中日友好医院
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Diagnosis and treatment of COVID-19

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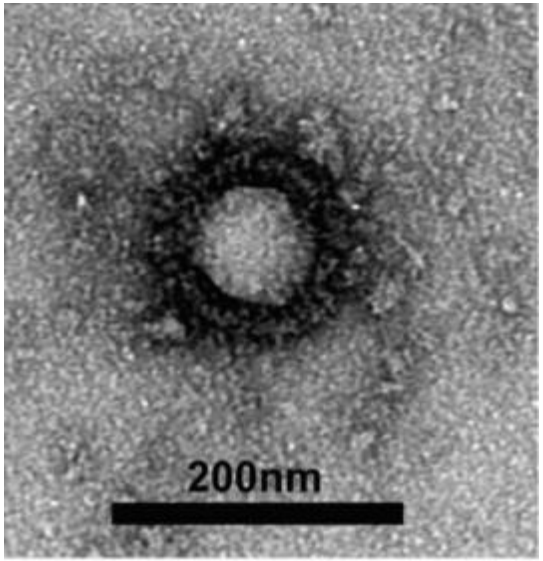
ERS COVID-19 Webinar, 28 March 2020

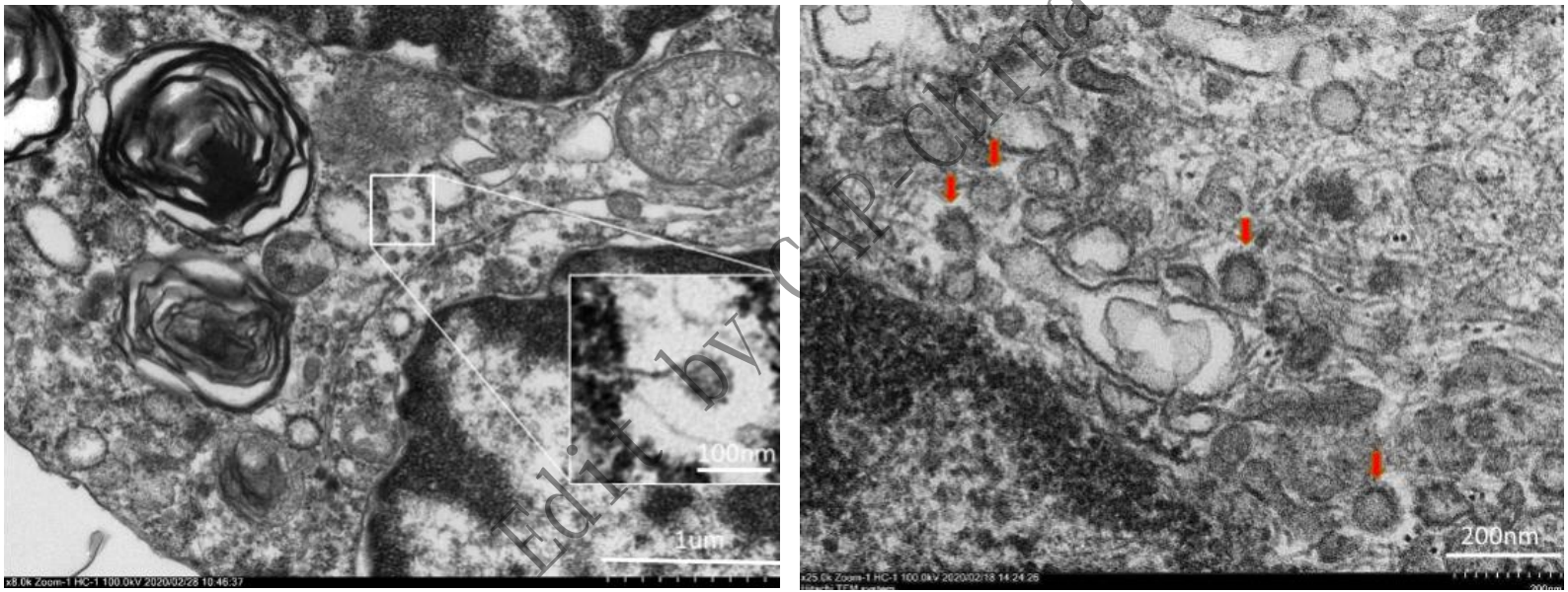
SARS-CoV-2

- 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



SARS-CoV-2 under Electron microscopy

- Viral particle in Alveolar type II cells



Xiaohong Yao et al. Zhonghua Bing Li Xue Za Zhi. 2020;49:E009

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
- High degree of morbidity and mortality
  - Mortality: Seasonal Influenza, 0.1%; COVID-19, 1-3%
- Devastating particularly to subset of population
  - Elderly, those with underlying conditions (heart disease, lung disease, diabetes, obesity)

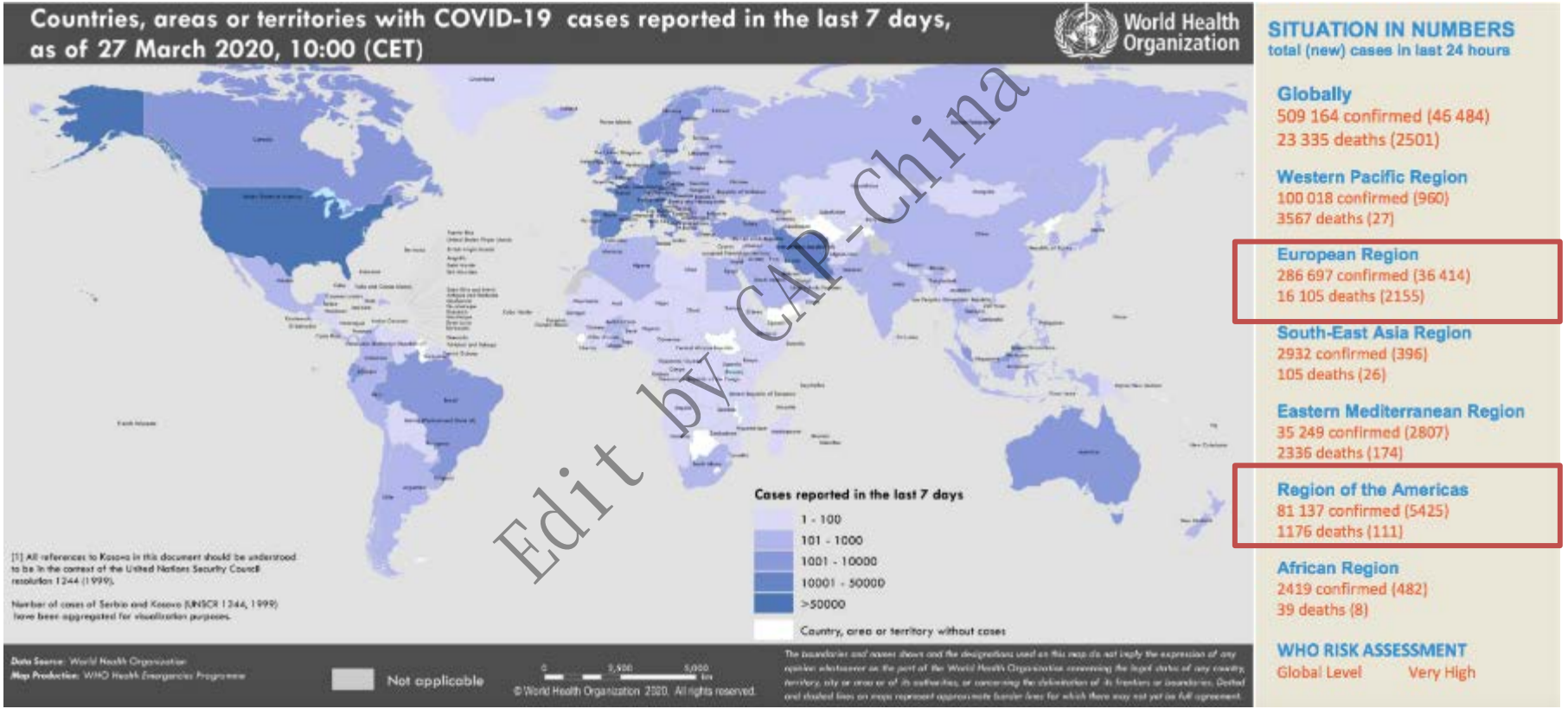
WHO Director General's remarks at the G20 Extraordinary Leaders' Summit on COVID-19 - 26 March 2020

- We are at war with a virus that threatens to tear us apart – if we let it.
- Almost half a million people have already been infected, and more than 20,000 have lost their lives.
- The pandemic is accelerating at an exponential rate.
- The first 100 thousand cases took 67 days. The second 100 thousand took 11 days, the third 100 thousand took just 4 days and the fourth 100 thousand just 2 days.

https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---20-march-2020

Epidemiology of COVID-19 globally

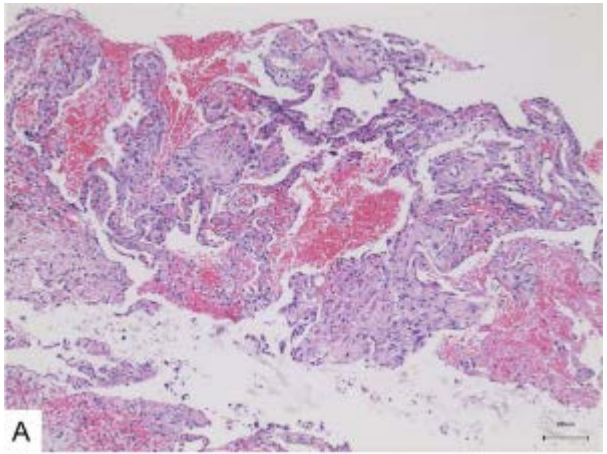
- COVID-19 has spread to the world rapidly. —— A threat of the word



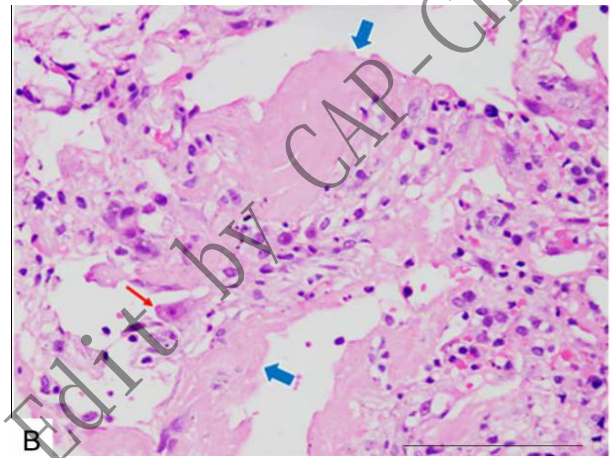
https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200327-sitrep-67-covid-19.pdf?sfvrsn=b65f68eb_4

Pathogenic changes of severe COVID-19 of lung

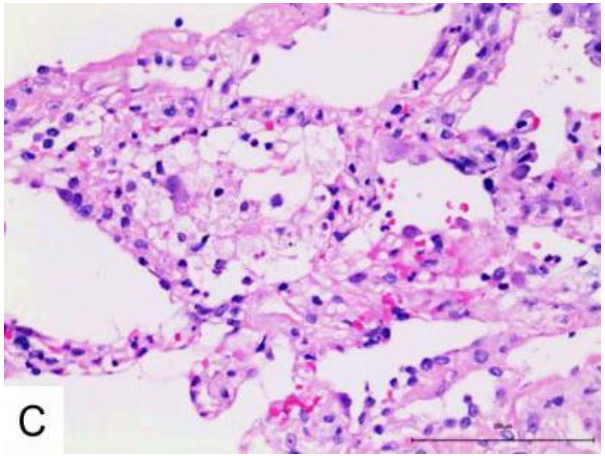
- The pathological features in lungs greatly resemble those seen in SARS and MERS infection
- Focal hemorrhage in lung tissue, organization of exudates in some alveolar cavities
- Bilateral diffuse alveolar damage with cellular fibromyxoid exudates



Hemorrhage in lung tissue, organization of exudates



Hyaline membrane formation（blue arrow)

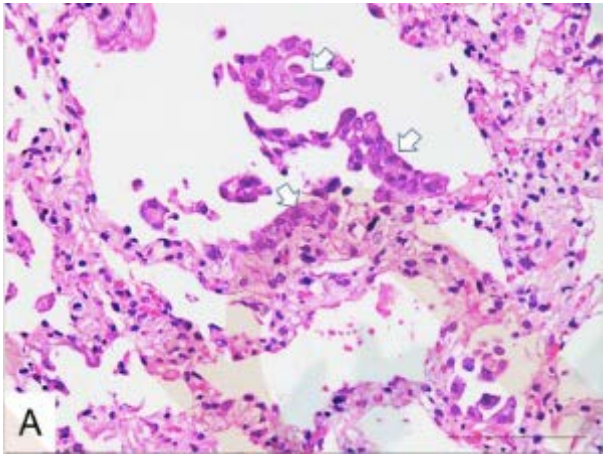


Interstitial mononuclear inflammatory infiltrates

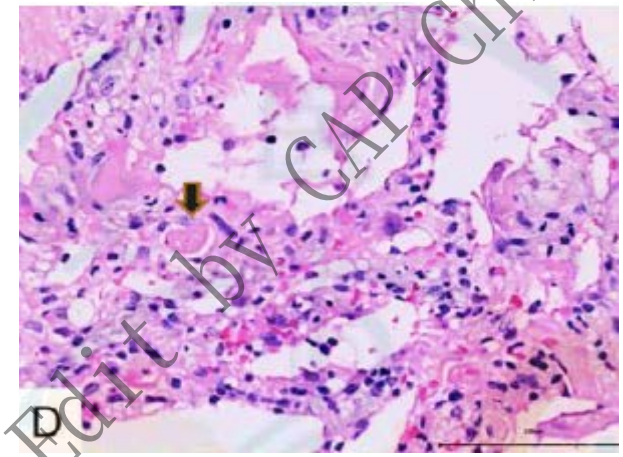
Xiaohong Yao et al. Zhonghua Bing Li Xue Za Zhi. 2020;49:E009

Pathogenic changes of severe COVID-19 of lung

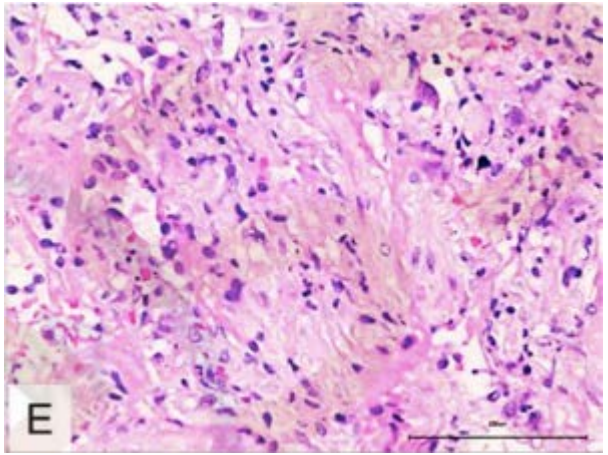
- Significant proliferation of type II alveolar epithelia and focal desquamation of alveolar epithelia
- Hyaline thrombi and inpulmonary interstitial fibrosis were found



proliferation of type II alveolar epithelia （white arrow)



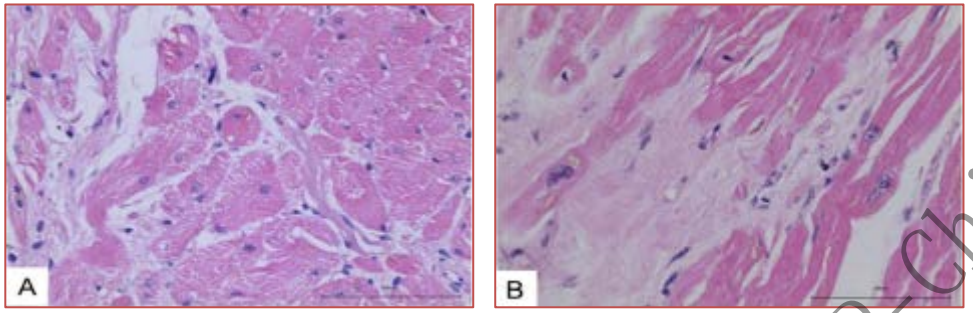
Thrombus in pulmonary arterioles (black arrow)



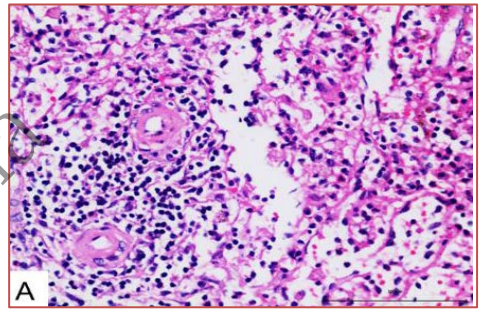
Pulmonary fibrosis

Xiaohong Yao et al. Zhonghua Bing Li Xue Za Zhi. 2020;49:E009

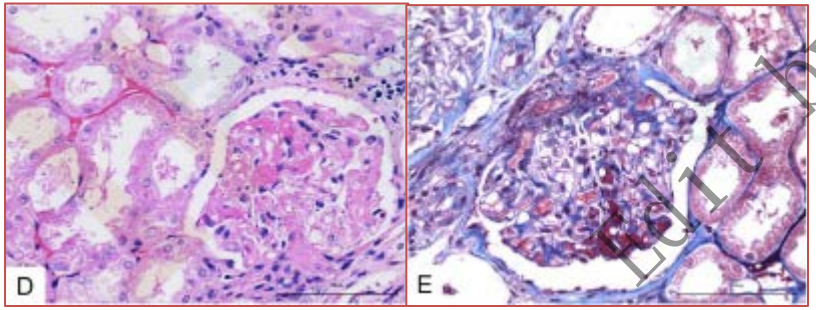
Pathogenic changes of severe COVID-19 of other organs



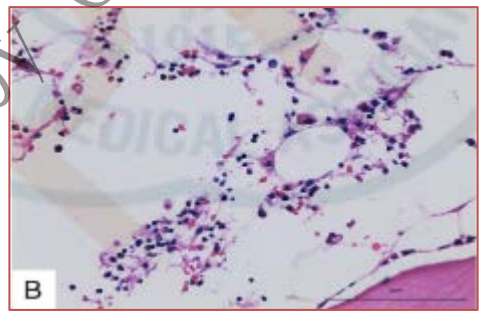
Hypertrophy, degeneration and necrosis of cardiomyocytes



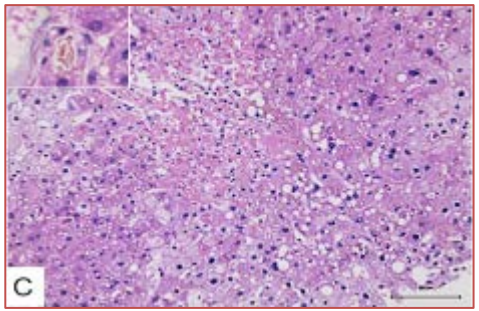
Decreased of lymphocyte, cell degeneration and necrosis in spleen



Edema, degeneration and exfoliation of renal tubular epithelial cells; hyaline thrombus glomerular capillary



Myelosuppression



Degeneration, focal necrosis, bile embolus in liver

Xiaohong Yao et al. Zhonghua Bing Li Xue Za Zhi. 2020;49:E009

Diagnostic criteria of COVID-19—Suspected case

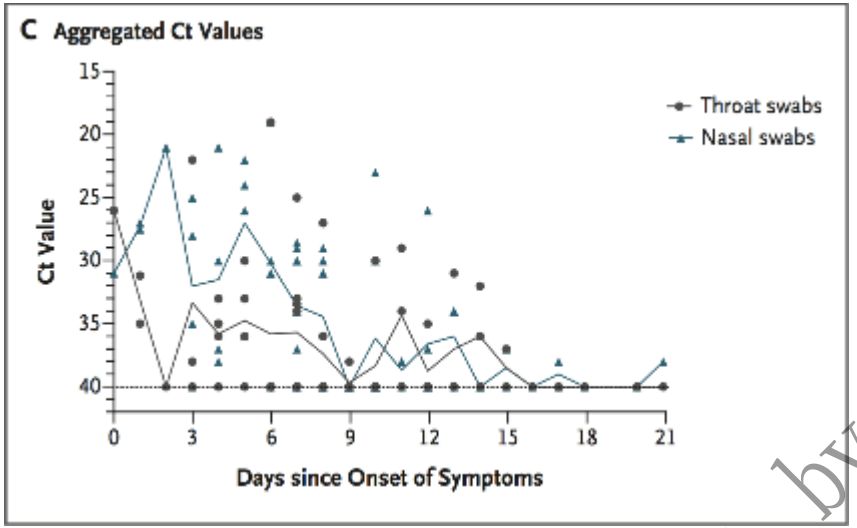
Suspected case	
Epidemiological history (≤14 days)	Clinical symptoms
➢ travel /residence in Wuhan and its surrounding areas,or other communities where COVID-19 has been found	➢ fever and/or respiratory symptoms
➢ contact with COVID-19 patients	➢ imaging characteristics of COVID-19
➢ Contact with patients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

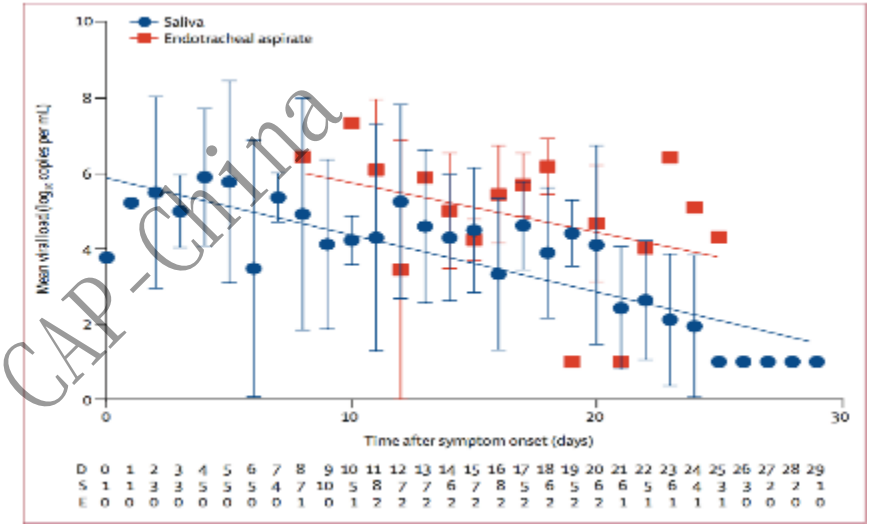
Diagnostic criteria of COVID-19—Confirmed case

Confirmed case	
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	

Nasal swabs and posterior oropharyngeal saliva for viral load detection



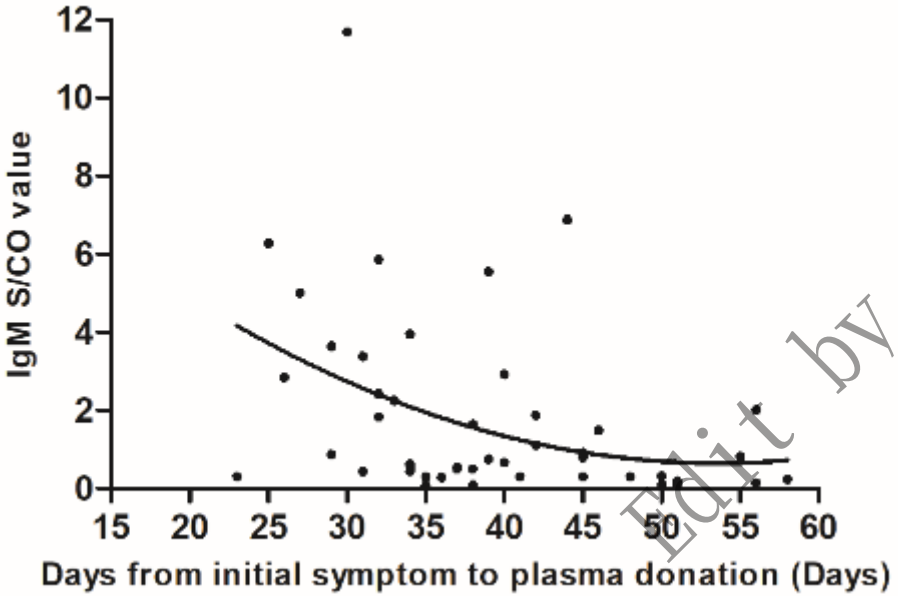
- Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat.

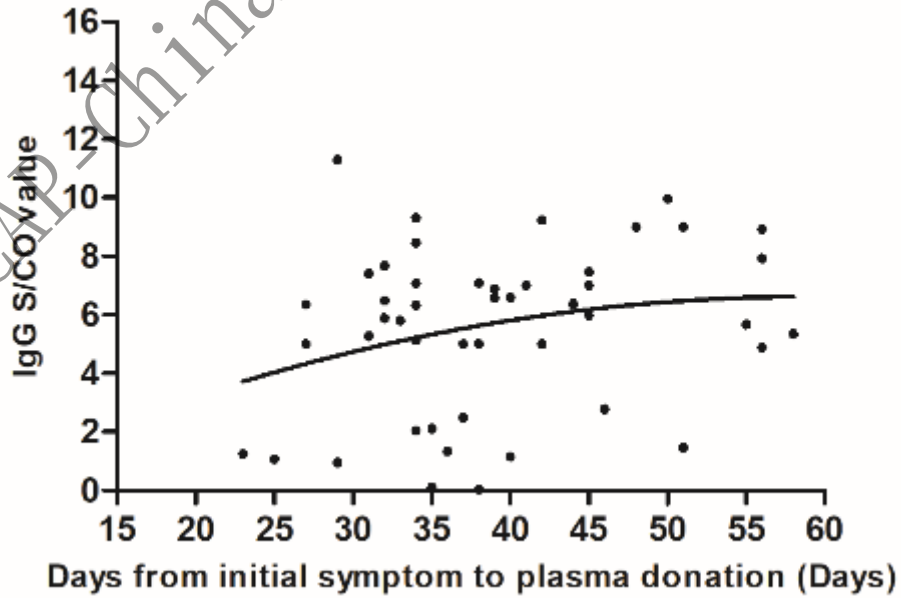


- Posterior oropharyngeal saliva specimens are non-invasive and acceptable to patients and can be used for initial diagnosis and subsequent viral load monitoring.

Lirong Zou et al. N Engl J Med , 382 (12), 1177-1179 2020 Mar 19
Kelvin Kai-Wang et al. Clin Infect Dis.2020. DOI: 10.1093/cid/ciaa149
Kelvin Kai-Wang To et al. Lancet Infect Dis. 2020. DOI: 10.1016/S1473-3099(20)30196-1

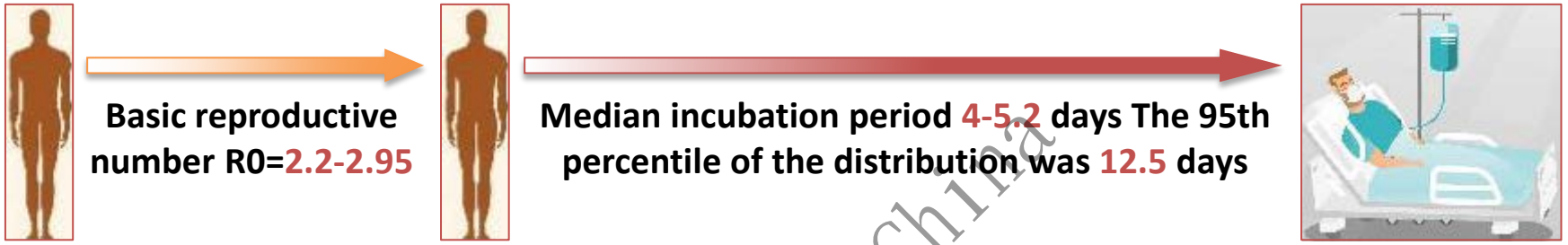
IgG/IgM Dynamic changes of Adults with COVID-19





Zhong Liu et al. unpublished data

Transmission and incubation of COVID-19

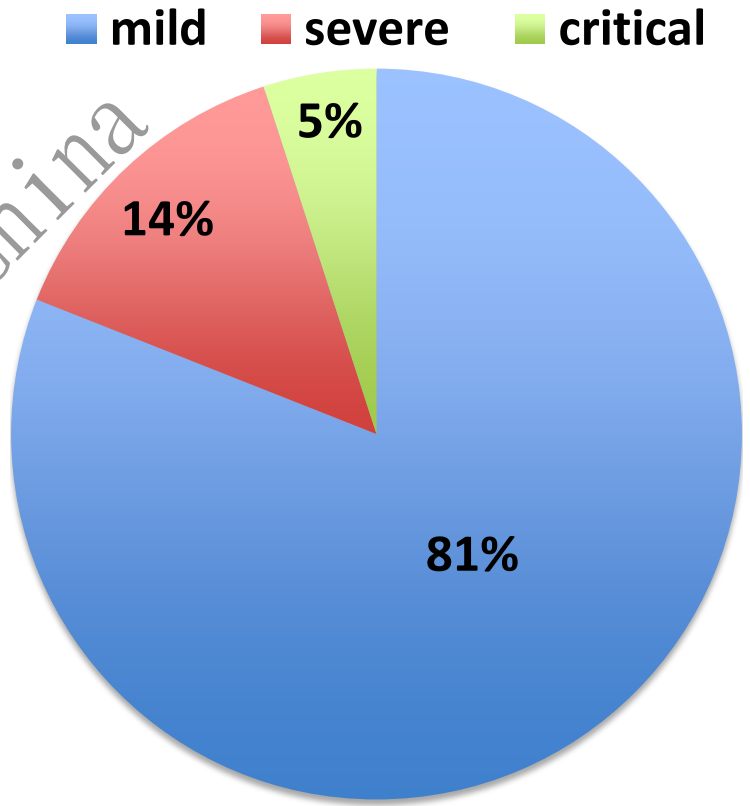


- **COVID-19 patients** including the **asymptomatic infected people** are the main source of infection
- Route of transmission
  - Respiratory **droplets** and close contact
  - Long-time exposure to the environment with a high concentrations of **aerosol**
  - Environment contaminated by feces/urine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

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

Disease spectrum of COVID-19

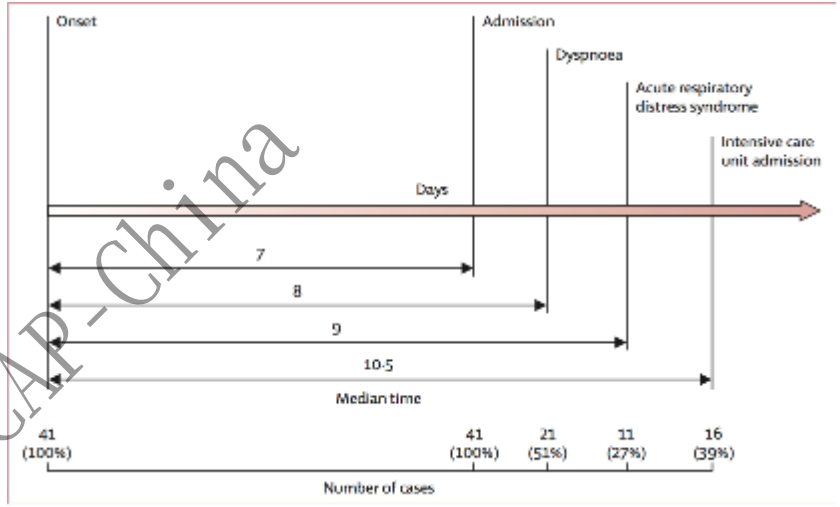
- **81% were mild status**
  - No pneumonia or mild pneumonia
- **14% were severe status**
  - Dyspnea or Respiratory Rate ≥ 30/min or SpO_2 < 93% or PaO_2/FiO_2 <300 mmHg
  - Lung infiltrates >50% within 24 to 48 hours
- **5% were critical ill status**
  - Needs mechanical ventilation
  - Shock
  -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

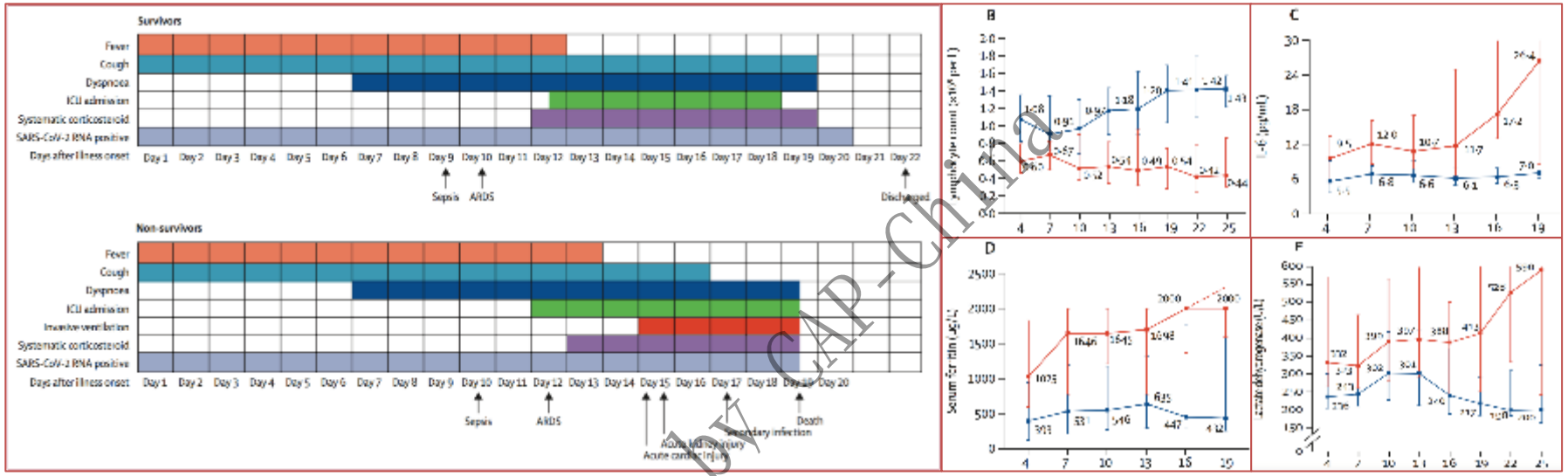
Symptoms and complications	N%
Fever	98%
Cough	76%
Myalgia or fatigue	44%
Sputum production	28%
Diarrhea	3%
WBC ≤ 10 × 10^9/L	70%
Lymphocytopnia	63%
ALT > 40 U/L	37%
Cr > 133 mmol/L	10%
LDH > 243 U/L	73%
Hypersensitive troponin I > 28 pg/ml	12%
Procalcitonin < 0.1 ng/ml	69%
Acute respiratory distress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

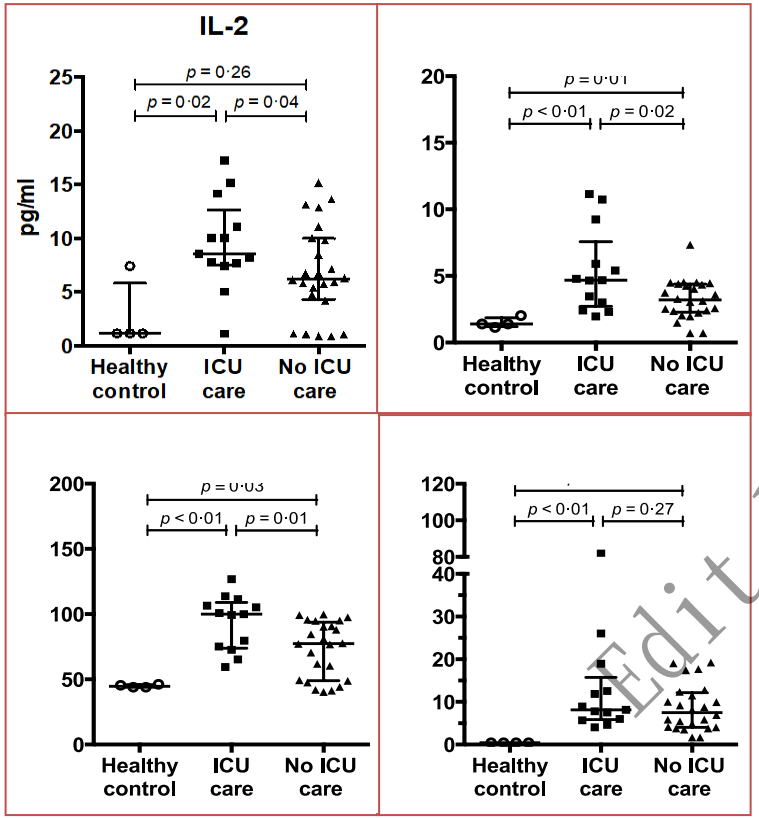
Clinical course of COVID-19—Severe and critical illness

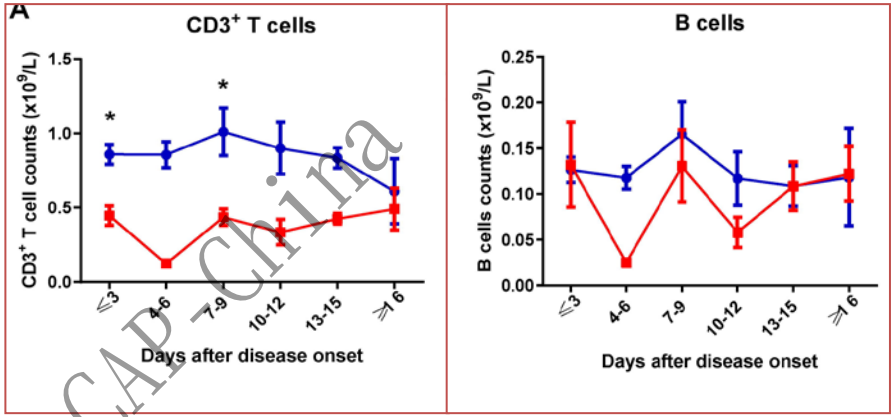


- Duration of dyspnea was 13 days in survivors
- 45% survivors still had cough on discharge
- Median duration of viral shedding was 20 days, could prolong as 37 days
- lymphocyte count was lowest on day 7 after illness onset and improved during hospitalisation in survivors but whereas severe lymphopenia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

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

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

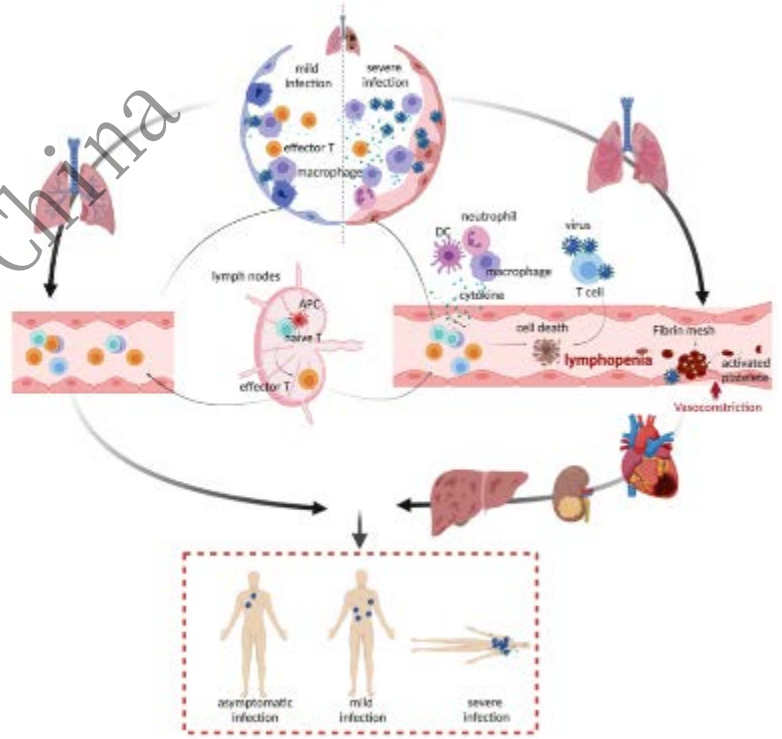
Host-directed therapies might be an option

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
- ……

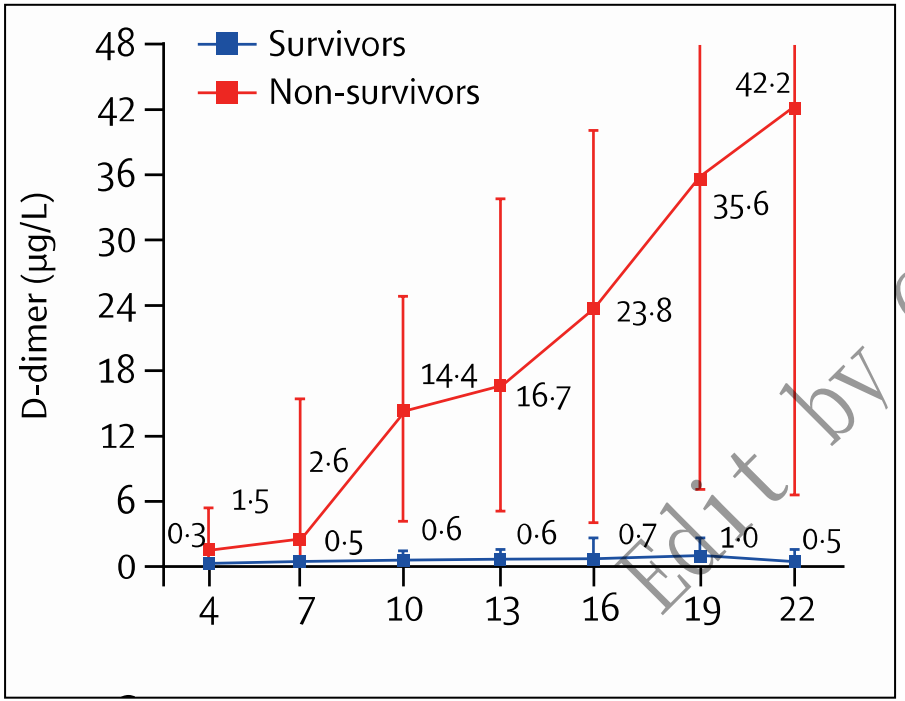


——Viral Sepsis

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; accepted, online soon

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.

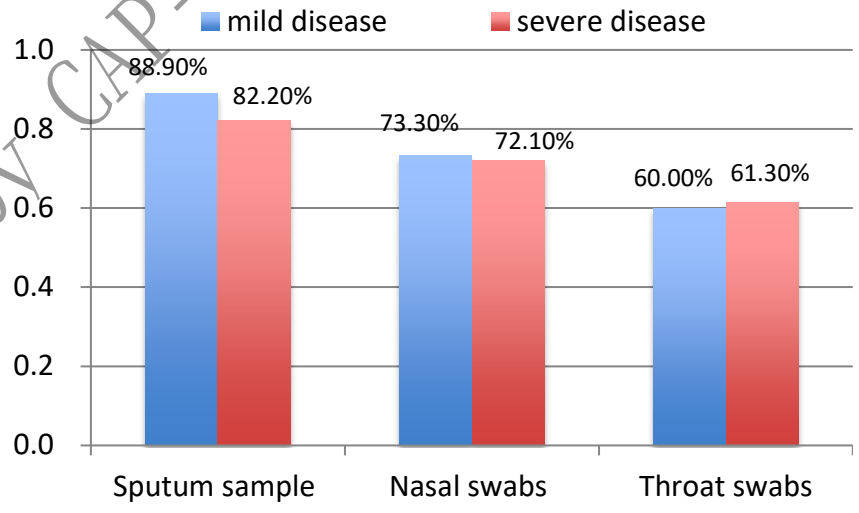
Zhou F, et al. Lancet 2020; DOI:10.1016/S0140-6736(20)30566-3; Hamming I, et al. J Pathol 2004; 203(2): 631-7.

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 specimens
- The specimens should be submitted for testing as soon as possible after collection

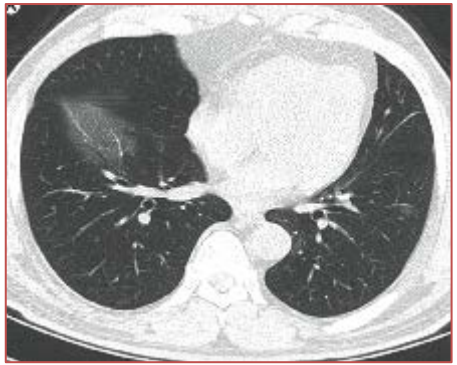
Table 1. Molecular detection of 2019-nCoV in swabs and blood. Samples were from oral swabs (OS), anal swabs (AS) and blood. Data were shown as qPCR Ct values. Patients in severe condition during investigation were shown.

	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

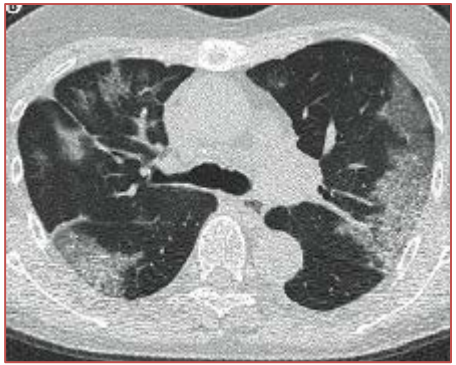


Wei Zhang et al.Emerg Microbes Infect, 9 (1), 386-389; Yang Y et al. medRxiv 2020.

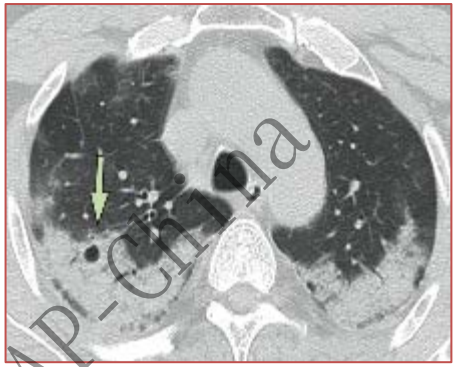
Features of CT scan of COVID-19



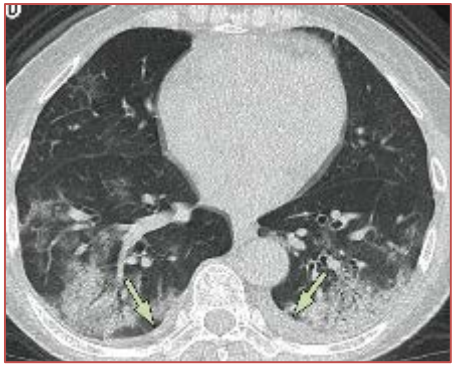
56-year-old man
Day 3 after symptom onset
Focal ground-glass opacity



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

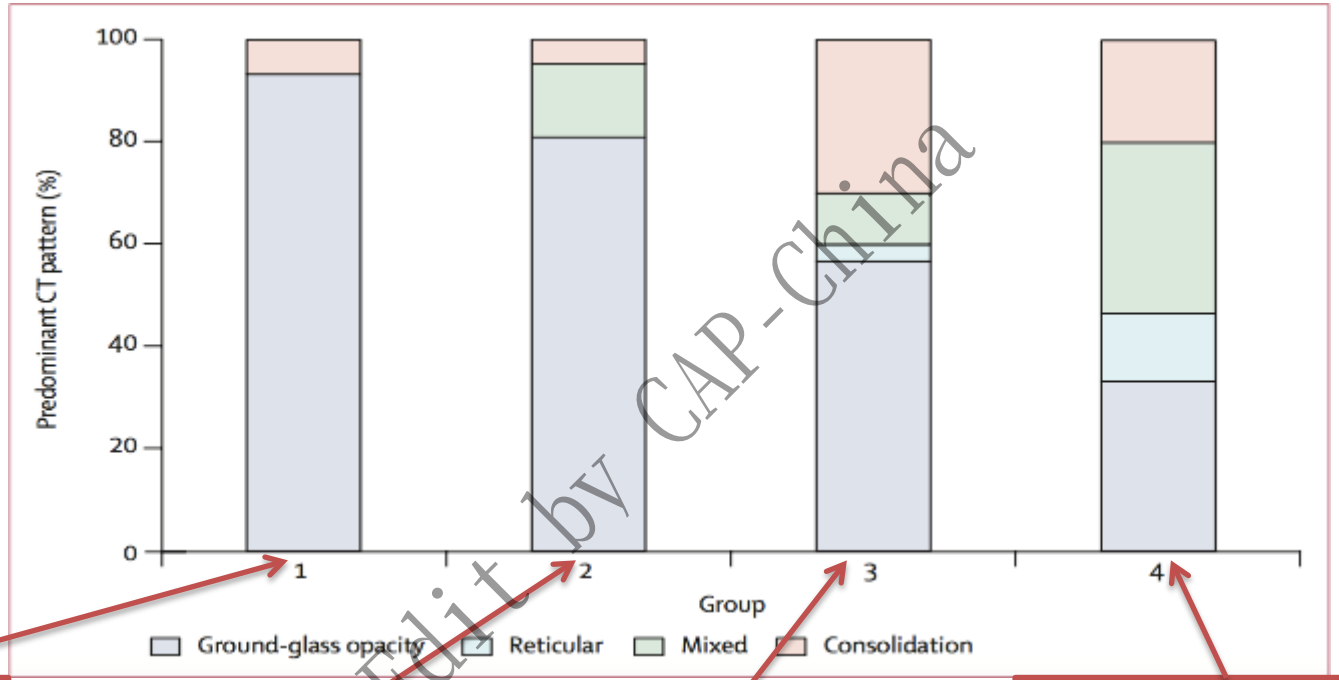


63-year-old woman
Day 17 after symptom onset
Bilateral, peripheral mixed pattern； Air bronchogram；
Pleural effusion

- 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

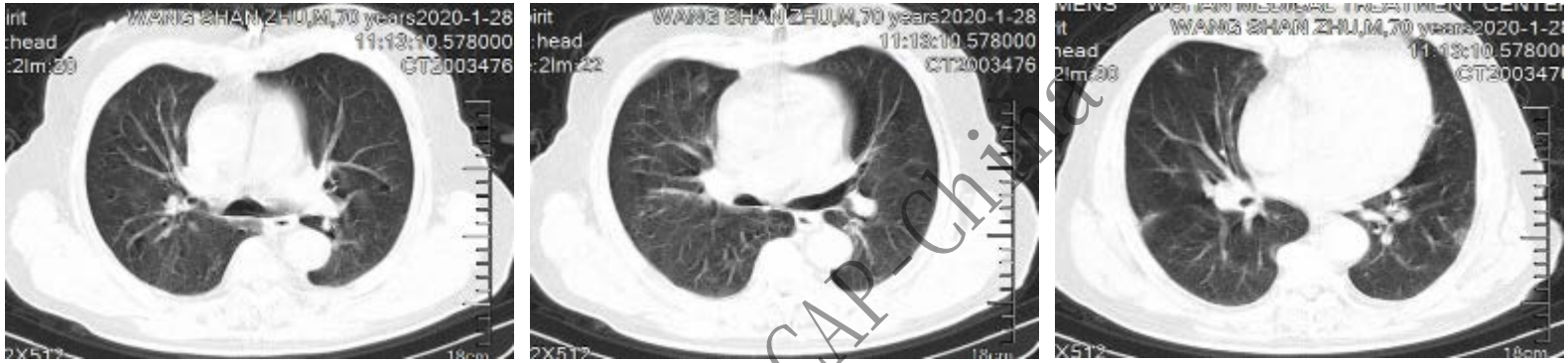
>1 week to 2 weeks after symptom onset

>2 weeks to 3 weeks after symptom onset

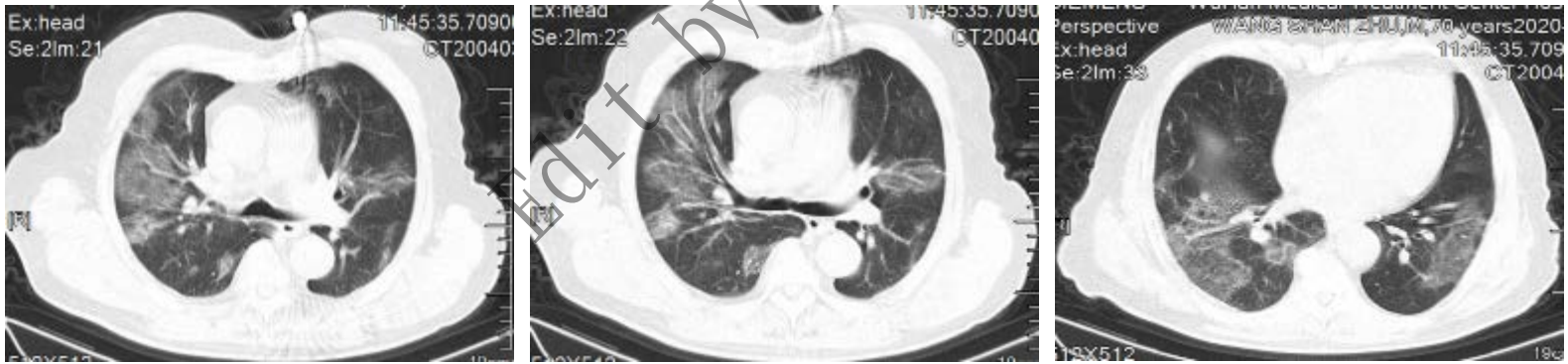
Heshui Shi et al. Lancet Infect Dis.2020; DOI: 10.1016/S1473-3099(20)30086-4

Rapid deterioration on CT scan-case 1

Male, 70 years old



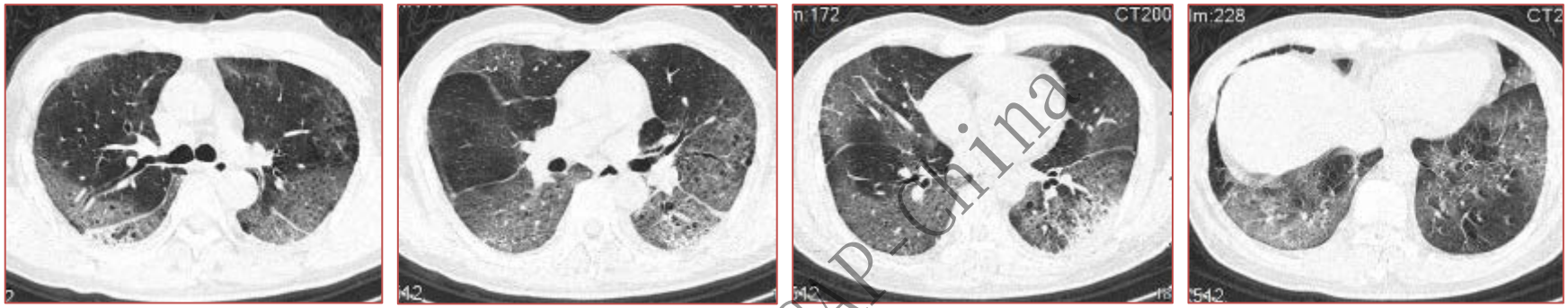
2020-1-28 Day 9 after illness onset



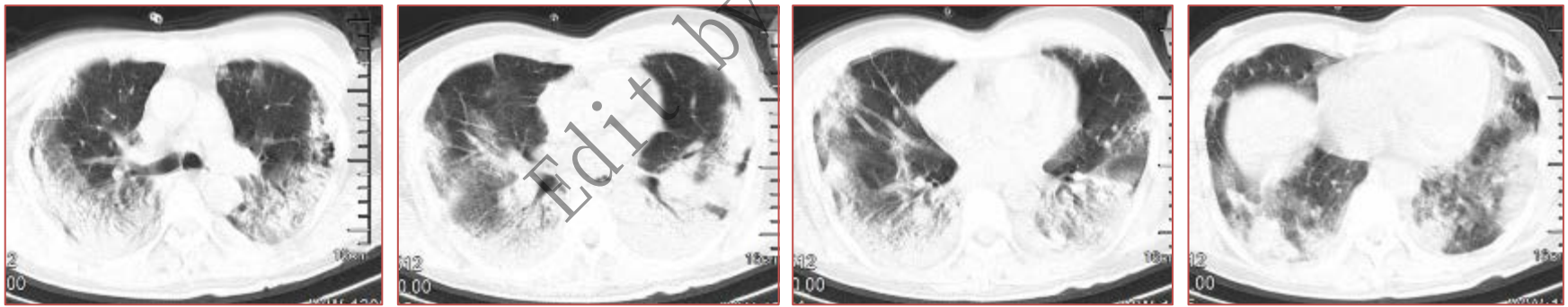
2020-2-1 Day 13 after illness onset. Died 2 weeks later.

Rapid deterioration on CT scan-case 2

Male, 62 years old



2020-2-7 Day 12 after illness onset

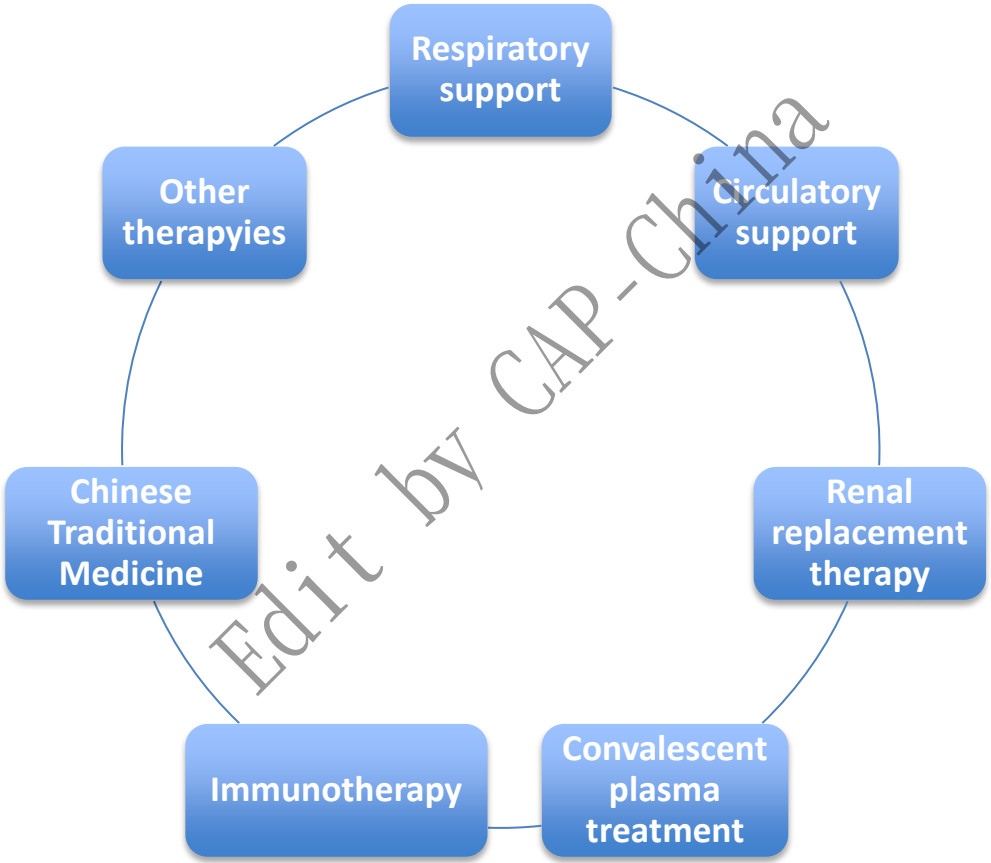


2020-2-7 Day 19 after illness onset. Died 15 days later

Isolation and Close monitoring 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
- Closely monitoring vital sign and laboratory (**progress rapidly in severe patients**)
  - Blood pressure, HR, RR, Oxygen Saturation
  - water and electrolyte balance
  - 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***
    - Encouraging results
  - CAP China Remdesivir 1 (mild-moderate pneumonia, NCT04252664): ***ongoing***
  - CAP China Remdesivir 2 (severe-critical pneumonia, NCT04257656): ***ongoing***
  - Meplazumab treats COVID-19 pneumonia (NCT04275245)

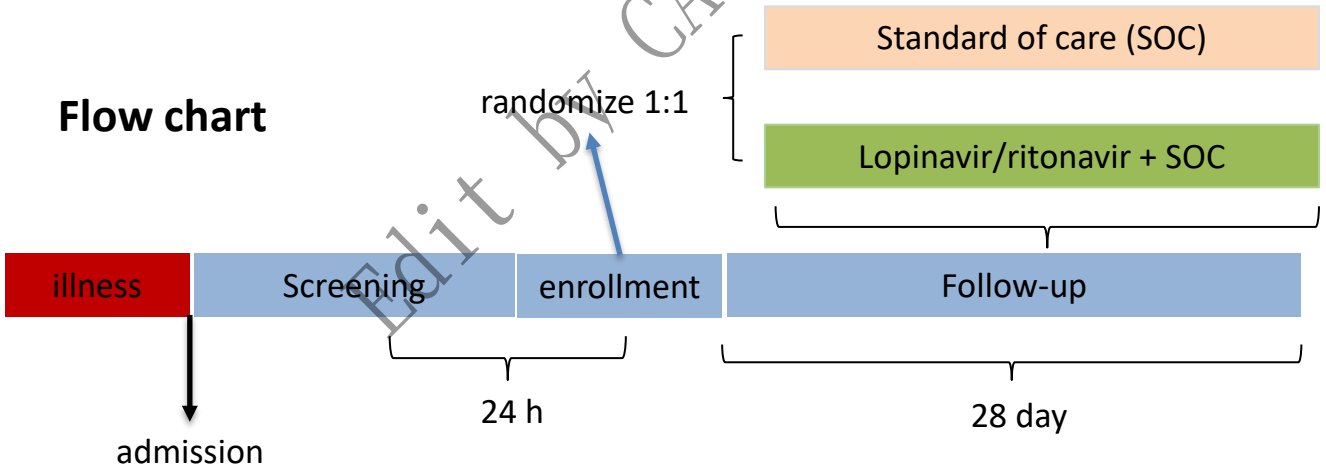
Bin Cao, et al. N Engl J Med. 2020; DOI: 10.1056/NEJMoa2001282; Yeming wang, et al. Trials. 2020; under peer review

Lopinavir Trial for Suppression of SARS-CoV-2 in China-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

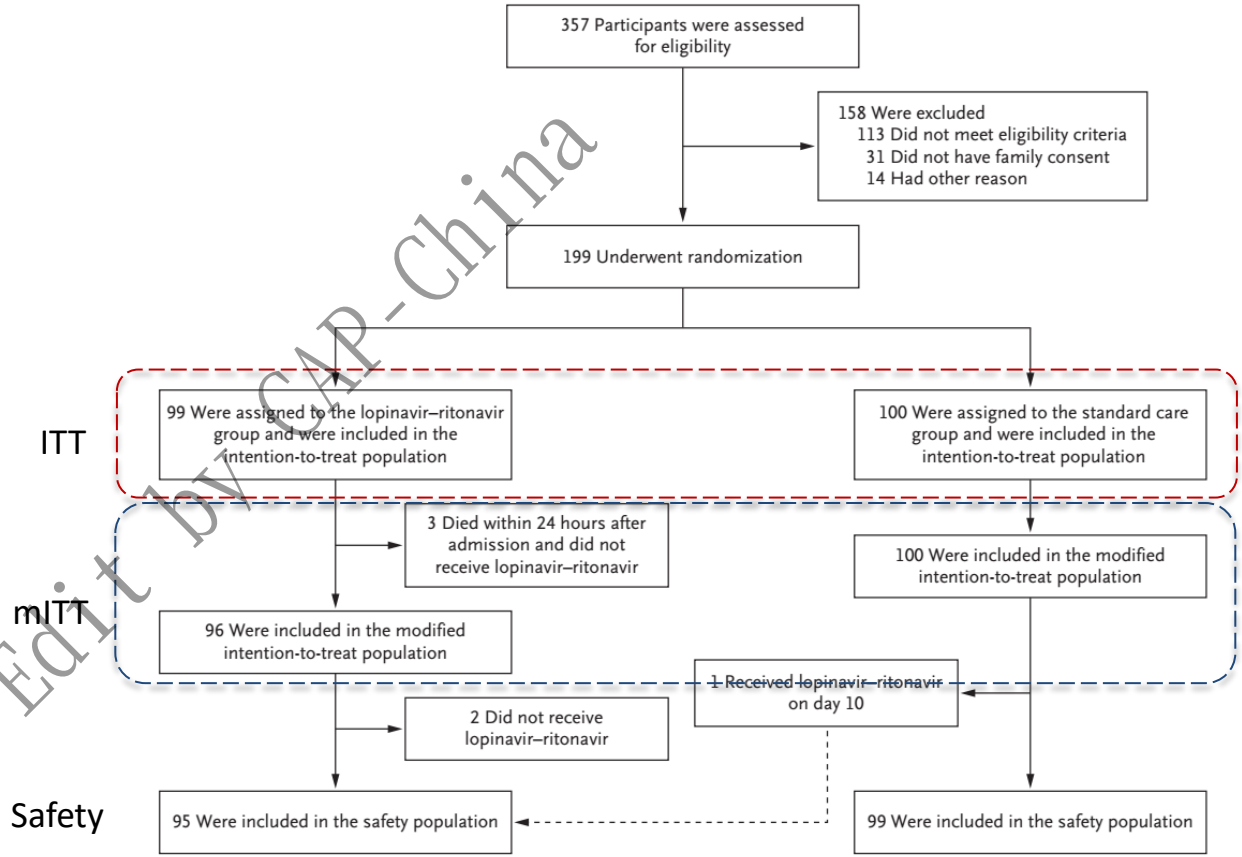
(2)Oxygen saturation (Sao2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) of less than 300 mmHg



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

End points and Enrollment-LOTUS China

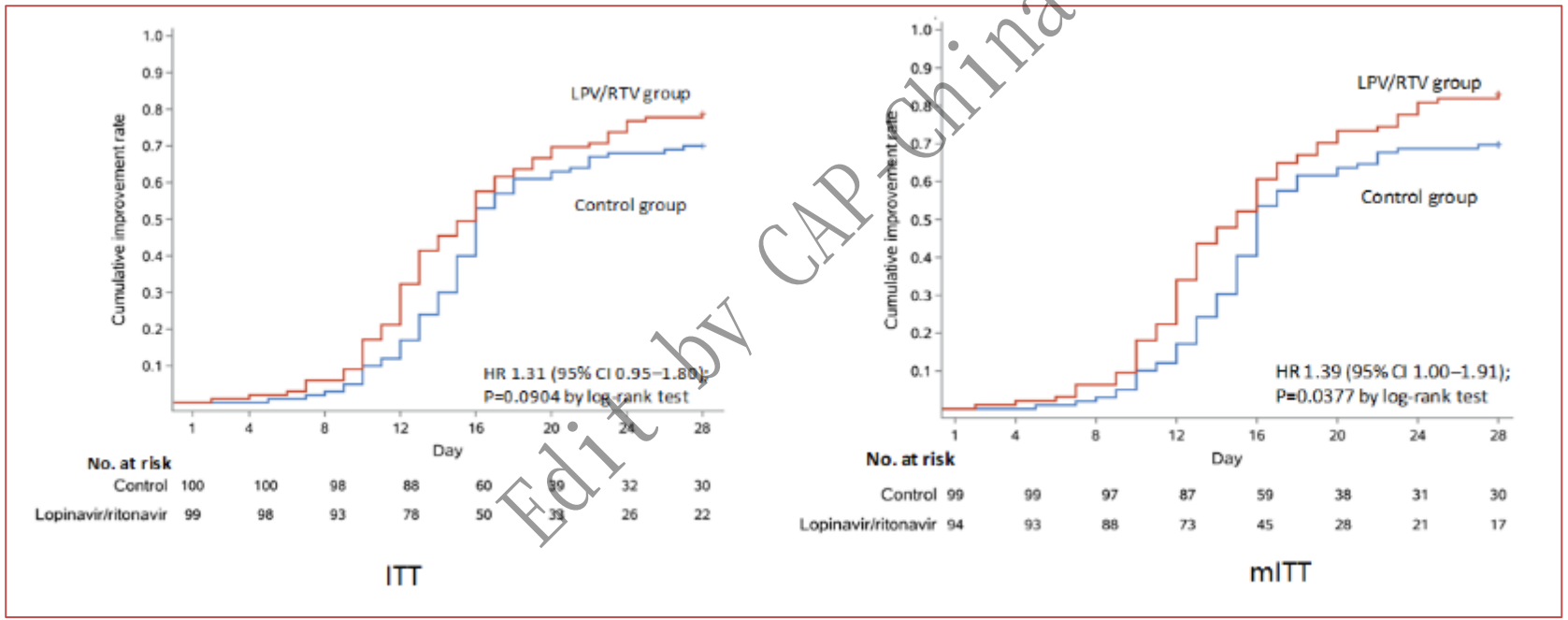
- Primary end point:
  - time to clinical improvement
- Secondary end points:
  - ICU length
  - 28 day mortality
  - Rate of clinical improvement at 14 days or 28 days



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

Time to clinical improvement-ITT and mITT

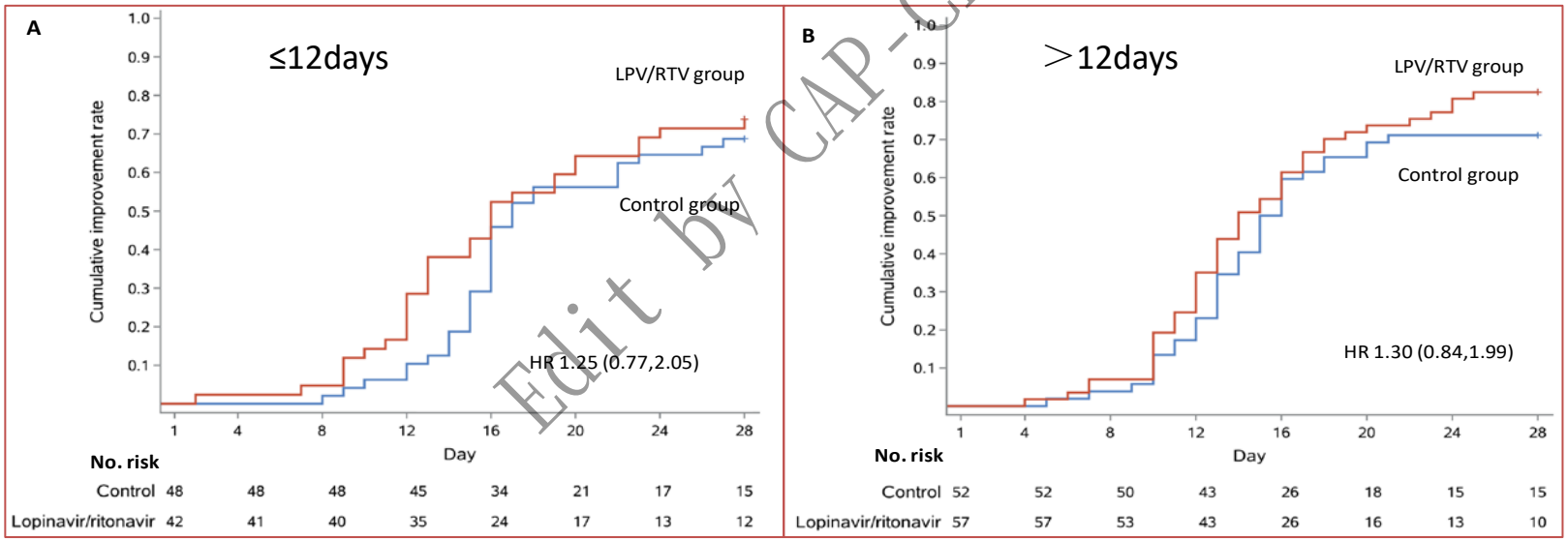
- No benefit was observed with lopinavir–ritonavir treatment beyond standard care?



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

Time to clinical improvement-ITT received antiviral treatment ≤ 12 days VS > 12 days after illness onset

- The difference of 28-days mortality between the lopinavir–ritonavir and standard-care group was numerically higher among patients treated within 12 days after the onset of symptoms [−8.0 (−25.3 to 9.3)] than among those treated later[−3.8 (−19.1 to 11.6)].



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

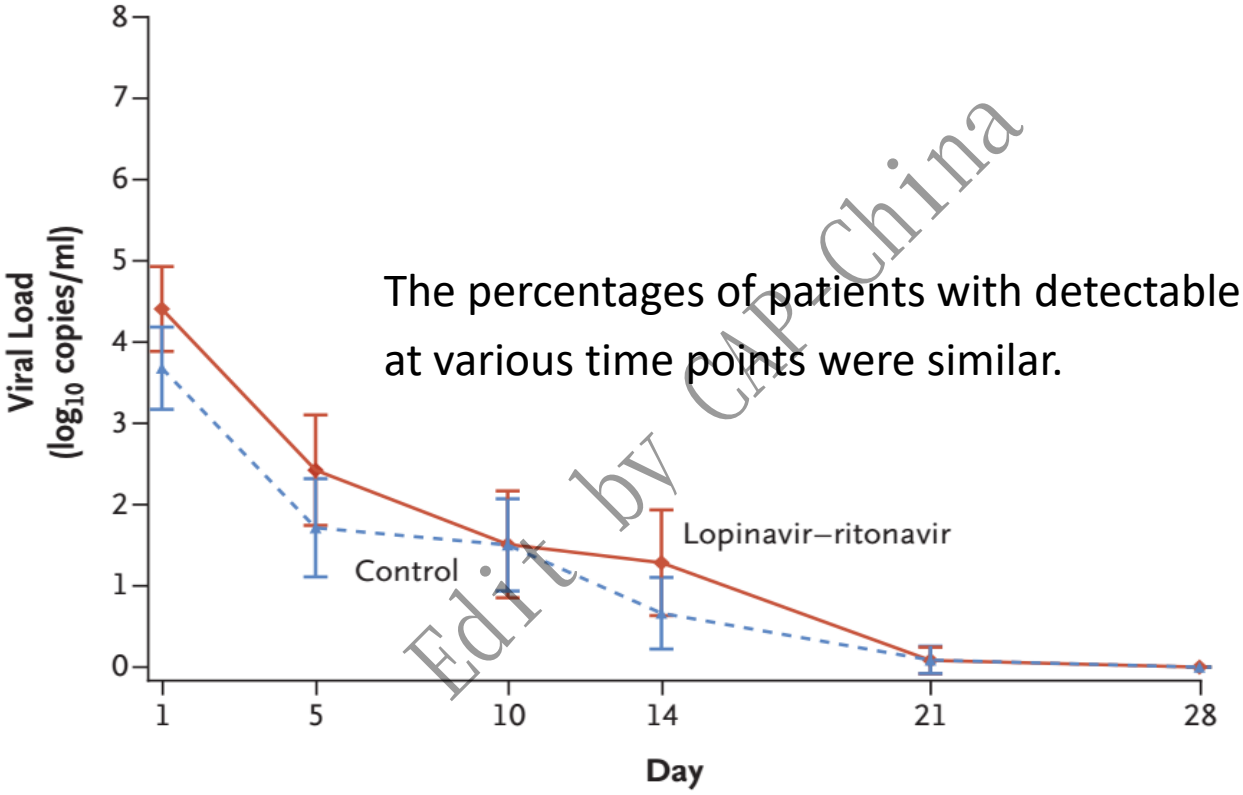
Secondary Endpoints-ITT

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

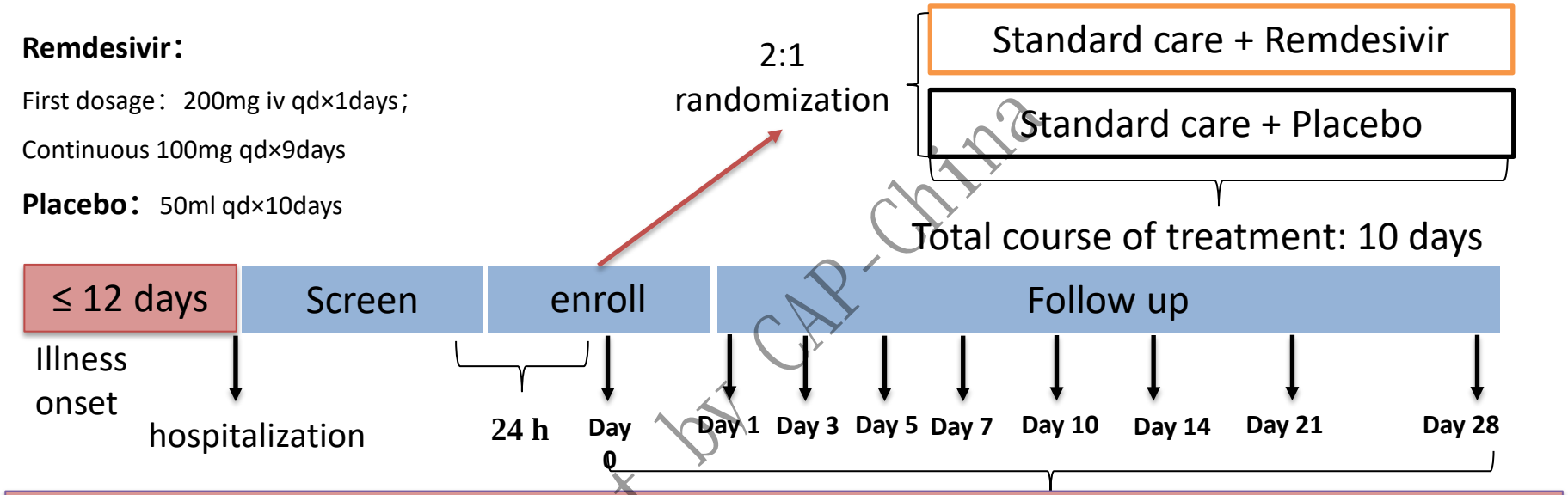
Table 4. Summary of Adverse Events in the Safety Population.*

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



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. Trials. 2020; under peer review

Antiviral for COVID-19: other potential choices

- Convalescent plasma treatment: infusion dose 200-500ml (4-5 ml/kg)×2
- Hydroxychloquine 200mg Tid + azithromycin 500mg D1, 250mg another 4 days
- Favipiravir: 1600mg Bid D1, 600mg Bid
- Alpha-interferon: 5 MU, atomization inhalation twice daily
- 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
- Ribavirin: used together with interferon or lopinavir/ritonavir, 500 mg twice or three times of intravenous injection daily, no longer than 10 days

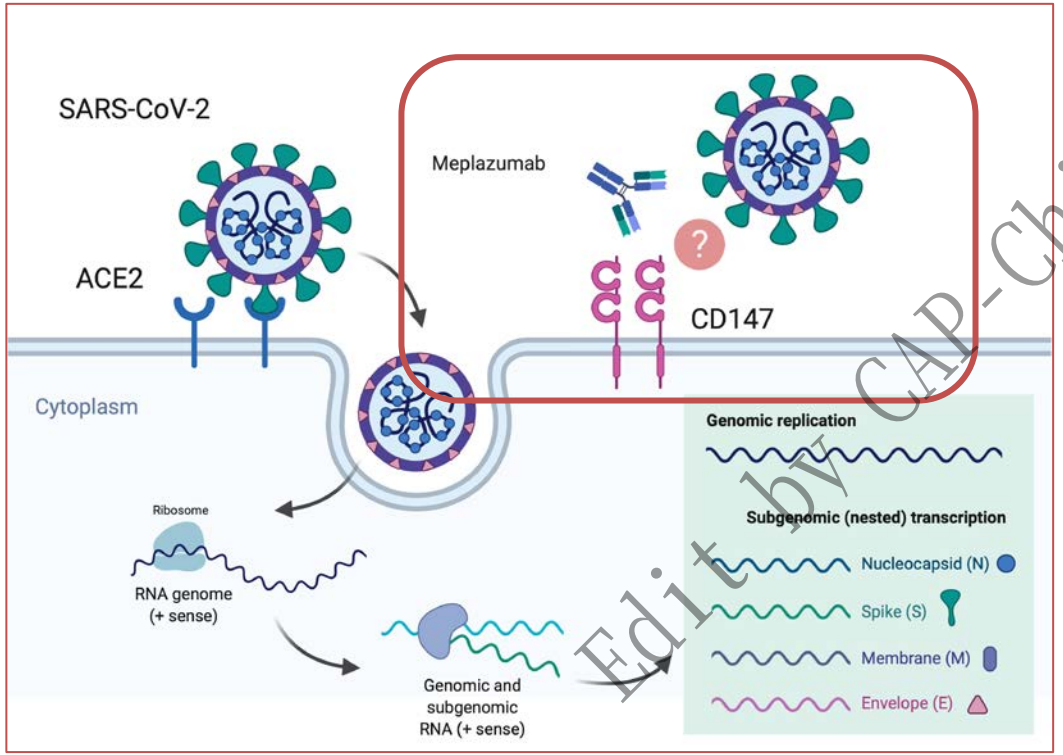
Philippe Gautret et al. IJAA. 2020; DOI : 10.1016/j.ijantimicag.2020.105949
Qingxian Cai, et al. Engineering. 2020; online first

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

Lianhan Shang et al. Lancet. 2020; 395(10225):683–684. DOI: 10.1016/S0140-6736(20)30361-5
JianPing Zhao, et al. Zhonghua Jie He He Hu Xi Za Zhi 2020,43(03) : 183-184 (in Chinese).

SARS-CoV-2 invades host cells via a novel route: CD147-spike protein

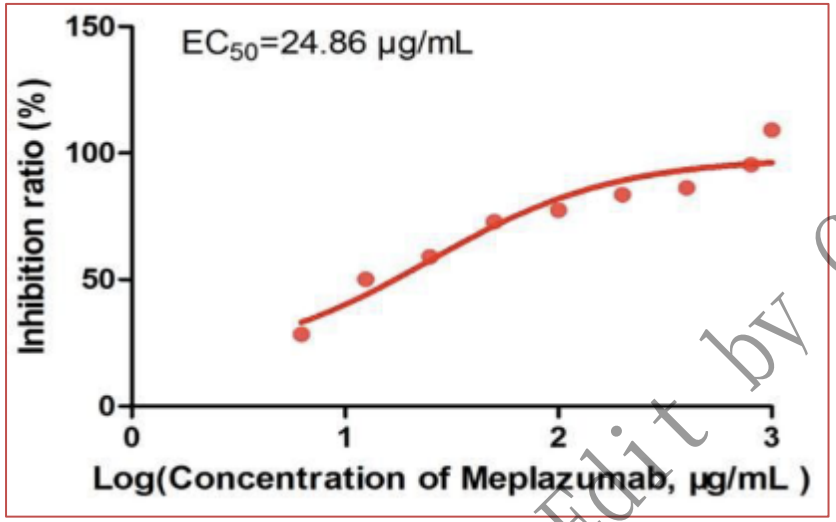


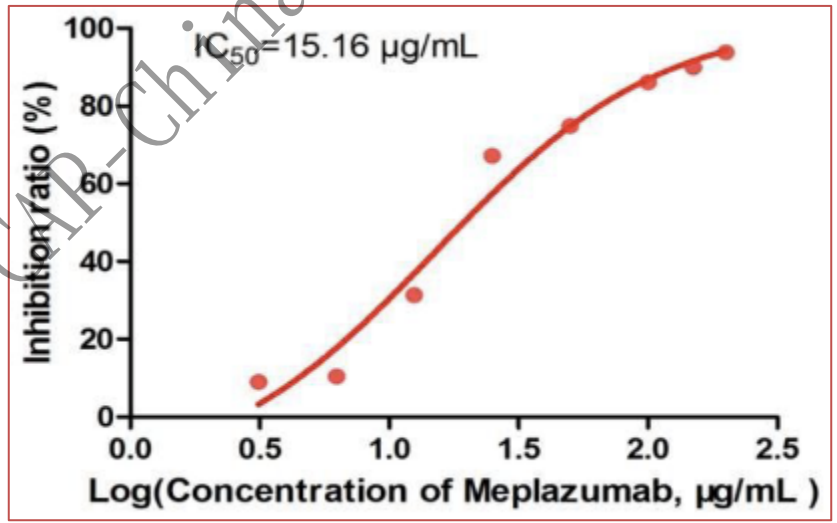
- CD147 is a transmembrane glycoprotein CD147 plays a functional role in facilitating SARS-CoV invasion for host cells
- The interaction between CD147 and S protein on SARS-CoV-2： affinity constant of 1.85×10-7M

Ke Wang et al. bioRxiv preprint.2020. DOI:10.1101/2020.03.14.988345

Anti-CD147 humanized antibody can block virus invading host cells

- Meplazumab, an anti-CD147 humanized antibody, compete with S Protein for CD147 binding, significantly inhibited the viruses from invading host cells

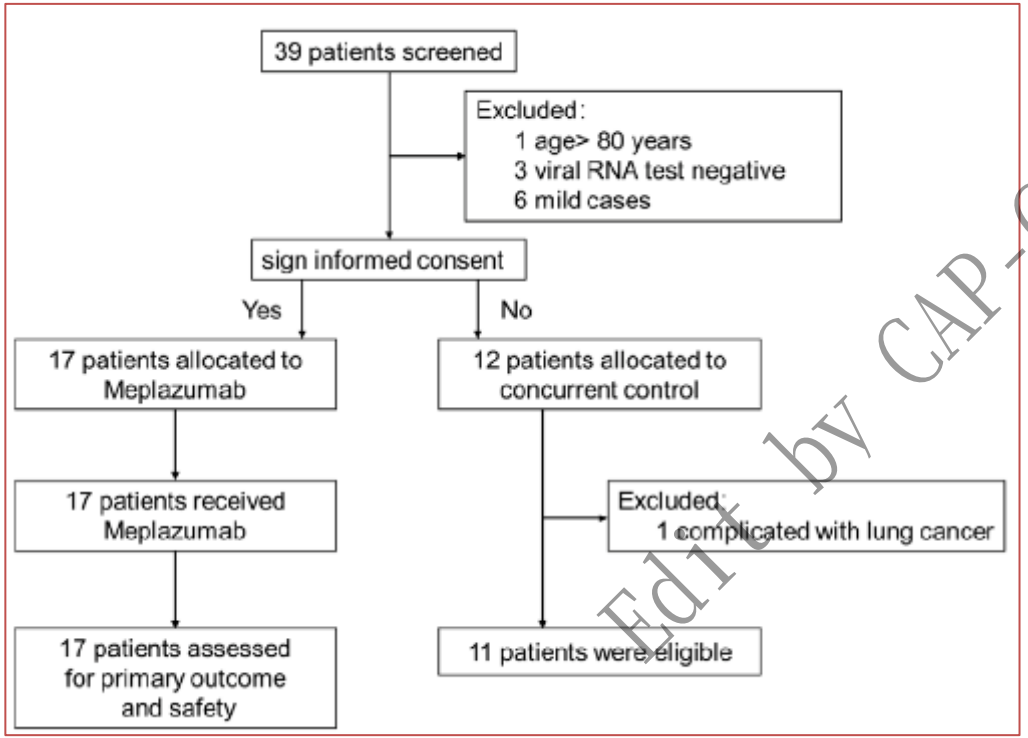




The inhibitory rate for viruses was significantly increased in CD147-blocking group in a dose-dependent manner, with a concentration for 50% of maximal effect (EC50) of 24.86 μg/mL and the half maximal inhibitory concentration (IC50) of 15.16 μg/mL

Ke Wang et al. bioRxiv preprint.2020. DOI:10.1101/2020.03.14.988345

Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial



Flow Chart

Methods and Patients:

- Open-labelled, concurrent controlled add-on clinical trial
- Aged 18 to 78 years
- With common, severe, or critical COVID-19 pneumonia

Procedure:

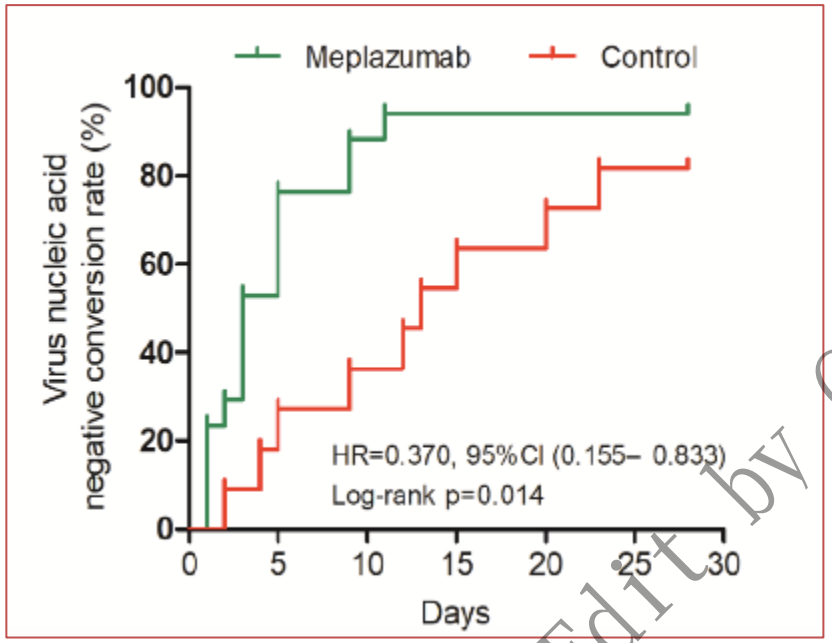
- 10mg meplazumab IV on day 1, day 2 and day 5

Primary outcome:

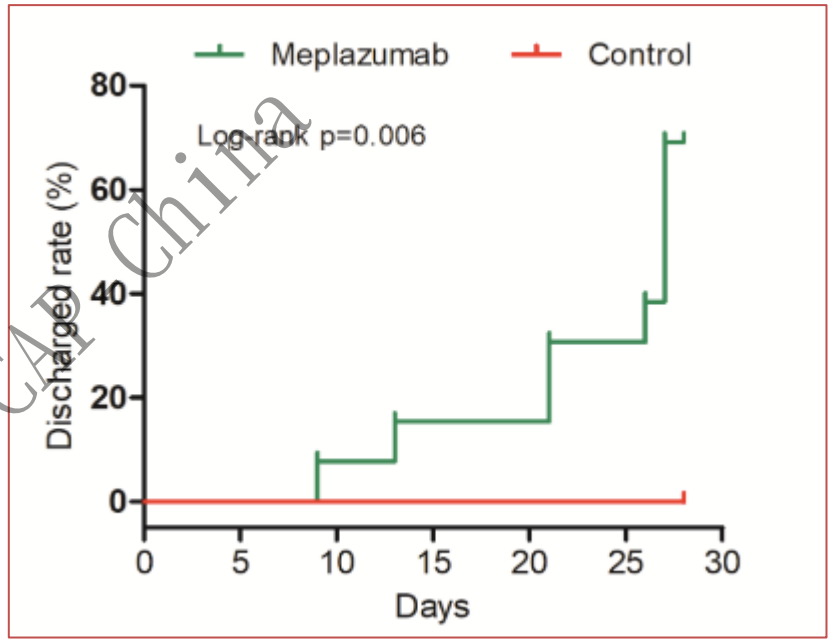
- Virological clearance

Huijie Bian et al. medRxiv preprint.2020. DOI:10.1101/2020.03.21.20040691

Meplazumab treatment reduce the time to virus negative conversion



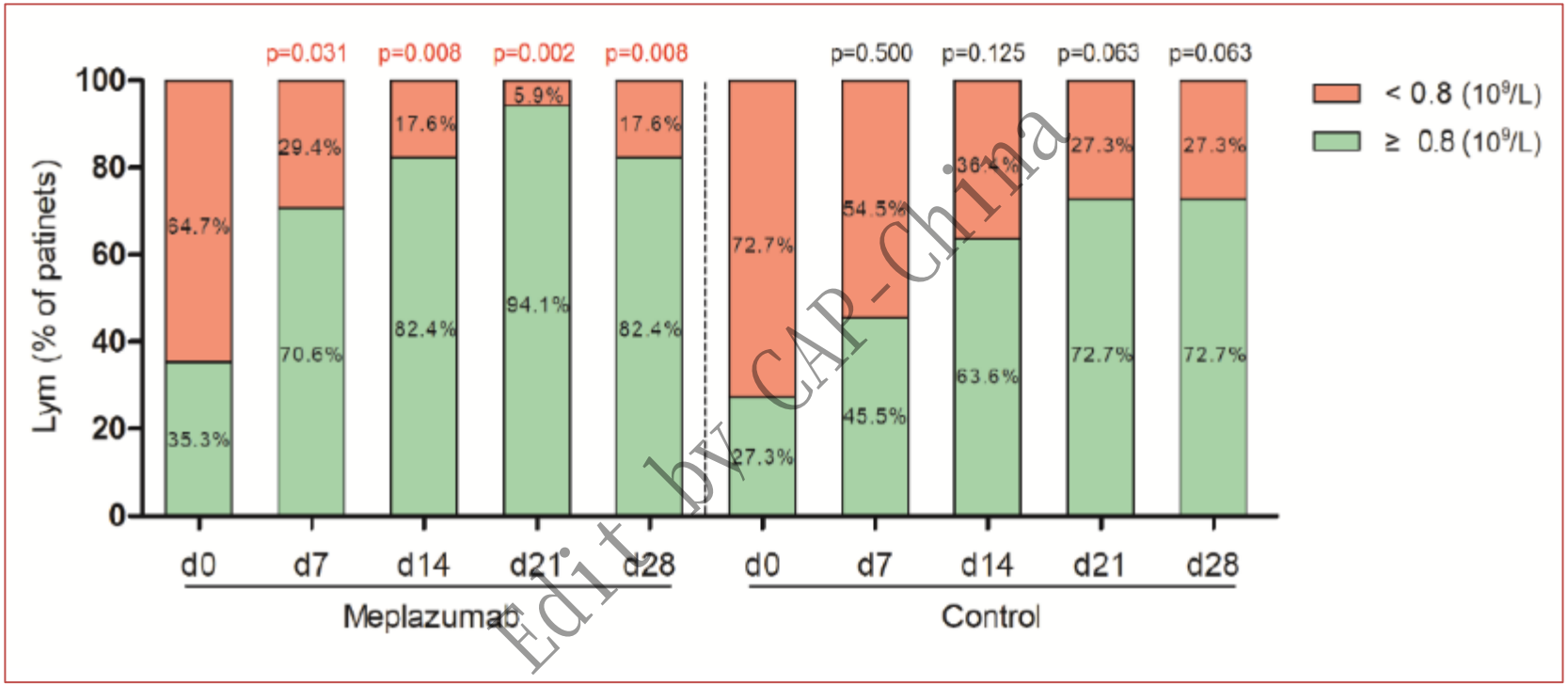
The time to virus negative conversion was shorter in Meplazumab treatmet group



Among severe and critical ill cases, discharge rate was higher in Meplazumab treatmet group

Huijie Bian et al. medRxiv preprint.2020. DOI:10.1101/2020.03.21.20040691

Lymphocyte count in Meplazumab improved earlier than control



Lymphocyte count improved earlier in Meplazumab treatment group

Huijie Bian et al. medRxiv preprint.2020. DOI:10.1101/2020.03.21.20040691

Tocilizumab (anti-human IL-6R) trials for COVID-19 on going now

- Multicenter, single-arm, open-label, phase 2 study for COVID-19 pneumonia in Italy (NCT04317092)
  - 330 participants; primary outcome: 30-day mortality
- multicenter, randomized controlled trial for COVID-19 pneumonia in China (ChiCTR2000029765)
  - Tocilizumab + standard care vs standard care
  - 198 participants; primary outcome: clinical cure rate
- Three arms, multi-center, randomized and controlled study for COVIA-19 patients with increased IL-6 in China (NCT04310228)
  - Favipiravir vs Tocilizumab vs Favipiravir Combined With Tocilizumab
  - 150 participants; primary outcome: clinical cure rate

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 hypertension was only 23% (32/137) in survivors. The OR of hypertension is 3.05 (1.57-5.92).
- At present, there is no evidence to abandon Renin-Angiotensin System Blockers.

A.H Jan Danser, et al. Hypertension. 2020; DOI: 10.1161/HYPERTENSIONAHA.120.15082.
Zhou F, et al. Lancet. 2020; DOI:10.1016/S0140-6736(20)30566-3

China 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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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 in Wuhan