Abstract. Coronavirus disease 2019 (COVID-19) is a highly infectious type of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has rapidly become a global pandemic. COVID-19, SARS and Middle East respiratory syndrome (MERS) are all caused by members of the Coronaviridae family. As expected, emerging genetic and clinical evidence from patients with COVID-19 has indicated that the pathway of infection is similar to that of SARS and MERS. Additionally, much like SARS and MERS, chest imaging serves an important role in the diagnosis, management and follow-up of patients with COVID-19. Although these related viruses present a similar pneumonic pathogenesis, the imaging results have distinguishable features. The current review evaluated the imaging results of patients with SARS and MERS and explored the potential similarities and differences among patients with COVID-19, SARS and MERS at early, progressive, severe and recovery stages, with the aim of improving our understanding of SARS-CoV-2 infections by comparing the features of COVID-19 images with those of SARS and MERS. The current review assessed whether imaging results had implications for the administration of corticosteroids as treatment for COVID-19. Whether corticosteroids can inhibit inflammatory cytokine storms and reduce the mortality of patients with viral pneumonia remains controversial. However, his review may help radiologists and clinicians to identify viral pneumonia and guide appropriate COVID-19 treatment.

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1. Introduction

The outbreak and subsequent pandemic of Coronavirus disease 2019 (COVID-19) is a public health emergency of international concern (1). As of December 16, 2020, a total of 71,581,532 confirmed cases and 1,618,374 deaths have been reported by the World Health Organization (WHO) (2). COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was most likely transmitted to humans from wild bats (3). SARS-CoV-2 closely resembles SARS-CoV (79% sequence identity) and Middle East respiratory syndrome coronavirus (MERS-CoV) (51.8% identity) (4), both of which are also believed to have originated in bats (5,6). All three of these viruses are members of the Coronaviridae family.

Coronaviruses often cause a series of diseases in humans and animals, ranging from the common cold to more severe illness, such as pneumonia. Zoonotic transmission of coronaviruses, such as SARS-CoV, SARS-CoV-2 and MERS-CoV, may be associated with severe lower respiratory tract infections. These related infections present as pneumonia as the primary clinical feature, sharing symptoms including fever, cough and shortness of breath (7).
Although viruses within the same family often share similarities in the pathogenesis of pneumonia, their imaging results may exhibit distinguishable features. As for the Coronaviridae family, imaging is an important basis for the diagnosis and evaluation of the underlying viral infections. However, to the best of our knowledge, no studies have summarized the imaging features at different stages of coronavirus pneumonias. To highlight the differences, the current review presents imaging features at the early, progressive, severe and recovery phases of these viruses.

2. Pathogenesis and pathological manifestations of coronavirus

Coronavirus infections first enter susceptible host cells by binding to specific receptors (8). Angiotensin converting enzyme 2 (ACE-2) is a receptor of SARS-CoV and is expressed in tracheobronchial epithelial cells, alveolar epithelial cells and in monocytes and macrophages (9). The downregulation of ACE-2 is considered to be associated with SARS-CoV-induced lung injury (10). The structure of SARS-CoV-2 is similar to that of SARS-CoV, suggesting that the virus may utilize ACE-2 receptors in alveolar type II epithelial cells for cell invasion, thereby replicating into bronchial epithelial cells (11). Smoking and obesity increases the expression of the ACE-2 gene, which explains why smokers and obese individuals are susceptible to infection (12,13). Smoking and obesity are also independent risk factors for the deterioration of COVID-19 infection (12,13). ACE-2 receptors are present in many animals, which enables inter-species contamination (14). The efficiency of binding depends on the affinity between the receptor-binding domain of the virus and the species-specific ACE-2 receptor (14). As such, it is likely that the clinical characteristics and infectivity of SARS and COVID-19 are similar, especially in severe cases (15). Dipeptidyl peptidase-4 is a receptor for MERS-CoV, which is a versatile cell surface protein (16). This virus demonstrates high homology in its primary and tertiary structure with the receptor-binding domain of SARS-CoV (16). However, the simulation of their protein structure exhibits a disparity in the receptors (ACE-2 and dipeptidyl peptidase-4) between the two coronaviruses, and the mechanism that causes this phenomenon remains unclear (17).

Pathological changes of the lung observed in patients with SARS-CoV infection are usually diffuse, involving several lung lobes and manifesting as diffuse alveolar damage (18,19). Histopathological assessment of MERS-CoV infection has indicated necrotizing pneumonia, pulmonary diffuse alveolar damage and acute kidney injury (20). On 27 January 2020, a death attributed to COVID-19 was pathologically dissected for the first time in China. The pulmonary manifestations were diffuse alveolar injury and hyaline membranes, which are consistent with acute respiratory distress syndrome (ARDS) (21). However, another report of five cases revealed that no viral cytopathic changes were observed in COVID-19. Moreover, diffuse alveolar injury with hyaline membrane formation, inflammation and type II pneumocyte hyperplasia were not prominent (22). Therefore, microvascular injury alongside thrombosis may serve an important role when hyaline membrane formation is not prominent in certain patients. Although the overall pathological manifestations of the lungs are similar to SARS and MERS, there are also differences.

3. Imaging at different stages of disease progression

COVID-19, SARS and MERS are novel infectious diseases with general stages of progression that are consistent with other infectious diseases, such as influenza. These can manifest as different clinical types following the natural course of the disease and during the pathophysiological changes that occur (18,19,23). Combined with clinical classification and imaging features (18,23), the progression of these diseases is currently classed into four stages: Early, progressive, severe and recovery.

Early stage. In this stage, clinical symptoms exhibited by patients with COVID-19 are mild to moderate, although some patients are asymptomatic. Usually there is no imaging evidence of pneumonia in patients that are asymptomatic or those with mild symptoms, and the changes of imaging are often atypical, which may result in omissions. For example, Zhang et al (24) demonstrated that high-resolution computed tomography (HRCT) exhibited multiple instances of ground-glass opacity (GGO) and may be accompanied by consolidation in patients with early stage COVID-19. The study also revealed that certain patients did not present imaging results that were indicative of pneumonia, and others exhibited normal chest radiographs, but HRCT results revealed pneumonia. Therefore, with imaging as an important supplement to the screening of COVID-19, HRCT should be recommended as the initial imaging technique, as X-rays often result in missed diagnoses in the early stage. Pulmonary CT manifestations are usually as follows: i) GGO or consolidation changes, in which multiple lesions on the bilateral lung are common. The scope of consolidation is small and localized (25); ii) the density of the lesions is uneven, and they are distributed in a localized manner. Generally, only parts of the lung segment are affected, mostly within the extrapulmonary zone and the lower lung (25); iii) there are no manifestations of mediastinal or hilar lymphadenopathy, pleural thickening or pleural effusion (26). Typical HRCT patterns of patients with early stage COVID-19 are presented in Fig. 1A and B.

SARS is an acute infectious disease with fever as the first and primary symptom, often occurring without upper catarrhal symptoms (18). At the early stage, the time from clinical symptom presentation to chest imaging abnormalities is generally only 2-3 days. X-rays and CT scans of the lungs demonstrate small or round-shaped GGO, with some patients presenting this alongside lung consolidation. Single lesions are more common, and those involving the lung segment are rare. Most of the lesions are distributed in the lower field and lateral bands of both lungs (18).

The early stage of MERS usually manifests as an acute respiratory infection. Patients with low immune function or underlying diseases, including coronary heart disease and diabetes, may have more severe symptoms, such as dyspnea (27). However, for those without underlying disease, symptoms are mild or asymptomatic, and some patients do not exhibit imaging changes (28). The primary features of the lung that are visible in HRCT images are GGO changes...
and occasionally mixed consolidation or small nodules, most of which are distributed in the subpleural and basal lung regions (29,30). Some cases may demonstrate varying degrees of pleural effusion (31,32).

Early imaging features of the three diseases share several similarities. GGO is the primary symptom, and a small degree of consolidation may be observed. Lesions generally do not affect the entire lung segment and are most common in the lower lung field and lateral bands. However, certain patients with COVID-19 do not present changes in chest images in the early stage, whereas patients with SARS demonstrate pneumonia within a short period of time (2-3 days). The reasons for this difference may be the duration of the viral incubation period, the method of virus detection used or the popularity of pulmonary HRCT. The reason of pulmonary HRCT being not commonly used is attributed to the cost of the CT examination and the doctors' cognitive level of the characteristics of different coronavirus diseases. The aforementioned similarities and differences of early-stage features of COVID-19, SARS and MERS are summarized in Tables I and II.

Progressive stage. There are several pulmonary HRCT imaging features of COVID-19: i) The confluence or expansion of GGO lesions may be demonstrated, with some being accompanied by certain reticular changes, such as the ‘crazy-paving pattern’. Sometimes lesions appear as consolidations, and signs of air bronchogram may be observed. GGO can also appear around consolidations or other lung fields (26). ii) The lesion area may increase due to multiple lesions fusing together or through diffusion into multiple lung lobes, demonstrating asymmetric distribution in the lungs. This is most commonly observed feature in the middle and lateral bands. iii) Enlargement of the mediastinum and hilar lymph nodes may occur, although this is rare. The lesions progress rapidly and clear changes in imaging morphology appears within a short period (several days) (25,26). Active treatment is required and the possibility of ARDS must be considered (26). Typical imaging patterns of progressive stage COVID-19 are presented in Fig. 1C and D.

In the progressive stage of SARS, fever and other symptoms of infection persist, with imaging demonstrating progressive
deterioration within 3-7 days after onset (18). The features of pulmonary CT imaging are as follows: i) GGO increases or occurs alongside consolidation, and the lesions are large or diffuse; and ii) the lesions may spread from one lung field to multiple lung fields, with lesions of the unilateral lung progressing into the bilateral lung. Lesions are distributed in
multiple lung lobes, but primarily in the lower lobe, with a mixed distribution in the inner and outer lung fields (18,33). However, central distributions are rare (18). At this stage, pulmonary lesions proliferate.

From the date of onset, MERS can progress within 2-3 weeks. Additionally, certain patients may progress rapidly from asymptomatic infection to pneumonia within 4-7 days (34-36), demonstrating pneumonia-associated clinical symptoms and typical imaging changes (37). Multifocal nodular consolidation with rapid progression in the lower lung and the lateral zone of the lung may be demonstrated in pulmonary HRCT images. This is often accompanied with a GGO halo. The similarities and differences in images at the progressive stage of COVID-19, SARS and MERS are summarized in Tables I and II.

### Severe stage.

A retrospective study by Guan et al (39) summarized the clinical characteristics of 1,099 patients with COVID-19 in 552 hospitals located in China. The results revealed that 15.7% of patients developed severe pneumonia. An additional study demonstrated this value to be 25.5% (40). For COVID-19 to be classified as severe, patients must meet any of the following criteria: i) Respiratory distress (respiratory rate, ≥30 breaths/min), ii) oxygenation index ≤300 mmHg, iii) finger oxygen saturation ≤93% in a resting state and iv) chest images presenting >50% lesion progression within 24-48 h (23).

Pulmonary HRCT images suggest that as the GGO density increases, the lesions fuse and progress into multiple, large and diffuse consolidations on the bilateral lung from the periphery to the center, involving multiple lobes and presenting as “white lung”. Additionally, certain patients demonstrate a small degree of pleural effusion. This phase of treatment is difficult, and the mortality rate is 49%. Certain patients may exhibit insignificant changes in imaging, despite worsening clinical symptoms. This is most common in patients with other underlying diseases, such as cerebral vascular disease (26). Typical imaging patterns of patients with severe COVID-19 are presented in Fig. 1E and F.

The majority of patients with SARS enter the very severe stage 2-3 weeks after onset. Imaging morphology and lesion range change rapidly at this stage, with some changes in chest imaging occurring within 1-3 days (33,41). Patients may demonstrate ‘white lung’ in images, which indicates that ARDS had occurred (41). ARDS may develop in 10-15% of patients with SARS (41,42), which is a life-threatening condition. The presentation of ‘white lung’ in images may indicate poor prognosis and death, but it can also disappear after treatment in certain patients (18). In addition, SARS in the severe stage is prone to relapse. The imaging of certain patients may indicate that the lesion has disappeared; however, it may then reappear or become aggravated in a short period of time (18).

Most severe cases of MERS progress into severe pneumonia within 1 week. This can lead to ARDS, acute renal failure, septic shock or multiple organ failure. Patients with MERS are more prone to acute renal failure than those with SARS (29,37). The WHO reported that 12.4% of patients with MERS develop ARDS (43). The primary imaging feature of this stage is bilateral interstitial infiltration that progresses rapidly (44). Furthermore, imaging typically indicates the deterioration of lesions, including those patients previously presenting with ‘white lung’. The changes in images are rapid and require attentive monitoring (30).

The differences in imaging features between COVID-19, SARS and MERS include the progression rate of lesions, the likelihood of pleural effusion, the main clinical manifestations of consolidation or GGO and whether the consolidation or GGO is the primary manifestation. The similarities and differences in images at the severe stage of these diseases are summarized in Tables I and II.

#### Recovery stage.

The recovery stage of COVID-19 typically occurs 1-2 weeks after the onset of pneumonia. The imaging features include a decrease in the scope and density of lesions, a gradual disappearance in consolidation lesions and the beginning of organizing pneumonia. The lesions may completely disappear, or part of the funicular shadow may remain (25,26). Changes in imaging at the recovery stage generally lag behind the improvement of clinical symptoms (25). However, the lesions may subsequently enlarge, or new lesions may appear in certain cases (25). Typical imaging patterns of patients in recovery stage of COVID-19 are presented in Fig. 1G and H.

The majority of SARS cases proceed to the recovery stage within 2-3 weeks after onset. The range and density of the lesions observed in images may exhibit a gradual decrease, or they may disappear entirely. Pulmonary fibrosis is also a common imaging feature during recovery (18). Patients with severe cases are more prone to pulmonary fibrosis compared with those with ordinary infection, with fibrosis disappearing at a slower rate (45). The majority of patients recover within 2-3 months post-discharge (18) and 7-8% of patients demonstrate pronounced sequelae of pulmonary fibrosis (46).

The imaging features of patients with MERS during the recovery stage include the scope of lesions decreasing significantly and certain patients experiencing left pulmonary fibrosis. The rate of improvement in clinical symptoms is slightly faster than what is exhibited by images (30,34). A case study reporting imaging follow-up revealed that abnormalities in multiple nodules combined with GGO declined after treatment, but progression in fibrosis was observed (34).

The overall condition of patients with COVID-19, SARS and MERS during the recovery stage tends to be stable, and images usually indicate that the lesions have gradually disappeared. In general, changes in imaging occur later than improvements in clinical manifestations. Regarding disease progression, the recovery stage of COVID-19 is earlier than that of SARS; however, some patients with COVID-19 may exhibit recurrent conditions that require attention (47). The similarities
and differences in images at the recovery stage of COVID-19, SARS and MERS are summarized in Tables I and II.

4. Suggestions for viral pneumonia chest imaging

Chest imaging is important to the diagnosis, management and prognosis of patients with viral pneumonia. The benefits of imaging are numerous.

Evaluation of imaging when diagnosing patients at their first hospital visit. The majority of chest images obtained at the first hospital visit in patients with SARS or MERS are abnormal, which aids the successful and early diagnosis of patients (18,31). However, for patients exhibiting early stage COVID-19, the interpretation of imaging results requires careful attention. Guan et al (39) demonstrated that radiologic abnormalities were not identified in the initial presentation of 17.9 and 2.9% of non-severe and severe cases, respectively. Although the detection of viral nucleic acid is the first method used to diagnose COVID-19, and while chest imaging should not replace this method, many countries are still facing a shortage of nucleic acid reagents, particularly in poor and developing countries (48,49). During the early stages of COVID-19 outbreaks or during large-scale outbreaks, the flowchart for screening COVID-19 presented in Fig. 2, which was constructed based on our previous clinical experience in Wuhan, may be used as a reference for diagnosis in the absence of nucleic acid testing kits.

Evaluation of lesion scope for prognosis. A previous study that assessed the clinical outcome of 70 patients with MERS revealed that the imaging manifestations of the bilateral lung were a risk factor for intensive care unit admission (44). Imaging manifestations of patients with severe COVID-19 include bilateral lung involvement and interstitial change, which indicates poor prognosis (39). Patients with SARS may demonstrate multiple lung lobe lesions. If the range of lesions usually exceeds one third of the lung lobe, the patient may be at the severe stage of infection (54).

Effect of early diagnosis on prognosis. As of December 16, 2020, the mortality rate of patients with COVID-19 has been reported to be 2.26% worldwide (2). However, among male patients aged ≥60, an initial diagnosis of severe pneumonia
and a delay in diagnosis were associated with elevated mortality rates (40). Early diagnosis is an important measure for the prevention of severe pneumonia or death, and imaging examination may therefore be helpful. The majority of patients with severe cases demonstrate imaging abnormalities at the time of onset, and consolidation generally indicates disease progression. Pleural effusion, pneumomthorax, bilateral lung involvement and the rapid progression of lesions can be indicative of severe cases. If necessary, chest X-rays or pulmonary CT scans should be re-examined within 48 h (25,56). Chest imaging can be used for early diagnosis, the early identification of severe cases and for early treatment guidance. It can also reduce the risk of death (25).

5. Imaging implications for corticosteroid therapy

The current COVID-19 pandemic has urged the scientific community internationally to find methods in terms of therapeutics and vaccines to control SARS-CoV-2. Despite the rapidly increasing volume of scientific data on the possible treatments of COVID-19, none have yet demonstrated unequivocal clinical utility against the virus (57). For COVID-19, the immunization of a population through vaccination is recognized as a public health priority (58). WHO and other national organizations collaborate on the response and tracking of the COVID-19 pandemic, advising on critical interventions and attempting to develop safe and effective vaccines (2). As of 12 December 2020, three COVID-19 vaccines (Pfizer, Moderna and AstraZeneca) have been authorized by certain national regulatory authorities. None have yet received WHO emergency use listing authorization, but an assessment of the Pfizer vaccine by WHO is expected by WHO (59).

As research and clinical trials continue to develop vaccines and therapies, scientists have gained an increased understanding of Coronaviridae characteristics. For example, the acute aggravation of SARS and MERS is considered to be associated with cytokine storms. Previous studies have suggested that prolonged and dysregulated cytokine production occurs in SARS (60), and large increases in pro-inflammatory cytokines in the serum of patients with SARS have been associated with extensive inflammatory damage to the lungs (61). Additionally, Mahallawi et al (62) analyzed cytokine responses in plasma samples obtained from patients with MERS. The results demonstrated a marked pro-inflammatory cytokine response during the acute phase of MERS-CoV infection. Furthermore, Liu et al (63) suggested that a cytokine storm may also be associated with disease severity and should be considered as an important cause of death in patients with severe and critical COVID-19.

Corticosteroids are commonly used to treat patients with severe pneumonia, with the purpose of inhibiting abnormal pathological immune responses and reducing systemic inflammation. Chest imaging evaluation may also provide a basis for assessing the severity of lung injury to guide the use of corticosteroids (64). The evaluation of lung images may help to determine whether corticosteroids can be used in patients with SARS. The imaging features of corticosteroid use correspond to an X-ray exhibiting large or multiple pulmonary shadows that progress rapidly, and a lesion area that increases >50% within 48 h and accounts for over one quarter of the bilateral lung area. However, previous studies have demonstrated that corticosteroids may increase the mortality rate of patients with SARS and delay viral clearance (65,66). At present, there are conflicting opinions on whether to administer corticosteroids to patients with MERS. The Chinese expert consensus recommendation for the use of corticosteroids for COVID-19 suggests that imaging-confirmed pneumonia and rapid progression are conditions for which corticosteroid application must be considered (67). According to China’s Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Version 7) (3), patients with progressive deterioration of the oxygenation index, rapid progression that is visible following imaging and patients exhibiting an increased inflammatory response may receive a short course of corticosteroids for 3-5 days as appropriate. An early short course of methylprednisolone in hospitalized patients with moderate to severe COVID-19 has been confirmed to reduce escalation of care and length of hospital stay (68).

It is important to avoid high-dose corticosteroid shock therapy, as this approach delays the clearance of coronavirus due to immunosuppression (69). The dosage and course of treatment should be adjusted based on the severity of the patient’s condition and disease status, with an overall goal of medium dosage and short course of treatment (67,70). For example, methylprednisolone is usually administered at a dosage of 40-160 mg once per day for 5 days, with a maximum course lasting no more than 7-10 days (70).

Whether corticosteroids can prevent inflammatory cytokine storms and reduce the mortality of patients with viral pneumonia remains unclear. It is expected that high-quality clinical studies (large sample, multicenter, randomized, double-blind, placebo-controlled trials) will provide more evidence to guide practice. Once corticosteroid therapy is required, chest imaging evidence is a crucial factor to consider.

6. Conclusion

Although the imaging results of COVID-19, SARS and MERS demonstrate clear similarities, there are also differences that must be considered. The present review has summarized the key imaging features of coronavirus pneumonia at different stages in order to aid its diagnosis. The imaging features of SARS and MERS provide a reference for the better prevention and control of COVID-19.

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Authors’ contributions

LL and YGW conceived the project. YBC and LYG contributed to drafting the manuscript. YQI, FTF and JL contributed to searching the electronic databases and interpreting the image data. LL, YGW, MC and HPY revised the contents and polished the language of the translation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The images in the manuscript came from a clinical study of Chinese medicine in the treatment of COVID-19, which was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese medicine (Guangzhou, China; approval no. 2020-049-01). All participants provided informed consent for participation in the study. In the informed consent form, it was clearly stated that the participant agreed that their data and biological specimens of this project may be used for other studies.

Patient consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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