COVID-19 Clinical Spectrum, Complications, and Coinfections

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The ongoing COVID-19 Pandemic

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

Overview of COVID-19

- Emerging Infectious Disease
- Presented mainly as viral pneumonia-respiratory borne illness, easily spread person to person
- It is insidious and treacherous
  - Asymptomatic infected people can spread the disease
- Relatively high degree of morbidity and death risk
- Devastating particularly to subset of population
  - Elderly, those with underlying conditions (heart disease, lung disease, diabetes, obesity)
SARS-CoV-2

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

*China National Health Commission. Clinical Protocols for the Diagnosis and Treatment of COVID-19 (Trial 7th version); 2020*
SARS-CoV-2 transmission

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

Examples of potential transmission routes of SARS-CoV-2

Thushara Galbadage et al. Front Public Health. 2020; 8:163
W. Joost Wiersinga et al. JAMA. 2020; 324(8):782-793
SARS-CoV-2 interacts with ACE2 as host cell receptor and the Spike protein is primed by protease TMPRSS2

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

Arno R. Bourgonje et al. J Pathol. 2020; DOI:10.1002/path.5471
Daniel Wrapp et al. Science. 2020; 367, 1260–1263
Disease spectrum of COVID-19

- **81% were mild status**
  - No pneumonia or mild pneumonia

- **14% were severe status**
  - Dyspnea or Respiratory Rate ≥ 30/min or SpO$_2$ < 93% or PaO$_2$/FiO$_2$ <300 mmHg
  - Lung infiltrates >50% within 24 to 48 hours

- **5% were critical ill status**
  - Needs mechanical ventilation
  - Shock
  - Complicated with other organ failure required ICU admission

Zunyou Wu et al. JAMA. 2020; 323(13):1239-1242
Disease onset of COVID-19 patients

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

<table>
<thead>
<tr>
<th>Common symptoms</th>
<th>N%</th>
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</thead>
<tbody>
<tr>
<td>Fever</td>
<td>83-99%</td>
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<tr>
<td>Cough</td>
<td>60-82%</td>
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<tr>
<td>Fatigue</td>
<td>44-70%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>40-84%</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>31-40%</td>
</tr>
<tr>
<td>Myalgias</td>
<td>11-35%</td>
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<tr>
<td>Other non-specific symptoms</td>
<td></td>
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<tr>
<td>Sore throat, nasal congestion,</td>
<td></td>
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<tr>
<td>Headache, diarrhea, nausea and</td>
<td></td>
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<tr>
<td>Vomiting</td>
<td></td>
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<tr>
<td>Olfactory and/or gustatory</td>
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</tr>
<tr>
<td>Dysfunctions are also reported</td>
<td></td>
</tr>
<tr>
<td>in many patients, ranging from</td>
<td></td>
</tr>
<tr>
<td>5-98% in different cohort. Most</td>
<td></td>
</tr>
<tr>
<td>studies used patient-reported</td>
<td></td>
</tr>
<tr>
<td>symptoms but not objective function tests.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Common comorbidities</th>
<th>N%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>48-57%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17-34%</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>21-28%</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>4-10%</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3-13%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6-8%</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

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

Tom Wai-Hin Chung et al. Open Forum Infect Dis;7(6)
W. Joost Wiersinga et al. JAMA. 2020; 324(8):782-793
WHO. Clinical management of COVID-19: Interim guidance
Duration of dyspnea was 13 days in survivors

45% survivors still had cough on discharge

Median duration of viral shedding was 20 days, could prolong as 37 days

lymphocyte count was lowest on day 7 after illness onset and improved during hospitalization in survivors but whereas severe lymphopenia was observed until death in non-survivors.
CT patterns change over time

Hyperinflammatory response in severe COVID-19 patients

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

Host-directed therapies might be an option

Chaolin Huang et al. Lancet. 2020; 395(10223): 497-506
Jing Liu et al. EBioMedicine. 2020;55:102763
Risk factors for severe/critical illness or death
Listed in the literature

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

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

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

Rachel E Jordan. BMJ 2020;368:m1198
Disease severity is influenced by both viral infection and host response

- **Direct mechanism** – SARS-CoV-2 infection:
  - SARS-CoV-2 infiltration, replication;
  - Death and injury of virus-infected cells/tissues;
  - Primary organ damage;

- **Indirect mechanism** – Host response:
  - Dysfunctional immune response;
  - Cytokine storm syndrome;
  - Secondary organ damage;

_Akbarshakh Akhmerov et al. Circ Res. 2020;126:1443–1455_  
SARS-CoV-2 Viral sepsis—Observations and Hypotheses

Multi-organ dysfunction

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

——Viral Sepsis

Lili Ren et al. Chin Med J 2020; 133(9):1015-1024
Chaolin Huang et al. Lancet 2020; 395(10223): 497-506
Hui Li et al. Lancet. 2020;395(10235):1517-1520
COVID-19 ARDS — Perspective from a large cohort in Spain

- A total of 742 patients were analyzed with complete 28-day outcome data: 128 (17.1%) with mild, 331 (44.6%) with moderate, and 283 (38.1%) with severe ARDS.

- Clinical features are similar with non-COVID-19 ARDS:
- At baseline, defined as the first day on invasive MV, median (IQR) values were: tidal volume 6.9 (6.3–7.8) ml/kg predicted body weight, positive end-expiratory pressure 12 (11–14) cmH₂O. Values of respiratory system compliance 35 (27–45) ml/cmH₂O, plateau pressure 25 (22–29) cmH₂O, and driving pressure 12 (10–16) cmH₂O were similar to values from non-COVID-19 ARDS patients observed in other studies.

- The risk of 28-day mortality was lower in mild ARDS [RR 0.56 (95% CI 0.33–0.93), p = 0.026] and moderate ARDS [RR 0.69 (95% CI 0.47–0.97), p = 0.035] when compared to severe ARDS.

- The 28-day mortality was similar to other observational studies in non-COVID-19 ARDS patients.

Common extrapulmonary manifestations and complications

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

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

Jutzeler CR, et al. Travel Med Infect Dis. 2020; 37:101825
COVID-19 and hyper-coagulation

D-Dimer > 1μg/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.

Autopsy Findings from 12 patients in German

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

COVID-19 and kidney injury

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

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

COVID-19 and cardiac injury

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

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

Akbarshakh Akhmerov et al. Circ Res. 2020;126:1443–1455
Searching for magic bullets of COVID-19

1804 randomized trials have been registered globally

Potential therapeutic targets

- Potential anti-viral drugs:
  - Remdesivir
  - Lopinavir-Ritonavir
  - Hydroxychloroquine
  - Favipiravir
  - Ribavirin
  - Monoclonal antibody

- Potential immunomodulator:
  - Corticosteroids
  - Convalescent plasma
  - IL-6R inhibitors
  - JAK inhibitors
  - Interferon beta

Antiviral + Immunomodulatory drugs might be the future
Drug treatments for covid-19: A living network meta-analysis

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

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Mortality</th>
<th>Mechanical ventilation</th>
<th>Admission to hospital</th>
<th>Duration of hospital stay</th>
<th>ICU length of stay</th>
<th>Duration of mechanical ventilation</th>
<th>Time to symptom resolution</th>
<th>Time to viral clearance</th>
</tr>
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<tbody>
<tr>
<td>Glucocorticoids</td>
<td>233/130 to 472b</td>
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<tr>
<td>Remdesivir</td>
<td>91/115 to 46b</td>
<td>22/24 to 83b</td>
<td>22/24 to 83b</td>
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</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>900/000 to 23b</td>
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Reed Ac Siemieniuk et al. BMJ 2020; 370:m2980
Uncertainties still remain for systemic corticosteroids

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

Fully evaluation of benefits and risks before initiation of systemic corticosteroids
A question to discuss: What is the real death risk of COVID-19?

- As of 2020/9/23, there has been 31425029 confirmed cases and 967164 confirmed deaths (WHO data).
- Is the death risk of COVID-19 3.1% (967164/31425029)?
- Case fatality rate of COVID-19 = \( \frac{\text{Number of COVID-19 deaths}}{\text{Total Number of COVID-19 patients}} \)
- Both the numerator and denominator of the above formula is not accurate in the pandemic:
  - Numerator: In pandemic-stricken area with limited medical resources, some COVID-19 related deaths failed to be attributed to COVID-19.
  - Denominator: A large number of cases are not diagnosed in the pandemic.
    - First, the ability of nucleic testing in many countries/regions will influence the diagnosis rate of COVID-19, especially in the areas with rapidly rising suspected cases.
    - Second, the asymptomatic infected individuals may not receive test and will not be diagnosed.
  - The condition of medical resources will also influence the risk of death
- A nationwide sero-epidemiological study in Iceland estimated that only 56% infected individuals were confirmed with PCR
  - The estimated death risk in Iceland is 0.3% (95% CI, 0.2 to 0.6).
- The data from Iceland provided us with some confidence that, if under proper medical care, the death risk of COVID-19 might be controlled under 1%
- Before the vaccines are widely available, more efforts need to be done on enlarging testing scale, quarantine and providing high-quality medical care

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

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

<table>
<thead>
<tr>
<th>China-Japan Friendship Hospital</th>
<th>University of Virginia</th>
<th>Third Military Medical University (Army Medical University)</th>
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<tbody>
<tr>
<td>Chen Wang; Yeming Wang; Fei Zhou; Guohui Fan; Hui Li; Zhibo Liu; Yi Zhang</td>
<td>Frederick G Hayden Oxford University Peter W Horby</td>
<td>Xiuwu Bian</td>
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### Cooperators:

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<thead>
<tr>
<th>Wuhan Jinyintan Hospital</th>
<th>Wuhan Tongji Hospital</th>
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<tbody>
<tr>
<td>Wuhan Lung Hospital</td>
<td>The Central Hospital of Wuhan</td>
</tr>
<tr>
<td>Zhongnan Hospital of Wuhan University</td>
<td>Renmin Hospital of Wuhan University</td>
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<tr>
<td>Union Hospital</td>
<td>Wuhan First hospital</td>
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<tr>
<td>Wuhan Third hospital</td>
<td>Wuhan Fourth hospital</td>
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*All health-care workers involved in the diagnosis and treatment of patients*