Treatment Strategies to Prevent Mild to Severe Progression of COVID-19 Cases

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Translated by Center for Global Public Health, Chinese Center for Disease Control and Prevention

Outline

- Pathogenesis and pathological changes
- Diagnostic criteria
- Early-warning indicators of severe cases
- Clinical management strategies to prevent mild to severe progression of COVID-19 cases
  - ✓ Principles of clinical management: classified treatment and full-process management
  - ✓ Monitoring and evaluation
  - ✓ Antiviral therapy
  - ✓ Immunoregulation
  - ✓ Others

COVID-19 CORONAVIRUS PANDEMIC

Last updated: July 01, 2020, 08:21 GMT

Graphs - Countries - Death Rate - Symptoms - Incubation - Transmission - News

Coronavirus Cases:

10,600,203

view by country

Deaths:

514,298

Recovered:

5,812,076

COVID-19 CORONAVIRUS PANDEMIC

Last updated: July 21, 2020, 07:59 GMT

Countries - Death Rate - Symptoms - Incubation - Transmission - News

Coronavirus Cases:

14,866,394

view by country

Deaths:

613,542

Recovered:

8,923,956

COVID-19 CORONAVIRUS PANDEMIC

Last updated: July 25, 2020, 17:22 GMT

Countries - Death Rate - Symptoms - Incubation - Transmission -

Coronavirus Cases:

16,073,398

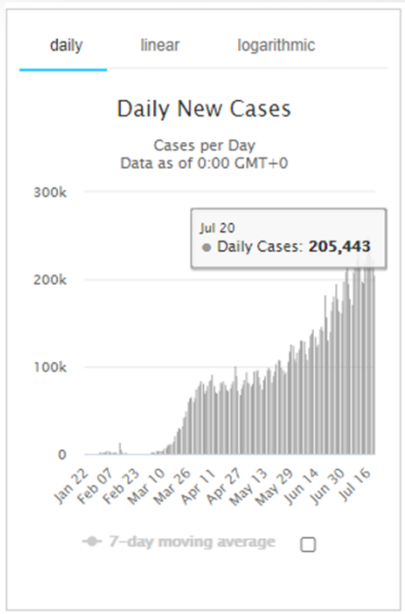
view by country

Deaths:

645,207

Recovered:

9,821,594


daily
linear
logarithmic
Daily New Cases
Cases per Day
Data as of 0:00 GMT+0
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200k
100k
0
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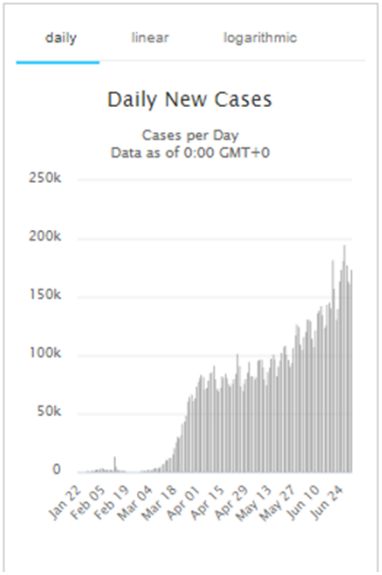
Feb 07
Feb 23
Mar 10
Mar 26
Apr 11
Apr 27
May 13
May 29
Jun 14
Jun 30
Jul 16
7-day moving average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Cases per Day
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Mar 04
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Apr 15
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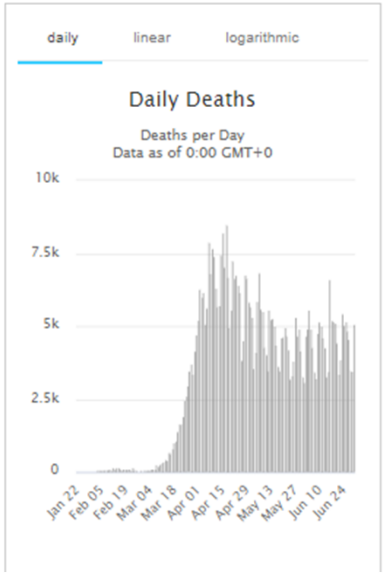
May 27
Jun 10
Jun 24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Daily Deaths
Deaths per Day
Data as of 0:00 GMT+0
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7.5k
5k
2.5k
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Mar 18
Apr 01
Apr 15
Apr 29
May 13
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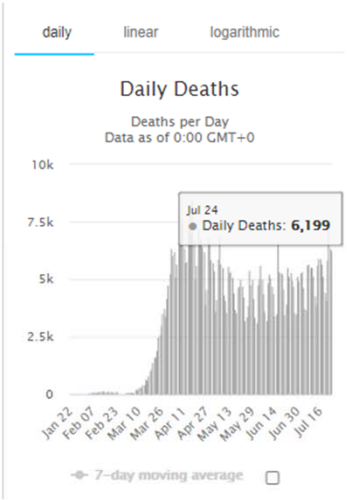
Jun 10
Jun 24


daily
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Daily Deaths
Deaths per Day
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7.5k
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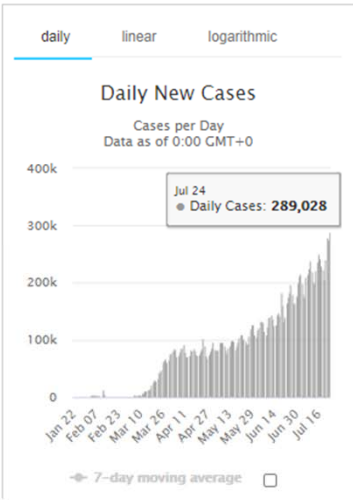
Jul 24
Daily Deaths: 6,199
Jan 22
Feb 07
Feb 23
Mar 10
Mar 26
Apr 11
Apr 27
May 13
May 29
Jun 14
Jun 30
Jul 16
7-day moving average


daily
linear
logarithmic
Daily New Cases
Cases per Day
Data as of 0:00 GMT+0
400k
300k
200k
100k
0
Jul 24
Daily Cases: 289,028
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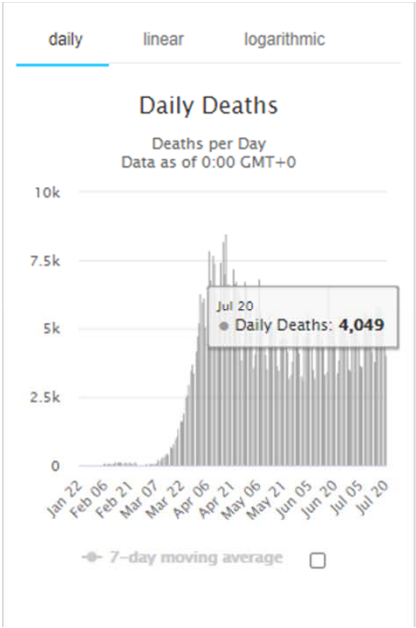
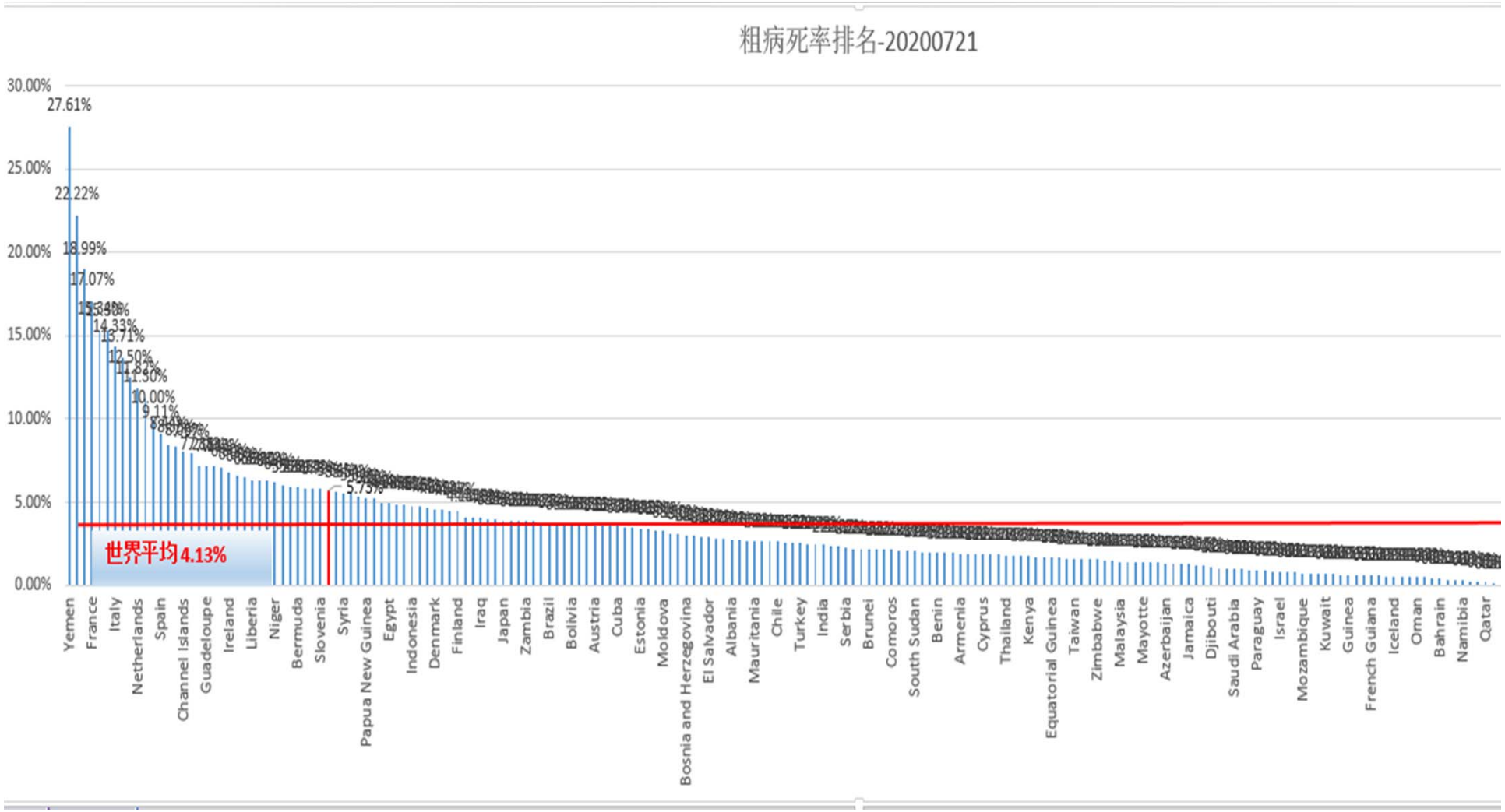
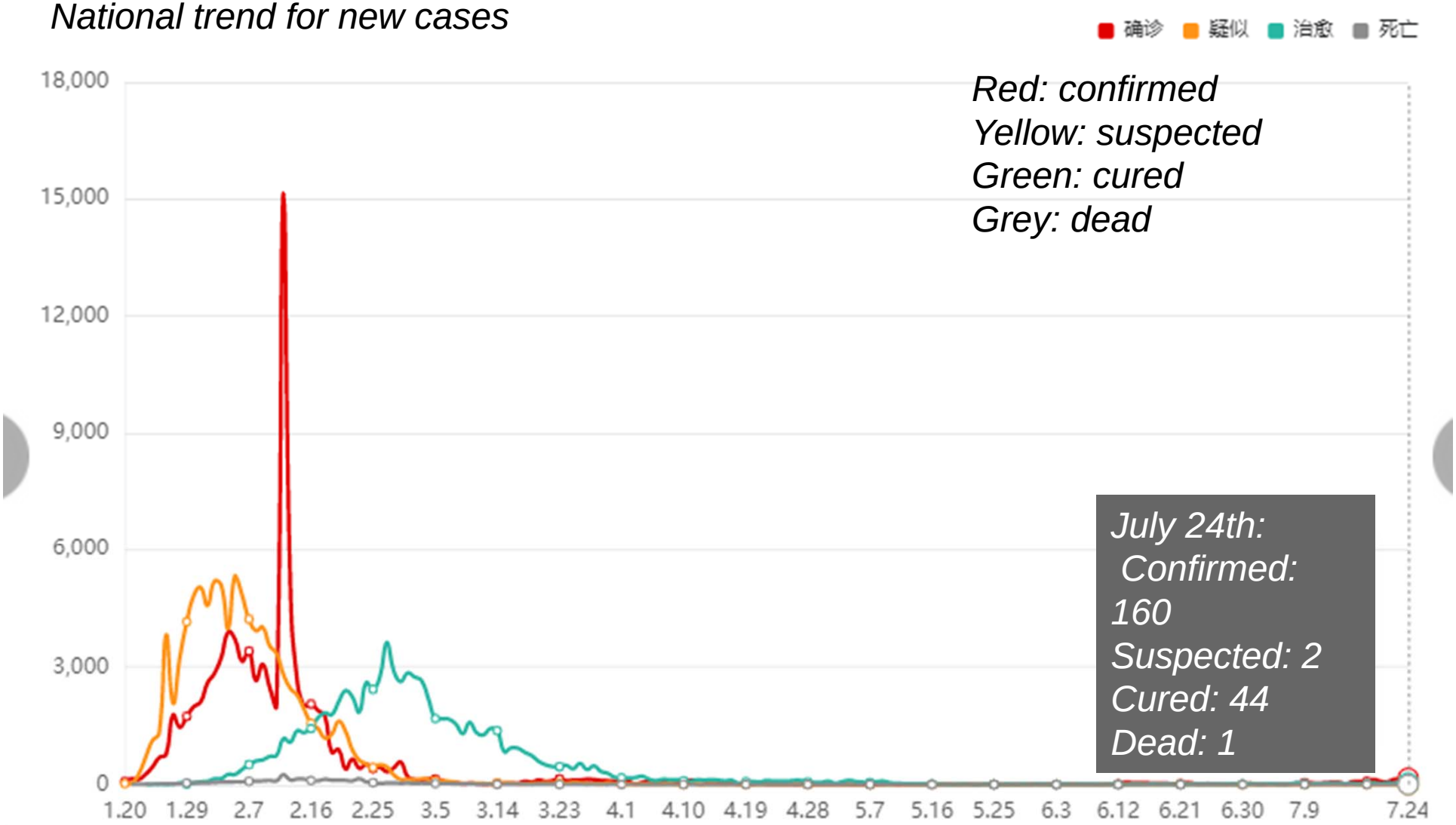
Feb 07
Feb 23
Mar 10
Mar 26
Apr 11
Apr 27
May 13
May 29
Jun 14
Jun 30
Jul 16
7-day moving average


daily
linear
logarithmic
Daily Deaths
Deaths per Day
Data as of 0:00 GMT+0
10k
7.5k
5k
2.5k
0
Jul 20
Daily Deaths: 4,049
Jan 22
Feb 06
Feb 21
Mar 07
Mar 22
Apr 06
Apr 21
May 06
May 21
Jun 05
Jun 20
Jul 05
Jul 20
7-day moving average

Crude Fatality Rate Worldwide



National trend for new cases



Red: confirmed
Yellow: suspected
Green: cured
Grey: dead

July 24th:
Confirmed: 160
Suspected: 2
Cured: 44
Dead: 1


1 in 2 COVID-19 patients could not identify a person with COVID-19 with whom they had close contact in the last 2 weeks*
*Random sample of adults with positive RT-PCR tests at 11 U.S. academic medical centers in nine states
CDC.GOV
Many people might be getting infected in their communities
Protect yourself and others:
• Limit close contact with people who don't live in your household
• Wear a cloth face covering in public
• Wash hands frequently
bit.ly/MMWR63020
MMWR

Pathogenesis and Pathological Changes

- The 2019-nCoV mainly damages the lungs, immune system, and vascular endothelium.
- Damage to other organs varies with the underlying disease, mostly secondary damage.

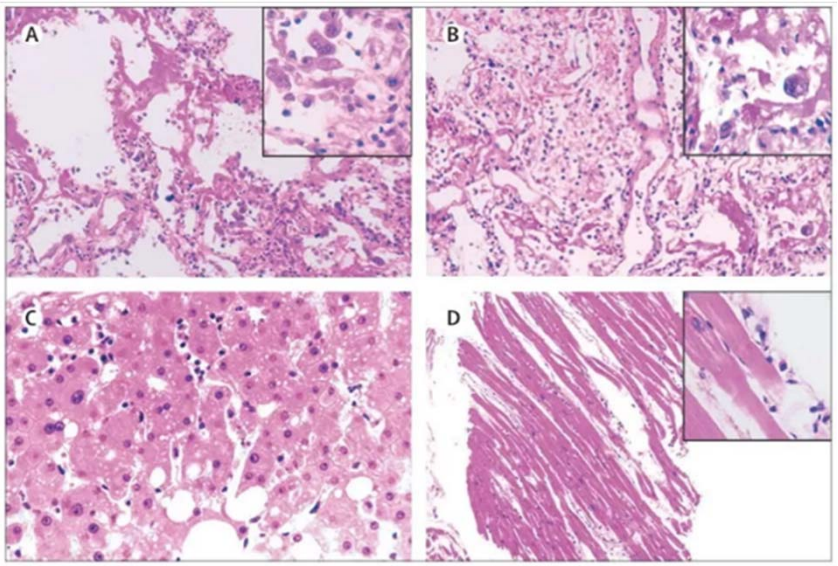


图2: 一个感染SARS-CoV-2重症肺炎患者的右肺（A）和左肺（B）组织，肝组织（C），和心脏组织（D）的病理学表现

The Lancet Respiratory Medicine, Published: February 18, 2020

COVID-19 causes widespread formation of microthrombi

- The incidence of alveolar capillary thrombosis caused by COVID-19 is 9 times that caused by influenza (P <0.001)
- The number of new blood vessels caused by COVID-19 is 2.7 times that caused by influenza pneumonia (P <0.001)

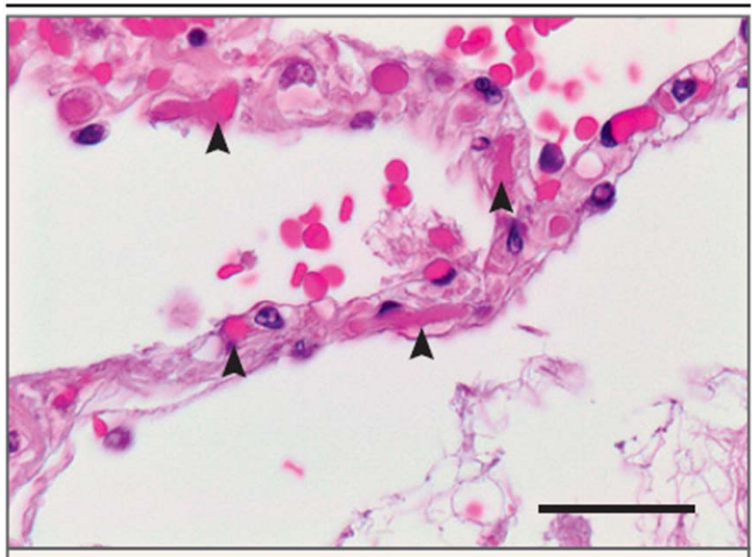


Figure 2. Microthrombi in the Interalveolar Septa of a Lung from a Patient Who Died from Covid-19.

N Engl J Med 2020;383:120-8.DOI: 10.1056/NEJMoa2015432

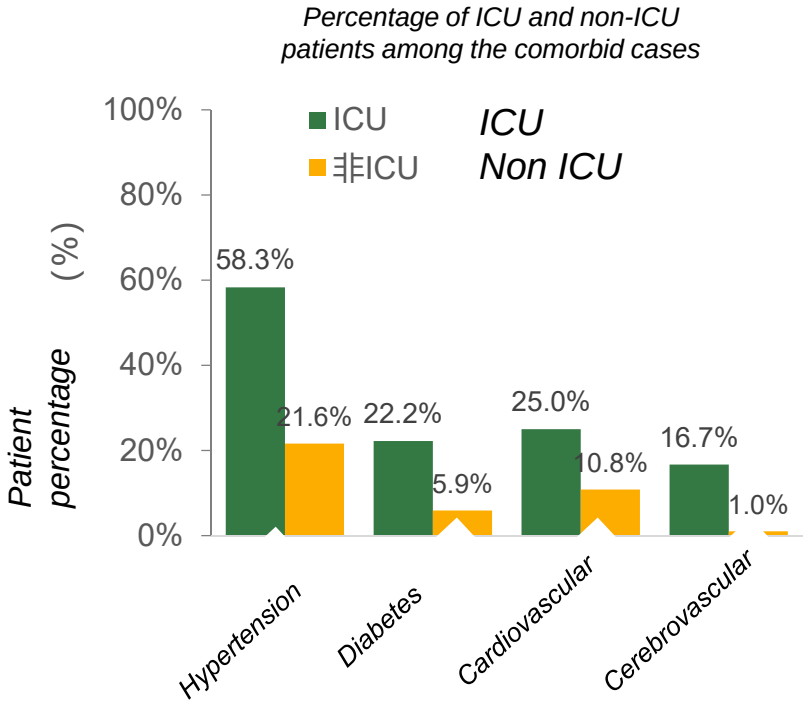
The elderly are at high risk

- The case-fatality rate for COVID-19 varies markedly by age, ranging from **0.3 deaths per 1,000 cases** among patients aged **5 to 17 years** to **304.9 deaths per 1,000 cases** among patients **aged 85 years or older** in the US.

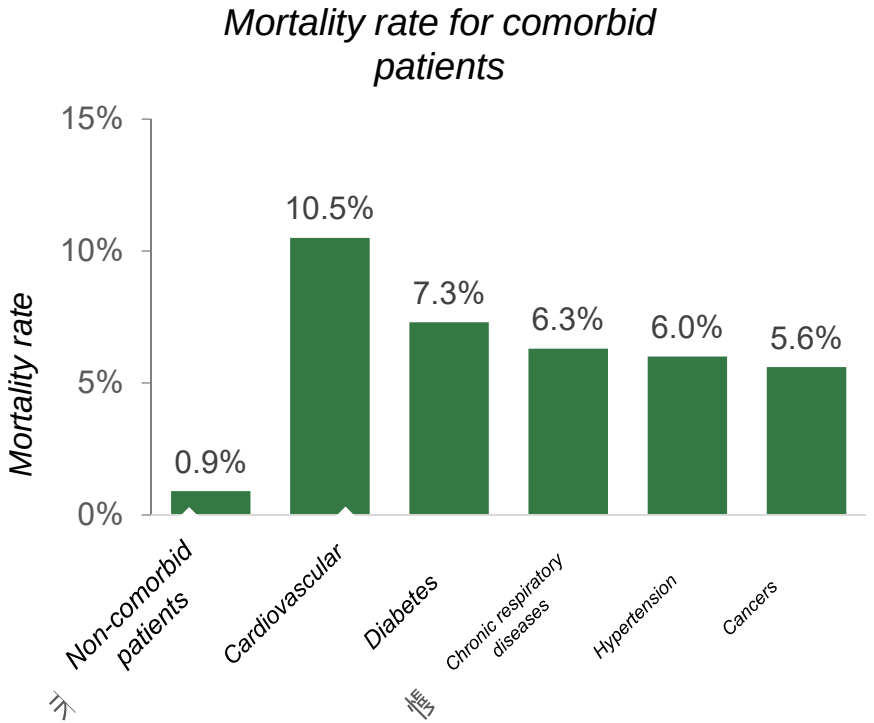
JAMA Published online July 10, 2020

Patients with COVID-19 combined with underlying diseases are more critically ill and have a higher mortality rate.

- *Compared with non-ICU patients, more patients with COVID-19 combined with underlying diseases were admitted to ICU and their mortality rate were higher.*

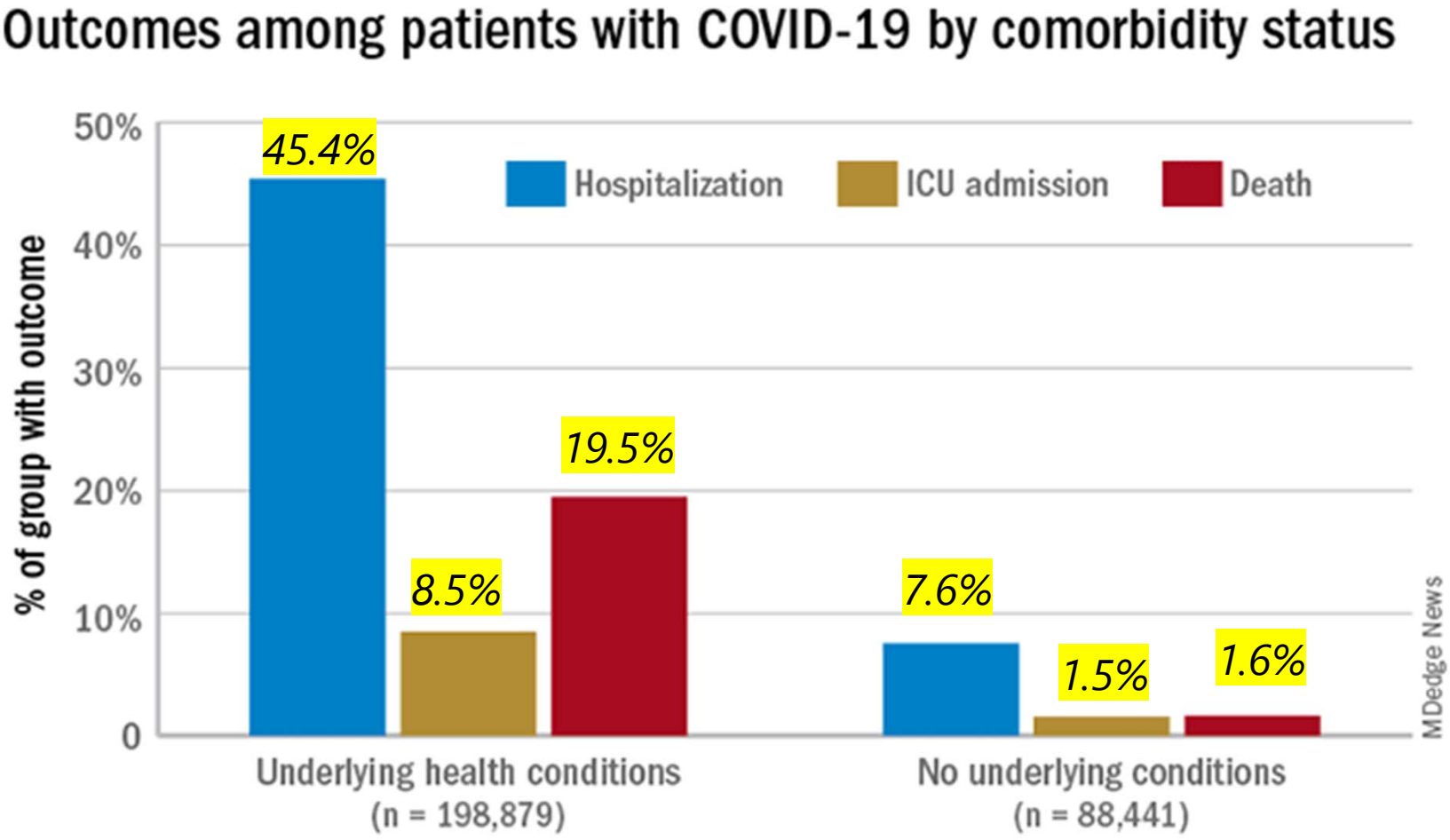


—A single-center, retrospective study admitted a total of 138 consecutive hospitalized patients diagnosed with COVID-19 infection in the Zhongnan Hospital of Wuhan University, Wuhan City, China. The epidemiological and clinical features of NCIP were described by collecting clinical and laboratory data and treatment methods, and analyzing the mortality rate, so as to inform the clinical diagnosis and treatment.



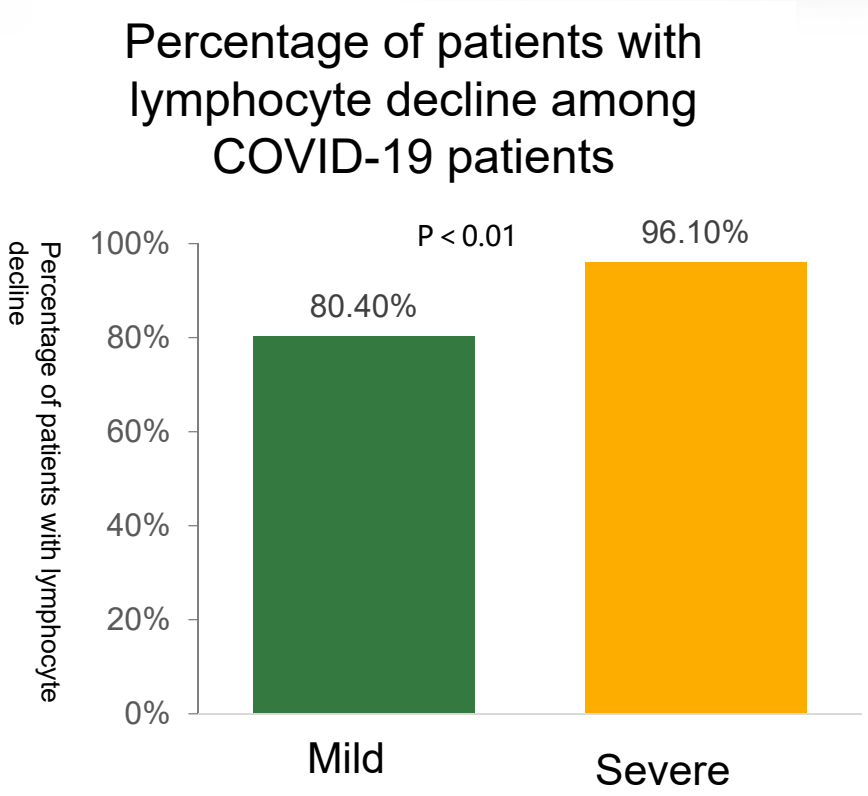
A multi-center retrospective study, which selected 72,314 or all the COVID-19 cases reported to the Infectious Disease Reporting System in Mainland China as of February 11, 2020, and described the epidemiological features of COVID-19 by analyzing patient characteristics and mortality.

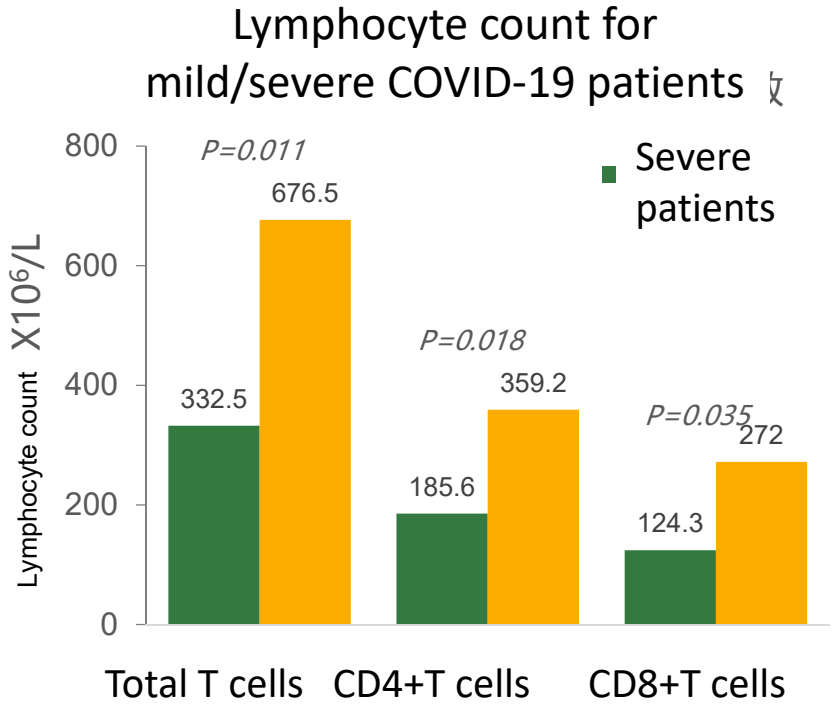
Wang D, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published online ahead of print, 2020 Feb 7].
Zhang Yanping. Analysis of Epidemiological Characteristics of Corona Virus Disease 2019. Chinese Journal of Epidemiology, 2020, 41 (2): 145-151.



MMWR Morb Mortal Wkly Rep. ePub: 15 June 2020.

Lymphocyte decline is a common feature for patients with COVID-19, especially in severe cases.





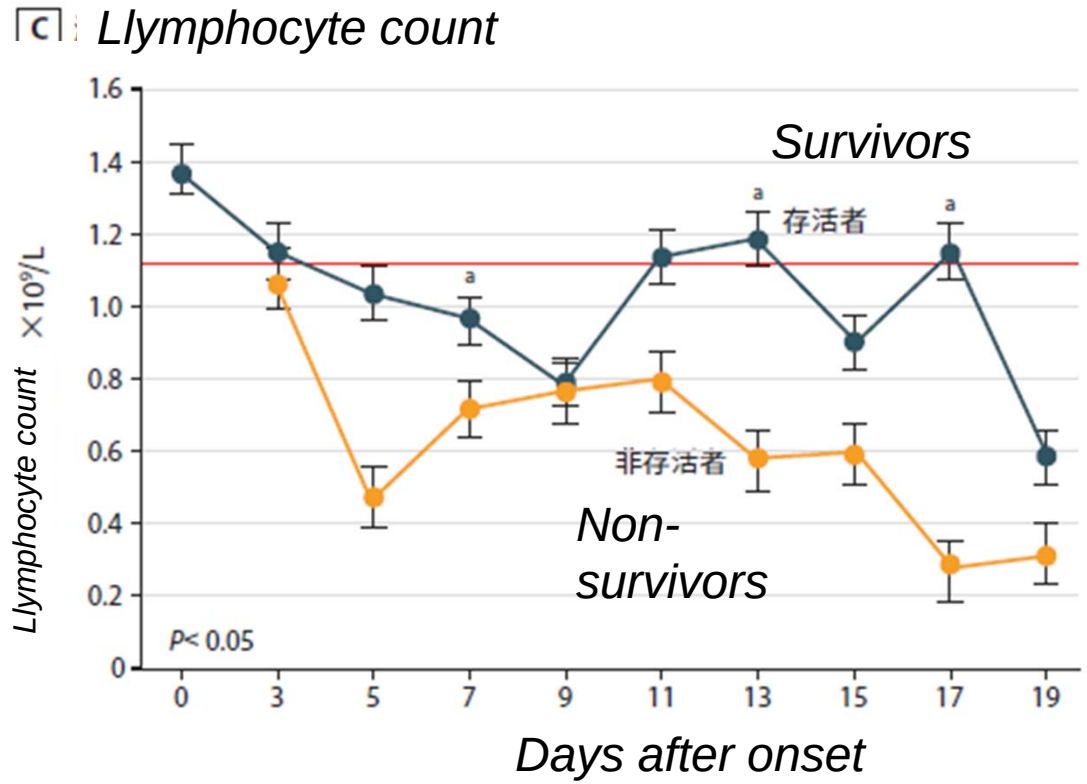
A multi-center clinical study involving 1,099 laboratory-confirmed COVID-19 patients from 552 hospitals in 30 provinces/autonomous regions/municipalities across the country from December 11, 2019 to January 29, 2020. The main composite endpoint is admission to the intensive care unit (ICU), mechanical ventilation, or death.

In a retrospective study, a total of 21 COVID-19 patients were included, who were divided into severe and mild cases according to blood oxygen saturation and respiratory rate, then the immunological evaluation results of the two groups were evaluated and analyzed.

Guan WJ, et al. Clinical Characteristics of Coronavirus Disease 2019 in China.N Engl J Med. 2020 Feb 28. doi: 10.1056/NEJMoa2002032.
Chen G,et al. Clinical and immunologic features in severe and moderate forms of Coronavirus Disease 2019[J]. medRxiv, 2020.

Significant decrease in lymphocyte count may be related to poor clinical outcome of COVID-19

- During hospitalization, most COVID-19 patients experienced significant lymphopenia, for non-surviving patients it was even more severe.



Note: The timetable shows the lymphocyte count in 33 patients with COVID-19. The solid red line indicates the lower limit of normal lymphocyte count.a P< 0.05, non-survivor and survivor.

A single-center, retrospective study admitted a total of 138 consecutive hospitalized patients diagnosed with COVID-19 infection in the Zhongnan Hospital of Wuhan University, Wuhan City, China. The epidemiological and clinical features of NCIP were described by collecting clinical and laboratory data and treatment methods, and analyzing the mortality rate, so as to inform the clinical diagnosis and treatment.

Wang D, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7. doi: 10.1001/jama.2020.1585.

Thrombosis is a high-risk factor for severe cases

Table 2 Coagulation parameters of COVID-19 patients

	All patients ($n = 150$)
Baseline coagulation parameters	
Platelet count (10^9/L)—normal range: 150–400.10^9/L	200 [152; 267]
aPTT—normal range: 0.7–1.2	1.2 [1.1; 1.3]
PT (%)—normal range: > 70%	84 [73; 91]
INR—normal range: 1.00–1.15	1.12 [1.05; 1.25]
D-dimers (mg/L)—normal range: < 0.5 mg/L	2.27 [1.16; 20]
Fibrinogen (g/L)—normal range: 2–4 g/L	6.99 [6.08; 7.73]
Antithrombin activity (%)—normal range: 50–150%	91 [78; 102]
Factor V (%)—normal range: > 70%	136 [115; 150]
Factor VIII (%)—normal range: 60–150%	341 [258; 416]
vWF activity (%)	328 [212; 342]
vWF antigen (%)—normal range: 50–150%	455 [350; 521]
Lupus anticoagulant[a]—*n* (%)	50/57 (87.7)
Screen patient (s)	68.6 [59.5; 85.4]
Screen ratio—normal range: < 1.2	1.63 [1.43; 2.04]
Confirm patient (s)	43.9 [40.9; 48.4]
Confirm ratio—normal range: < 1.2	1.25 [1.13; 1.46]
Screen/confirm ratio—normal range: < 1.2	1.4 [1.25; 1.48]

All results are given in median [IQR], except if specified otherwise

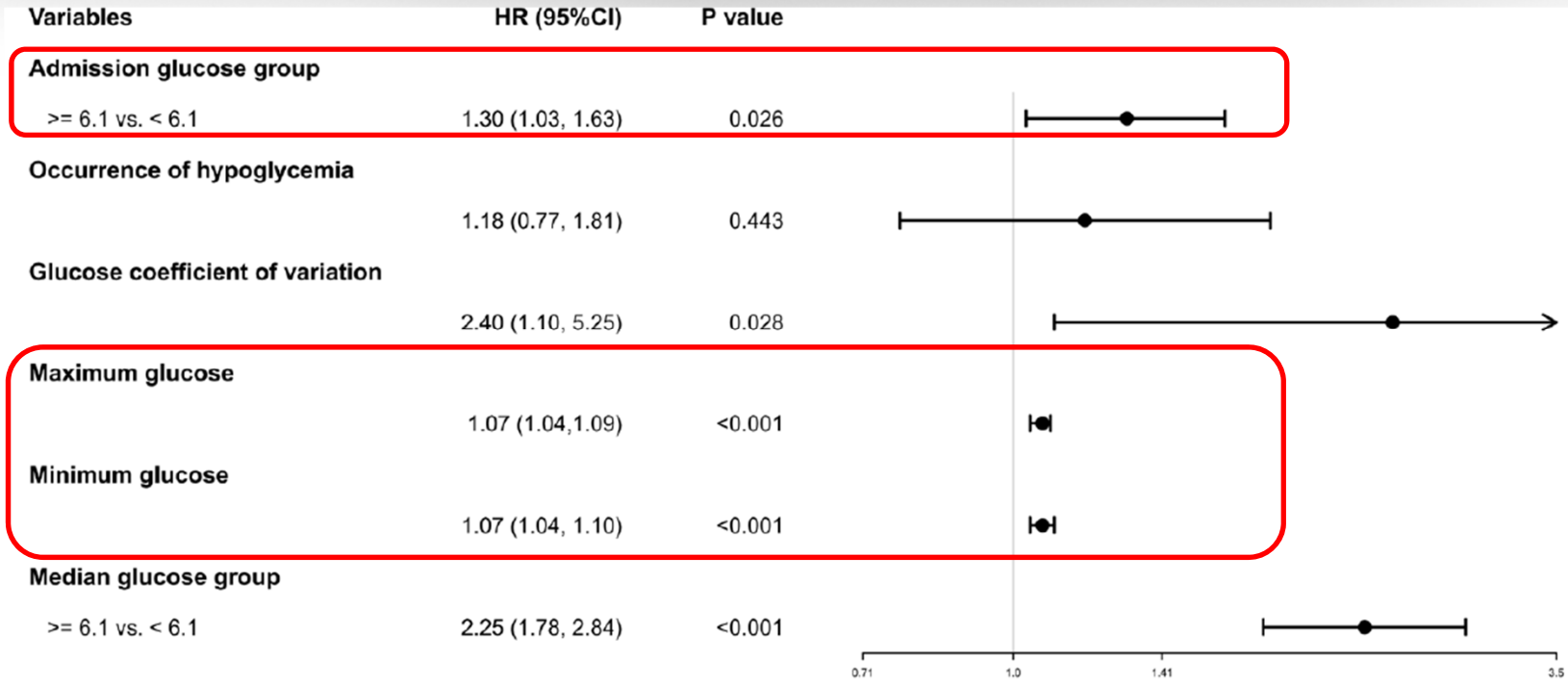
aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; vWF, von Willebrand factor

[a] Measured during ICU stay

- *D-dimer and fibrinogen were elevated in most severe cases.*
- *Activity and antigens of coagulation factor VIII and vWF were also significantly increased*
- *Abnormal blood coagulation in severe cases may be closely related to epithelial inflammation. Hypoxemia activates the HIF pathway, which leads to the overexpression of PAI-1 gene. Weakened scavenging capacity of fibrin is weakened, and normal gas exchange is obstructed, which is closely related to poor outcome.*

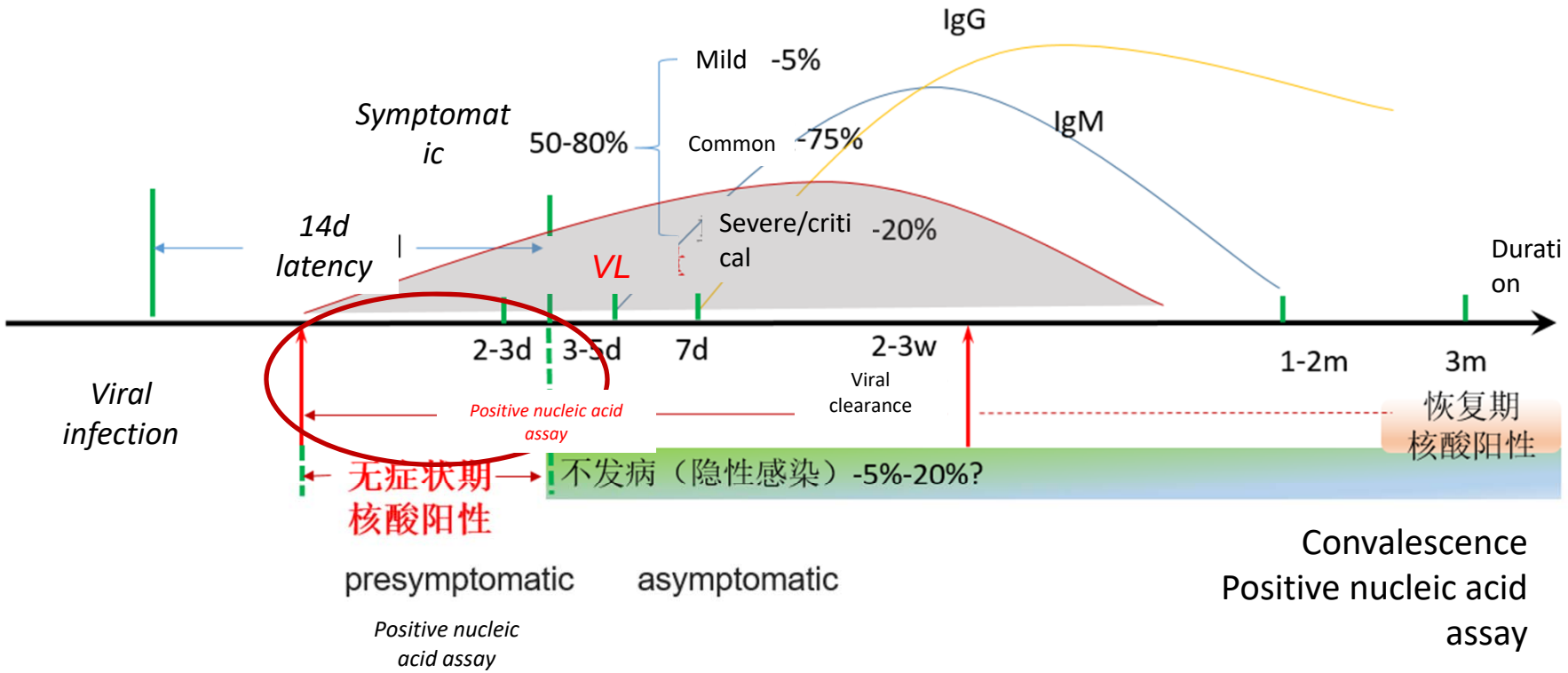
Helms J et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020 Jun;46(6):1089-1098.

Elevated blood glucose is a high-risk factor for the aggravation of inpatients with mild symptoms

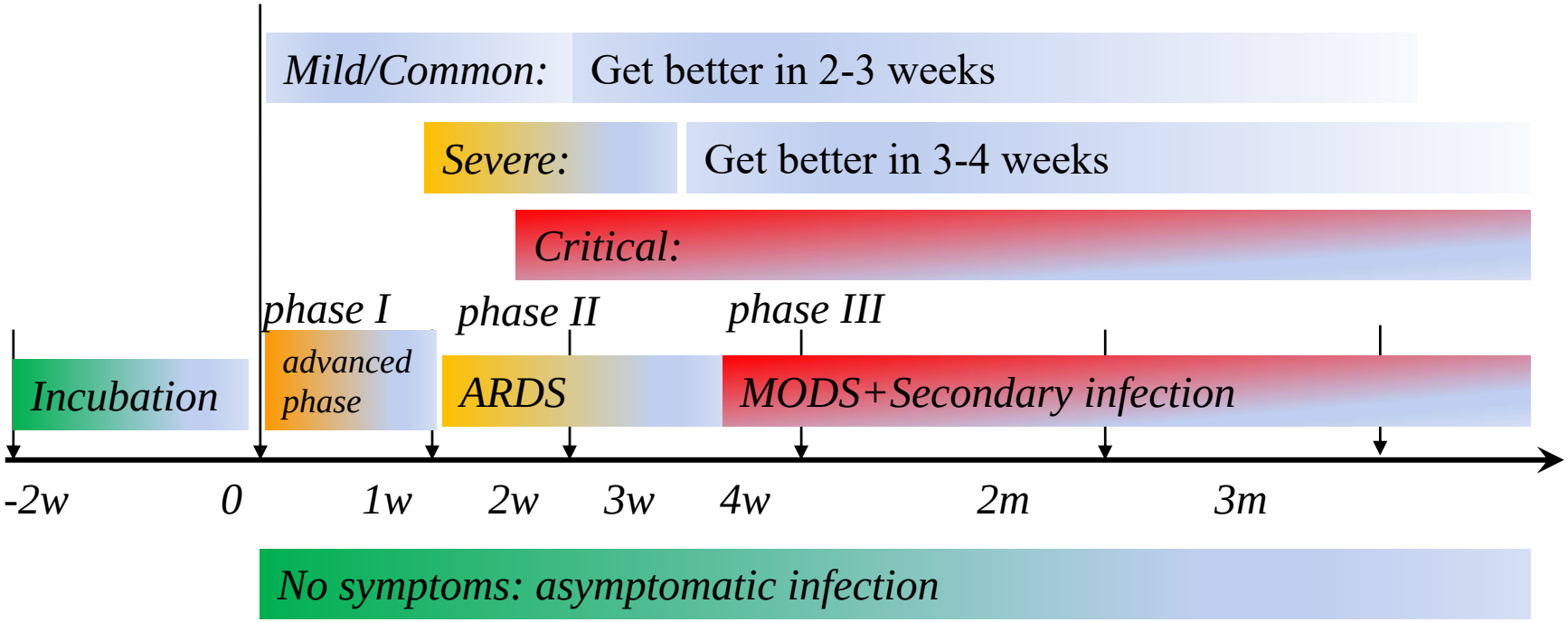


- *Admission glucose is an independent risk factor for aggravation (HR=1.30, 95% CI 1.03 to 1.63, p=0.026)*
- *Maximum glucose (HR=1.07, 95% CI 1.04 to 1.09) and minimum glucose (HR=1.07, 95% CI 1.04 to 1.10) are important independent risk factors for aggravation*
- *Median in-hospital glucose is closely related to the aggravation of mild patients (HR=2.25, 95% CI 1.78 to 2.84, p<0.001)*

Wu JF et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diabetes Res Care . 2020 Jun;8(1):e001476.



Transformation of SARS-CoV-2



The transformation process of various types of COVID-19

Diagnostic criteria

- (1) Suspected cases
- (2) Confirmed cases

(1) Suspected cases

1. Epidemiological history

(1) Travel or residence history in the community where the case was reported within 14 days before the onset;

(2) Contact history with 2019-nCov infected persons (nucleic acid test positive) within 14 days before onset;

(3) Contact history with patients with fever or respiratory symptoms from communities with case reports within 14 days before onset;

(4) Cluster outbreak (2 or more cases of fever and/or respiratory symptoms occurred in a small area such as home, office, school, etc.) within 2 weeks.

2. Clinical manifestations

(1) Clinical manifestations of COVID-19, such as fever and/or respiratory symptoms;

(2) The above-mentioned imaging characteristics of COVID-19;

（(3) The total number of white blood cells is normal or decreased in the early stage of the disease, and the lymphocyte count is normal or decreased.

Patient who has any one of the epidemiological history, and meets any 2 of the clinical manifestations should be diagnosed as suspected cases.

No clear epidemiological history, or in line with 3 of the clinical manifestations.

(2) Confirmed cases

Suspected cases with one of the following etiological or serological evidence:

- 1.2019-nCov nucleic acid positive detected by real-time fluorescent RT-PCR
- 2. Viral gene sequencing, highly homologous to the known 2019-nCov;
- 3. Specific IgM and IgG antibody of 2019-nCov are positive;
- 4. Specific IgG antibody of 2019-nCov turns from negative to positive, or the recovery period' is 4 times or more higher than the acute period'.

Mild and Common cases

- Mild cases (about 5%)
  - ✓ The clinical symptoms were mild, and no manifestations of pneumonia were found on imaging

- Common cases (about 75%)
  - ✓ With fever, respiratory symptoms and other symptoms, imaging can show pneumonia

Severe cases（7-8 days） （about 15%）

- One of the following situations:

1. Increased respiratory rate (≥30 times/min), dyspnea, cyanosis

2. In the resting state, the oxygen saturation is ≤93%

3. $PaO_2/FiO_2 \leq 300mmHg$

（1mmHg=0.133kPa）

4. Pulmonary imaging shows that the lesion has progressed significantly> 50% within 24 to 48 hours;

5.Age> 70 years old, combined with serious chronic diseases, including hypertension and diabete, coronary heart disease, malignant tumor, structural lung disease, pulmonary heart disease and immunosuppression.

- In high altitude (altitude over 1000 meters), PaO2/FiO2 should be corrected according to the following formula: PaO2/FiO2 × [Atmospheric pressure (mmHg)/760]".

Critical cases（about 5%）

- Meet any of the following:

1. Respiratory failure occurs and mechanical ventilation is required

2. Shock

3. Combined with other organ failure, ICU monitoring and treatment is required

Risk assessment of severe cases

High risk

- Age ≥65 years
- background disease：
  - Chronic lung disease or moderate to severe asthma
  - Cardiovascular disease (including hypertension)
  - Diabetes mellitus
  - Chronic kidney disease (undergoing dialysis)、Chronic liver disease
- Immunocompromising condition
- Severe obesity (body mass index [BMI] ≥30 kg/m^2)
- Residence in a nursing home or long-term care facility
- Tobacco use

Early-warning indicators of severe and critical cases

• Adult

- Progressive decline of peripheral blood lymphocytes;

-Progressive increase of peripheral inflammatory factors such as IL-6 and C-reactive protein;

- Progressive increase of lactic acid;

- Progressive increase of D- dimer

- Intrapulmonary lesions progress rapidly in a short time.

Clinical management strategies for non-severe cases

- Principle: classified treatment, full-process management
- Monitoring: vital signs (especially RR, SpO2), laboratory tests
- Symptomatic, supportive treatment, psychological support
- Etiological treatment: Antiviral therapy?
- TCM therapy
- Simultaneous treatment of background diseases and complications

Determine the treatment site based on the severity of the condition

- Suspected and confirmed cases should be isolated and treated in designated hospitals;
- Suspected cases should be treated in isolation in a single room;
- Multiple confirmed cases can be admitted to the same ward;
- Critical and severe cases should be admitted to the ICU for treatment as soon as possible.

Vital signs + SpO2 monitoring

- Patients within 2 weeks of onset or within 1 week of admission:
  - ✓T, RR, HR, BP, SpO2:
  - ✓Asymptomatic and mild cases: monitored twice a day
  - ✓Common and high-risk cases: monitored at least 4 times a day

Laboratory inspection and monitoring

- WBC and its classification, especially L (conditional T cell subsets)
- Full set of biochemistry (liver function, kidney function, blood sugar, etc.)
- Cardiac enzymes: creatine kinase (CK), lactate dehydrogenase, myoglobin, troponin
- Ferritin
- Inflammation indicators: C reactive protein (CRP), PCT, IL-6
- Coagulation function: prothrombin time (PT)/partial prothrombin time (APTT)/fibrinogen/D-dimer
- Electrocardiogram (ECG)/QTc (extended)
- Lung CT

- Severe high-risk cases and cases with early warning indicators of severe cases : review every 3 days
- Asymptomatic, mild, and cases with no high-risk factors: review every 7 days
- Critical value: treatment and review on the same day, such as hypoxemia, hypokalemia, high lactate, etc.

Ward management recommendations

Take 40 beds as an example:

- Recommended number: doctors: 9-11; nurses: 20-32
  - ✓ 4-8 people in day shift, 2-4 people in night shift
  - ✓ 1 director, 2 attending physicians; 1 head nurse, 2 nurses group leader

夜：Night
白： Day

	姓名	Mon	Tus	Wed	Thurs	Fri	Sat	Sun
Doctor 1	医生1	夜		白	白	夜		白
Doctor 2	医生2	夜		白	白	夜		白
Doctor 3	医生3	白	夜		白	白	夜	
Doctor 4	医生4	白	夜		白	白	夜	
Doctor5	医生5	白	白	夜		白	白	夜
Doctor 6	医生6	白	白	夜		白	白	夜
Doctor 7	医生7		白	白	夜		白	白
Doctor8	医生8		白	白	夜		白	白
Attendin g 1	主诊1	白	白	白		白	白	
Attendin g 2	主诊2	白	白	白	白			白
Director	主任	白	白	白	白	白		

Treatment goals for non-ICU patients

- Reduce or avoid the occurrence of severe illness
- Identify severe cases in time and transfer them to ICU

What about those with high risk factors or tendency to severe illness?

- Symptomatic and supportive treatment, cooling, nutrition, psychological support
- Pathogen treatment:
  - ✓ Convalescent plasma
  - ✓ Antiviral drugs
- Immunomodulatory: thymosin
- Hormone therapy:
- Treatment of basic diseases, heart disease, hypertension, diabetes, etc
- Oxygen therapy: nasal catheter, mask oxygen, transnasal high flow, autonomic prone position
- Back pat, sputum drainage

Specific treatment for COVID-19?

- **Interferon α/β atomization**
- **Lopinavir-ritonavir**
- **Ribavirin**
- **Hydroxychloroquine/chloroquine** : potential toxicity
- **Arbidol**
- **Convalescent plasma**
- **IL-6 pathway inhibitors** — Tocilizumab
- **Which is not listed in the diagnosis and treatment plan:**
  - ✓ **Remdesivir**
  - ✓ **Favipiravir**

Remdesivir

- Remdesivir is endorsed for severely ill COVID-19 patients in the United States, India, and South Korea, and it's approved in Japan.
- The European Medicines Agency has recommended the conditional approval of remdesivir for COVID-19 patients over 12 years of age with pneumonia who require oxygen support.

Prevention of venous thromboembolism (VTE)

- Increased D-dimer levels are associated with poor prognosis (e.g., 6 times or more than the upper limit of the normal)
- Prevention: Low molecular heparin (LMWH;e.g, enoxaparin 40 mg SC once Daily)
- Intensification: 0.5 mg/kg enoxaparin every 12 hours/7500 units of unfractionated heparin every 8 hours and/or use of mechanical devices (patients with creatinine clearance <30 mL/min, enoxaparin should be reduced to 30 mg per day, or according to the severity of renal insufficiency and the patient's weight change to unfractionated heparin)
- Fondaparinux (clotting factor Xa inhibitor): For patients with heparin-induced thrombocytopenia

Others

- Antibacterial drugs:
  - ✓If there is no clear evidence of bacterial infection, routine use of antibacterial drugs is not recommended.
  - ✓Actively monitor respiratory tract pathogens and carry out targeted anti-infective treatment.
- Management of medication for underlying disease

Dexamethasone

- The National Institutes of Health COVID-19 Treatment Guidelines Panel

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**.

Glucocorticoids

Section last reviewed and updated 6/25/20

Recommendation 4. Among hospitalized patients with severe* COVID-19, the IDSA guideline panel suggests glucocorticoids rather than no glucocorticoids. (Conditional recommendation, Moderate certainty of evidence)

- **Remark:** Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

*Severe illness is defined as patients with SpO_2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or extracorporeal mechanical oxygenation (ECMO).

Recommendations for hormone use

- Indications: persistent high fever, significantly increased inflammatory markers, rapid lung imaging progress
- Equivalent to methylprednisolone 0.5 ~ 1mg/kg/ day, 3-5 days
- Attention should be paid to the immune suppression, the effect of blood sugar, the delay in virus clearance, etc， caused by hormones

Immunomodulatory

- Thymosin 1 is recommended for severe patients with low lymphocyte count and low cellular immune function;
- The intestinal microecological regulator can be used to maintain the intestinal microecological balance;
- As for the use of proprietary Chinese medicines, xuebijing may be considered, although it is currently in clinical trials.

National Health Comission: Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia(Trial Version 7)

Convalescent plasma

Table 3. Primary and Secondary Clinical Outcomes at Day 28[a]

	Convalescent plasma group (n = 52)	Control group (n = 51)	Absolute difference (95% CI)[b]	Effect estimate (95% CI)	*P* value[c]
All patients					
Primary clinical outcome					
Time to clinical improvement, median (IQR),d[d]	28.00 (13.00-Indeterminate)	Indeterminate (18.00-Indeterminate)	−2.15 (−5.28 to 0.99)	HR, 1.40 (0.79-2.49)	.26
Clinical improvement rate, No./total (%)[e]					
At day 7	5/52 (9.6)	5/51 (9.8)	−0.2% (−11.6% to 11.2%)	OR, 0.98 (0.30-3.19)	.97
At day 14	17/52 (32.7)	9/51 (17.6)	15.0% (−1.4% to 31.5%)	OR, 1.85 (0.91-3.77)	.08
At day 28	27/52 (51.9)	22/51 (43.1)	8.8% (−10.4% to 28.0%)	OR, 1.20 (0.80-1.81)	.37
Secondary clinical outcomes					
Discharge rate at 28 d, No./total (%)	26/51 (51.0)	18/50 (36.0)	15.0% (−4.1% to 34.1%)	OR, 1.42 (0.90-2.24)	.13
Time from randomization to discharge, median (IQR), d[d]	28.00 (13.00-Indeterminate)	Indeterminate (19.00-Indeterminate)	−2.43 (−5.56 to 0.69)	HR, 1.61 (0.88-2.93)	.12
Time from hospitalization to discharge, median (IQR),d[d]	41.00 (31.00-Indeterminate)	53.00 (35.00-Indeterminate)	−11.95 (−26.33 to 2.43)	HR, 1.68 (0.92-3.08)	.09
Mortality at 28 d, No./total (%)	8/51 (15.7)	12/50 (24.0)	−8.3% (−23.8% to 7.2%)	OR, 0.65 (0.29-1.46)	.30
Time from randomization to death, median (IQR), d[d]	Indeterminate	Indeterminate (26.00-Indeterminate)	0.52 (−2.10 to 3.14)	HR, 0.74 (0.30-1.82)	.52
Viral nucleic acid negative rate, No./total (%)					
At 24 h	21/47 (44.7)	6/40 (15.0)	29.7% (11.7% to 47.7%)	OR, 4.58 (1.62-12.96)	.003
At 48 h	32/47 (68.1)	13/40 (32.5)	35.6% (15.9% to 55.3%)	OR, 4.43 (1.80-10.92)	.001
At 72 h	41/47 (87.2)	15/40 (37.5)	49.7% (32.0% to 67.5%)	OR, 11.39 (3.91-33.18)	<.001

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Convalescent plasma

Patients with severe disease					
Primary clinical outcome					
Time to clinical improvement, median (IQR), d[d]	13.00 (9.00-21.00)	19.00 (15.00-Indeterminate)	−4.94 (−9.33 to −0.54)	HR, 2.15 (1.07-4.32)	.03
Clinical improvement rate, No./total (%)[e]					
At day 7	3/23 (13.0)	4/22 (18.2)	−5.1% (−26.3% to 16.1%)	OR, 0.72 (0.18-2.85)	.70
At day 14	14/23 (60.9)	6/22 (27.3)	33.6% (6.3% to 60.9%)	OR, 2.23 (1.05-4.76)	.02
At day 28	21/23 (91.3)	15/22 (68.2)	23.1% (−3.9% to 50.2%)	OR, 1.34 (0.98-1.83)	.07
Secondary clinical outcomes					
Discharge rate at 28 d, No./total (%)	21/23 (91.3)	15/22 (68.2)	23.1% (−3.9% to 50.2%)	OR, 1.34 (0.98-1.83)	.07
Time from randomization to discharge, median (IQR), d[d]	13.00 (10.00-16.00)	19.00 (11.00-Indeterminate)	−4.09 (−8.44 to 0.27)	HR, 1.97 (1.00-3.88)	.05
Time from hospitalization to discharge, median (IQR), d	32.00 (26.00-40.00)	41.00 (30.00-53.00)	−9.38(−23.63 to 4.88)	HR, 1.74 (0.89-3.41)	.11
Mortality at 28 d, No./total (%)	0/23	2/22 (9.1)	−9.1% (−25.6% to 7.4%)		.49
Time from randomization to death, median (IQR), d[d]	Indeterminate	Indeterminate (26.00-Indeterminate)	1.42 (−0.88 to 3.71)	HR, 0.00	>.99
Viral nucleic acid negative rate, No./total (%)					
At 24 h	7/21 (33.3)	2/17 (11.8)	21.6% (−9.1% to 52.2%)	OR, 3.75 (0.66-21.20)	.15
At 48 h	13/21 (61.9)	6/17 (35.3)	26.6% (−4.2% to 57.4%)	OR, 2.98 (0.79-11.25)	.10
At 72 h	19/21 (90.5)	7/17 (41.2)	49.3% (22.7% to 75.9%)	OR, 13.57(2.36-77.95)	<.001

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Convalescent plasma

Patients with life-threatening disease					
Primary clinical outcome					
Time to clinical improvement, median (IQR), d[d]	Indeterminate	Indeterminate	0.23 (−3.11 to 3.57)	HR, 0.88 (0.30-2.63)	.83
Clinical improvement rate, No./total (%)[e]					
At day 7	2/29 (6.9)	1/29 (3.4)	3.4% (−11.4% to 18.3%)	OR, 2.00 (0.19-20.86)	>.99
At day 14	3/29 (10.3)	3/29 (10.3)	0.0% (−19.1% to 19.1%)	OR, 1.00 (0.22-4.55)	>.99
At day 28	6/29 (20.7)	7/29 (24.1)	−3.4% (−24.9% to 18.0%)	OR, 0.86 (0.33-2.24)	.75
Secondary clinical outcomes					
Discharge rate at 28 d, No./total (%)	5/28 (17.9)	3/28 (10.7)	7.1% (−14.7% to 28.9%)	OR, 1.67 (0.44-6.32)	.71
Time from randomization to discharge, median (IQR), d[d]	Indeterminate	Indeterminate	−0.80 (−3.74 to 2.14)	HR, 1.77 (0.42-7.40)	.44
Time from hospitalization to discharge, median (IQR), d[d]	Indeterminate (46.00-Indeterminate)	Indeterminate	−4.61 (−15.07 to 5.85)	HR, 1.90 (0.45-8.04)	.38
Mortality at 28 d, No./total (%)	8/28 (28.6)	10/28 (35.7)	−7.1% (−31.5% to 17.2%)	OR, 0.80 (0.37-1.72)	.57
Time from randomization to death, median (IQR), d[d]	Indeterminate (22.00-Indeterminate)	Indeterminate (15.00-Indeterminate)	−0.04 (−3.86 to 3.77)	HR, 0.86 (0.34-2.17)	.74
Viral nucleic acid negative rate, No./total (%)					
At 24 h	14/26 (53.8)	4/23 (17.4)	36.5% (11.8% to 61.1%)	OR, 5.54 (1.47-20.86)	.01
At 48 h	19/26 (73.1)	7/23 (30.4)	42.6% (17.3% to 68.0%)	OR, 6.20 (1.79-21.46)	.003
At 72 h	22/26 (84.6)	8/23 (34.8)	49.8% (25.9% to 73.7%)	OR, 10.31(2.63-40.50)	<.001

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Evaluation and management of severe cases

- Most of the severe cases get worse within 1 week of onset
- Determining when endotracheal intubation should be performed is very important
- After intubation, patients should receive lung-protective ventilation with plateau pressure less than or equal to 30 cm of water
- Prone positioning is a potential treatment strategy for refractory hypoxemia.
- Thrombosis and renal failure are well-recognized complications of severe COVID-19.
- the benefits and risks of antiviral or immunomodulatory therapies for severe COVID-19 need to be evaluated.

Treatment of severe and critical cases

Therapeutic principles

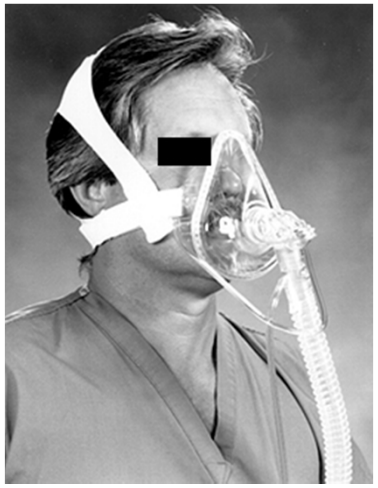
- Rest in bed, support treatment, and ensure adequate calories;
- Maintain water, electrolyte and acid-base balance, and blood sugar control;
- Fever management;
- Timely oxygen therapy, mechanical ventilation and other life support measures to prevent and treat complications;
- Treatment of underlying diseases;
- Prevention of secondary infection (protective isolation);
- Clotting function, stress ulcer;
- Patients often have anxiety and fear, so psychological counseling should be strengthened.

National Health Commission: Diagnosis and Treatment Protocol for the Severe and Critcial Novol Coronavirus Pneumonia Cases (Trial Version 2)

2. Oxygen therapy and respiratory support

- (1) In patients with hypoxemia, PaO2/FiO2 is 200-300mmhg.
- 1) Nasal catheter or mask should be used for oxygen inhalation, and whether respiratory distress and/or hypoxemia is relieved should be evaluated in a timely manner
  - ✓ The oxygen flow of nasal cannula generally does not exceed 5L/min;
  - ✓ The oxygen flow of mask oxygen therapy is generally 5-10L/min.

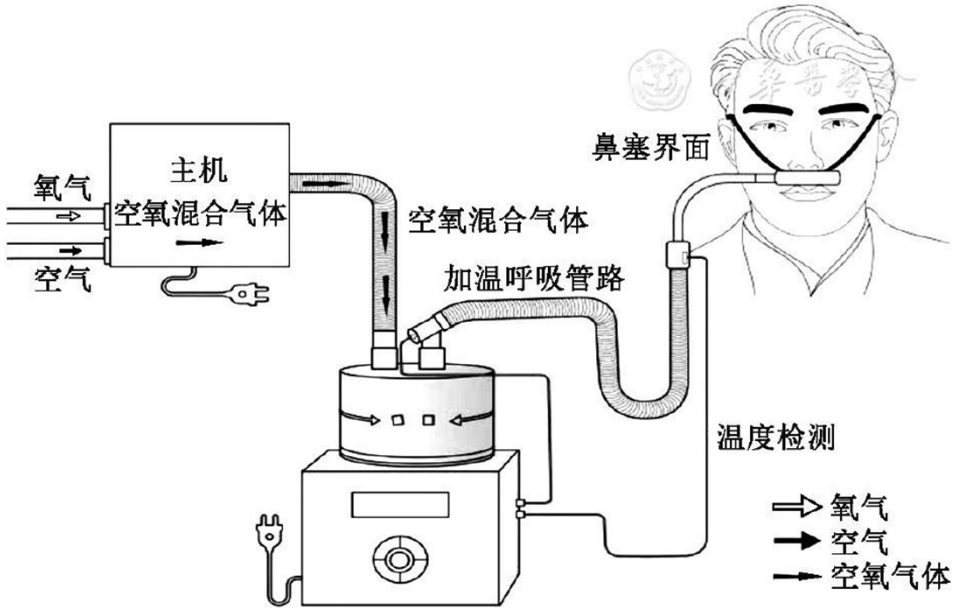




National Health Commission: Diagnosis and Treatment Protocol for the Severe and Critical Novel Coronavirus Pneumonia Cases (Trial Version 2)

2. Oxygen therapy and respiratory support

- (1) In patients with hypoxemia, PaO2/FiO2 is 200-300mmhg.
- 2) **High-flow nasal cannula oxygen therapy (HFNC)**： HFNC should be used when respiratory distress and/or hypoxemia does not improve 2 h after patients receive nasal catheter or mask oxygen therapy.



National Health Commission: Diagnosis and Treatment Protocol for the Severe and Critical Novel Coronavirus Pneumonia Cases (Trial Version 2)

2. Oxygen therapy and respiratory support

- (2) In patients with hypoxemia, PaO2/FiO2 is 150-200mmHg.
- NIV treatment is preferred.
- The initial parameters are set to 8-10 cmH2O for inspiratory positive airway pressure (IPAP), 5-8 cmH2O for expiratory positive airway pressure (EPAP), and FiO2 100%.
- Previous studies on the treatment of ARDS with NIV have suggested that Vt>9 ml/kg is an independent risk factor for NIV failure and even increased mortality.
- The failure rate of treatment with noninvasive mechanical ventilation in such patients is high and should be closely monitored.
- If the condition does not improve or even worsen within a short time (1-2h), endotracheal intubation and invasive mechanical ventilation should be performed in time.

Crit Care Med, 2016, 44(2): 282-290.
National Health Commission: Diagnosis and Treatment Protocol for the Severe and Critical Novel Coronavirus Pneumonia Cases (Trial Version 2)

Mask oxygen/transnasal high flow/non-invasive ventilator

- Implement "awake prone position": at least 12 hours a day
- Aerosol transmission?
- Aerosol inhalation?
- Endotracheal intubation?

2. Oxygen therapy and respiratory support

- (3) In patients with hypoxemia, PaO2/FiO2 is less than 150mmHg.
- 1) Invasive mechanical ventilation.

-In the following cases, intubation and invasive mechanical ventilation should be performed in a timely manner.

-Increased respiratory distress or excessive inspiratory effort: hypoxemia cannot be improved during HFNC or NIV treatment (SpOz≤93%), or increased respiratory frequency (RR≥35 beats/min), excessive tidal volume (> 9～10ml/kg ideal body weight), or excessive inhalation effort.

-Tissue hypoxia or progressive increase in lactic acid: when HFNC or NIV treatment is performed, tissue hypoxia is aggravated, such as progressive increase in lactic acid or progressive decrease in central venous oxygen saturation (ScvOz).

-Hemodynamic instability or disturbance of consciousness: When HFNC or NIV treatment is performed, if consciousness disturbance or shock still exists, invasive mechanical ventilation treatment should be started immediately.

Clinical application of respiratory support therapy and extracorporeal membrane oxygenation in severe patients with COVID-19 (trial)

2. Oxygen therapy and respiratory support

- (3) In patients with hypoxemia, PaO2/FiO2 is less than 150mmHg.
- 1) Invasive mechanical ventilation.
- Implement lung protective mechanical ventilation strategy, that is, low tidal volume (4-6ml/kg ideal body weight) and low inspiratory pressure (platform pressure <30cmH2O) for mechanical ventilation to reduce ventilator-related lung injury;
- Recruitability of the lungs should be evaluated, and PEEP should be set according to the optimal oxygen method or FiO2-PEEP correspondence table (ARDSnet's low PEEP setting method).
- SpO2 remained at 88%-95%.

Ideal weight (kg) for male =50+0.91× [height (cm) -152.4]

Ideal weight (kg) for women =45.5+0.91× [height (cm) -152.4]

NHC China: Protocol on diagnosis and treatment of severe and critical COVID-19 cases (trial version 2)

2. Oxygen therapy and respiratory support

- 2) Lung recruitment.
- If invasive mechanical ventilation with FiO2 above 0.5 is required to achieve the goal of oxygenation (or meet the criteria for moderate to severe ARDS), lung recruitment therapy can be adopted.Before lung recruitment,recruitability of the lungs should be evaluated through ultrasound, P-V curve, and electrical impedance imaging (EIT), etc.
- 3) Prone ventilation.
- If PaO2/FiO2 is consistently below 150mmHg, prone ventilation should be considered for more than 16 hours per day.

NHC China: Protocol on diagnosis and treatment of severe and critical COVID-19 cases (trial version 2)

Conclusion

- Severe cases are converted from non-severe cases (7-8 days)
- In order to prevent the transformation from non-severe to severe,it is necessary to pay close attention to the high-risk group and the early warning indicators of severe cases,provide symptomatic supportive treatment, immune regulation, and take into account the underlying disease. When ARDS is complicated, timely non-invasive/invasive ventilation is required to prevent secondary infections.
- Case fatality rate:
  - ✓ 0 death in Wuhan Sanmin Community: 7 confirmed cases, 5 of htem over 70 years old, 3 severe cases and 1 critical case (ECMO)
  - ✓ 0 death of imported cases from abroad
  - ✓ 0 deaths from the epidemic in Xinfadi, Beijing

Thank you!