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COVID-19 PANDEMIC AND PULMONOLOGY: A COMPREHENSIVE REVIEW

Lazaro Javier Diaz Iglesias*[1], Okoma Shed Akolokwu[2], Edelyn M. Manning Pagan[3], Nimisha Madas[3], Prem Kumar Sah[5], Julissa Nicole Jaca Castro[6], Karar Alameedi[3], Julio Perez Rodriguez[6], Eli C Garcia Bautista[6], Agustina Rajendra Putri[7], Tony Alarcon[8], Lea Bach-Bachich[9], Naglaa Ghobriel[10], Shravanti Muthu[11], Anand Reddy Maligireddy[12], Anam Hamid[13], Jennis Singla[14] and Roshan Niraula[15]

[1]University of Science, Art and Technology of Montserrat, College of Medicine, CO, USA.
[2]Avalon University School of Medicine, Curacao.
[3]Caribbean Medical University, Willemstad, Curacao.
[4]Mamata Medical College, Khammam, Telangana, India.
[5]Manipal College of Medical Sciences, Pokhara, Nepal.
[6]Universidad Autónoma de Guadalajara, Mexico.
[7]Lampung University, Indonesia.
[8]St. George's University School of Medicine, St. George, Grenada.
[9]University of Zagreb, School of Medicine, Croatia.
[10]Faculty of Medicine Alexandria, Egypt.
[11]Melmaruvathur Adhiparasakthi Institute of Medical Sciences and Research, India.
[12]Kamineni Institute of Medical Sciences, India.
[13]Dow University of Health and Sciences, Pakistan.
[14]University College Dublin, Ireland.
[15]B.P. Koirala Institute of Health Sciences, Dharan, Nepal.

***Corresponding Author: Lazaro Javier Diaz Iglesias**
University of Science, Art and Technology of Montserrat. College of Medicine, CO, USA.

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ABSTRACT

The pandemic of the coronavirus disease-19 (COVID-19), the causative agent of the severe acute respiratory syndrome-2 (SARS-CoV-2), has become a public health emergency of international concern. The majority of the population is exhibiting signs and symptoms similar to the flu and common cold. COVID-19 affects various systems, but the respiratory system has been principally affected by the virus. Respiratory involvement in SARS-COV-2 usually corresponds to four situations: (a) respiratory manifestation of acute viral infection, (b) respiratory manifestation of post-viral infection, (c) manifestation in patients with comorbidities (d) ARDS and respiratory failure in COVID-19. The actual disease pathogenesis is the expression of the ACE2 receptor, expressed by the lower respiratory tract. These receptors are responsible for the viral invasion and subsequent progression of the disease. However, direct viral injury, inflammation due to markers, and the complement system's activation might be the contributing causes. Various respiratory manifestations have been observed and reported in many cases. Starting with mild symptoms ranging from flu, fever, cough, sore throat, dyspnea, and tachypnea, patients with lung involvement can develop pneumonia, respiratory failure, heart failure, septic shock, and death. SARS-CoV-2 pandemic has become a significant challenge for the pulmonologists specifically, considering the degree of lung damage that it causes. Most of the COVID-19 complications may be caused by a condition known as cytokine release syndrome, also referred to as cytokine storm. In this review, we have condensed the information from published literature including, case reports and open-source data sets, to describe the spectrum of respiratory manifestation and complication observed in COVID-19 cases and future prognosis.

KEYWORDS: COVID-19, SARS-CoV-2, infection, pandemic, coronavirus.

INTRODUCTION

Since when the first case of coronavirus disease (COVID-19) was reported in Hubei province of China in December 2019, this infection, caused by a novel coronavirus namely Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2),[1] has globally caused 41,332,899 confirmed cases and 1,132,879 deaths as of October 23, 2020.[2] The World Health Organization declared COVID-19 a pandemic on March 11, 2020.[3] COVID-19 patients can be asymptomatic or present with symptoms of a viral respiratory illness such

as dry cough, fever, dyspnea, malaise, myalgia, sore throat, and loss of taste and/or smell. The direct human-to-human transmission of SARS-CoV-2 occurs via inhalation of infective droplets released into the air by sneezing or coughing; contact with fomites and contamination of conjunctival, oral, and nasal mucosa leads to indirect transmission.[1] COVID-19 can be confirmed by the genome-detection of SARS-CoV-2 on reverse transcriptase-polymerase chain reaction or IgM/IgG serology. Lymphopenia, leukopenia, thrombocytopenia, elevated C-reactive protein levels, lactate dehydrogenase, cardiac biomarkers, and decreased albumin are the characteristic laboratory findings in this disease.[4] The radiological and pathological findings present in the lungs in the SARS-COV-2 infection given in the table below.

Table. Pathological and Radiological (CT) Findings in lungs in COVID-19.

Pathological Findings[4]	**CT Findings[1]**
1. Type II pneumocyte hyperplasia 2. Alveolar epithelial damage 3. Hyaline membrane formation and fibrin deposition 4. Thrombotic microangiopathy and platelet aggregation 5. Mononuclear cell accumulation and activated local megakaryocytes	1. Bilateral pulmonary parenchymal ground-glass opacities 2. Diffuse bilateral pulmonary consolidations and nodules 3. Infrequent interlobar pleural thickening and pleural effusion

CT: Computerised Tomography

Pathophysiology of pulmonary disease in COVID-19

In the pathophysiology of COVID-19, angiotensin-converting-enzyme-2 (ACE-2) and its receptor are of prime importance. ACE-2 receptor, found abundantly in type-II pneumocytes, is the primary binding site and point of entry for S (spike) protein of SARS-CoV-2.[1,4] The function of ACE-2 is to break down angiotensin-II and neutralize its effects. Another enzyme, angiotensin-converting-enzyme (ACE), converts angiotensin-I to angiotensin-II. However, ACE-2 can also hydrolyze angiotensin-I and decrease its availability for conversion into angiotensin-II by ACE. When SARS-CoV-2 occupies the ACE-2 receptor, ACE-2 is unable to bind to its receptor and cannot hydrolyze angiotensin-I and angiotensin-II. Moreover, due to the higher concentration of ACE than ACE-2, more angiotensin-I is converted to angiotensin-II when ACE-2 is not functioning. Hence, increased local angiotensin-II levels cause inflammatory damage to the pulmonary vascular endothelium.[4]

On the other hand, when SARS-CoV-2 enters an alveolar epithelial cell through the ACE-2 receptor, it replicates rapidly and triggers a robust immune response known as 'cytokine storm.' Cytokine storm refers to the uncontrolled production of pro-inflammatory cytokines resulting in pulmonary and other systemic complications.[5,6]

COVID-19-associated Pneumonia

SARS-CoV-2 mainly infects the lung parenchymal tissue; thus, the patients develop pneumonia symptoms, such as fever and cough. COVID-associated pneumonia is more severe than seasonal influenza pneumonia, even in young adults without any comorbidities.[7] A case series from China consisting of hospitalized COVID-19 patients with severe pneumonia suggested that approximately 80% of the patients have mild disease, 20% require hospital admission, and around 5% require intensive care admission.[8] The mortality rate is higher among patients above 60 years of age, particularly those with comorbidities such as hypertension, diabetes, and cardiovascular disease.[7]

Dry Cough

The most common respiratory manifestation of COVID-19 is a dry cough, having an average incidence of 59.4–82% in presenting patients.[9] 45.8% of the 262 COVID-19 patients and 81.80% of the 99 COVID-19 patients were found to have dry cough in studies done by Tian et al and Chen et al, respectively.[10,11] In a large meta-analysis of 1994 COVID-19 patients, dry cough was present in 68.6% cases.[12]

Pulmonary Microthrombi/Pulmonary Embolism

Acute thromboembolic events may occur in approximately 20.6–25% of admitted COVID-19 patients with no prior history or associated risk factors.[13] Pulmonary involvement can occur, as seen in a case of a 75-year-old female with severe COVID-associated pneumonia; her lung CT revealed a bilateral filling defect suggestive of pulmonary embolism.[14] COVID-related bilateral pulmonary embolism was also reported by Cellina et al. in a 60-year-old male.[15] Massive pulmonary embolism in the setting of SARS-CoV-2 infection was found in a 62-year-old male who presented with cardiac arrest and was managed with catheter-mediated thrombolysis.[16] These thrombo-embolic events can be attributed mainly to COVID-19-associated coagulopathy, as indicated by increased D-dimers and decreased fibrinogen levels,[17] and to a small extent to the transient hypercoagulability imposed by an acute infection,[14] Hence, a chest CT angiogram is recommended to exclude pulmonary embolism in patients with COVID-19 pneumonia who develop worsening respiratory symptoms.[15]

Pulmonary Fibrosis

Post-COVID pulmonary fibrosis has been observed on the chest CT of the patients. Zhou et al., in their study, reported fibrotic changes in 21 out of 62 (33.9%) patients.[18] whereas Pan et al. reported fibrotic changes in 11 out of 63 patients (17.4%).[19] Histopathological examination on lung autopsy has confirmed areas of diffuse alveolar damage with fibrotic consolidation and fibrin deposition, which indicate an attempted fibroblastic proliferation to repair the damaged lung tissue.[20,21] Fibrosis is more likely to occur 8-14 days after the disease onset.[18]

Acute Respiratory Distress Syndrome (ARDS)

Diffuse alveolar damage caused by SARS-CoV-2 can lead to Acute Respiratory Distress Syndrome or ARDS, an acute parenchymal inflammation due to a direct or indirect lung injury. It can be potentially fatal, particularly in elderly COVID-19 patients with comorbidities,[22] and has an incidence of 15.6–31%.[9] COVID-19-associated ARDS differs from the ARDS due to other etiologies. According to the Berlin criteria, ARDS's onset must be within 1 week of a known insult.[23] However, studies have shown that ARDS in COVID-19 patients can develop after a period of one week, as its median time of onset was indicated by Huang et al and Zhou et al to be 8.0 days and 12.0 days, respectively.[9,24] Moreover, COVID-19 patients with ARDS can show relatively normal or high lung compliance, contrary to patients with non-COVID ARDS.[22] The pathological features found on lung biopsy in a patient who died of COVID-related ARDS were prominent desquamation of pneumocytes and hyaline membrane formation.[25]

Pleural effusion

The ongoing lung injury in SARS-CoV-2 infection can lead to the development of pleural effusion, which can be observed in the lung CT of the patient. As reported by Zhou S. et al, pleural effusion was confirmed in six out of 62 patients.[18] 7 out of 83 COVID-19 patients (8.4%) were found to have pleural effusion in a study carried out by Li K.[26]

Dyspnea

Dyspnea has a variable incidence in COVID-19 patients. It is more common in elderly patients with comorbidities, as reported in a study by Shahid Z, et al where as much as 76% of the 21 COVID-19 patients having a median age of 70 years presented with dyspnea.[27] Dyspnea was present in 6.9% of the 262 COVID-19 patients as reported by Tian S et al in their study.[10]

Respiratory failure

Hypoxemic respiratory failure can occur as a complication of SARS-CoV-2 infection. A multicenter study in Seattle showed that during the first 3 weeks of the Covid-19 outbreak, the most common reasons for admission to the ICU were hypoxemic respiratory failure leading to mechanical ventilation, hypotension requiring vasopressor treatment, or both. The earliest extubation occurred 8 days after initiation of invasive mechanical ventilation, suggesting that Covid-associated acute respiratory failure may require prolonged mechanical ventilation lasting days to weeks.[28]

Silent or 'Happy' hypoxia

In some COVID-19 patients, low oxygen levels are present without apparent dyspnea. This phenomenon is known as silent or 'happy' hypoxia. In a case series of three patients, none of them reported any difficulty in breathing even on oxygen saturation levels of 62%, 68% and 83%. The mechanism behind this is not well-understood. However, an idiosyncratic action of SARS-CoV-2 on oxygen chemosensitive receptors has been speculated.[29]

CONCLUSION

The pulmonary complications associated with coronavirus disease can progress to life-threatening situations such as acute respiratory distress syndrome and respiratory failure. Elderly patients with associated disorders, including diabetes and hypertension, are particularly susceptible to these conditions. Also, we recommend that apart from providing acute management for such complications, one should be wary of their long-term implications. For example, COVID-associated pulmonary fibrosis can cause persistent respiratory difficulty in a patient. Hence, accurate diagnosis and timely treatment are required in order to prevent any chronic disabilities.

Abbreviations

ACE-2: Angiotensin-converting-enzyme-2
ARDS: Acute Respiratory Distress Syndrome
COVID-19: Coronavirus disease
CT: Computerised tomography
ICU: Intensive care unit
RT-PCR: Reverse Transcriptase-Polymerase chain reaction
SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

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