Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **December 2021; 7(3):439-445**

REVİEW **DOI:** 10.19127/mbsjohs.959305

Approach to Respiratory System Involvement and the Symptom of Dyspnea in Covid-19 Disease

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Received: 29 June 2021, Accepted: 06 December 2021, Published online: 31 December 2021

Abstract

The Covid-19 pandemic, China at the end of 2019 and was declared a global pandemic by the World Health Organization on March 11, is still a serious public health problem. The international virus taxonomy committee named this virus as SARSCoV-2 and the disease caused by the virus as Covid-19 disease. The disease is transmitted from person to person through droplets. When the infected person coughs, sneezes, or speaks, the virus found in respiratory secretions is transmitted by direct contact with the mucosa. In addition, it can be transmitted upon bringing one's hands to the mucous membranes of the mouth, nose, or eyes after hand-to-hand contact with droplets produced by the coughing and sneezing of a sick individual.

The respiratory system is the system most affected by Covid-19 infection. The virus affects the respiratory system in 3 ways: acute respiratory distress syndrome (ARDS) with diffuse alveolar damage, diffuse thrombotic alveolar microvascular occlusion, and inflammatory mediator-associated airway inflammation. As a result of these 3 effects of the virus, impaired alveolar oxygenation, hypoxemia, acidosis and, consequently, dyspnea develops. Dyspnea occurs when breathing becomes disturbingly noticeable. Dyspnea is an important symptom that affects the prognosis of Covid-19 disease. The severity of the disease ranges from asymptomatic infection to critical illness. Dyspnea symptoms and respiratory system involvement are more common in critical illness. Primary care physicians should be familiar with respiratory system pathologies caused by the Covid-19 disease.

Keywords: Covid-19, Dyspnea, Pandemic

Suggested Citation: Demir GH, Tetik BK. Approach to Respiratory System Involvement and the Symptom of Dyspnea in Covid-19 Disease Mid Blac Sea Journal of Health Sci, 2021; 7(3):439-445

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Introduction

The Covid-19 pandemic, which emerged in Wuhan, China at the end of 2019 and was declared a global pandemic by the World Health Organization on March 11, is still a serious public health problem (1).

Iatrotropic stimulus, a term frequently used in family medicine, is defined as the reason that prompts a patient to seek out the care of a physician (2). Dyspnea is an important iatrotropic stimulus in Covid-19 disease. Furthermore, dyspnea is a symptom that should be alarming for family physicians. Distinctive problem-solving skills, which is one of the leaves of the WONCA tree of competencies in general practice, is the core competency that every family doctor should have. These such problem-solving skills should be used in the management of Covid-19 disease and in managing the symptom of dyspnea due to the disease. In this context, we aimed to examine in depth the respiratory system involvement in Covid-19 disease and the symptom of dyspnea associated with this involvement.

Taxonomy and Structural Features of the Coronavirus

According to the classification determined by the International Committee on Virus Taxonomy (ICTV), coronaviruses belong to the Nidovirales class of the Riboviria kingdom. The virus that causes the Covid-19 disease is the SARS-CoV-2 strain belonging to the Betacoronavirus genus in the Coronaviridea family. The international virus taxonomy committee named this virus as SARSCoV-2 and the disease caused by the virus as Covid-19 disease (3).

Coronaviruses are 65-125 nm in diameter and contain single-stranded ribonucleic acid (RNA) and feature rod-like extensions on their surface. These viruses were named Coronavirus (crowned virus) due to these rod-like extensions, based on the Latin meaning of "corona" meaning "crown"(4).

Coronavirus Infection Chain

According to epidemiological studies, wild animals (bat?) sold in the Huanan Seafood Wholesale Market are thought to be the first source of the infection chain. The disease is transmitted from person to person through droplets. When the infected person coughs, sneezes, or speaks, the virus found in respiratory secretions is transmitted by direct contact with the mucosa. In addition, it can be transmitted upon bringing one’s hands to the mucous membranes of the mouth, nose, or eyes after hand to hand contact with droplets produced by the coughing and sneezing of a sick individual. The majority of society is susceptible to the Covid-19 disease. Health workers, people over 50 years old, people with comorbidities (hypertension (HT), heart disease, diabetes mellitus (DM), malignancy, chronic obstructive pulmonary disease (COPD), kidney disease, etc.), people in care and rehabilitation centers, schools, military barracks, prisons, people living in migrant camps, and seasonal agricultural workers are especially vulnerable groups in terms of disease (5).

Pathogenesis of Coronavirus

Coronaviruses attach to the host cells via the spike (S) protein on the outer surface and thus enter the cell. The S protein regulates the entry of the virus into the host cell by recognizing the receptor in the target cell. The life cycle of the virus begins with the binding of the S protein to the Angiotensin-Converting Enzyme 2 (ACE2) receptor on the host cell surface (6). After the virus enters the host cell, viral antigens are presented to macrophages and T lymphocytes by antigen-presenting cells (7). Thus, the chain of inflammation, the severity of which varies according to the immune system and age of the person, develops. Infection primarily affects the innate immune system and causes the release of cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-18, etc.), especially interferon (7).

Clinical Symptoms of Covid-19 Disease

The most common symptoms in Coronavirus patients are fever, malaise, and cough. According to a study conducted in China, common clinical symptoms include fever (88.7%), cough (67.8%), fatigue (38.1%), dyspnea (18.7%), sore throat (13.9%), myalgia (14.9%), and headache (13.6%). In the same study, diarrhea (3.8%) and vomiting (5.0%) were found to be gastrointestinal symptoms of the virus (8).

Laboratory Findings of Covid-19 Disease

The most common laboratory findings in Covid-19 diagnosis were found to be lymphocytopenia (83.2%), thrombocytopenia (36.2%), and leukopenia (33.7%). High levels of infection markers such as C-reactive protein (CRP), ALT/AST in liver function tests, and D-Dimer, have also been frequently reported.

Changes in general laboratory values are summarized in the table 1 below (9).

Table 1. Changes in LaboratoryValues in Covid-19 Disease

Lab Test Name	Change in Test
Complete Blood Count	Decreased lymphocyte thrombocyte count Increase in the number of leukocytes and neutrophils
CD4+ T Cell Count	Decrease
CD8+ T Cell Count	Decrease
Ferritin	Increase
C Reactive Protein (CRP)	Increase
Sedimentation Rate	Increase
Procalcitonin	Increase
Interleukin 6 (IL-6)	Increase
CreatinineKinase	Increase
LactateDehydrogenase	Increase
D-Dimer	Increase
Troponin	Increase
AST	Increase
ALT	Increase

Radiological Findings of Covid-19 Disease

In Covid-19 pneumonia, bilateral, localized (especially in the middle and lower zone), peripherally weighted, irregularly boardered density increases and consolidation are seen on chest radiograph (10).

In the early stages of the disease, unilateral or bilateral subpleural ground-glass opacities are seen mainly in the lower lobes on Computed Tomography (CT). In the later stages of the disease, diffuse ground-glass opacities, interlobular and intralobular septal thickenings (curbstone appearance) and consolidations are detected with bilateral and multilobar distribution. Ground glass densities with more intense consolidation in a crescent or ring shape are called “reverse halo sign” and are frequently seen in Covid-19 disease (11).

Clinical Course in Covid-19 Disease

While mild infection is observed in 81% of symptomatic patients infected with Covid-19 disease, severe disease occurs in 14% of patients and critical illness occurs in 5% of patients (12).

Severe disease is predominantly seen in people with advanced age and underlying comorbidities. Studies have found that cardiovascular disease, DM, HT, chronic lung disease, cancer, chronic kidney disease, and obesity (body mass index (BMI) ≥ 30) are associated with severe disease and mortality (13). The severity of the disease ranges from asymptomatic infection to critical illness. The clinical severity of Covid-19 disease is defined in 5 groups as asymptomatic, mild, moderate, severe, and critical as indicated in the table 2 below (12,13).

Table 2. Clinical Course in Covid-19 Disease

Asymptomatic infection:	Cases with positive SARS-CoV-2 PCR test and noclinical symptoms. Asymptomatic infection is important because it increases the risk of transmission in the community. Especially asymptomatic infants and children play an important role in human-to-human transmission.
Mildillness:	Patients have mild symptoms such as fever, fatigue, myalgia, sorethroat, cough, runnynose and sneezing. There are noradiographic findings.
Moderateillness:	Pneumonia, fever and cough; patients may have wheezing, but no severe hypoxemia. Radiographic findings are present.
Severe illness:	Rapid progression, dyspnea, centra lcyanosis. Inpatients: Respiratory rate > 30 Oxygen Saturation (SpO2) < 93 There are signs of PaO 2/FiO2 < 300 mm/Hg.
Critical illness:	Akut Respiratory Distress Syndrome (ARDS), respiratory failure, sepsis, septic shock, multiple organ dysfunction are seen.

Covid-19 Disease and the Respiratory System

The course of the Covid-19 disease in the respiratory system can be categorized as early period, pulmonary period, and hyperinflammation period. In the early period, the virus is active and causes symptoms such as dry cough, fever, and weakness. In the pulmonary period, shortness of breath and hypoxemia develop. During the hyperinflammation period, the host response is dominant. During this period, ARDS, shock, and organ failure may develop (14).

Covid-19 Disease and Pneumonia

Radiological imaging shows infiltration and ground glass opacities (20). Mild cases may present with fever, chills, and dry cough. Tachypnea (>30/min), dyspnea, respiratory distress, and hypoxia (SpO2 < 90% in room air) are seen in severe cases (15).

Covid-19 Disease and ARDS

ARDS is considered according to clinical and respiratory parameters. The diagnosis of ARDS should be considered in the presence of bilateral

infiltration in radiology if acute respiratory distress cannot be explained by the association of cardiogenic edema. ARDS causes diffuse alveolar damage to the lung. In an acute situation, hyaline membrane formation in the alveoli, followed by interstitial enlargement, edema, and fibroblast proliferation develops (16).

Covid-19 Disease and Cytokine Storms

A cytokine storm is a severe immune system hyperreaction in which large amounts of cytokines are rapidly released into the systemic circulation. Chemokines and high plasma inflammatory cytokines, interleukins (IL-1, IL-6, IL-8, IL-12, IL-18), tumor necrosis factor (TNF-α), and interferon (INF) play a role in the cytokine storm. The inflammatory response caused by excessive cytokine release seen with T cell and monocyte/macrophage activation increases vascular permeability, leading to exudative fluid accumulation in the alveoli and causes respiratory failure (17).

Fever that does not decrease despite treatment, elevated D-dimer, high ferritin and CRP values, cytopenia, low fibrinogen, and abnormal liver function tests should suggest a cytokine storm. Looking at ferritin, CRP, liver enzymes, triglyceride, D-dimer, lymphocyte count, and platelet count values in terms of hyperinflammation in all severe Covid-19 cases; it is important to recognize the cytokine storm early and to identify the subgroups that may benefit from immunosuppression (5).

Treatment of Covid-19 Disease

Favipravir

Favipiravir is recommended in probable or definite cases in the Covid-19 treatment guide of the Ministry of Health. In asymptomatic, uncomplicated, mild-to-moderate pneumonia patients, a 5-day treatment is recommended as 2x1600 mg/day on the first day and 2x600 mg/day on the next 4 days. In cases aged >50 years and with comorbidities, a total of 10 days of treatment is recommended, with the dose of Favipravir being 2x1800 mg on the first day and 2x800 on the other days (18).

Anticoagulant Therapy

Thrombosis prophylaxis should be applied in all hospitalized Covid-19 patients unless there is active bleeding or thrombocytopenia (<25-30.000/µl). Low molecular weight heparin (LMWH) is preferred over standard heparin in thrombosis prophylaxis. Because LMWH causes thrombocytopenia less commonly (18).

Other Treatments:

Oxygen therapy, steroid therapy, Tocilizumab, and plasma therapy can be applied to hospitalized patients.

Definition of Dyspnea

While breathing is an unnoticed condition in normal physiology, when it becomes disturbingly noticeable, it is called dyspnea (19). It describes the feeling of difficulty in breathing. The word dyspnea is formed by the combination of the words “dys” meaning bad or difficult and “pnea” meaning breath or breathing. It is a subjective term and people may express dyspnea in different ways. Patients may express the symptoms of dyspnea as shortness of breath, chest tightness, panting, and air hunger.

The mechanisms involved in the formation of dyspnea sensation are as follows:

Increased respiratory demand: Increased ventilation at vigorous exercise levels in healthy individuals, and even mild exercise in patients with lung and heart disease causes dyspnea. This increased effort stimulates the central nervous system, resulting in an increase in motor stimulation. The dyspnea cycle results in decreased activity, decreased fitness, even less movement, and occurrence of dyspnea*. Age, nutritional disorders, and hypoxemia due to disease also cause a decrease in exercise capacity (20).

Abnormalities of the respiratory muscles: Weakness or mechanical failure of the respiratory muscles causes an incoordination between the central motor response and lung ventilation. This disharmony explains the dyspnea that occurs in neuromuscular diseases and respiratory muscle fatigue. In those with COPD, excessive inflammation of the lung and increased enlargement of the thorax lead to shortening of the inspiratory muscles and reduced pressure-generating effect. The decrease in the mechanical strength of the inspiratory muscles creates the feeling of dyspnea (20).

Conditions that prevent breathing: Increased airway resistance with narrowing of the airways in diseases such as asthma and COPD, and decreased lung elasticity in lung parenchymal diseases such as pulmonary fibrosis cause dyspnea. The emergence of conditions that prevent breathing results in central motor commands trying to increase ventilation.

Dyspnea occurs when increased respiratory effort cannot provide the necessary ventilation (20).

Blood gas abnormalities: Blood gas disorders are one of the most serious conditions to occur in heart and lung diseases. Hypoxemia increases the motor activity of respiration via chemoreceptors. Hypoxia also has a direct dyspnea-causing effect (20).

Dyspnea can also be classified as acute and chronic. Acute dyspnea develops within minutes to hours. It mostly happens in diseases that affect the heart or lungs. Pericardial tamponade and pneumothorax are examples of acute dyspnea that life threatening and often need urgent treatment. Chronic dyspnea is dyspnea lasting longer than one month. Chronic dyspnea is usually progressive. Initially, shortness of breath with exertion may increase over time and can be felt without exertion. COPD and asthma are the most common examples of chronic dyspnea (20)

The Symptom of Dyspnea in Covid-19 Disease

The respiratory system is the system most affected by the Covid-19 infection. The virus affects the lungs in 3 ways: acute respiratory distress syndrome with diffuse alveolar injury (ARDS), diffuse thrombotic alveolar microvascular occlusion, and airway inflammation associated with inflammatory mediators. As a result of these 3 effects of the virus, impaired alveolar oxygenation, hypoxemia, acidosis, and dyspnea develop as a result. (21).

Dyspnea is an important symptom affecting the prognosis of Covid-19 disease. In their meta-analysis study, which included 13 studies and 3027 patients, Zheng et al. categorized the disease as critical/mortal and non-critical. Dyspnea symptoms were significantly higher in patients categorized as critical/mortal (22). In another meta-analysis study in which 4062 patients were examined, statistically significant data was found suggesting that patients who were old, male, had a high BMI, and had dyspnea and fever symptoms experienced a more severe form of the illness (23). In a study conducted by Xie et al. in Wuhan, 49.2% of Covid-19 patients had dyspnea symptoms. As a result of this study, researchers found an independent relationship between shortness of breath and death (24). In another meta-analysis study conducted by Jain et al., in which they examined 1813 patients; dyspnea was found to be the only predictive symptom for severe Covid-19 disease and ICU admission (25).

There are studies in the literature showing that Covid-19 disease causes both acute and chronic dyspnea in patients. (26.27) In a cohort study by Lerum et al., in which they followed 103 Covid-19 patients for 3 months, it was found that dyspnea continued in 56% of the patients after 3 months. As a result of this research, they thought that Covid-19 might be the cause of chronic dyspnea (28).

The Concept of Non-Dyspneic Hypoxemia (Happy Hypoxemia, Silent Hypoxemia) in Covid-19 Disease

Hypoxemia is an insufficient amount of O2 in the arterial blood (PaO2<80 mmHg). In diseases such as pneumonia, COPD, and asthma, hypoxemia in the blood is usually seen along with the symptom of dyspnea. Likewise, in Covid-19 disease, hypoxemia is seen in the blood together with dyspnea. Silent hypoxemia (Happy hypoxemia) is severe hypoxemia without symptoms of dyspnea (29). Some COVID-19 patients have been labelled with 'happy hypoxia', in which patient complaints of dyspnoea and observable signs of respiratory distress are reported to be absent. A perplexing clinical aspect of COVID-19 is presentation of patients with pronounced hypoxemia without expected signs of respiratory distress or dyspnea, even when cyanotic. Nonetheless, these patients frequently leapfrog clinical evolution stages and suffer ARDS with concomitant cardiorespiratory arrest and death. This phenomenon is referred to as silent or 'happy' hypoxemia. Although the prevalence is not clear in Covid-19 Disease, silent hypoxemia can also be seen. There are many hypotheses in the literature regarding the pathophysiology of silent hypoxemia that can be seen in Covid-19 disease. Inability to stimulate the respiratory center due to insufficient increase in CO2 in the blood, the fact that the coronavirus binds to ACE receptors in peripheral chemoreceptors and desensitizes them, and its the relationship to thrombi in the pulmonary vessels are among the hypotheses of silent hypoxemia that occurs without the feeling of dyspnea (30, 31, 32, 33, 34).

In Summary, How Should Primary Care Physicians Approach Respiratory System Involvement and the Sympton of Dyspnea in Covid-19 Disease?

In a newly diagnosed or follow-up Covid-19 patient, shortness of breath should be questioned in the taking of medical history. Among the vital signs, respiratory rate and oxygen saturation should be checked. Patients with respiratory rate >30 and oxygen saturation <93 should be referred to a higher

level of care. In addition, since one of the causes of dyspnea in Covid-19 disease is microvascular thrombosis, the use of anticoagulants should be questioned, and anticoagulants should be started in patients who do not use anticoagulants by using the coagulopathy management guide of the Ministry of Health. In regards to the blood test results of the patient; if the blood lymphocyte count is approximately 10x the upper limit of the normal value or ferritin>500 ng/ml or D-dimer>1000 ng/ml or CRP > approximately 10x the upper limit of the normal value, the patient should be referred to an upper level of care on suspicion of cytokine storm (5.9) Physicians should not forget that in Covid-19 disease, patients may have hypoxemia without symptoms of dyspnea, and should be alert to silent hypoxemia.

In Turkey, covid-19 follow-up is not done so comprehensively by primary care physicians. However, these recommendations should be taken into account by primary care physicians.

Peer-review: Externally peer-reviewed.
Author Contributions: *Concept:* G.H.D, B.K.T, *Design: G.H.D,* B.K.T *Literature Search:* G.H.D, *Data Collection and Processing:* G.H.D, B.K.T, *Analysis and/or Interpretation:* G.H.D, B.K.T, *Writing:* G.H.D, B.K.T
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study hasn't received no financial support.

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