

An overview of COVID-19,
with emphasis on radiological features



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Introduction

The latest threat to local and global health is the ongoing outbreak of Coronavirus Disease 2019 (COVID-19). Amidst the pandemic, the Hong Kong College of Radiologists (HKCR) aligned radiologists from all her Radiology Training Centers in Hospital Authority (HA) and the Department of Diagnostic Radiology of the University of Hong Kong (HKU) to publish this feature article on the updates of scientific knowledge, in particular the radiological features, of COVID-19. Our objectives are to enhance the knowledge of our Fellows and members on the available information and further equip them in their daily medical practice. At the time of writing, COVID-19 is still continuously spreading at fast pace around the world. The condition is shifting rapidly and most of the relevant guidelines and scientific knowledge will need to be updated from day to day. Every attempt has been made to ensure the content of this article is up to date to the time of printing on 27 March 2020. We hope our publication can provide useful background and radiological information to facilitate our Fellows and members in following the evolvement of the COVID-19 pandemic.

Background

COVID-19 was first reported to the World Health Organization (WHO) Country Office in China as a cluster of cases of pneumonia of unknown etiology from Wuhan, the capital city of Hubei Province, on 31 December 2019. Since then, the disease rapidly spread and resulted in an epidemic in Mainland China. On 12 January 2020, the Chinese Center for Disease Control and Prevention (China CDC) announced that the causative agent of this outbreak was a novel coronavirus, which was phylogenetically in the SARS-CoV clade, hence referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak was declared by WHO as Public Health Emergency of International Concern on 30 January 2020 and the disease was formally named as Coronavirus Disease 2019 (COVID-19) on 11 February 2020.

Various measures in prevention and control work were implemented in Mainland China to reduce the intensity of the epidemic, such as implementation of strict traffic restrictions and building of new hospitals. While the number of new cases in Mainland China had started to drop since late February 2020, the COVID-19 caseload around the world continued to rise rapidly, with the pace of increase overtaking that of Mainland China and the epicenter of outbreak shifting to Europe and other western countries. WHO officially declared the COVID-19 outbreak a pandemic on 11 March 2020. By 27 March 2020, over 486,000 cases have been diagnosed in more than 200 countries / areas, including over 22,500 fatalities, with the disease affecting all continents except Antarctica^[1].

Hong Kong logged the first confirmed patient of COVID-19 on 23 January 2020, the same day that China declared a lockdown in Wuhan. After the Chinese New Year, clusters of local cases emerged, including two largest clusters of infection known as the “hot pot family” and worshippers of a Buddhist hall located in North Point. With mobilization of the healthcare system and enhancement of infective control measures by the whole society, the number of confirmed cases in Hong Kong has been controlled at low level comparing with the rest of the world. However, the recent surge of imported cases of COVID-19 has put us at risk of a second wave of infection. In Hong Kong, as of 27 March 2020, a cumulative total of 518 confirmed cases of COVID-19 were reported. Four patients died while 111 patients had recovered from the illness^[2].



The virus causing COVID-19: SARS-CoV-2

SARS-CoV-2 belongs to the Coronavirus family and is a member of the subgenus Sarbecovirus. It is an enveloped, positive-sense, single stranded RNA virus similar to the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) viruses. The genome of SARS-CoV-2 is about 96% identical to the bat coronavirus BatCoV RaTG13^[3], thus suggesting that bats may be the natural reservoir of this virus.

SARS-CoV-2 contains four structural proteins, including the transmembrane spike (S), envelope (E) and membrane (M) proteins which together form the viral envelope; as well as the nucleocapsid (N) protein which holds the RNA genome^[4]. The S glycoprotein on the virion surface allows the virus to bind to the host cell receptors and mediates fusion of the viral and cellular membranes^[5]. SARS-CoV-2 in particular accesses host cells via a receptor binding domain in the S protein, allowing cross-species transmission to human by binding to the angiotensin-converting enzyme 2 (ACE-2) receptors in human cells, which are found in various organs (in lungs, heart, vasculature, kidneys and intestines etc.) but are most abundant in Type 2 alveolar cells in the lungs, and facilitates cell-cell fusion and virus entry^[3].

Clinical features of COVID-19

Early cases of COVID-19 identified in Wuhan were believed to have acquired the infection from a zoonotic source, while later cases suggested transmission from person to person^[6-8]. Like SARS and MERS, transmission through droplets, contact and contaminated inanimate objects are observed in COVID-19^[9]. Current evidence does not support routine airborne transmission of COVID-19, but the potential occurrence of airborne transmission can be envisaged during aerosol-generating procedures, such as tracheal intubation and bronchoscopy^[6]. Opportunistic airborne/ aerosol transmission was reported for SARS and MERS^[10] while a recent study^[11] has shown similar aerosol stability of SARS-CoV-2 and SARS-CoV-1 under experimental conditions. Fecal viral shedding is occasionally demonstrated in patients with COVID-19, but fecal oral route does not appear to be a main route of transmission^[6].

COVID-19 has a median incubation period of five to six days, which is similar to SARS (median 4.6 days) and MERS (median 5 days)^[10] and is thought to be up to 14 days. However, it remains prudent to consider the incubation period to be of at least 14 days^[6, 12]. Transmission of COVID-19 through asymptomatic contact has been described^[13, 14], but is not thought to be a major driver of transmission^[12]. COVID-19 shows considerable transmission among close contact, such as family households^[7]. Basic reproduction number (R_0) of COVID-19 is estimated to be two to three^[12], while it is 2.2 to 3.7 for SARS^[10] and less than 1 (with significant heterogeneity) for MERS^[15]. SARS and MERS are also known to have “super-spreading events”^[16], which is also suspected for COVID-19^[17].

According to the WHO-China Joint Mission report^[6], fever (87.9%) and dry cough (67.7%) were typical symptoms in COVID-19. Other symptoms included fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), headache (13.6%), myalgia or arthralgia (14.8%), and chills (11.4%). Gastrointestinal symptoms such as nausea or vomiting (5%) or diarrhea (3.7%)



were uncommon. Patients with severe disease developed dyspnea or hypoxia at one week from symptom onset. The median time from onset to clinical recovery was approximately 2 weeks for mild cases and 3 to 6 weeks for patients with severe or critical disease. Among patients who died of COVID-19, the time from symptom onset to outcome ranged from 2 to 8 weeks^[6, 18]. Most COVID-19 patients had mild disease and recovered. About 80% of patients had mild to moderate disease, with or without pneumonia; 13.8% had severe disease; 6.1% were critical with respiratory failure, septic shock or multiple organ dysfunction or failure. The proportion of infected asymptomatic individuals was estimated to be 1% to 3% in China^[6, 12], but could be as high as 44% in Italy, and 51% in a rapidly evolving cruise ship outbreak^[12]. The case-fatality rate was reported to be 2.3% in the largest case series in China^[7], 2.8% in Italy, and 0.5% in South Korea^[12]. The rate was higher at Wuhan than other locations, and higher in the early stage of the outbreak^[6]. On the other hand, MERS showed higher critical and mortality rates, 58% to 84% and 36.0% (65% for hospitalized) whilst SARS had critical and mortality rates of 34% to 37% and 9.6% (28% for hospitalized)^[10, 20]. For COVID-19, individuals at highest risk for severe disease and death included people aged over 60 years and those with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer. Male gender was also associated with increased fatality^[6, 20]. These were also observed in MERS^[21] and SARS^[22]. Disease appeared to be relatively rare and mild in children. A very small proportion of those aged under 19 years developed severe (2.5%) or critical disease (0.2%)^[6]. Pregnant women with COVID-19 did not appear to be at higher risk of severe disease, with 8% having severe disease and 1% being critical^[6, 18].

Laboratory investigations

Laboratory investigation is the cornerstone for the diagnosis of COVID-19. The decision of performing laboratory testing for SARS-CoV-2 should be based on clinical features and epidemiological risk factors, depending on the reporting criteria and surveillance guidelines of the local health authority.

Laboratory testing for SARS-CoV-2 relies on the detection of unique sequences of virus RNA by nucleic acid amplification tests (NAAT), such as real-time reverse-transcription polymerase chain reaction (RT-PCR), with confirmation by nucleic acid sequencing when necessary^[23]. Various types of specimens can be obtained for RT-PCR, such as sputum, tracheal aspirate, bronchoalveolar lavage, nasopharyngeal flocculated swab (NPFS), nasopharyngeal aspirate (NPA), throat swab, early morning deep throat saliva, blood and stool. A number of external factors may affect the RT-PCR testing result including sampling methods, specimen sources (upper or lower respiratory tract), sampling timing (different periods of the disease development) and performance of detection kits. Previous study showed that the sensitivity of RT-PCR assay for sputum and NPFS ranged from 74.4% to 88.9% and 53.6% to 73.3% respectively^[24].

Serological survey can aid investigation of an ongoing outbreak and retrospective assessment of the attack rate or extent of an outbreak. They are under development and are not widely used^[6, 23]. SARS-CoV-2 virus specific IgM was reported to be positive at 3 to 5 days from symptom onset and IgG titer showed 4-fold rise in titer between acute and convalescent phase sera^[18]. Serology tests may avoid false negative result due to sampling and allow less stringent specimen quality. However, cross-reaction with other coronaviruses may be of concern^[25].



Viral culture and isolation is not recommended as a routine diagnostic procedure, and requires Biosafety Level 3 laboratory^[23, 26].

Patients with COVID-19 may also reveal abnormalities in hematological and biochemical investigations. Lymphopenia was reported in 33%^[27] to 82%^[28] of the patients. Lymphocyte count predicted poor clinical outcome^[28] and was significantly lower in those requiring intensive care unit (ICU) admission^[29] and fatal cases^[30]. Total white cell count may be low, normal or raised^[29]. Thrombocytopenia was observed in 36% of the patients^[28]. Liver function abnormality was common with 14% to 53% reporting alanine aminotransferase (ALT) or aspartate transaminase (AST) abnormality, and was more frequently found in patients with severe disease^[31]. Raised lactate dehydrogenase (LDH) and creatine kinase (CK) may be observed while most patients show raised c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Raised procalcitonin, troponin, D-dimer, and progressive leukopenia may occasionally be found in severe disease^[18, 29].

Radiological features of COVID-19

Chest radiograph and chest CT, in particular high-resolution thoracic CT (HRCT), are the two main radiological investigations performed in patients with suspected or confirmed COVID-19. Nevertheless, radiological investigations cannot replace laboratory investigations in confirming the diagnosis. Both laboratory and radiological investigations have limitations in detecting the disease at its early stage. It should be of note that during the outbreak in Mainland China, CT was used early on and also frequently in the investigation of suspected cases, as well as in monitoring of disease progress.

Chest radiograph

With enhanced surveillance undertaken in different parts of the world, many patients with COVID-19 are diagnosed at early stage and the patients may be asymptomatic or only have mild symptoms. In China, around 80% of the patients at diagnosis were non-pneumonia or mild pneumonia cases^[32]. Only 33% to 59.1% of them had abnormal radiographic findings^[26, 33]. It is therefore considered that chest radiograph may not be sensitive enough to play a significant role in the detection of COVID-19 pneumonia at early stage. However, chest radiograph remains as an important initial tool for diagnosing or excluding alternative conditions such as lobar collapse, pneumothorax or pleural effusion. Being readily available in wards and Accident and Emergency Departments (AEDs), portable chest radiograph can be used to assess and follow up the patients with established COVID-19 pneumonia when the consolidation can be well delineated (Fig. 1, 2). Despite being commonly utilized as an initial investigation tool, the exact role of chest radiograph in the overall management of COVID-19 requires further research to delineate.

Chest CT

Initial findings of COVID-19 pneumonia on chest CT are small ground-glass opacities (GGOs), which would then grow larger with crazy paving pattern and consolidation as patient deteriorates^[34-36]. At an early stage, some patients may only show a single patch of GGO^[35]. Patients may even present with a completely normal CT if they are imaged 0-2 days after symptom onset. In severe and critical patients, the occurrence rates of consolidation, linear opacities, crazy-paving and bronchial thickening would increase, as well as the extent of lung involvement^[34]. 'White lung' appearances would ensue eventually,

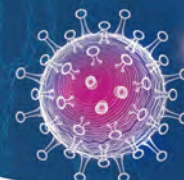


Fig. 1. Serial CXRs in an adult patient with confirmed COVID-19. Initial CXR taken on Day 1 of +ve RT-PCR test (A) showed area of air space opacity in right upper and mid zone at the periphery. Follow-up CXR on Day 5 (B) showed progression to consolidation in right upper and mid zone, coincided with the peak of symptoms and biochemical & haematological abnormalities. Patient gradually improved clinically and further CXR on Day 11 (C) showed corresponding radiographic improvement.

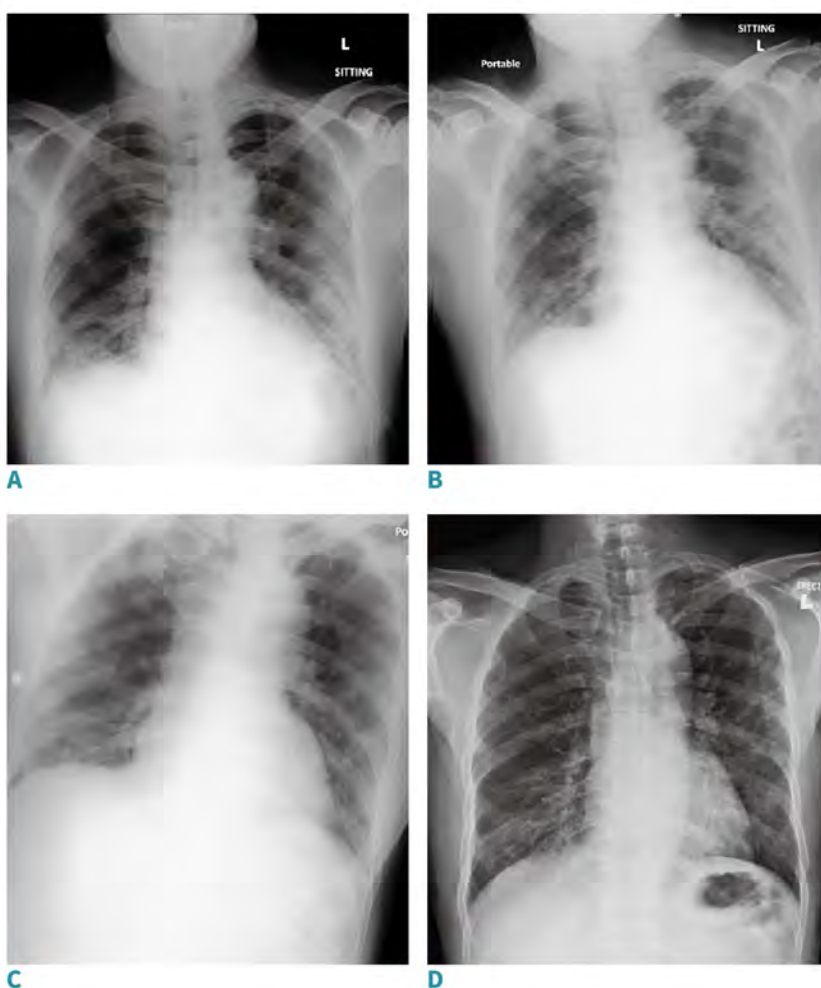
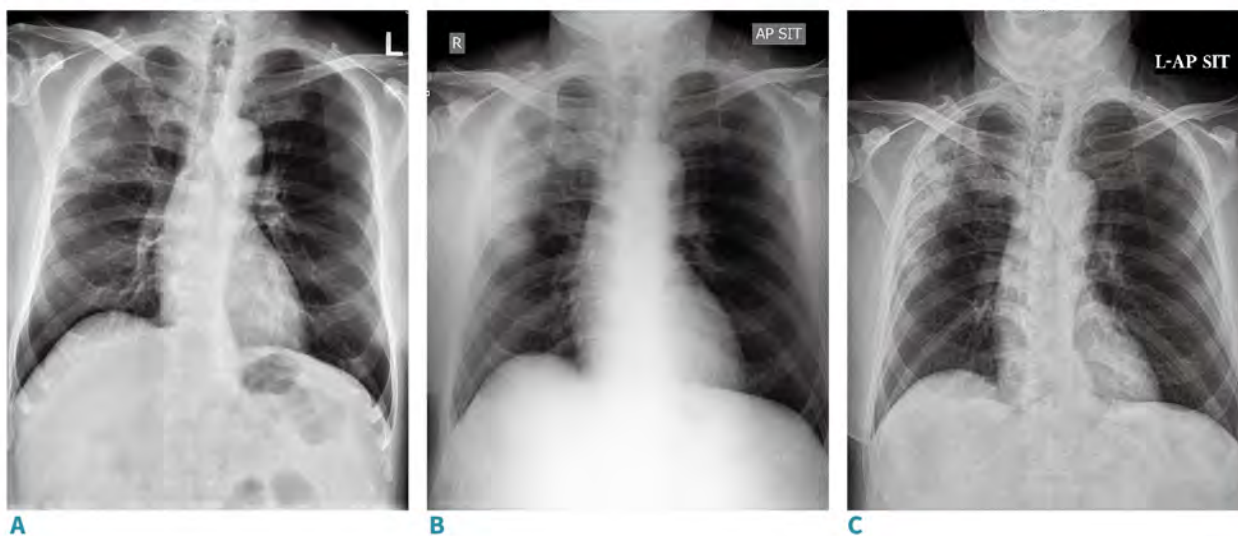


Fig. 2. Serial CXRs in an adult patient with confirmed COVID-19. First CXR taken on Day 1 of +ve RT-PCR test (A) showed bilateral patchy consolidations, more on left side. Second CXR on Day 5 (B) showed deterioration of bilateral consolidations which became more extensive especially in left lung. Follow-up CXR on Day 14 (C) showed radiographic improvement of bilateral pneumonia. Further follow-up CXR at 1 month (D) showed further improvement of consolidations while some fibrotic changes were noted in the previously involved areas.



which would seriously affect patient's lung function^[36]. Pleural effusion, multiple tiny pulmonary nodules and mediastinal lymphadenopathy are regarded as atypical CT findings in COVID-19 pneumonia. Their appearance should raise concern for bacterial superinfection or alternative diagnosis^[37].

As the number of confirmed cases of COVID-19 in Hong Kong increases, we have accumulated certain understanding of the radiological patterns of the disease by combining the experience of radiology departments in multiple local hospitals.

From 22 January 2020 to 20 February 2020, Princess Margaret Hospital, the designated infectious disease hospital of Hong Kong, admitted more than 20 patients who subsequently became confirmed cases of COVID-19. They provided the earliest local experience on the radiological features of the disease. 19 of these patients had HRCT or conventional CT thorax scans performed after admission. Table [A] summarizes the radiological findings of these patients. GGOs with peripheral subpleural distribution (Fig.3-5) were found in all cases (100%). No specific zonal predominance was noted. All lobes were involved in 16 cases (84.2%). Focal subsegmental consolidations (Fig. 6,7) were seen in 14 cases (78.9%). Interlobular septal thickening and intralobular line opacities (Fig. 8,9) were present in 12 scans (63.2%). Other imaging features worth mentioning included bronchial dilatation or bronchial wall thickening (Fig. 10), and crazy-paving patterns (Fig. 11), which were found in up to around half of the patients. It should be noted that no mediastinal lymph node enlargement, centrilobular nodule or pleural effusion was detected in any of the scans. Such findings also coincide with several studies carried out in centers outside Hong Kong^[34, 36, 37, 39-41].

Chest CT has high sensitivity, making it useful in the early diagnosis of COVID-19 in high risk suspected cases. However, it should not be used as the sole method in achieving the diagnosis. Recent studies suggest that chest CT has higher sensitivity for the early diagnosis of COVID-19 when compared with initial RT-PCR swab samples. Varying between different studies, the sensitivity of chest CT was found to be 98%^[41] and 97%^[38]. Chest CT is particularly important when patients show clinical and epidemiological features compatible with COVID-19 but negative RT-PCR results. Xu et al reported a few cases of initially negative RT-PCR results which had bilateral GGOs in chest CT. Upon repeated testing, those patients were later converted to RT-PCR positive^[39]. Nevertheless, chest CT is unlikely a reliable standalone tool to rule out COVID-19 infection. Bernheim et al pointed out that if patients were imaged 'early' (0-2 days after symptoms onset), 56% of the patients would have a completely normal CT. On the contrary, 92% of those 'early' presented patients showed positive initial RT-PCR results^[40]. As shown in the above studies, discordance between results of RT-PCR and chest CT was not uncommonly encountered. The high sensitivity of chest CT in diagnosing COVID-19 also comes at a cost, which is low specificity. The specificity of chest CT in diagnosing COVID-19 could be as low as 25%^[38]. While alternative diagnosis such as other viral pneumonia can present with similar imaging features, atypical CT appearance can also be seen in some cases of COVID-19 pneumonia and may create diagnostic confusion. RT-PCR, which is believed to be highly specific, would be required to reach a definitive diagnosis. It could not be reiterated more that the diagnosis of COVID-19 requires multidisciplinary input. A combination of clinical history, clinical manifestations, imaging features and laboratory results are necessary to achieve a timely and accurate diagnosis.

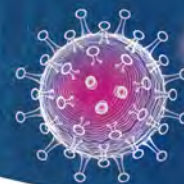


Table [A]. Summary of the radiological findings of 19 COVID-19 patients admitted into Princess Margaret Hospital from 22 January 2020 to 20 February 2020.

Total Chest CT performed	19
Age	63.7 (25-80)
Sex	
Male	11
Female	8
Days from diagnosis to CT	3.5 (1-10)
CT techniques	
HRCT	17
Conventional CT	2
CT findings	
GGO	19 (100%)
All lobes involvement	16 (84.2%)
Peripheral subpleural distribution	19 (100%)
Zonal predominance	
Upper	3 (15.8%)
Basal	5 (26.3%)
Diffuse	11 (57.9%)
Interlobular/ intralobular septal thickening	12 (63.2%)
Consolidation	14 (78.9%)
Bronchial wall thickening or dilatation	10 (52.6%)
Centrilobular nodule	0 (0%)
Pleural effusion	0 (0%)
Lymph node enlargement	0 (0%)

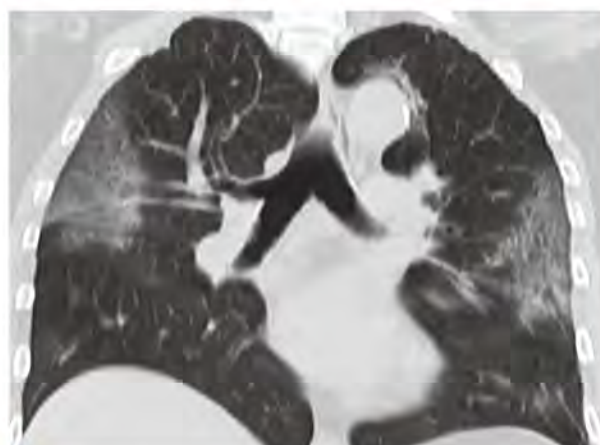
Age and days expressed in means with range in brackets

CT findings expressed in case number with percentage in brackets

Fig. 3. HRCT performed on Day 2 of +ve RT-PCR test in an adult patient with confirmed COVID-19, in axial (A) and coronal (B) planes. Note the typical appearance of GGOs with peripheral subpleural distribution, involving bilateral lungs in this case.



A



B

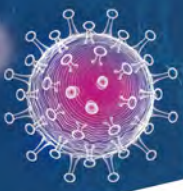


Fig. 4. HRCT performed on Day 4 of +ve RT-PCR test in an adult patient with confirmed COVID-19, reconstructed in coronal plane. Note that bilateral lungs are involved by GGOs.

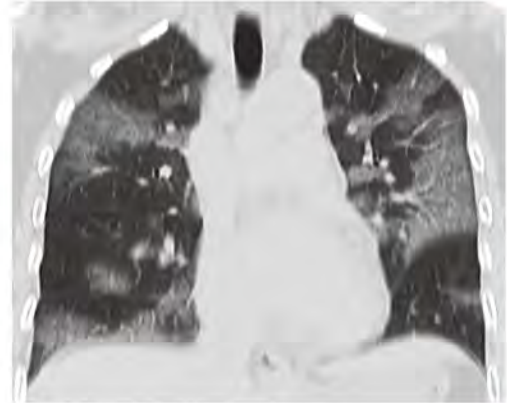


Fig. 5. HRCT performed on Day 2 of +ve RT-PCR test in an adult patient with confirmed COVID-19. Note the multiple patchy areas of GGOs involving bilateral lungs.



Fig. 6. HRCT performed on Day 2 of +ve RT-PCR test in an adult patient with confirmed COVID-19, reconstructed in coronal plane. Note the consolidations in bilateral lungs.

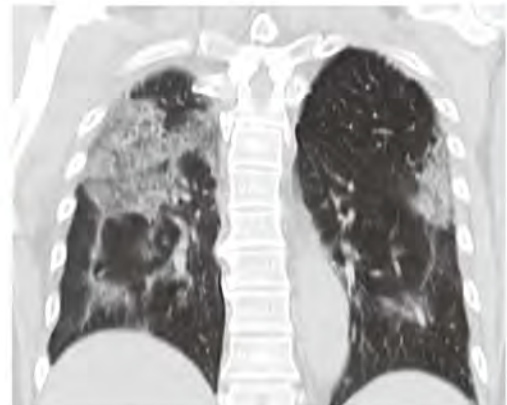
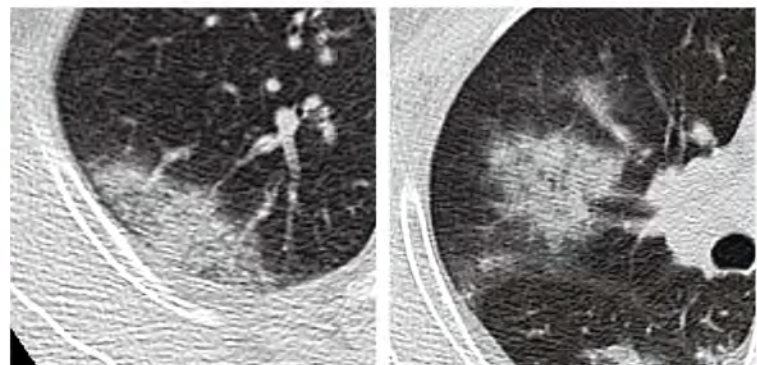


Fig. 7. HRCT performed on Day 3 of +ve RT-PCR test in an adult patient with confirmed COVID-19, showing areas of consolidations in right upper lobe.



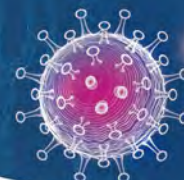


Fig. 8. HRCT performed on Day 2 of +ve RT-PCR test in an adult patient with confirmed COVID-19. In addition to bilateral GGOs, note the presence of septal thickening (arrows), best seen in left upper lobe.



Fig. 9. HRCT performed on Day 4 of +ve RT-PCR test in an adult patient with confirmed COVID-19. There are bilateral GGOs, more extensive in right lung. Also note the septal thickening (arrows).



Fig. 10. HRCT performed on Day 2 of +ve RT-PCR test in an adult patient with confirmed COVID-19. In addition to the typical GGOs, some areas of consolidations and septal thickening, note the presence of bronchial dilatation and wall thickening (arrows).

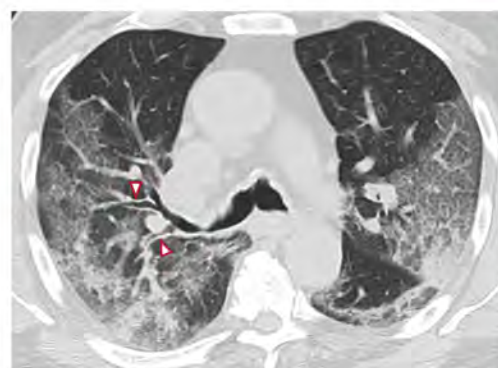
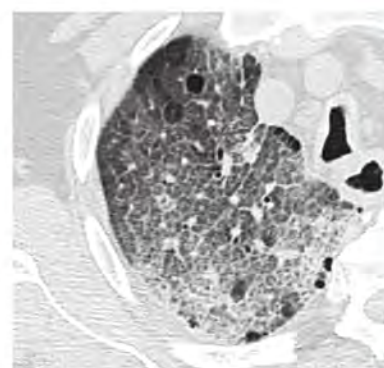


Fig. 11. HRCT performed on Day 2 of +ve RT-PCR test in an adult patient with confirmed COVID-19. Extensive GGO with septal thickening in right upper lobe, with crazy-paving pattern.





Apart from achieving initial diagnosis, chest CT may help in disease monitoring of COVID-19 pneumonia when necessary. Serial chest CT can accurately reflect disease evolution and monitor treatment effect^[35]. Up till now, the effective treatment of COVID-19 has not been established and current management is mainly supportive in nature. However, more aggressive therapies such as experimental antiviral treatments might be tried for critically ill patients^[42]. Whether chest CT could help to determine the management approach by assessing the imaging features of disease progression and treatment response would require further research.

Imaging findings on recovery

Most patients would recover from COVID-19. For patients who eventually recovered, they showed worst CT features at approximately 10 days after initial onset of symptoms. At approximately 14 days after initial onset of symptoms, radiological signs of improvement would be seen. In patients with improving condition, the consolidative changes seen previously would be gradually absorbed. Extensive GGOs; however, may still be observed as a demonstration of consolidation absorption^[35]. Small fibrous stripes may also be seen during the course of improvement^[36]. Ai et al observed that chest CT improvement would precede RT-PCR results turning negative in some patients^[38]. As it has only been 3 months since the disease was first reported, the long term radiological findings in survivors of COVID-19 remain unclear.

Comparing radiological findings among COVID-19, SARS and MERS

As the outbreaks of the current COVID-19, SARS in 2003 and MERS in 2012 are caused by viruses belonging to the same family coronaviridae^[43], they are often compared with each other. In fact, their imaging findings are mimics of each other. In the limited number of studies that reported detection rates of chest radiographs and CT separately in patients with COVID-19, abnormalities on radiographs were detected in up to 59.1% of patients at presentation^[28, 33]. This was in contrast to SARS and MERS where sensitivities of chest radiographs were reported to be up to 82.4%^[44, 45] and 83%^[46], respectively. Unilateral abnormalities are more commonly seen in SARS and MERS than in COVID-19, where changes more frequently involve both lungs^[47]. Severity of lung changes correlates with patients' clinical conditions and parameters in SARS and MERS, and is also likely the case in COVID-19 pneumonia^[9, 27, 44-46]. Pleural effusion is rarely seen in COVID-19 and SARS while it has been reported in MERS and is associated with poorer prognosis^[46, 47].

Epidemiological surveillance and disease diagnosis of COVID-19

With continuous outbreak of COVID-19, it is important for us to stay vigilant to the situation of the pandemic and be aware of the epidemiological surveillance and diagnosis of the disease, not only in Hong Kong but also the rest of the world. The epidemiological surveillance and disease diagnosis of COVID-19 adopted by Hong Kong and other regions/ organizations are summarized in Table [B].

Hong Kong

Hong Kong was one of the earliest places to make an official response to COVID-19 since the first reporting of the disease.



Since 31 December, 2019, the Centre for Health Protection (CHP) of Department of Health had enhanced surveillance for Severe Respiratory Disease associated with a Novel Infectious Agent. With effect from 8 January 2020, “Severe Respiratory Disease associated with a Novel Infectious Agent” became a statutorily notifiable disease under the Prevention and Control of Disease Ordinance (Cap 599) and the reporting criteria were updated from time to time to follow the evolution of the outbreak.

The latest Communicable Disease Surveillance Case Definitions for COVID-19 from the CHP was revised on 4 March, 2020 (Version 16.7)^[48]. The case has to be reported to the CHP for further investigation if an individual fulfils the following criteria:

1. Presented with fever* OR acute respiratory illness OR pneumonia;
- AND
2. Either one of the following conditions within 14 days before onset of symptom:
 - a. With travel history to a place with active community transmission of COVID-19[#]; OR
 - b. Had close contact with a confirmed case of COVID-19.

* Except fever due to a known etiology not related to respiratory infections

The list of places with active community transmission of COVID-19 is regularly uploaded to the CHP website (https://www.chp.gov.hk/files/pdf/statistics_of_the_cases_novel_coronavirus_infection_en.pdf)

In brief, the reporting criteria consists of a clinical component and an epidemiological component. When an individual fulfils both the clinical and epidemiological components, the case would become notifiable as a “suspected case” of COVID-19.

In Hong Kong, the diagnostic approach to a patient with suspected COVID-19 consists of both laboratory and radiological investigations. A patient would become a “confirmed case” of COVID-19 if he/she fulfils any of the following laboratory criteria (including asymptomatic patients):

1. Detection of nucleic acid of SARS-CoV-2 in a clinical specimen; OR
2. Isolation of SARS-CoV-2 from a clinical specimen; OR
3. Seroconversion or four-fold or greater increase in antibody titre to SARS-CoV-2 in paired serum specimens.

On the other hand, a patient would become a “probable case” of COVID-19 if he/she

1. has radiological evidence of pneumonia (by chest X-ray or computed tomography scan) AND epidemiological linkage to a confirmed case of COVID-19;
- OR
2. is a case (irrespective of any symptom) for whom testing for COVID-19 is inconclusive AND with epidemiological linkage to a confirmed case of COVID-19 or an outbreak of COVID-19

In Hong Kong, the Hospital Authority (HA) is managing most if not all of the confirmed and probable cases of COVID-19 while suspected cases may be encountered in both public and private sectors. In HA, RT-PCR test for SARS-CoV-2 would be arranged for all patients fulfilling the reporting criteria (i.e. suspected cases). Different types of specimens could be obtained^[49]:



1. Lower respiratory tract specimens (preferred if available): sputum or tracheal aspirate if intubated
2. Upper respiratory tract specimens: nasopharyngeal flocculated swab (NPFS) or nasopharyngeal aspirate (NPA) [pooled with throat swab in viral transport medium]
3. Stool: for patient fulfilling reporting criteria with diarrhea

For preliminarily positive cases, specimen should be re-tested and sent to Public Health Laboratory Services Branch (PHLSB) for confirmation.

On 3 February 2020, HA strengthened laboratory surveillance in public hospitals and extended the coverage of laboratory tests to include all in-patients with community acquired pneumonia, and any pneumonia case either with unknown cause (not responding to treatment in three days)/ requiring ICU care/ occurring in clusters/ who is a healthcare worker, irrespective of exposure or travel history. On 19 February 2020, the surveillance was further expanded to General Out-patient Clinics (GOPCs) and Accident and Emergency Departments (AEDs), where patients aged 18 or above, with fever and respiratory symptoms or mild chest infection but considered unnecessary for hospital admission according to clinical assessment, would be instructed to collect early morning deep throat saliva for SAR-CoV-2 laboratory testing.

In addition to the public sector, there was enhancement of laboratory surveillance for all clinics of private medical practitioners (PMPs) with free testing for COVID-19 by PHLSB since 6 March 2020^[50]. Respiratory specimen preferably nasopharyngeal swab could be taken from patients presenting with fever or respiratory symptoms, especially for those with travel history outside Hong Kong within 14 days before onset of symptoms. Alternatively, early morning deep throat saliva could be obtained. PMPs could send respiratory specimens to their existing laboratories for transfer to PHLSB if their laboratories offered such service. Since 12 March 2020, apart from early morning deep throat saliva, patients could also collect sputum by themselves at home and send the specimens to a collection point in one of the clinics of DH directly^[51]. All patients tested positive would be arranged by the CHP to be admitted to a public hospital for isolation and further management. The CHP would inform the patient directly for the arrangement.

In HA, for patients as suspected or confirmed cases of COVID-19 placed under isolation, the following principle^[52] for release are considered. For confirmed cases, when the clinical condition of the patient improves and he/she becomes afebrile and with two clinical specimens tested negative for SARS-CoV-2 taken at least 24 hours apart, the isolation order can be lifted after agreement with the Medical Control Officer (MCO) of the CHP. For suspected cases, the patient with negative RT-PCR test can be released from isolation unless he/she has strong epidemiological link or worsening clinical condition. With the accumulation of local clinical experience, the discharge criteria may be refined periodically and medical professionals should stay vigilant for future updates.

World Health Organization (WHO)

WHO issued interim technical guidance for the management of COVID-19 on 28 January 2020^[53], and further technical



guidance on epidemiological surveillance^[54] and laboratory testing^[23] in late February and early March respectively. The WHO guidance was mainly clinical, while radiological investigations were not employed for the purpose of diagnosing COVID-19.

Suspected cases are defined by both clinical and epidemiological features (See Table [B]). In particular, WHO provides definition on “contact”, which refers to a person who is exposed during the 2 days before and the 14 days after the symptom onset of a probable or confirmed case in any of the following ways:

1. Face-to-face contact within 1 meter and for more than 15 minutes
2. Direct physical contact
3. Direct care for patients with COVID-19 without using proper personal protective equipment (PPE)
4. Other situations as indicated by local risk assessment^[54]

Confirmation of the diagnosis of COVID-19 relies on laboratory testing, primarily by RT-PCR of respiratory specimens. Serological testing is also acceptable when RT-PCR is not available.

Mainland China

Since the start of the epidemic, the National Health Commission of the People's Republic of China (國家衛生健康委員會) has published national guidelines detailing the surveillance, diagnosis, management, and prevention of COVID-19. The guidelines has been continually updated, with the clinical management guidelines (新型冠狀病毒肺炎診療方案) currently at its Trial Version 7^[18].

The guidelines of Mainland China define suspected cases by both clinical and epidemiological features (See Table [B]). As patients are possibly contagious while asymptomatic, contact history includes close contact with a suspected/ confirmed symptomatic patient up to 2 days prior to symptom onset, or with asymptomatic patients up to 2 days prior to collection of respiratory specimens (that would later confirm the diagnosis)^[55].

The confirmation of COVID-19 relies on laboratory testing, mainly RT-PCR; while serology and viral genetic sequencing are also used. For some time in February, the Trial Version 5 of the clinical management guidelines contained a category “clinical diagnosis” (separated from “confirmed diagnosis”), which included CT findings in its criteria. However, this was only valid for Hubei province and was removed in the subsequent 6th revision.

Radiology has a more prominent role in the clinical management of COVID-19 under the guidelines of Mainland China. Imaging findings, mainly on chest CT, contribute as part of the assessment for distinguishing between mild, moderate, severe and critical cases, thereby guiding treatment. Improvement in imaging findings is also one of the criteria required for patient discharge^[18].



United States (US)

In the United States, individuals suspected to carry the SARS-CoV-2 virus are labelled as “Persons Under Interest” (PUI) and are defined by both clinical and epidemiological criteria (See Table [B]). The Centers for Disease Control and Prevention (CDC) recommends collection of specimens from the upper respiratory tract and, if possible, the lower respiratory tract for RT-PCR tests. Other additional specimens, such as stool and urine, can also be collected. After the initial testing, those with at least one positive respiratory specimen would be categorized as a “presumptive positive case”. These specimens would then be sent to the CDC for confirmation, until when these individuals would be labeled as “laboratory-confirmed COVID-19 cases”^[56]. On the other hand, a PUI with a negative RT-PCR test would be labeled as not infected.

European Union (EU)

On the other side of the Atlantic, the European Center for Disease Prevention and Control (ECDC) also defines suspected cases of COVID-19 according to both clinical and epidemiological criteria (See Table [B])^[57]. ECDC recommends collection of both upper respiratory and lower respiratory specimens for RT-PCR assay when possible. Additional specimens for later testing include urine, stool and serological testing of acute and convalescent sera. Confirmed cases are defined as a person with laboratory confirmation of virus causing COVID-19, irrespective of clinical signs and symptoms. Single positive test should be confirmed by a second RT-PCR assay targeting a different SARS-CoV2 gene when possible. In situations of large increase of cases and community transmission where a second confirmation test might not be feasible or would delay the confirmation, a single laboratory test is sufficient. ECDC also states that a single negative RT-PCR test (especially if from an upper respiratory tract specimen) does not exclude COVID-19 and another specimen should be tested with primary and secondary RT-PCR assays if there is strong suspicion. Discharge of hospitalized confirmed cases is based on laboratory evidence of SARS-CoV-2 clearance and clinical criteria, including pulmonary imaging showing obvious absorption of inflammation.

United Kingdom (UK)

In the UK, in the updated guidance by Public Health England on March 13, 2020^[58]. Instead of the previous clinical and epidemiological criteria for COVID-19 suspected cases, patients are now divided into inpatients and outpatients. Patients with cough and/ or fever who are well enough to remain in the community are advised to stay at home for 7 days. Those self-isolating for mild symptoms would not be tested for COVID-19. Only if inpatient criteria are met, of which radiological evidence of pneumonia is one of them, would further testing for COVID-19 be performed. Confirmation of COVID-19 again relies on laboratory investigations with RT-PCR testing on specimens from both upper and lower respiratory tracts if possible. Subsequent blood sample for serology would also be taken. Positive result on initial testing would be considered as a presumptive positive result and public health action would commence immediately. The presumptive positive sample would be referred for confirmatory testing.

Although there are variations in the epidemiological surveillance and disease diagnosis of COVID-19 across the world, most regions and organizations used both clinical and epidemiological criteria to identify suspected cases of COVID-19. Some



places would include radiological evidence of pneumonia as part of the clinical assessment. Nevertheless, the confirmation of COVID-19 is always based on laboratory testing, primarily RT-PCR, while serology is also included by some of the recommendations.

Treatment of COVID-19

Currently, the treatment of COVID-19 remains largely supportive. Most of the antiviral drug treatments currently employed are still controversial in their efficacies and are undergoing exhaustive clinical trials^[42]. The major proposed mechanism remains the inhibition of key components of the coronavirus infection life cycle, which include viral entry into the host cell (blocked by umifenovir, chloroquine, interferon etc.), viral replication (blocked by lopinavir/ritonavir, darunavir/cobicistat etc.), and viral RNA synthesis (inhibited by remdesivir, favipiravir, ribavirin etc.)^[59]. Recent studies have proposed the potential use of soluble recombinant human ACE2 (rhACE2) as a novel therapy for COVID-19, based on the proposed mechanism of rhACE2 binding to the viral S glycoprotein, and thereby prevents it from binding to ACE2 receptors of human cells at the cell membrane and subsequent virus entry^[60]. More researches are on-going to determine the appropriate therapy of COVID-19. Until today, there is still no vaccine that is proven effective against SARS-CoV-2.

Conclusion

Radiology is an important component in the diagnosis and management of COVID-19 pneumonia. The dominant radiological findings of COVID-19 on HRCT include GGOs, peripheral subpleural distribution, multiple lobes involvement without zonal predilection, subsegmental consolidation, septal thickening and relative lack of lymphadenopathy, pleural effusion and lung nodule. On the other hand, findings on chest radiograph are less sensitive than CT.

With emerging evidence that the epicenter of COVID-19 outbreak has shifted from Mainland China to Europe and other western countries, the pandemic is going to evolve. Local medical professionals including radiologists should stay vigilant to the situation and get prepared.



Table [B]. Epidemiological surveillance and disease diagnosis of COVID-19 adopted by Hong Kong and other regions / organizations

	HK	WHO	Mainland China ^[18]
Test	RT-PCR assay; Virus isolation; Serology ^[61]	RT-PCR assay; Serology if RT-PCR not available ^[23, 53]	RT-PCR assay; Viral genetic sequencing; Serology
Specimen Collection	Lower respiratory tract (sputum/ tracheal aspirate if intubated) Upper respiratory tract (nasopharyngeal flocked swab/ nasopharyngeal aspirate) Early morning deep throat saliva Additional specimens: stool if patient has diarrhoea ^[49, 52]	Upper respiratory tract (nasopharyngeal and oropharyngeal swab/ wash) Lower respiratory tract (sputum/ endotracheal aspirate/ bronchoalveolar lavage) ^[23]	Nasopharyngeal swab, sputum, endotracheal aspirate, bronchoalveolar lavage, blood, stool
Suspected cases	<u>Suspected case:</u> Presented with fever* or acute respiratory illness or pneumonia AND Either one of the following conditions within 14 days before onset of symptom: - with travel history to a place with active community transmission of COVID-19 [#] or - had close contact with a confirmed case of COVID-19 ^[61] <u>Probable case:</u> With radiological evidence of pneumonia (by CXR or CT) and epidemiological linkage to a confirmed case of COVID-19 OR With inconclusive test result for COVID-19 and with epidemiological linkage to a confirmed case of COVID-19 or an outbreak of COVID-19 ^[61]	<u>Suspected case:</u> With acute respiratory illness (fever and at least one sign or symptom of respiratory disease, e.g. cough, shortness of breath) and a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset OR With any acute respiratory illness and having been in contact with a confirmed or probable case of COVID-19 in the last 14 days prior to symptom onset OR With severe acute respiratory infection (fever and at least one sign or symptom of respiratory disease, e.g. cough, shortness of breath, and requiring hospitalization) and in the absence of an alternative diagnosis that fully explains the clinical presentation ^[54] <u>Probable case:</u> Suspected case for whom testing for COVID-19 is inconclusive OR A suspect case for whom testing could not be performed ^[54]	<u>Suspected case:</u> Epidemiological criteria (any 1): - travel history or residence in 14 days prior to symptom onset to Wuhan and surrounding areas or other areas with reported local transmission - contact with confirmed case in the 14 days prior to symptom onset - contact in the 14 days prior to symptom onset with individuals with fever or respiratory symptoms from Wuhan and surrounding areas or other areas with reported local transmission - clustered outbreak: 2+ cases of fever or respiratory symptoms within 2 weeks in small area, e.g. family, office, classroom AND Clinical criteria (any 2, all required if epidemiological criteria not met): - fever and/or respiratory symptoms - imaging suggestive of COVID-19 - normal or decreased WCC and lymphocytes in early disease
Confirmed cases	Suspected case with laboratory confirmation, followed by re-testing of specimen by Public Health Laboratory Services Branch for confirmation ^[49]	Laboratory confirmation of SARS-CoV-2 infection, irrespective of clinical signs and symptoms ^[54]	Suspected case with laboratory confirmation

* Except fever due to a known etiology not related to respiratory infections

The list of places with active community transmission of COVID-19 is regularly uploaded to the Centre for Health Protection (CHP) website (https://www.chp.gov.hk/files/pdf/statistics_of_the_cases_novel_coronavirus_infection_en.pdf)



	US	EU ^[57]	UK ^[58]
Test	CDC 2019-Novel Coronavirus RT-PCR Diagnostic Panel ^[62]	RT-PCR assay; Serology	RT-PCR assay
Specimen Collection	<p>Lower respiratory tract (bronchoalveolar lavage, tracheal aspirate)</p> <p>Upper respiratory tract (nasopharyngeal swab/ oropharyngeal swab)</p> <p>Collection of sputum should only be done for those patients with productive coughs. Induction of sputum is not recommended.^[63]</p>	<p>Upper respiratory tract (nasopharyngeal/ oropharyngeal swab/ nasopharyngeal aspirate/ nasal wash)</p> <p>Lower respiratory tract (expectorated sputum/ endotracheal aspirate/ bronchoalveolar lavage)</p> <p>Additional specimens for later testing: - serological testing of acute and convalescent phases (2-4 weeks after acute) serum - blood, urine, stool</p>	<p>Upper respiratory tract (individual/ combined nose and throat swabs/ nasopharyngeal aspirate)</p> <p>Lower respiratory tract (sputum)</p> <p>When admitted, take blood sample for acute serology</p>
Suspected cases	<p><u>Person Under Interest (PUI):</u></p> <p>Epidemiological criteria: - any persons, including healthcare workers, who have had close contact with a laboratory-confirmed COVID-19 patient within 14 days of symptom onset or - a history of travel from affected geographic areas within 14 days of symptom onset</p> <p>Clinical criteria: - fever (subjective or confirmed) and/or - symptoms of acute respiratory illness (e.g., cough, difficulty breathing)^[64]</p> <p><u>Presumptive positive case:</u></p> <p>Individual with at least one respiratory specimen that tested positive for the COVID-19 virus at a state or local laboratory. Confirmation will be made with CDC^[56]</p>	<p><u>Suspected case:</u></p> <p>- With acute respiratory tract infection (sudden onset of at least one of: cough, fever, shortness of breath) and with no other etiology that fully explains clinical presentation and a history of travel or residence in country/area reporting local or community transmission during 14 days prior to symptom onset</p> <p>OR</p> <p>- With acute respiratory illness and having in close contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset</p> <p>OR</p> <p>- With severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g. cough, shortness of breath)) and requiring hospitalization and with no other etiology that fully explains the clinical presentation</p> <p><u>Probable case:</u></p> <p>Suspected case for whom testing for COVID-19 virus is inconclusive or for whom testing was positive on a pan-coronavirus assay</p>	<p><u>Inpatient criteria:</u></p> <p>- requiring admission to hospital (a hospital practitioner has decided that admission to hospital is required with an expectation that the patient will need to stay at least one night)</p> <p>AND</p> <p>- have either clinical or radiological evidence of pneumonia or - acute respiratory distress syndrome or - influenza like illness (fever $\geq 37.8^{\circ}\text{C}$ and at least one of the following respiratory symptoms, which must be of acute onset: persistent cough (with or without sputum), hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing, sneezing)</p> <p>Only those who satisfy inpatient criteria would be tested for COVID-19</p> <p><u>Outpatient definition:</u></p> <p>Patients who have new continuous cough and or high temperature and are well enough to remain in the community should stay at home for 7 days. If symptoms worsen during self-isolation or not better after 7 days, then NHS 111 should be contacted online or by phone</p>
Confirmed cases	Positive CDC 2019-nCoV RT-PCR test, done by CDC or CDC-qualified lab	Laboratory confirmation of SARS-CoV-2 infection. Single positive test should be confirmed by a second RT-PCR assay targeting a different SARS-CoV-2 gene when possible. In situations of large increase of cases and community transmission where a second confirmatory test might not be feasible or would delay the confirmation, a single laboratory test is sufficient	Initial positive RT-PCR test will be considered as a presumptive positive result, followed by confirmatory testing by Public Health England Colindale



Table [B]. Epidemiological surveillance and disease diagnosis of COVID-19 adopted by Hong Kong and other regions / organizations

	HK	WHO	Mainland China ^[18]
Severity of illness	No specific classification	<p><u>Uncomplicated illness:</u></p> <ul style="list-style-type: none"> - non-specific symptoms - no dehydration, sepsis or shortness of breath <p><u>Mild pneumonia:</u></p> <ul style="list-style-type: none"> - pneumonia and no signs of severe pneumonia - child with cough or difficulty breathing + fast breathing (in breaths/min): <2 months, ≥ 60; 2–11 months, ≥ 50; 1–5 years, ≥ 40; and no signs of severe pneumonia <p><u>Severe pneumonia:</u></p> <ul style="list-style-type: none"> - adolescent or adult: fever or suspected respiratory infection, plus one of following: respiratory rate >30 breaths/min, or, severe respiratory distress, or, SpO₂ $<90\%$ on room air - child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO₂ $<90\%$, or, severe respiratory distress (e.g. grunting, very severe chest indrawing), or, signs of pneumonia with a general danger sign including inability to breastfeed or drink, lethargy, unconsciousness or convulsion^[53] 	<p><u>Mild:</u></p> <ul style="list-style-type: none"> - mild symptoms, no pneumonia on imaging <p><u>Moderate:</u></p> <ul style="list-style-type: none"> - fever, respiratory symptoms, pneumonia on imaging <p><u>Severe:</u></p> <ul style="list-style-type: none"> - adults (any 1): dyspnea (RR ≥ 30), SpO₂ $\leq 93\%$, PaO₂ / FiO₂ ≤ 300mmHg, $>50\%$ progression on imaging - children (any 1): dyspnea, SpO₂ $\leq 92\%$, use of accessory muscles for breathing, somnolence/ convulsions, difficult feeding, dehydration <p><u>Critical (any 1):</u></p> <ul style="list-style-type: none"> - respiratory failure requiring mechanical ventilation, shock, multiorgan failure requiring ICU support
Clear from suspected case	Negative RT-PCR test for SARS-CoV-2 unless patient has strong epidemiological link or worsening clinical conditions	No specific guidance	<p>Negative results from at least two consecutive RT-PCR tests for SARS-CoV-2 at least 24 hours apart</p> <p>AND</p> <p>Negative IgG and IgM antibodies against SARS-CoV-2 at least 7 days after symptom onset</p>
When to discharge a confirmed case	<p>Meeting ALL of the following criteria:</p> <ul style="list-style-type: none"> - improvement of clinical conditions and afebrile - with two clinical specimens tested negative for SARS-CoV-2 taken at least 24 hours apart - agreed by Medical Control Officer of Department of Health^[52] 	<p>For hospitalized patients, meeting ALL of the following criteria:</p> <ul style="list-style-type: none"> - Clinically recovered - Two negative tests on respiratory specimens at least 24 hours apart^[66] 	<p>Meeting ALL of the following criteria:</p> <ul style="list-style-type: none"> - afebrile for 3 days or more - significant improvement in respiratory symptoms - significant improvement in imaging findings - negative RT-PCR tests from 2 respiratory specimens taken 24 hours apart



	US	EU ^[57]	UK ^[58]
Severity of illness	<ul style="list-style-type: none"> - Requires hospitalization - Does not require hospitalization (i.e. homecare)^[65] 	No specific classification	No specific classification
Clear from suspected case	<p>Negative RT-PCR test for SARS-CoV-2 means that the PUI is not infected at time of specimen collection. However, negative test does not rule out false negative cases in early stages of infection</p> <p>If a higher level of clinical suspicion for COVID-19 exists, consider maintaining Transmission-Based Precautions and performing a second test for SARS-CoV-2</p>	A single negative RT-PCR test for SARS-CoV-2 (especially if from an upper respiratory tract specimen) or a positive test result for another respiratory pathogen result does not exclude COVID-19. If there is a strong suspicion, another specimen should be tested with the primary and secondary RT-PCR assays	Negative RT-PCR test for SARS-CoV-2
When to discharge a confirmed case	<p>Decision to discontinue transmission-based precautions can be assessed by:</p> <p>Test-based strategy:</p> <ul style="list-style-type: none"> - Resolution of fever without the use of medications, and - Improvement in respiratory symptoms, and - Negative results of SARS-CoV-2 from at least 2 consecutive nasopharyngeal swab specimens collected ≥ 24 hours apart <p>Or</p> <p>Non-test-based strategy:</p> <ul style="list-style-type: none"> - At least 3 days (72 hours) since recovery defined as resolution of fever without the use of medications and improvement in respiratory symptoms and, - At least 7 days have passed since symptoms first appeared 	<ul style="list-style-type: none"> - Clinical criteria (e.g. no fever for > 3 days, improved respiratory symptoms, pulmonary imaging showing obvious absorption of inflammation, no hospital care needed for other pathology, clinician assessment) - Laboratory evidence of SARS-CoV-2 clearance in respiratory samples with 2 to 4 negative RT-PCR tests for respiratory tract samples (nasopharynx and throat swabs with sampling interval ≥ 24 hours). - Serology: appearance of specific IgG when an appropriate serological test is available <p>Mild cases may be discharged provided that they are placed into home care equipped for self-isolation or another type of community care. After discharge, 14 days of further isolation with regular health monitoring can be considered^[66]</p>	If patient is clinically well, they can be discharged after appropriate clinical assessment and testing, risk assessment of their home environment and arrangements for safe transport are made



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