中日友好医院
CHINA-JAPAN FRIENDSHIP HOSPITAL

Chinese Guideline of Diagnosis and treatment of COVID-19

(7th Version)

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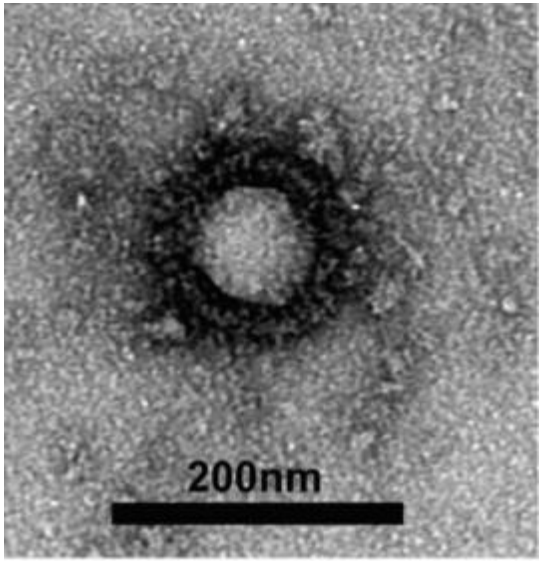
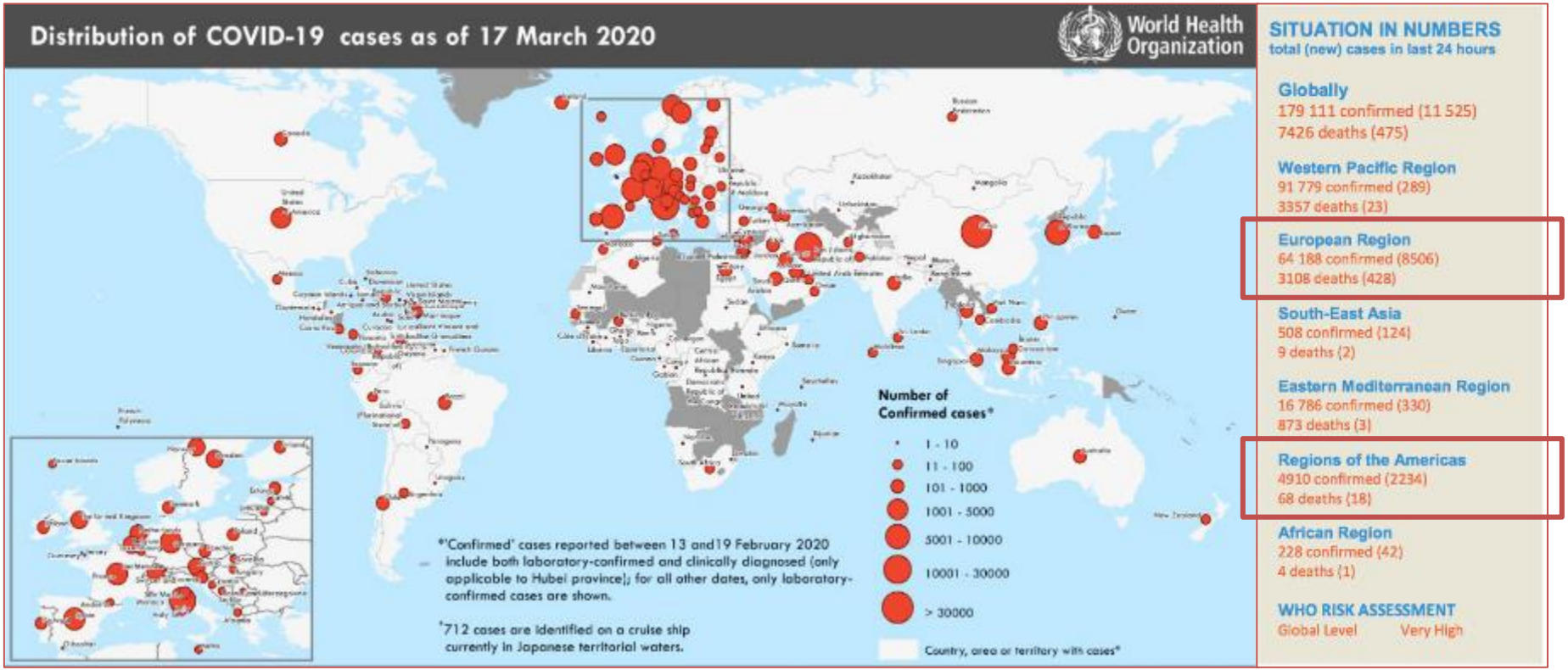
Severe Acute Respiratory Syndrome Coronavirus-2

- 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



Epidemiology of COVID-19 globally

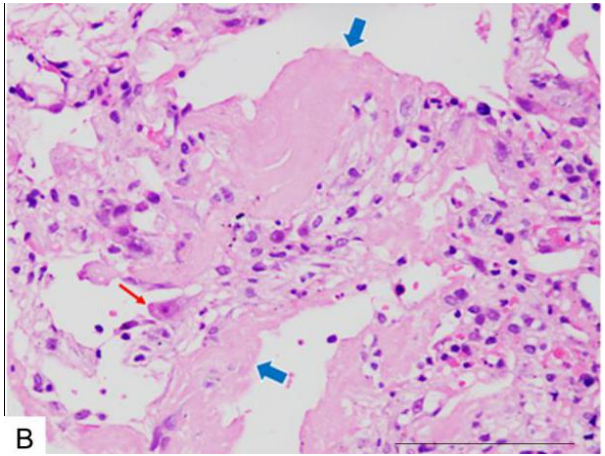
- COVID-19 has spread to the world rapidly. —— **A threat of the word**



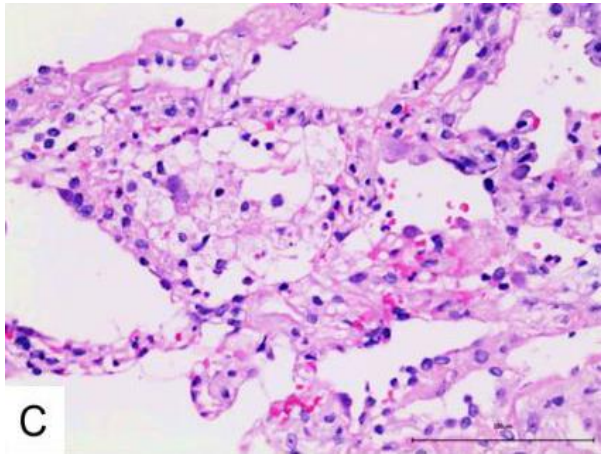
https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200317-sitrep-57-covid-19.pdf?sfvrsn=a26922f2_4

Pathogenic changes of severe COVID-19 in lung

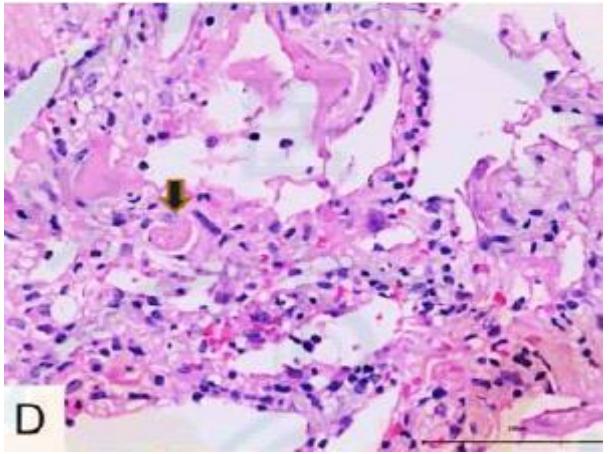
- The pathological features in lungs greatly resemble those seen in SARS and MERS infection
- bilateral diffuse alveolar damage with cellular fibromyxoid exudates



Hyaline membrane formation（blue arrow)



Interstitial mononuclear inflammatory infiltrates

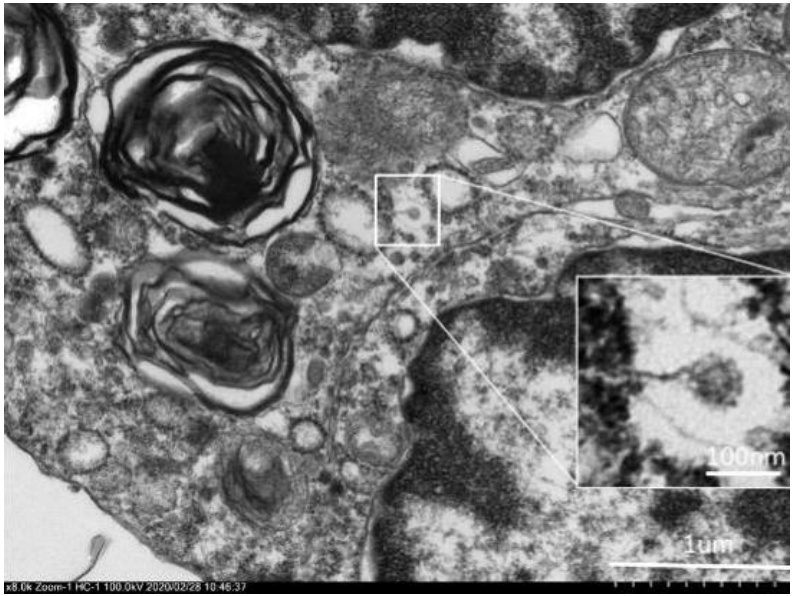


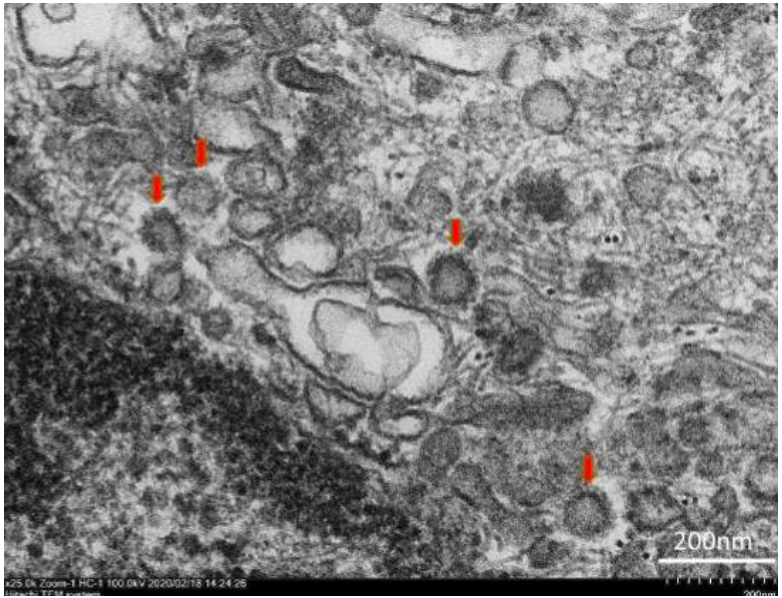
Thrombus in pulmonary arterioles (black arrow)

Xiaohong Yao et al. Chinese Journal of Pathology.2020,49 (2020-03-15).

Severe Acute Respiratory Syndrome Coronavirus-2

- Viral particle in Alveolar type II cells (Electron microscopy)

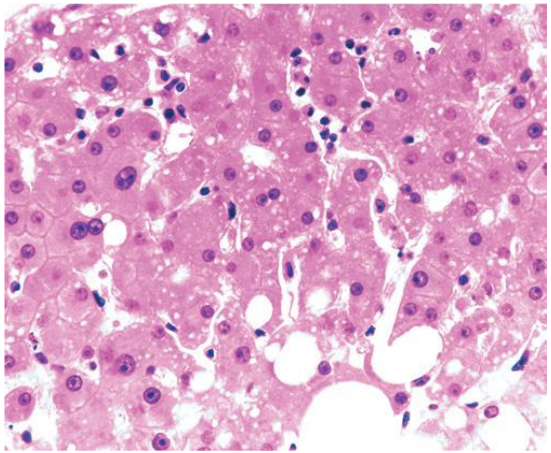


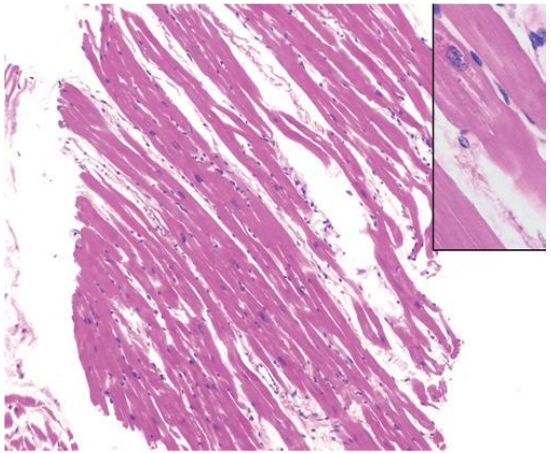


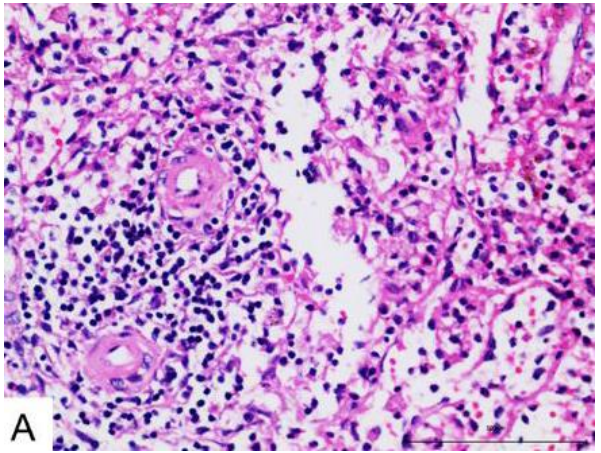
Zhe Xu et al. Lancet Respir Med.2020. DOI: [10.1016/S2213-2600(20)30076-X](10.1016/S2213-2600(20)30076-X)

Pathogenic changes of severe COVID-19 in other organs

- Degeneration and necrosis of parenchymal cells, formation of hyaline thrombus in small vessels, and pathological changes of chronic diseases were observed in other organs and tissues
- Decreased numbers of lymphocyte, cell degeneration and necrosis were observed in spleen







Zhe Xu et al. Lancet Respir Med.2020. DOI: [10.1016/S2213-2600(20)30076-X](10.1016/S2213-2600(20)30076-X)

Diagnostic criteria of COVID-19——Suspected cases

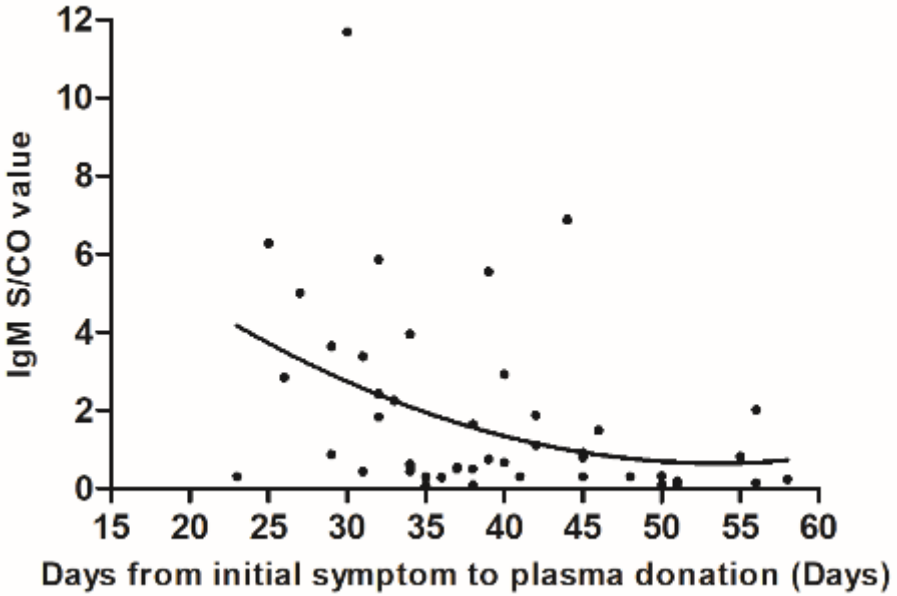
Suspected cases	
Epidemiological history (≤14 days)	Clinical symptoms
➢ travel /residence in Wuhan and its surrounding areas,or other communities where COVID-19 has been found	➢ fever and/or respiratory symptoms
➢ contact with COVID-19 patients	➢ imaging characteristics of COVID-19
➢ Contact with patients with fever or respiratory symptoms and from Wuhan and its surrounding areas, or from communities where COVID-19 has been found	➢ Normal or decreased of WBC ;Normal or decreased of Lymphocytes
➢ Clustered cases	

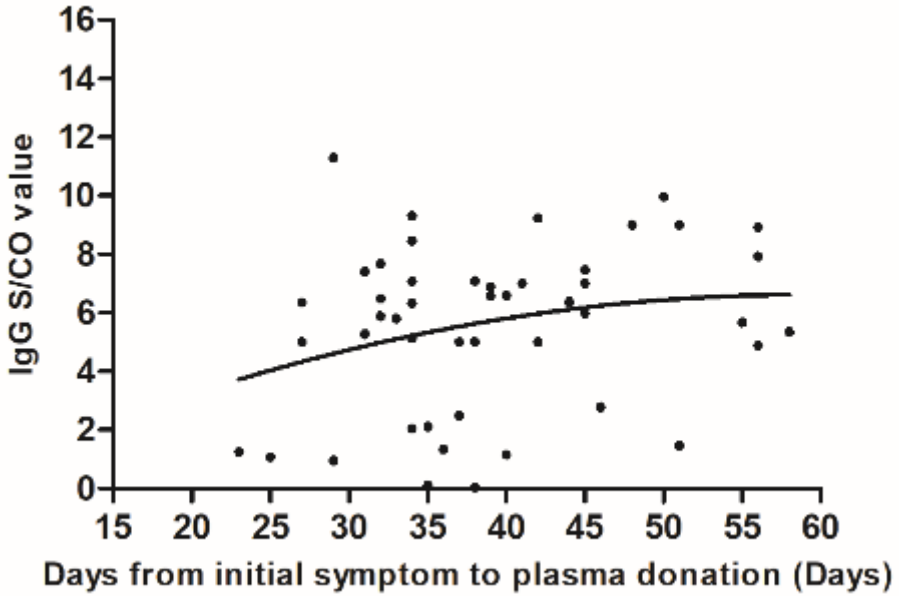
- **Any one criteria of Epidemiological history + Any two Clinical symptoms**
- **All three clinical symptoms**

Diagnostic criteria of COVID-19——Confirmed cases

Confirmed cases	
Etiological or serological evidences	
Nucleic acid testing	■ SARS-CoV-2 RNA was positive detected by real time RT-PCR
	■ Viral gene sequence is highly homologous to known new coronaviruses
Serum antibody testing	■ SARS-CoV-2 specific IgM and IgG are positive in serum
	■ SARS-CoV-2 specific IgG is detectable from negative to positive
	■ SARS-CoV-2 specific IgG antibody titer shows a 4-fold or higher change between the two sets of serum samples from acute and recovery phase
Suspect cases + one of etiological or serological evidences	

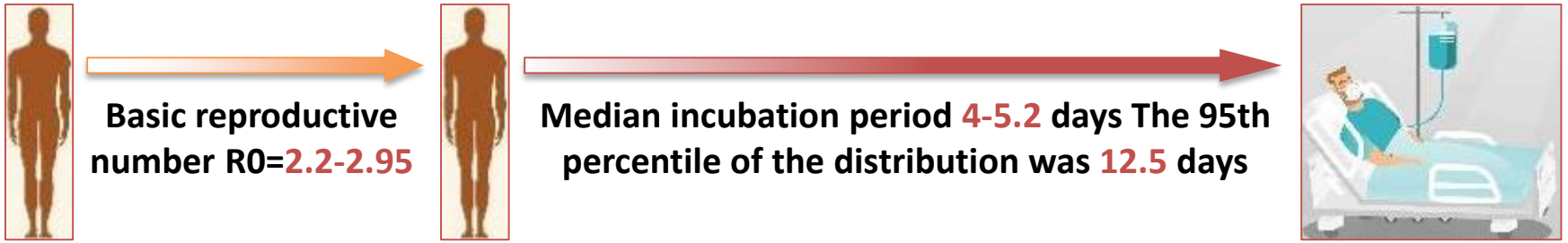
IgG/IgM Dynamic changes of Adults with COVID-19





Zhong Liu et al. unpublished data

Transmission and incubation of COVID-19

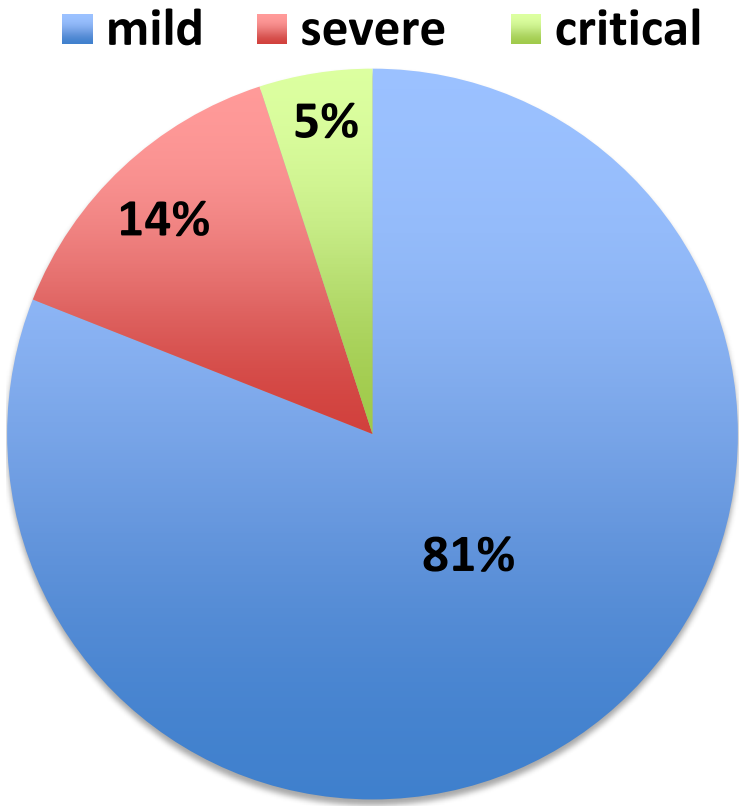


- **COVID-19 patients** including the asymptomatic infected people are the main source of infection
- Route of transmission
  - Respiratory droplets and close contact
  - Long-time exposure to the environment with a high concentrations of aerosol
  - Environment contaminated by feces/urine → aerosol or contact transmission
- All the population are generally susceptible

Y Wang et al. Zhonghua Liu Xing Bing Xue Za Zhi.41 (4), 476-479; Qun Li et al. N Engl J Med. DOI: 10.1056/NEJMoa2001316
Guan WJ et al. N Engl J Med. 2020. doi: 10.1056/NEJMoa2002032

Disease spectrum of COVID-19

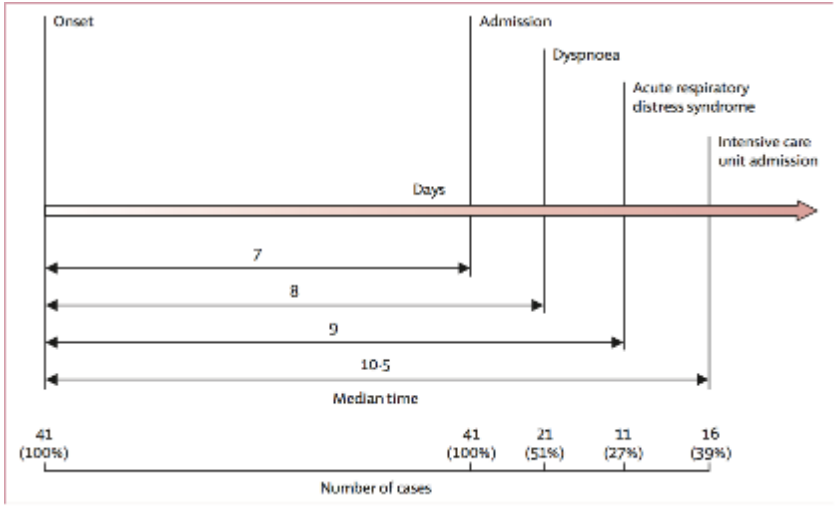
- **81% were mild status**
  - No pneumonia or mild pneumonia
- **14% were severe status**
  - Dyspnea or Respiratory Rate ≥ 30/min or SpO_2 < 93% or PaO_2/FiO_2 <300 mmHg
  - Lung infiltrates >50% within 24 to 48 hours
- **5% were critical ill status**
  - Needs mechanical ventilation
  - Shock
  -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



Zunyou Wu et al.JAMA.2020. DOI: 10.1001/jama.2020.2648

Clinical features of COVID-19 patients

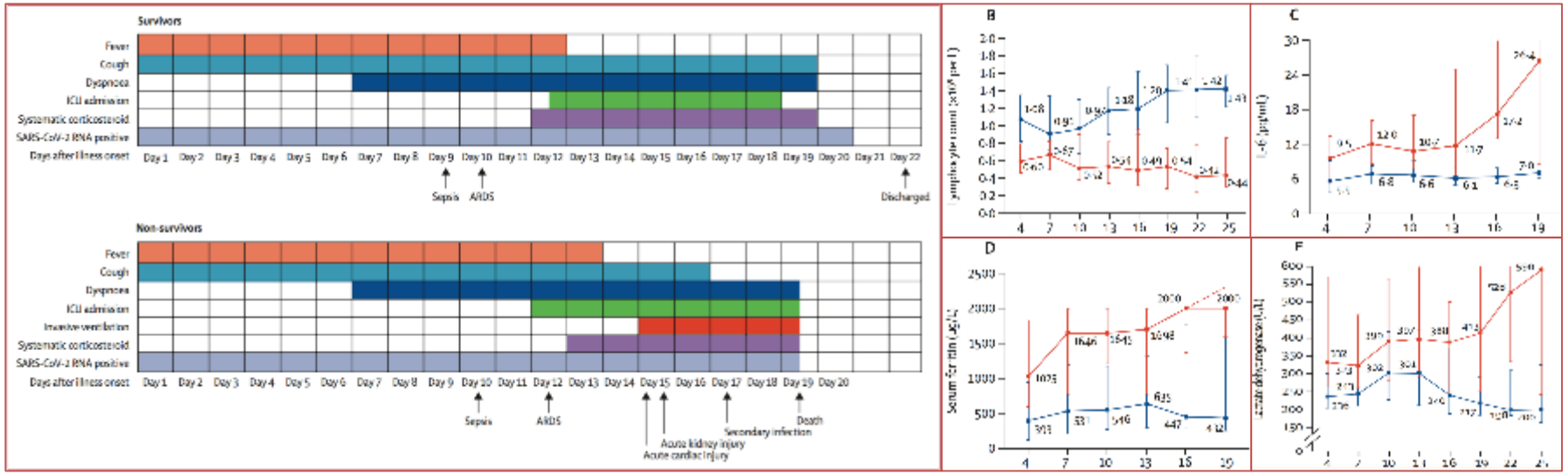
Symptoms and complications	N%
Fever	98%
Cough	76%
Myalgia or fatigue	44%
Sputum production	28%
Diarrhea	3%
WBC ≤ 10 × 10^9/L	70%
Lymphocytopnia	63%
ALT > 40 U/L	37%
Cr > 133 mmol/L	10%
LDH > 243 U/L	73%
Hypersensitive troponin I > 28 pg/ml	12%
Procalcitonin < 0.1 ng/ml	69%
Acute respiratory distress syndrome	29%



Symptoms and complications	N%
Acute cardiac injury	12%
Acute kidney injury	7%
Septic shock	7%
Secondary infection	10%

Huang C et al. Lancet. 2020;395(10223):497-506.

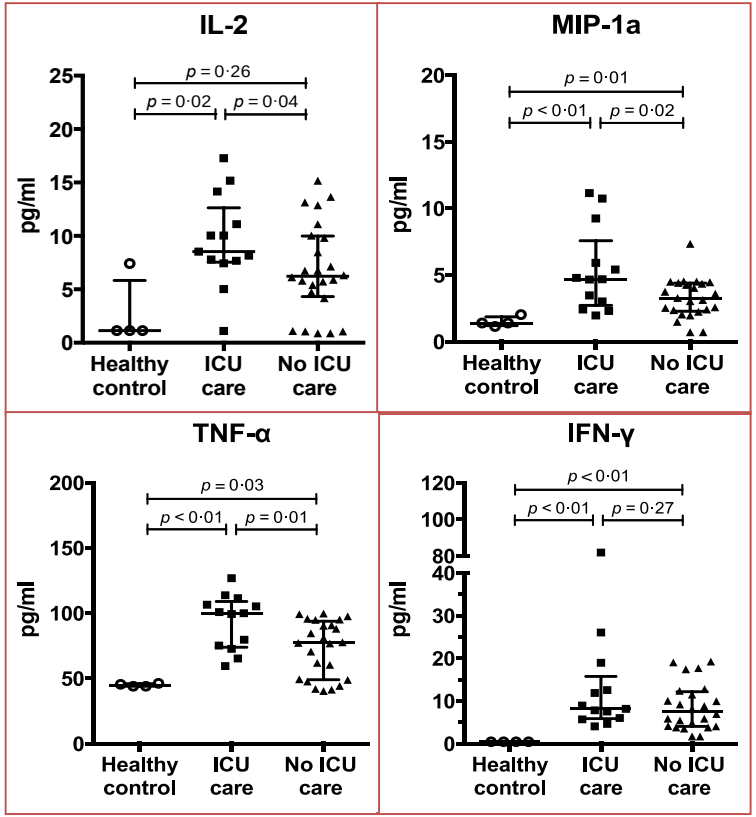
Clinical course of COVID-19——Severe and critical illness

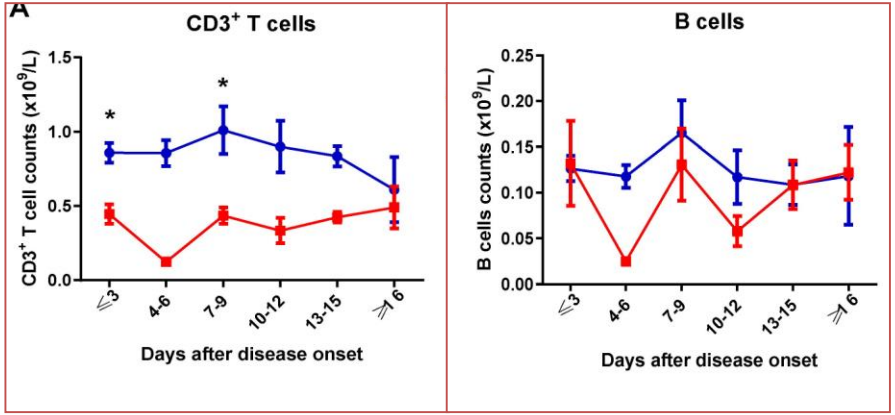


- Duration of dyspnea was 13 days in survivors
- 45% survivors still had cough on discharge
- Median duration of viral shedding was 20 days, could prolong as 37 days
- lymphocyte count was lowest on day 7 after illness onset and improved during hospitalisation in survivors but whereas severe lymphopenia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

Fei Zhou et al. Lancet.2020. DOI: [10.1016/S0140-6736(20)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)

Inflammation of COVID-19——Severe and critical illness





- IL-1β, IL-6, G-SCF, IP-10, and MCP1 were significantly elevated
- Peripheral lymphocyte counts, mainly T cells were substantially reduced in severe COVID-19 patients

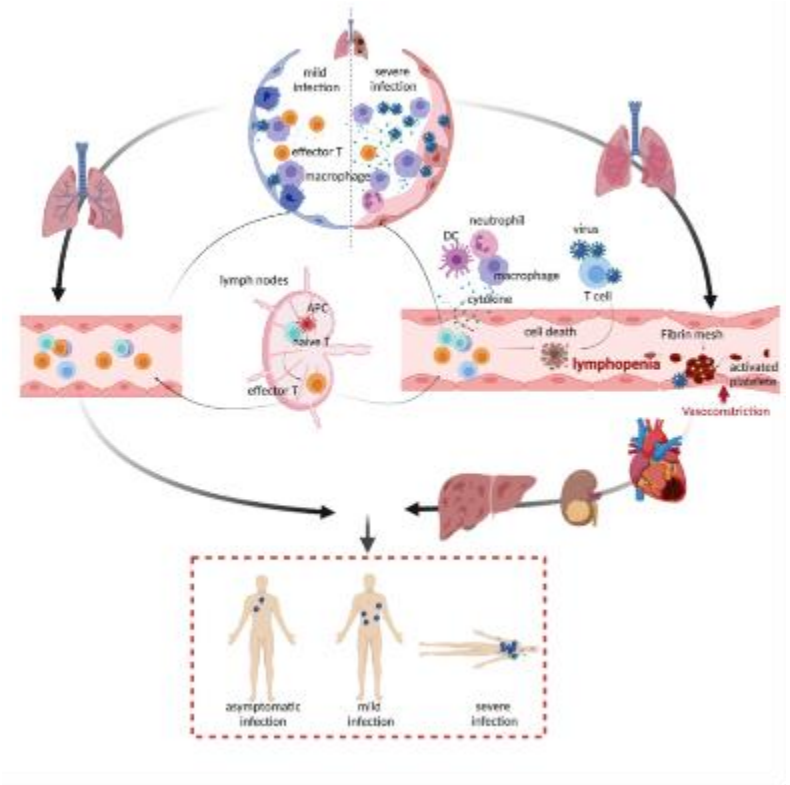
Host-directed therapies might be an option

Huang C, et al. Lancet 2020; 395(10223): 497-506; Liu J, et al. BMJ 2020;published online Feb 19.

SARS-CoV-2 Viral sepsis——From Bedside to Bench

Multi-organ dysfunction

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

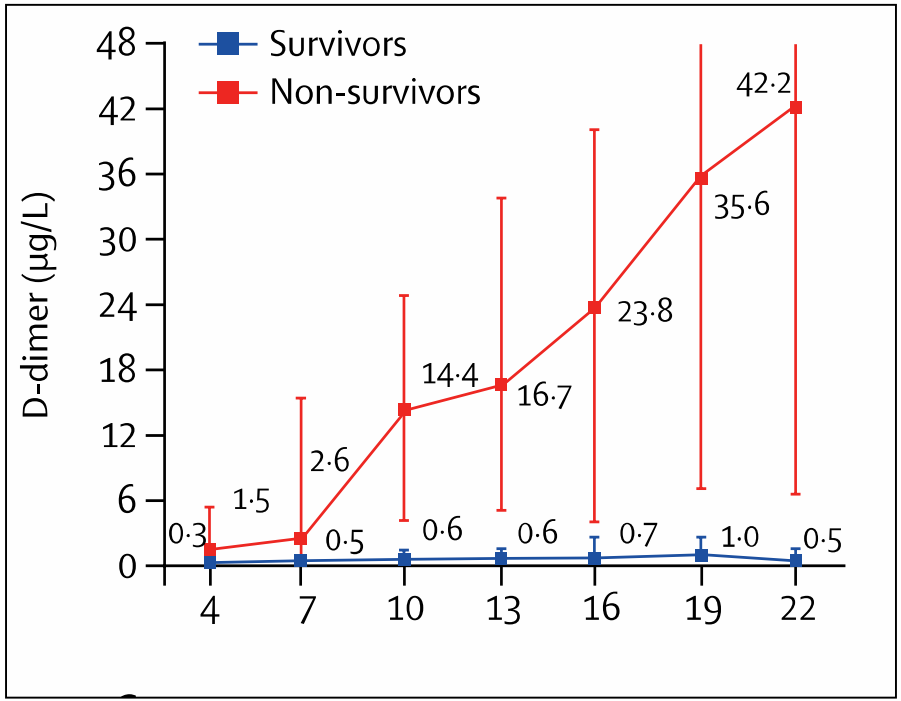


——Viral Sepsis

Ren L, et al. Chin Med J 2020; DOI: 10.1097/CM9.0000000000000722； Huang C, et al. Lancet 2020; 395(10223): 497-506
Hui Li, et al. 2020; unpublished, under revision

Abnormal coagulation is common in severe COVID-19

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.

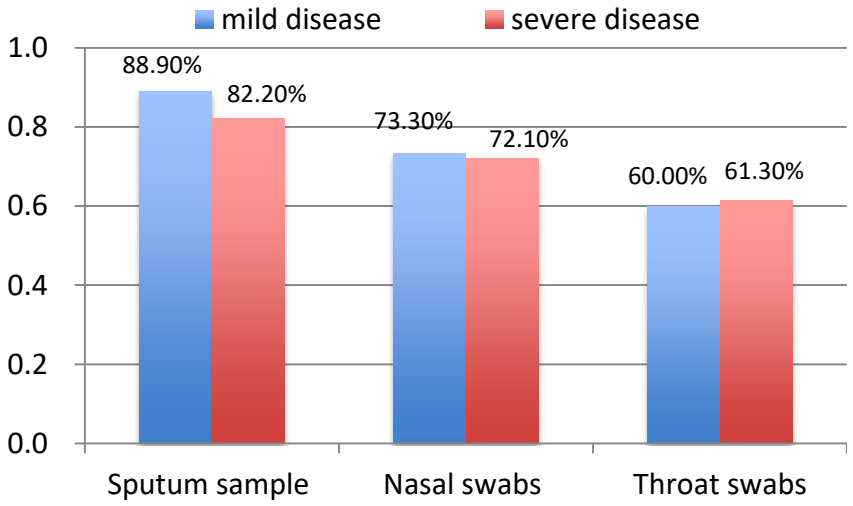
Zhou F, et al. Lancet 2020; DOI:10.1016/S0140-6736(20)30566-3; Hamming I, et al. J Pathol 2004; 203(2): 631-7.

SARS-CoV-2 RNA detection in COVID-19 patients

- SARS-CoV-2 RNA could be detected in nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, feces using RT-PCR and/or NGS methods
- Positive rate was higher in lower respiratory tract specimen
- The specimens should be submitted for testing as soon as possible after collection

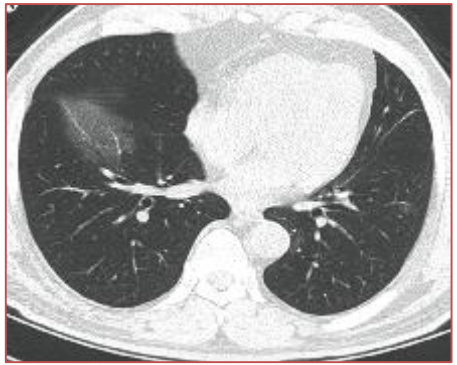
Table 1. Molecular detection of 2019-nCoV in swabs and blood. Samples were from oral swabs (OS), anal swabs (AS) and blood. Data were shown as qPCR Ct values. Patients in severe condition during investigation were shown.

	OS	AS	Whole blood	Serum	Severe disease
Patient 1	33.5				No
Patient 2			30.3	24.3	Yes
Patient 3	30.3				No
Patient 4			32.1		No
Patient 5		33.1			No
Patient 6			30.6		No
Patient 7	32.7	30.2			No
Patient 8		33.1			No
Patient 9			31.4	34.5	No
Patient 10			30.9	33.0	Yes
Patient 11	27.3				No
Patient 12	34.4				Yes
Patient 13	32.9	33.6			No
Patient 14	32.3				No
Patient 15			31.6		No



Wei Zhang et al.Emerg Microbes Infect, 9 (1), 386-389; Yang Y et al. medRxiv 2020.

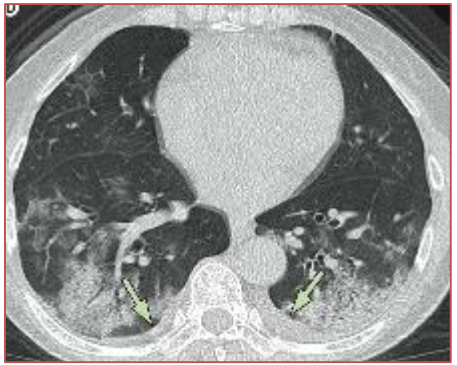
Features of CT scan of COVID-19



56-year-old man
Day 3 after symptom onset
Focal ground-glass opacity

74-year-old woman
Day 10 after illness onset
Bilateral, peripheral ground-glass opacity

61-year-old woman
Day 20 after symptom onset
Bilateral and peripheral predominant consolidation

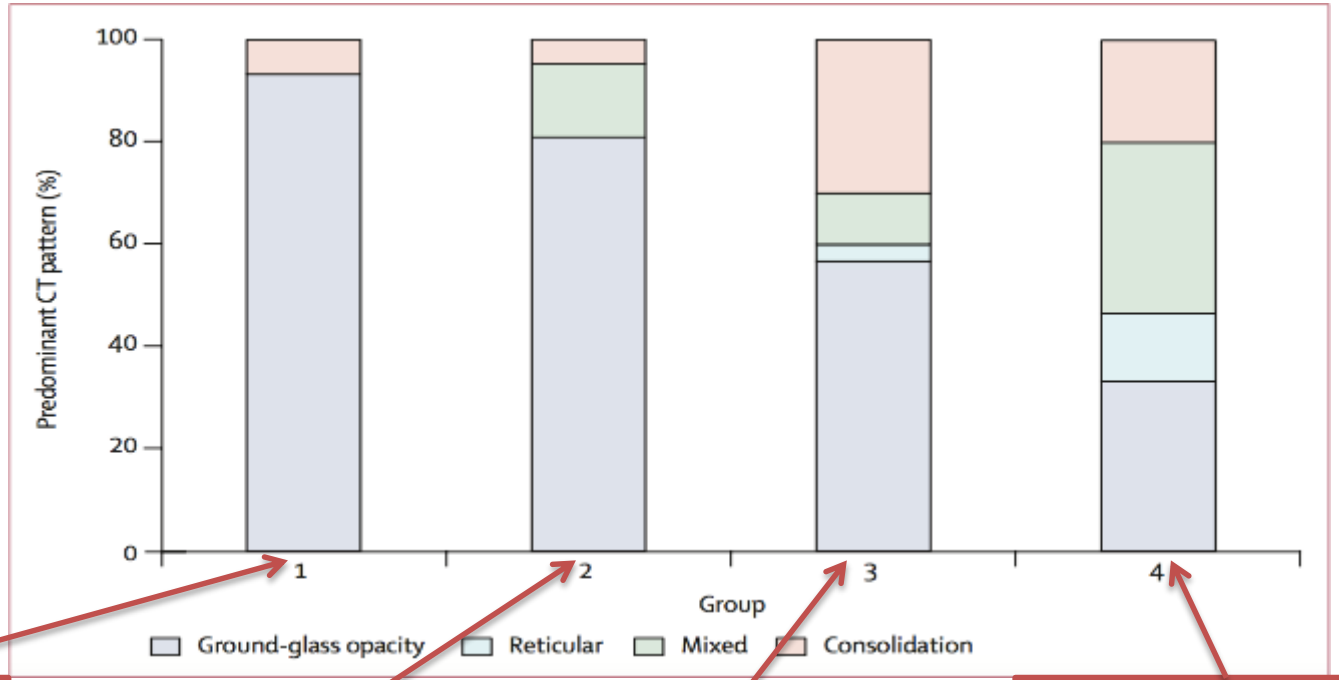


63-year-old woman
Day 17 after symptom onset
Bilateral, peripheral mixed pattern； Air bronchogram；
Pleural effusion

- Common:bilateral lung involvement(79%); peripheral distribution (54%); diffuse distribution (44%) ground glass opacity (65%); without septal thickening(65%).
- Less common: nodules (6%), cystic changes (10%), bronchiolectasis (11%), pleural effusion (5%).
- Not observed: Tree in bud signs, masses, cavitation, and calcifications

Heshui Shi et al. Lancet Infect Dis.2020. DOI: 10.1016/S1473-3099(20)30086-4

CT scan 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. DOI: 10.1016/S1473-3099(20)30086-4

Rapid deterioration on CT scan-case 1

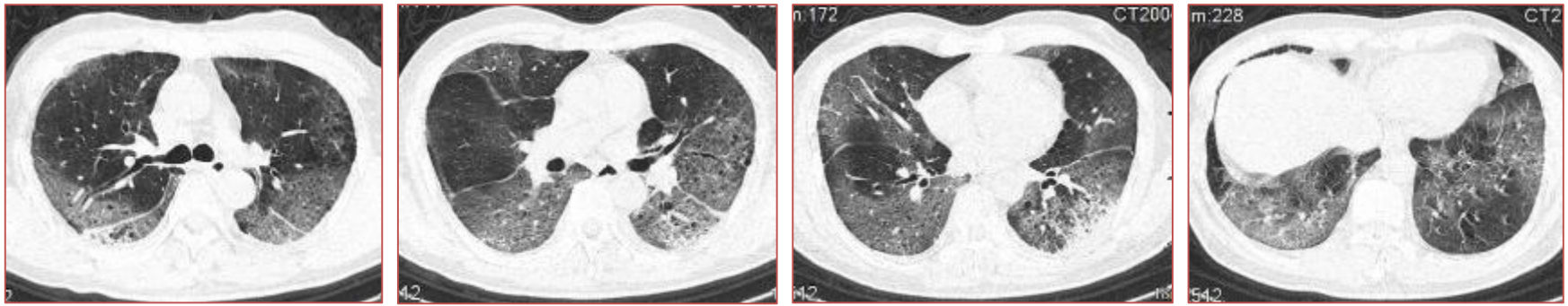
Male, 70 years old

2020-1-28 Day 9 after illness onset

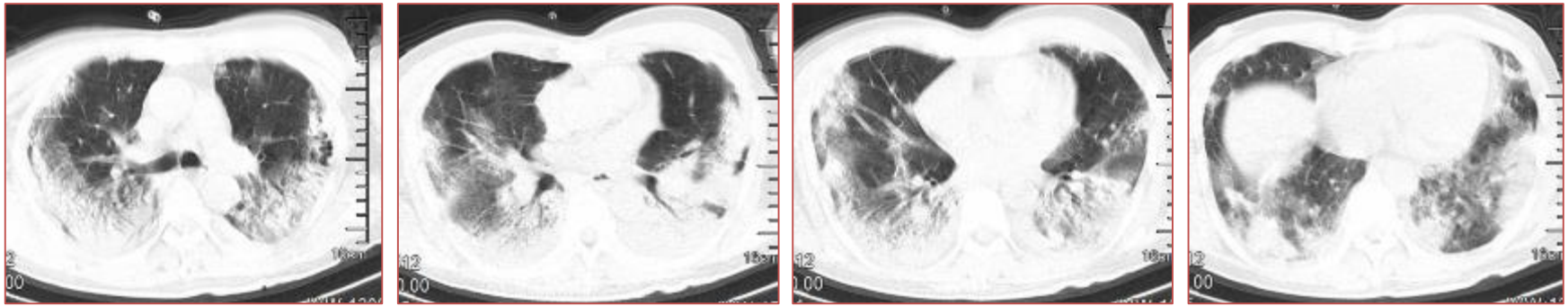
2020-2-1 Day 13 after illness onset. Died 2 weeks later.

Rapid deterioration on CT scan-case 2

Male, 62 years old



2020-2-7 Day 12 after illness onset

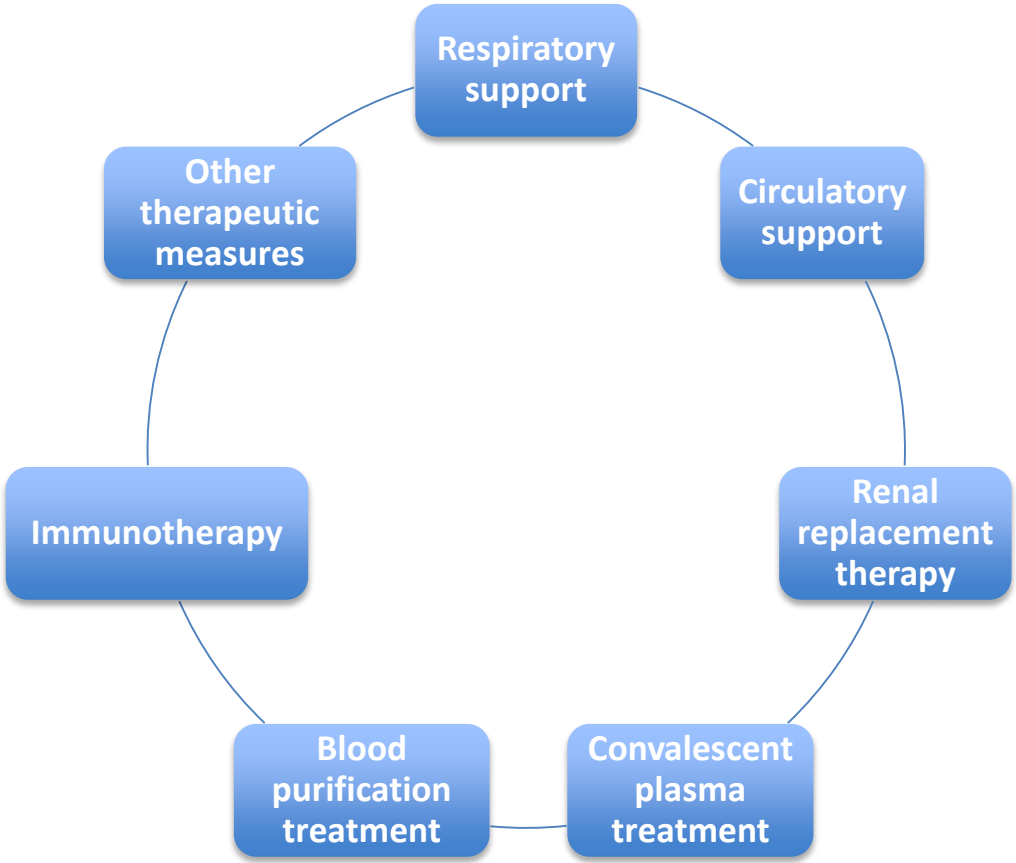


2020-2-7 Day 19 after illness onset. Died 15 days later

Isolation and Support treatment of COVID-19

- All confirmed patients should be isolation.
- Suspected case should be treated in isolation in a single room
- Hospital and ICU admission decision was according to disease severity
- Strengthening support treatment (most patients complicated with hypoproteinemia)
  - sufficient caloric
  - water and electrolyte balance
- Oxygen therapy
- Closely monitoring vital sign and laboratory **(progress rapidly in severe patients)**
  - WBC; Lymphocyte
  - Biochemical indicators (liver enzyme, myocardial enzyme, renal function .etc)
  - Marker of inflammation (serum ferritin, IL-6, cytokine)
  - Chest imaging

Treatment options for severe or critical COVID-19



Antiviral interventions

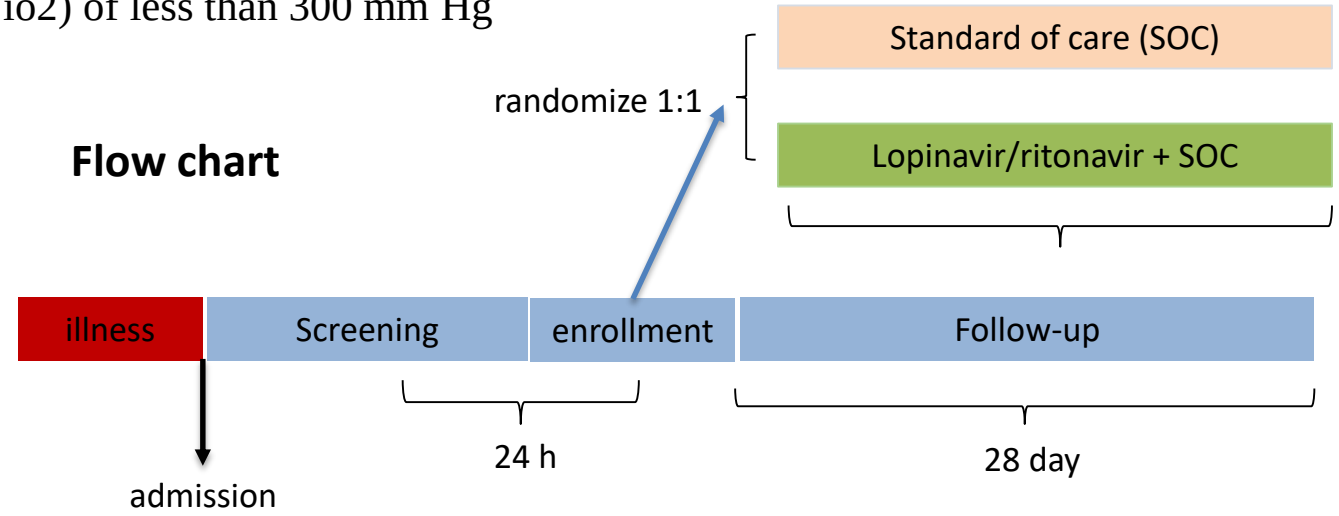
- So far, no specific antiviral against SARS-CoV-2 has been proved
- Clinically evaluated drugs：
  - Lopinavir/ritonavir monotherapy (LOTUS China, ChiCTR2000029308): ***completed, NEJM online (9 Mar, 2020)***
    - Encourging results
  - CAP China Remdesivir 1 (mild-moderate pneumonia, NCT04252664): ***ongoing***
  - CAP China Remdesivir 2 (severe-critical pneumonia, NCT04257656): ***ongoing***

Bin Cao, et al; N Engl J Med 2020; DOI: 10.1056/NEJMoa2001282
Yeming wang, et al. Trial, 2020, under peer review

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19-LOTUS China

- Method： a randomized, controlled, open-label trial (**ChiCTR2000029308**)

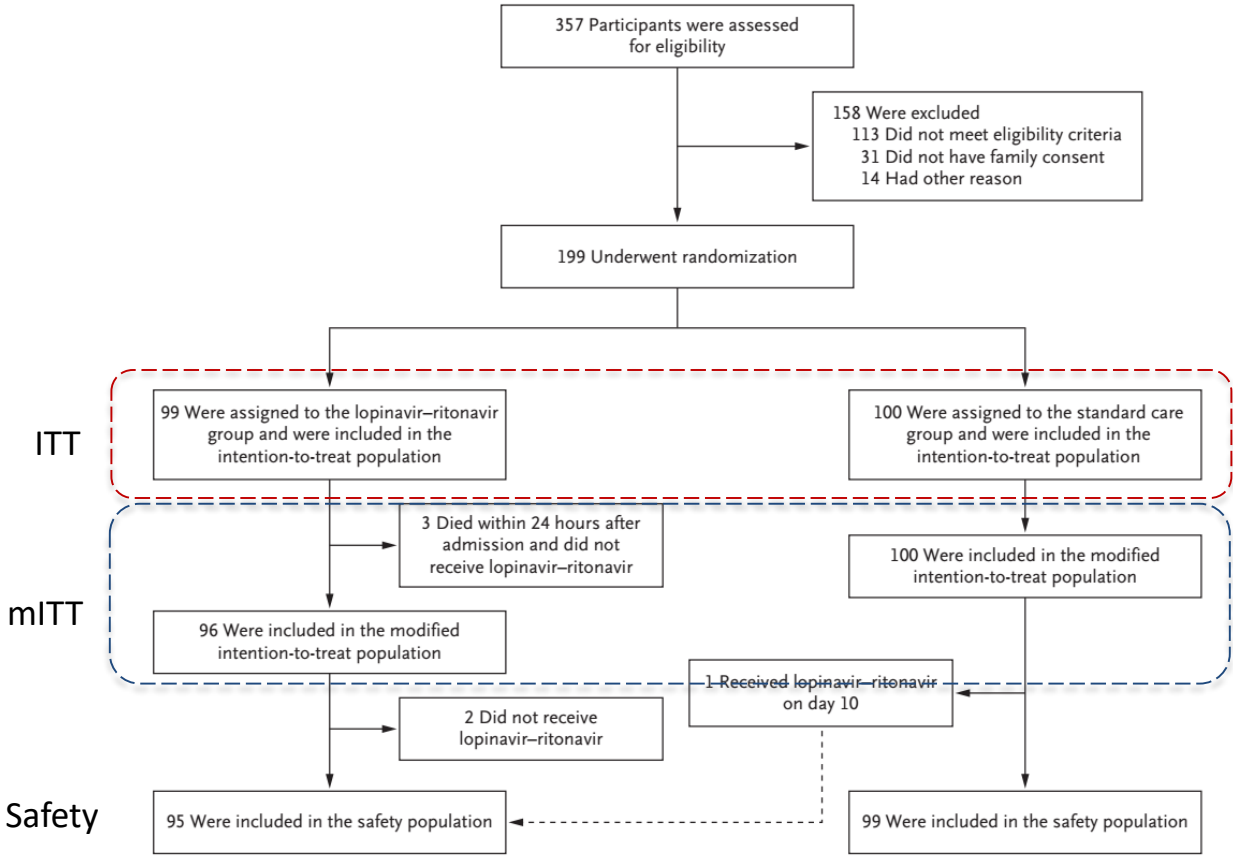
- Patients: 1) hospitalized adult patients with confirmed SARS-CoV-2 infection respiratory illness Covid-19; 2) an oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of less than 300 mm Hg



Bin Cao, et al; N Engl J Med 2020; DOI: 10.1056/NEJMoa2001282

End points and Enrollment-LOTUS China

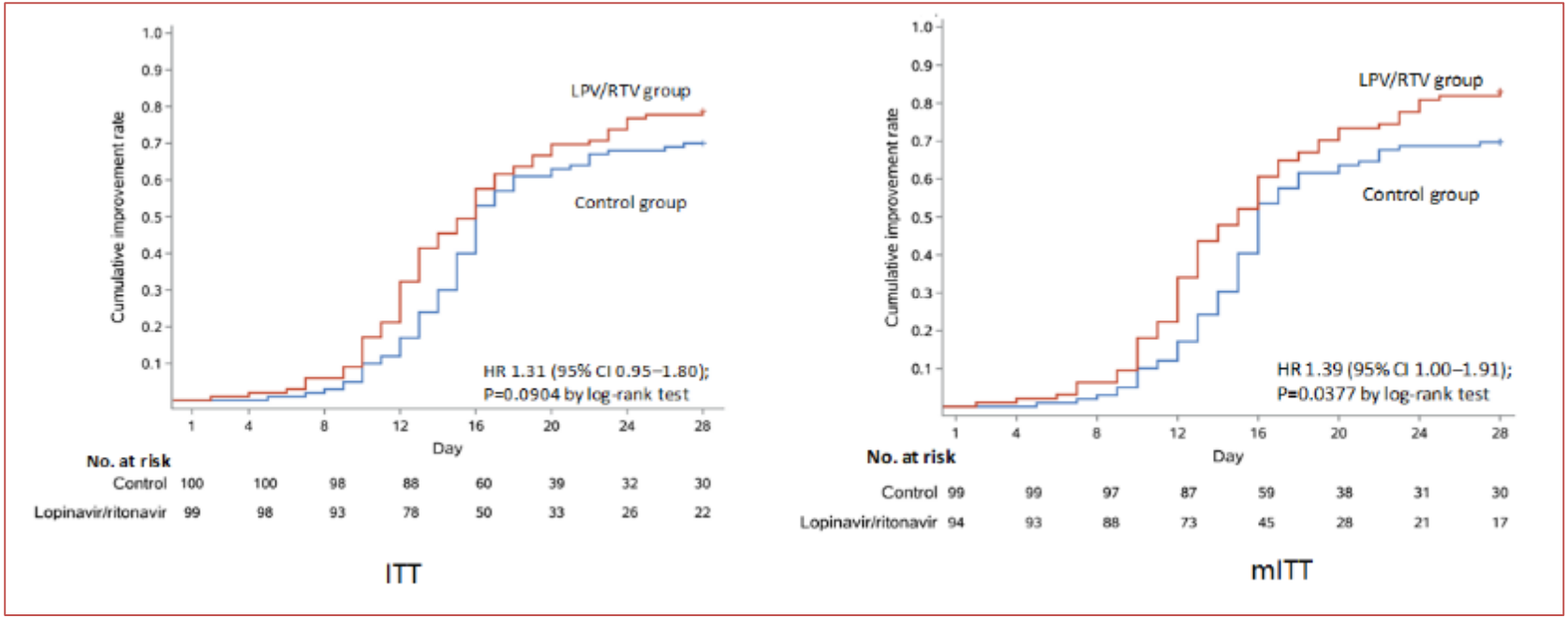
- Primary end point:
  - time to clinical improvement
- Secondary end points:
  - ICU length
  - 28 day mortality
  - Rate of clinical improvement at 14 days or 28 days



Bin Cao, et al; N Engl J Med 2020; DOI: 10.1056/NEJMoa2001282

Time to clinical improvement-ITT and mITT

- No benefit was observed with lopinavir–ritonavir treatment beyond standard care?



Bin Cao, et al; N Engl J Med 2020; DOI: 10.1056/NEJMoa2001282

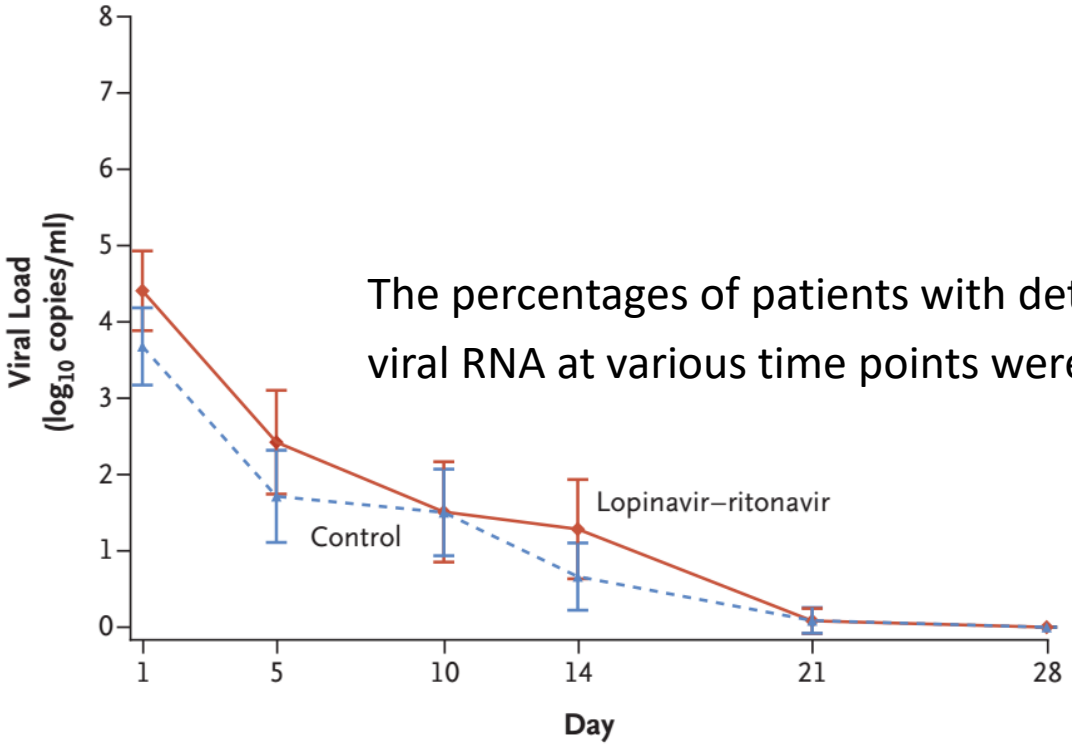
Secondary Endpoints-ITT

Table 3. Outcomes in the Intention-to-Treat Population.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)	Difference†
Time to clinical improvement — median no. of days (IQR)	16.0 (15.0 to 17.0)	16.0 (13.0 to 17.0)	16.0 (15.0 to 18.0)	1.31 (0.95 to 1.80)‡
Day 28 mortality — no. (%)	44 (22.1)	19 (19.2)§	25 (25.0)	−5.8 (−17.3 to 5.7)
Earlier (≤12 days after onset of symptoms)	21 (23.3)	8 (19.0)	13 (27.1)	−8.0 (−25.3 to 9.3)
Later (>12 days after onset of symptoms)	23 (21.1)	11 (19.3)	12 (23.1)	−3.8 (−19.1 to 11.6)
Clinical improvement — no. (%)				
Day 7	8 (4.0)	6 (6.1)	2 (2.0)	4.1 (−1.4 to 9.5)
Day 14	75 (37.7)	45 (45.5)	30 (30.0)	15.5 (2.2 to 28.8)
Day 28	148 (74.4)	78 (78.8)	70 (70.0)	8.8 (−3.3 to 20.9)
ICU length of stay — median no. of days (IQR)	10 (5 to 14)	6 (2 to 11)	11 (7 to 17)	−5 (−9 to 0)
Of survivors	10 (8 to 17)	9 (5 to 44)	11 (9 to 14)	−1 (−16 to 38)
Of nonsurvivors	10 (4 to 14)	6 (2 to 11)	12 (7 to 17)	−6 (−11 to 0)
Duration of invasive mechanical ventilation — median no. of days (IQR)	5 (3 to 9)	4 (3 to 7)	5 (3 to 9)	−1 (−4 to 2)
Oxygen support — days (IQR)	13 (8 to 16)	12 (9 to 16)	13 (6 to 16)	0 (−2 to 2)
Hospital stay — median no. of days (IQR)	15 (12 to 17)	14 (12 to 17)	16 (13 to 18)	1 (0 to 2)
Time from randomization to discharge — median no. of days (IQR)	13 (10 to 16)	12 (10 to 16)	14 (11 to 16)	1 (0 to 3)
Time from randomization to death — median no. of days (IQR)	10 (6 to 15)	9 (6 to 13)	12 (6 to 15)	−3 (−6 to 2)

Bin Cao, et al; N Engl J Med 2020; DOI: 10.1056/NEJMoa2001282

Quantitative RNA Detection-LOTUS China



The percentages of patients with detectable viral RNA at various time points were similar.

Bin Cao, et al; N Engl J Med 2020; DOI: 10.1056/NEJMoa2001282

Table 4. Summary of Adverse Events in the Safety Population.*

Event	Lopinavir–Ritonavir (N=95)		Standard Care (N=99)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number (percent)			
Any adverse event	46 (48.4)	20 (21.1)	49 (49.5)	11 (11.1)
Lymphopenia	16 (16.8)	12 (12.6)	12 (12.1)	5 (5.1)
Nausea	9 (9.5)	1 (1.1)	0	0
Thrombocytopenia	6 (6.3)	1 (1.1)	10 (10.1)	2 (2.0)
Leukopenia	7 (7.4)	1 (1.1)	13 (13.1)	0
Vomiting	6 (6.3)	0	0	0
Increased aspartate aminotransferase	2 (2.1)	2 (2.1)	5 (5.1)	4 (4.0)
Abdominal discomfort	4 (4.2)	0	2 (2.1)	0
Diarrhea	4 (4.2)	0	0	0
Stomach ache	4 (4.2)	1 (1.1)	1 (1.0)	0
Neutropenia	4 (4.2)	1 (1.1)	8 (7.6)	0
Increased total bilirubin	3 (3.2)	3 (3.2)	3 (3.0)	2 (2.0)
Increased creatinine	2 (2.1)	2 (2.1)	7 (7.1)	6 (6.1)
Anemia	2 (2.1)	2 (2.1)	5 (5.0)	4 (4.0)
Rash	2 (2.1)	0	0	0
Hypoalbuminemia	1 (1.1)	1 (1.1)	4 (4.0)	1 (1.0)
Increased alanine aminotransferase	1 (1.1)	1 (1.1)	4 (4.0)	1 (1.0)
Increased creatine kinase	0	0	1 (1.0)	0
Decreased appetite	2 (2.1)	0	0	0
Prolonged QT interval	1 (1.1)	0	0	0
Sleep disorders and disturbances	1 (1.1)	0	0	0
Facial flushing	1 (1.1)	0	0	0

- Gastrointestinal adverse events were more common in lopinavir–ritonavir group
- Serious adverse events were more common in standard-care group.

Bin Cao, et al; N Engl J Med 2020; DOI: 10.1056/NEJMoa2001282

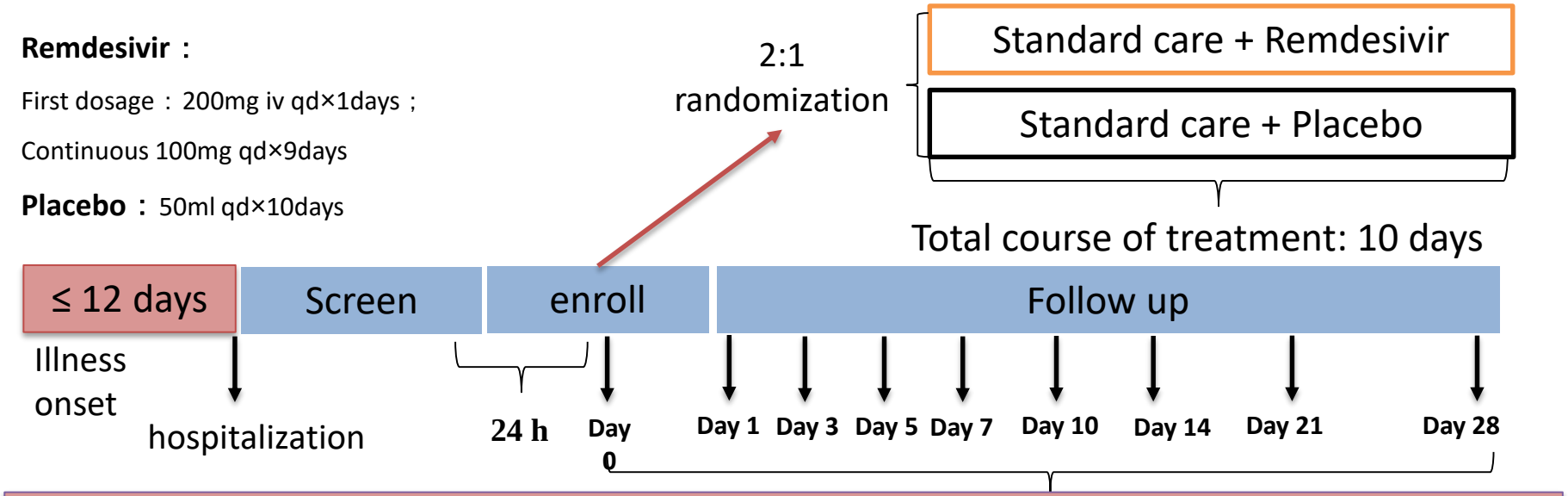
CAP-China Remdesivir trials on going for COVID-19

Remdesivir：

First dosage：200mg iv qd×1days；

Continuous 100mg qd×9days

Placebo：50ml qd×10days



Primary outcome：Clinical improvement on day 28

Secondary outcome：The time from randomization to clinical improvement

- The clinical trail of Remdesivir treatment for severe COVID-19 is on going

Yeming wang, et al. Trial, 2020, under peer review

Antiviral for COVID-19: other potential choices

- Alpha-interferon: 5 MU, atomization inhalation twice daily
- Ribavirin: used together with interferon or lopinavir/ritonavir, 500 mg twice or three times of intravenous injection daily, no longer than 10 days
- Chloroquine phosphate: 500 mg bid for 7 days for adults aged 18-65 with body weight over 50 kg; 500 mg bid for Days 1&2, and 500 mg daily for Days 3-7 for adults with body weight below 50 kg
- Arbidol: 200 mg three time daily for adults, no longer than 10 days
- Convalescent plasma treatment: infusion dose 200-500ml (4-5 ml/kg)×2
- Favipiravir

Use of corticosteroid is still controversial

- Only for patients with rapid progressive deterioration oxygenation, radiology imaging and excessive inflammation
- Contraindications: allergy; un-controlled diabetes; uncontrolled hypertension; glaucoma; GI bleeding; immunodepression; lymphocyte less than 300/ul; severe bacterial and/or fungal infections
- Short term, 3-5 days
- Low-moderate dosage
  - no more than methylprednisolone 1-2 mg/kg/day

Lianghan Shang et al. Lancet.2020. https://doi.org/10.1016/PII
JianPing Zhao, et al. Zhonghua Jie He He Hu Xi Za Zhi 2020; 43: E007 (in Chinese).

Dilemma of ARB/ACEi

- Letter from Prof. Giovanni de Simone, Chair, Council on Hypertension, European Society of Cardiology
  - Anti-RAS meds of course reduce angio-II activity, which is good for lung inflammatory response.
  - However, too much inhibition of angio-II might increase ACE2 activity, because angio-II increase ACE2 cleavage through AT1R-activated TNF-alfa-ACE, and this might not be good for the COVID-19 action.
- Bin Cao' response to Prof. Giovanni de Simone
  - In our cohort, 48% (26/48) non-survivors had hypertension, whereas the percentage of hypertension was only 23% (32/137) in survivors. The OR for hypertension in ANOVA is 3.05 (1.57-5.92).
  - No definite answer to the question of ARB/ACEi

Zhou F, et al. Lancet 2020; DOI:10.1016/S0140-6736(20)30566-3

Discharge criteria of COVID-19

- Body temperature is back to normal for more than three days
- Respiratory symptoms improved obviously
- Pulmonary imaging shows obvious absorption
- Two consecutive negative nucleic acid tests for respiratory specimens (sampling interval being at least 24 hours)

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Wuhan Third hospital	Wuhan Fourth hospital

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

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