

Outline

I. Introduction

II. Clinical Features

III. Detection and Diagnostic Methods

IV. Prevention and Control Strategies

V. Treatment Options

VI. Long COVID

I. Introduction

COVID-19 (Coronavirus Disease 2019) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). As of 24 December 2023, there were 773,119,173 confirmed cases of COVID-19, including 6,990,067 deaths reported to the World Health Organisation [1].

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus belonging to the *Coronaviridae* family, genus *Betacoronavirus* [2].

To enter host cells, the SARS-CoV-2 spike protein binds to its cellular receptor, human angiotensin-converting enzyme 2 (hACE2), through its receptor-binding domain (RBD). The virus undergoes clathrin-mediated endocytosis, viral RNA is then released into the cytoplasm, followed by viral replication [3].

Human-to-human transmission occurs primarily through respiratory droplets of infected individuals [4, 5]. The incubation period of pre-Omicron variants is 5 days with a range of 2 to 14 days after initial exposure. Studies on the Omicron variant have estimated the incubation period to be 2 to 3 days [6].

SARS-CoV-2 continues to mutate, and new variants and subvariants emerge with the ability to evade existing host immunity [7]. Thus, reinfection may occur multiple times in an individual as protection from previous infections and/or vaccinations wanes over time. Protection is lost more rapidly especially for the Omicron variant as compared to previous variants [8]. Reinfections are often mild, but severe disease may still occur. However, protection against severe disease has been shown to be high for all SARS-CoV-2 variants [8].

II. Clinical Features

The clinical features of COVID-19 resemble infections by other respiratory viruses. These include but are not limited to:

Table 1: Presenting symptoms and signs of COVID-19. [2]

Respiratory	Cough, dyspnea, coryza or nasal congestion, sore throat, chest pain or tightness
Constitutional	Fever, chills/rigors, myalgia, fatigue, headache, arthralgia
Olfactory/gustatory	Anosmia, ageusia, dysgeusia
Gastrointestinal	Diarrhea, abdominal pain, nausea, vomiting
Dermatologic	Rash, vascular eruptions, pseudo-chilblains (COVID toes)
Others	Conjunctivitis

There is no single symptom or combination of symptoms that can be used to sufficiently discriminate COVID-19 from other respiratory infections [9]. Although the loss of sense of taste or smell has been reported to serve as a red flag for SARS-CoV-2 infections, these symptoms cannot be considered to adequately diagnose or exclude COVID-19 [2].

Most individuals with COVID-19 display mild respiratory symptoms. However, the severity of disease ranges from asymptomatic to severe. There are 5 general categories in which COVID-19 can be classified:

Table 2: Five categories of severity of COVID-19 ranging from asymptomatic/presymptomatic infection to critical disease. [10]

Category	Criteria
Asymptomatic or presymptomatic	Individuals who have no symptoms consistent with COVID-19 but test positive for SARS-CoV-2 using a virologic test, i.e., a nucleic acid amplification test (NAAT) or an antigen test.
Mild	Individuals who exhibit any of the signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.
Moderate	Individuals who show evidence of lower respiratory disease during clinical assessment or imaging, and who have an oxygen saturation measured by pulse oximetry (SpO ₂) \geq 94% on room air at sea level.
Severe	Individuals who have SpO ₂ $<$ 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO ₂ /FiO ₂) $<$ 300 mm Hg, a respiratory rate $>$ 30 breaths/minute, or lung infiltrates $>$ 50%.
Critical	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

III. Detection and Diagnostic Methods

- **Real-time reverse transcriptase PCR or RT-PCR (gold standard)**
 - Performed on respiratory samples obtained from the nasopharynx, oropharynx, sputum, saliva.
 - A threshold cycle (Ct) value less than 40 is clinically reported as PCR positive [11]. Lower Ct values indicate higher viral RNA loads.
 - However, detection may not indicate “live” virus replication.
- **Antigen rapid test kits (point-of-care tests)**

- Usually to detect SARS-CoV-2 nucleocapsid protein (most abundant).
- Inexpensive and rapid, can be done at point-of-care.
- Specificity is high (>97%), sensitivity is variable [2].
- Best performance in patients with high viral loads (Ct values $\leq 25-30$), 1 to 3 days prior to onset of symptoms and during the first 5 to 7 days of illness [12].
- Less sensitive as compared to real-time RT-PCR.
- **Serological assays such as ELISA, virus neutralisation tests**
 - To detect antibodies to SARS-CoV-2 (after infection and/or vaccination).

IV. Prevention and Control Strategies

- Use of face-masks or respirators
- Contact tracing
- Quarantine, isolation, and safe-distancing measures
- Hygiene measures (hand-washing, surface disinfection, etc)
- Vaccines

Approved in Singapore

Pfizer-BioNTech/Comirnaty (mRNA vaccine)

Moderna/Spikevax (mRNA vaccine)

Novavax/Nuvaxovid (protein subunit vaccine)

Sinovac-CoronaVac (inactivated virus vaccine)

Singapore's National COVID-19 Vaccination Program [13]

Table 3: Vaccine recommendations for individuals aged 5 and above.

5-11 years	Pfizer-BioNTech/Comirnaty vaccine only
12 and above	Pfizer-BioNTech/Comirnaty or Novavax/Nuvaxovid vaccines
18 years and above	Pfizer-BioNTech/Comirnaty, Moderna/Spikevax, Novavax/Nuvaxovid or Sinovac-CoronaVac vaccines

≥5 years old: Minimum protection should be received via:

3 doses of Pfizer-BioNTech/Comirnaty, Moderna/Spikevax or Novavax/Nuvaxovid. The 1st and 2nd doses should be spaced 8 weeks apart, while the recommended interval between the 2nd and 3rd doses is 5 months; *OR*

4 doses of Sinovac-CoronaVac. The 1st and 2nd doses should be spaced 8 weeks apart. Thereafter, the recommended interval between the 2nd and 3rd, as well as the 3rd and 4th doses is 3 months [13].

6 months to 4 years old: 2 doses of Moderna/Spikevax, administered 8 weeks apart, *OR* 3 doses of Pfizer-BioNTech/Comirnaty, administered 8 weeks apart. A booster dose should be taken after their 5th birthday, and the interval between the booster dose and the last dose should be more than 5 months.

V. Treatment Options

Table 4: Treatment options of COVID-19 based on severity of disease [14].

Severity	Treatment
Mild to moderate (not requiring supplemental oxygen)	Most patients do not require specific antiviral treatment, beyond supportive care - observation till recovery. Patients with high-risk of progression to severe disease: consider Remdesivir or oral antivirals (Nirmatrelvir/Ritonavir or Molnupiravir).
Severe (requiring supplemental oxygen)	Dexamethasone (or equivalent steroid) alone <i>or</i> Dexamethasone (or equivalent steroid) + Remdesivir <i>or</i> Dexamethasone (or equivalent steroid) + Baricitinib with or without Remdesivir <i>or</i> Baricitinib + Remdesivir
Critical illness (mechanical ventilation, extracorporeal membrane oxygenation or ECMO)	Dexamethasone (or equivalent steroid) alone <i>or</i> Dexamethasone (or equivalent steroid) + Tocilizumab <i>or</i> Dexamethasone + Baricitinib

VI. Long COVID

“Long COVID” or “post-acute sequelae of COVID-19” or “post COVID-19 condition” is defined by WHO as “the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation” [15].

According to WHO, an estimated 10 to 20% of COVID-19 patients develop symptoms which may include and are not limited to: fatigue, shortness of breath and cognitive dysfunction [16]. A meta-analysis of 36 studies identified fatigue, cognitive impairment, joint pain, anxiety and depression as primary clinical features within five categories of general, neurological, neuropsychiatric, cardiopulmonary, and gastrointestinal symptoms.

Table 5: Categories of long-COVID clinical symptoms. Adapted from [17].

Category	Symptoms
General	Pain (e.g. general pain, muscle or joint pain, and mobility dysfunction), fatigue, fever, hair fall, skin rash, weight loss
Neurological	Headache, cognitive impairment, loss of smell, taste or hearing
Neuropsychiatric	Depression, anxiety, post-traumatic stress disorder or PTSD, sleep disturbances
Cardiopulmonary	Chest pain, sore throat, dyspnea, palpitations, cough
Gastrointestinal	Poor appetite, diarrhea, nausea, vomiting, abdominal pain

Singapore has several “Long COVID” clinics at National University Hospital, Ng Teng Fong General Hospital, and the National Centre for Infectious Diseases (NCID).

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