

COVID-19 Clinical Update for Pediatric Hematology/Oncology/BMT

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Tuesday, March 17th, 2020



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Disclosures and Notes

- No personal/financial COI.
- Will be discussing non-FDA/non-Health Canada approved use of medications.
- Situation is fluid/changing hourly, especially epidemiologic data.
- Many peer-reviewed manuscripts are 'early online access' or 'early view,' - check for title if looking for reference, final published versions will change.
- Some manuscripts included here are pre-print/not peer reviewed; will notify which.
- Talk includes some data especially regarding clinical situation/presentation pulled from Social Media (e.g. Twitter), sources are relatively reliable (e.g. physicians actively treating patients w COVID-19).
- Papers used here are freely available; journals are assisting in disseminating COVID-19-associated literature.



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Reminders:

- Social Distancing!



Reminders:

- Don't touch your face!



Reminders:

- Or other people's faces!



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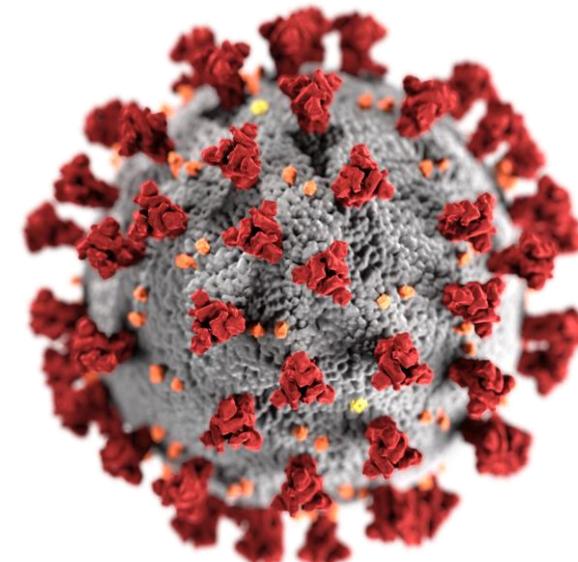
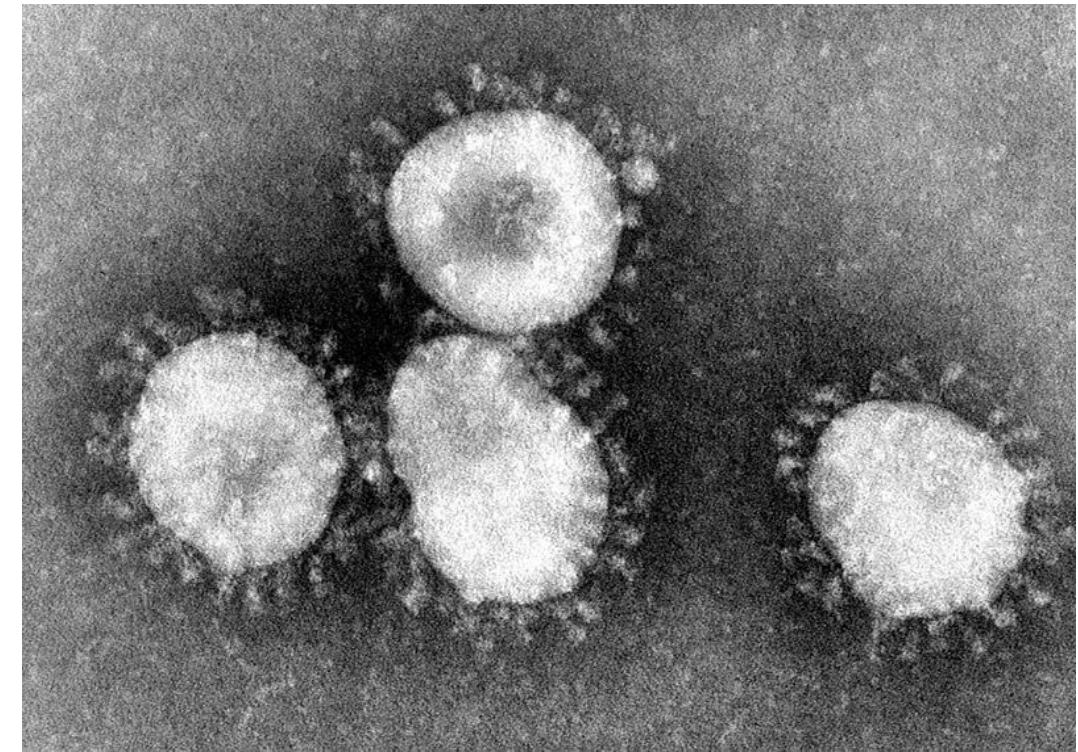
Reminders:

- Wash hands frequently/use hand sanitizer.



Nomenclature

- **Coronaviruses** -
 - Name is derived from the Latin corona, meaning "crown" or "halo."
 - Refers to characteristic appearance reminiscent of a crown around the virions when viewed under two-dimensional transmission electron microscopy
 - Appearance due to the surface covering of club-shaped protein spikes.



Nomenclature

- Coronaviruses -
 - Other famous coronas:



The Coronas: "We have such an unfortunate name"

"Someone mentioned that maybe we should do a co-headline tour with The Vaccines"

Andrew Trendell 11 hours ago

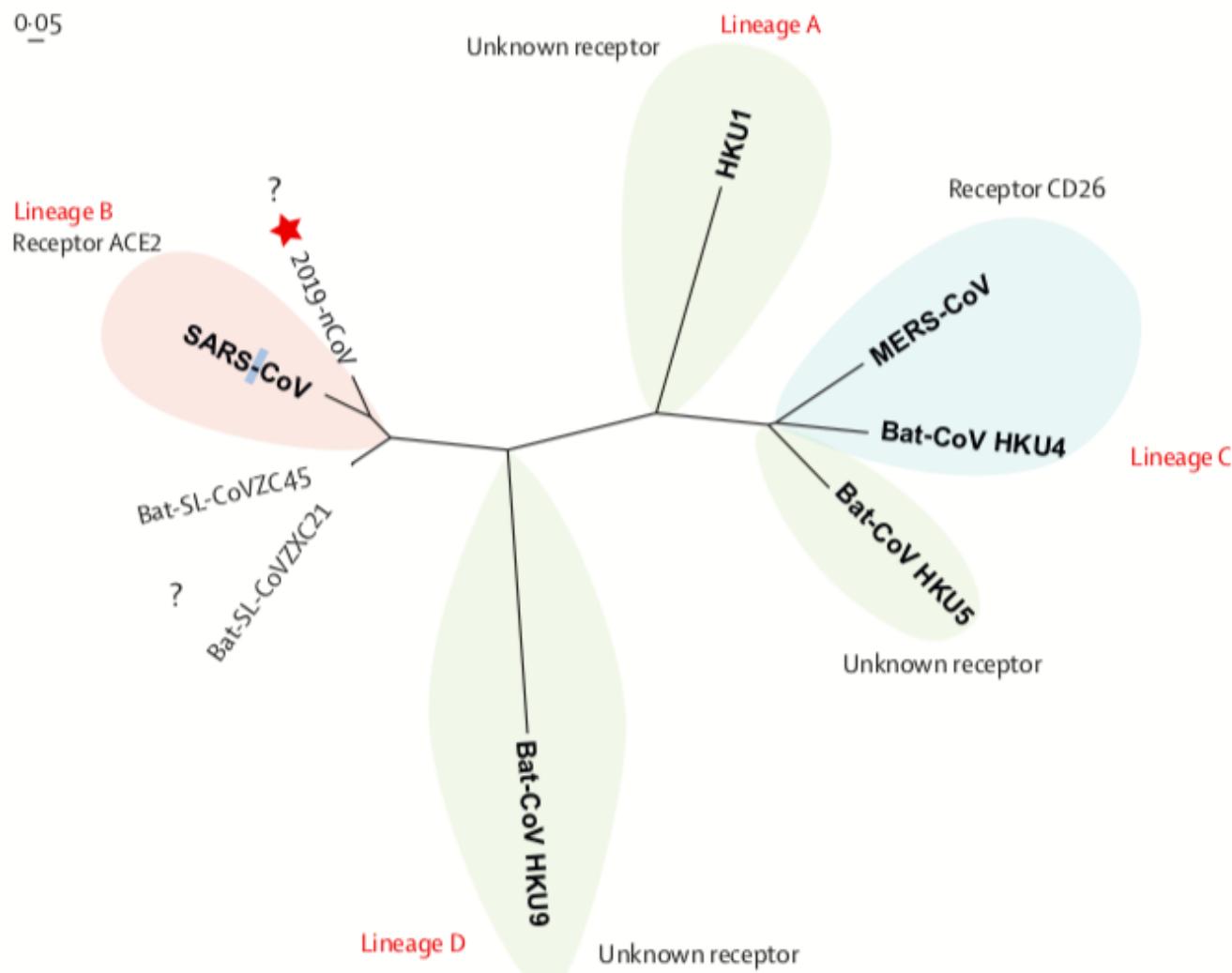


Epidemiology

- In early December 2019, the first pneumonia cases of unknown origin were identified in Wuhan, the capital city of Hubei province. These cases were traced to a seafood ‘wet market,’ suggesting animal-to-person spread. Subsequently, large number of patients identified who did not have exposure to animal markets, indicating person-to-person spread.
- The pathogen was identified as a novel enveloped RNA beta-coronavirus with substantial phylogenetic similarity to SARS-CoV, and was therefore named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Nomenclature

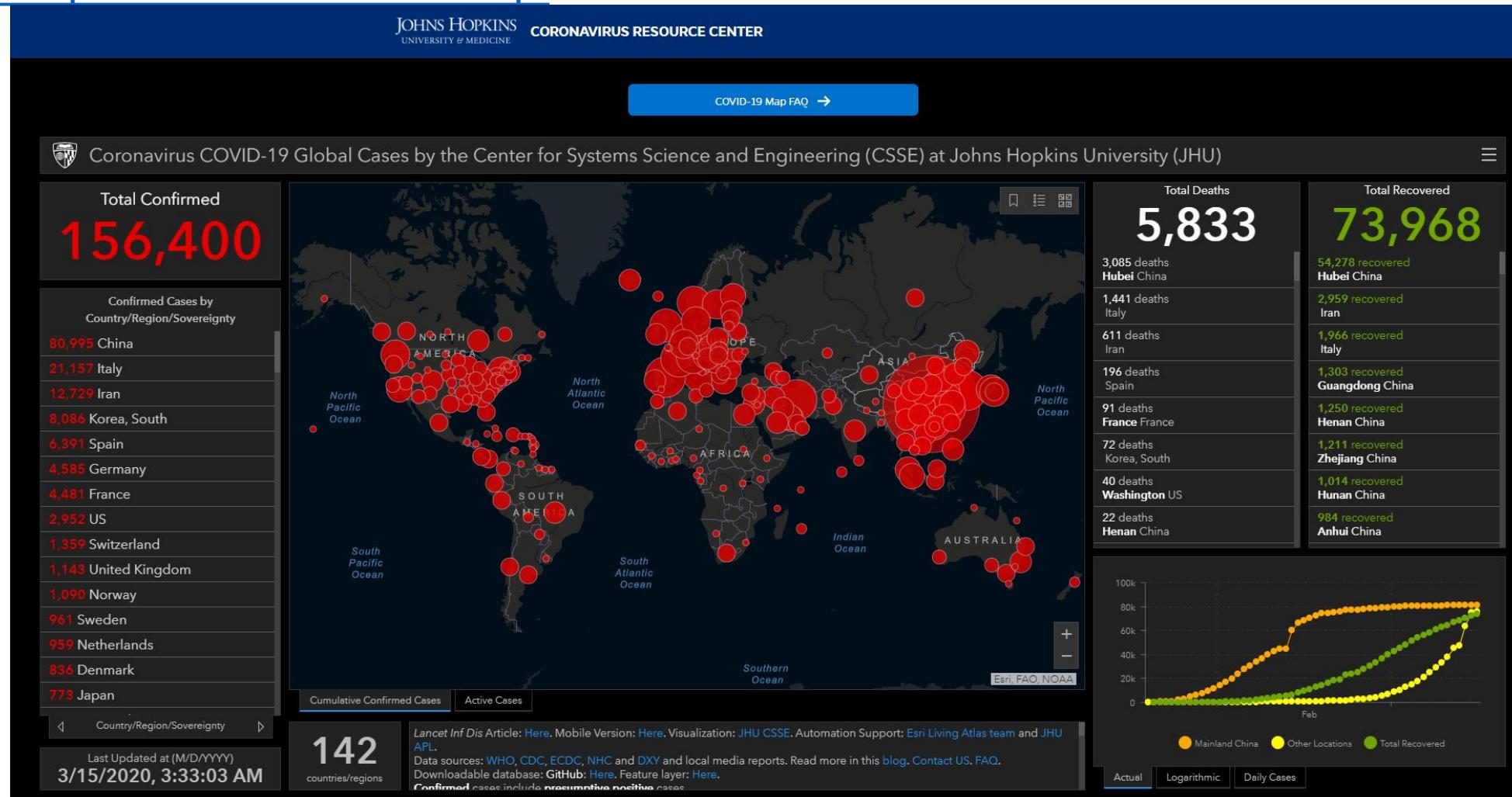
- COVID-19: Disease name
 - COrona Virus Infectious Disease-19
- SARS-CoV-2: Virus itself
 - Causative agent of COVID-19
 - HCoV-19 – Human Coronavirus-19 (old name)
- SARS-CoV: Severe Acute Respiratory Syndrome - COronaVirus
 - Causative agent of SARS (outbreak 2002 – 2003)
- MERS-CoV: Middle East Respiratory Syndrome-COronaVirus
 - Causative agent of MERS (outbreak 2012)



Lu et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor Binding. Lancet 2020

Epidemiology

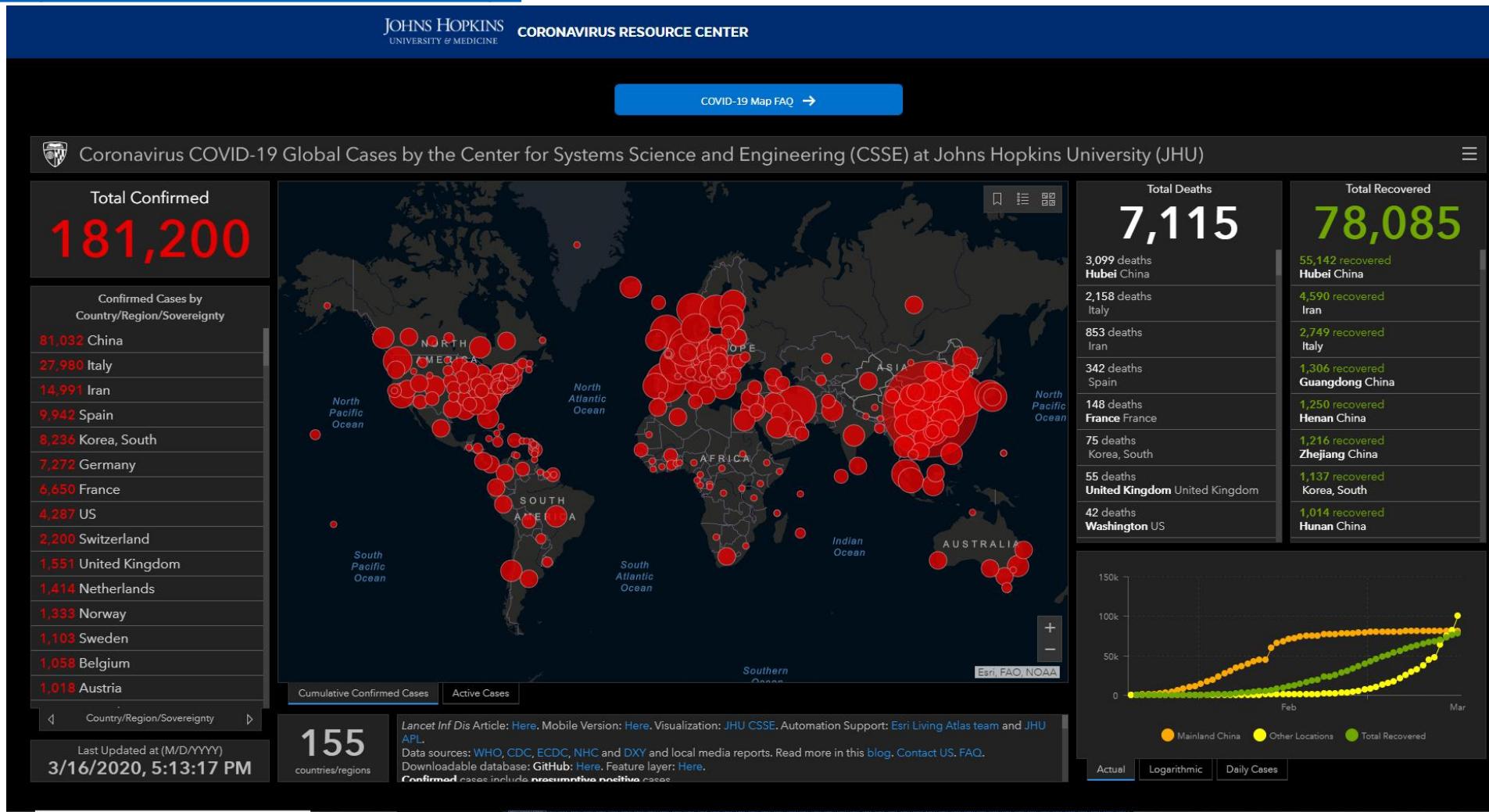
- Johns Hopkins 'Coronavirus Map'



<https://coronavirus.jhu.edu/map.html>

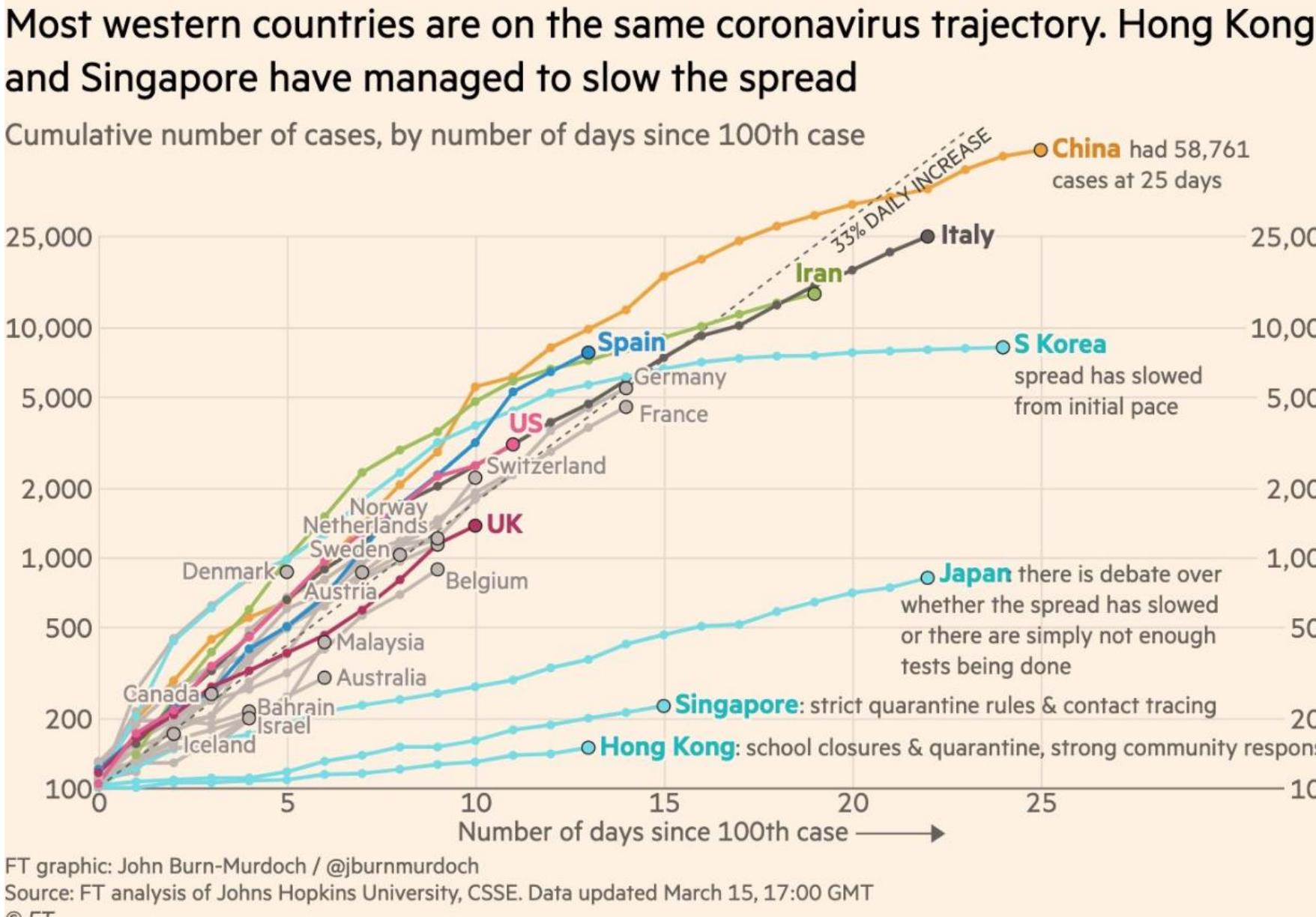
Epidemiology

- Johns Hopkins 'Coronavirus Map'



Epidemiology

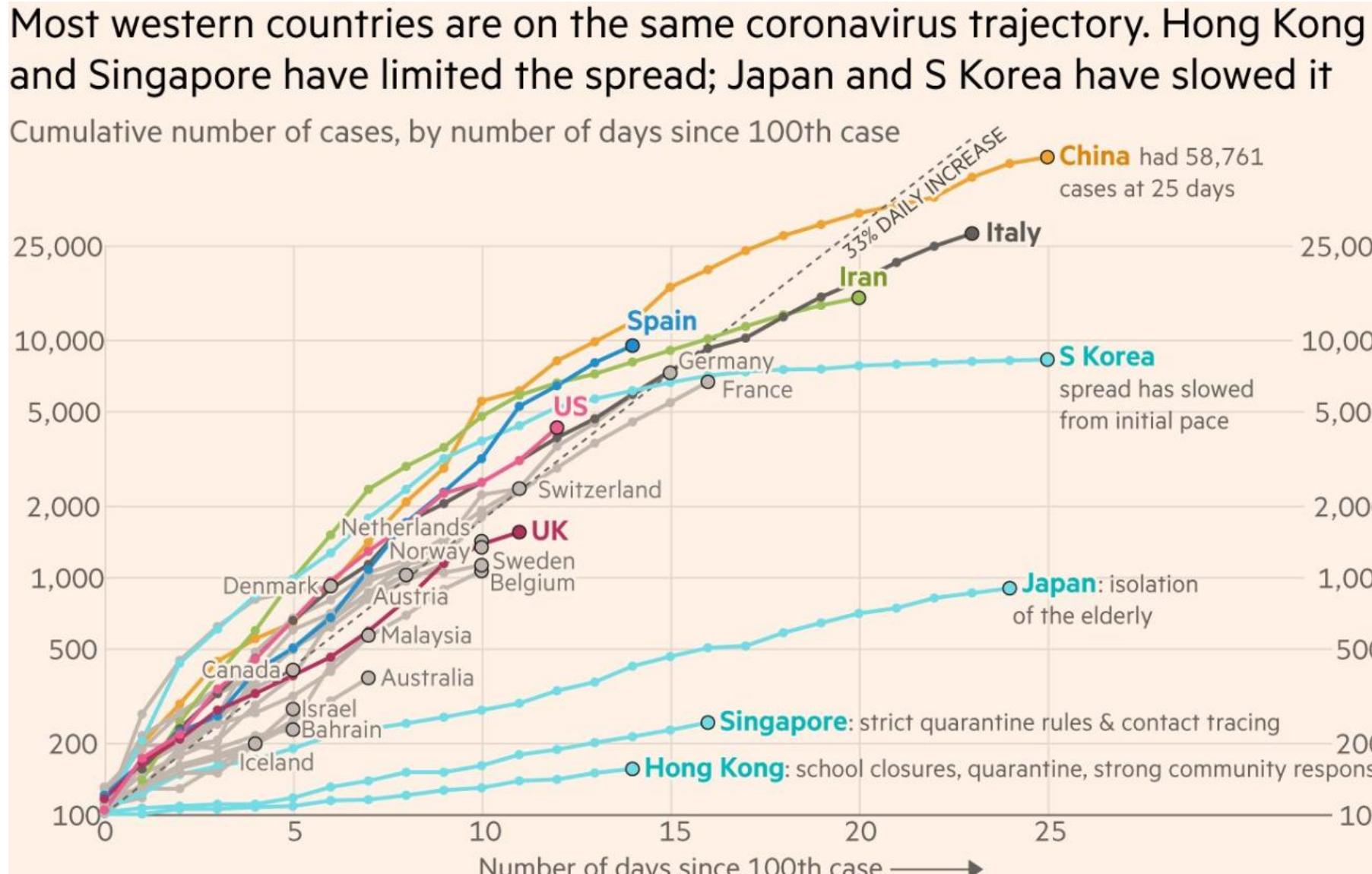
- My favorite, least-favorite graphical overview of the situation.
- A.K.A. 'lesson in data confounding.'
- ``We are not doing better than Italy or Iran – we are just further behind.``



Credit: John Burn-Murdoch; @jburnmurdoch + <https://coronavirus.jhu.edu/map.html>

Epidemiology

- My favorite, least-favorite graphical overview of the situation.
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FT graphic: John Burn-Murdoch / @jburnmurdoch

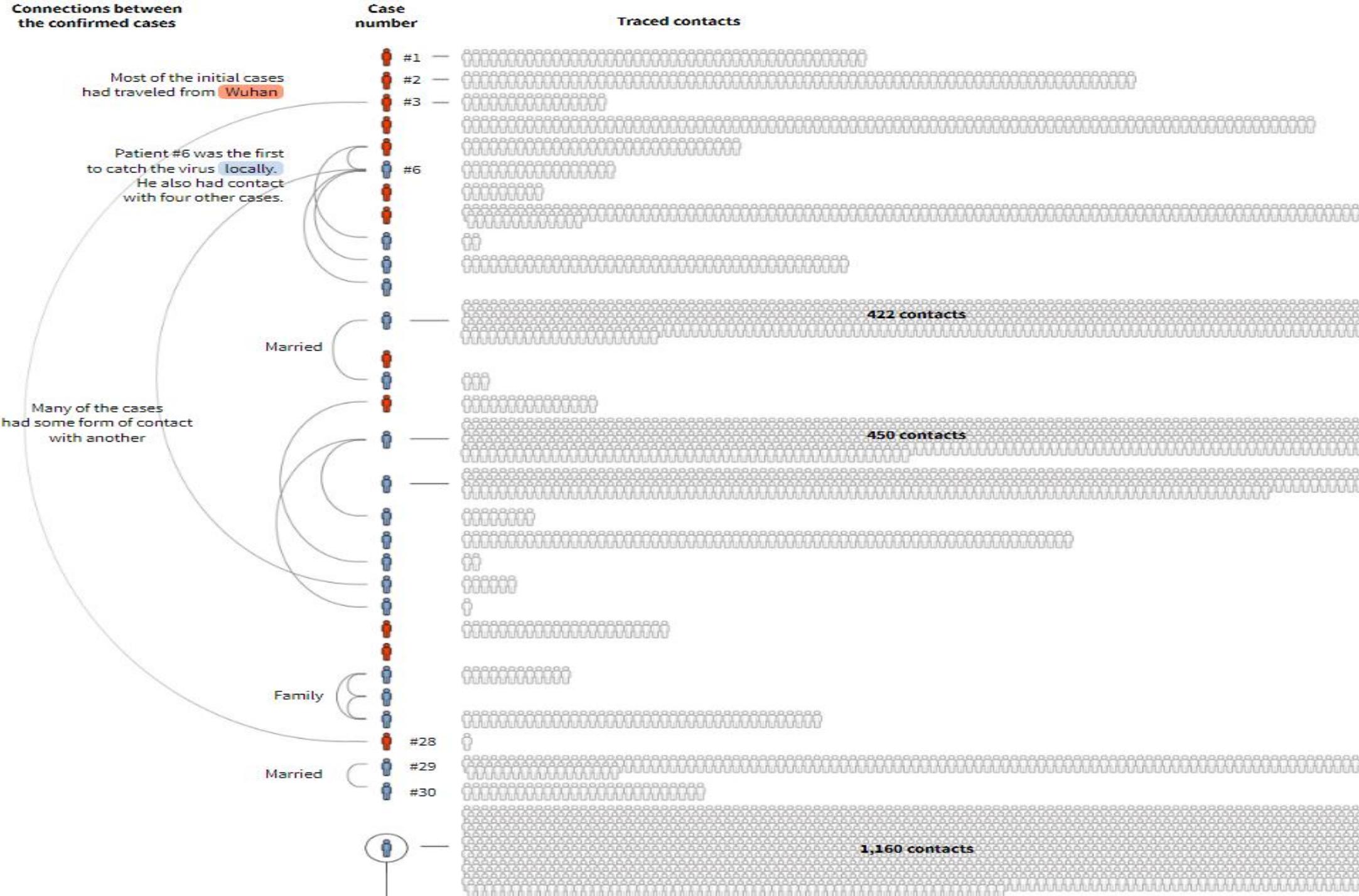
Source: FT analysis of Johns Hopkins University, CSSE; Worldometers. Data updated March 16, 20:00 GMT

© FT

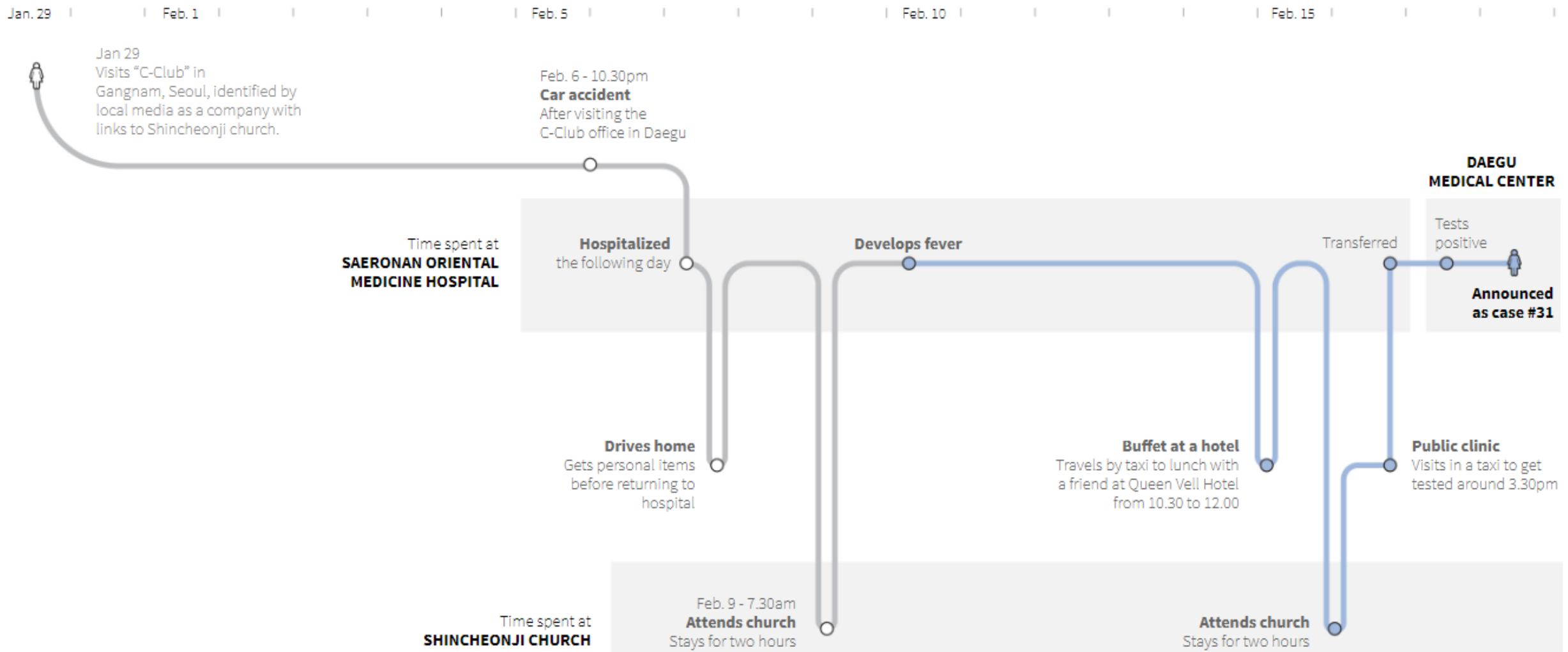
Epidemiology – the importance of isolation.

- "The Korean clusters: How coronavirus cases exploded in South Korean churches and hospitals"
- The virus was first confirmed in South Korea on Jan. 20 when a 35-year-old Chinese woman who flew from Wuhan, China to Incheon international airport, which serves Seoul, and was isolated upon entry into the country.
- In the four weeks following, South Korea managed to avoid a major outbreak with only 30 people contracting the virus, despite many interactions between those later confirmed as being sick and hundreds more people being identified as contacts of the sick patients.
- This changed with the emergence of “Patient 31.”

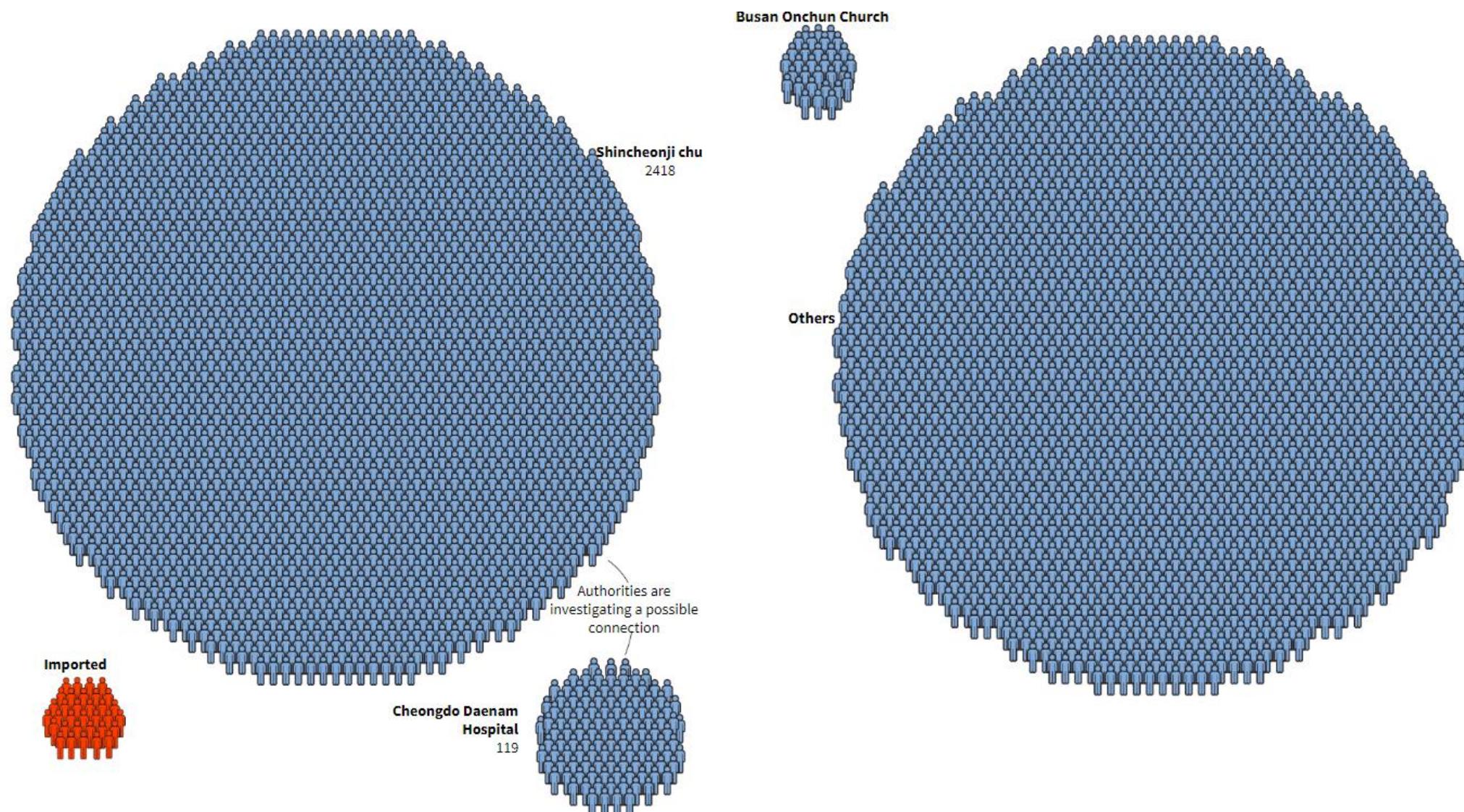
**Connections between
the confirmed cases**



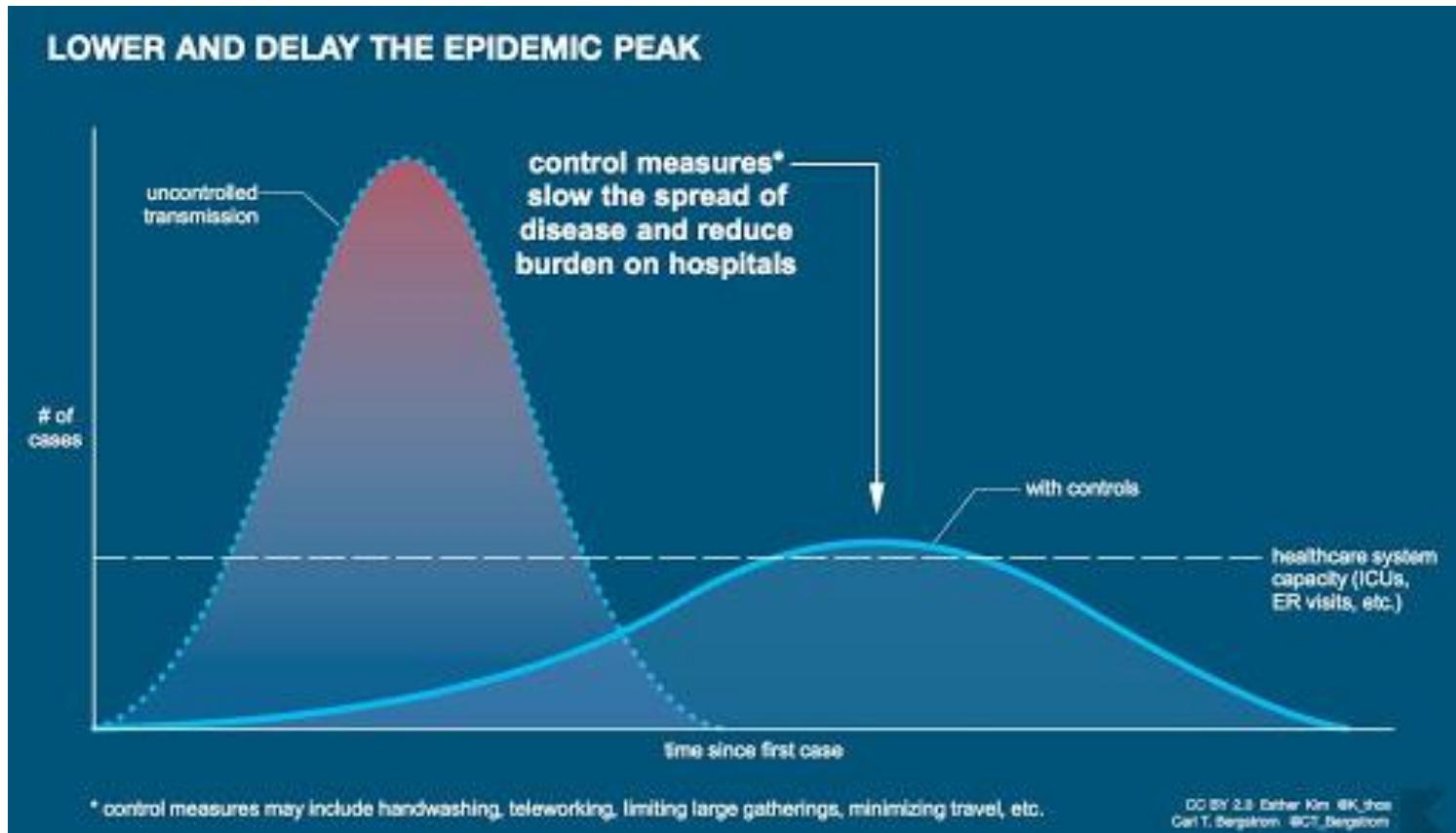
- Patient 31: travelled to Daegu, and Seoul. Involved in a minor traffic accident in Daegu, and checked herself into a hospital. While at that hospital, attended services at the Daegu branch of the Shincheonji Church of Jesus. In between those visits, developed a fever, and went to a buffet lunch with a friend at a hotel. Twice refused to self-isolate and be tested. Finally was tested 2 days later and became the country's 31st confirmed case.



- Caused at least 2 clusters, to which approx 80% of South Korea's current cases can be traced.



Epidemiology – “Flattening the Curve.”

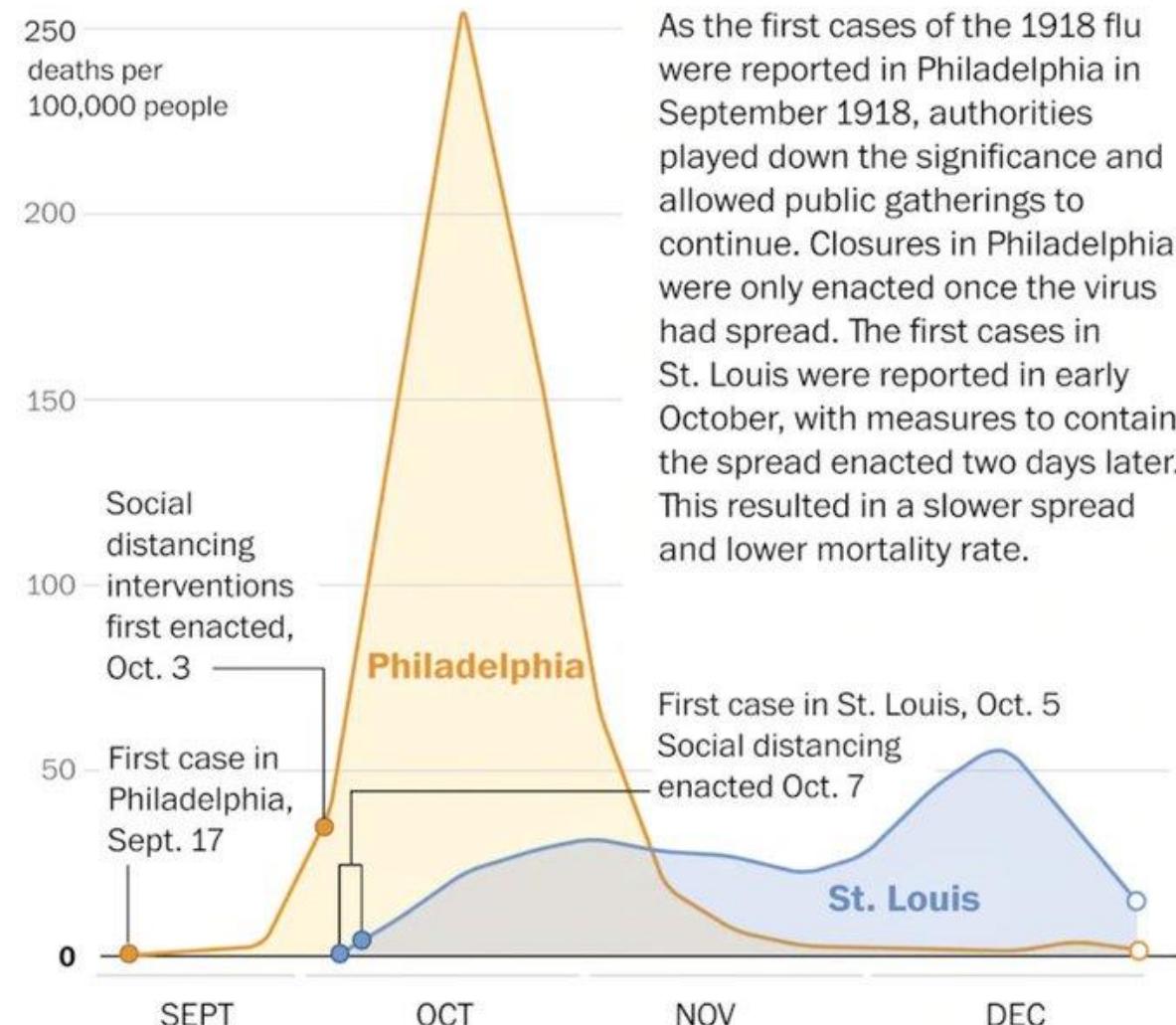


Epidemiology – “Flattening the Curve.” Lessons from 1918

- “The first cases of disease among civilians in Philadelphia were reported on September 17, 1918, but authorities downplayed their significance and allowed large public gatherings, notably a city-wide parade on September 28, 1918, to continue.
- Social distancing interventions were not implemented until October 3, when disease spread had already begun to overwhelm local medical and public health resources.
- In contrast, the first cases of disease among civilians in St. Louis were reported on October 5, and authorities moved rapidly to introduce a broad series of measures designed to promote social distancing, implementing these on October 7.
- The difference in response times between the two cities (14 days, when measured from the first reported cases) represents approximately 3-5 doubling times for an influenza epidemic.”

Hatchett RJ et al. Public health interventions and epidemic intensity during the 1918 influenza pandemic. PNAS 2007. 104 (18) 7582-7587

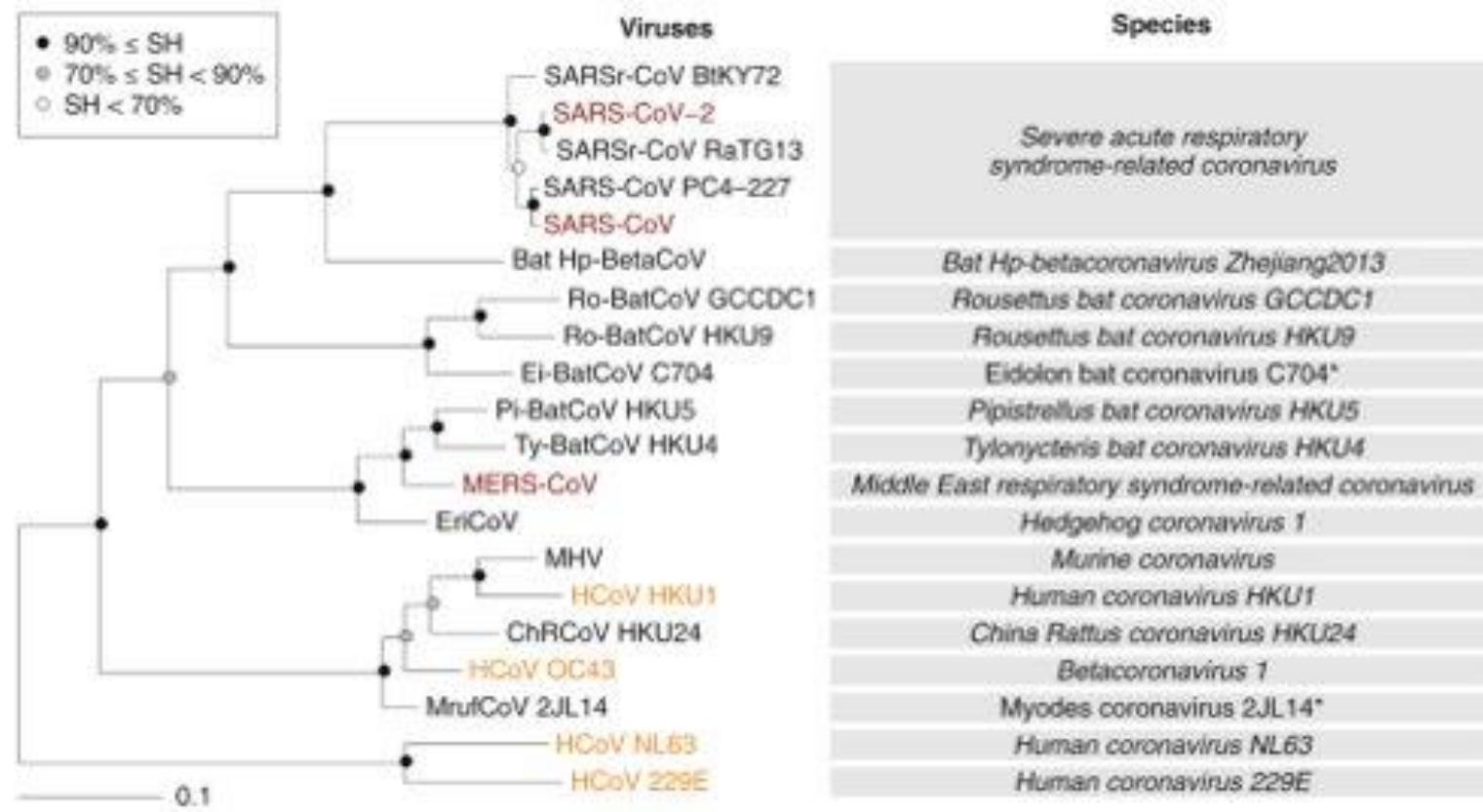
Effects of social distancing on 1918 flu deaths



Biology

- Coronaviruses:

- Common human coronaviruses
 - 229E (alpha coronavirus)
 - NL63 (alpha coronavirus)
 - OC43 (beta coronavirus)
 - HKU1 (beta coronavirus)
- Other human coronaviruses
 - MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS)
 - SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS)
 - SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19)



Biology

- Coronaviruses:
 - Viruses of the family Coronaviridae: single- strand, positive-sense RNA viruses
 - Genome 26 to 32 kilobases in length (relatively large for viruses).
 - Identified in avian hosts, and many species of mammal - camels, bats, masked palm civets, mice, dogs, and cats.
 - Many exist; several pathogenic to human hosts.

Biology

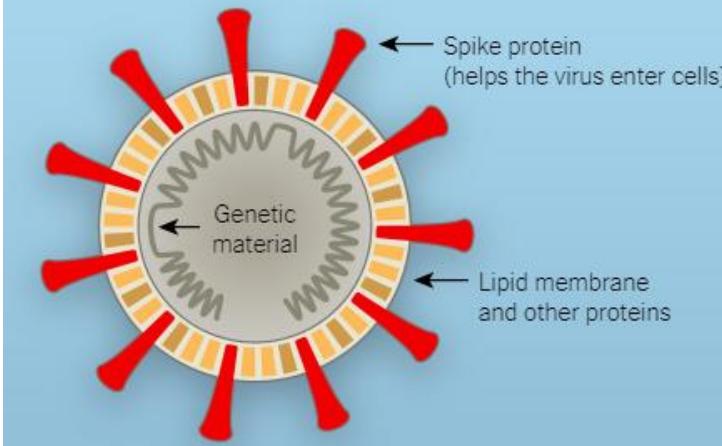
- Coronaviruses:
 - Most associated with mild clinical symptoms; notable exceptions include:
 - Severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV), a novel betacoronavirus, first detected in Guangdong, southern China, in November, 2002,
 - Resulted in over 8000 infections and 774 deaths
 - Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), which was first detected in Saudi Arabia in 2012
 - Resulted in 2494 infections and 858 deaths
- Novel Viruses:
 - Population – little or no immunity
 - Past examples – pandemic influenza, Zika
 - Novel coronaviruses: (SARS-CoV, SARS-CoV-2, MERS-CoV)



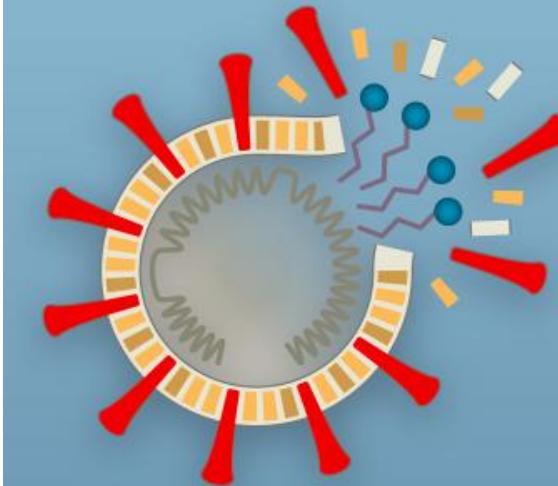
Soap, Water, and Transmission

- Soap: possess a hydrophobic tail + hydrophilic head.
- Hydrophobic tails of soap molecules attempt to evade water via insertion into the lipid envelope bacteria or viruses.
- Disrupt chemical bonds allowing adhesion to surfaces.
- Micelle formation around particles of dirt and viral or bacterial fragments, which are washed away.
- Hand sanitizers are not as reliable; assuming at least 60 percent ethanol, lipid membrane is destroyed.

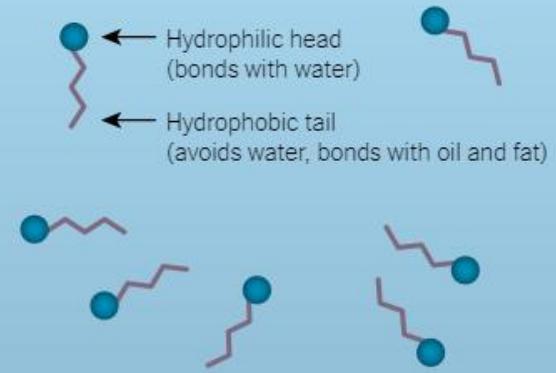
THE CORONAVIRUS has a membrane of oily lipid molecules, which is studded with proteins that help the virus infect cells.



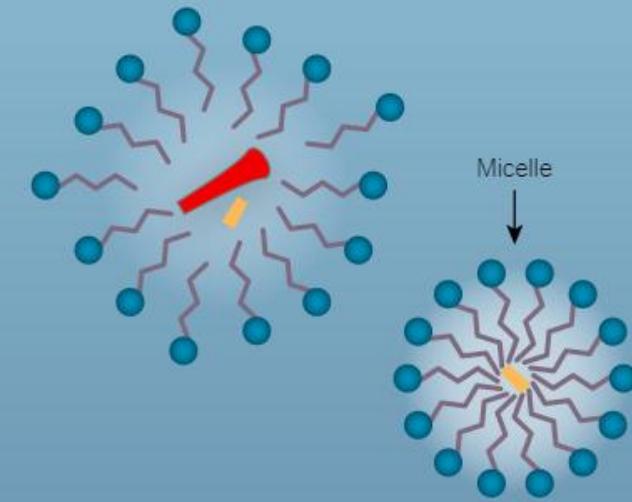
SOAP DESTROYS THE VIRUS when the water-shunning tails of the soap molecules wedge themselves into the lipid membrane and pry it apart.



SOAP MOLECULES have a hybrid structure, with a head that bonds to water and a tail that avoids it.



SOAP TRAPS DIRT and fragments of the destroyed virus in tiny bubbles called micelles, which wash away in water.

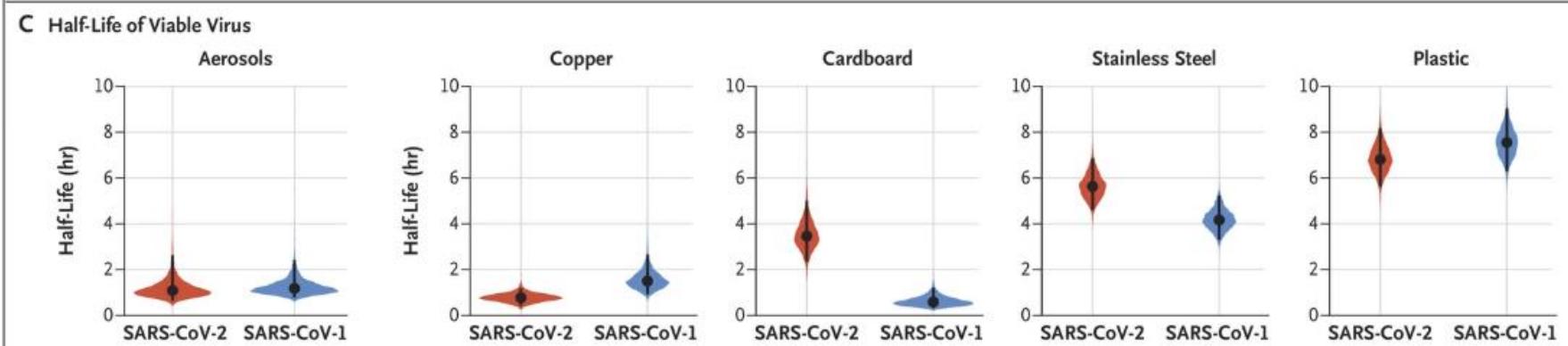
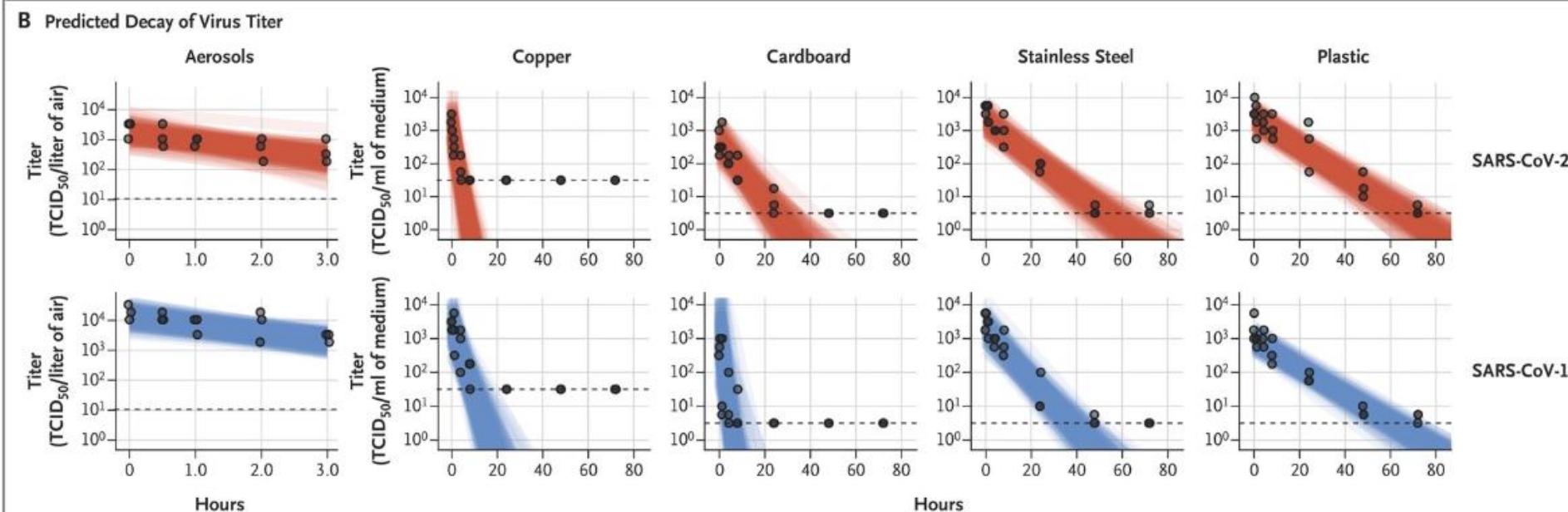
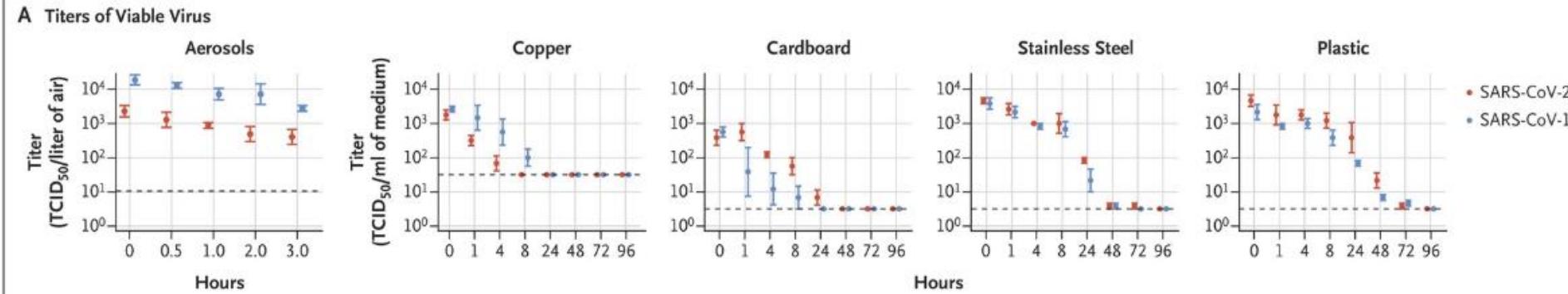


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Soap, Water, and Transmission

- Coronaviruses in general - known to be transmitted via droplet + surface fomites.
- Van Doremalen et al (NIH) – pre-peer review data via medRxiv preprint server - Investigation into the stability of viable SARS-COV and SARS-COV-2.
 - droplets (>5 microns) or aerosols (<5 microns)
- Viable virus could be detected in aerosols up to 3 hours post aerosolization. Similar half-lives in aerosols, median 2.7 hours.
- On surfaces:
 - Up to 4 hours on copper,
 - Up to 24 hours on cardboard
 - Up to 2-3 days on plastic and stainless steel. Median half-life 13 hours on steel and 16 hours on polypropylene.
- Therefore authors conclude aerosol and fomite transmission of SARS-COV2 is plausible, as the virus can remain viable in aerosols for multiple hours and on surfaces for multiple days.



Preprint/Pre-peer review: van Doremalen et al. Aerosol and surface stability of HCoV-19 (SARS-CoV-2) compared to SARS-CoV-1. medRxiv preprint doi: <https://doi.org/10.1101/2020.03.09.20033217>

Transmission: Presence in bodily fluids?

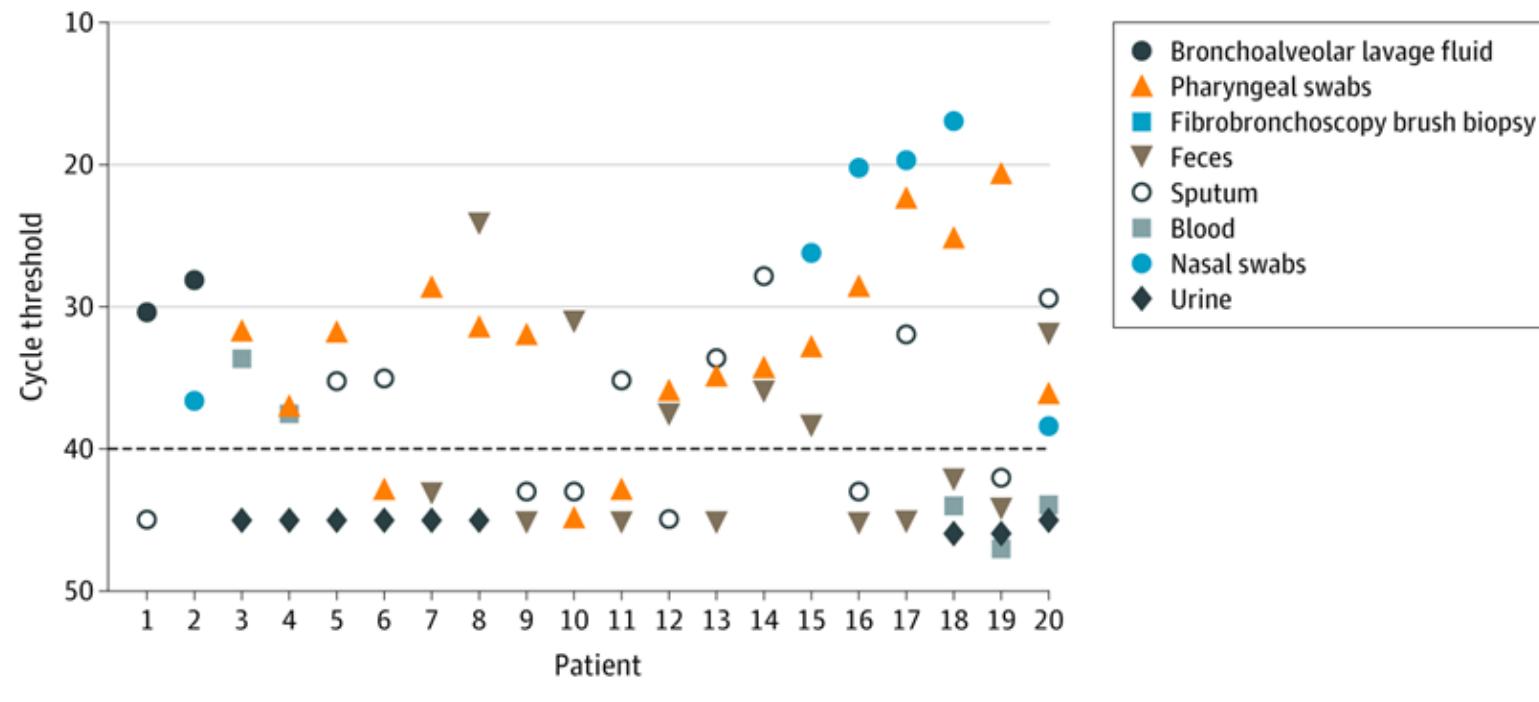
- Real-time reverse transcriptase–polymerase chain reaction (rRT-PCR) of nasopharyngeal swabs is most often used to confirm clinical diagnosis (e.g. isolate SARS-CoV-2 in suspected COVID-19 cases)
- However, whether the virus can be detected in specimens from other sites, and therefore potentially transmitted in other ways than by respiratory droplets, is unknown.
- Wang et al – collected pharyngeal swabs 1 to 3 days after hospital admission + blood, sputum, feces, urine, and nasal samples throughout the illness.
 - RNA was extracted from clinical specimens and determined by rRT-PCR – used the open reading frame 1ab gene to detect.
 - Fecal specimens with high copy numbers were cultured, and electron microscopy was performed to detect live virus.
 - Patterns in a subgroup of patients with multiple specimens collected during hospitalization were explored.



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Transmission: Presence in bodily fluids?

- 1070 specimens collected from 205 patients with COVID-19
- Most of the patients presented with fever, dry cough, and fatigue; 19% of patients had severe illness.
- Bronchoalveolar lavage fluid specimens (14 of 15; 93%),
- Sputum (72 of 104; 72%),
- Nasal swabs (5 of 8; 63%),
- Fibrobronchoscope brush biopsy (6 of 13; 46%),
- Pharyngeal swabs (126 of 398; 32%),
- Feces (44 of 153; 29%)
- Blood (3 of 307; 1%)
- None of the 72 urine specimens tested positive



Severe Acute Respiratory Syndrome Coronavirus 2 Distribution and Shedding Patterns Among 20 Hospitalized Patients

The specimen with a cycle threshold value above the dashed line is interpreted as positive for SARS-CoV-2 RNA; those under, negative.

Transmission: Presence in bodily fluids?

- The mean cycle threshold values of all specimen types were more than 30 ($<2.6 \times 10^4$ copies/mL) except for nasal swabs with a mean cycle threshold value of 24.3 (1.4×10^6 copies/mL), indicating high viral loads in nasal swabs, lower elsewhere.
- Twenty patients had multiple specimens collected simultaneously. Viral RNA was detected in single specimens from 6 patients (respiratory specimens, feces, or blood), while 7 patients excreted virus in respiratory tract specimens and in feces (n = 5) or blood (n = 2).
- Live SARS-CoV-2 was observed in the stool sample from 2 patients who did not have diarrhea.

Table. Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase-Polymerase Chain Reaction

Specimens and values	Bronchoalveolar lavage fluid (n = 15)	Fibrobronchoscope brush biopsy (n = 13)	Sputum (n = 104)	Nasal swabs (n = 8)	Pharyngeal swabs (n = 398)	Feces (n = 153)	Blood (n = 307)	Urine (n = 72)
Positive test result, No. (%)	14 (93)	6 (46)	75 (72)	5 (63)	126 (32)	44 (29)	3 (1)	0
Cycle threshold, mean (SD)	31.1 (3.0)	33.8 (3.9)	31.1 (5.2)	24.3 (8.6)	32.1 (4.2)	31.4 (5.1)	34.6 (0.7)	ND
Range	26.4-36.2	26.9-36.8	18.4-38.8	16.9-38.4	20.8-38.6	22.3-38.4	34.1-35.4	
95% CI	28.9-33.2	29.8-37.9	29.3-33.0	13.7-35.0	31.2-33.1	29.4-33.5	0.0-36.4	

Abbreviation: ND, no data.

Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase-Polymerase Chain Reaction



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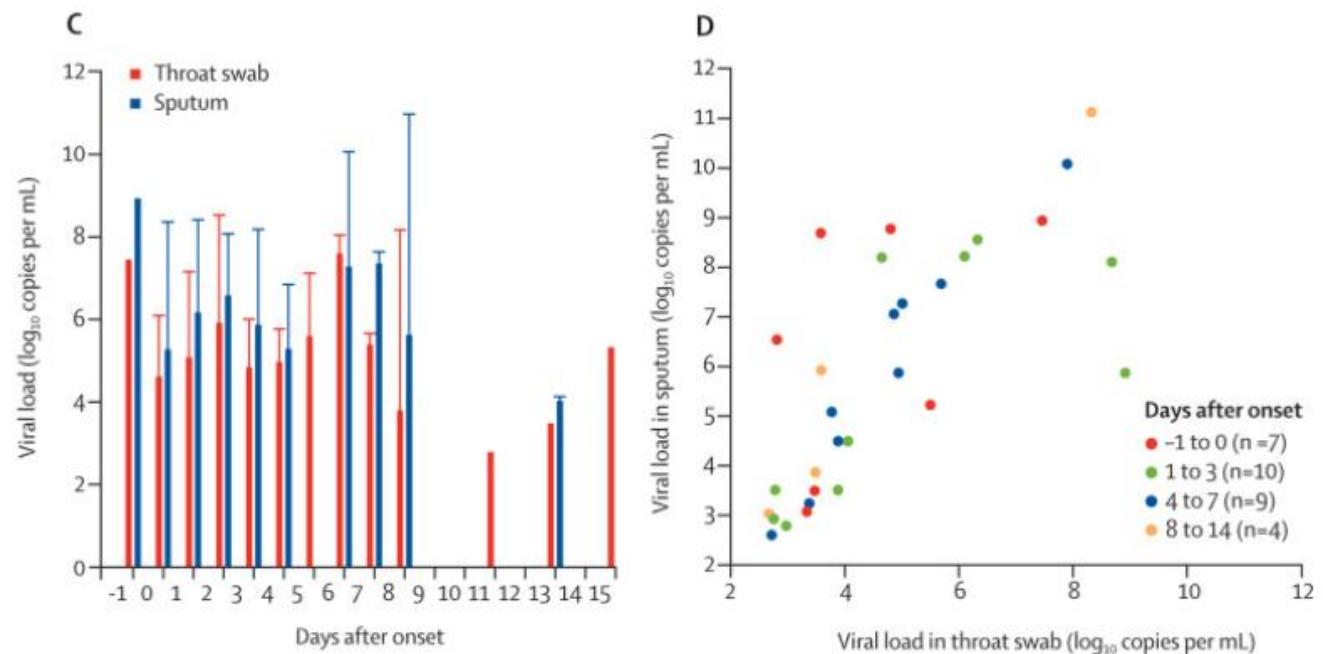
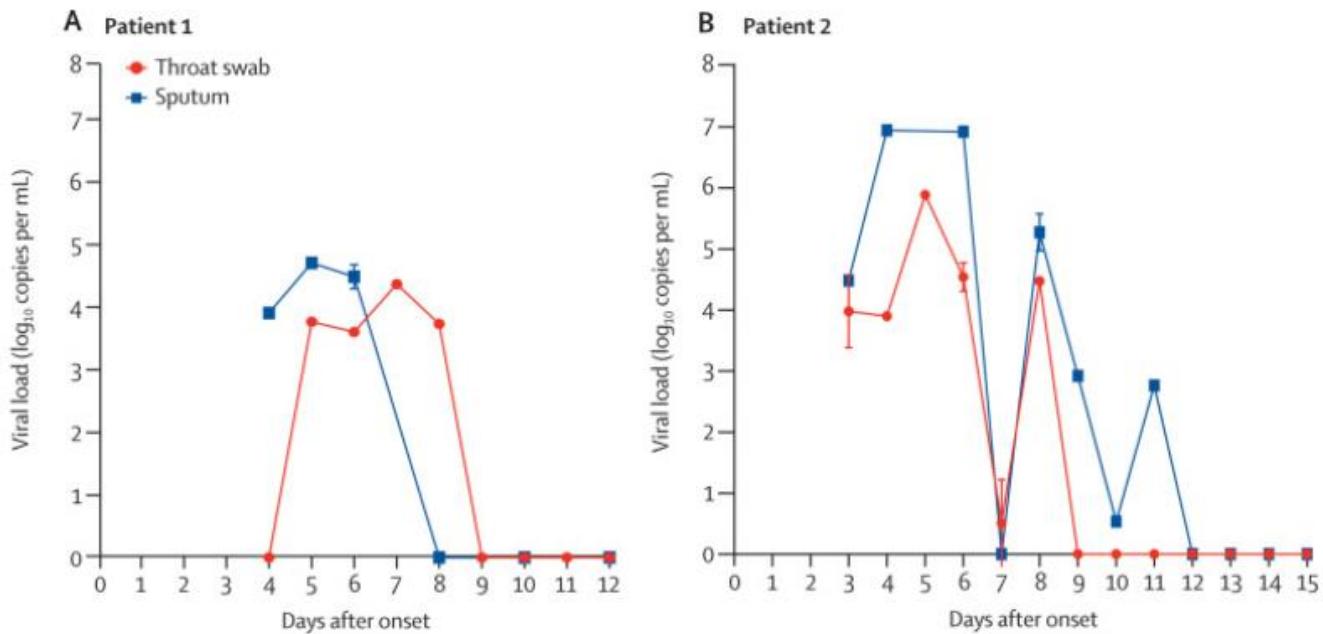
Transmission: Presence in bodily fluids?

- Viral load of SARS-CoV-2 in clinical samples.
- Pan et al: Obtained serial samples (throat swabs, sputum, urine, and stool) from patients in Beijing daily after hospitalization. These samples were examined by an N-gene-specific quantitative RT-PCR assay.
- The viral loads in throat swab and sputum samples peaked at around 5–6 days after symptom onset, ranging from around 10^4 to 10^7 copies per mL during this time.
- Pattern of changes in viral load is distinct from the one observed in patients with SARS, which peaked at 10 days after onset.
- Sputum samples showed higher viral loads than throat swab samples. No viral RNA was detected in urine or stool samples.



Transmission: Presence in bodily fluids?

- 2 representative patients:



Days after onset	-1	0	1	2	3	4	5	6	7	8	11	13	15
Throat swab, n	1	10	12	4	12	12	3	4	2	4	1	1	1
Sputum, n	1	9	4	3	5	9	0	3	2	4	0	2	0

Transmission: Presence in bodily fluids?

- Additionally, assessed viral loads across sample types – at various time points.
- Overall, the viral load early after onset was high ($>1 \times 10^6$ copies per mL).
- Two individuals, who were under active surveillance because of a history of exposure to SARS-CoV-2-infected patients showed positive results on RT-PCR a day before onset, suggesting that infected individuals can be infectious before they become symptomatic.
- Confirmed low level presence of SARS-CoV-2 in fecal samples.



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Transmission: Pre/Post COVID-19 detection

- European Center for Disease Control and Prevention:
 - Technical Report released over the weekend "Discharge Criteria for Confirmed COVID-19 Cases." Focuses on 4 key questions:
 - What is the duration of SARS-CoV-2 virus shedding in bodily fluids of symptomatic patients after remission of symptoms?
 - What is the duration of SARS-CoV-2 virus shedding in bodily fluids of asymptomatic patients?
 - Which tests are available to document the lack of infectivity in a previously diagnosed infection?
 - What is the longest documented transmission from an asymptomatic person?

Transmission: Pre/Post COVID-19 detection

- What is the duration of SARS-CoV-2 virus shedding in bodily fluids of symptomatic patients after remission of symptoms?
 - SARS-CoV-2 virus can be detected 1–2 days prior to symptom onset in upper respiratory tract samples; viral detection persists for 7–12 days in moderate cases and up to 2 weeks in severe cases
 - Fecal detection in up to 30% of patients from day 5 after onset for up to 4 to 5 weeks in moderate cases. Unclear significance for transmission.
 - Prolonged viral shedding from nasopharyngeal aspirates – up to at least 24 days after symptom onset – has been reported as detected by qRT-PCR (viability of SARS-CoV-2 detected by qRT-PCR unknown).
 - Prolonged viral shedding observed among convalescent children after mild infections in respiratory tract samples (up to 22 days from diagnosis) and faeces (2-4 weeks from diagnosis).
- ECDC comment: "Although the oral-faecal route does not appear to be a driver of transmission, its significance remains to be determined. Discharged patients should be advised to strictly follow personal hygiene precautions in order to protect household contacts. This applies to all convalescing patients, but particularly to convalescent children."

Transmission: Pre/Post COVID-19 detection

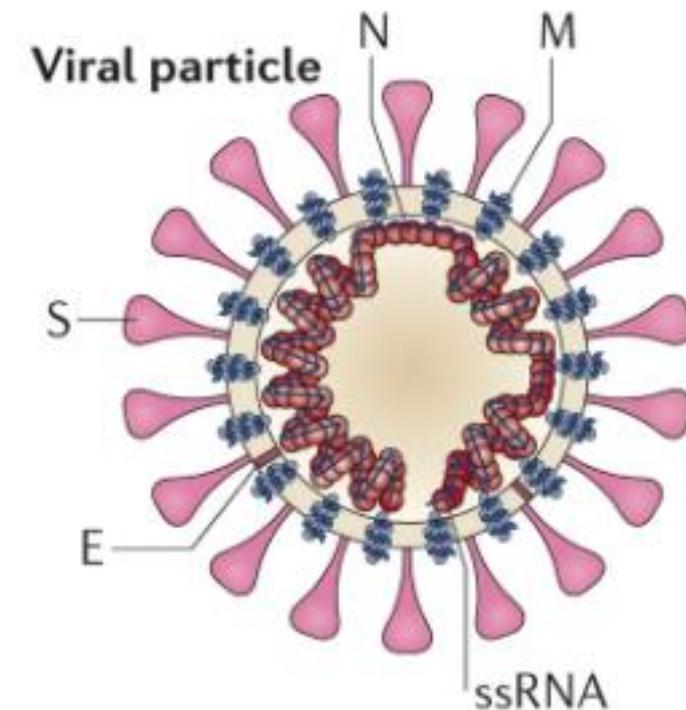
- What is the duration of SARS-CoV-2 virus shedding in bodily fluids of asymptomatic patients?
 - Virus has been detected in asymptomatic persons, by both viral culture and qRT-PCR.
 - Viral load of asymptomatic patients was similar to symptomatic patients, indicating the transmission potential of asymptomatic or pre-symptomatic patients. Patients with few or no symptoms may have modest levels of detectable viral RNA in the oropharynx for at least 5 days.
 - Confirmed transmission from asymptomatic individuals has been documented.
- ECDC comment: Provided that there are sufficient resources, there is a clear benefit in testing asymptomatic patients before they are released from isolation. However, in the context of limited resources for healthcare and laboratories during the COVID-19 epidemic, the testing of symptomatic persons should have priority over the testing of asymptomatic patients before release from isolation.
- What is the longest documented transmission from an asymptomatic person?
 - There is insufficient evidence to provide a qualified answer to this question.

Transmission: De-isolation

- An overview of recommendations for the de-isolation of COVID-19 patients from national bodies in countries is available in the linked document.
 - Some differences in practice, but consensus exists to combine a) the evidence for viral RNA clearance from the upper respiratory tract with b) the clinical resolution of symptoms.
 - At least two upper respiratory tract samples negative for SARS-CoV-2, collected at \geq 24-hour intervals are recommended to document SARS-CoV-2 clearance.
 - For symptomatic patients, following resolution of symptoms, samples should be collected at least seven days from disease onset or after > 3 days without fever.
 - For asymptomatic SARS-CoV-2-infected persons, the tests to document virus clearance should be taken at a minimum of 14 days after the initial positive test.
 - Italian experience indicates that serology to document IgG antibody specific to SARS-CoV-2 will be of value.

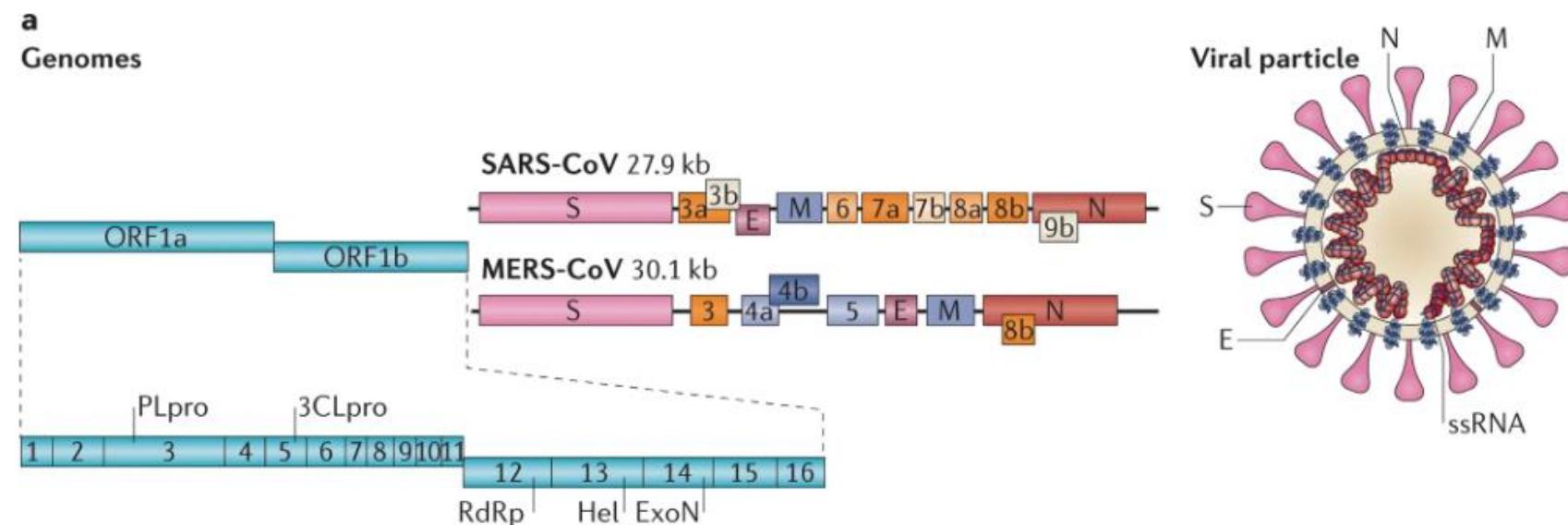
Biology

- SARS-CoV-2 form spherical particles that consisting of four structural proteins.
- The envelope glycoprotein spike (S) forms a layer of glycoproteins that protrude from the envelope.
- Two additional transmembrane glycoproteins are incorporated in the virion: envelope (E) and membrane (M).
- Inside the viral envelope is the helical nucleocapsid, which consists of the viral positive-sense RNA ((+)RNA) genome encapsulated by protein nucleocapsid (N)



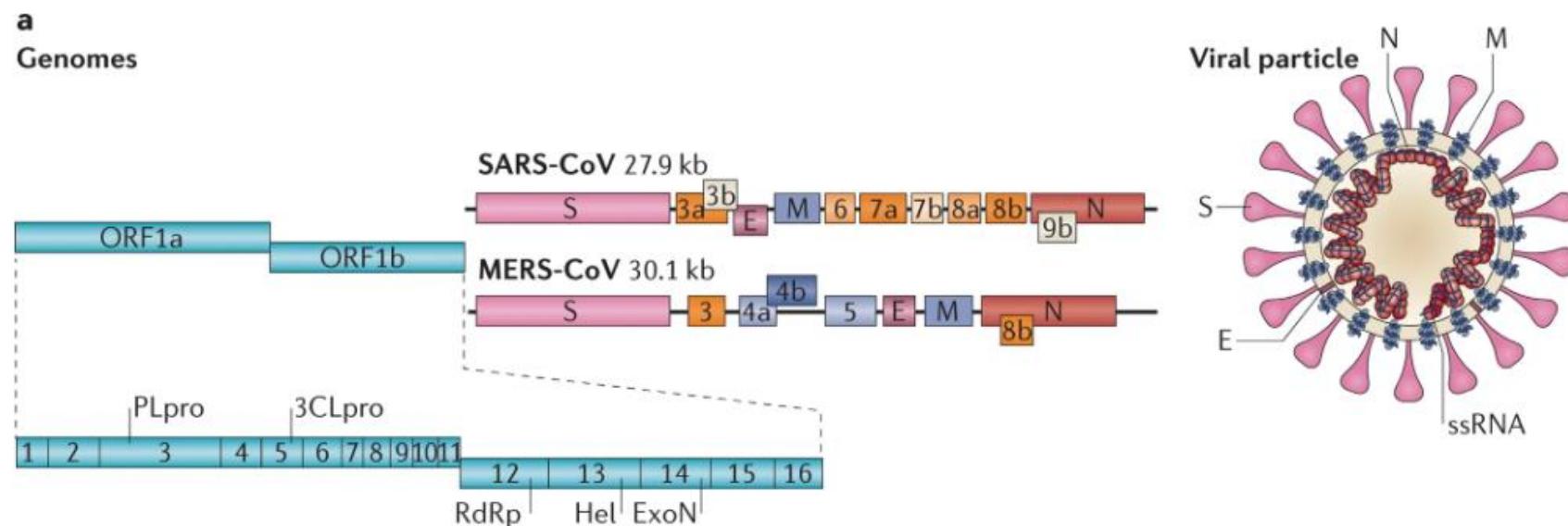
Biology

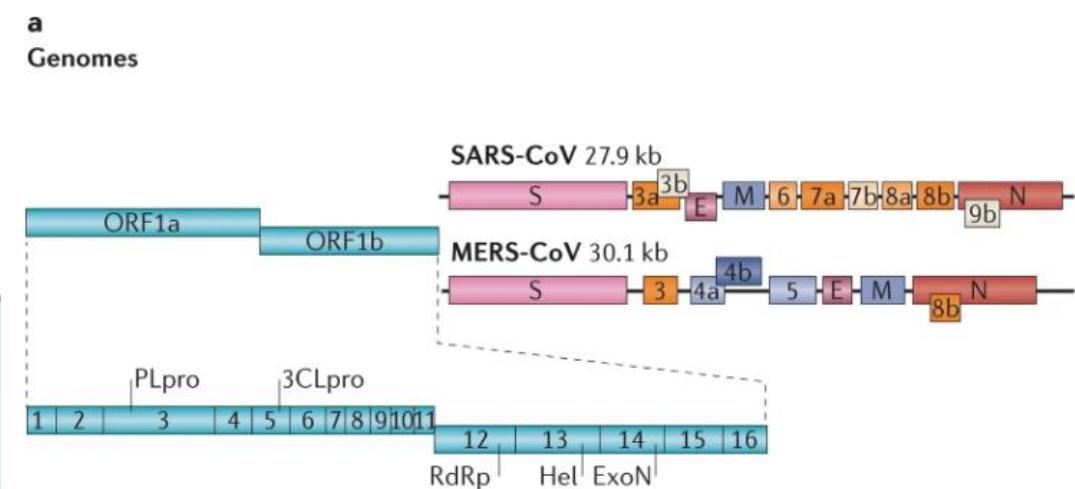
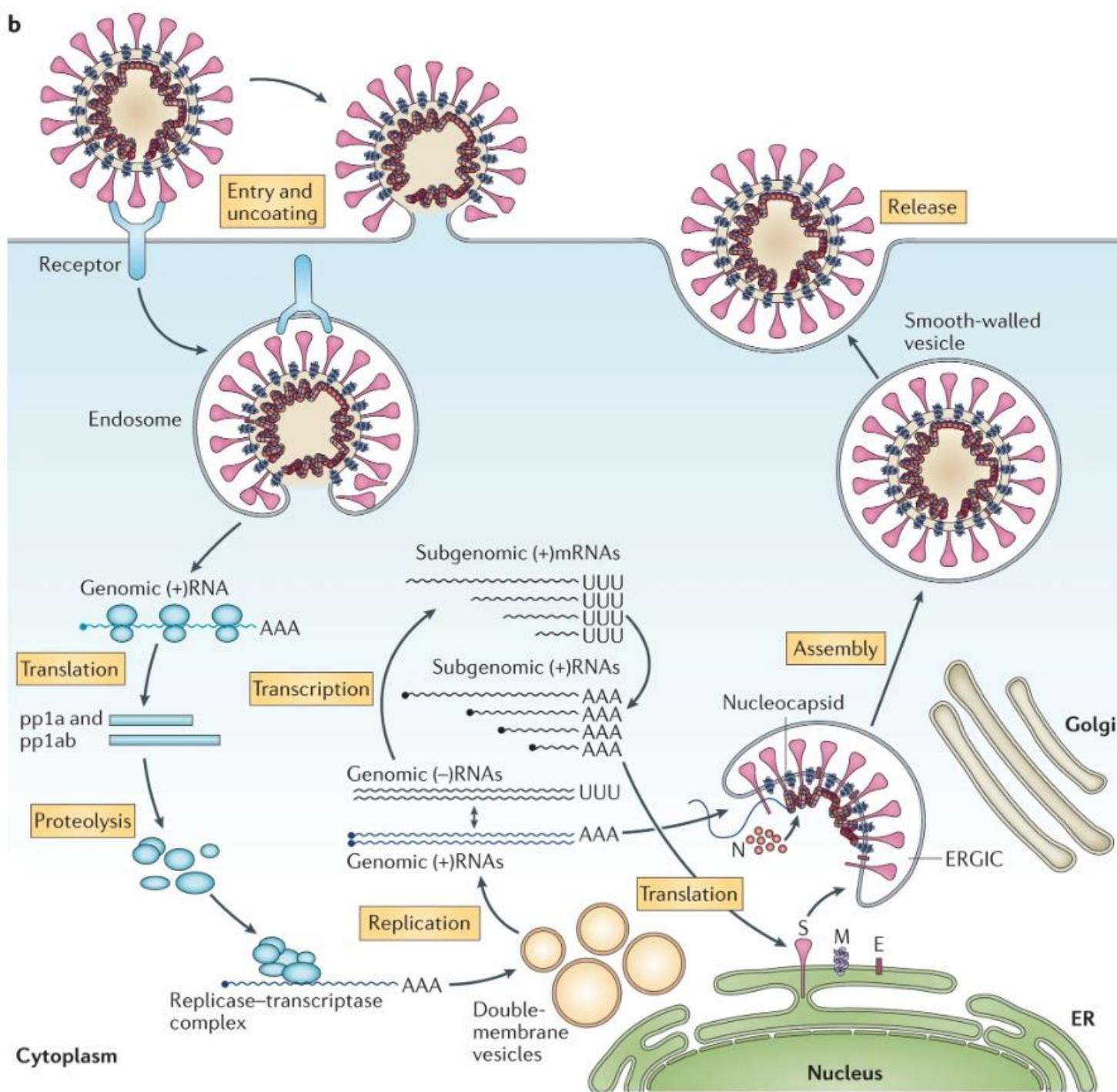
- Two-thirds of the viral RNA is translated into two large polyproteins, and the remainder of the viral genome is transcribed into a nested set of subgenomic mRNAs.
- The two polyproteins, pp1a and pp1ab, encode 16 non-structural proteins (nsp1–nsp16) that make up the viral replicase–transcriptase complex.



Biology

- The polyproteins are cleaved by two proteases, papain-like protease (PLpro; corresponding to nsp3) and, 3C-like protease (3CLpro; corresponding to nsp5).
- The non-structural proteins rearrange membranes that are derived from the rough endoplasmic reticulum (RER) into double-membrane vesicles, in which viral replication and transcription occur.





- Following entry of the virus into the host cell, the viral RNA is uncoated in the cytoplasm.
- Entry is via receptor-mediated endocytosis, and receptor for SARS-CoV-2 (and SARS-CoV) is angiotensin-converting enzyme 2 (ACE2); dipeptidyl peptidase 4 (DPP4) for MERS-CoV.

Biology

- Angiotensin converting enzyme 2 (ACE2): transmembrane metallocarboxypeptidase with homology to ACE, an enzyme long-known to be a key part of the Renin-Angiotensin system (RAS) and a target for the treatment of hypertension.
- ACE is expressed in vascular endothelial cells, the renal tubular epithelium, and in Leydig cells in the testes.
- ACE-2 is expressed in these tissues, as well as in lung, kidney, and gastrointestinal tract tissues - target sites for SARS-CoV-2 and SARS-CoV.
- Major substrate for ACE2 is Angiotensin II. ACE2 degrades Angiotensin II to generate Angiotensin 1-7, negatively regulating RAS.

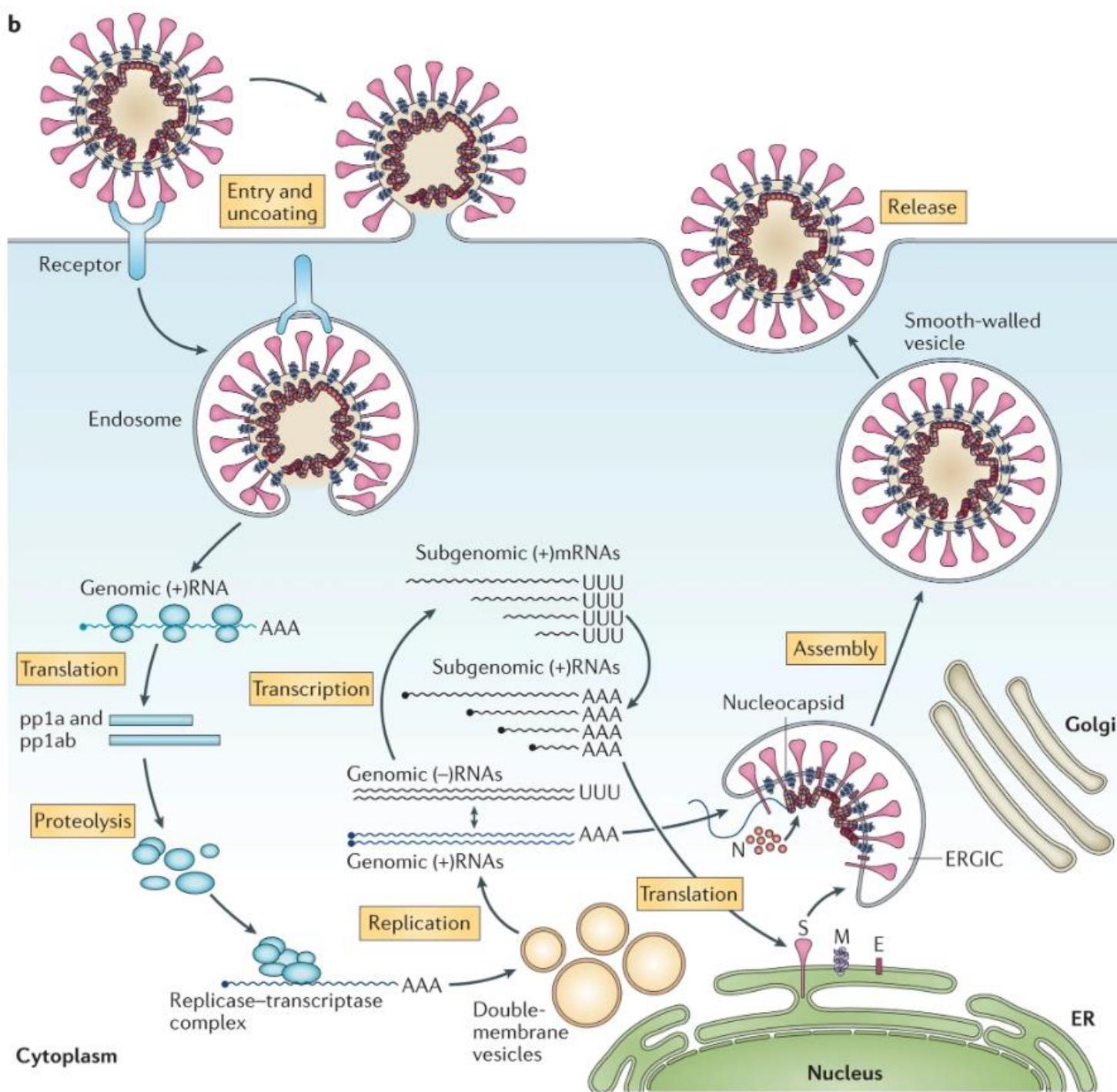


Biology

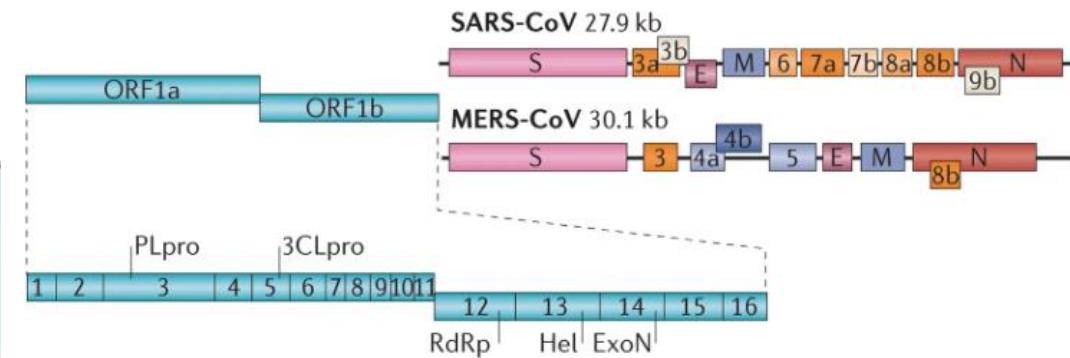
- SARS-CoV-2 can use ACE-2 from humans, Chinese horseshoe bats, civet cats, bats, monkeys, and pigs to gain entry into ACE-2-expressing HeLa cells.
- To enter a cell, Spike (S) protein needs to be cleaved by cellular proteases at 2 sites, termed S protein priming, so the viral and cellular membranes can fuse.
- Specifically, S protein priming by the serine protease TMPRSS2 is crucial for infection of target cells.
- TMPRSS2 inhibitors exist - serine protease inhibitor 'camostat mesylate' - partially blocks viral entry.
- More on ACE, ARB, and TMPRSS2 later.



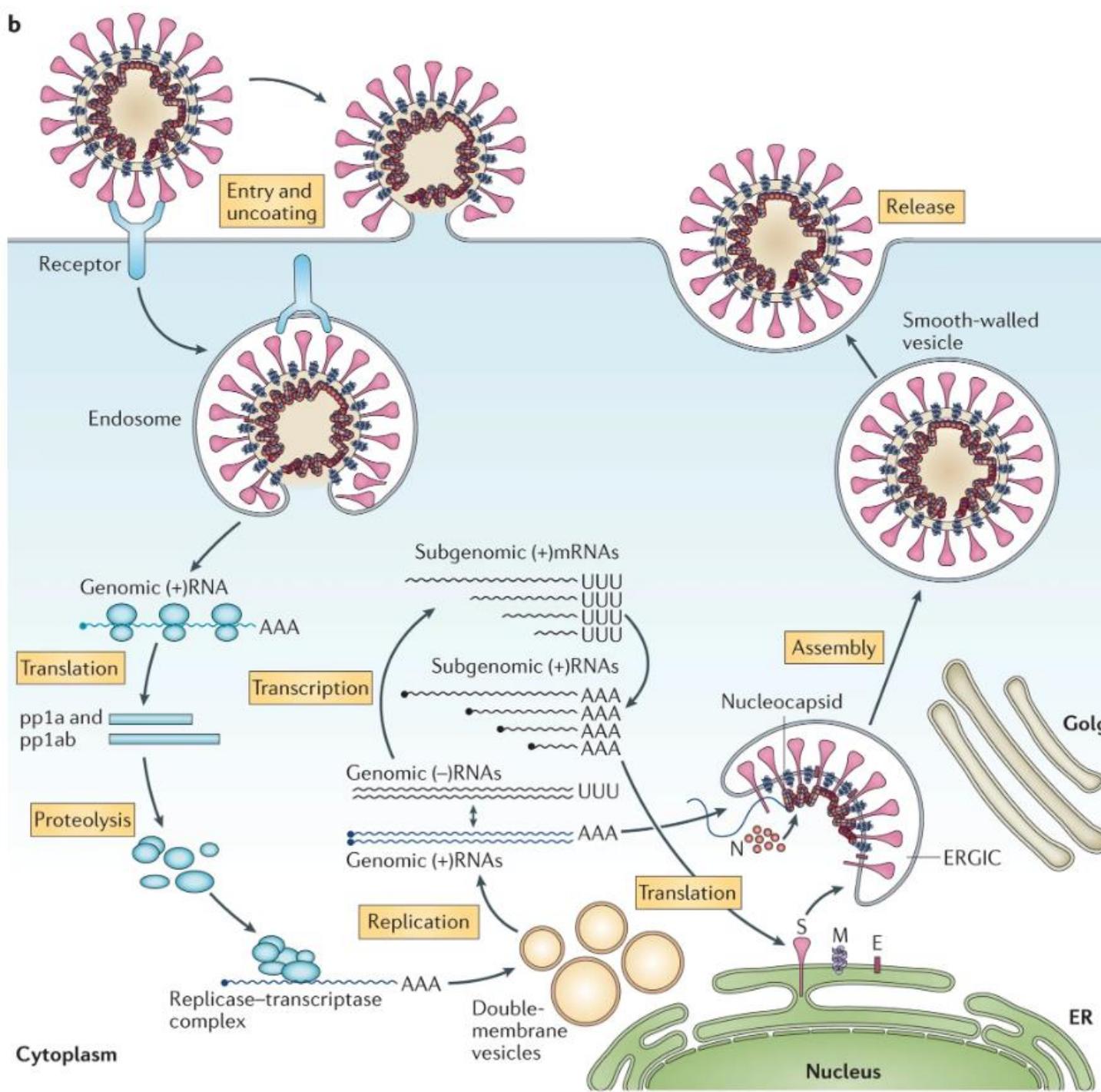
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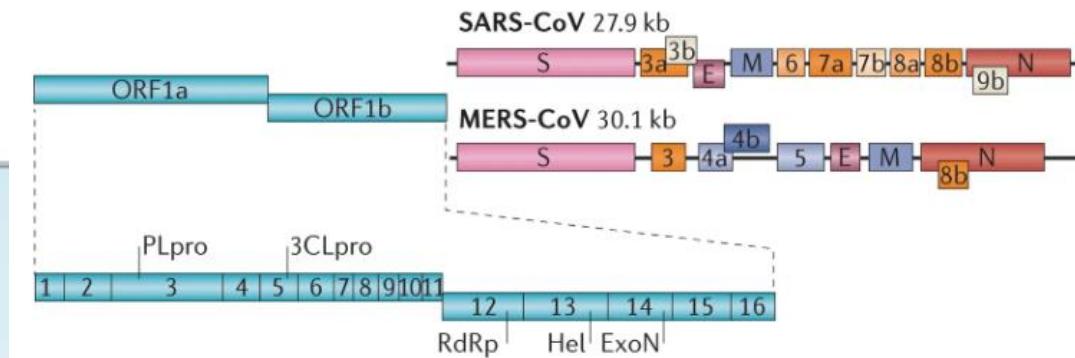
a
Genomes



- Once inside, open reading frame (ORF)1a and (ORF)1ab are translated to produce pp1a and pp1ab, which are cleaved by the proteases that are encoded by ORF1a to yield 16 non-structural proteins that form the RNA replicase-transcriptase complex.



a
Genomes



- Undergo subsequent replication, transcription, and translation.
- The resulting structural proteins are assembled into the nucleocapsid and viral envelope at the ER–Golgi intermediate compartment (ERGIC), followed by release of the virion from the infected cell.

Clinical Presentation – COVID-19

- R₀ for SARS-CoV-2 is estimated at 2.7. The incubation period is estimated at 5–6 days, but may be up to 14 days. The serial interval is estimated to be 8 days.
- The most common symptoms on admission are fever and cough, followed by sputum production and fatigue.

Clinical Presentation – COVID-19

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
Age, years	56·0 (46·0–67·0)	69·0 (63·0–76·0)	52·0 (45·0–58·0)	<0·0001
Sex	0·15
Female	72 (38%)	16 (30%)	56 (41%)	..
Male	119 (62%)	38 (70%)	81 (59%)	..
Exposure history	73 (38%)	14 (26%)	59 (43%)	0·028
Current smoker	11 (6%)	5 (9%)	6 (4%)	0·21
Comorbidity	91 (48%)	36 (67%)	55 (40%)	0·0010
Hypertension	58 (30%)	26 (48%)	32 (23%)	0·0008
Diabetes	36 (19%)	17 (31%)	19 (14%)	0·0051
Coronary heart disease	15 (8%)	13 (24%)	2 (1%)	<0·0001
Chronic obstructive lung disease	6 (3%)	4 (7%)	2 (1%)	0·047
Carcinoma	2 (1%)	0	2 (1%)	0·37
Chronic kidney disease	2 (1%)	2 (4%)	0	0·024
Other	22 (12%)	11 (20%)	11 (8%)	0·016

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	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
Respiratory rate >24 breaths per min	56 (29%)	34 (63%)	22 (16%)	<0.0001
Pulse ≥125 beats per min	2 (1%)	2 (4%)	0	0.024
Systolic blood pressure <90 mm Hg	1 (1%)	0	1 (1%)	0.53
Fever (temperature ≥37.3°C)	180 (94%)	51 (94%)	129 (94%)	0.94
Cough	151 (79%)	39 (72%)	112 (82%)	0.15
Sputum	44 (23%)	14 (26%)	30 (22%)	0.55
Myalgia	29 (15%)	8 (15%)	21 (15%)	0.93
Fatigue	44 (23%)	15 (28%)	29 (21%)	0.33
Diarrhoea	9 (5%)	2 (4%)	7 (5%)	0.67
Nausea or vomiting	7 (4%)	3 (6%)	4 (3%)	0.40
SOFA score	2.0 (1.0–4.0)	4.5 (4.0–6.0)	1.0 (1.0–2.0)	<0.0001
qSOFA score	1.0 (0.0–1.0)	1.0 (1.0–1.0)	0.0 (0.0–1.0)	<0.0001
CURB-65 score	0.0 (0.0–2.0)	2.0 (1.0–3.0)	0.0 (0.0–1.0)	<0.0001
0–1	141/188 (75%)	16 (30%)	125/134 (93%)	<0.0001*
2	32/188 (17%)	23 (43%)	9/134 (7%)	..
3–5	15/188 (8%)	15 (28%)	0/134	..
Disease severity status	<0.0001
General	72 (38%)	0	72 (53%)	..
Severe	66 (35%)	12 (22%)	54 (39%)	..
Critical	53 (28%)	42 (78%)	11 (8%)	..
Time from illness onset to hospital admission, days	11.0 (8.0–14.0)	11.0 (8.0–15.0)	11.0 (8.0–13.0)	0.53

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	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Laboratory findings				
White blood cell count, ×10 ⁹ per L	6·2 (4·5–9·5)	9·8 (6·9–13·9)	5·2 (4·3–7·7)	<0·0001
<4	32 (17%)	5 (9%)	27 (20%)	<0·0001*
4–10	119 (62%)	24 (44%)	95 (69%)	..
>10	40 (21%)	25 (46%)	15 (11%)	..
Lymphocyte count, ×10 ⁹ per L	1·0 (0·6–1·3)	0·6 (0·5–0·8)	1·1 (0·8–1·5)	<0·0001
<0·8	77 (40%)	41 (76%)	36 (26%)	<0·0001
Haemoglobin, g/L	128·0 (119·0–140·0)	126·0 (115·0–138·0)	128·0 (120·0–140·0)	0·30

(Table 1 continues on next page)

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
(Continued from previous page)				
Anaemia	29 (15%)	14 (26%)	15 (11%)	0·0094
Platelet count, $\times 10^9$ per L	206·0 (155·0–262·0)	165·5 (107·0–229·0)	220·0 (168·0–271·0)	<0·0001
<100	13 (7%)	11 (20%)	2 (1%)	<0·0001
Albumin, g/L	32·3 (29·1–35·8)	29·1 (26·5–31·3)	33·6 (30·6–36·4)	<0·0001
ALT, U/L	30·0 (17·0–46·0)	40·0 (24·0–51·0)	27·0 (15·0–40·0)	0·0050
>40	59/189 (31%)	26 (48%)	33/135 (24%)	0·0015
Creatinine >133 $\mu\text{mol}/\text{L}$	8/186 (4%)	5 (9%)	3/132 (2%)	0·045
Lactate dehydrogenase, U/L	300·0 (234·0–407·0)	521·0 (363·0–669·0)	253·5 (219·0–318·0)	<0·0001
>245	123/184 (67%)	53 (98%)	70/130 (54%)	<0·0001
Creatine kinase, U/L	21·5 (13·0–72·4)	39·0 (19·5–151·0)	18·0 (12·5–52·1)	0·0010
>185	22/168 (13%)	11/52 (21%)	11/116 (9%)	0·038
High-sensitivity cardiac troponin I, pg/mL	4·1 (2·0–14·1)	22·2 (5·6–83·1)	3·0 (1·1–5·5)	<0·0001
>28	24/145 (17%)	23/50 (46%)	1/95 (1%)	<0·0001
Prothrombin time, s	11·6 (10·6–13·0)	12·1 (11·2–13·7)	11·4 (10·4–12·6)	0·0004
<16	171/182 (94%)	47 (87%)	124/128 (97%)	0·016*
≥ 16	11/182 (6%)	7 (13%)	4/128 (3%)	..

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	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
D-dimer, µg/mL	0·8 (0·4–3·2)	5·2 (1·5–21·1)	0·6 (0·3–1·0)	<0·0001
≤0·5	55/172 (32%)	4 (7%)	51/118 (43%)	<0·0001*
>0·5 to ≤1	45/172 (26%)	6 (11%)	39/118 (33%)	..
>1	72/172 (42%)	44 (81%)	28/118 (24%)	..
Serum ferritin, µg/L	722·0 (377·2–1435·3)	1435·3 (728·9–2000·0)	503·2 (264·0–921·5)	<0·0001
>300	102/128 (80%)	44/46 (96%)	58/82 (71%)	0·0008
IL-6, pg/mL	7·4 (5·3–10·8)	11·0 (7·5–14·4)	6·3 (5·0–7·9)	<0·0001
Procalcitonin, ng/mL	0·1 (0·1–0·1)	0·1 (0·1–0·5)	0·1 (0·1–0·1)	<0·0001
<0·1	114/164 (70%)	19/51 (37%)	95/113 (84%)	<0·0001*
≥0·1 to <0·25	30/164 (18%)	16/51 (31%)	14/113 (12%)	..
≥0·25 to <0·5	6/164 (4%)	3/51 (6%)	3/113 (3%)	..
≥0·5	14/164 (9%)	13/51 (25%)	1/113 (1%)	..
Imaging features				
Consolidation	112 (59%)	40 (74%)	72 (53%)	0·0065
Ground-glass opacity	136 (71%)	44 (81%)	92 (67%)	0·049
Bilateral pulmonary infiltration	143 (75%)	45 (83%)	98 (72%)	0·090

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	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Treatments*				
Antibiotics	181 (95%)	53 (98%)	128 (93%)	0·15
Antiviral treatment	41 (21%)	12 (22%)	29 (21%)	0·87
Corticosteroids	57 (30%)	26 (48%)	31 (23%)	0·0005
Intravenous immunoglobin	46 (24%)	36 (67%)	10 (7%)	<0·0001
High-flow nasal cannula oxygen therapy	41 (21%)	33 (61%)	8 (6%)	<0·0001
Non-invasive mechanical ventilation	26 (14%)	24 (44%)	2 (1%)	<0·0001
Invasive mechanical ventilation	32 (17%)	31 (57%)	1 (1%)	<0·0001
ECMO	3 (2%)	3 (6%)	0	0·0054
Renal replacement therapy	10 (5%)	10 (19%)	0	<0·0001

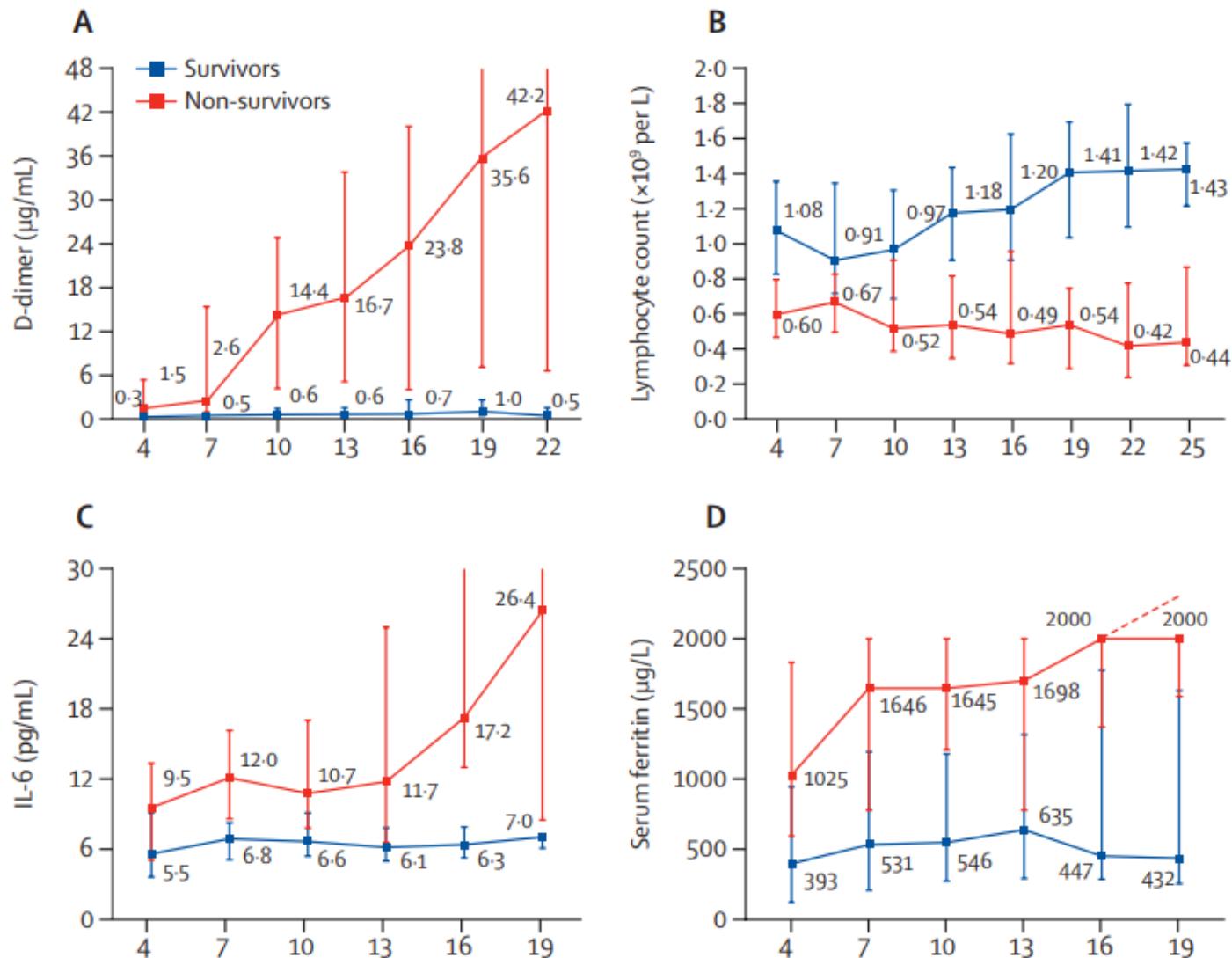
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Outcomes	Total	Non-survivor	Survivor	p value
Sepsis	112 (59%)	54 (100%)	58 (42%)	<0·0001
Respiratory failure	103 (54%)	53 (98%)	50 (36%)	<0·0001
ARDS	59 (31%)	50 (93%)	9 (7%)	<0·0001
Heart failure	44 (23%)	28 (52%)	16 (12%)	<0·0001
Septic shock	38 (20%)	38 (70%)	0	<0·0001
Coagulopathy	37 (19%)	27 (50%)	10 (7%)	<0·0001
Acute cardiac injury	33 (17%)	32 (59%)	1 (1%)	<0·0001
Acute kidney injury	28 (15%)	27 (50%)	1 (1%)	<0·0001
Secondary infection	28 (15%)	27 (50%)	1 (1%)	<0·0001
Hypoproteinaemia	22 (12%)	20 (37%)	2 (1%)	<0·0001
Acidosis	17 (9%)	16 (30%)	1 (1%)	<0·0001
ICU admission	50 (26%)	39 (72%)	11 (8%)	<0·0001

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	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
ICU length of stay, days	8·0 (4·0–12·0)	8·0 (4·0–12·0)	7·0 (2·0–9·0)	0·41
Hospital length of stay, days	11·0 (7·0–14·0)	7·5 (5·0–11·0)	12·0 (9·0–15·0)	<0·0001
Time from illness onset to fever, days	1·0 (1·0–1·0)	1·0 (1·0–1·0)	1·0 (1·0–1·0)	0·16
Time from illness onset to cough, days	1·0 (1·0–3·0)	1·0 (1·0–1·0)	1·0 (1·0–4·0)	0·30
Time from illness onset to dyspnoea, days	7·0 (4·0–9·0)	7·0 (4·0–10·0)	7·0 (4·0–9·0)	0·51
Time from illness onset to sepsis, days	9·0 (7·0–13·0)	10·0 (7·0–14·0)	9·0 (7·0–12·0)	0·22
Time from illness onset to ARDS, days	12·0 (8·0–15·0)	12·0 (8·0–15·0)	10·0 (8·0–13·0)	0·65
Time from illness onset to ICU admission, days	12·0 (8·0–15·0)	12·0 (8·0–15·0)	11·5 (8·0–14·0)	0·88
Time from illness onset to corticosteroids treatment, days	12·0 (10·0–16·0)	13·0 (10·0–17·0)	12·0 (10·0–15·0)	0·55
Time from illness onset to death or discharge, days	21·0 (17·0–25·0)	18·5 (15·0–22·0)	22·0 (18·0–25·0)	0·0003
Duration of viral shedding after COVID-19 onset, days	20·0 (16·0–23·0)	18·5 (15·0–22·0)†	20·0 (17·0–24·0)	0·024

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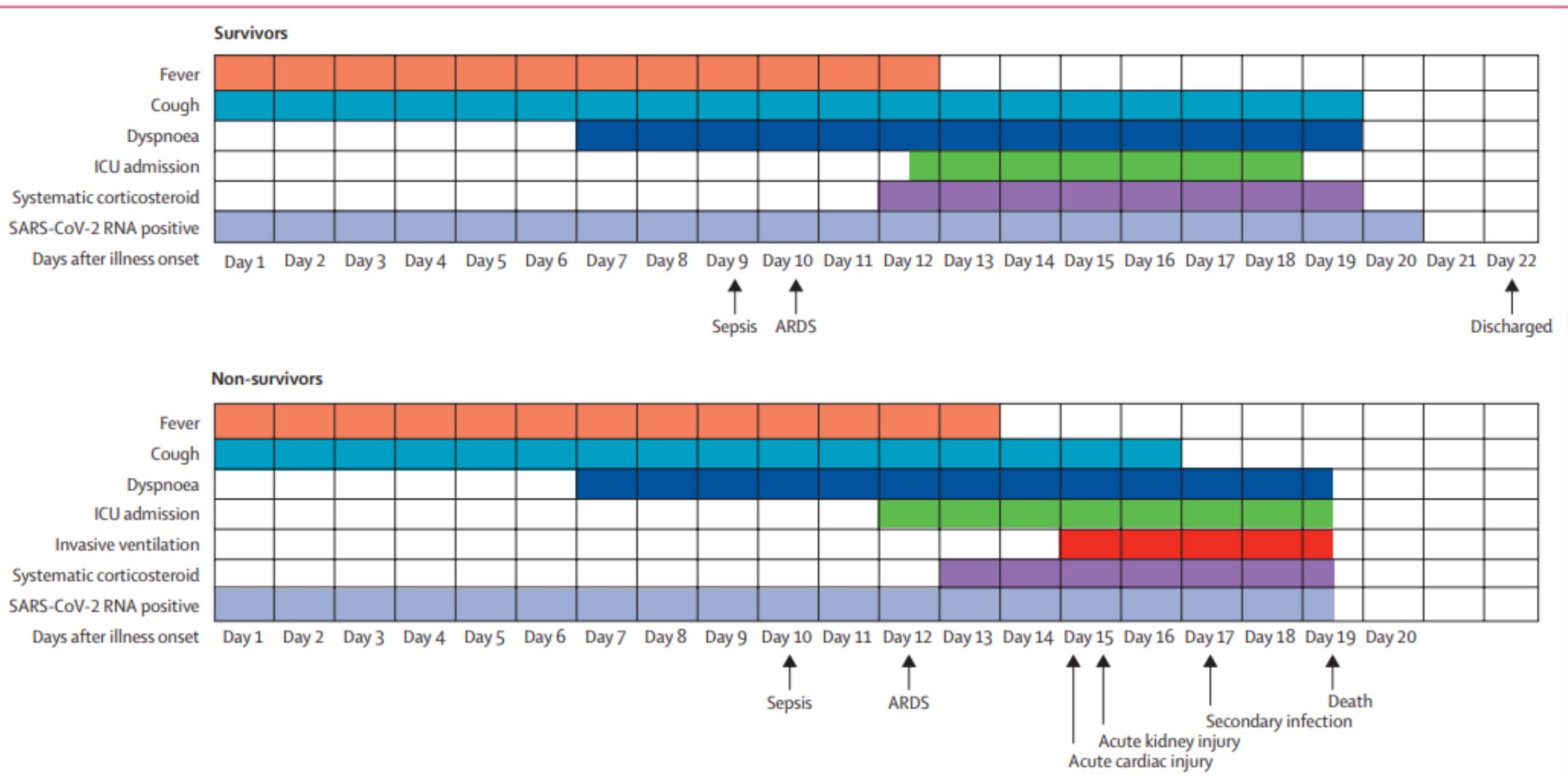


Figure 1: Clinical courses of major symptoms and outcomes and duration of viral shedding from illness onset in patients hospitalised with COVID-19

Figure shows median duration of symptoms and onset of complications and outcomes. ICU=intensive care unit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ARDS=acute respiratory distress syndrome. COVID-19=coronavirus disease 2019.

Clinical Presentation – COVID-19

- [Video: ARDS in a COVID-19 patient](#)
- Courtesy: Giuseppe Curigliano, MD, PhD, Associate Professor at University of Milan.
 - **G Curigliano MD PhD @curijoey**

Clinical Presentation – COVID-19

2.3% of all cases died

1,023 of the 44,415 infected people, for which the breakdown is shown on the right, died. The case fatality rate is therefore 2.3%.

5% Critical cases

Critical cases include patients who suffered respiratory failure, septic shock, and/or multiple organ dysfunction/failure.

14% Severe cases

Severe cases include patients suffer from shortness of breath, respiratory frequency \geq 30/minute, blood oxygen saturation $\leq 93\%$, PaO₂/FiO₂ ratio <300 , and/or lung infiltrates $>50\%$ within 24–48 hours.

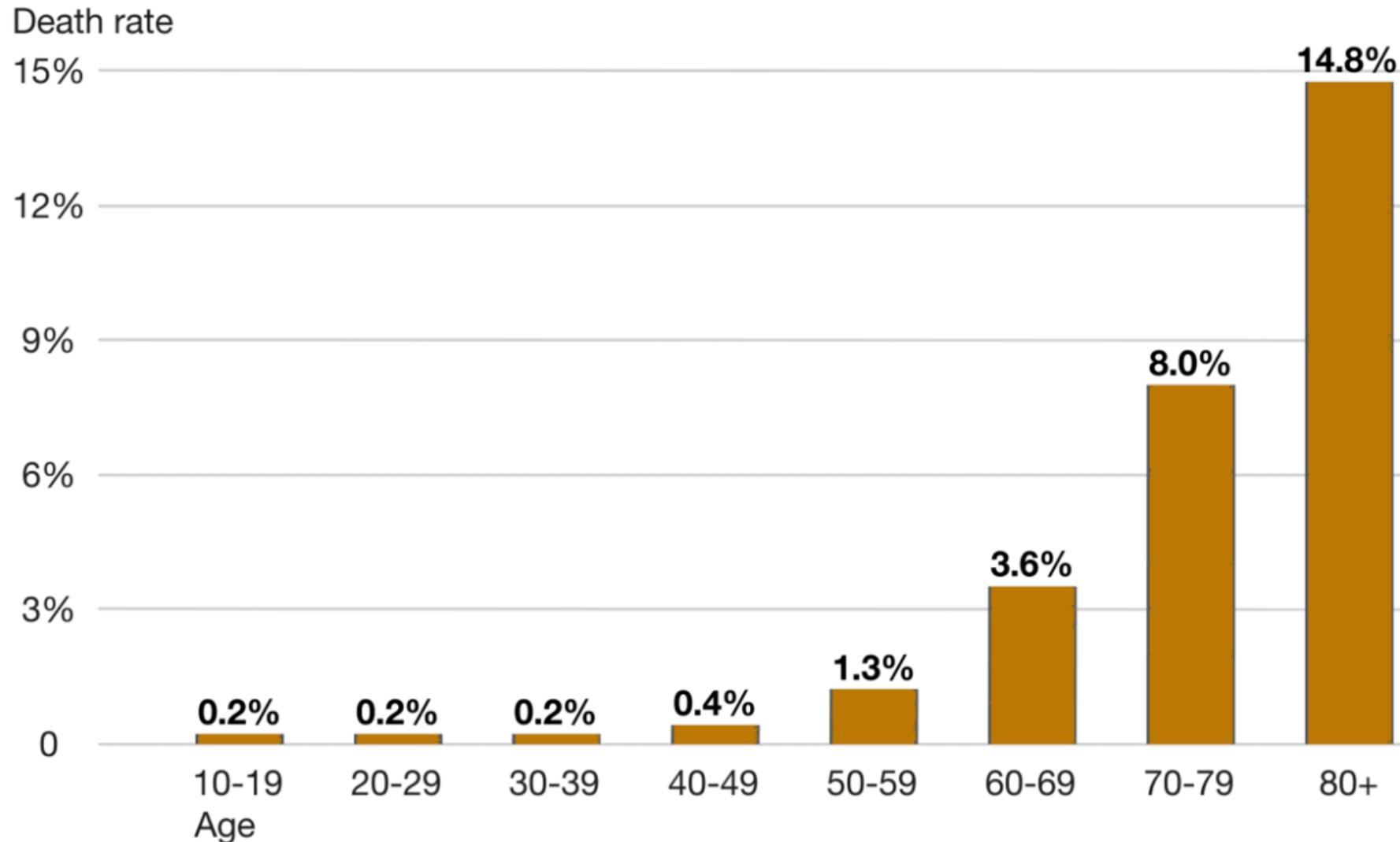
81% Mild cases

Mild cases include all patients without pneumonia or cases of mild pneumonia.

Cases that were not identified and not diagnosed

Clinical Presentation – COVID-19

COVID-19 Fatality Rate by AGE



Clinical Presentation – COVID-19 – In Oncology Patients

- Retrospective registry analysis. 18 (1%; 95% CI 0.61–1.65) of 1590 COVID-19 cases had a history of cancer, out of proportion to incidence of cancer in the overall Chinese population (285.83 [0.29%] per 100 000 people).
- Lung cancer was the most frequent type (five [28%] of 18 patients).
- Four (25%) of 16 patients (two of the 18 patients had unknown treatment status) with cancer + COVID-19 had received chemotherapy or surgery within the past month, and the other 12 (75%) patients were cancer survivors in routine follow-up after treatment.

Clinical Presentation – COVID-19 – In Oncology Patients

- Compared with patients without cancer, patients with cancer were:
 - Older (mean age 63.1 years [SD 12.1] vs 48.7 years [16.2]),
 - More likely to have a history of smoking (four [22%] of 18 patients vs 107 [7%] of 1572 patients),
 - Had more severe baseline CT manifestation (17 [94%] of 18 patients vs 1113 [71%] of 1572 patients), but had no significant differences in sex, other baseline symptoms, other comorbidities, or baseline severity of x-ray.

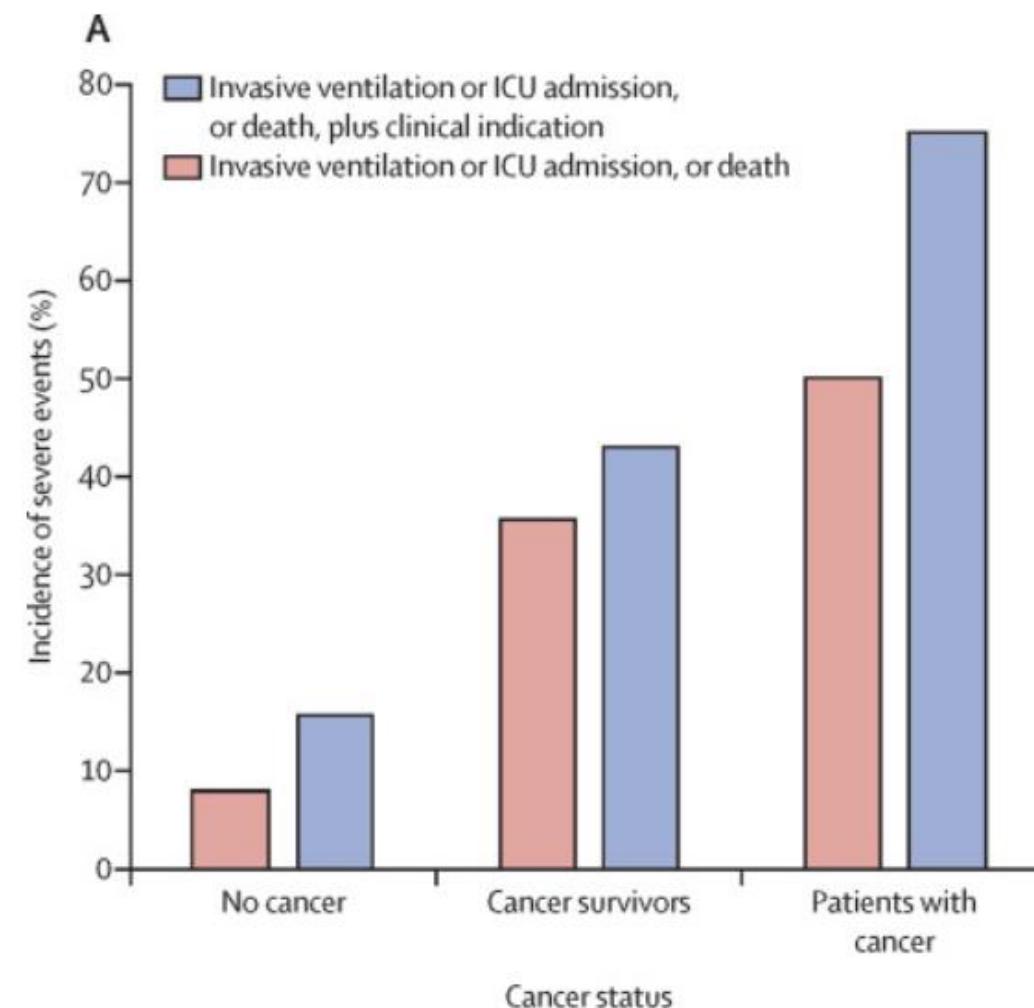
Table S1. Baseline Information of Cases with Cancer History

ID	District*	Time*	Sex	Complication	Age	Course*(year)	Tumor Type	Phase	Severe events (Yes/No)
NO.1	Hubei	2020/1/22	Male	No	83	4	Bladder cancer	Postoperative routine follow-up	Yes
NO.2	Hubei	2020/1/9	Male	Diabetes, Hypertension	87	2	Colonic tubular adenocarcinoma	Postoperative routine follow-up	Yes
NO.3	Hubei	2020/1/3	Male	No	67	0	Adrenal neoplasms	3 weeks after operation	Yes
NO.4	Hubei	2020/1/9	Female	No	68	8	Breast cancer	Surgical resection plus adjuvant chemotherapy 8 years ago	Yes
NO.5	Hubei	2020/1/14	Male	No	58	7	CRCC*	Recurrence, in immunotherapy	Yes
NO.6	Zhejiang	2020/1/20	Female	No	62	4	Breast cancer	Surgical resection plus adjuvant chemotherapy 4 years ago	Yes
NO.7	Zhejiang	2020/1/20	Male	No	56	5	Rectal carcinoma	Surgical resection plus adjuvant chemotherapy 5 years ago	No
NO.8	Guangdong	2020/1/19	Male	No	53	16	Transverse colon cancer	Surgical resection plus adjuvant chemotherapy 16 years ago	No
NO.9	Hubei	2020/1/13	Female	No	63	1	Papillary thyroid microcarcinoma	Postoperative, in TSH inhibition therapy	No
NO.10	Shanxi	2020/1/23	Male	No	47	1	Lung adenocarcinoma	In chemotherapy for advanced tumor	No
NO.11	Zhejiang	2020/1/20	Female	No	52	0.5	Breast cancer	Postoperative, loss of chemotherapy information	No
NO.12	Shandong	2020/1/25	Male	No	47	1	Lymphoma	N.A.	No
NO.13	Hubei	2020/1/12	Male	Diabetes, Hypertension, Cerebrovascular disease	80	4	Bladder cancer	Postoperative, no chemotherapy information	Yes
NO.14	Hubei	2019/12/27	Male	COPD*	79	5	Colorectal carcinoma	Surgical resection plus adjuvant radiotherapy 5 years ago	Yes
NO.15	Hubei	2020/1/17	Male	No	63	1	Lung adenocarcinoma	In chemotherapy for advanced tumor	Yes
NO.16	Hubei	2020/1/23	Female	CKD*	58	2	Lung carcinoma in situ	Postoperative routine follow-up	No
NO.17	Hubei	2020/1/17	Male	No	58	2	Lung adenocarcinoma	Postoperative, In targeted therapy	No
NO.18	Hubei	2020/1/26	Female	No	55	6	Lung adenocarcinoma	Advanced, In targeted therapy	No

* District: District of Diagnosis; Time: Time of Preliminary Diagnosis; Course: Course of Tumor; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CRCC: chromophobe renal cell carcinoma

Clinical Presentation – COVID-19 – In Oncology Patients

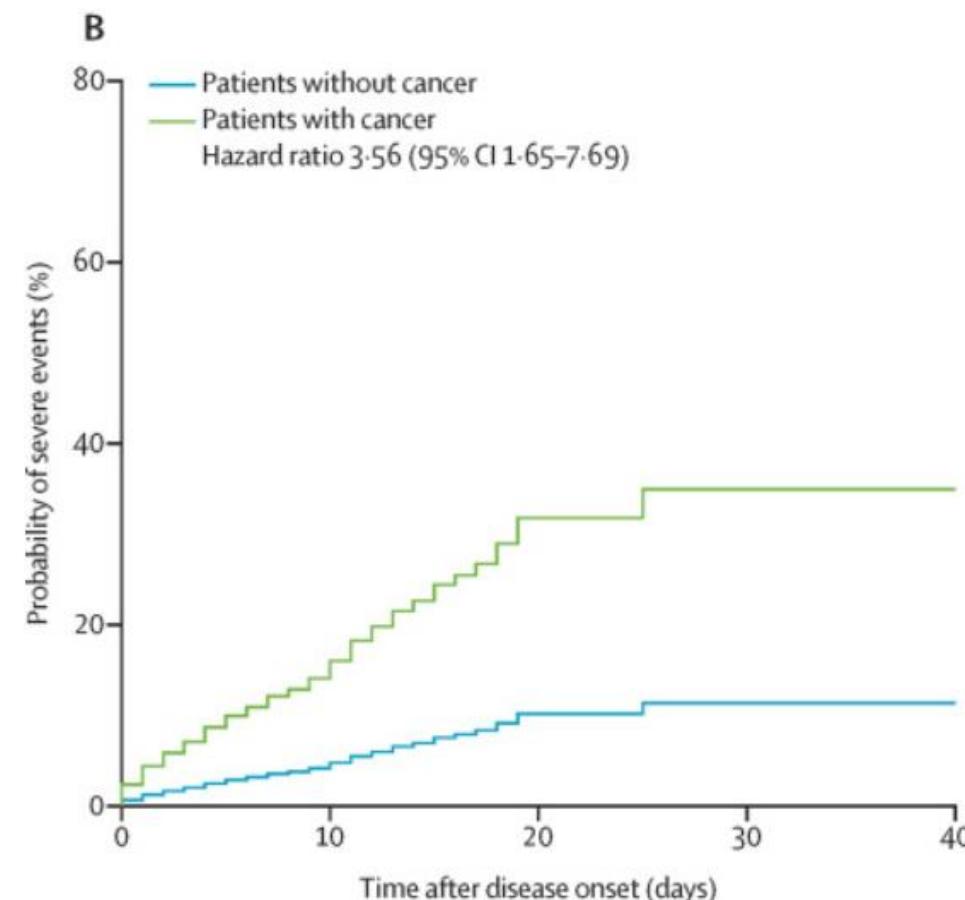
- Oncology patients – higher risk of severe events compared with patients without cancer (seven [39%] of 18 patients vs 124 [8%] of 1572 patients; $p=0.0003$).
- Similar results when the severe events were defined both by the severe events + by physician evaluation (nine [50%] of 18 patients vs 245 [16%] of 1572 patients; $p=0.0008$).
- Patients who underwent chemotherapy or surgery in the past month had further increased risk (three [75%] of four patients) of clinically severe events versus those not receiving chemotherapy or surgery (six [43%] of 14 patients).



Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020; S1470-2045(1420):30096.

Clinical Presentation – COVID-19 – In Oncology Patients

- Outcome remained true after adjusting for other risk factors, including age, smoking history, and other comorbidities (odds ratio [OR] 5.34, 95% CI 1.80–16.18; $p=0.0026$).
- Cancer history represented the highest risk for severe events.
- Patients with lung cancer did not have a higher probability of severe events compared with patients with other cancer types.
- Patients with cancer deteriorated more rapidly than those without cancer (median time to severe events 13 days vs 43 days $p<0.0001$; hazard ratio 3.56, 95% CI 1.65–7.69).



Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020; S1470-2045(1420):30096.

Clinical Presentation – COVID-19 – In Pediatric Patients

- Children are less commonly affected by SARS-CoV-2. Based on Chinese Centers for Disease Control and Prevention reporting, of 72,314 cases reported as of publication, only 2% were in children.
- There are 3 case series of children who have been infected with SARS-CoV-2.
 - The first included 20 children up to January 31, 2020, in the Province of Zhejiang,
 - The second 34 children between January 19, 2020, and February 7, 2020, in the Province of Shenzhen,
 - The third 9 infants from different provinces in China.



Clinical Presentation – COVID-19 – In Pediatric Patients

- The case series with 34 children provides the most clinical details:
 - None of the children had an underlying disease,
 - 65% had common respiratory symptoms,
 - 26% had mild disease and
 - 9% were asymptomatic.
 - The most common symptoms were fever (50%) and cough (38%).
- In the case series of 20 children, presentation was with low to moderate or no fever, rhinitis, cough, fatigue, headache, diarrhea and, in more severe cases, with dyspnea, cyanosis and poor feeding, but the numbers were not specified.
- In the series of 9 infants, only 4 were reported to have fever. One infant was asymptomatic. Additional asymptomatic children infected with SARS-CoV-2 outside these case series.
- Most infected children recover 1–2 weeks after the onset of symptoms and no deaths from SARS-CoV-2 had been reported as of publication.



Clinical Presentation – COVID-19 – In Pediatric Patients

- Based on the series, it appears that children have milder clinical symptoms than adults. Implicaiton - children might not be tested for SARS-CoV-2 as frequently as adults.
- It has therefore been suggested that asymptomatic or mildly symptomatic children might transmit the disease.
- However, the majority of children infected with SARS-CoV-2 thus far have been part of a family cluster outbreak [100% in the infants series, in which other family member had symptoms before the infants in all cases; 82% in the case series of 34 children; and the majority in the one with 20 children (exact number not specified)].
- A study prepublished in early March 2020 suggests that children are just as likely as adults to become infected with SARS-CoV-2 but are less likely to be symptomatic or develop severe symptoms.
- From a small case series of 9 mothers who were infected with SARS-CoV-2, there is, to date, no evidence that SARS-CoV-2 can be vertically transmitted to the infant.



Clinical Presentation – COVID-19 – In Pediatric Patients

- The WBC is typically normal or reduced with decreased neutrophil and/or lymphocyte counts. Thrombocytopenia may occur.
- C-reactive protein and procalcitonin levels are often normal.
- In severe cases, elevated liver enzymes, lactate dehydrogenase levels, as well as abnormal coagulation and elevated D-dimers have been reported.
- In the case series of 34 children, the white blood cell count was normal in 83%, neutropenia and lymphopenia were each found in 1 case (3%). The lactate dehydrogenase level was elevated in 30% of cases. C-reactive protein and procalcitonin levels were each elevated in 1 case only (3%)



Clinical Presentation – COVID-19 – In Pediatric Patients

- Similar to the laboratory findings, radiologic findings from children are also similar across infections with different novel CoVs.
- On chest radiography, children mostly show bilateral patchy airspace consolidations often at the periphery of the lungs, peribronchial thickening and ground-glass opacities.
- Chest CT mostly shows bilateral multiple patchy, nodular ground-glass opacities, speckled ground-glass opacities and/or infiltrating shadows in the middle and outer zone of the lung or under the pleura.
- These findings are unspecific and milder compared with those in adults.

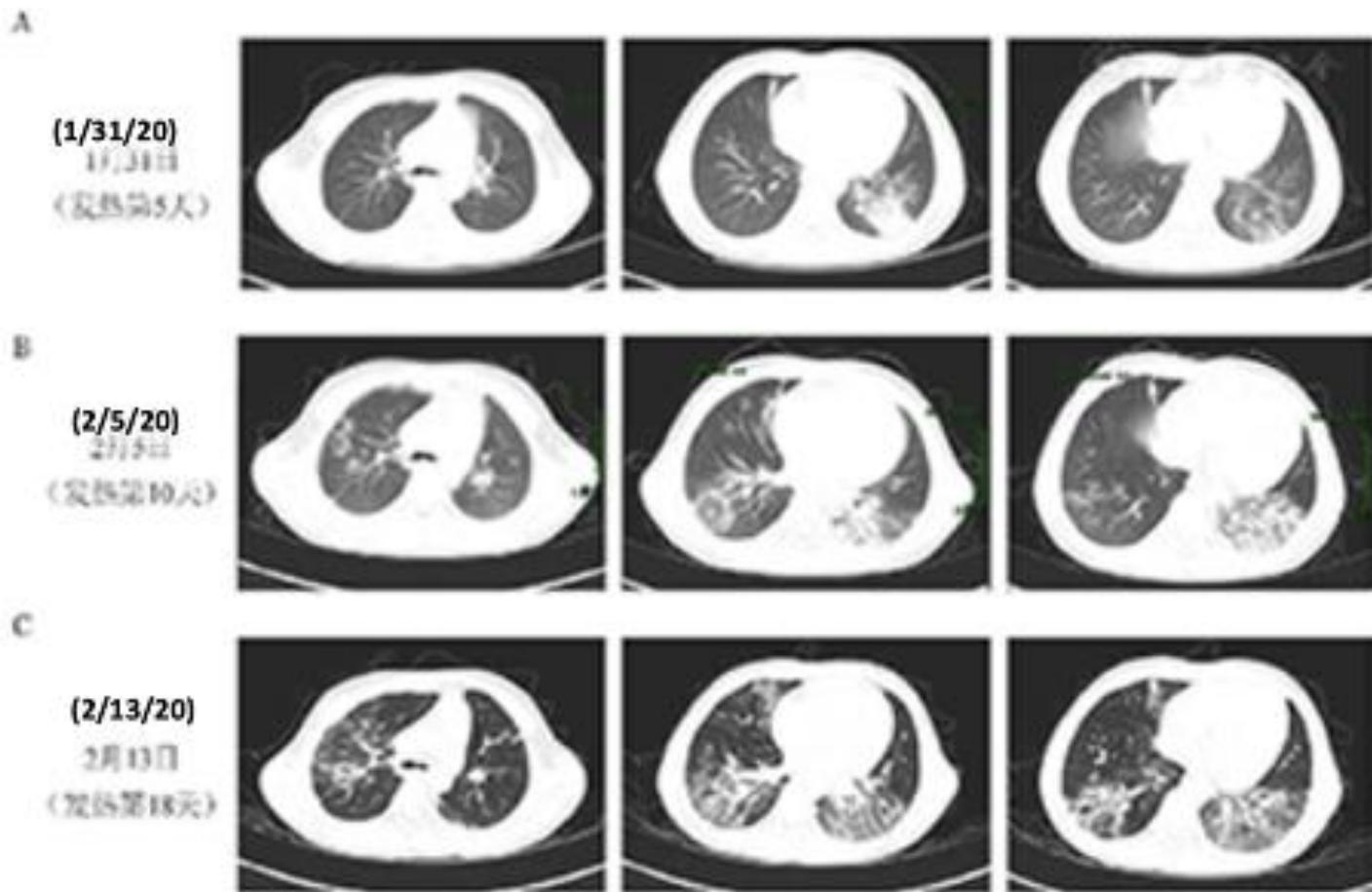


Clinical Presentation – COVID-19 – In Pediatric Immunocompromised Patients

- Minimal data available. First published report identified of single patient
- Chinese Language, translation provided courtesy of Joshua Wolf, PhD, MBBS (@JoshuaWolf) (Pediatric Infectious Disease, St Jude).
- "Most descriptions of children with COVID-19 have been reassuring, few have had severe disease and most recover rapidly. However, there is some concern that immunocompromised children will fare worse."
- "The patient developed severe disease despite multiple therapies. Here are a few important features:"
 - Patient is an 8 year old male with T-cell acute lymphoblastic leukemia, 1 year into therapy and in remission, and on maintenance chemotherapy.
 - The suspected incubation period was 14 days (1/13/20 - 1/27/20). This is relatively long compared with other reports.

Clinical Presentation – COVID-19 – In Pediatric Immunocompromised Patients

- The child had a slow deterioration, starting with fever and cough, then progression to respiratory failure 22 days after presentation.
- CT chest was abnormal throughout and worsened over time. It showed bilateral ground glass opacities with some areas of dense consolidation and small pleural effusions.



Clinical Presentation – COVID-19 – In Pediatric Immunocompromised Patients

- The deterioration did not seem to be related to the hyperinflammatory syndrome described in adults; CRP (max. 8.4mg/L) and IL6 (max 36.5 ng/L) were only mildly elevated despite high fever and severe lung disease.
- In contrast to CRP and IL6, ferritin was very elevated (first measured on Day 9 at 15,000 ng/mL) but fell as the illness worsened (6400 ng/mL on Day 24 at transfer to ICU). Deterioration coincided with increase in ANC and decrease in ALC.

日期	(Values)						(cytokines) (ng/L)					
	WBC ($\times 10^3/L$)	ANC ($\times 10^3/L$)	ALC ($\times 10^3/L$)	(Monos) ($\times 10^3/L$)	CRP (mg/L)	(Procalc.) (Ferritin) ($\mu g/L$)	IL-2 (ng/L)	IL-4 (ng/L)	IL-6 (ng/L)	IL-10 (ng/L)	TNF- α (ng/L)	IFN- γ (ng/L)
(1/28/20)	0.88	0.01	0.54	0.08	6.48	0.25 (N/A)	1.53	2.97	36.46	11.59	1.36	3.37
(2/6/20)	1.65	0.78	0.69	0.17	2.98	0.11 15 758	1.52	2.54	15	7.62	1.04	4.48
(2/14/20)	1.24	0.62	0.39	0.22	1.63	0.18 8 725	1.25	2.71	7.79	6.10	2.73	4.52
(2/17/20)	2.55	1.98	0.36	0.21	1.38	0.16 7 295	1.27	2.30	18.28	7.02	0.90	5.80
(2/19/20)	1.98	1.66	0.15	0.17	8.84	0.20 6 417	1.53	1.44	16.14	5.65	1.24	5.38
(Normal range)	5.50-12.20	1.08-3.90	1.15-6.00	0.26-2.40	0-3.00	0-0.05 22-322	0-11.4	0-12.9	0-20.9	0-5.9	0-5.5	0-17.3

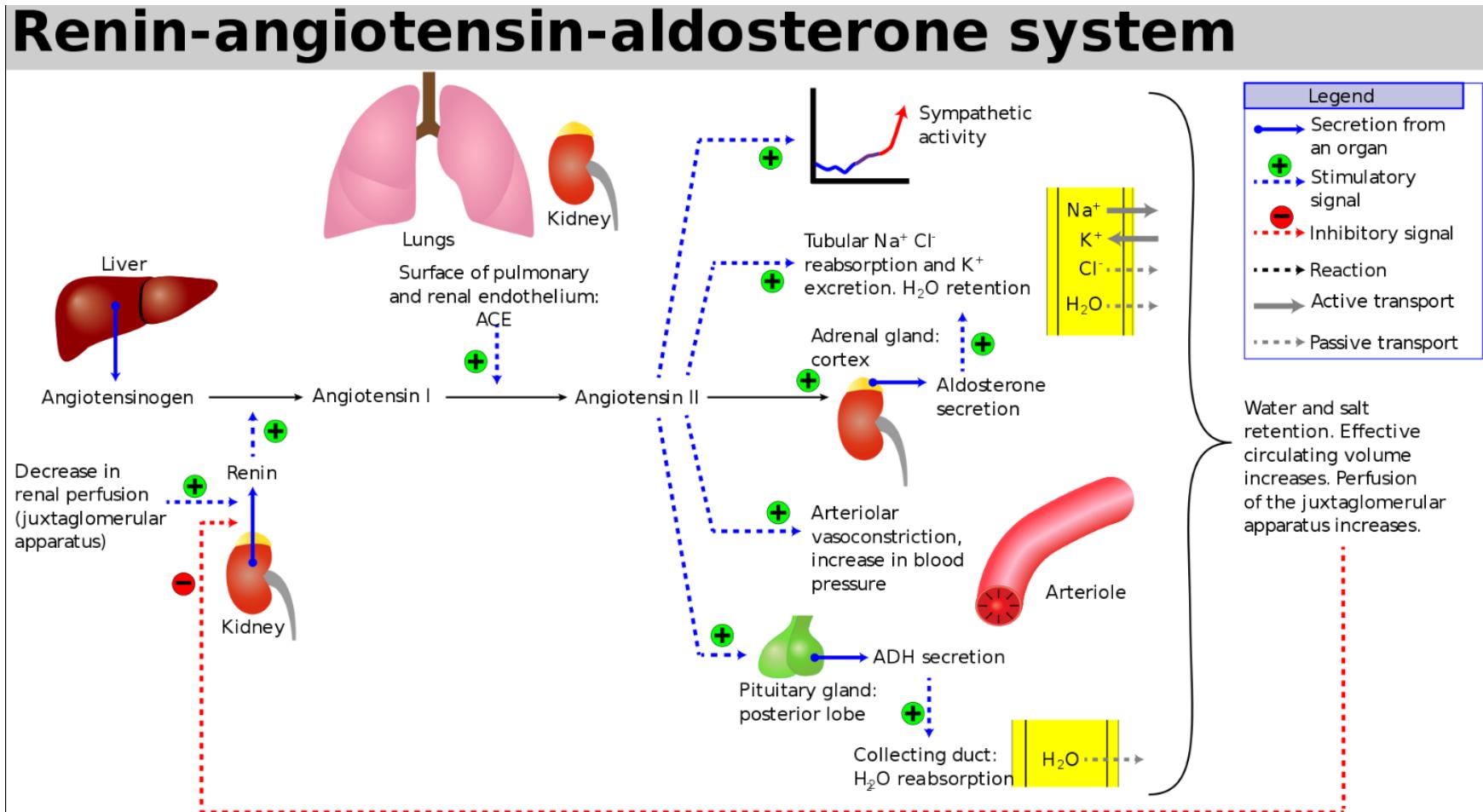
注：ANC：中性粒细胞绝对计数 ALC：淋巴细胞绝对计数；CRP：超敏 C 反应蛋白

Clinical Presentation – COVID-19 – In Pediatric Immunocompromised Patients

- Attempted treatments at various doses and routes included:
Empiric antibiotics and antifungals, oseltamivir, IVIG, methylprednisolone, ribavirin, Interferon alpha-1b, arbidol (umifenovir).
- The eventual outcome of the patient is not included in the report.

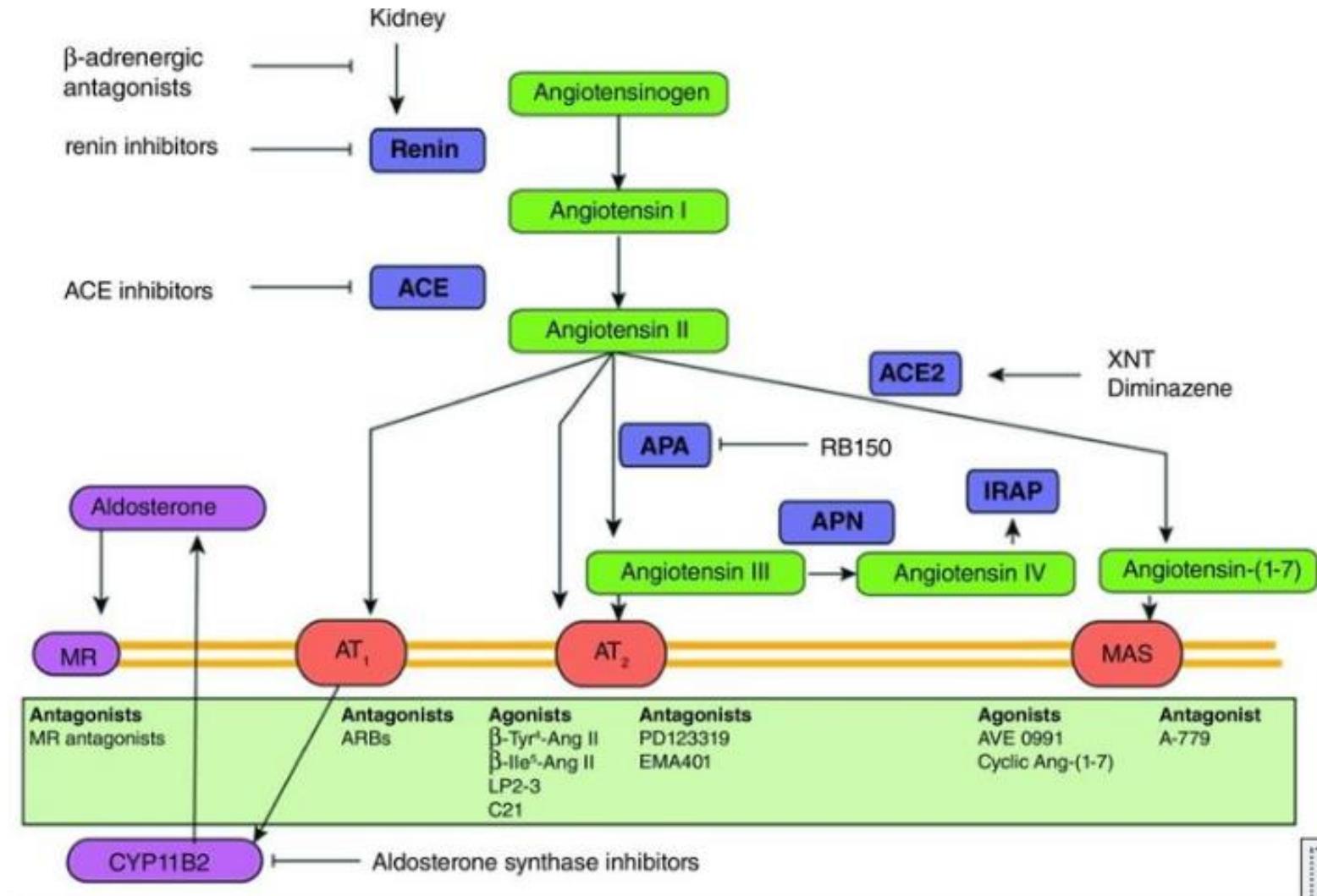
Potential Therapeutic Options – ACE Inhibitors?

- ACE inhibitors reduce the activity of the renin–angiotensin–aldosterone system (RAAS); block the conversion of Angiotensin 1 to Angiotensin 2.
- (E.g. benazepril, zofenopril, perindopril, trandolapril, captopril, enalapril, lisinopril, and ramipril.)
- Renin activates the angiotensinogen via by proteolytic cleavage to angiotensin I.
- ACE then further cleaves angiotensin 1, converting it to angiotensin 2 (active).
- SARS-COV-2 – ACE2 is receptor, not ACE.



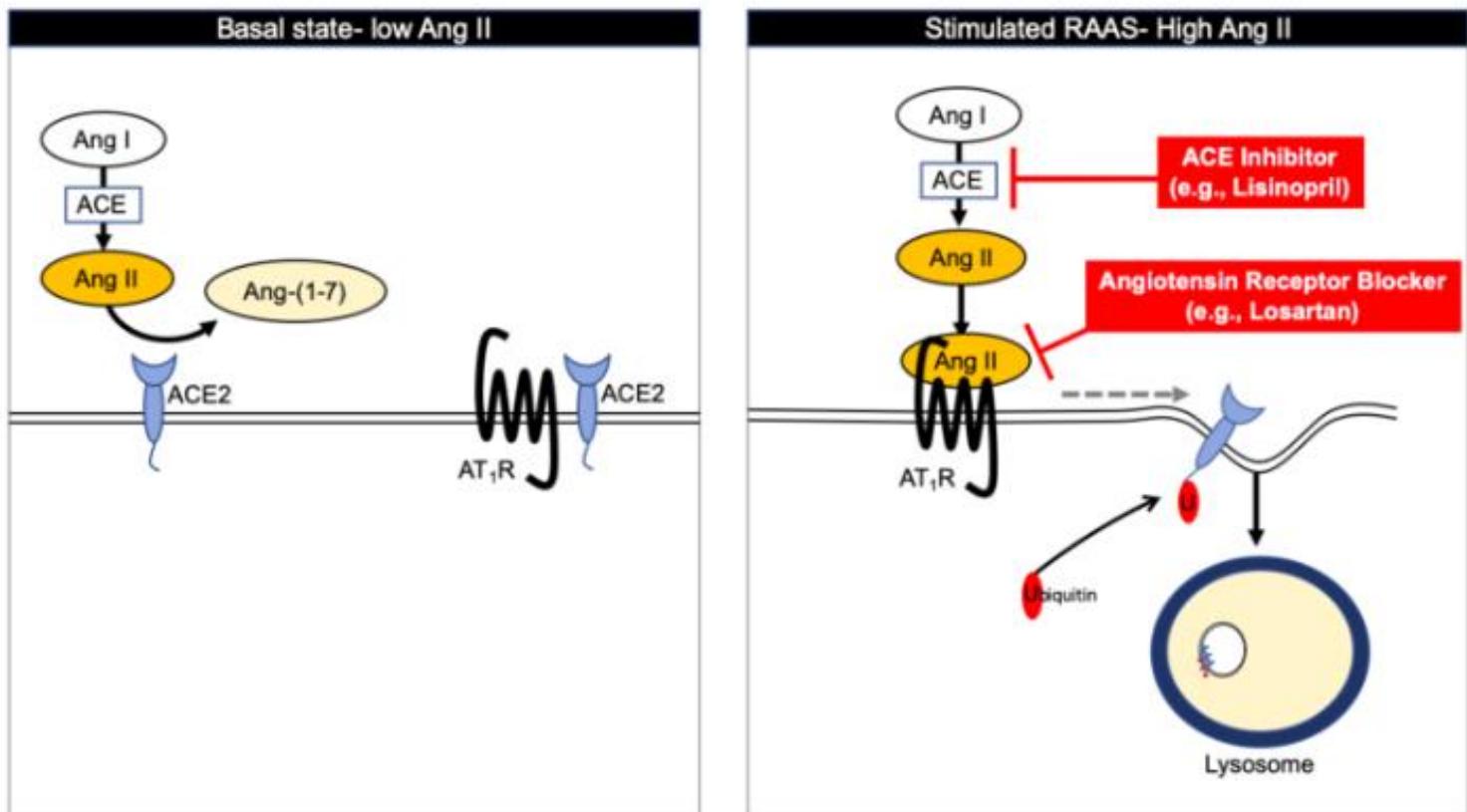
Potential Therapeutic Options – ARBs?

- Angiotensin II receptor blockers- ARBS (e.g. losartan, irbesartan, olmesartan, candesartan, valsartan, fimasartan and azilsartan).
- Angiotensin converting enzyme 2 (ACE2) is a homolog of ACE.
- ACE2 negatively regulates the renin angiotensin system by converting angiotensin 2 to angiotensin 1-7.
- Effect of this is two-fold:
 - Reducing amount of primary effector of the RAS, angiotensin 2, thus decreasing vasoconstriction.
 - Production of the vasodilatory Ang 1-7.
- Net effect is less vasoconstriction, hence use for hypertension.



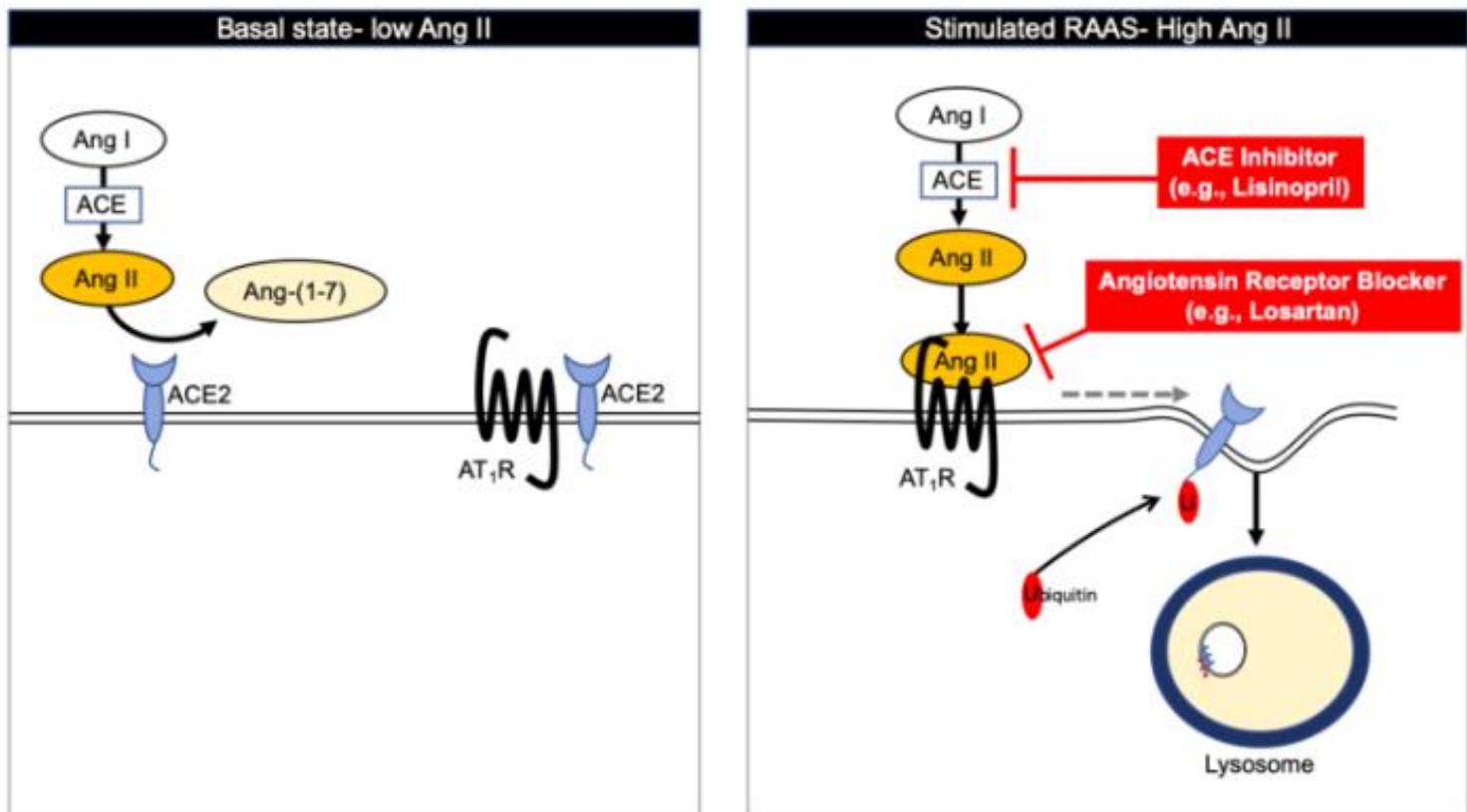
Potential Therapeutic Options – ARBs?

- ACE2 interacts with the type I angiotensin receptor, AT1R. ACE2+AT1R form complexes on the cell membrane.
- AT1R is the site of action/target of ARBS.
- Angiotensin 2 causes reduced expression of ACE2, because after AT1R binds to angiotensin 2, ACE2 is internalized.
- This internalization is prevented by AT1R antagonism by the ARBs.



Potential Therapeutic Options – ARBs?

- The clinical impact of this remains uncertain, but could provide another mechanism by which ACE inhibition or ARBs could prevent COVID-19 viral entry.
- If the viral protein interaction with ACE2 is reduced in ACE2-AT1R complexes, then ARBs could prove beneficial, as administration of an ARB could stabilize the ACE2-AT1R interaction and prevent viral protein-ACE2 interaction and internalization.
- It remains unknown if prevention of ACE2 internalization could prevent viral infection with the SARS or COVID-19 virus.

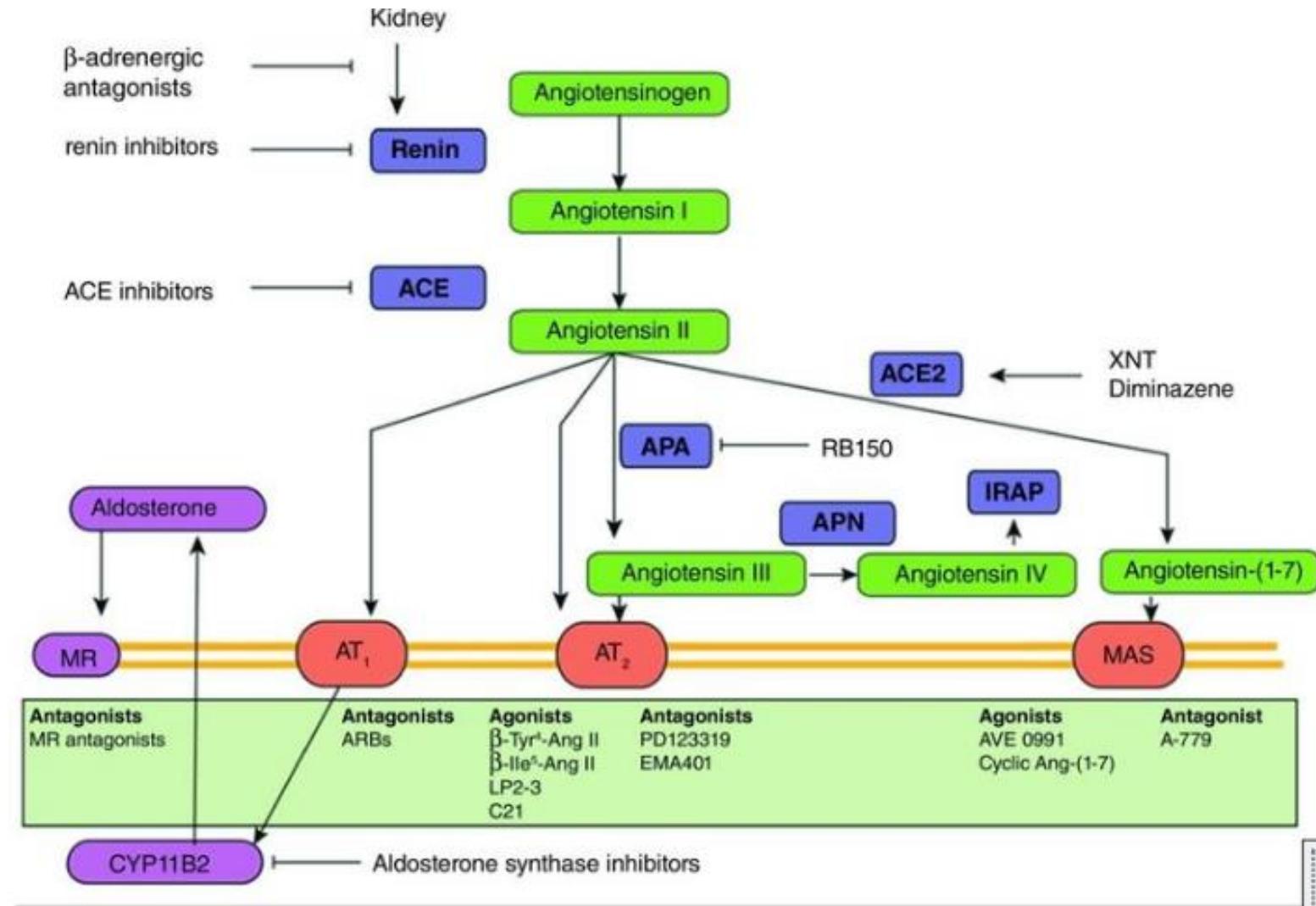


Potential Therapeutic Options – ARBs?

- ARBs increase ACE2 expression 3x following chronic treatment, in multiple tissues. Additionally, higher urinary ACE2 levels are observed in hypertensive patients treated with ARBs.
- Therefore suggestion to treat COVID-19 patients with ARBs to increase ACE2 expression seems counter-intuitive.

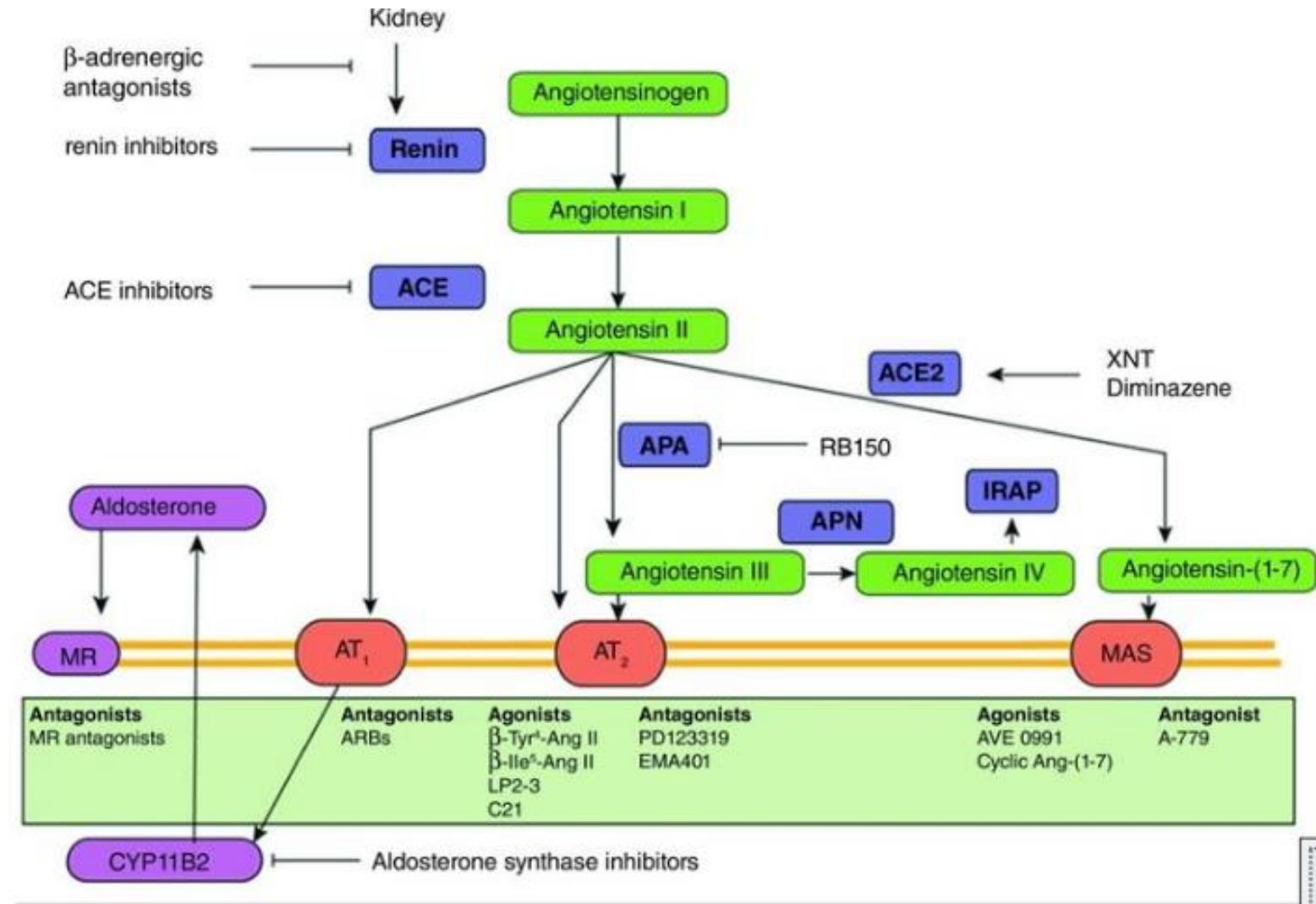
Potential Therapeutic Options – ARBs?

- However, several observations exist that make this an option:
 - Binding of the coronavirus to ACE2 leads to ACE2 downregulation, resulting in preserved high levels of angiotensin 2, with less angiotensin 1–7 produced.
 - This contributes to lung injury, as angiotensin-stimulated AT1R results in increased pulmonary vascular permeability.



Potential Therapeutic Options – ARBs?

- However, several observations exist that make this an option:
 - Therefore, higher ACE2 expression that would result from treatment of SARS-CoV-2 infected patients with ARBs, while seemingly paradoxical, may protect them against acute lung injury.
 - This is due to (a) blocking the excessive angiotensin-mediated AT1R activation caused by the viral infection, and (b) upregulating ACE2, thereby reducing angiotensin production by ACE and increasing the production of the vasodilator angiotensin 1–7.



Potential Therapeutic Options - TMPRSS2 blockade?

- Inhibiting TMPRSS2 activity blocks SARS-CoV-2 entry – recall, for SARS-CoV-2 to enter a host cell, S protein needs to be cleaved by cellular proteases at 2 sites, termed S protein priming, so the viral and cellular membranes can fuse.
- Specifically, S protein priming by the serine protease TMPRSS2 is crucial for SARS-CoV-2 infection of target cells and spread throughout the host.
- TMPRSS2 - Transmembrane protease, serine 2. Involved with androgen receptor signaling - "aberrant activation of the ERG oncogenic pathway due to the TMPRSS2-ERG gene fusion is the major event that contributes to prostate cancer development."

Potential Therapeutic Options - TMPRSS2 blockade?

- Camostat mesylate, a serine protease inhibitor and inhibitor of TMPRSS2, partially blocks entry of SARS-CoV-2 into respiratory epithelial cells in vitro.
- FDA-approved for treatment of pancreatitis. Has also been used for hepatic, renal fibrosis.
- No available data regarding use in humans for COVID-19.

Potential Therapeutic Options - Convalescent Plasma/Sera?

- Passive antibody therapy - administration of antibodies against a given agent to a susceptible individual, to prevent/treat an infectious disease due to that agent.
- Compare with active vaccination - requires induction of an immune response.
- Passive antibody administration is therefore able to provide immediate, temporary immunity.
- Convalescent plasma/sera - derived from recovered individuals.
- Experience from prior outbreaks e.g. SARS-COV in 2002/2003 shows such convalescent sera contain neutralizing antibodies to the relevant virus.

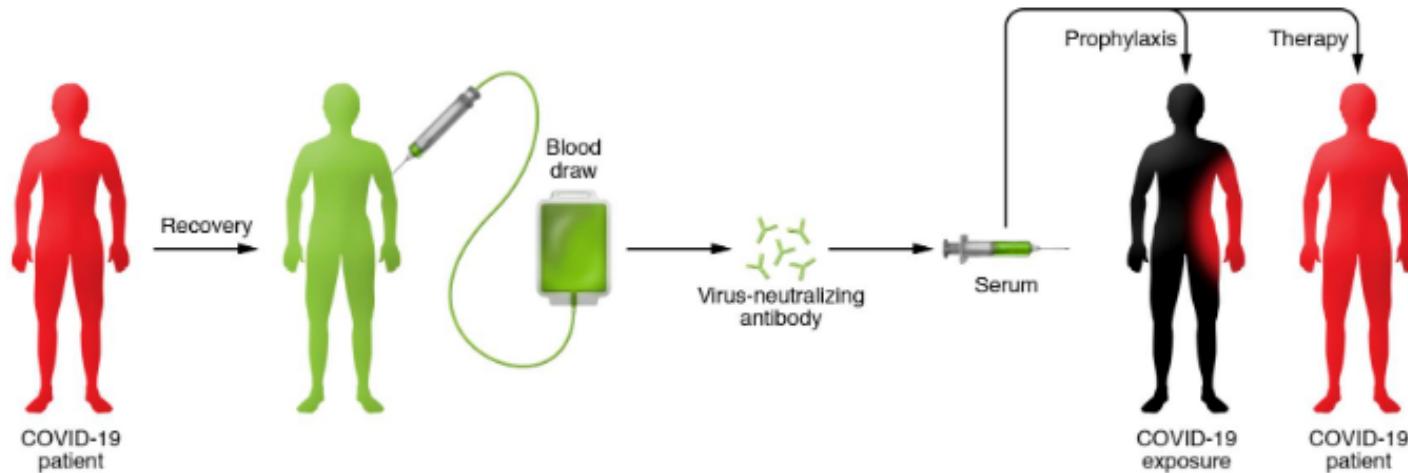


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Potential Therapeutic Options - Convalescent Plasma/Sera?

Schematic of the use of convalescent sera for COVID-19.

Options: [Click-Drag image to reposition](#) | [View smaller image](#) | [Reduce to browser width](#)



An individual who is sick with COVID-19 and recovers has blood drawn and screened for virus-neutralizing antibodies. Following identification of those with high titers of neutralizing antibody, serum containing these virus-neutralizing antibodies can be administered in a prophylactic manner to prevent infection in high-risk cases, such as vulnerable individuals with underlying medical conditions, health care providers, and individuals with exposure to confirmed cases of COVID-19. Additionally, convalescent serum could potentially be used in individuals with clinical disease to reduce symptoms and mortality. The efficacy of these approaches is not known, but historical experience suggests that convalescent sera may be more effective in preventing disease than in the treatment of established disease.

Potential Therapeutic Options - Convalescent Plasma/Sera?

- Convalescent SARS patients exhibit a neutralizing antibody response directed against the viral S protein. Antibody appears to persist for at least 24 months in convalescent patients, before becoming undetectable.
- This antibody also appears to block SARS-CoV-2-S-driven entry, implying that antibody responses raised against SARS-CoV during infection or vaccination might offer some level of protection against SARS-CoV-2 infection.

Hoffman M et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, 2020 (Early Online Access)

Liu W et al. Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. *J. Infect. Dis.*, 193 (2006), pp. 792-795

Potential Therapeutic Options - Convalescent Plasma/Sera?

- In the SARS outbreak, largest available study involved treatment of 80 patients with SARS in Hong Kong.
 - Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective.
 - In addition, those who were PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis .
- There is also some anecdotal information on the use of convalescent serum in seriously ill individuals.
 - Three patients with SARS in Taiwan were treated with 500 mL convalescent serum, resulting in a reduction in serum virus titer, and each survived .
- For current outbreak, small amount of data available, but suggests that convalescent serum administration reduced viral load and was safe.
 - 245 COVID-19 patients reported to have received, and 91 cases have showed improvement.

Potential Therapeutic Options - JAK1/2 Inhibition?

- BenevolentAI's knowledge graph is a large repository of structured medical information, including numerous connections extracted from scientific literature by machine learning.
- Together with customisations bespoke to 2019-nCoV, authors used BenevolentAI to search for approved drugs that could help, focusing on those that might block the viral infection process.
- Identified baricitinib, which is predicted to reduce the ability of the virus to infect lung cells.

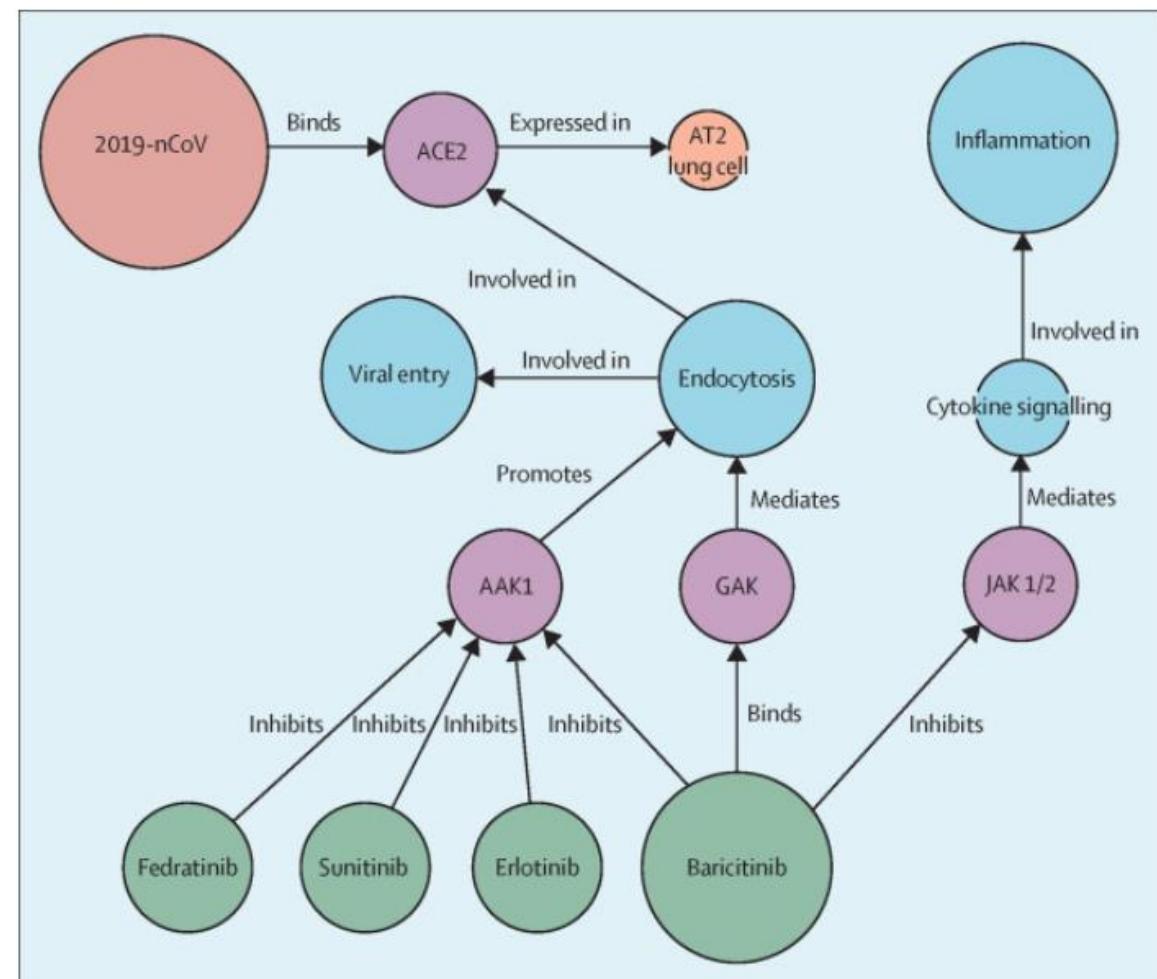
Richardson P. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020.



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Potential Therapeutic Options - JAK1/2 Inhibition?

- Most viruses enter cells through receptor-mediated endocytosis. The receptor that 2019-nCoV uses to infect lung cells is ACE2, a cell-surface protein on cells in the kidney, blood vessels, heart, and, importantly, lung AT2 alveolar epithelial cells.
- These AT2 cells are particularly prone to viral infection.
- One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1).
- Disruption of AAK1 might, in turn, interrupt the passage of the virus into cells and also the intracellular assembly of virus particles.



Potential Therapeutic Options - JAK1/2 Inhibition?

- Of the identified AAK1 inhibitors in the knowledge graph, a number of oncology drugs such as sunitinib and erlotinib were identified, both of which inhibit viral infection of cells through the inhibition of AAK1.
- However, these compounds have serious side-effects, and our data infer high doses to inhibit AAK1 effectively. Authors do not consider these drugs would be a safe therapy for a population of sick and infected people.
- However, one of the six high-affinity AAK1-binding drugs was the JAK 1/2 baricitinib.
- Because the plasma concentration of baricitinib on therapeutic dosing (either as 2 mg or 4 mg once daily) is sufficient to inhibit AAK1, authors suggest it could be trialled, using an appropriate patient population with 2019-nCoV acute respiratory disease, to reduce both the viral entry and the inflammation in patients.

Potential Therapeutic Options - Glucocorticoids?

- Commonly being utilized. Mixed evidence in ARDS:
 - No evidence that corticosteroids prevent the development of ARDS among patients at risk
 - High dose and short course treatment with steroids does not improve the outcomes of patients with ARDS.
 - There is compelling data that low dose and prolonged treatment with steroids improves pulmonary physiology in patients with ARDS, but additional studies are needed to recommend treatment with steroids for ARDS.

Potential Therapeutic Options - Glucocorticoids?

- Commonly being utilized. Experience in SARS/MERS available.
 - SARS: "29 studies of steroid use, 25 were inconclusive and four were classified as causing possible harm."
 - MERS: "Corticosteroid therapy in patients with MERS was not associated with a difference in mortality after adjustment for time-varying confounders but was associated with delayed MERS coronavirus RNA clearance"

Arabi YM et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. Am J Respir Crit Care Med. 2018. 15;197(6):757-767.

Stockman LJ et al. SARS: systematic review of treatment effects. PLoS Med. 2006. 3(9):e343.

Potential Therapeutic Options - Glucocorticoids?

- Commonly being utilized. Mixed evidence of efficacy in COVID-19. Multiple trials underway.
- Background: Acute lung injury and acute respiratory distress syndrome are partly caused by host immune responses. Corticosteroids suppress lung inflammation but also inhibit immune responses and pathogen clearance.
- In SARS-CoV infection, as with influenza, systemic inflammation is associated with adverse outcomes, and persists after viral clearance.
- Pulmonary histology in both SARS and MERS infections reveals inflammation and diffuse alveolar damage, and in some cases haemophagocytosis.
- Therefore, theoretically, corticosteroid treatment could have a role to suppress lung inflammation.

Potential Therapeutic Options - Glucocorticoids?

- Life-threatening acute respiratory distress syndrome occurs in 2019-nCoV infection. However, generalising evidence from acute respiratory distress syndrome studies to viral lung injury is problematic because these trials typically include a majority of patients with acute respiratory distress syndrome of non-pulmonary or sterile cause.
- A review of treatments for acute respiratory distress syndrome of any cause, based on six studies with a total of 574 patients, concluded that insufficient evidence exists to recommend corticosteroid treatment.

Potential Therapeutic Options - Glucocorticoids?

- Septic shock has been reported in a small subset of patients with COVID-19. Corticosteroids are widely used in septic shock despite uncertainty over their efficacy.
- Most patients in septic shock trials have bacterial infection, leading to vasodilatory shock and myocardial insufficiency. In this group, there is potential that net benefit might be derived from steroid treatment in severe shock.
- However, shock in severe hypoxaemic respiratory failure is often a consequence of increased intrathoracic pressure (during invasive ventilation) impeding cardiac filling, and not vasodilation. In this context, steroid treatment is unlikely to provide a benefit.

Potential Therapeutic Options - Glucocorticoids?

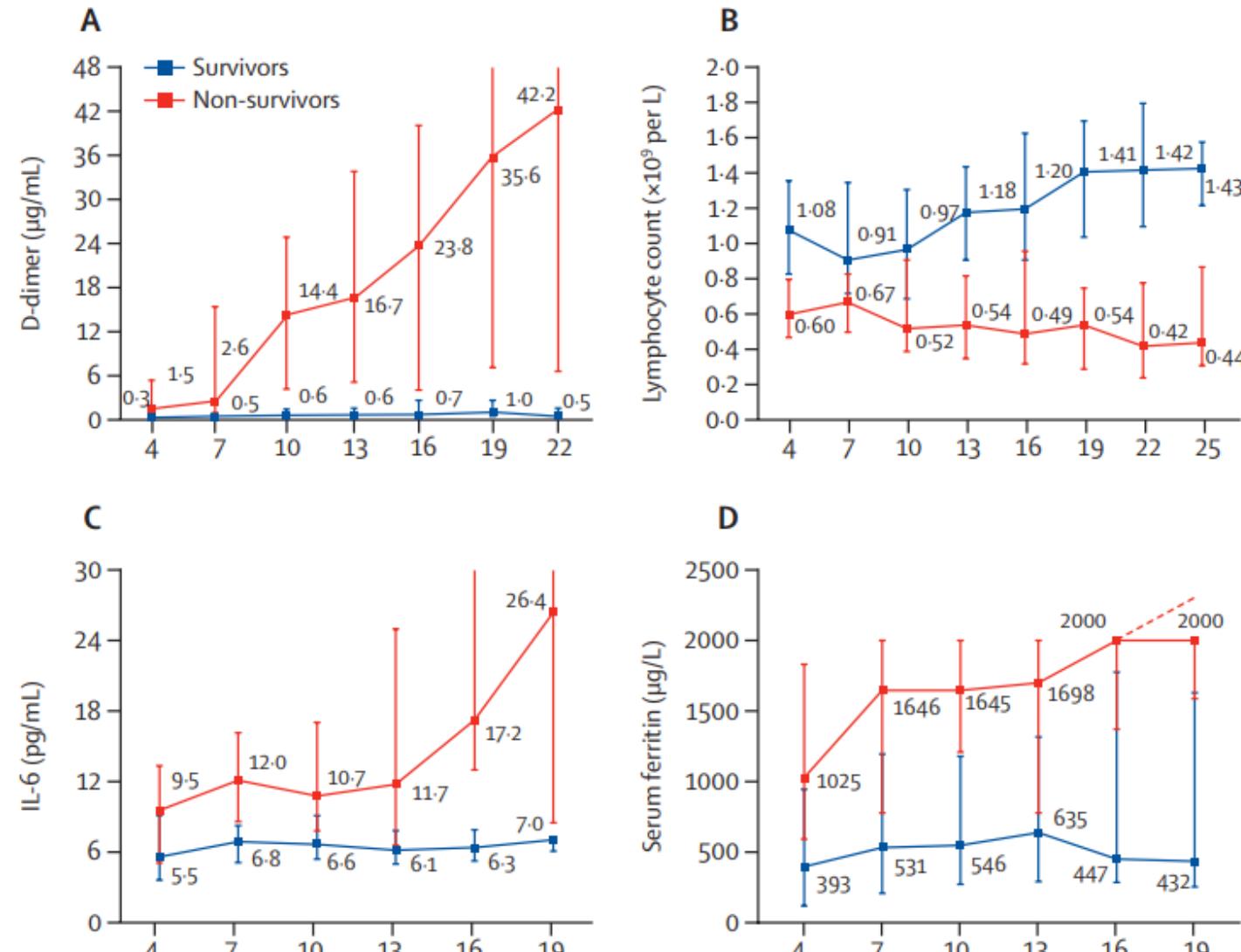
- No clinical data exist to indicate that net benefit is derived from corticosteroids in the treatment of respiratory infection due to RSV, influenza, SARS-CoV, or MERS-CoV.
- The available observational data suggest increased mortality and secondary infection rates in influenza, impaired clearance of SARS-CoV and MERS-CoV, and complications of corticosteroid therapy in survivors.
- If it is present, the effect of steroids on mortality in those with septic shock is small, and is unlikely to be generalizable to shock in the context of severe respiratory failure due to COVID-19
- Overall, no unique reason exists to expect that patients with 2019-nCoV infection will benefit from corticosteroids, and they might be more likely to be harmed with such treatment. We conclude that corticosteroid treatment should not be used for the treatment of 2019-nCoV-induced lung injury or shock outside of a clinical trial.

Potential Therapeutic Options - Tocilizumab?

- Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome.
- Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality.
- A cytokine profile resembling secondary HLH is associated with COVID-19 disease severity, characterized by:
 - increased interleukin (IL)-2, IL-7, GCSF, interferon- γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- α , and tumour necrosis factor- α .
- Predictors of fatality include elevated ferritin (mean 1297.6 ng/ml in non-survivors vs 614.0 ng/ml in survivors; $p<0.001$) and IL-6 ($p<0.0001$), suggesting that mortality might be due to virally driven hyperinflammation.

Potential Therapeutic Options - Tocilizumab?

- Cytokine Profile



Zhou F et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020

Potential Therapeutic Options - Tocilizumab?

- A multicenter, randomized controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in patients with COVID-19 pneumonia and elevated IL-6 in China (ChiCTR2000029765).



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Potential Therapeutic Options - Tocilizumab?

- No peer-reviewed data available.
- Preprint/Pre-peer review; abstract only available:
- 21 patients, diagnosed with 'severe COVID-19' administered tocilizumab.
- All patients enrolled met severe or critical criteria. Diagnosis was by RT-PCR assay. Severity was defined as any of the following conditions:
 - (1) respiratory rate \geq 30 breaths/min; (2) SpO₂ \leq 93% while breathing room air; (3) PaO₂/FiO₂ \leq 300 mmHg.
 - A critical case was diagnosed if any of (1) respiratory failure which requiring mechanical ventilation; (2) shock; (3) combined with other organ failure, admitted to ICU.

Potential Therapeutic Options - Tocilizumab?

- All patients received standard care including lopinavir, methylprednisolone, and oxygen therapy, and received tocilizumab 400 mg via IV.
- Eighteen patients (85.7%) received tocilizumab once, and 3 patients (14.3%) received a second dose due to persistence of fever after 12 hours.
- Body temperature of all patients returned to normal on the first day after receiving tocilizumab and remained stable thereafter.
- Clinical symptoms were significantly improved in the following days; one patient needed no further oxygen therapy. Fifteen patients (15/20, 75.0%) had reduced oxygen requirement. One patient was extubated on the first day after tocilizumab. One critical patient was extubated and regained consciousness on the fifth day after therapy.

Potential Therapeutic Options - Tocilizumab?

- On the fifth day after treatment, only two patients (2/19, 10.5%) had persistent WBC abnormality; mean for all patients was $5.25 \pm 2.11 \times 10^9/L$.
- The percentage of lymphocytes in 10 patients (10/19, 52.6%) returned to normal (mean, $22.62 \pm 13.48\%$).
- CRP decreased significantly and returned to normal in 84.2% patients (16/19, mean, $2.72 \pm 3.60 \text{ mg/L}$) after treatment on the fifth day.
- After treatment, CT scans showed that the lesions were absorbed in 19 patients (90.5%) and a little improvement in the others.
- Nineteen patients (90.5%) discharged including two critical patients and the rest remained under hospital observation, but body temperatures remained normal and all symptoms improved remarkably.

Potential Therapeutic Options - Tocilizumab?

- The mean hospitalization time was 13.5 ± 3.1 d after the treatment with tocilizumab.
- There have been no reports of subsequent pulmonary infection and deterioration/illness or death.
- During the treatment with tocilizumab, no adverse drug reactions were reported.

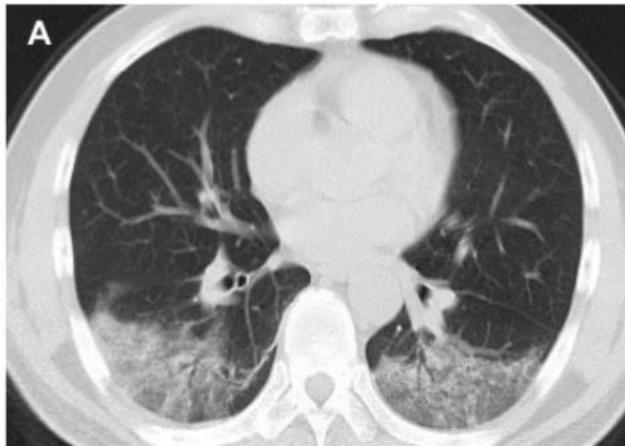
Potential Therapeutic Options - Tocilizumab?

Table 2 Laboratory Tests before and after Tocilizumab

	Range	Before the tocilizumab	After the tocilizumab		
			D1	D3	D5
White-cell count, $\times 10^9/L$	3.5-9.5	6.30 ± 2.77 (4/20, 20.0%)	8.05 ± 4.39 (8/18, 44.4%)	6.02 ± 3.05 (9/21, 42.9%)	5.25 ± 2.11 (2/19, 10.5%)
Lymphocyte percentage, %	20-50	15.52 ± 8.89 (17/20, 85.0%)	11.78 ± 11.36 (16/18, 88.9%)	16.93 ± 13.59 (14/21, 66.7%)	22.62 ± 13.48 (9/19, 47.4%)
C-reactive protein, mg/L	0-5	75.06 ± 66.80 (20/20, 100%)	38.13 ± 54.21 (17/18, 94.4%)	10.61 ± 13.79 (10/20, 50.0%)	2.72 ± 3.60 (3/19, 15.8%)
Procalcitonin, ng/ml	0-0.5	0.33 ± 0.78 (2/20, 10.0%)	0.21 ± 0.35 (2/16, 12.5%)	0.09 ± 0.13 (1/19, 5.3%)	0.12 ± 0.15 (1/18, 5.6%)

Potential Therapeutic Options - Tocilizumab?

Before tocilizumab

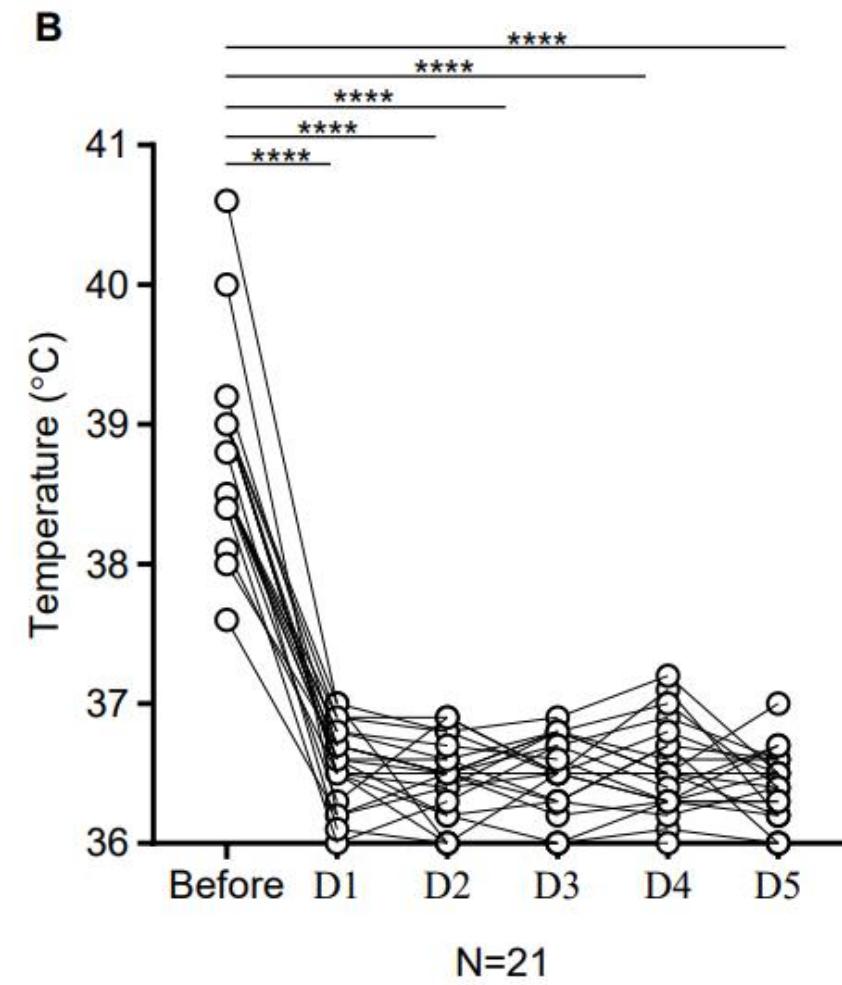
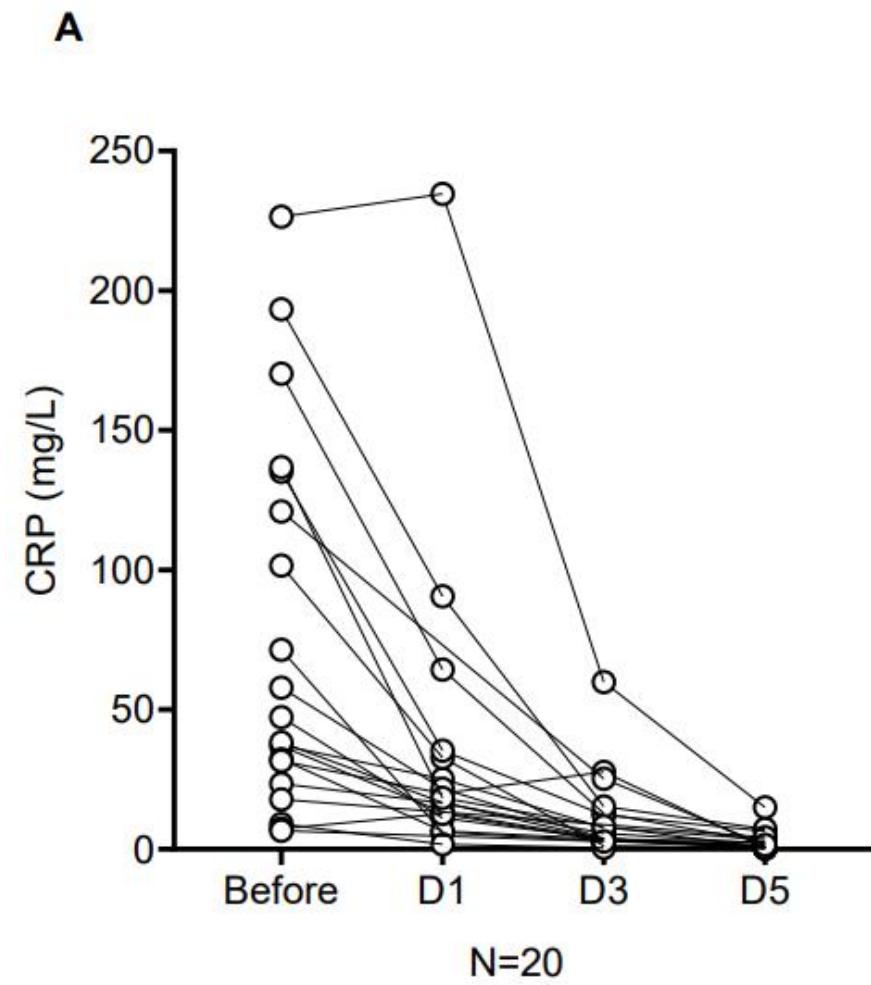


After tocilizumab



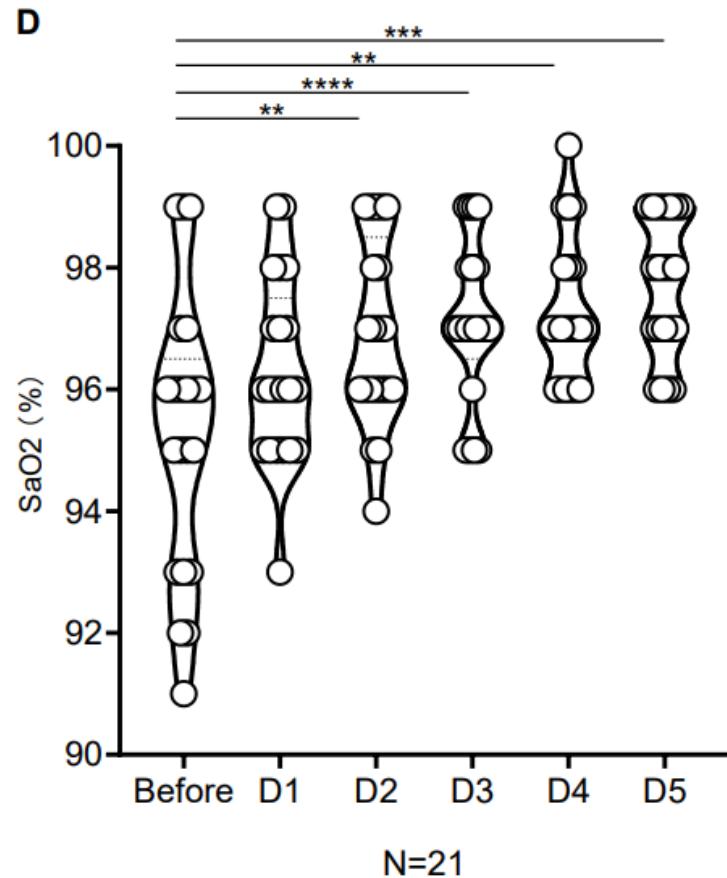
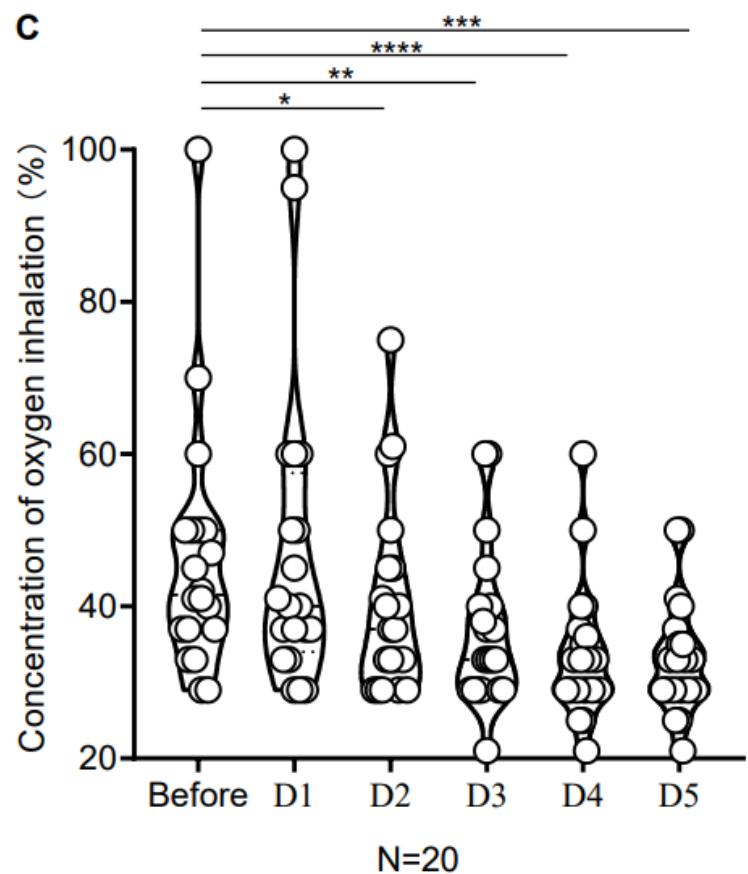
Preprint/Pre-Peer review: Xu et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. <http://www.chinaxiv.org/abs/202003.00026>

Potential Therapeutic Options - Tocilizumab?



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Potential Therapeutic Options - Tocilizumab?

- Conclusions: In summary, tocilizumab effectively improve clinical symptoms and repress the deterioration of severe COVID-19 patients.
- Therefore, tocilizumab is an effective treatment in severe patients of COVID-19, which provided a new therapeutic strategy for this fatal infectious disease

Potential Therapeutic Options - Other areas under Investigation:

- Fixed dose of the anti-HIV combination, lopinavir–ritonavir, is currently in clinical trials with ribavirin.
- Remdesivir, developed by Gilead Sciences Inc., was previously tested in humans with Ebola virus disease and has shown promise in animal models for MERS and SARS. The drug is currently being studied in phase III clinical trials in both China and the USA.
- Favipiravir, a purine nucleoside leading to inaccurate viral RNA synthesis has recently been approved for a clinical trial as a drug to treat COVID-19.
- Chloroquine, an antimalarial drug, has proven effective in treating coronavirus in China.

A Seattle Intensivist's One-pager on COVID-19

Nick Mark, MD
@nickmmark

Nomenclature

Infection: Coronavirus Disease 2019 a.k.a. COVID-19

Virus: SARS-CoV-2, 2019 Novel Coronavirus

NOT "Wuhan Virus"

Biology

- 30 kbp, +ssRNA, enveloped coronavirus
- Likely zoonotic infection; source/reservoir unclear (Bats? / Pangolins? → people)
- Now spread primarily person to person;
 - Can be spread by asymptomatic carriers!
- Viral particles enter into lungs via droplets
- Viral S spike binds to ACE2 on type two pneumocytes
- Effect of ACE/ARB is unclear; not recommended to change medications at this time.
- Other routes of infection (contact, enteric) possible but unclear if these are significant means of spread

Epidemiology

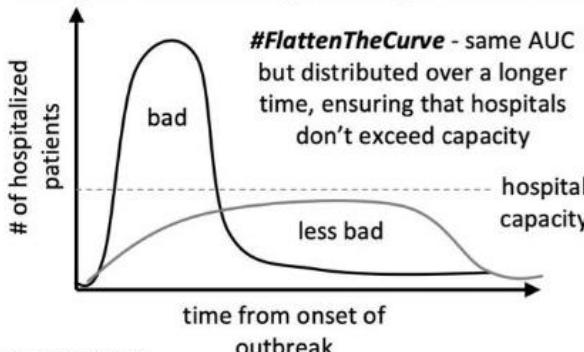
- Attack rate = 30-40%
- R₀ = 2-4
- Case fatality rate (CFR) = 3.4% (worldwide numbers)
- Incubation time = 4-14 days (up to 15 days)
- Viral shedding – median 20 days (max 37 days)

Timeline:

- China notifies WHO 2019-12-31
- First US case in Seattle 2020-1-15
- WHO Declared pandemic 2020-3-11
- National emergency 2020-3-12

Disease clusters: SNFs, Conferences, other

Strategies: contact tracing, screening, social distancing



v2.3.0 2020-03-15

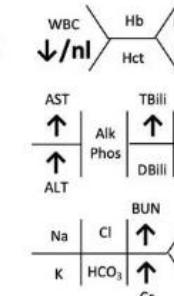
Diagnosis/Presentation

Symptoms

- 65-80% cough
- 45% febrile on presentation (85% febrile during illness)
- 20-40% dyspnea
- 15% URI symptoms
- 10% GI symptoms

Labs

- CBC: Leukopenia & lymphopenia (80%+)
 - BMP: ↑BUN/Cr
 - LFTs: ↑AST/ALT/Tbili
 - ↑ D-dimer, ↑ CRP, ↑ LDH
 - ↑ IL-6, ↑ Ferritin
 - ↓ Procalcitonin
- *PCT may be high w/ superinfxn (rare)*



Imaging

- CXR: hazy bilateral, peripheral opacities
- CT: ground glass opacities (GGO), crazy paving, consolidation, *rarely may be unilateral*



- POCUS: numerous B-lines, pleural line thickening, consolidations w/ air bronchograms

Isolation

- Phone call is the best isolation (e.g. move to telemed)
- Place patient in mask, single room, limit/restrict visitors

Precautions

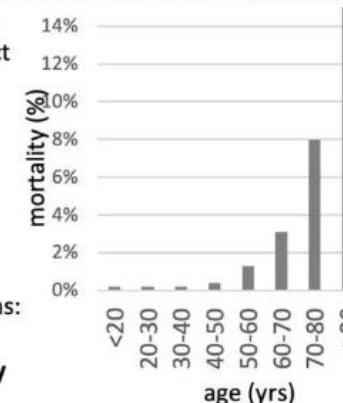
- In correct sequence: STANDARD + CONTACT (double glove) + either AIRBORNE (for aerosolizing procedures: intubation, extubation, NIPPV, suctioning, etc) or DROPLET (for everything else)
- N95 masks must be fit tested; wear eye protection
- PPE should be donned/doffed with trained observer
- Hand hygiene: 20+ seconds w/ soap/water or alcohol containing hand gel

Treatment

- Isolate & send PCR test early (may take days to result)
- GOC discussion / triage
- Notify DOH, CDC, etc
- Fluid sparing resuscitation
- ± empiric antibiotics
- Intubate early under controlled conditions if possible
- Avoid HFNC or NIPPV (aerosolizes virus) unless individualized reasons exist (e.g. COPD, DNI status, etc); consider helmet mask interface (if available) if using NIPPV
- Mechanical ventilation for ARDS
 - LPV per ARDSnet protocol
 - 7 P's for good care of ARDS patients: e.g. PEEP/Paralytics/Proning/inhaled Prostacyclins, etc
 - ? High PEEP ladder may be better
 - ? ECMO in select cases (unclear who)
- Consider using POCUS to monitor/evaluate lungs
- Investigational therapies:
 - Remdesivir --| block RNA dependent polymerase
 - Chloroquine --| blocks viral entry in endosome
 - Oseltamivir --| block neuraminidase
 - Lopinavir/ritonavir --| protease inhibitor
 - Tocilizumab --| block IL-6 (reduce inflammation)
 - Corticosteroids --| block T-cells (reduce inflammation)
- None of these investigational therapies is proven, but literature is evolving quickly.

Prognosis

- Age and comorbidities (DM, COPD, CVD) are significant predictors of poor clinical outcome; admission SOFA score also predicts mortality.
- Lab findings also predict mortality
 - ↑ d-dimer,
 - ↑ ferritin
 - ↑ troponin
 - ↑ cardiac myoglobin
- Expect prolonged MV
- Watch for complications: Secondary infection (VAP), Cardiomyopathy



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