

Chinese Guideline of Diagnosis and treatment of COVID-19

(7th Version)

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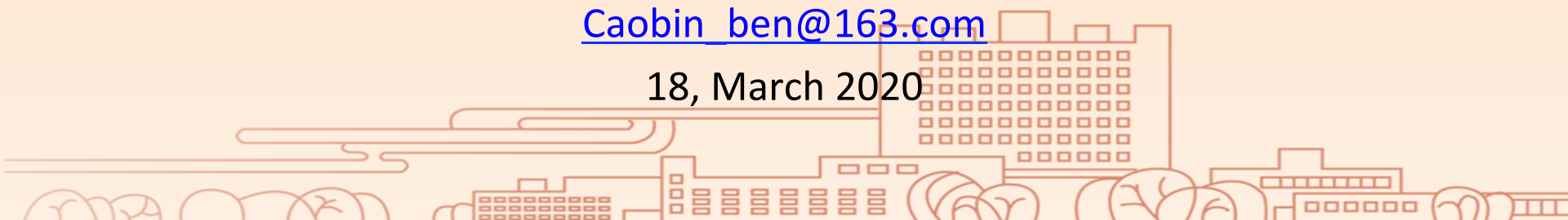
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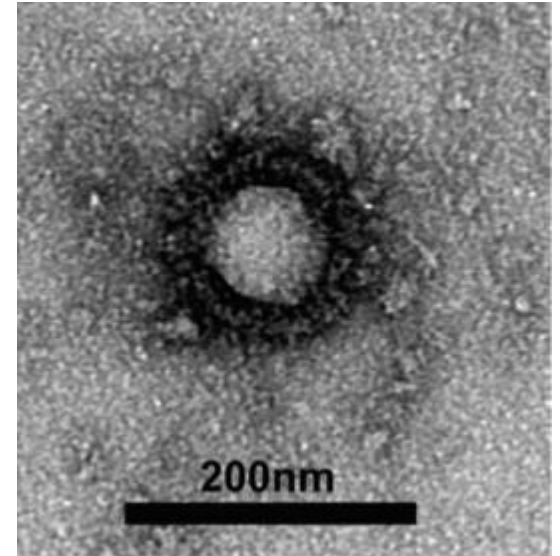
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18, March 2020



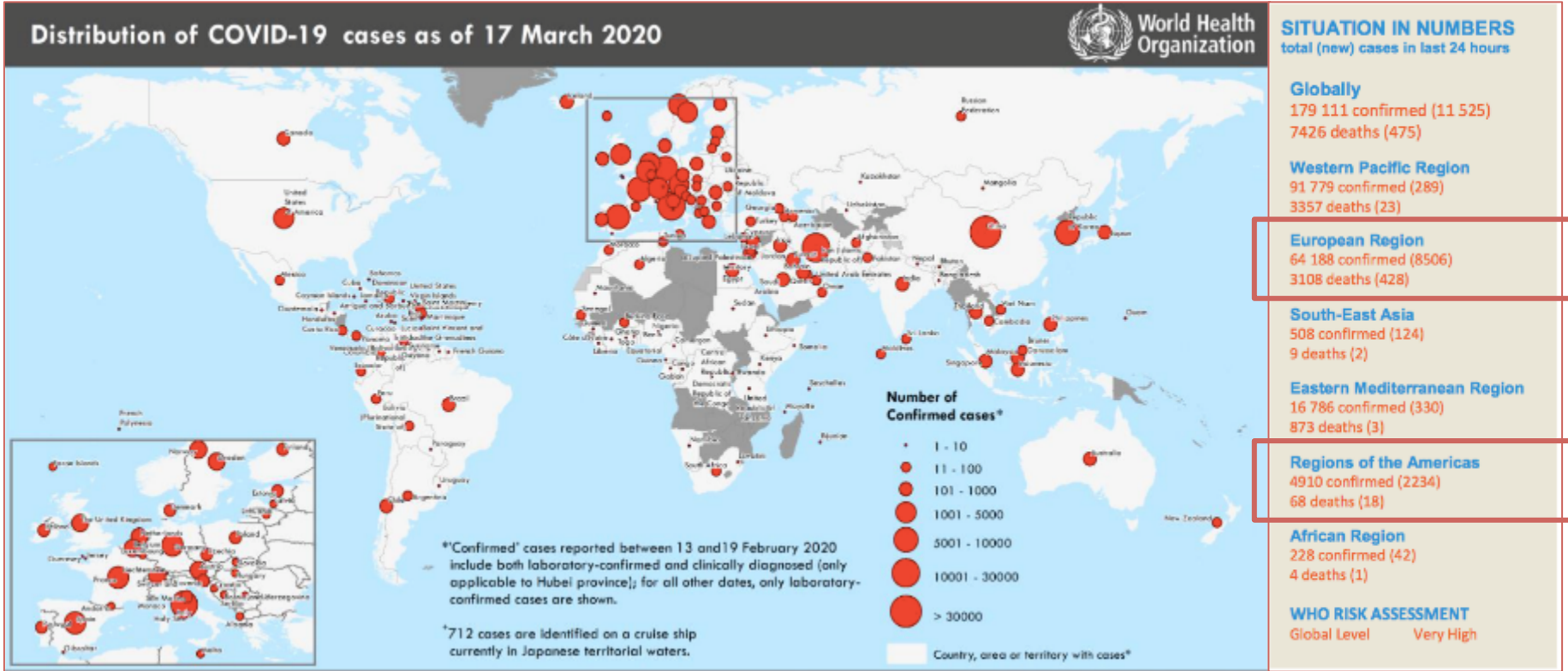
Severe Acute Respiratory Syndrome Coronavirus-2

- 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



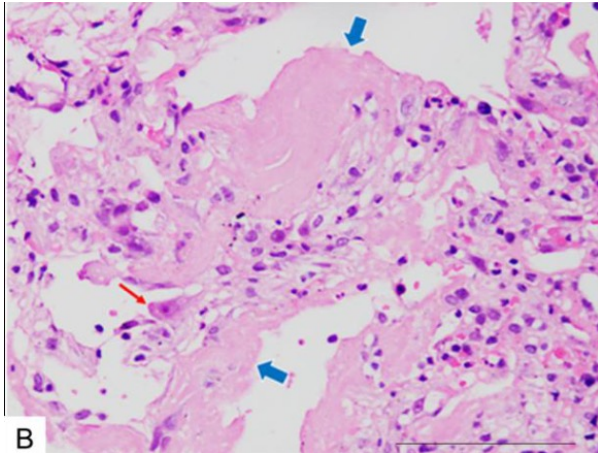
Epidemiology of COVID-19 globally

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

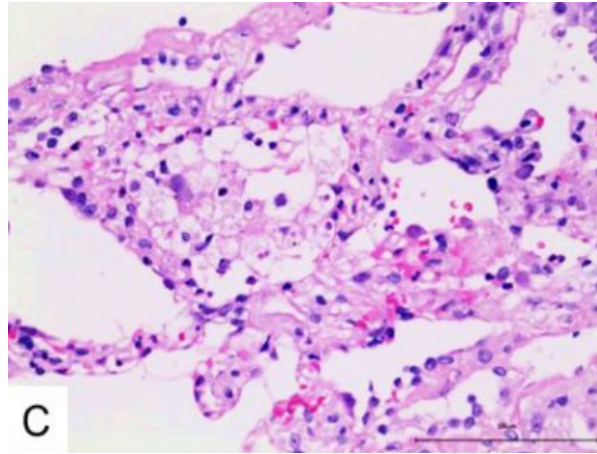


Pathogenic changes of severe COVID-19 in lung

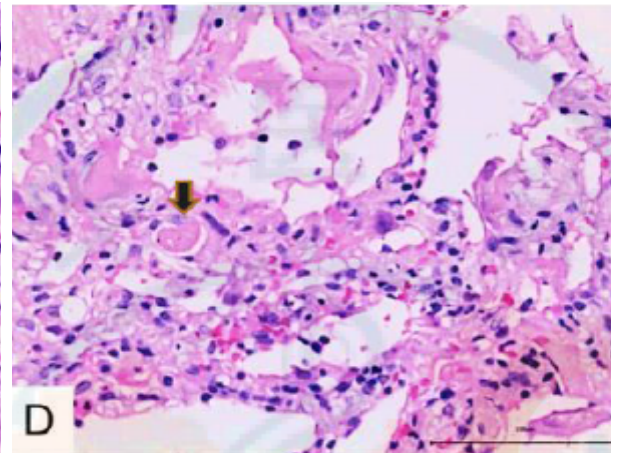
- The pathological features in lungs greatly resemble those seen in SARS and MERS infection
- bilateral diffuse alveolar damage with cellular fibromyxoid exudates



Hyaline membrane formation (blue arrow)



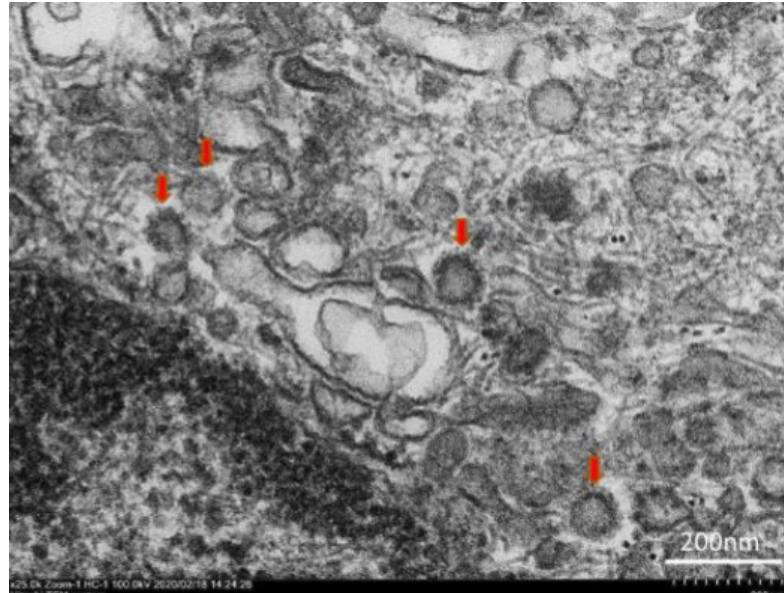
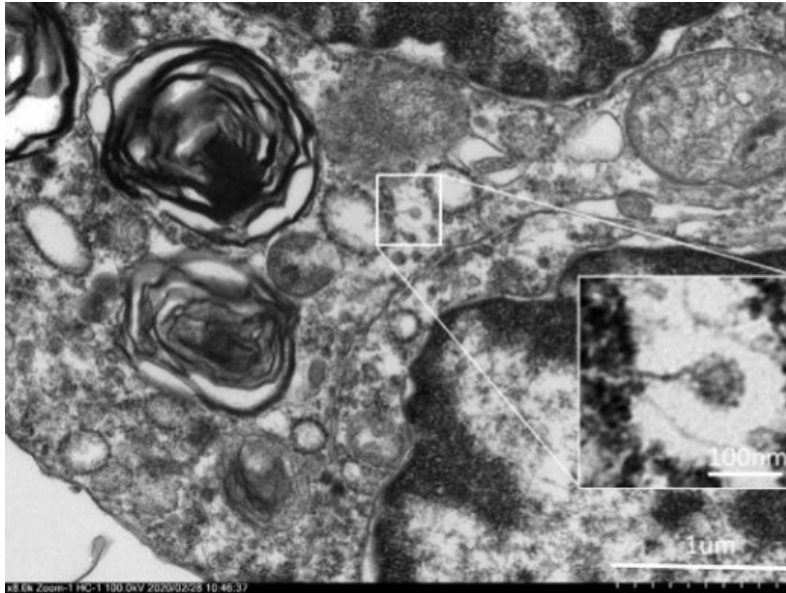
Interstitial mononuclear inflammatory infiltrates



Thrombus in pulmonary arterioles (black arrow)

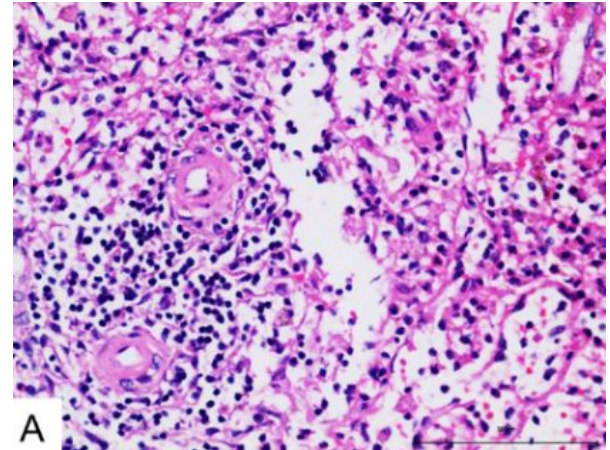
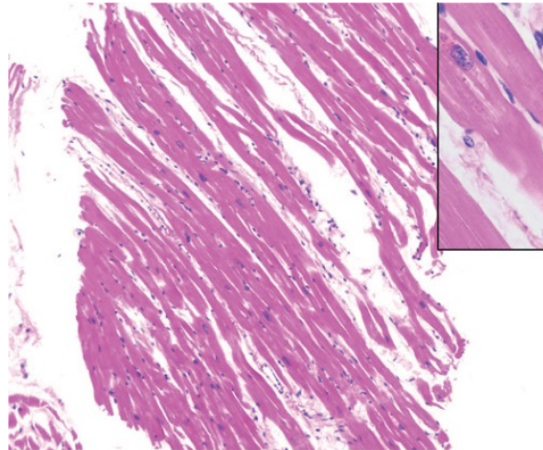
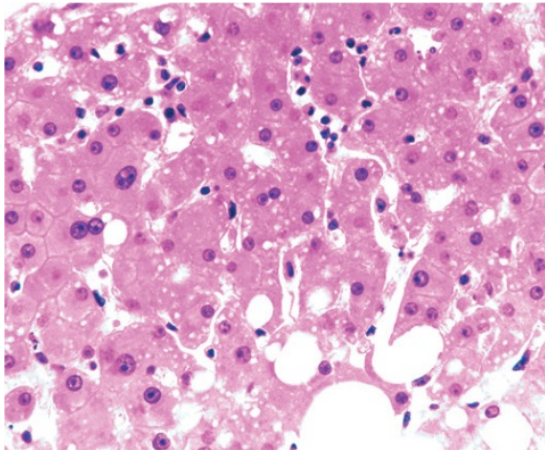
Severe Acute Respiratory Syndrome Coronavirus-2

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



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



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

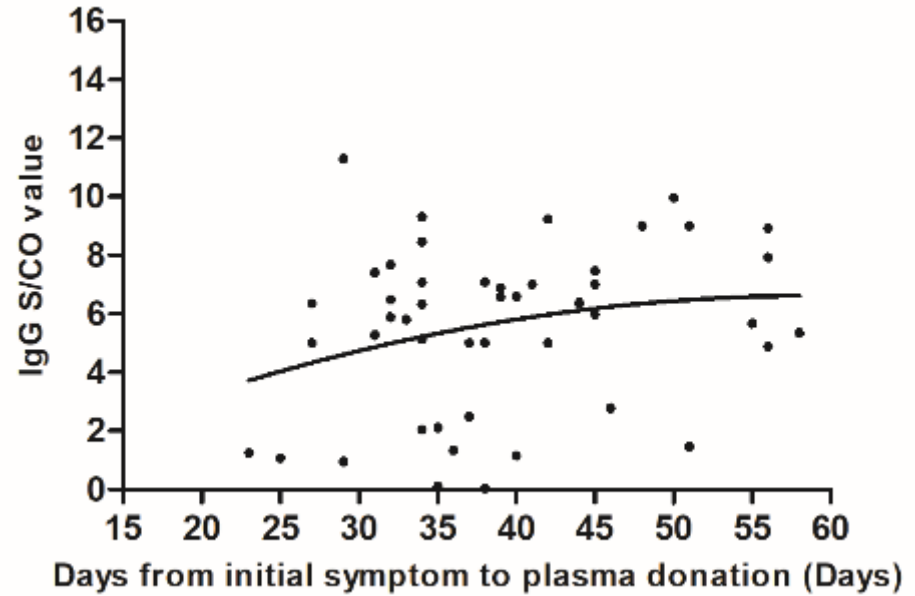
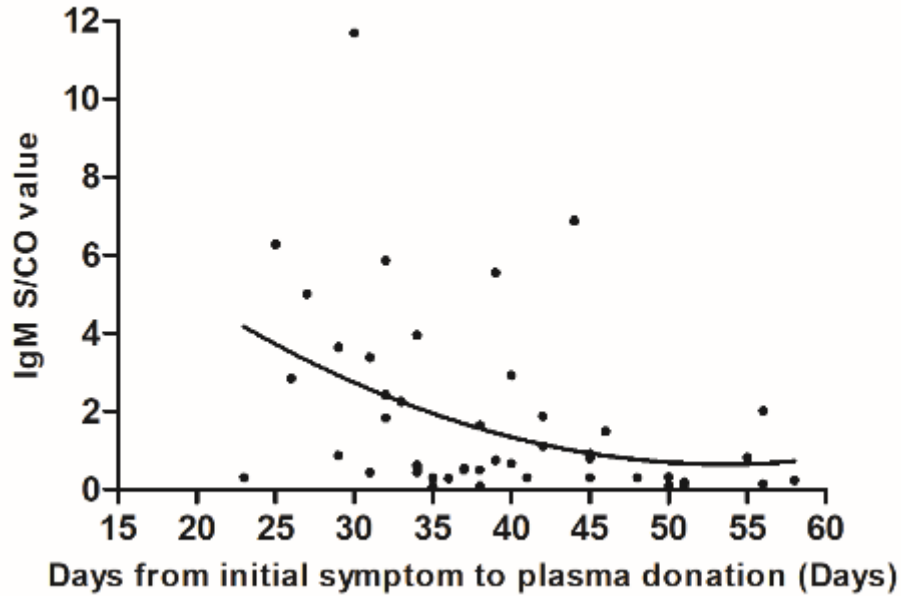
- SARS-CoV-2 RNA was positive detected by real time RT-PCR
- Viral gene sequence is highly homologous to known new coronaviruses

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

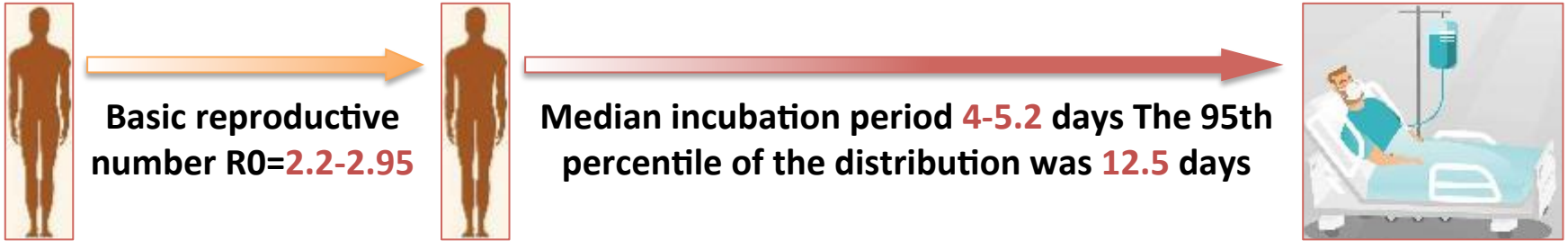
Suspect cases + one of etiological or serological evidences

IgG/IgM Dynamic changes of Adults with COVID-19



Zhong Liu et al. unpublished data

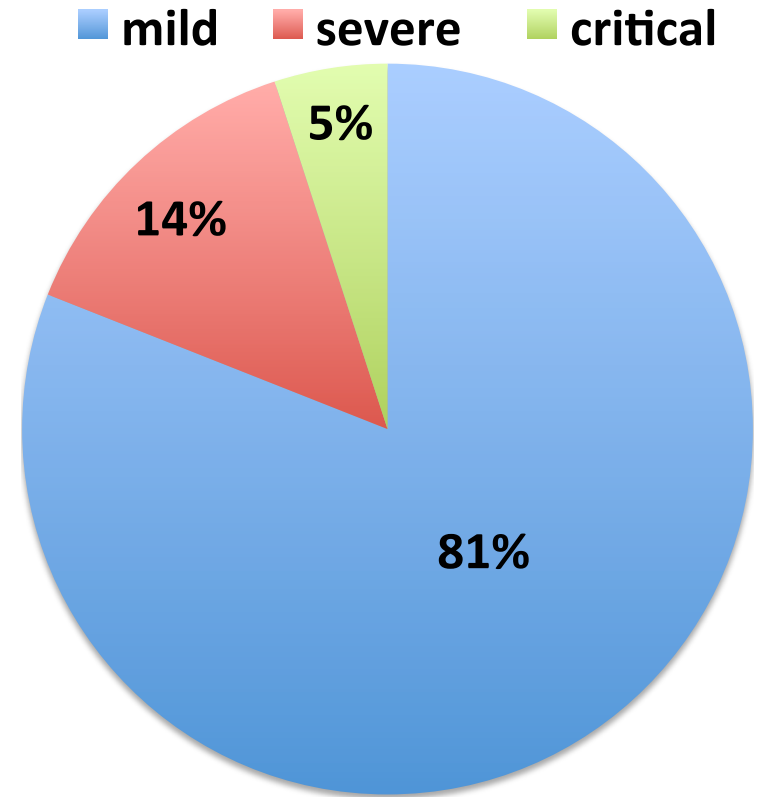
Transmission and incubation of COVID-19



- **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

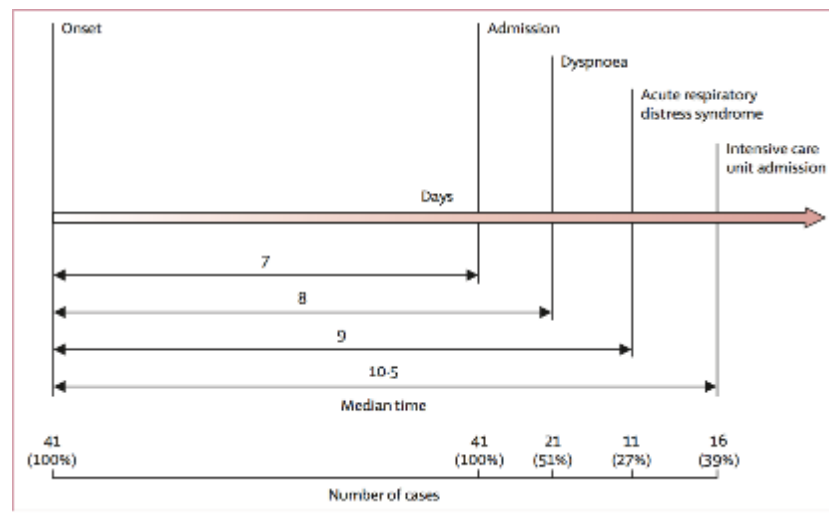
Disease spectrum of COVID-19

- **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



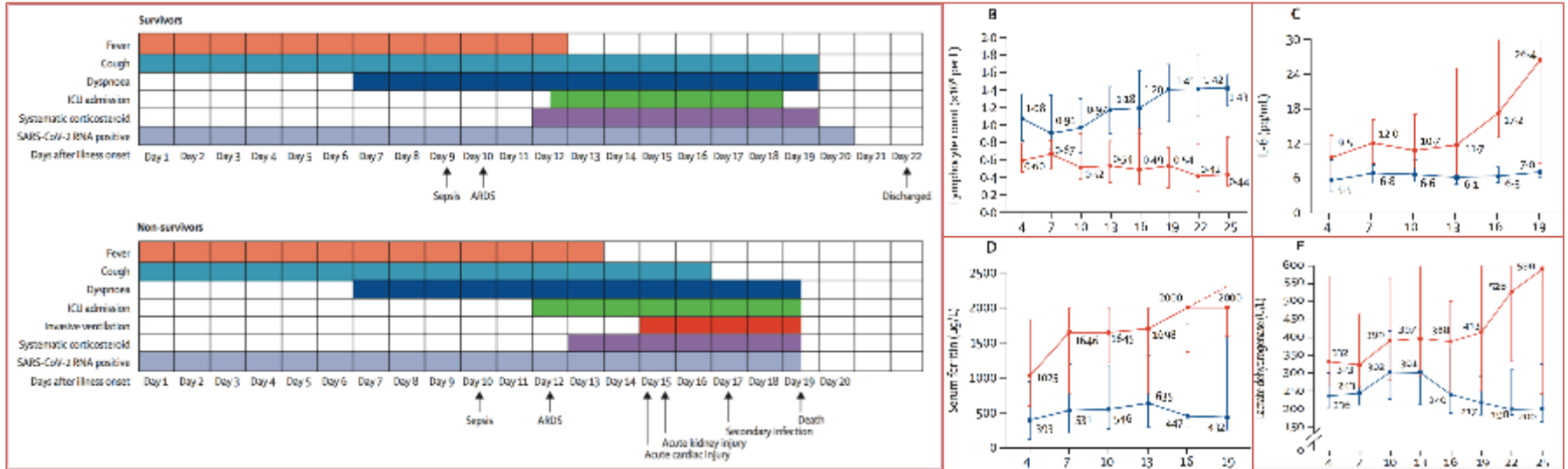
Clinical features of COVID-19 patients

Symptoms and complications	N%
Fever	98%
Cough	76%
Myalgia or fatigue	44%
Sputum production	28%
Diarrhea	3%
WBC $\leq 10 \times 10^9/L$	70%
Lymphocytopenia	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%



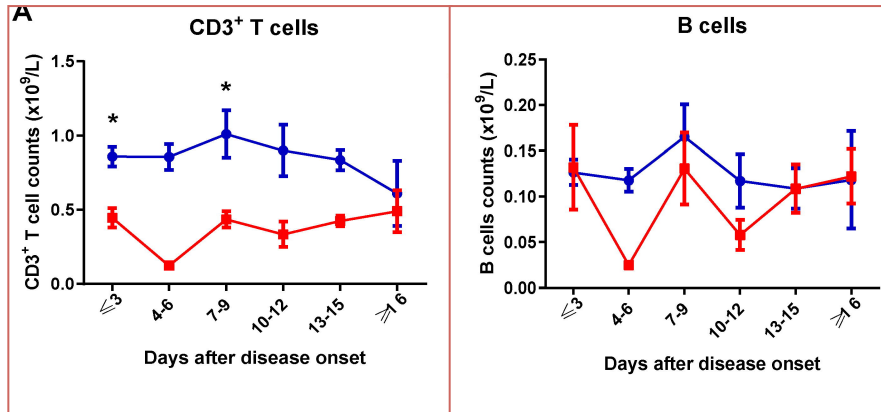
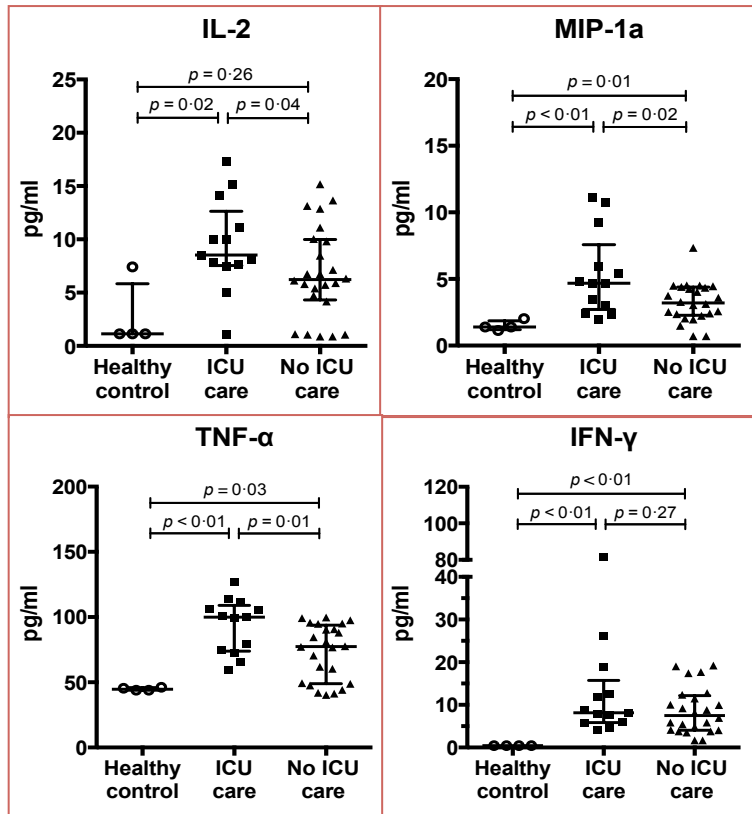
Symptoms and complications	N%
Acute cardiac injury	12%
Acute kidney injury	7%
Septic shock	7%
Secondary infection	10%

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.

Inflammation of COVID-19—Severe and critical illness



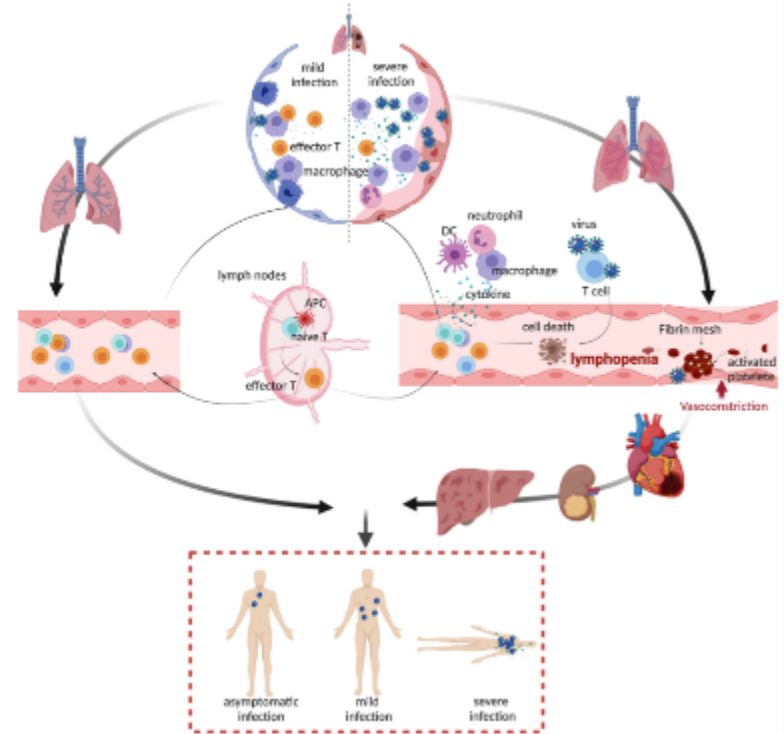
- IL-1 β , IL-6, G-SCF, IP-10, and MCP1 were significantly elevated
- Peripheral lymphocyte counts, mainly T cells were substantially reduced in severe COVID-19 patients

Host-directed therapies might be an option

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

Multi-organ dysfunction

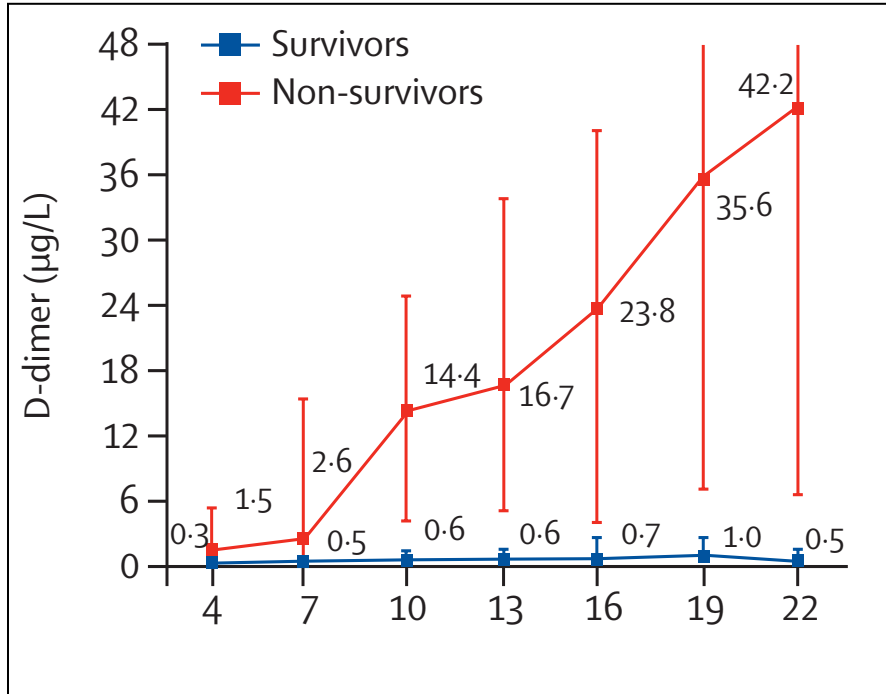
- Pneumonia, Respiratory failure, Acute respiratory distress syndrome
- Metabolic acidosis and internal environment disorders
- Acute kidney injury
- Acute cardiac injury
-



——Viral Sepsis

Abnormal coagulation is common in severe COVID-19

D-Dimer > 1 μ g/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



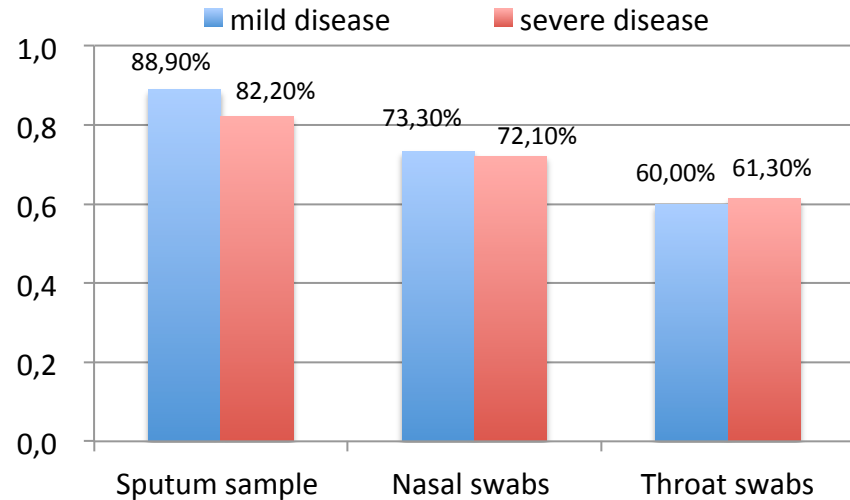
Anticoagulation therapy should be initiated for severe COVID-19 patients if otherwise contraindicated.

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

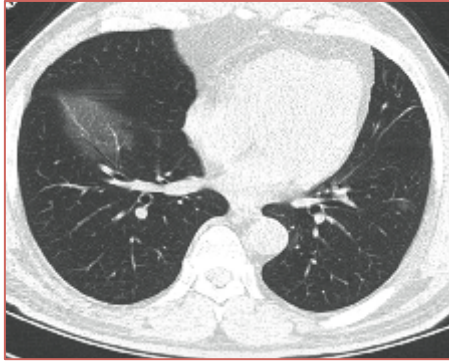
- SARS-CoV-2 RNA could be detected in nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, feces using RT-PCR and/or NGS methods
- Positive rate was higher in lower respiratory tract specimen
- The specimens should be submitted for testing as soon as possible after collection

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



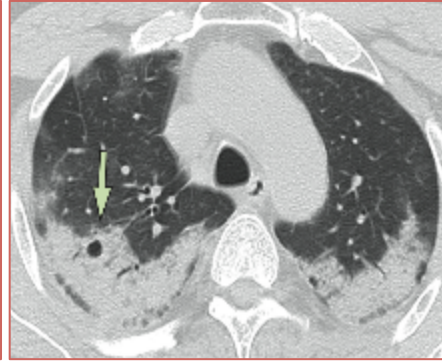
Features of CT scan of COVID-19



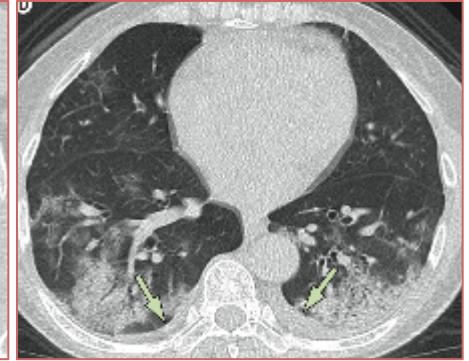
56-year-old man
Day 3 after symptom onset
Focal ground-glass opacity



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



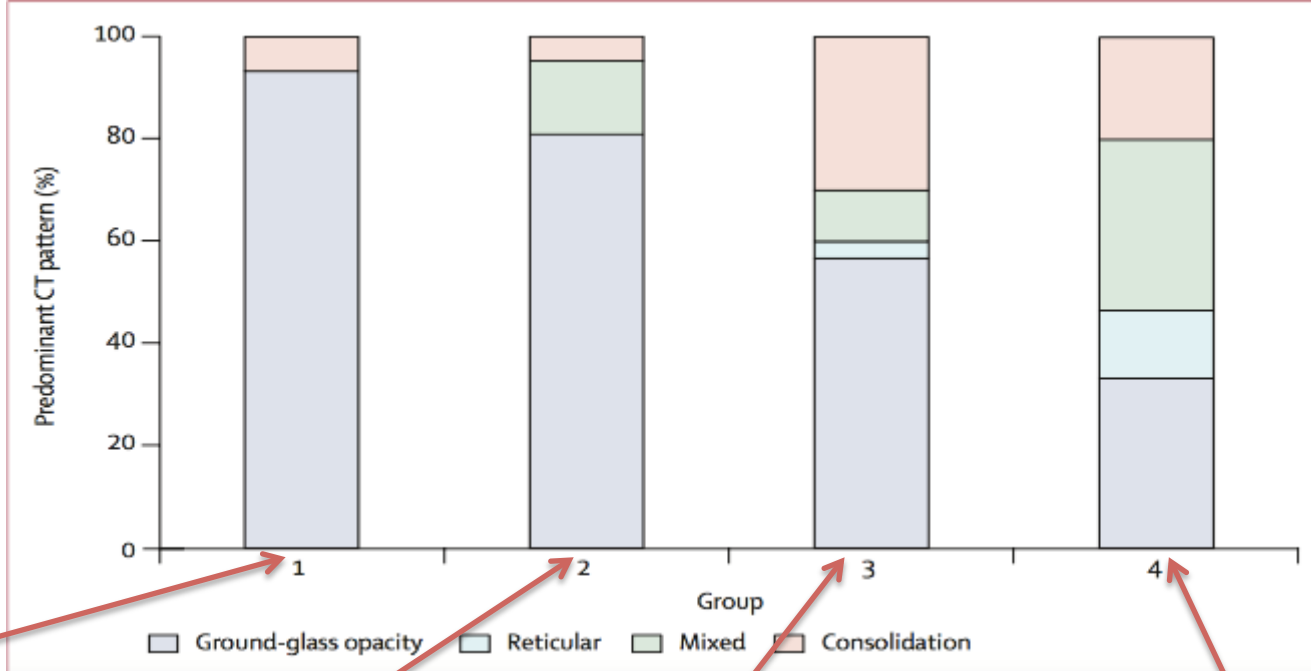
61-year-old woman
Day 20 after symptom onset
Bilateral and peripheral predominant consolidation



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

Features of imagine change over time



Ct scan before illness onset

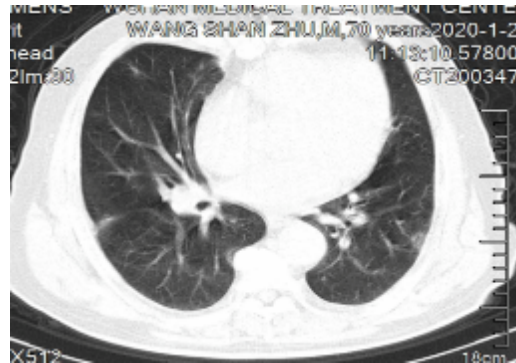
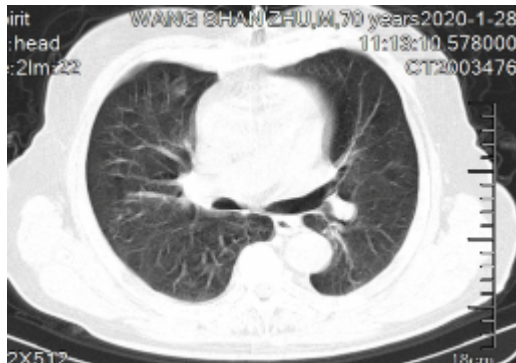
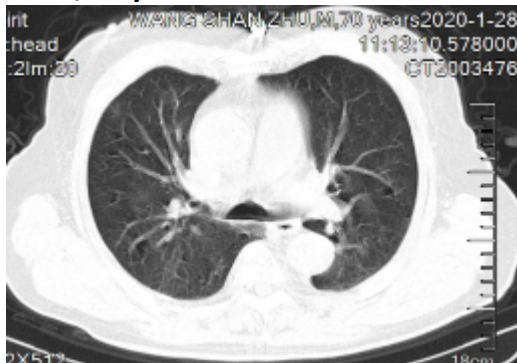
≤ 1 week after symptom onset

>1 week to 2 weeks after symptom onset

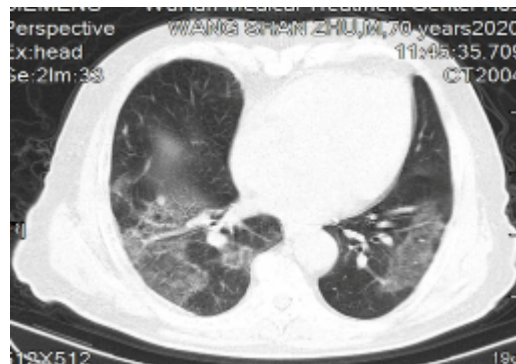
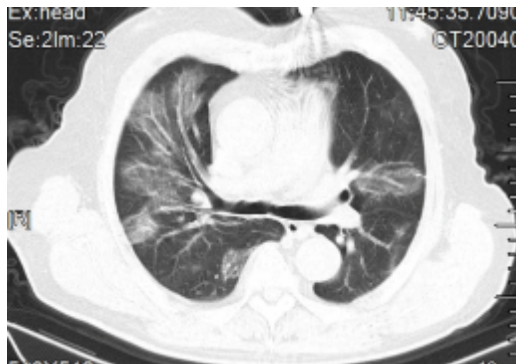
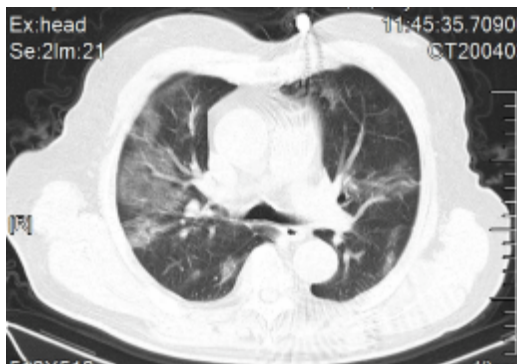
>2 weeks to 3 weeks after symptom onset

Rapid deterioration on CT scan-case 1

Male, 70 years old



2020-1-28 Day 9 after illness onset



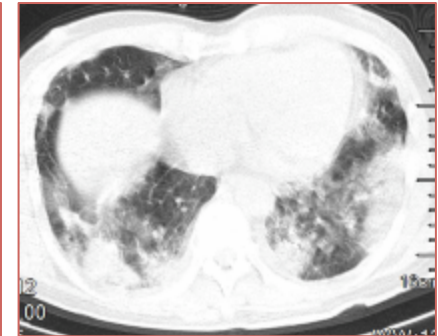
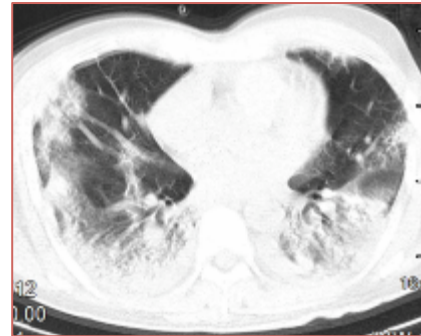
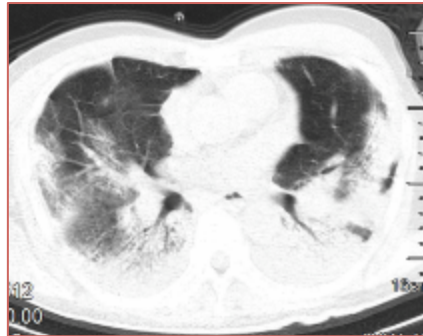
2020-2-1 Day 13 after illness onset. Died 2 weeks later.

Rapid deterioration on CT scan-case 2

Male, 62 years old



2020-2-7 Day 12 after illness onset

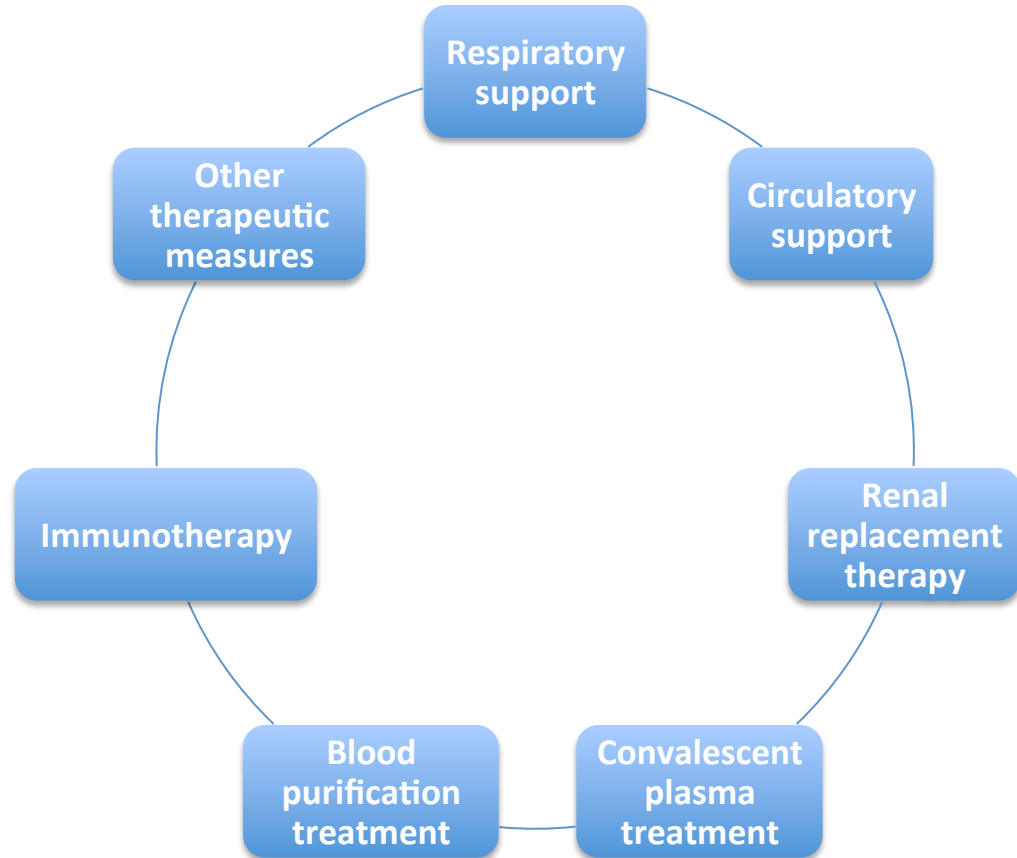


2020-2-7 Day 19 after illness onset. Died 15 days later

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, manuscript accepted, online tomorrow***
 - Promising results
 - CAP China Remdesivir 1 (mild-moderate pneumonia, NCT04252664): ***ongoing***
 - CAP China Remdesivir 2 (severe-critical pneumonia, NCT04257656): ***ongoing***

Emmie de Wit et al. Nature Reviews Microbiology 2016; 14, 523 - 534

Timothy P Sheahan; Nat Commun 2020; 11 (1), 222

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

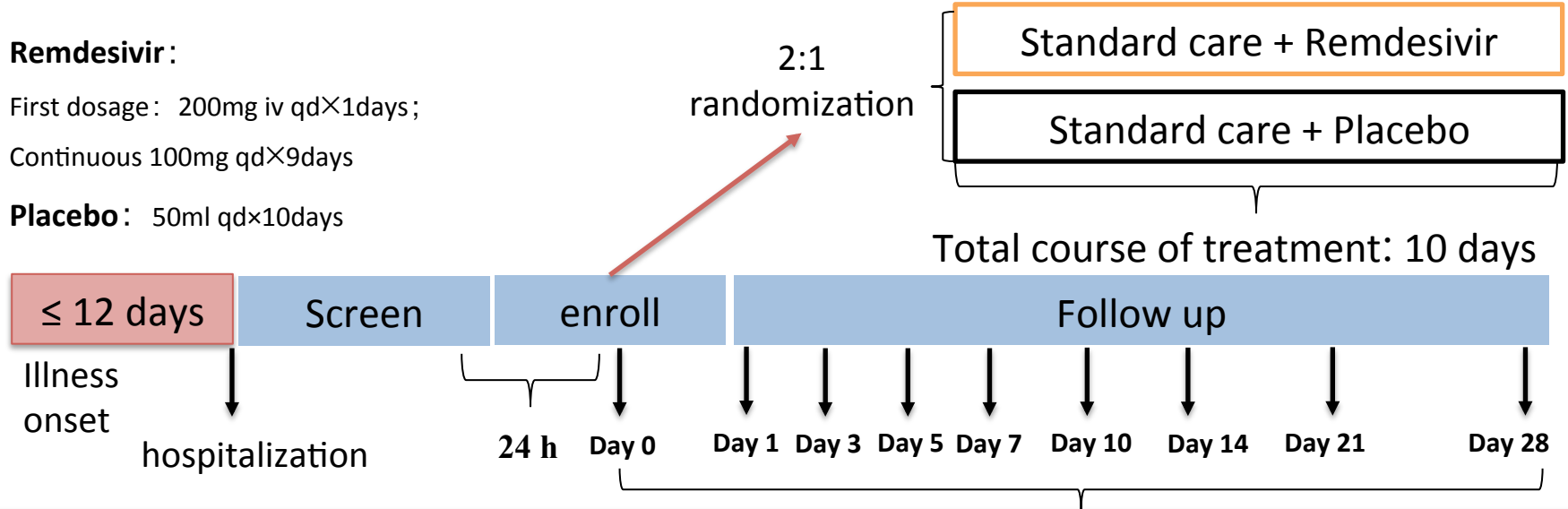
CAP-China Remdesivir trials on going for COVID-19

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

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/Pll>
Zhao JP, 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

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)

Acknowledgements

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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

