# Supplementary Methods

## The 5th edition 2019 Novel Coronavirus Disease (COVID-19) Diagnostic criteria

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### I. Clinical definitions of severe/critical symptoms

1. **Severe symptoms**

Adults who meet any one of the following:

1) Shortness of breath, RR>30 breaths/minute;

2) Oxygen saturation<93% at rest;

3) Arterial oxygen partial pressure (PaO2)/ fraction of inspired oxygen (FiO2)<300mmHg(1mmHg =0.133kPa);

4) The patient should be managed as a severe case if lung imaging shows a substantial progression of lesions (greater than 50%) within 24-48 hours.

**2. Critical symptoms**

Meeting any of the following criteria:

1) Respiratory failure occurs and mechanical ventilation is required;

2) Shock;

3) Combined failure of other organs than require ICU monitoring.

### II. Definitions of severe/critical complications

**Shock and acute respiratory distress syndrome (ARDS)** were defined in accordance with the WHO interim guidance.[1]

**Acute kidney injury** was defined based on the highest serum creatinine level and urine output.[2] Specifically, the diagnosis could be made based on any of the following criterion: an increase in serum creatinine levels by 0.3 mg/dl or greater (26.5 μmol/l or greater) within 48 hours; or increase in serum creatinine levels to 1.5 times of the baseline level or greater, which was known or presumed to have occurred within 7 days; or urine volume of below 0.5 ml/kg/h for 6 consecutive hours.

**Disseminated intravascular coagulation** was diagnosed on the constellation of laboratory markers and a consistent history of an illness known to cause DIC. Laboratory markers consistent with DIC include: Characteristic history, Prolongation of the prothrombin time (PT), the activated partial thromboplastin time (aPTT), fibrinogen level, a rapidly declining platelet count, high levels of fibrin degradation products, the peripheral blood smear may show fragmented red blood cells.[3]

**Rhabdomyolysis** was diagnosed if the muscle pain or muscle weakness took place on admission and the creatine kinase level was greater than 10 times the upper limit of normal.[4]

### III. Diagnostic Criteria, Inclusion/ Exclusion criteria

#### 1. Diagnostic Criteria

**Other provinces except Hubei province**

1. Suspected cases by clinical criteria

Comprehensive screening of the following epidemiological information and clinical manifestations:

1) Epidemiological information

a) Cases reporting a history of travel to or reside in Wuhan city and surrounding areas, or other communities with reported cases within 14 days prior to onset of illness.

b) Cases have been exposed to patients with COVID-19 (confirmed by laboratory diagnosis of SARS-CoV-2 RNA detection) within 14 days prior to onset of illness.

c) Cases have been exposed to patients with fever or respiratory symptoms from Wuhan city and surrounding areas, or other communities with reported cases within 14 days prior to onset of illness.

d) Has contact history with a cluster.

2) Clinical manifestations

a) Fever and/or respiratory symptoms

b) Computed tomography (CT) changes for viral pneumonia

c) Normal or below normal absolute leukocyte count, or low absolute lymphocyte count below normal range in the early stages of the disease.

2. Diagnosis of COVID-19 is made if meeting one of the following:

1) cases report any one of above epidemiological information and harbor any two of the clinical manifestations;

2) cases without the above epidemiological information, but harbor all of the above clinical manifestations.

**Hubei province**

**1.Suspected cases.**

Comprehensively analyze combinations of the following epidemiological history and clinical presentations:

1) Eidemiological history

a) Within 14 days prior to onset, had history of travel or residence in Wuhan or surrounding regions, or other communities reporting cases.

b) Within 14 days prior to symptom onset, having had contact with patients infected with 2019-nCoV (positive nucleic acid test).

c) Within 14 days prior to onset, had contact with patients who had a fever or respiratory tract symptoms that had come from Wuhan, its surrounding regions, or other communities reporting cases.

d) Clustered onset (Within a span of 2 weeks, 2 or more cases with fever and/or respiratory symptoms appear in a small area, such as a family, an office, or a school class).

2) Clinical presentations

a) Fever and/or respiratory tract symptoms;

b) Having the imaging features of novel coronavirus pneumonia discussed above;

c) During the early stages of the disease, white blood cell count is normal or reduced, while the lymphocyte count is normal or reduced;

Diagnosis of COVID-19 is made if meeting one of the following:

1) any of the epidemiologic history items, and any 2 of the clinical presentions are met;

2) there is no clear epidemiological history, and at least 3 of the clinical presentations are met.

**2. Confirmed cases**

1) Clinically diagnosed cases

CT chest changes that are consistent with atypical viral pneumonia.

2) Laboratory confirmed cases

a) Respiratory tract or blood specimen test positive for SARS-CoV2 by real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay.

b) The sequence of the virus is highly homologues to that of SARS-CoV-2.

**2. Inclusion criteria**

Cases diagnosed based on the 2019 Novel Coronavirus Disease (COVID-19) Diagnostic criteria 5th edition will be included.

**3.Exclusion criteria**

No exclusion criteria apply provided that the clinical profiles of the patients are as complete as possible, which would not prevent from the analysis of the composite endpoint.

**IV. Laboratory testing**

Laboratory confirmation of SARS-CoV-2 was achieved through the Chinese Center for Disease Prevention and Control (CDC) before January 23rd. Since January 24th, the National Health Commission has officially approved for confirmation of diagnosis in certified tertiary hospitals across all provinces/autonomous regions/provincial municipalities.[5]

The uniform laboratory testing procedures were adopted across all provinces/autonomous regions/provincial municipalities in China.

The reverse-transcription polymerase chain reaction (RT-PCR) assay was conducted in accordance with the protocol established by the World Health Organization. Extraction of nucleic acids from the respiratory samples was performed with the commercialized nucleic acid extraction kits. The extracted nucleic acids were tested for SARS-CoV-2. The following sequences of SARS-CoV-2 were adopted for the RT-PCR assays. For Open reading frame 1 ab fragment, the forward primer sequence was 5’-CCC

TGTGGGTTTTACACTTAA-3', the reverse primer sequence was 5'-ACGATTGTGCATCAGCTGA-3', and probe sequence was5'-FAM-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3'. For the N region of the viral sequence, the forward primer sequence was 5'-GGGGAACTTCTCCTGCTAGA AT-3', the reverse primer sequence was 5'-CAGACATTTTGCTCTCAAGCTG-3', and the probe sequence was 5'-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3'.

Amplifications were initially done at 50 degree for 10 min and subsequently at 95 degree for 5 min, followed by 40 cycles of 95 degree for 10s and 55 degree for 40s.

The cycle threshold (Ct) of 40 or greater denoted negative findings, whereas the Ct of less than 37 denoted the SARS-CoV-2 being detected. A Ct of greater than 37 but lower than 40 was considered susceptible value, and should be subject to re-testing. SARS-CoV-2 was reported as having been detected if the repeated Ct-value was less than 40 and an obvious peak was observed, or if the repeated Ct-value was less than 37.

**References:**


1. WHO. Clinical management of severe acute respiratory infection when Novel coronavirus (nCoV) infection is suspected: interim guidance. Jan 11, 2020. https://www.who. int/internal-publications-detail/clinical-managementof-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected(accessed February 4th, 2020)

2. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. March, 2012. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf (accessed3 on January 30, 2020)

3.National Heart, Lung and Blood Institute. Disseminated intravascular coagulation. 2016. https://www. nhlbi.nih.gov/health-topics/disseminated-intravascularcoagulation. Accessed December 15, 2017.

4.Graham DJ, Staffa JA, Shatin D, et al. Incidence of Hospitalized Rhabdomyolysis in Patients Treated With Lipid-Lowering Drugs. JAMA 2004;292:2585-90。

5.Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020.