最快可在下周進行收集的程序。

而第二階段則是利用此高免疫球蛋白以治療嚴重人類豬型流感患者。

研究人員會在冬季時，進行一項雙盲研究，將收集到的血漿，提煉成高免疫球蛋白，並注射入 63 名嚴重人類豬流感的患者身上，同時亦有 63 名嚴重患者接受普通免疫球蛋白的治療，以評估高免疫球蛋白的成效，分析有關的死亡率、深切治療日數、留院日數、病毒數量和肺部損壞程度。

HK Red Cross 2020

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Convalescent Plasma Therapy in Severe Covid-19

Figure 2. Time to Clinical Improvement in Patients With COVID-19

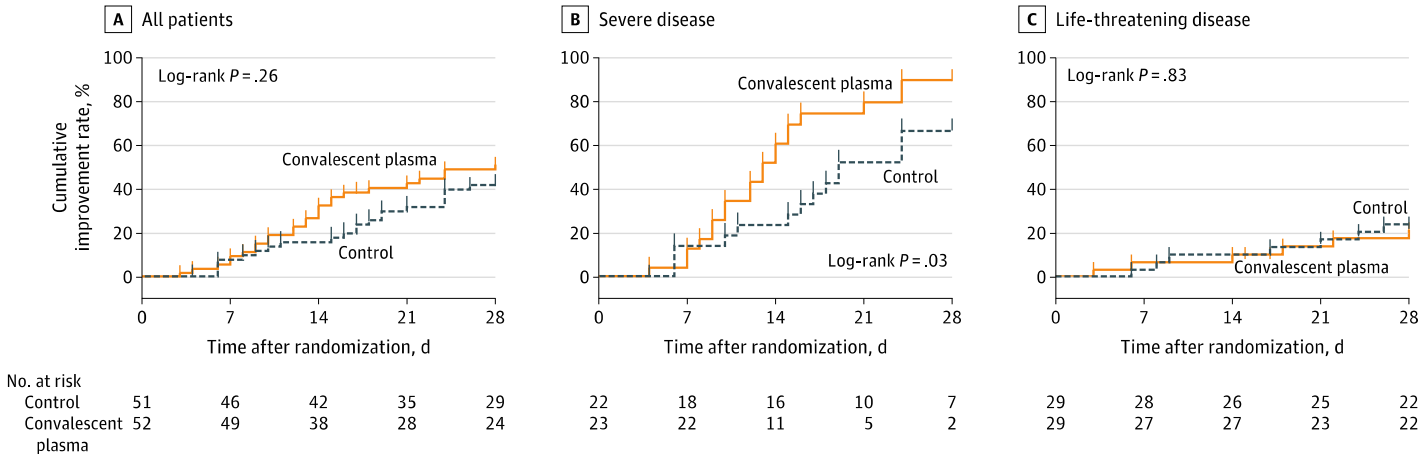
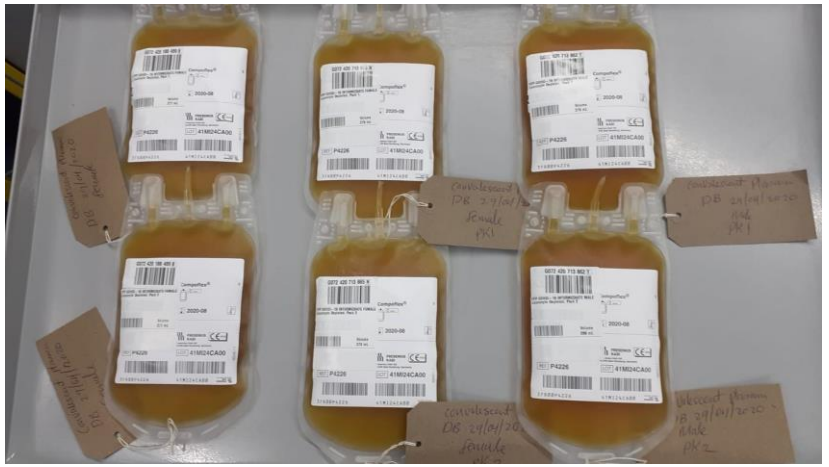


Table 3. Primary and Secondary Clinical Outcomes at Day 28[a] (continued)

	Convalescent plasma group (n = 52)	Control group (n = 51)	Absolute difference (95% CI)[b]	Effect estimate (95% CI)	*P* value[c]
Mortality at 28 d, No./total (%)	8/28 (28.6)	10/28 (35.7)	−7.1% (−31.5% to 17.2%)	OR, 0.72 (0.23-2.22)	.57
Time from randomization to death, median (IQR), d[d]	Indeterminate (22.00-Indeterminate)	Indeterminate (15.00-Indeterminate)	−0.04 (−3.86 to 3.77)	HR, 0.86 (0.34-2.17)	.74
Viral nucleic acid negative rate, No./total (%)					
At 24 h	14/26 (53.8)	4/23 (17.4)	36.5% (11.8% to 61.1%)	OR, 5.54 (1.47-20.86)	.01
At 48 h	19/26 (73.1)	7/23 (30.4)	42.6% (17.3% to 68.0%)	OR, 6.20 (1.79-21.46)	.003
At 72 h	22/26 (84.6)	8/23 (34.8)	49.8% (25.9% to 73.7%)	OR, 10.31(2.63-40.50)	<.001



HKU Med

Ling Li, et al. JAMA;2020;324:460-470

Convalescent Plasma Therapy

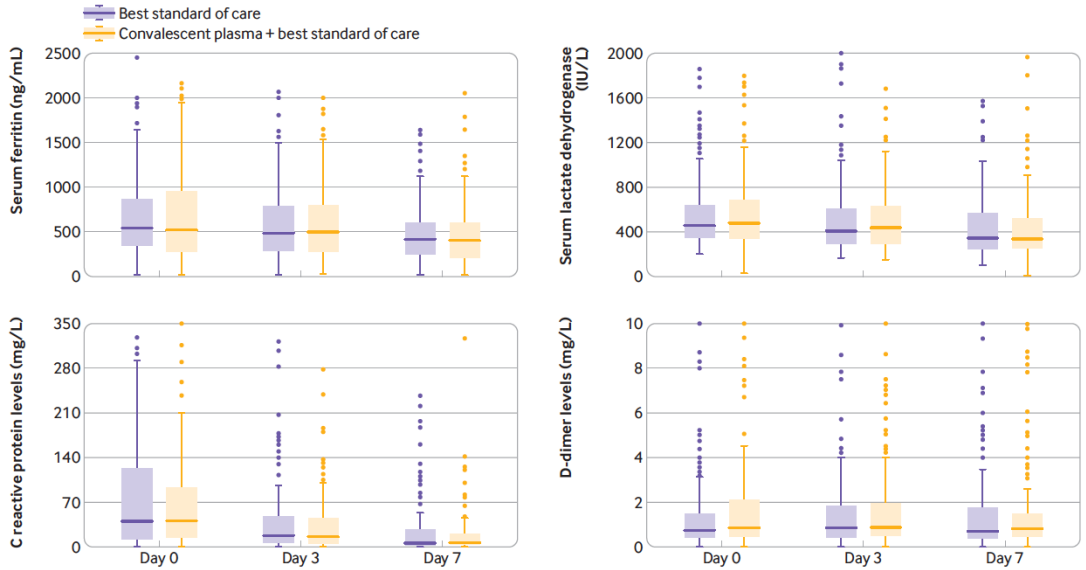


Fig 2 | Comparison of biomarkers between intervention (convalescent plasma therapy+best standard of care) and control (best standard of care) arms, by days post-enrolment. The dark line in the box represents the median and the upper and lower edges of the box represent the interquartile range. The upper and lower extreme of the whiskers represent the upper and lower range, respectively, excluding outliers

Table 3 | Comparison of primary outcomes between convalescent plasma therapy (intervention arm) and best standard of care (control arm) in intention-to-treat analysis

Composite outcome	No (%) in intervention arm (n=235)	No (%) in control arm (n=229)	Unadjusted risk difference (95% CI)	Unadjusted risk ratio (95% CI)	Adjusted risk ratio (95% CI)
All cause mortality at 28 days or progression to severe disease	44 (19)	41 (18)	0.008 (–0.062 to 0.078)	1.04 (0.71 to 1.54)	1.07 (0.73 to 1.58)

Adjusted for trial sites and presence of diabetes mellitus.

Table 4 | Comparison of secondary outcomes between convalescent plasma therapy (intervention arm) and best standard of care (control arm) in per protocol analysis (n=451). Values are numbers (percentages) unless stated otherwise

Secondary outcomes	Intervention arm	Control arm	Unadjusted risk ratio (95% CI)
Resolution of symptoms on day 7:			
Shortness of breath (n=362)	140/183 (76)	119/181 (66)	1.16 (1.02 to 1.32)
Fever (n=138)	66/67 (98)	65/71 (92)	1.08 (0.99 to 1.16)
Cough (n=274)	102/127 (80)	111/147 (76)	1.06 (0.94 to 1.2)
Fatigue (n=306)	114/156 (73)	92/153 (60)	1.21 (1.02 to 1.42)
Negative conversion of SARS-CoV-2 RNA:			
Day 3 (n=367)	79/184 (43)	67/183 (37)	1.2 (0.9 to 1.5)
Day 7 (n=342)	117/173 (68)	93/169 (55)	1.2 (1.04 to 1.5)
Median (interquartile range) total hospital stay (days); No with event	14 (10-19); n=227	13 (10-18); n=224	0.2*
Median (interquartile range) total days of respiratory support; No with event	9 (6-13); n=227	10 (6-13); n=224	0.7*
Median (interquartile range) days of respiratory support post-enrolment; No with event	6 (3-9); n=227	6 (4-10); n=224	0.5*
Type of mechanical ventilation during hospital stay:			
Invasive	19/227 (8)	19/224 (8)	0.99 (0.54 to 1.81)
Non-invasive	31/227 (14)	37/224 (16)	0.8 (0.5 to 1.3)
Vasopressor support after enrolment	10/225 (4)	8/221 (4)	1.2 (0.5 to 3.05)

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; RNA=ribonucleic acid.
*Continuous variables—Mann-Whitney U test applied and P values reported. All changes are measured from day of enrolment.

HKU Med

Agarwal A et al. BMJ 2020;371:m3939

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Convalescent Plasma (N=228)	Placebo (N=105)
Median age (IQR) — yr	62.5 (53–72.5)	62 (49–71)
Age category — no. (%)		
<65 yr	126 (55.3)	54 (51.4)
≥65 to <80 yr	75 (32.9)	43 (41)
≥80 yr	27 (11.8)	8 (7.6)
Female sex — no. (%)	67 (29.4)	41 (39.0)
Median time to onset of symptoms (IQR) — days	8 (5–10)	8 (5–10)
Coexisting conditions — no. (%)		
No other conditions	80 (35.1)	37 (35.2)
Body-mass index >30	104 (45.6)	52 (49.5)
Hypertension	111 (48.7)	48 (45.7)
Diabetes	40 (17.5)	21 (20)
Chronic obstructive pulmonary disease	23 (10.1)	2 (1.9)
Asthma	9 (3.9)	5 (4.8)
Chronic renal failure	10 (4.4)	4 (3.8)
Hematologic cancer	4 (1.8)	3 (2.9)
Solid tumors	23 (10.1)	11 (10.5)
Current tobacco use	6 (2.6)	6 (5.7)
Previous tobacco use	101 (44.3)	37 (35.2)
Congestive heart failure	8 (3.5)	3 (2.9)
Thromboembolic disease	5 (2.2)	2 (1.9)
Previous medications used — no. (%)		
ACEI or ARB 2	69 (30.3)	32 (30.5)
Frequent or recent use of NSAID	37 (16.2)	13 (12.4)
Anticoagulation	14 (6.1)	6 (5.7)
Corticosteroids	7 (3.1)	2 (1.9)
Immunosuppressants	6 (2.6)	3 (2.9)
Statins	61 (26.8)	21 (20)
Laboratory values		
Median total SARS-CoV-2 antibody titer (IQR)	1/50 (0–1:800)	1:50 (0–1:1600)
Negative total SARS-CoV-2 antibody titer — no./total no. (%)	65/145 (44.8)	34/70 (48.6)
Median D-dimer level (IQR) — ng/ml	697 (470–1150)	797 (550–1224)
Median ferritin level (IQR) — ng/ml	939 (441–1634)	645 (362–1180)
Severity inclusion criteria — no. (%)		
Oxygen saturation <93% at FiO_2 0.21	224 (98.2)	100 (95.2)
mSOFA or SOFA ≥2	32 (14)	17 (16.2)
Hospitalization area at enrollment — no. (%)		
Emergency department	11 (4.8)	3 (2.9)
General ward	150 (65.8)	77 (73.3)
Critical care unit	67 (29.4)	25 (23.8)

Table 2. Clinical Outcomes in Patients Who Received Convalescent Plasma as Compared with Placebo.*

Outcomes	Convalescent Plasma (N=228)	Placebo (N=105)	Odds Ratio or Hazard Ratio (95% CI)	P value
Primary outcome, clinical status at 30 days — no. of patients (%)			Odds ratio, 0.81 (0.50–1.31)	0.396
Death	25 (11)	12 (11.4)		
Invasive ventilatory support	19 (8.3)	10 (9.5)		
Hospitalized with supplemental oxygen requirement	5 (2.2)	2 (1.9)		
Hospitalized without supplemental oxygen requirement	8 (3.5)	1 (1)		
Discharged without full return to baseline physical function	30 (13.2)	8 (7.6)		
Discharged with full return to baseline physical function	141 (61.8)	72 (68.6)		
Secondary Outcomes				
Median time from intervention (IQR) — days				
To hospital discharge	13 (8–30)	12 (7–ND)	Subhazard ratio, 1 (0.76–1.32)	—
To discharge from the ICU	ND (8–ND)	ND (6–ND)	Subhazard ratio, 0.94 (0.48–1.82)	—
To complete restoration of physical functions†	15 (9–ND)	15 (7–ND)	Subhazard ratio, 0.89 (0.66–1.18)	—
To start of invasive ventilation	ND (9–ND)	ND	Subhazard ratio, 1.14 (0.72–1.81)	—
To death	ND	ND	Hazard ratio, 0.93 (0.47–1.86)	—
To improvement of 2 categories in the ordinal outcome or hospital discharge within 30 days	12 (7–29)	12 (6–ND)	Hazard ratio, 1 (0.76–1.32)	—
Adverse events — no (%)				
Any event	153 (67.1)	66 (62.9)	Odds ratio, 1.21 (0.74–1.95)	—
Serious event	54 (23.7)	19 (18.1)	Odds ratio, 1.40 (0.78–2.51)	—
Infusion-related event	13 (5.7)	2 (1.9)	Odds ratio, 3.13 (0.69–14.11)	—

HKU Med

Simonovich VA et al. NEJM 2020:10:1056

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

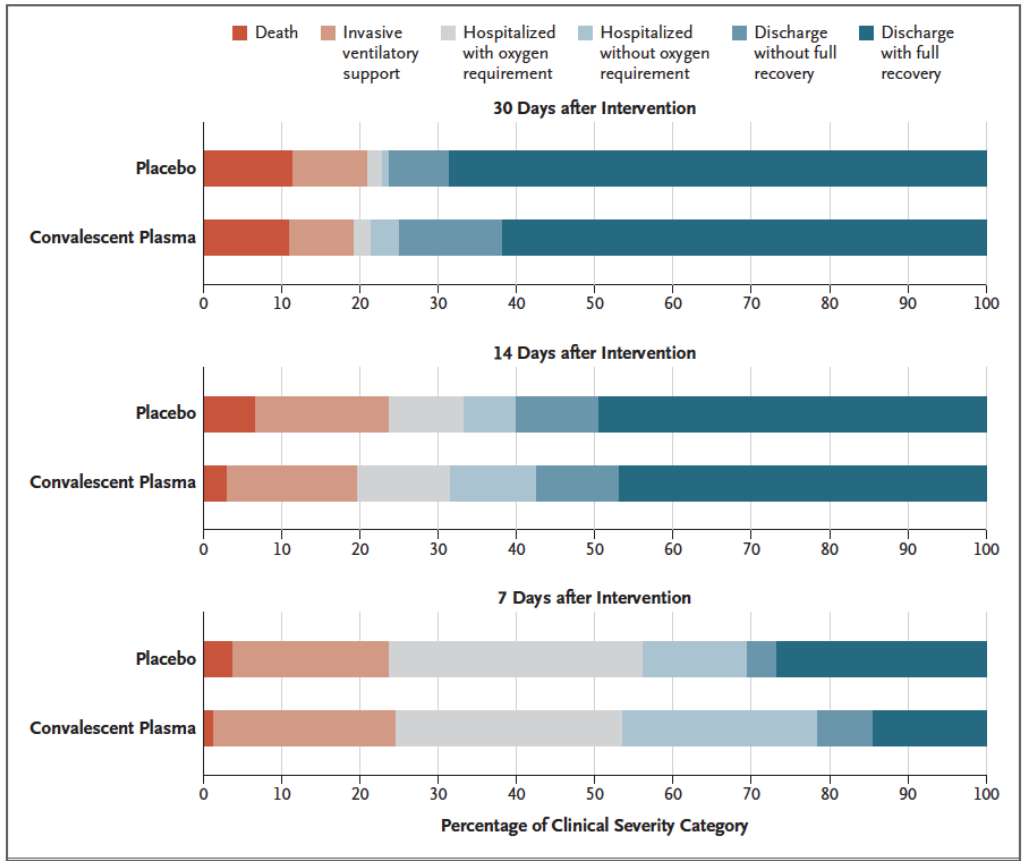


Figure 2. Clinical Outcomes among Patients Treated with Convalescent Plasma as Compared with Placebo.
The distribution of the clinical status according to the ordinal scale is shown at 30 days, 14 days, and 7 days after the intervention.

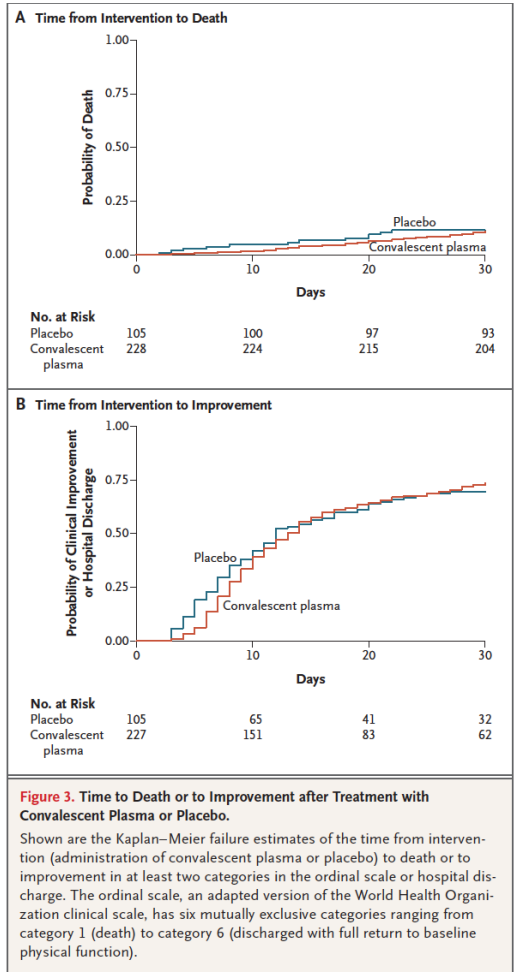


Figure 3. Time to Death or to Improvement after Treatment with Convalescent Plasma or Placebo.
Shown are the Kaplan–Meier failure estimates of the time from intervention (administration of convalescent plasma or placebo) to death or to improvement in at least two categories in the ordinal scale or hospital discharge. The ordinal scale, an adapted version of the World Health Organization clinical scale, has six mutually exclusive categories ranging from category 1 (death) to category 6 (discharged with full return to baseline physical function).

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Simonovich VA et al. NEJM 2020:10:1056

REGN-CoV2 Antibody Cocktail

- Two monoclonal Ab: REGN10933
  and REGN10987
- Derived from humanized mice and human convalescent plasma
- Ab against SARS-CoV-2 spike protein
- Two Ab to prevent rapid mutational escape
- RECOVERY trial

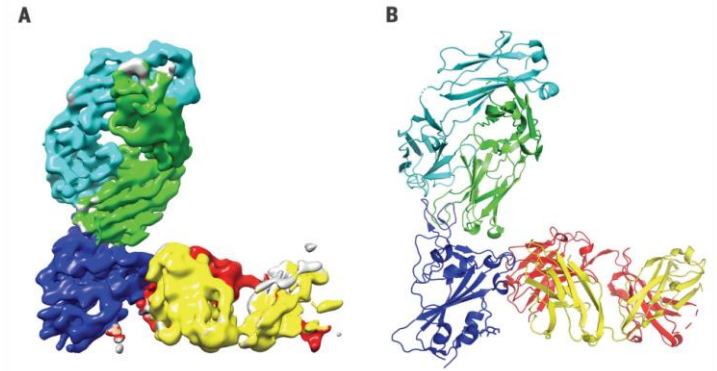
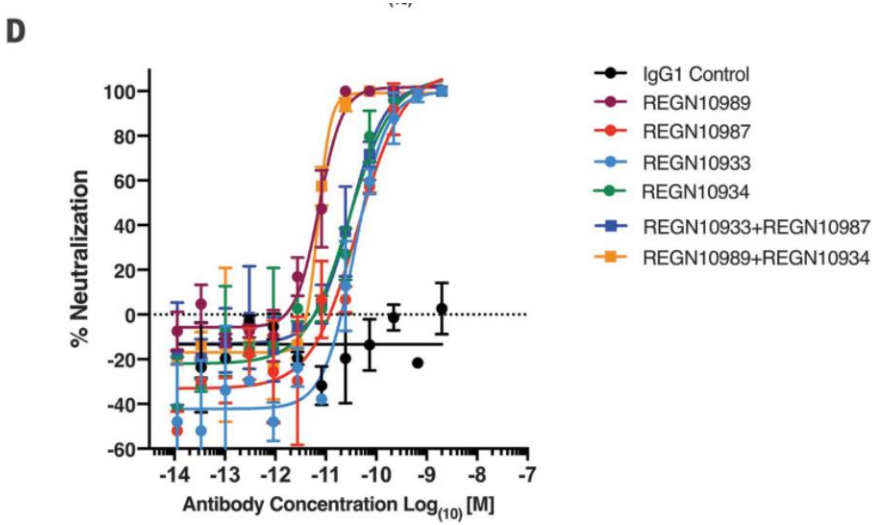


Fig. 4. Complex of REGN10933 and REGN10987 with the SARS-CoV-2 RBD. (A) 3.9-Å cryo-EM map of the REGN10933-RBD-REGN10987 complex, colored according to the chains in the refined model (B). RBD is colored dark blue; REGN10933 heavy and light chains are green and cyan, respectively; and REGN10987 heavy and light chains are yellow and red, respectively.



Hansen J et al. Science 369;1010-1014
Baum A et al. Science 369;1014-1018

HKU Med

Tocilizumab (anti-IL6)

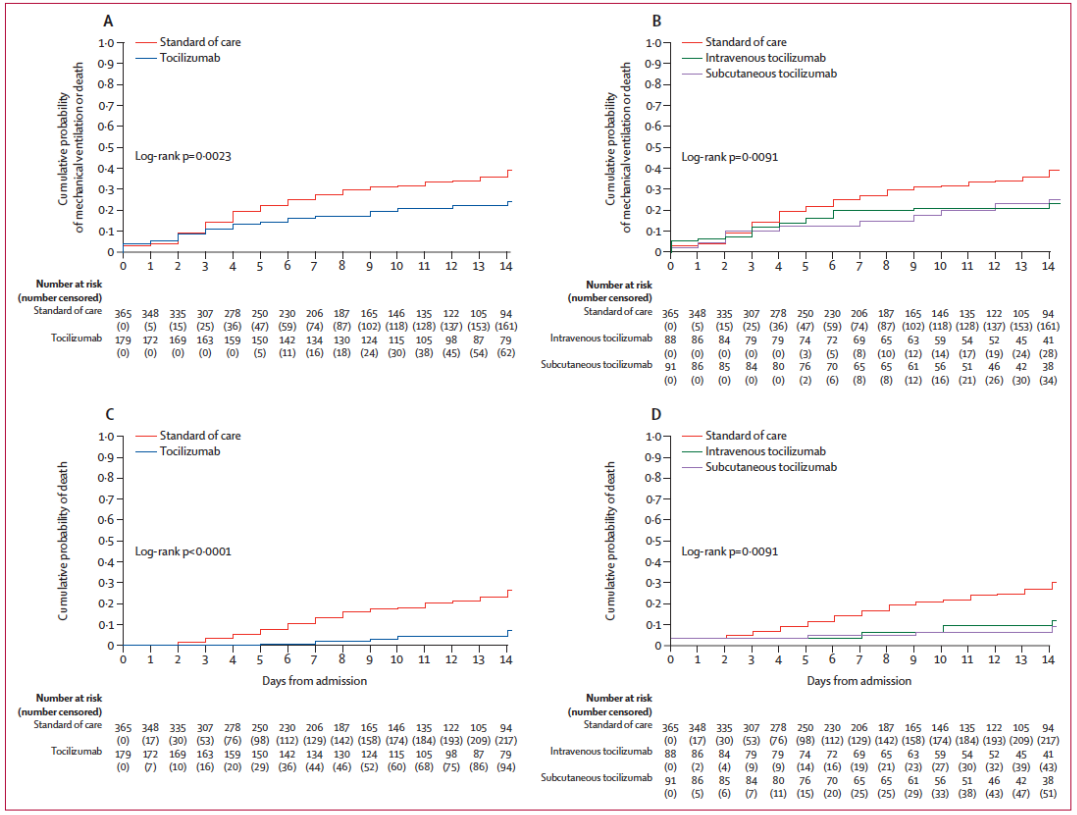
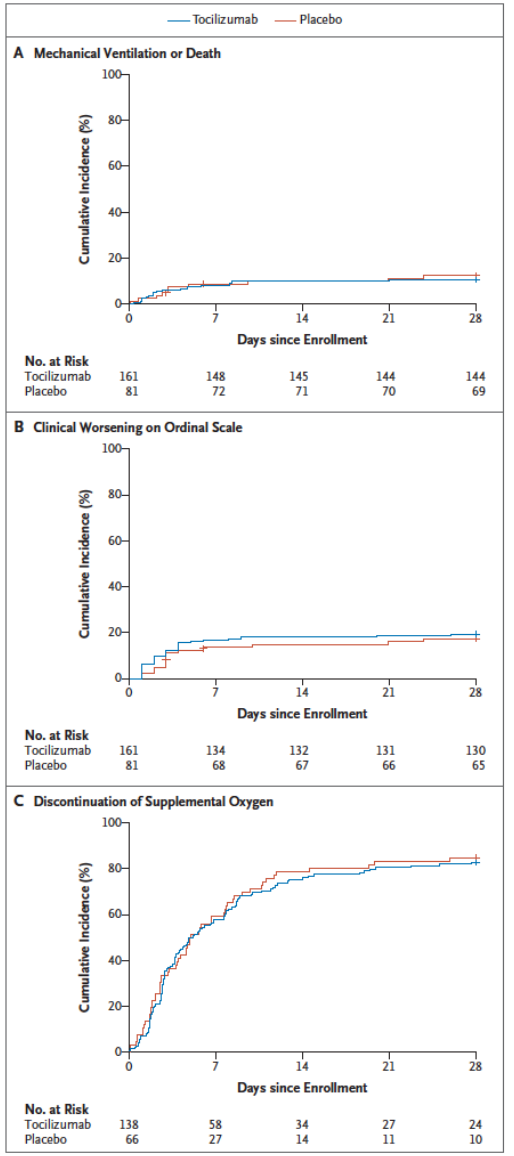


Figure 2: Kaplan-Meier estimates of the cumulative probability of mechanical ventilation or death (A, B) and death (C, D) by treatment group



Guaradldi G et al. 2020 Lancet Rheumatology
Stone JH et al. NEJM 2020

Anticoagulant treatment in Covid-19

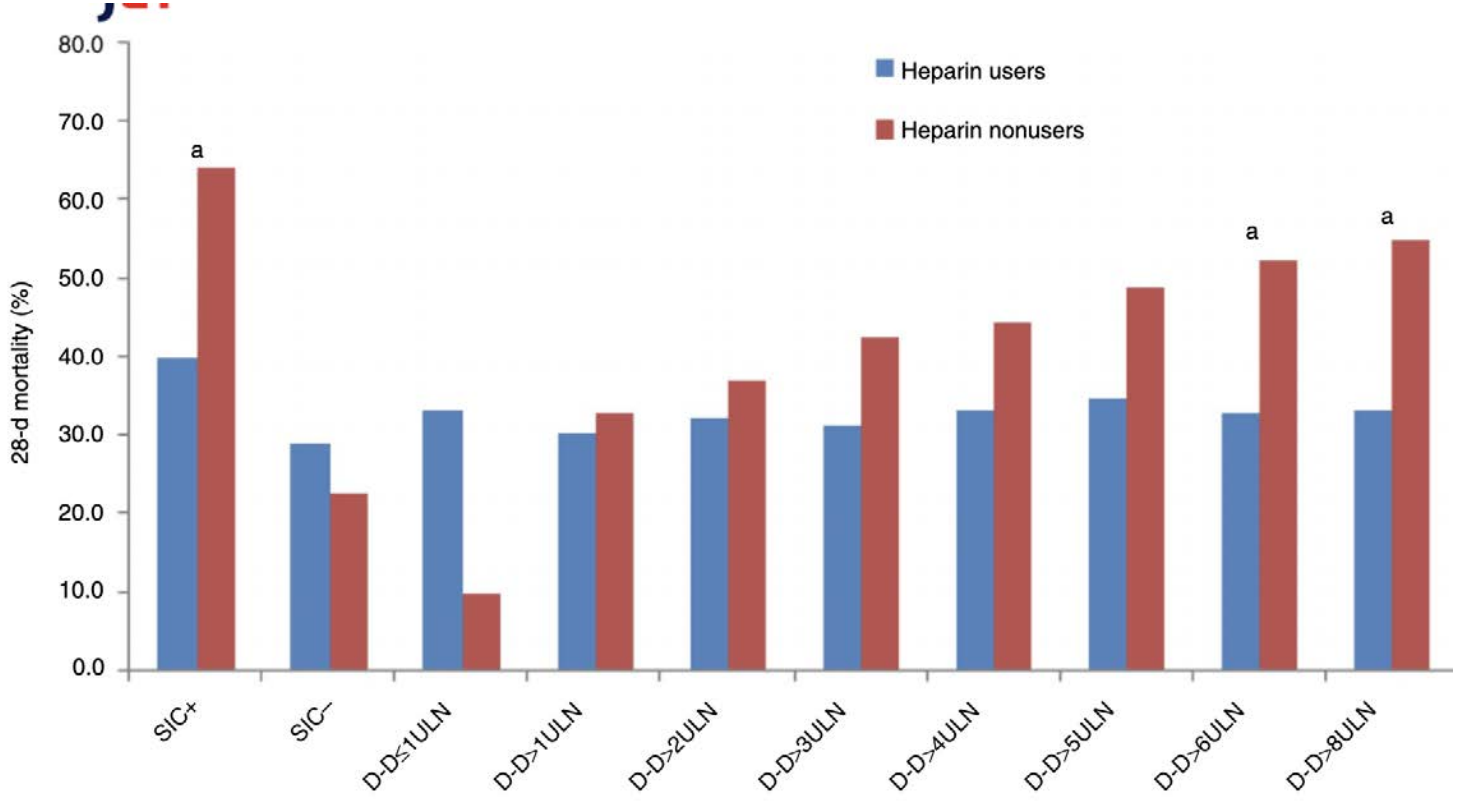
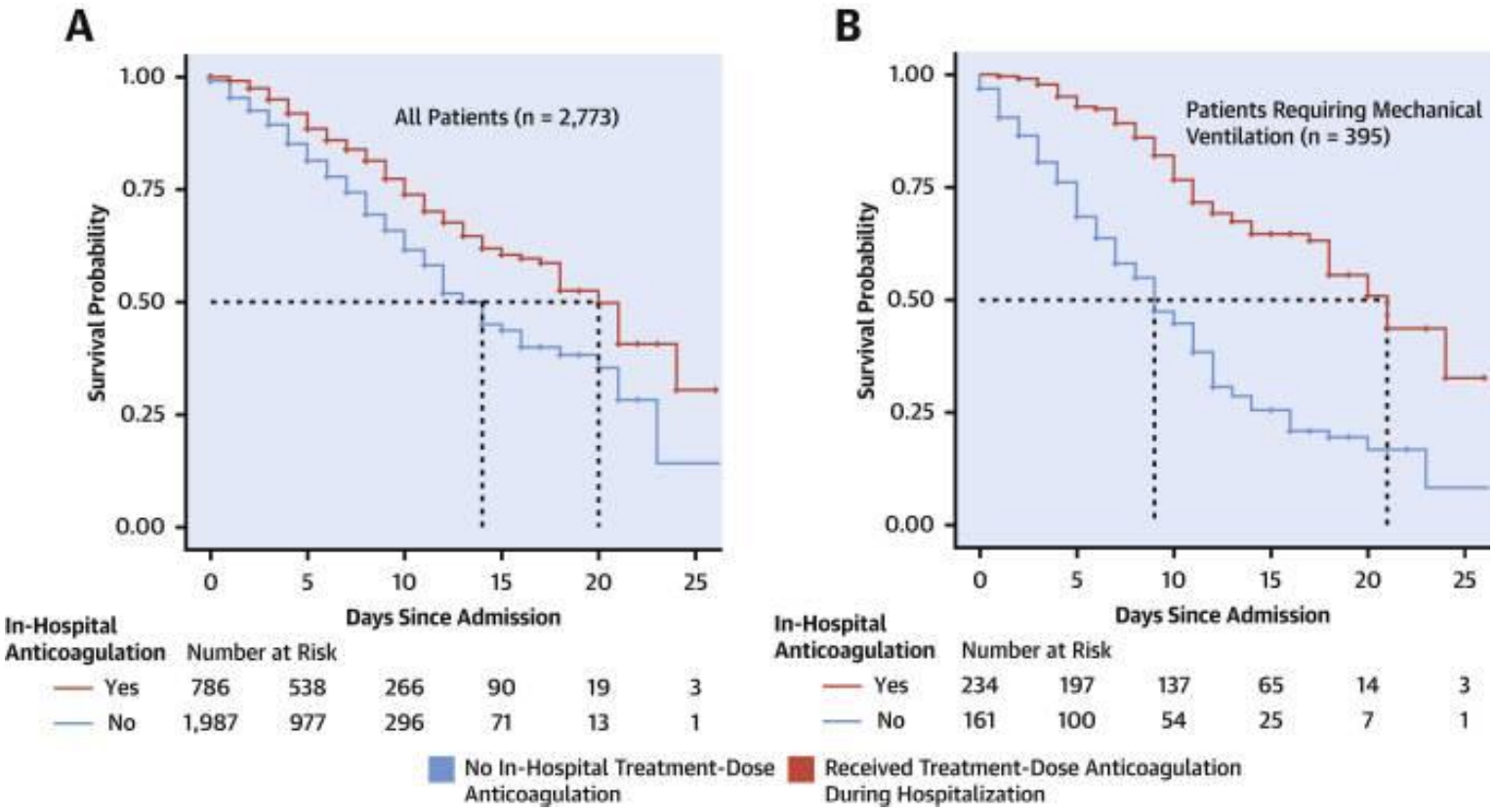


FIGURE 2 A paired bar chart showing the mortality between heparin users and nonusers in stratified patients. D-D, D-dimer; SIC+, SIC score ≥ 4; SIC−, SIC score < 4; ULN, upper limit of normal (0.5 μg/mL); a, $P < .05$ between heparin users and nonusers

HKU Med

Tang N et al. J Thromb Haemost 2020

Treatment Dose Anticoagulant with In-Hospital Survival in Patients with Covid-19



Mortality 29.1% vs 62.7%

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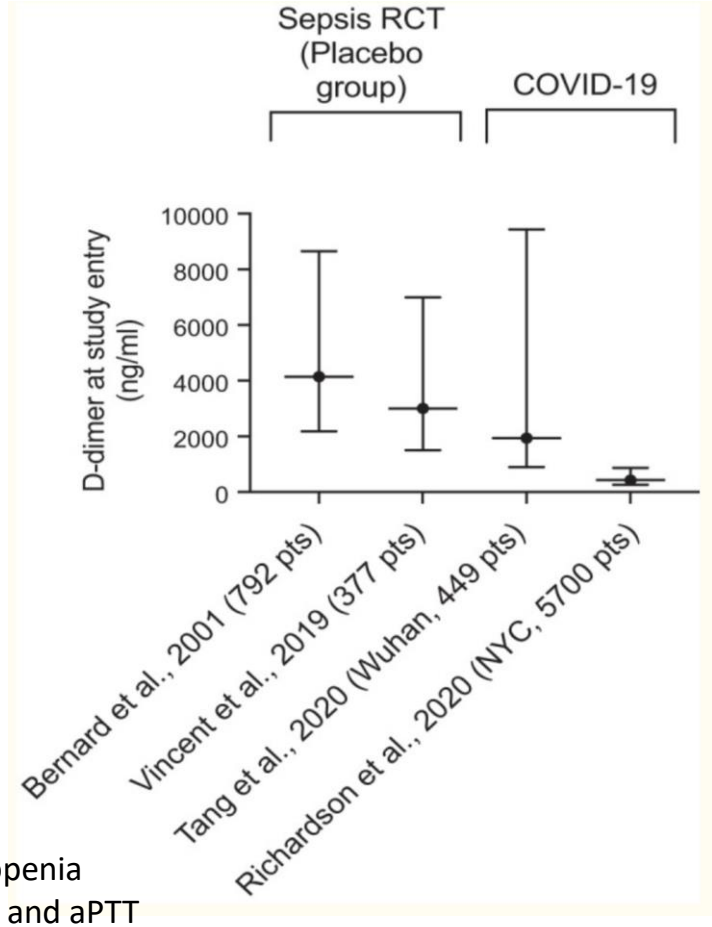
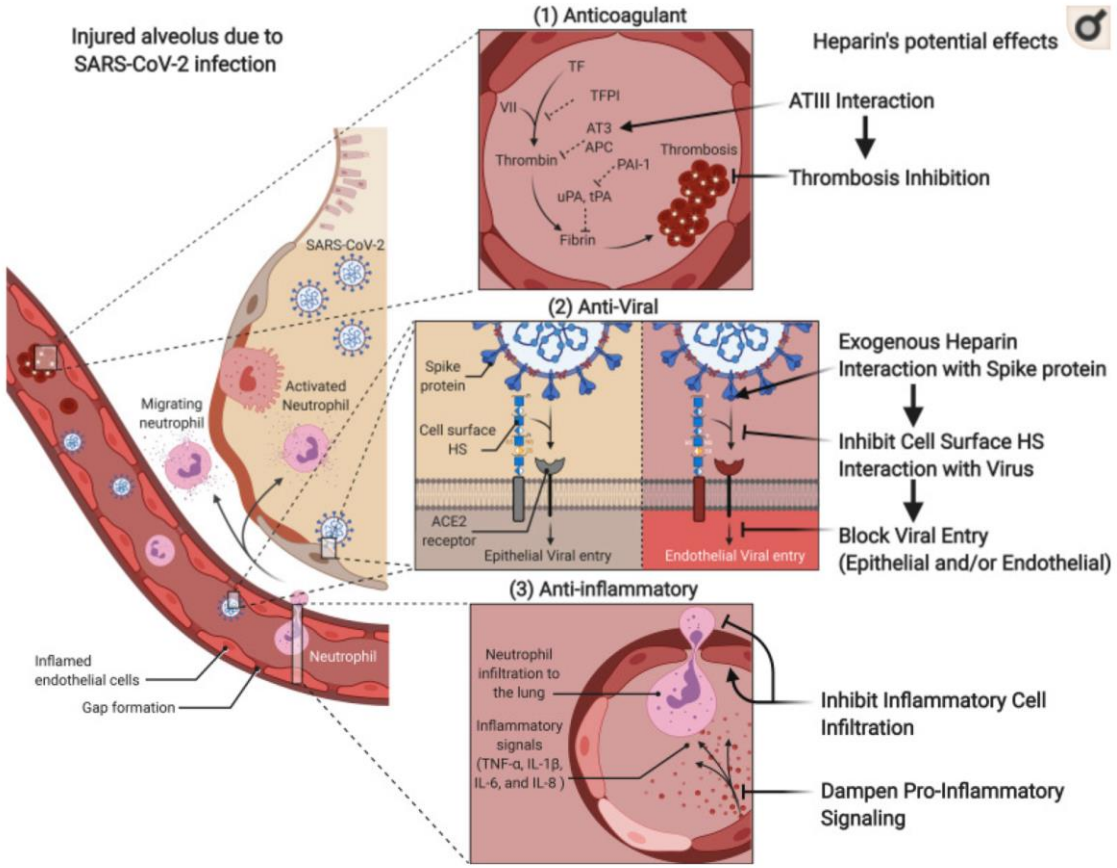
Paranjpe I et al. J Am Coll Cardiol 2020

Heparin as a therapy for COVID-19: current evidence and future possibilities





Coagulopathy

1. Thrombocytopenia
2. Prolonged PT and aPTT
3. Raised D-dimer and fibrinogen
4. Endothelial injury, microangiopathy

Adverse effects

1. 10-15% bleeding risks
2. Heparin induced thrombocytopenia

Hippensteel JA et al. Am J Physiol Lung Cell Mol Physiol 2020

Ongoing Heparin Trial in Covid-19

Showing: 1-20 of **20** studies 100 studies per page

Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Nebulized **Heparin** in Severe Acute Respiratory Syndrome **COVID-19**	• **Covid19** • Pneumonia	• Drug: Heparin sodium • Drug: Enoxaparin	• Clinica San Camilo Ciudad Autonoma de Buenos Aire, Buenos Aires, Argentina
2	☐	Not yet recruiting	Clinical Efficacy of **Heparin** and Tocilizumab in Patients With Severe **COVID-19** Infection: a Randomized Clinical Trial	• **Covid19**	• Drug: Tocilizumab • Drug: Heparin - Therapeutic dosage • Drug: Heparin - Prophylactic dosage	
3	☐	Recruiting	**Heparins** for Thromboprophylaxis in **COVID-19** Patients: HETHICO Study in Veneto	• **COVID-19** • Hypercoagulability	• Drug: Low Molecular Weight Heparin	• Giuseppe Camporese Padova, Italy
4	☐	Recruiting	Efficacy Assessment of Methylprednisolone and **Heparin** in Patients With **COVID-19** Pneumonia	• **COVID-19**	• Drug: Methylprednisolone • Drug: Heparin	• D'Or Institute for Research and Education Rio de Janeiro, Brazil
5	☐	Recruiting NEW	Inhaled **Heparin** for Hospitalised **COVID-19** Patients	• **Covid19**	• Drug: Unfractionated heparin	• San Camilo Clinic Buenos Aires, Argentina • 15th May hospital Cairo, Egypt
6	☐	Recruiting	Nebulised **Heparin** in Patients With Severe **COVID-19**	• **Covid19** • Respiratory Failure	• Drug: Nebulised unfractionated heparin (UFH)	• Frederick Health Hospital Frederick, Maryland, United States
7	☐	Recruiting	Full Dose **Heparin** Vs. Prophylactic Or Intermediate Dose **Heparin** in High Risk **COVID-19** Patients	• **Sars-CoV2** • **COVID**	• Drug: Enoxaparin • Drug: Prophylactic/Intermediate Dose Enoxaparin	• Beth Israel Newark Newark, New Jersey, United States • Southside Hospital Bay Shore, New York, United States • Huntington Hospital Huntington, New York, United States • (and 3 more...)
8	☐	Enrolling by invitation	Nebulized **Heparin** for the Treatment of **COVID-19** Induced Lung Injury	• **Covid-19** • ARDS, Human • Acute Lung Injury	• Drug: Heparin • Drug: 0.9% Sodium-chloride	• Frederick Health Hospital Frederick, Maryland, United States
9	☐	Not yet recruiting NEW	Factor Xa Inhibitor Versus Standard of Care **Heparin** in Hospitalized Patients With **COVID-19** (XACT)	• **Covid19**	• Drug: Enoxaparin • Drug: Rivaroxaban	
10	☐	Recruiting	D-dimer Adjusted Versus Therapeutic Dose Low-molecular-weight **Heparin** in Patients With **COVID-19** Pneumonia	• Coronavirus Disease (**COVID**)19	• Drug: low-molecular-weight heparin	• Faculty of Medicine Ain Shams University Research Institute- Clinical Research Center Cairo, Non-US, Egypt
11	☐	Not yet recruiting	Steroids and Unfractionated **Heparin** in Critically Ill Patients With Pneumonia From **COVID-19** Infection	• **Covid19** • SARS-CoV Infection • Pneumonia, Viral • Coagulopathy	• Drug: Enoxaparin • Drug: Methylprednisolone • Drug: unfractionated heparin	
12	☐	Not yet recruiting	Early Prophylactic Low-molecular-weight **Heparin** (LMWH) in Symptomatic **COVID-19** Positive Patients	• **COVID-19**	• Drug: Enoxaparin	
13	☐	Active, not recruiting	Intranasal **Heparin** Tolerability Study	• **Covid19**	• Drug: Intranasal heparin sodium (porcine)	• The University of Mississippi National Center for Natural Products Research University, Mississippi, United States

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Conclusions

Conclusion

Antivirals

- More robust multicenter trials with similar ICU support needed
- Early commencement of combination of antiviral treatment
- Prevention of deterioration
- Focus in high risk population and elderly
- Profile in viral load and inflammatory markers
- Novel antiviral therapies

Vaccines

- Long-term efficacy of vaccines
- Safety profile
- Viral mutations
- Combination of vaccine antigens

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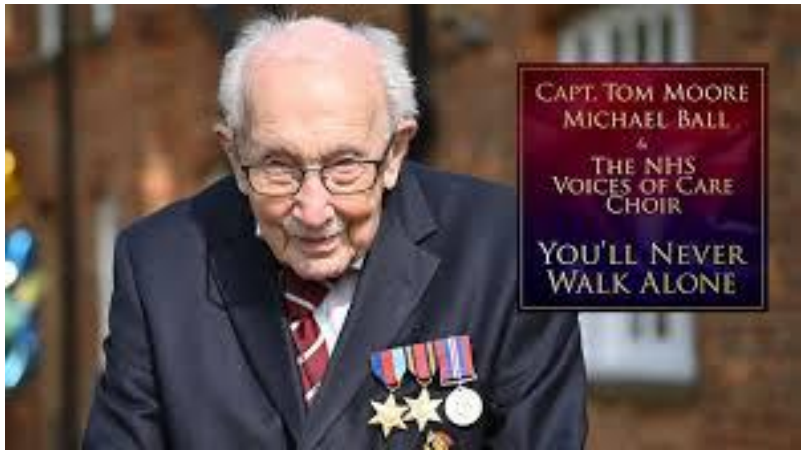
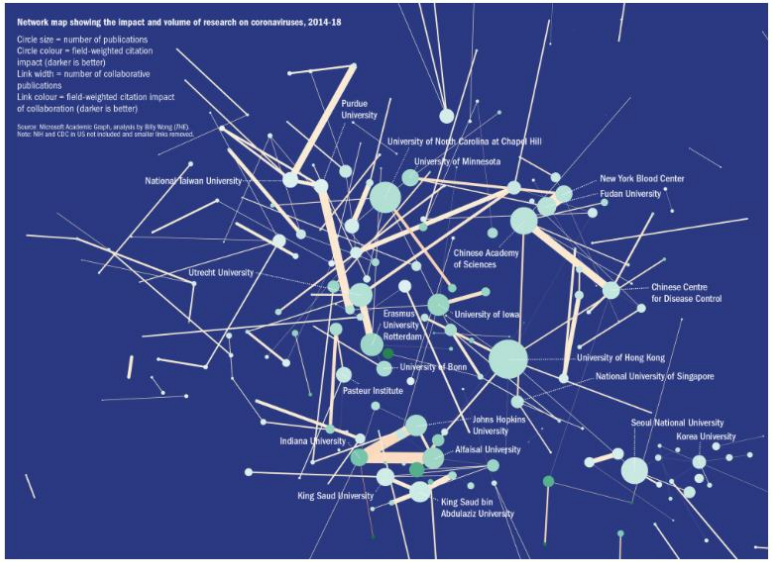
You'll Never Walk Alone!





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Acknowledgement

Gratitude to:

- Isolation wards medical and nursing colleagues all HA hospitals
- A&E and other departments
- DH/ CHP colleagues
- HA, HKU, DH laboratory colleagues

Support from the RGC/ HMRF

- Prof KY Yuen
- Dr. KC Lung
- Dr. Eugene Tso
- Dr. Alan Wu
- Dr. TC Wu
- Dr. KM Sin
- Dr. YY Ng
- Dr. Tom Chung
- Dr. Anthony Tam
- Dr. Jenny Lo
- Dr. WL Law
- Dr. MY Chu
- Dr Veronica Chan
- Dr Alwin Yeung
- Dr. Rodney Lee
- Dr. KH Chan
- Dr. Li Xin
- Dr. Derek Hung
- Dr. Kelvin Chiu
- Dr Raymond Liu
- Dr Owen Tsang
- Dr. Albert Lie
- Prof CS Lau
- Dr WM Chan
- Dr WW Yan
- Dr HP Shum
- Dr. WS Leung
- Dr. Jacky Chan
- Dr. Jasper Chan
- Dr. Kelvin To
- Dr. Vincent Cheng
- Dr. Johnny Chan
- Dr. David Lung
- Dr. Kitty Fung
- Dr TL Que

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