Review Article

COVID-19 and Pulmonary Involvement

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Abstract

The COVID-19 pandemic results in the largest global health crisis. Most patients are asymptomatic. Pneumonia usually develops in about one week after infection, with approximately 5% of patients needing ICU admission due to hypoxemia or acute respiratory failure. The common symptoms of patients with COVID-19 pneumonia are fever, cough, and sputum production. Typical radiographic features of pneumonia are bilateral lower lobe lesions with ground-glass opacities or consolidations. N95 respirator in combination with personal protective equipment are necessary to prevent COVID-19 from spreading among healthcare workers during aerosol-generating procedures. Hemodynamic and ventilation management of critically ill patients with COVID-19 should follow established guidelines. Remdesivir and dexamethasone are beneficial in hospitalized patients with COVID-19 pneumonia who require supplemental oxygen or mechanical ventilation. Favipiravir can reduce the duration of hospital stay and time for clinical treatment in hospitalized COVID-19 patients. Evidence regarding the benefits of other medications remains conflicting.

Keywords: Acute respiratory distress syndrome, COVID-19, Ground-glass opacity, Pneumonia

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Introduction

Coronaviruses are enveloped ribonucleic acid (RNA) viruses belonging to the family Coronaviridae. They are important human and animal respiratory pathogens. In the past, there were the two strains of these viruses causing spreading i.e. severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are zoonotic in origin and have been linked to sometimes fatal illness.[1] SARS-CoV was the causal organism of the severe acute respiratory syndrome outbreaks in 2002 and 2003 in Guangdong Province, China.[2] MERS-CoV was the pathogen causing severe respiratory disease outbreaks in 2012 in the Middle East.[3] At late December 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China.[1, 4] It rapidly spread, resulting in a global pandemic. The disease is designated coronavirus disease 2019 (COVID-19).[5] The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as novel coronavirus 2019 (2019-nCoV).[6]

Clinical features and respiratory manifestations

Asymptomatic infection

For confirmed COVID-19 cases in some settings, asymptomatic at the time of diagnosis were 56 - 78%.[7, 8] Of those, approximately 43 - 89% remained asymptomatic over time.[4, 7, 8] Some people who are asymptomatic at the time of diagnosis go on to develop symptoms occurred a median of 4 days (range in 3 - 7 days) after the initial positive reverse-transcription polymerase chain reaction (RT-PCR) test.[7]

Symptomatic infection

In a large study in China reported 44,672 confirmed infections showing varying in disease severity.[9] They were mild disease (no or mild pneumonia) in 81%, severe disease (eg, dyspnea, hypoxia, or > 50% lung involvement on imaging within 24 - 48 hours) in 14%, critical disease (eg, with respiratory failure, shock, or multiorgan dysfunction) in 5%, and the overall mortality rate was 2.3%. No deaths were reported among noncritical cases in this report.[9] Among hospitalized patients, the proportion of critical or fatal disease is higher. In a study of 2,741 COVID-19 patients in a New York City who were hospitalized, 24% died or were discharged to hospice.[10] Of 647 patients who received invasive mechanical ventilation, 60% died, 13% were still ventilated, and 16% were discharged by the end of the study.[10] In a study from China found 1,099 patients with laboratory-confirmed COVID-19. 5.0% were admitted to the intensive care unit (ICU), 2.3% underwent invasive mechanical ventilation, and 1.4% died.[11] Mortality rates in China studies are lower than the U.S. study because the severity of illness may be lower in Chinese patients.

The presenting symptoms included fever (43.8 - 83%),[11-13] cough (67.8 - 82%),[11-13] shortness of breath (31 - 56%),[12, 13] myalgias (11 - 23.8%),[12, 13] sore throat (5%), rhinorrhea (4%), chest pain (2%),[12] diarrhea (2 - 23%),[11-13] and nausea and vomiting (1 - 19%).[12, 13] The median incubation period was 4 days (interquartile range in 2 - 7 days).[11]

In a study of patients with COVID-19 pneumonia at China, more common symptoms were fever (86%), cough (78%), sputum production (18%), and myalgias (18%). Less common symptoms were headache (10%), dyspnea (10%), abdominal pain or diarrhea (8%), pharyngeal discomfort (7%), and chest pain (6%).[14]

Only approximately 25% of COVID-19 patients have comorbidities, but 60-90% of hospitalized infected patients have comorbidities.[15, 16] The most common comorbidities in hospitalized patients include hypertension (48 - 57%), diabetes (17 - 34%), cardiovascular disease (21 - 28%), chronic pulmonary disease (4 - 10%), chronic kidney disease (3 - 13%), malignancy (6 - 8%), and chronic liver disease (<5%).[15, 16]

COVID-19 pneumonia can be classified to 2 proposed phenotypes.[17] Type L and Type H are best identified by CT scan and are affected by different pathophysiological mechanisms. Type L is characterized by low elastance (i.e., high compliance), low ventilation-to-perfusion ratio, low lung weight, and low recruitability. Type H is characterized by high elastance, high right-to-left shunt, high lung weight, and high recruitability.[17]

Radiographic imaging in COVID-19 pneumonia

In a study from China of 1,099 COVID-19 patients, ground-glass opacity (GGO) was the most common radiologic finding (56.4%) on chest computed tomography (CT) in hospitalized patients on the admission.[11] No radiographic or CT abnormality was found in 17.9% with non-severe disease and in 2.9% with severe disease.[11]

In a study of 101 cases with COVID-19 pneumonia from China, most patients had typical imaging features; GGO (86.1%) or mixed GGO and consolidation (64.4%), vascular enlargement in the lesion (71.3%), and traction bronchiectasis (52.5%). Lesions present on CT images were more likely to have a peripheral distribution (87.1%) and bilateral involvement (82.2%) and be lower lung predominant (54.5%) and multifocal (54.5%).[18] Similar to a study of 99 cases with COVID-19 pneumonia in China, 75% showed bilateral pneumonia, 14% showed multiple mottling and ground-glass opacity, and 1% had pneumo-thorax. 17% developed acute respiratory distress syndrome (ARDS) and 11% worsened in a short period of time and died of multiple organ failure.[12]

The imaging pattern of multifocal peripheral ground glass or mixed opacity with predominance in the lower lung is highly suspicious of COVID-19 in the first week of disease onset. However, some patients can present with a normal chest finding despite testing positive for COVID-19.[11, 19]

In 83 patients with COVID-19 pneumonia in China, the risk factors for severe or critical pneumonia were age more than 50 years, comorbidities, dyspnea, chest pain, cough, sputum production, decreased lymphocytes, and increased inflammatory biomarkers i.e. C-reactive protein and procalcitonin.[14] CT findings of consolidation, linear opacities, crazy-paving pattern, bronchial wall thickening, high CT scores, and extrapulmonary lesions were features of severe or critical pneumonia.[14]

In a study from Thailand of 193 COVID-19 patients, the incidence of pneumonia was 39%. The median time from onset of illness to pneumonia detection was 7 days (rage in 5 - 9 days). Bilateral pneumonia was more prevalent than unilateral pneumonia. Predictive factors for COVID-19 pneumonia were increasing age (OR 2.5 per 10-year increase from 30 years old), obesity (OR 8.7), and higher temperature at presentation (OR 4.5 per 1˚C increase from 37.2˚C).[20]

In 132 patients with COVID-19 pneumonia in a respiratory care unit at Thammasat University Hospital, Thailand between 1st April 2021 and 31st July 2021 (preliminary internal audits), bilateral pneumonia was found in 132 patients (100%) especially in the lower lobes. GGO on chest radiograph was found in 99 patients (75%) (Figures 1 and 2).

Differences in chest radiographic findings of coronavirus pneumonia between severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19 are summarized in Table 1.[21] Interestingly, CT scan has significantly higher sensitivity than RT-PCR for detection in patients with COVID-19 pneumonia (69 - 100 %vs. 59 - 57%).[21] In this epidemic situation, CT plays an important role for early detection of COVID-19 pneumonia.[22] Typical CT features include peripheral GGOs with multifocal distribution, and a progressive evolution towards organizing pneumonia patterns.[22]

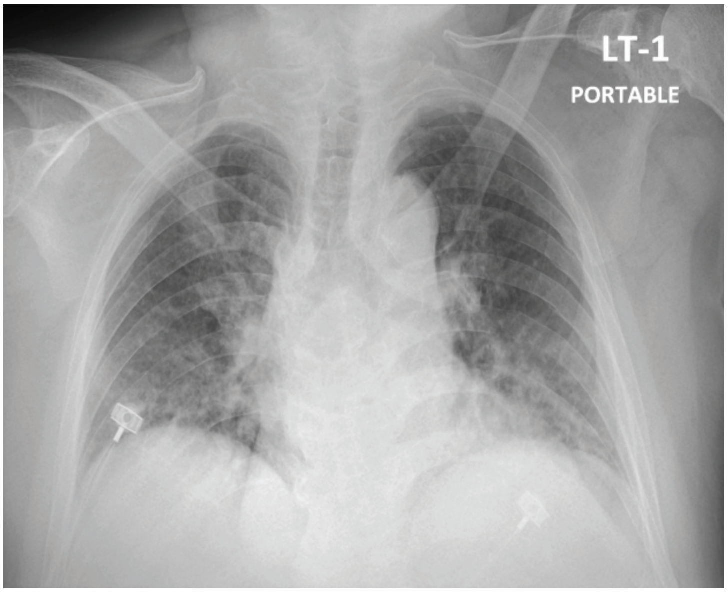

Figure 1 Chest X-ray shows bilateral infiltrates with grounglass opacities and consolidations of a 57-year-old man with COVID-19 pneumonia in a respiratory care unit at Thammasat University Hospital, Thailand (day 6 after onset of illness).

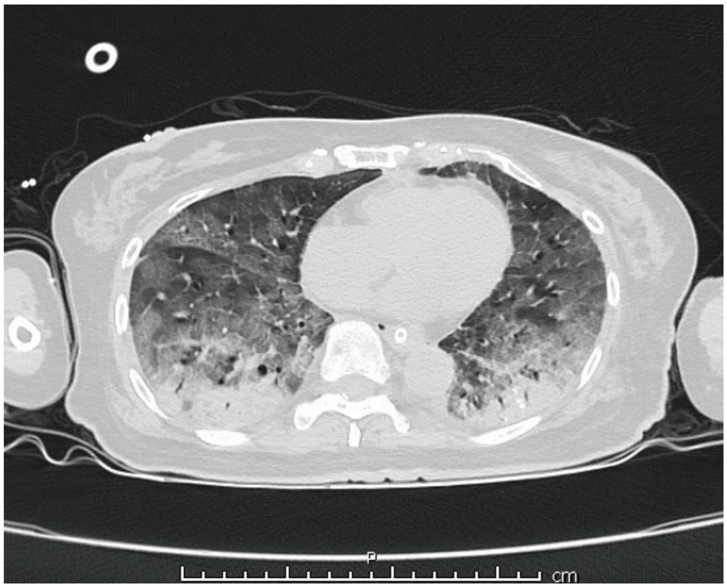

Figure 2 Chest computed tomography shows ground-glass opacities at anterior part of bilateral lungs and consolidations at bilateral posterior lobes of a 71-year-old woman with COVID-19 pneumonia in a respiratory care unit at Thammasat University Hospital, Thailand (day 14 after onset of illness).

Table 1 Chest radiography of coronavirus pneumonia[21]

Pneumonia	Abnormality	Imaging manifestation	Lesions location
SARS	58 - 90%	GGO 33%, Consolidation 78%	Unifocal 55%, Multifocal 45%, Unilateral 61%, Bilateral 39%, Low lung zone 74%
MERS	60 - 100%	GGO 65%, Consolidation 18%, Bronchovascular markings 17%, Diffuse reticulonodular pattern 4%, Air bronchogram 11%	Unifocal 40%, Multifocal 60%, Unilateral 23%, Bilateral 77%, Interstitial 67%
COVID-19	15 - 100%	GGO 24% Pneumothorax 1%	Unifocal 48%, Multifocal 52%, Unilateral 22%, Bilateral 78%, Interstitial 7%

COVID-19 = coronavirus disease 2019, GGO = ground-glass opacity, MERS = Middle East respiratory syndrome, SARS = severe acute respiratory syndrome

Other laboratory data

In 393 COVID-19 patients in a New York City, most of the patients (90.0%) had lymphopenia, 27% had thrombocytopenia, and many had elevated liver function values and inflammatory markers.[13] In a study from China, lymphocytopenia was present in 83.2% of the patients on admission.[11]

Patients who received invasive mechanical ventilation were more likely to be male, to have obesity, and to have elevated liver-function values and inflammatory biomarkers (ferritin, d-dimer, C-reactive protein, and procalcitonin) than were patients who did not receive invasive mechanical ventilation.[13] Bacterial infection was more common in critically ill patients (8.1%).[23]

Management of critically ill patients with COVID-19

Patients with severe disease often need oxygenation support. High-flow oxygen and non-invasive positive-pressure ventilation may be used, and they should be considered aerosol-generating procedures that warrant specific isolation precautions. Some patients may develop ARDS and warrant intubation with mechanical ventilation. Management of ARDS in patients with COVID-19 and other critical care issues are reviewed.

Guidelines for management of critically ill patients with COVID-19 have been issued by several societies and organizations.[24-27]

Infection control and testing

- For healthcare workers who are performing aerosol-generating procedures (AGP) on patients with COVID-19, the guidelines recommend using an N95 respirator (or equivalent or higher-level respirator eg, FFP2) rather than surgical masks, in addition to other personal protective equipment (PPE) (i.e., gloves, gown, and eye protection such as a face shield or safety goggles).[24, 25]
- The guidelines recommend minimizing the use of AGP on ICU patients with COVID-19 and carrying out any necessary AGP in a negative-pressure room (known as an airborne infection isolation room) when available.[24, 25]
- For healthcare workers who are providing usual care for non-ventilated patients with COVID-19, the guideline recommends using an N95 respirator (or equivalent or higher-level respirator) or a surgical mask in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles).[25]
- For healthcare workers who are performing non-AGP on patients with COVID-19 who are on

closed-circuit mechanical ventilation, the guideline recommends using an N95 respirator (or equivalent or higher-level respirator) in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) because ventilator circuits may become disrupted unexpectedly.[25]

- The guidelines recommend that endotracheal intubation in patients with COVID-19 be performed by healthcare providers with extensive airway management experience in order to minimize the number of attempts and risk of transmission, if possible.[24, 25]

- The guidelines recommend that intubation be performed using video laryngoscopy, over direct laryngoscopy, if possible.[24, 25]

- The diagnostic testing for intubated and mechanically ventilated adults with suspicion of COVID-19, the guideline suggests obtaining lower respiratory tract samples in preference to upper respiratory tract (nasopharyngeal or oropharyngeal) samples.[24]

- For intubated and mechanically ventilated adults with suspicion of COVID-19: With regard to lower respiratory samples, the guideline suggests obtaining endotracheal aspirates in preference to bronchial wash or bronchoalveolar lavage samples.[24]

Hemodynamics

- For adults with COVID-19 and shock, the guidelines recommend using dynamic parameters, skin temperature, capillary refilling time, and/or lactate levels over static parameters to assess fluid responsiveness.[24, 25]

- For the acute resuscitation of adults with COVID-19 and shock, the guidelines recommend using crystalloids over colloids, and buffered/balanced crystalloids over unbalanced crystalloids.[24, 25]

- For the acute resuscitation of adults with COVID-19 and shock, the guidelines **recommend against** the initial use of albumin for resuscitation.[24, 25]

- The guidelines **recommend against** using hydroxyethyl starches, gelatins, or dextrans for intravascular volume replacement in patients with sepsis or septic shock.[24, 25]

- The guidelines recommend norepinephrine as the first-choice vasopressor. The guide-lines recommend adding either vasopressin (up to 0.03 units/min) or epinephrine to norepinephrine to raise mean arterial pressure to target or adding vasopressin (up to 0.03 units/min) to decrease norepinephrine dosage.[24, 25]

- For adults with COVID-19 and shock, the guideline suggests titrating vasoactive agents to target mean arterial pressure (MAP) of 60 - 65 mmHg, rather than higher MAP targets.[24]

- When norepinephrine is available, the guidelines **recommend against** using dopamine for patients with COVID-19 and shock.[24, 25]

- The guidelines **recommend against** using low-dose dopamine for renal protection.[25]

- The guidelines recommend using dobutamine in patients with shock who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents.[24, 25]

- The guidelines recommend that all patients who require vasopressors have an arterial catheter placed as soon as practical, if resources are available.[25]

- For adults with COVID-19 and refractory septic shock who are not receiving corticosteroids to treat their COVID-19, the guidelines recommend using low-dose corticosteroid therapy (shock-reversal) over no corticosteroid therapy.[24, 25] A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses.[24]

Oxygenation and ventilation

- For adults with COVID-19, the guideline suggests starting supplemental oxygen if the peripheral oxygen saturation (SpO_2) is < 92%, and recommend starting supplemental oxygen if SpO_2 is < 90%.[24] The author recommends starting oxygen therapy when SpO_2 is < 92%.

- For adults with COVID-19 and acute hypoxemic respiratory failure on oxygen, we recommend that SpO_2 be maintained no higher than 96%.[24]

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the guideline suggests using high-flow nasal cannula (HFNC) over conventional oxygen therapy.[24]

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the guidelines recommend HFNC oxygen over noninvasive positive pressure ventilation (NIPPV).[24, 25] Helmet NIPPV with PEEP of 10 - 12 cmH_2O and pressure support of 10 - 12 cmH_2O significantly reduced the rate of endotracheal intubation but did not improve the number of days free of respiratory support within 28 days when compared to HFNC in patients with COVID-19 and moderate to severe hypoxemia.[28]

- In the absence of an indication for endotracheal intubation, the guidelines recommend a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available.[24, 25]

- For adults with COVID-19 receiving HFNC or NIPPV, the guideline recommends close monitoring for worsening of respiratory status, and early intubation in a controlled setting if worsening occurs.[24]

- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the guidelines recommend considering a trial of awake prone positioning to improve oxygenation.[25]

- The guidelines **recommend against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation.[25]

- In critically ill patients with COVID-19, the timing of intubation for acute respiratory failure is challenging and there are no standard recommendations. The author suggests that do not delay intubation until the patient has features of impending respiratory arrest (eg, respiratory rate > 30/minutes, accessory muscle use, abdominal paradox) or is on maximum noninvasive supportive care. Some authors suggest criteria for tracheal intubation in patients with COVID-19 pneumonia are alteration of consciousness, risk of airway inhalation, severe decompensated acidosis (pH < 7.2 - 7.25), severe hypoxemia (PaO_2 < 50 mmHg or SaO_2 < 90%) despite maximal noninvasive support, signs or symptoms of significant respiratory distress or tissue hypoxia (eg, respiratory rate > 25 - 30/minute, use of accessory respiratory muscles, sweating, dyspnea, tachycardia, increased blood lactate levels, etc.), and decision to implant venoarterial extracorporeal membrane oxygenation (VA-ECMO).[29]

- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of SARS-CoV-2 exposure to healthcare practitioners during intubation.[25]

- For mechanically ventilated adults with COVID-19 and ARDS[24, 25]:
    - o The guidelines recommend using low tidal volume (VT) ventilation (VT 4 - 8 mL/kg of predicted body weight) over higher VT ventilation (VT > 8 mL/kg).
    - o The guidelines recommend targeting plateau pressures of < 30 cmH_2O.
    - o The guidelines recommend using a conservative fluid strategy over a liberal fluid strategy.
    - o The guidelines **recommend against** the routine use of inhaled nitric oxide.

- For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS[24, 25]:
    - o The guidelines recommend using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy. If using a higher PEEP strategy (i.e. PEEP > 10 cmH_2O), clinicians should monitor patients for barotrauma. For Type H pneumonia patients should be treated as severe ARDS, including higher PEEP.[17] Whereas Type L pneumonia patients should be considered lower PEEP (8 - 10 cmH_2O).[17]
    - o For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the guidelines recommend prone ventilation for 12 - 16 hours per day over no prone ventilation.
    - o The guidelines recommend using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation.
    - o In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the guidelines recommend using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled.

- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies[24, 25]:

o The guidelines recommend using recruitment maneuvers rather than not using recruitment maneuvers.

o If recruitment maneuvers are used, the guidelines **recommend against** using staircase (incremental PEEP) recruitment maneuvers.

o The guidelines recommend using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off.

o There are insufficient data to recommend either for or against the use of extracorporeal membrane oxygenation in patients with COVID-19 and refractory hypoxemia.[25]

Pharmacologic interventions

- In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication.[25]
- If antimicrobials are initiated, the guideline recommends that their use should be reassessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy.[25]
- For critically ill adults with COVID-19 who develop fever, the guideline suggests using acetaminophen/paracetamol for temperature control, over no treatment.[24]
- For hospitalized patients with COVID-19 pneumonia who require supplemental oxygen or are mechanically ventilated, the guideline suggests remdesivir.[27] Remdesivir reduced the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection.[30]
- For hospitalized patients with COVID-19 pneumonia who require supplemental oxygen or are mechanically ventilated, the guideline suggests dexamethasone.[27] In patients hospitalized with COVID-19, the use of dexamethasone (6 mg daily for 10 days) reduced the 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone.[31]
- For adults who were hospitalized with COVID-19 pneumonia and had confirmed venous thromboembolism, the guideline suggests therapeutic anticoagulant therapy for 3 months to reduce the risk of recurrent venous thromboembolism.[27]
- For hospitalized patients with COVID-19 pneumonia who require supplemental oxygen or are mechanically ventilated, the guideline suggests not using hydroxychloroquine (HCQ).[27]
- In critically ill adults with COVID-19, the guideline suggests against the routine use of standard intravenous immunoglobulins, convalescent plasma, and lopinavir/ritonavir (LPV/r).[24]
- In COVID-19 patients who were admitted to ICU, favipiravir was significantly lower the length of hospital stay compared to LPV/r although there were no difference in the mortality rate from an observational study.[32] Moreover, favipiravir significantly improved in time to clinical cure but could not reduce time to the cessation of viral shedding in hospitalized patients with mild to moderate COVID-19 from a randomized controlled trial.[33]
- In hospitalized patients with COVID-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the progression to the composite outcome of mechanical ventilation or death, but it did not improve survival.[34]

Discussion

COVID-19 pneumonia is found about one-fourth to one-third of total infected cases. Only 14% and 5% are severe and critical disease, respectively. The common symptoms of patients with COVID-19 pneumonia are fever, cough, sputum production, and myalgias. Predictors for COVID-19 pneumonia are old age, obesity, and high temperature. Risk factors for severe or critical pneumonia are age > 50 years, comorbidities, dyspnea, chest pain, cough, sputum production, lymphopenia, increased inflammatory biomarkers (C-reactive protein and procalcitonin), and some CT findings. Typical chest imaging features were GGO and consolidation at bilateral lower lobes of lungs, however pneumothorax might be found (1%). The updated guidelines are considered for management of patients with COVID-19 pneumonia and critically illness. Helpful medications especially remdesivir and dexamethasone show positive clinical outcomes for patients with COVID-19 pneumonia. Favipiravir could reduce the length of hospital stay and time to clinical cure. Several medications including immunobiological drug (equine hyperimmune serum F(ab')2), bevacizumab, mefloquine, silymarin, vitamin C, vitamin D, herbal medicines (eg, *Andrographis paniculate*), and traditional Chinese medicine are still being investigated in ongoing clinical trials.

In summary, the COVID-19 pandemic results in the largest global health crisis. Pneumonia develops about one week after infection and approximately 5% needing ICU admission. Fever, cough, and sputum production are common symptoms of patients with COVID-19 pneumonia. Ground-glass opacities and bilateral lower lobe lesions are typical radiographic features of pneumonia. Hemodynamic and ventilation management of critically ill patients with COVID-19 should follow the established guidelines. Remdesivir and dexamethasone are beneficial in hospitalized patients with COVID-19 pneumonia who require supplemental oxygen or mechanical ventilation.

Conflict of interest

The author declares no conflict of interest.

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