中日友好医院
CHINA-JAPAN FRIENDSHIP HOSPITAL

COVID-19 Clinical Spectrum, Complications, and Coinfections

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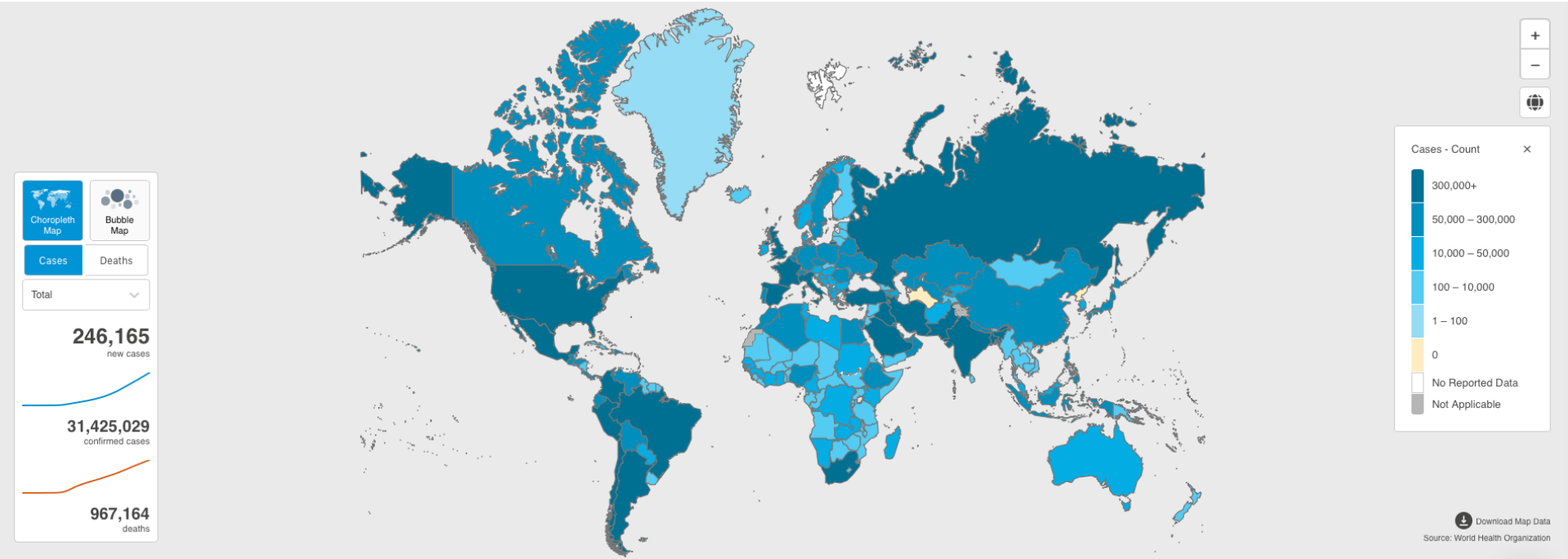
The ongoing COVID-19 Pandemic



As of 2020/9/23, there has been more than 30 million cases with nearly 1 million death

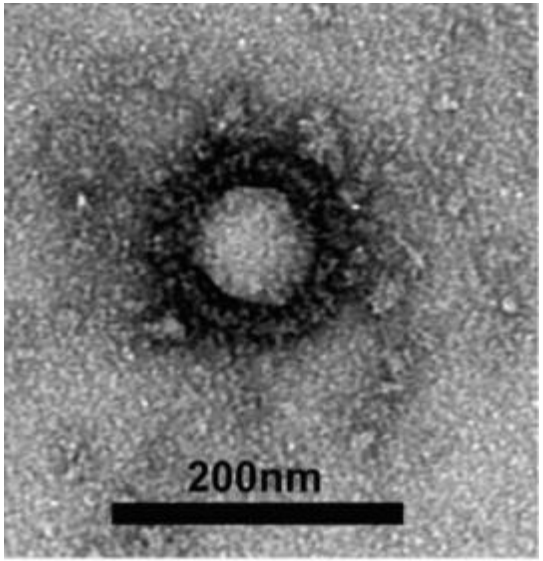
World Health Organization, https://covid19.who.int, data as of 2020/9/23, 4:47pm CEST

Overview of COVID-19

- Emerging Infectious Disease
- Presented mainly as viral pneumonia-respiratory borne illness, easily spread person to person
- It is insidious and treacherous
  - Asymptomatic infected people can spread the disease
- Relatively high degree of morbidity and death risk
- Devastating particularly to subset of population
  - Elderly, those with underlying conditions (heart disease, lung disease, diabetes, obesity)

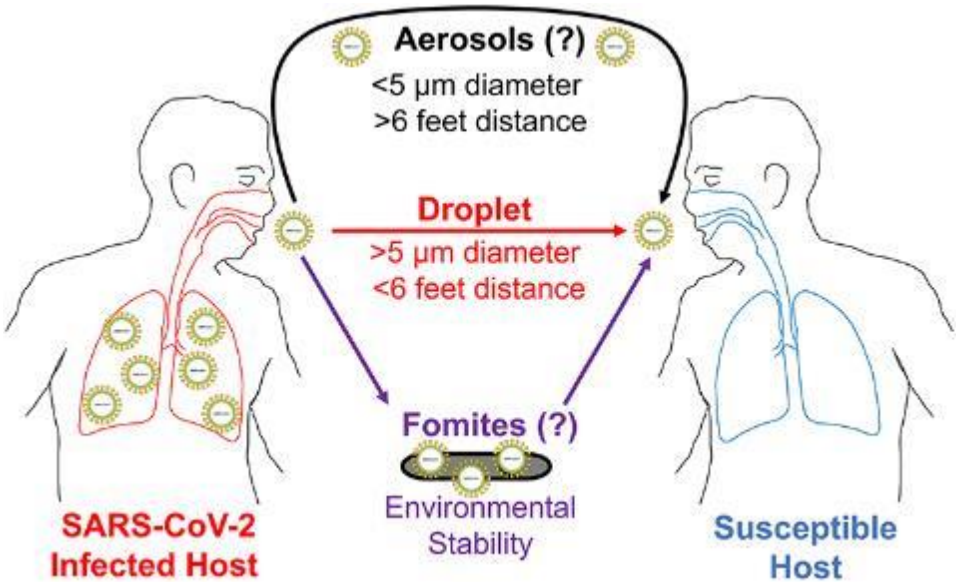
SARS-CoV-2

- Belong to the β genus; Have envelopes; Round or oval; diameter being 60 to 140 nm
- showed 79.0% nucleotide identity with the sequence of SARS-CoV and 51.8% identity with the sequence of MERS-CoV.
- Sensitive to ultraviolet and heat. 75% ethanol, chlorine-containing disinfectant, peracetic acid, and chloroform can effectively inactivate the virus.
- Chlorhexidine was not effective



China National Health Commission. Clinical Protocols for the Diagnosis and Treatment of COVID-19 (Trial 7th version); 2020

SARS-CoV-2 transmission

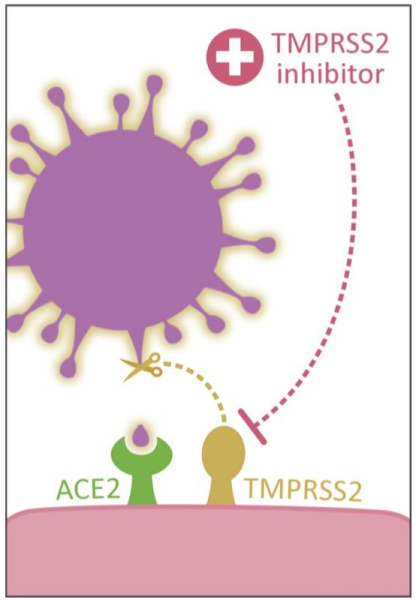


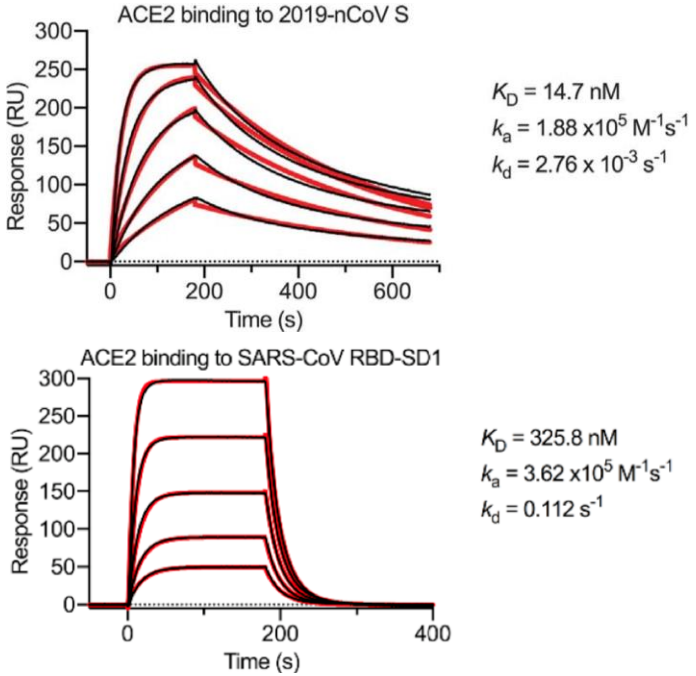
Examples of potential transmission routes of SARS-CoV-2

- **Droplet (Main transmission route):** The droplets emitted by patients during speech, cough or sneezing
- **Fomite (Possible):** Contact with the contaminated surfaces or equipment
- **Aerosol (Possible)**
- Viruses can be detected in fecal samples or anal swabs, but oral-fecal transmission is not confirmed
- No evidence for vertical transmission
- All the population is generally vulnerable

Thushara Galbadage et al. Front Public Health. 2020; 8:163
W. Joost Wiersinga et al. JAMA. 2020; 324(8):782-793
Lian Chen et al. N Engl J Med. 2020; 382(25):e100

SARS-CoV-2 infection





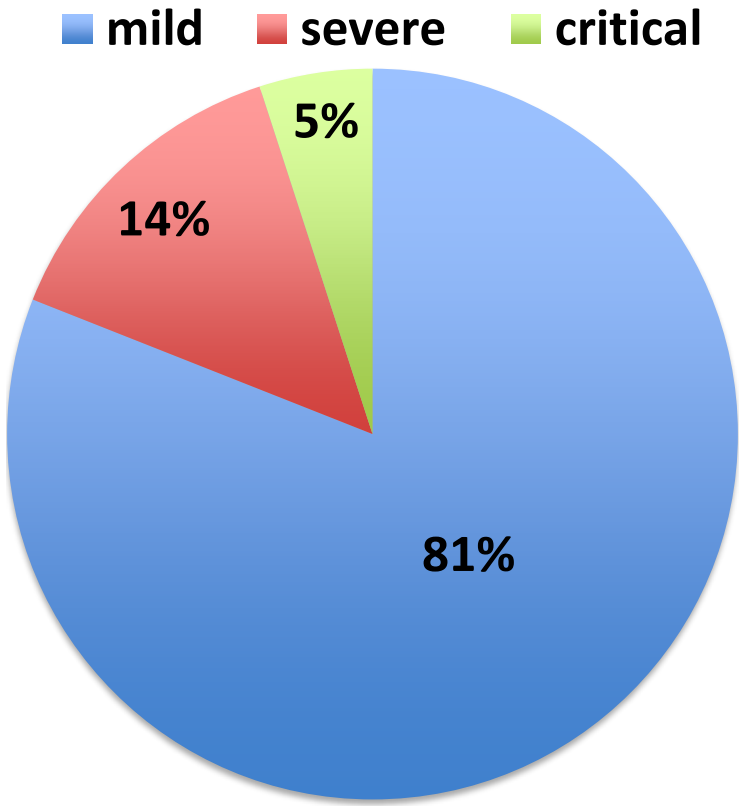
SARS-CoV-2 interacts with ACE2 as host cell receptor and the Spike protein is primed by protease TMPRSS2

The binding affinity of ACE2 to the SARS-CoV-2 S ectodomain is 10- to 20-fold higher than that of SARS-CoV S ectodomain

Arno R. Bourgonje et al. J Pathol. 2020; DOI:10.1002/path.5471
Daniel Wrapp et al. Science. 2020; 367, 1260–1263

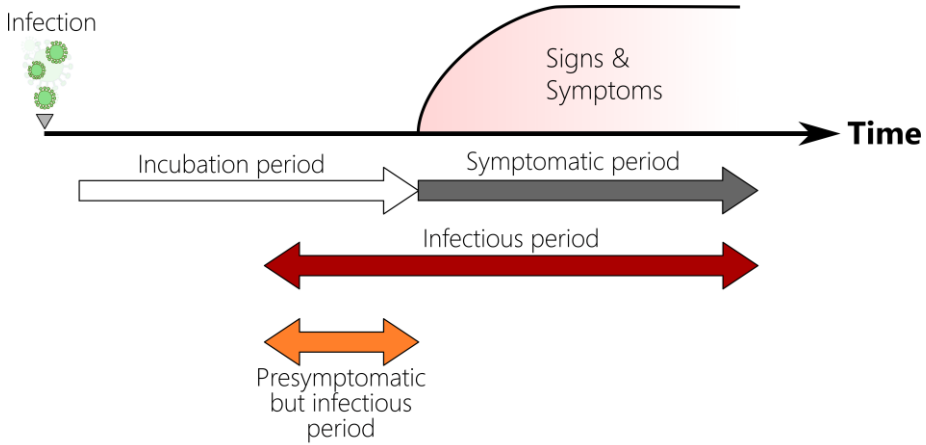
Disease spectrum of COVID-19

- **81% were mild status**
  - No pneumonia or mild pneumonia
- **14% were severe status**
  - Dyspnea or Respiratory Rate ≥ 30/min or SpO_2 < 93% or PaO_2/FiO_2 <300 mmHg
  - Lung infiltrates >50% within 24 to 48 hours
- **5% were critical ill status**
  - Needs mechanical ventilation
  - Shock
  - Complicated with other organ failure required ICU admission



Zunyou Wu et al. JAMA. 2020; 323(13):1239-1242

Disease onset of COVID-19 patients



- The incubation period for COVID-19 is on average 5–6 days, but can be up to 14 days.
- Some infected persons can be contagious, from 1–3 days before symptom onset.
- The median (IQR) interval from symptom onset to hospital admission is 7 (3-9) days.

Ian M. Mackay. https://virologydownunder.com (the picture)

W. Joost Wiersinga et al. JAMA. 2020; 324(8):782-793
WHO. Clinical management of COVID-19: Interim guidance

Clinical features of COVID-19 patients

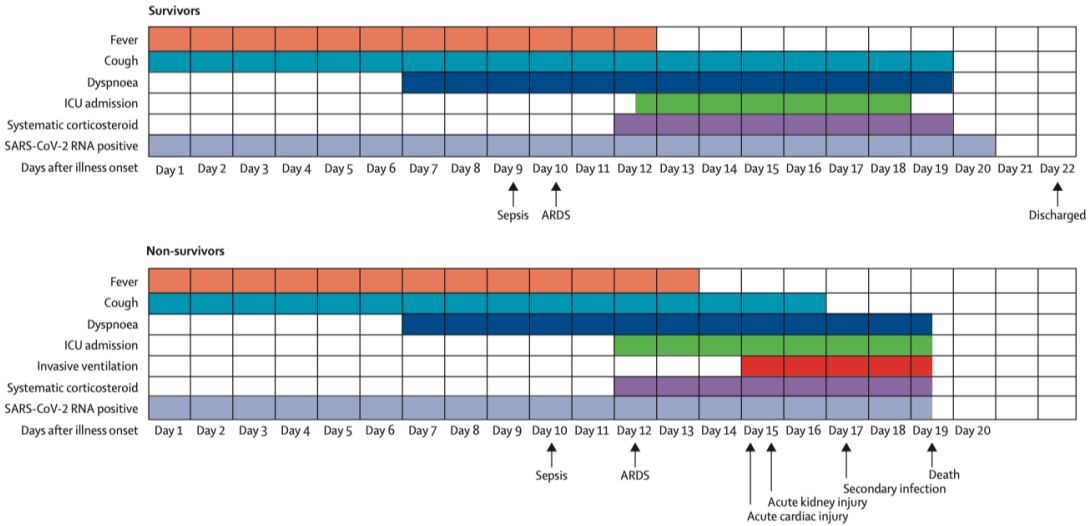
Common symptoms	N%
Fever	83-99%
Cough	60-82%
Fatigue	44-70%
Anorexia	40-84%
Shortness of breath	31-40%
Myalgias	11-35%
Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, have also been reported.	
Olfactory and/or gustatory dysfunctions are also reported in many patients, ranging from 5-98% in different cohort. Most studies used patient-reported symptoms but not objective function tests.	

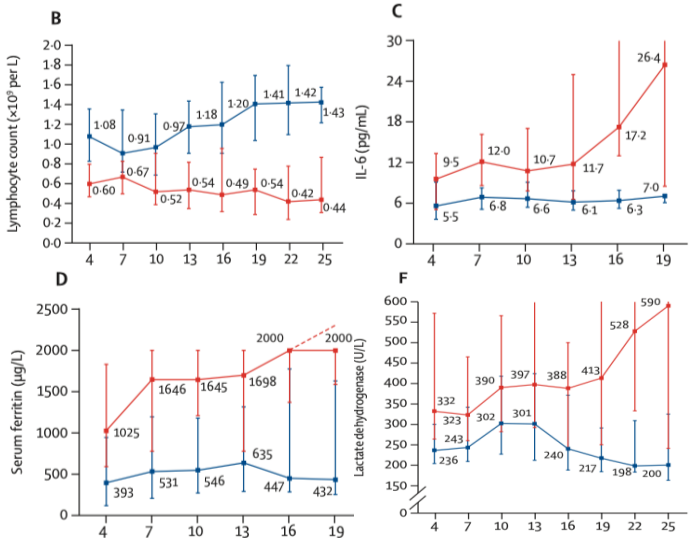
Common comorbidities	N%
Hypertension	48-57%
Diabetes	17-34%
Cardiovascular disease	21-28%
Chronic pulmonary disease	4-10%
Chronic kidney disease	3-13%
Malignancy	6-8%
Chronic liver disease	<5%

- Approximately 17% to 35% of hospitalized patients with COVID-19 are treated in an ICU, most commonly due to hypoxemic respiratory failure.
- Among patients in the ICU with COVID-19, 29% to 91% require invasive mechanical ventilation.

Tom Wai-Hin Chung et al. Open Forum Infect Dis;7(6)
W. Joost Wiersinga et al. JAMA. 2020; 324(8):782-793
WHO. Clinical management of COVID-19: Interim guidance

Clinical course of COVID-19—severe and critical illness

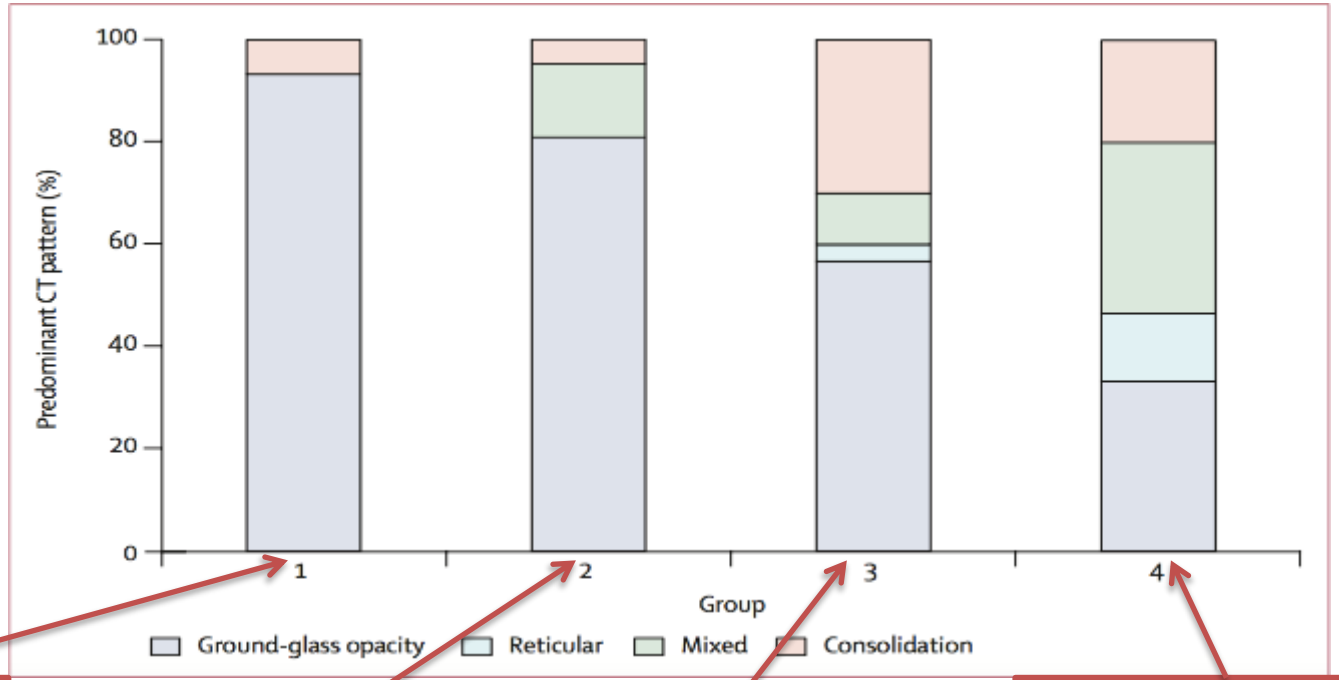




- Duration of dyspnea was 13 days in survivors
- 45% survivors still had cough on discharge
- Median duration of viral shedding was 20 days, could prolong as 37 days
- lymphocyte count was lowest on day 7 after illness onset and improved during hospitalization in survivors but whereas severe lymphopenia was observed until death in non-survivors.

Fei Zhou et al. Lancet. 2020; 395(10229):1054-1062

CT patterns change over time



Ct scan before illness onset

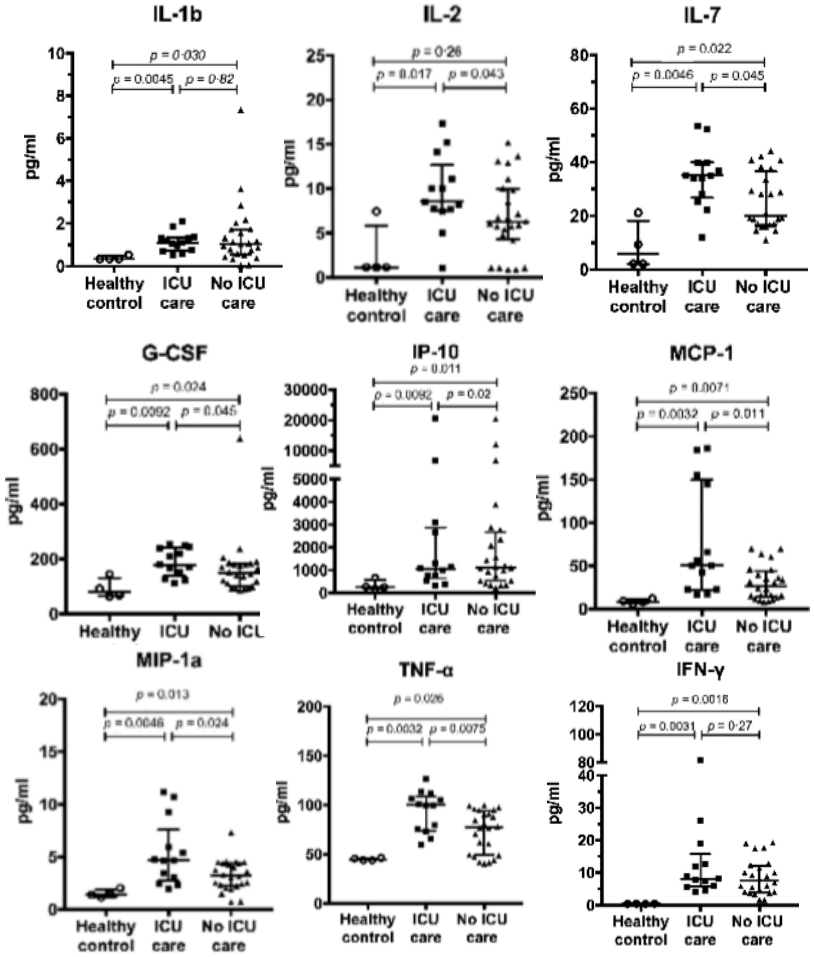
≤ 1 week after symptom onset

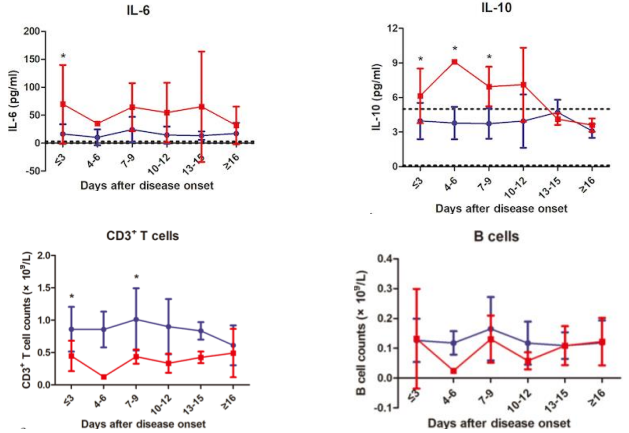
>1 week to 2 weeks after symptom onset

>2 weeks to 3 weeks after symptom onset

Heshui Shi et al. Lancet Infect Dis.2020; 20(4):425-434

Hyperinflammatory response in severe COVID-19 patients





- Cytokines including IL-1β, IL-2, IL-6, IL-7, IL-10, G-CSF, IP-10, MCP1, IFN-γ, etc. were significantly elevated
- Peripheral lymphocyte counts, mainly T cells were substantially reduced in severe COVID-19 patients

Host-directed therapies might be an option

Chaolin Huang et al. Lancet. 2020; 395(10223): 497-506
Jing Liu et al. EBioMedicine. 2020;55:102763

Risk factors for severe/critical illness or death Listed in the literature

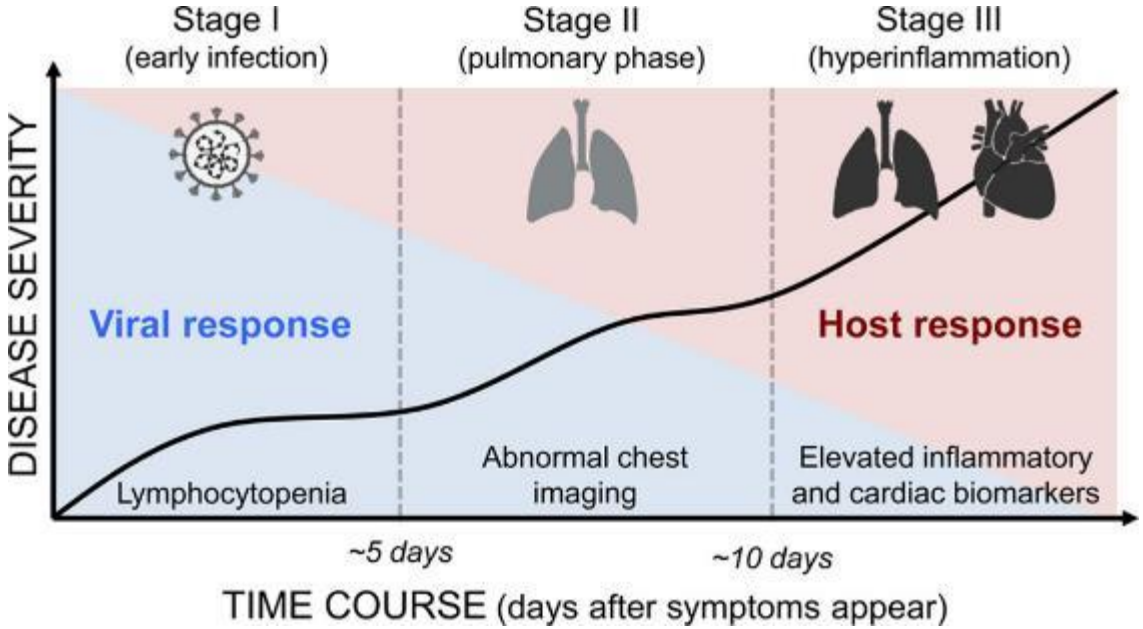
- Elder age
- Obesity
- Comorbidity
- Hypertension, Diabetes, etc.
- Higher D-dimer (＞ 1ug/ml)
- Higher SOFA score
- Smoking
- Lymphopenia
- ……

When reading literature regarding risk factors, several points to consider:

- Definition of severe/critical illness
- Adjusted for confounders?
- Sufficient follow-up?
- Sufficient reporting of pre-existing condition?

Fei Zhou et al. Lancet. 2020; 395(10229):1054-1062
Rachel E Jordan. BMJ 2020;368:m1198

Disease severity is influenced by both viral infection and host response



- Direct mechanism – SARS-CoV-2 infection:

SARS-CoV-2 infiltration, replication;

Death and injury of virus-infected cells/tissues;

Primary organ damage;

- Indirect mechanism – Host response:

Dysfunctional immune response;

Cytokine storm syndrome;

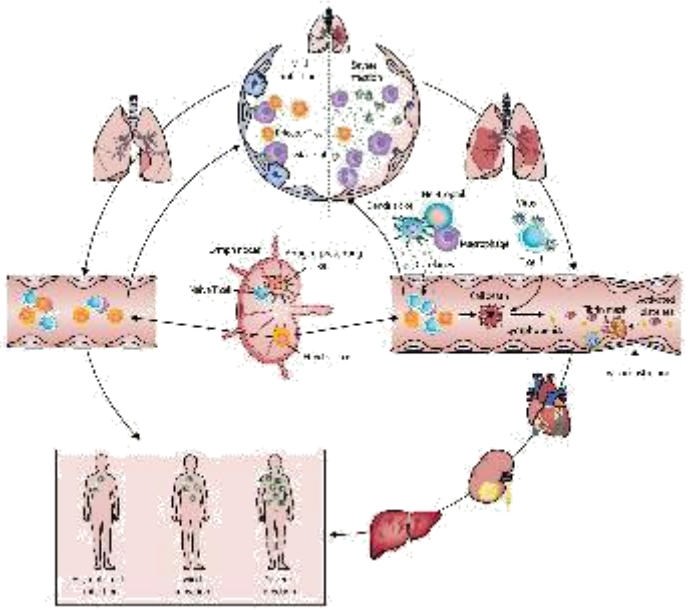
Secondary organ damage;

Akbarshakh Akhmerov et al. Circ Res. 2020;126:1443–1455
Matthew Zirui Tay et al. Nat Rev Immunol. 2020;20:363-374

SARS-CoV-2 Viral sepsis—Observations and Hypotheses

Multi-organ dysfunction

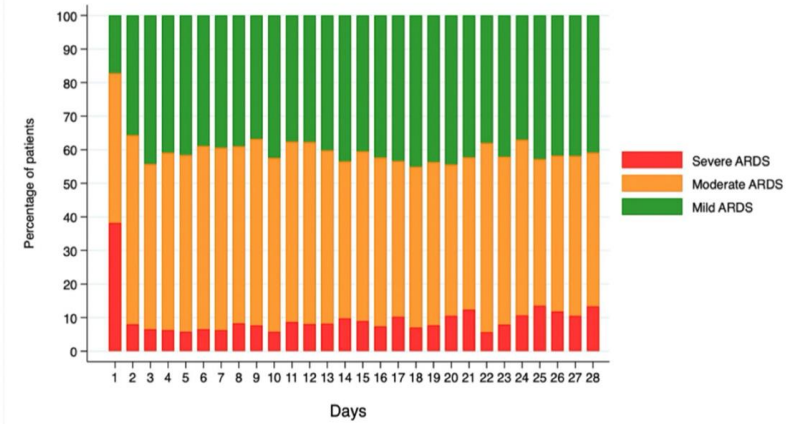
- Pneumonia, Respiratory failure, Acute respiratory distress syndrome
- Metabolic acidosis and internal environment disorders
- Acute kidney injury
- Acute cardiac injury
- ……



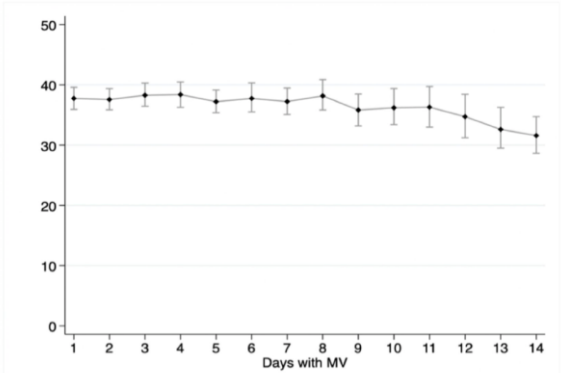
——Viral Sepsis

Lili Ren et al. Chin Med J 2020; 133(9):1015-1024
Chaolin Huang et al. Lancet 2020; 395(10223): 497-506
Hui Li et al. Lancet. 2020;395(10235):1517-1520

COVID-19 ARDS — Perspective from a large cohort in Spain



Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N	742	613	629	593	576	537	514	484	445	419	393	360	355	308
Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28
N	281	257	244	215	208	191	170	142	152	132	126	110	105	105

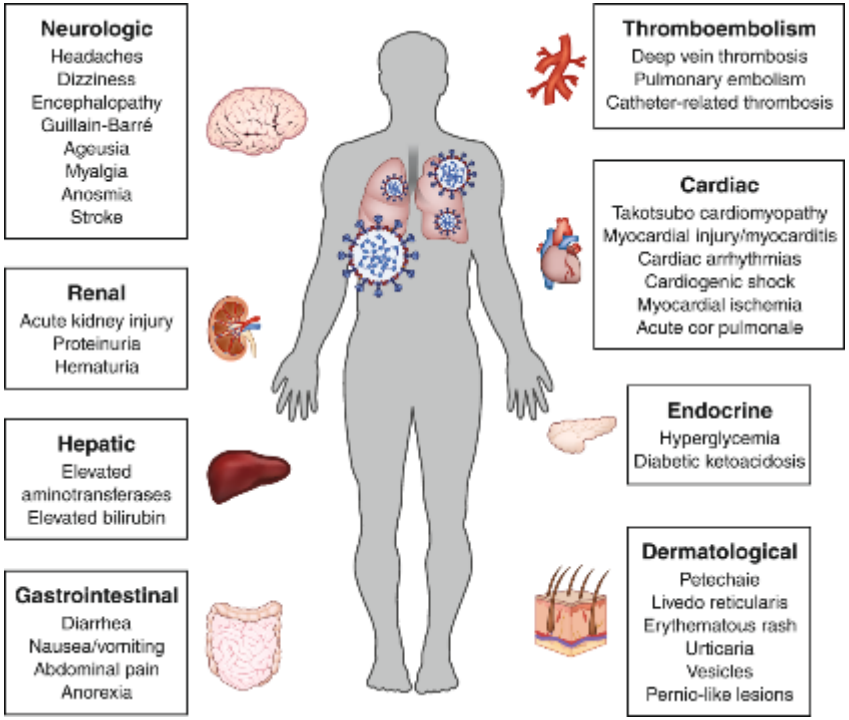


Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N	296	275	267	229	209	188	171	145	114	103	95	77	73	61

- A total of 742 patients were analyzed with complete 28-day outcome data: 128 (17.1%) with mild, 331 (44.6%) with moderate, and 283 (38.1%) with severe ARDS
- Clinical features are similar with non-COVID-19 ARDS:
- At baseline, defined as the first day on invasive MV, median (IQR) values were: tidal volume 6.9 (6.3–7.8) ml/kg predicted body weight, positive end-expiratory pressure 12 (11–14) cmH_2O. Values of respiratory system compliance 35 (27–45) ml/cmH_2O, plateau pressure 25 (22–29) cmH_2O, and driving pressure 12 (10–16) cmH_2O were similar to values from non-COVID-19 ARDS patients observed in other studies
- The risk of 28-day mortality was lower in mild ARDS [RR 0.56 (95% CI 0.33–0.93), p = 0.026] and moderate ARDS [RR 0.69 (95% CI 0.47–0.97), p = 0.035] when compared to severe ARDS
- The 28-day mortality was similar to other observational studies in non-COVID-19 ARDS patients

Ferrando C, et al. Intensive Care Med. 2020; doi:10.1007/s00134-020-06192-2

Common extrapulmonary manifestations and complications



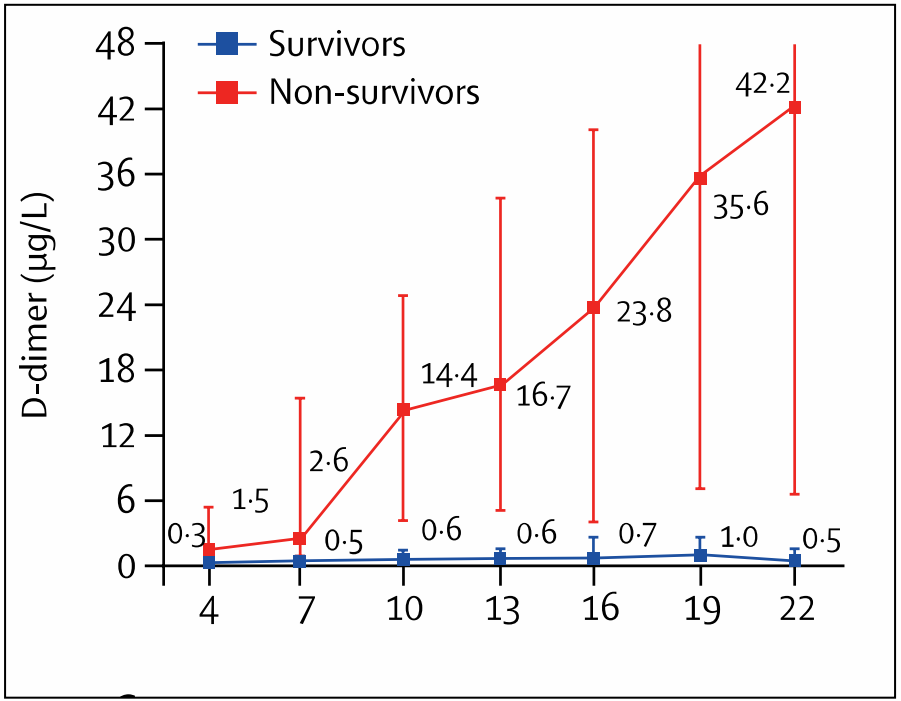
Complications	Prevalence (95%CI)
Admission to ICU	9.68% (5.41-16.73%)
Acute kidney injury	7.17% (3.75-13.28%)
Acute cardiac injury	13.54% (8.58-20.72%)
All secondary infections	9.73% (6.11-15.15%)
Secondary infections (bacteria)	2.48% (1.03-5.81%)
Heart Failure	10.34% (2.71-32.07%)

- The data is from a meta-analysis including studies as of March 28, 2020.
- As the included studies are mainly early studies, the data reflect the status of relatively severe patients and may overestimate the real prevalence of these complications in all COVID-19 patients

Gupta A, et al. Nat Med. 2020; 26(7):1017-1032
Jutzeler CR, et al. Travel Med Infect Dis. 2020; 37:101825

COVID-19 and hyper-coagulation

D-Dimer ＞ 1ug/ml was independent risk factor of in-hospital death



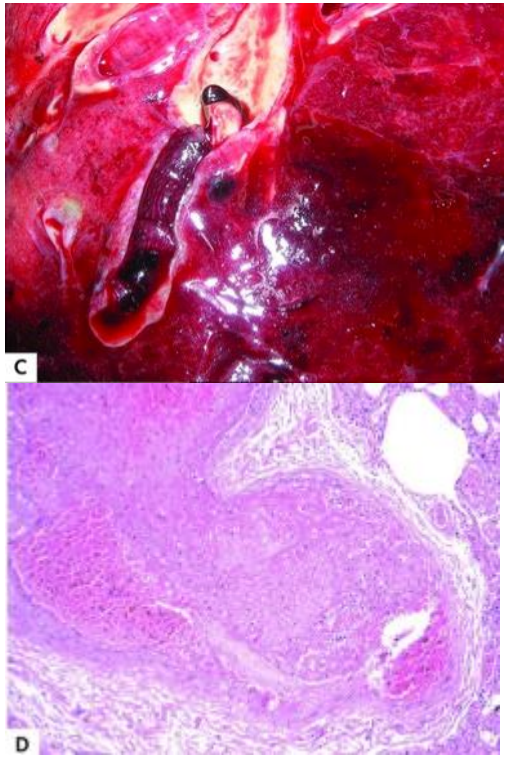
- Significantly increased D-dimer and FDP were associated with poor prognosis
- Vascular endothelium inflammation, Extensive intravascular microthrombosis on autopsy
- Vascular endothelial cells express high levels of ACE2

Anticoagulation therapy should be initiated for severe COVID-19 patients if otherwise contraindicated.

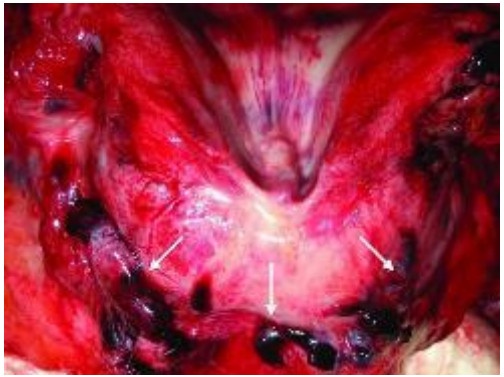
Fei Zhou et al. Lancet. 2020; 395(10229):1054-1062
Hamming I, et al. J Pathol 2004; 203(2): 631-637

COVID-19 and hyper-coagulation

Autopsy Findings from 12 patients in German

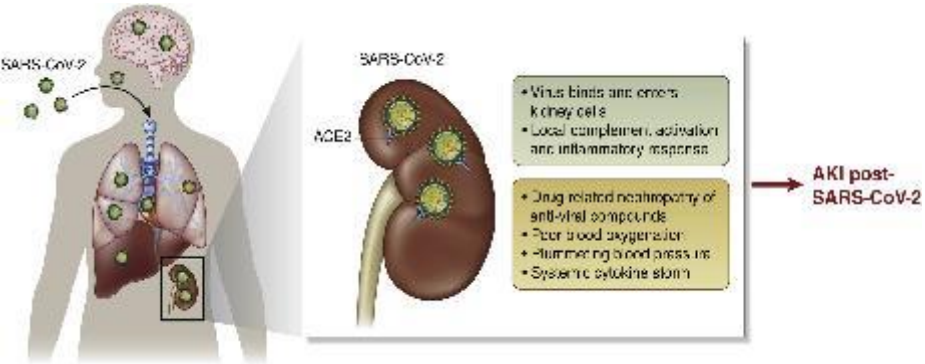


- Pulmonary embolism was the direct cause of death in 4 patients
- Autopsy revealed deep venous thrombosis in 7 of 12 patients (58%) in whom venous thromboembolism was not suspected before death



Dominic Wichmann, et al. Ann Intern Med. 2020; 173(4):268-277

COVID-19 and kidney injury

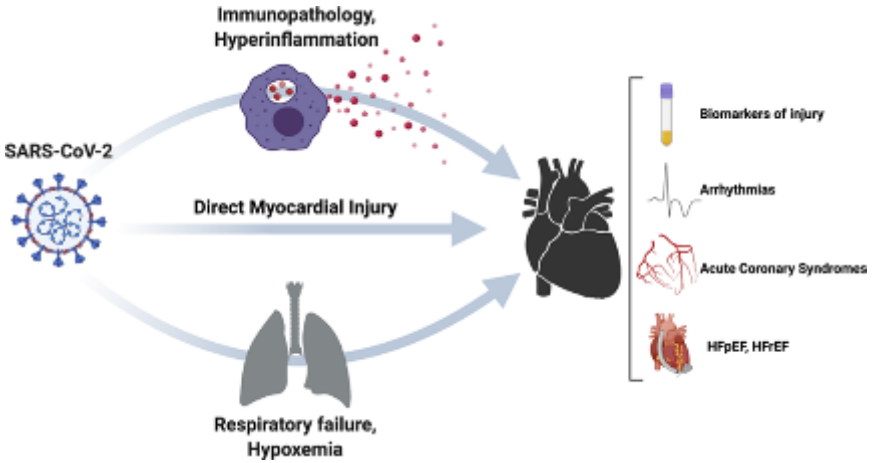


- Direct mechanism: SARS-CoV-2 bind directly to ACE2 expressed on kidney cells
- Indirect mechanism: Drug nephrotoxicity or systemic events like poor blood oxygenation, lowered blood pressure or cytokine storms

- Clinical manifestations:
  - AKI
  - Electrolyte abnormalities (hyperkalemia, hyponatremia, and hypernatremia, among others)
  - Proteinuria
  - Hematuria
  - Metabolic acidosis
  - Clotting of extracorporeal circuits used for RRT

Marina Noris et al. Kidney Int. 2020; 98(2):314-322
Gupta A, et al. Nat Med. 2020; 26(7):1017-1032

COVID-19 and cardiac injury



- Direct mechanism: viral infiltration into myocardial tissue, resulting in cardiomyocyte death and inflammation
- Indirect mechanism: Cardiac stress due to respiratory failure and hypoxemia; Cardiac inflammation secondary to severe systemic hyperinflammation

- Clinical manifestations:
  - Myocardial ischemia and MI (type 1 and 2)
  - Myocarditis
  - Arrhythmia: new-onset atrial fibrillation and flutter, sinus tachycardia, sinus bradycardia, QTc prolongation (often drug induced), torsades de pointes, sudden cardiac death, pulseless electrical activity
  - Cardiomyopathy: biventricular, isolated right or left ventricular dysfunction
  - Cardiogenic shock

Akbarshakh Akhmerov et al. Circ Res. 2020;126:1443–1455
Gupta A, et al. Nat Med. 2020; 26(7):1017-1032

Searching for magic bullets of COVID-19

1804 randomized trials have been registered globally

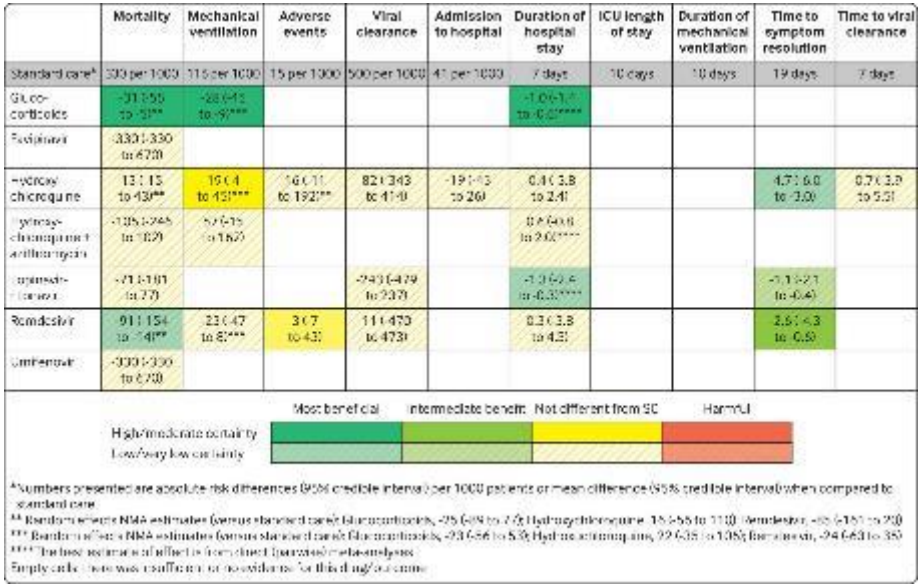
WHO Covid-19 - living NMA initiative. https://www.covid-nma.com/dataviz/

Potential therapeutic targets

- Potential anti-viral drugs:
  - Remdesivir
  - Lopinavir-Ritonavir
  - Hydroxychloroquine
  - Favipiravir
  - Ribavirin
  - Monoclonal antibody
- Potential immunomodulator:
  - Corticosteroids
  - Convalescent plasma
  - IL-6R inhibitors
  - JAK inhibitors
  - Interferon beta

Antiviral + Immunomodulatory drugs might be the future

Drug treatments for covid-19: A living network meta-analysis



- The literature search of this version was up to July 29, 2020
- Corticosteroids probably reduce death (moderate certainty), mechanical ventilation (moderate certainty), and duration of hospitalization (moderate certainty). Besides, a systematic review published in *JAMA* on Sept 2 further confirmed the benefits of corticosteroids in 28-day mortality.
- The impact of remdesivir on mortality, mechanical ventilation, and length of hospital stay is uncertain, but it probably reduces duration of symptoms (moderate certainty) and probably does not substantially increase adverse effects leading to drug discontinuation (moderate certainty)
- Hydroxychloroquine may not reduce risk of death (low certainty) or mechanical ventilation (moderate certainty)
- The effects of most drugs are highly uncertain and the evidences are still emerging

Reed Ac Siemieniuk et al. BMJ 2020; 370:m2980
WHO REACT Working Group. JAMA. 2020; doi:10.1001/jama.2020.17023

Uncertainties still remain for systemic corticosteroids

- Long-term effect of systemic corticosteroids on mortality and functional outcomes in COVID-19 survivors
- Systemic corticosteroids combination with antivirals vs corticosteroids alone
- Impact of corticosteroids on immunity and the risk of a subsequent infection, which may impact the risk of death after 28 days
- Contraindication of systemic steroids, including immucompromised patients, patients with tuberculosis, et al.
- Adverse Effects on viral replication

Fully evaluation of benefits and risks before initiation of systemic corticosteroids

A question to discuss: What is the real death risk of COVID-19?

- As of 2020/9/23, there has been 31425029 confirmed cases and 967164 confirmed deaths (WHO data).
- Is the death risk of COVID-19 3.1% (967164/31425029)?
- Case fatality rate of COVID-19 = $\frac{Number\ of\ COVID{-}19\ deaths}{Total\ Number\ of\ COVID{-}19\ patients}$
- Both the numerator and denominator of the above formula is not accurate in the pandemic:
  - Numerator: In pandemic-stricken area with limited medical resources, some COVID-19 related deaths failed to be attributed to COVID-19.
  - Denominator: A large number of cases are not diagnosed in the pandemic.
    - First, the ability of nucleic testing in many countries/regions will influence the diagnosis rate of COVID-19, especially in the areas with rapidly rising suspected cases.
    - Second, the asymptomatic infected individuals may not receive test and will not be diagnosed.
  - The condition of medical resources will also influence the risk of death
- A nationwide sero-epidemiological study in Iceland estimated that only 56% infected individuals were confirmed with PCR

  The estimated death risk in iceland is 0.3% (95% CI, 0.2 to 0.6).
- The data from Iceland provided us with some confidence that, if under proper medical care, the death risk of COVID-19 might be controlled under 1%
- Before the vaccines are widely available, more efforts need to be done on enlarging testing scale, quarantine and providing high-quality medical care

World Health Organization, https://covid19.who.int, data as of 2020/9/23, 4:47pm CEST
Gudbjartsson DF, et al. N Engl J Med. 2020; doi:10.1056/NEJMoa2026116

Summary

- The main transmission route of SARS-CoV-2 is face-to-face exposure of droplets
- SARS-CoV-2 interacts with ACE2 as host cell receptor and the Spike protein is primed by protease TMPRSS2
- Disease severity of COVID-19 is influenced by both viral infection and host response
- The extrapulmonary symptoms and complications are common
- Corticosteroid is the only drug with confirmed mortality benefit, but the individualized use remains to be explored
- Antiviral + Immunomodulatory drugs might be the future
- What we know is still very limited and the knowledge is rapidly emerging

Acknowledgements

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Peter W Horby

Third Military Medical University (Army Medical University)
Xiuwu Bian

Cooperators:

Wuhan Jinyintan Hospital	Wuhan Tongji Hospital
Wuhan Lung Hospital	The Central Hospital of Wuhan
Zhongnan Hospital of Wuhan University	Renmin Hospital of Wuhan University
Union Hospital	Wuhan First hospital
Wuhan Third hospital	Wuhan Fourth hospital

All health-care workers involved in the diagnosis and treatment of patients

World Health Organization
国家自然科学基金委员会 National Natural Science Foundation of China
中国肺炎研究 CAP-China