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COVID-19: Clinical Manifestations and Management in Outpatient/Hospitalized Adults

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ABSTRACT

A new coronavirus, emerging toward the end of 2019, rapidly disseminated around the world and resulted in a pandemic. The virus was named as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the disease caused by the virus as coronavirus disease-2019 (COVID-19). The clinical spectrum of COVID-19 in adults varies from asymptomatic infection to acute respiratory distress syndrome and multi-organ dysfunction. Information on the disease and its management has been continuously updated, especially with the development of SARS-CoV-2 variants and vaccines against the virus. The disease is generally mild in most patients with COVID-19 and requires no medical intervention or hospitalization; follow-up and treatment in an outpatient setting are adequate. Patients with a risk of severe disease or unvaccinated patients, and elderly patients with comorbidities with dyspnea and deteriorated oxygenation should be admitted, treated and followed up at hospital. Current local sources and the individual evaluation of the patients is important in the management of the disease.

Keywords: Clinical findings, COVID-19, management, SARS-CoV-2

Introduction

Clinical Findings and Patient Management

Coronavirus disease-2019 (COVID-19), a newly emerging disease, originally emerged with symptoms of respiratory tract infection alone. In time, we learned that it is a disease with possible clinical findings in a spectrum from asymptomatic infection and mild respiratory tract symptoms to acute respiratory distress syndrome (ARDS), severe pneumonia and cardiovascular complications. Experience with the diagnosis, clinical properties and treatment of COVID-19 has gradually increase. Our understanding of the disease spectrum and optimal management strategies, particularly in the presence of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) variants and the vaccines, has been developing continuously. The clinical severity of the disease might be variable according to the viral load received and the immune response of the individual. Asymptomatic disease is quite common with a reported rate of 20%-40% varying on the population analyzed (1,2,3,4).

Individuals, asymptomatic at the time of the polymerase chain reaction (PCR) test might later develop symptoms, hence be presymptomatic. The start of the symptoms was an average of four days (3-7 days) after the first positive RT-PCR test in a study (5).

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The incubation period was 2-14 days in 98% of the patients, with a mean of 4-5 days (6,7,8). The median incubation period in SARS-CoV-2 Omicron variant (B.1.1.159) seems to be a little shorter and the first symptoms emerged in about three days (8,9).

Clinical Presentation

The most commonly reported symptoms in patients with COVID-19 are cough, muscle pain and headache. The fatigue, weakness, diarrhea, sore throat and abnormalities in taste and smell can also be seen. Mild upper respiratory tract symptoms (i.e. nasal congestion and sneeze) are seen more commonly in Delta and Omicron variants (10). Pneumonia is the most serious clinical picture (6,11). Some complaints such as loss of taste and smell are seen more frequently in COVID-19 compared with other viral respiratory tract infections; however, there are no specific and reliable symptoms to differentiate COVID-19. Nevertheless, the development of dyspnea approximately a week after the start of the first symptoms may suggest COVID-19. Clinical findings of Delta and Omicron variants were compared in an observational study evaluating the clinical symptoms of 63.000 confirmed COVID-19 cases. The most common symptoms in both variants were nasal congestion, headache, sore throat and sneezing, while sore throat was seen more frequently and abnormalities in the sensation of taste and smell were seen less commonly in the Omicron variant (10,12).

Symptoms are variable according to the severity of the disease. For example; fever, cough and dyspnea have been reported more widely in hospitalized individuals compared to outpatients. Atypical signs might be seen in the elderly and individuals with comorbidities, and manifestation of fever and respiratory symptoms might be delayed (13,14). However, the presence of fever and cough is inadequate to differentiate mild and severe cases and to reflect the prognosis (15). Dyspnea, on the other hand, is a powerful marker of severe disease. Dyspnea, in general, may develop in the second week of the disease course and might advance into hypoxemia (6). A clinical picture of viral pneumonia, possibly with fever, cough and hypoxia is dominant. Bilateral ground glass images and infiltration are seen in chest imaging (16).

Clinical Course of the Disease

The severity of COVID-19 infection is generally mild but can be variable from mild to a critical course (11,17). There is no definite and accepted clinical classification; although some authors have used the following grading (18):

· Mild cases: Symptomatic cases with no pneumonia in imaging studies,

· Ordinary cases: Fever and pneumonia in imaging studies,

· Severe cases: Dyspnea, hypoxia (SpO_2 ≤93%), abnormal blood gas analysis (PaO_2 <60 mmHg, $PaCO_2$ >50 mmHg),

· Critical cases: Dyspnea requiring mechanical ventilation, shock and other organ failure requiring admission to intensive care unit (ICU).

The risk of severe disease varies according to the age, underlying comorbidity and status of vaccination. Also, different variants of SARS-CoV-2 have been associated with varying severity of disease risks. For example, the Omicron variant seems to be associated with a less severe disease (10,19).

The case fatality rate reflects the death rate only among the confirmed cases. The infection fatality ratio (namely, expected death rate among all individuals with infection) is quite low since asymptomatic infection is common and many mild infections get undiagnosed, and should be around 0.15%-1% among unvaccinated individuals, though quite variable depending on the localization and risk groups (20,21,22). The rate of critical illness and mortality is higher among hospitalized and unvaccinated patients (15,23).

Advanced age is a significant risk factor for severe disease, the development of complications and death (6,11). The rates of severe disease and mortality may be higher in populations with a low socioeconomic level due to the scarcity of the sources. Cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer (especially hematologic malignancies, lung cancer, and metastatic disease), chronic kidney disease and obesity are significant comorbidities increasing the risk of severe disease (13,23,24,25). Vaccination decreases the risk of severe disease substantially and is associated with decreased mortality.

Complications

The most common complications are ARDS, arrhythmia, myocardial damage, heart failure, shock, thromboembolic complications, encephalopathy, stroke, motility disorders, ataxia, seizures and inflammatory complications.

Laboratory Findings

The most commonly seen laboratory findings in patients diagnosed with COVID-19 are lymphopenia, high levels of aminotransferase, lactate dehydrogenase (LDH) and inflammatory markers [i.e. ferritin, C-reactive protein (CRP), erythrocyte sedimentation rate] and abnormalities in coagulation tests (6,11,18,25). Lymphopenia is the most frequent laboratory sign of COVID-19; is present in 83% of hospitalized patients (6,11) and with a high D-dimer level, has

been associated with mortality (25). Procalcitonin, although in normal ranges at admission, is probably elevated in patients admitted to the ICU (11,17).

Outpatient Management

The clinical course is mild in the great majority of patients with COVID-19 and no medical intervention or hospitalization is required (26,27).

The phone consultation is appropriate to decrease the risk of communal spread whenever an individual with a definitive diagnosis has no complaints. However, patients should be encouraged to apply to hospitals when they have complaints such as high fever and dyspnea.

The risk of severe disease should be evaluated to deciding to hospitalize a patient presenting at the hospital. Hypoxia (SpO_2 <93%), tachypnea and infiltration in more than 50% of the lungs using imaging techniques and requirement of respiratory support have been defined as criteria for admission to the hospital in many countries, though they are still controversial. Other indications for hospitalization are conditions such as immunosuppression and acute renal failure. Patients with severe and critical disease (18) should absolutely be hospitalized. Dyspnea is an indication of hospitalization in the clinical picture of intermediate disease (28). In this country, according to the guidelines of the Ministry of Health, uncomplicated patients and cases with pneumonia with a mild-intermediate course are recommended to be followed up as outpatients and receive their drugs from hospital pharmacies (29).

Patients with the following criteria were assessed as having severe disease:

· Over 50 years of age (higher risk if over 65 years)

· Unvaccinated or inadequately vaccinated (30)

· Have comorbidities (13,23,25)

Dyspnea and impairment in oxygenation with the risk factors for developing severe disease might be used to guide clinicians for a decision to hospitalization. Anamnesis related to dyspnea, even when talking, should be carefully obtained. The patient can be hospitalized when the SpO_2 is ≤93% at admission, regardless of the severity of the dyspnea. Note that dyspnea can be manifested 4-8 days, and in some cases, even 10 days after the start of the symptoms (11,31). Outpatients with no dyspnea should be educated about the possible development of dyspnea later. Increasing dyspnea, dyspnea particularly at rest and chest pain, suggest development or advancement of pulmonary involvement.

Patients followed up at home, though not every patient, was asked to check their oxygen level by a pulse oximeter, if possible, twice daily and to inform their physicians if case the value was less than 95%.

Other than the respiratory status, orthostasis, dizziness, fall, hypotension, changes in consciousness (i.e. lethargy, confusion, behavioral changes, difficulty in weakening), cyanosis, and decreased urinary output are conditions that the outpatients should inform their physicians when present and should apply to the hospital. In that case, the patient should absolutely be re-examined and re-evaluated for hospitalization.

We observed that the clinical condition of the patient was more important in deciding the type of treatment in most patients with COVID-19 whom we had evaluated, rather than the laboratory tests and imaging of the lungs since the latter provided a limited benefit.

Patients followed up at home should be told about the appropriate infection control and isolation precautions during the disease and recovery periods (including to use a separate bedroom, whenever possible). Patients should be told who to call when they need help and how and when they should reach the emergency medical services. The home environment and social factors should be considered when deciding to determine whether the outpatient follow-up and treatment is appropriate.

Management of Hospitalized Patients

A patient admitted to the hospital is asked to wear a medical mask and is placed in a separate area so that the distance between the patient and other patients would be 2 meters. The patient is admitted into a single bed room, if available, and droplet isolation and personal protective precautions are applied both for the patient and the attending persons. Regular ventilation and cleaning of the room is provided. The vital signs of the patient (heart rate, rhythm, respiratory rate, blood pressure, body temperature, and oxygen saturation) are observed (32).

Our experience in the management of patients hospitalized for COVID-19 has substantially accumulated compared with the early days of the disease. Updated national and international guidelines should be followed on this subject (28,32).

Levels of CRP, D-dimer, LDH, troponin, CPK, ferritin, absolute lymphocyte count, associated with serious disease but with unknown prognostic value, and the tests reflecting organ dysfunctions and various comorbidities (i.e. alanine aminotransferase, aspartate aminotransferase, urea,

creatinine) that might affect the potential treatment should be assessed. Some of those tests are repeated daily, every other day and some when there is clinical deterioration.

Chest X-ray can be used in the follow-up of hospitalized patients. Computed tomography is necessary when a chest X-ray is inadequate or in cases of clinical deterioration (33). A routine electrocardiogram is initially obtained; however, no echocardiogram (ECHO) is necessary. ECHO should be obtained in cases of hemodynamic deterioration, increased troponin, or in cases suggesting cardiomyopathy.

The risk of secondary bacterial infections is quite low in COVID-19. Nevertheless, two sets of blood cultures and a sputum culture should be obtained and procalcitonin level should be checked when suspected. Laboratory values must be carefully evaluated not to reach unnecessary conclusions. For example, high levels of troponin do not necessarily show acute coronary syndrome in a patient with COVID-19 (34).

Clinical deterioration and ARDS might develop immediately after the emergence of dyspnea. Advancement into ARDS was seen to occur in a mean of 2.5 days after the start of dyspnea in patients with COVID-19 and development of ARDS in the initial studies (13). Supportive oxygen treatment is applied in most of the patients with dyspnea and SpO_2 ≤93%. Antiviral, anticytokine, anti-inflammatory and other current treatment modalities should be applied based on the oxygen requirement, presence of macrophage activation syndrome, level of chest involvement in imaging studies and the laboratory findings. No empirical antibiotic treatment should be administered to the patients diagnosed with COVID-19 for bacterial pneumonia. Secondary infection is not a prominent specification of this disease. However, when the diagnosis is uncertain, empirical bacterial pneumonia treatment can be started after obtaining samples such as sputum culture and urinary antigen test.

Anticoagulation should be started in all patients for venous thromboembolism prophylaxis in all hospitalized patients. However, recommendations for the intensity of the dosage are dynamic and the new evidence obtained from the clinical studies during the pandemics has changed to reflect the changes in the disease severity, such as in the milder disease with omicron variant and in vaccinated individuals. Additionally, the decision of prophylactic or therapeutic dose is based on a risk-benefit evaluation.

No negative effects of the non-steroidal anti-inflammatory drug have been proven in recent studies, in spite of concerns about their potential negative effects of them during the early days of COVID-19 (35,36).

The respired drugs should be applied through a measuring inhaler instead of a nebulizer, if possible to prevent the risk of aerosolization of SARS-CoV-2 by nebulization. Patients receiving angiotensin-converting enzyme inhibitor or angiotensin receptor blockers should continue to receive those medications, unless there is otherwise a need to stop the treatment (i.e. hypotension, acute renal damage) (37). No supportive evidence was found for associating use of renin-angiotensin system inhibitors and severe disease, in spite of the speculation about the possible high risk of COVID-19 patients taking these agents. Statin or aspirin should not be started in COVID-19 patients who had no indications for these drugs before the disease. No benefit of these medications was demonstrated in randomized studies. However, patients already on aspirin or statin should continue to receive their drugs.

Severe disease can be characterized as severe respiratory tract infection, ARDS, sepsis, septic shock, myocarditis, arrhythmia and cardiogenic shock, metabolic acidosis and coagulation dysfunction, acute renal damage, exacerbations of chronic lung disease and clinical pictures of multi-organ failure. ICU admission is required in such critical diseases.

Patients are evaluated for discharge with decreased oxygen requirement, regression of fever and improvement in the laboratory values. Patients should be followed up for a while by outpatient appointments or by phone calls after the discharge.

Ethics

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