Respiratory manifestations of COVID-19

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Corona virus disease 2019 (COVID-19), is the biggest health challenge faced by the world in the recent years. It rapidly spread to the rest of the world, over a short period of time, after its appearance in Wuhan, China. WHO declared it a pandemic on the 11th of March. At the time of writing, 5,556,574 people are affected worldwide with 348,223 deaths¹.

In Sri Lanka, the first local case was detected in early March 2020, and 2 months later, despite the much lower population compared to the severely affected countries such as China, US and Italy, there are over 1000 cases with 9 deaths².

COVID-19 is primarily a disease affecting the respiratory system. The corona virus that leads to COVID-19 is a beta coronavirus and belongs to the same subgenus as the Severe Acute Respiratory Syndrome [SARS] virus. COVID-19 virus is known as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS COV2)³. The virus binds to Angiotensin Converting Enzyme 2 (ACE 2) protein to enter human cells⁴. ACE 2 proteins are expressed in the airway epithelium, lung parenchyma and vascular endothelium⁵. ACE 2 is expressed more on the apical surface of the airway epithelium as opposed to the baso-lateral surface. Thus, rendering the lung susceptible to infection by SARS COV2.

The respiratory involvement in COVID-19 can manifest in several ways –

• Upper respiratory tract infection
• Pneumonia and Acute respiratory distress syndrome [ARDS]
• Pulmonary embolism and pulmonary vascular thrombosis
• Other presentations

This article will briefly describe each of these.

Upper respiratory tract infection

Fever, cough, fatigue and dyspnoea are the commonest symptoms seen in those admitted to hospital with COVID-19, according to the data from 3 centers in Wuhan, China⁶,⁷,⁸. This is comparable to the first 100 patients from Sri Lanka⁹ (Table 1). The Chinese data are from patients who required hospital admission, however in Sri Lanka, as per government policy, all patients with COVID-19 positive PCR is admitted to a hospital. Therefore, the Sri Lankan data includes patients who do not require in-ward care.

The cough is predominantly a dry cough¹⁰. Interestingly, occurrence of rhinorrhea is not common in the Chinese data⁸. However, in Sri Lanka, rhinorrhea is seen in 11% of patients, and nasal congestion in 21% of the patients⁸. Haemoptysis was seen in 2 out of 39 (5%) patients in one center in China⁷ and in another center out of 99 patients studied, 1 patient had a pneumothorax⁸.

Dyspnoea was obviously more prominent in those needing ICU care. The other symptoms didn’t differ much in those needing ICU care as opposed to those in inward care. However, anorexia was noted to be more common in the former⁶.

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There is a growing body of evidence for the presence of olfactory dysfunction (anosmia/hyposmia). Importance of considering anosmia as a symptom of COVID-19 was stated in a statement issued by the ENT UK and the British Rhinological Society following a number of reports on anosmia from US, France and Northern Italy. A multi-center European study on olfactory dysfunction in mild to moderate COVID-19 (n= 417), showed that 85.6% had olfactory dysfunction. Interestingly the olfactory dysfunction has preceded other symptoms in 11.8% of patients. This is a very important finding as this indicates that anosmia can be an early sign to identify COVID-19 patients. Similar findings were noted in several other studies across the world. A more recent study from France looking at 54 patients with confirmed COVID-19 having anosmia found that the median duration for anosmia was 8.9 days. Sri Lankan data on 58 patients show that 5% had anosmia.

**Table 1. Hospitalized patients with pneumonia from 3 centers in Wuhan, China and the first 100 patients from Sri Lanka**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Center 1&lt;sup&gt;a&lt;/sup&gt; n=138 (%)</th>
<th>Center 2&lt;sup&gt;b&lt;/sup&gt; n=41 (%)</th>
<th>Center 3&lt;sup&gt;c&lt;/sup&gt; n=99 (%)</th>
<th>Sri Lanka&lt;sup&gt;d&lt;/sup&gt; n=100 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>136 (98.6)</td>
<td>40 (98)</td>
<td>82 (83)</td>
<td>66</td>
</tr>
<tr>
<td>Cough</td>
<td>82 (59.4)</td>
<td>31 (76)</td>
<td>81 (82)</td>
<td>48 (48)</td>
</tr>
<tr>
<td>Sputum production</td>
<td>37 (26.8)</td>
<td>11 (28)</td>
<td>-</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>24 (17.4)</td>
<td>-</td>
<td>5 (5)</td>
<td>29 (29)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>43 (31.2)</td>
<td>22 (55)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>31 (31)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>-</td>
<td>-</td>
<td>4 (4)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>-</td>
<td>2 (5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anorexia</td>
<td>55 (39.9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>96 (69.6)</td>
<td>18 (44)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>-</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>48 (34.8)</td>
<td>11 (11)</td>
<td>26 (26)</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (6.5)</td>
<td>3 (8)</td>
<td>8 (8)</td>
<td>21 (21)</td>
</tr>
</tbody>
</table>

<sup>a</sup> dry cough, <sup>b</sup> myalgia or fatigue, <sup>c</sup> 12 (29%) patients had a respiratory rate > 24

Pneumonia and ARDS

The disease can progress to the development of pneumonia, severe pneumonia, sepsis, septic shock and ARDS.

Pneumonia in COVID-19 can range from mild to severe. The common radiological, including computed tomography (CT) features are multiple lung opacities and multiple types of opacities such as ground glass shadows, ground glass shadows with consolidations and bilateral consolidations. Multiple lobes are affected especially the lower lobes. Crazy paving pattern and organising pneumonia are seen at a later stage in the disease. Extensive consolidation is associated with a poor prognosis. Bilateral consolidations and bilateral patchy opacities were the X ray findings of 5 critically ill patients with COVID-19 in Sri Lanka. However, in one patient there was a unilateral lung shadow (blunting of the costo-phrenic angle) in the chest X ray done on day 3 of the illness and patient had died on day 9. X ray chest is not sensitive to pick up subtle changes seen in early lung involvement.
Figure 1. X-ray chest image of a patient with SARS COV2 pneumonia showing bilateral lower zone shadows more prominent on the right than the left.

(Courtesy Dr Aruna Jayawardena, Consultant Physician (acting), Welikanda COVID-19 treatment center)

Figure 2. Chest Computed Tomographic images of a patient with severe COVID-19 pneumonia.
A & B – Bilateral ground glass shadows
C & D – Bilateral consolidation of lungs – no air visible. (The patient was moved to ECMO after failed ventilation)
(Courtesy Dr Keith Hattotuwa, Consultant Respiratory Physician, Mid Essex Hospital Services NHS Trust.)
Acute respiratory distress syndrome (ARDS): In the study by Wang et al. out of the thirty-six patients who were transferred to the intensive care unit (ICU), 22 (61.1%) had acute respiratory distress syndrome\(^9\). The median time from first symptom to ARDS was 8 days.

In a retrospective case series of 1591 critically ill COVID-19 patients admitted to intensive care unit (ICU) in Lombardy, Italy it was noted that, 99% (1287 of 1300 patients) required respiratory support. 88% required endotracheal intubation and 11% needed non-invasive ventilation. The mortality in the ICU was 26%\(^{20}\). However, the ICU mortality varies from center to center.

According to the Sri Lankan data of the first 100 patients, 2 were considered severely ill and 6 were critical. All critically ill patients were treated in the ICU and had required endotracheal intubation. There had been one death on admission. The rest of the critically ill patients have subsequently died following a period of stay in the ICU\(^9\).

One of the interesting observations in COVID-19 is a category of patients with severe hypoxemia disproportionate to dyspnoea. The severe pneumonia in all patients does not behave the same way. Gattinoni et al proposed an explanation to this by observation of the presence of two different COVID-19 pneumonia phenotypes\(^{21,22}\).

The two phenotypes described are L type and the H type. The L type is characterized by low elastance; therefore, the lungs are compliant, and are easy to oxygenate. The amount of non-aerated lung tissue is very low. The low ventilation perfusion (V/Q) ratio leading to hypoxemia is believed to be a consequence of vasoplegia, or the loss of hypoxic vasoconstriction of the pulmonary vasculature. Hypoxemia increases the minute ventilation by stimulation of the peripheral chemoreceptors. Partial pressure of CO\(_2\) (PaCO\(_2\)) in the blood is the main determinant of the respiratory rate. In the presence of near normal lung compliance, a slight increase in minute volume will decrease the PCO\(_2\) and therefore an increase in respiratory rate is not seen. This explains the severe hypoxemia without dyspnoea noted in certain patients\(^{21}\).

The High-resolution computed tomography (HRCT) images of the lungs in L type show bilateral ground glass opacities, mainly in the subpleural areas and along the fissures. The H type on the other hand has a low lung compliance. The lungs are heavy, sometimes the lung weight is > 1.5kg with areas of non-aerated lung tissue\(^7\). There is a high right to left shunt because of the pulmonary perfusion to non-aerated tissue. This is associated with a high lung recruitability. This is the basis for prone ventilation in such patients. The HRCTs show bilateral consolidations.

L type can either remain as it is or progress to H type. The differentiation between the 2 types is important as the ventilator strategies employed are different.

**Pulmonary embolism and pulmonary vascular thrombosis**

Pulmonary embolism (PE) is common in COVID-19 pneumonia\(^23\). In a series of 107 patients admitted to ICU with pneumonia, it was noted to have high number of PE (20.6%). This was compared with a similar number of ICU admissions with pneumonia during the same time interval the previous year. The frequency of PE in the COVID-19 series was twice as high as the frequency in the control period. A similar study done in a center in Paris, found 24% of COVID-19 patients with pneumonia had PE\(^{24}\).

PE should be suspected in those with sudden worsening of hypoxia, hypotension, tachycardia and new onset arrhythmia. It is more common in patients in critical care units and in those requiring mechanical ventilation\(^{25}\). An advice paper from the European Society of Radiology and the European Society of Thoracic Imaging suggested that PE should be suspected if supplementary oxygen is needed in a patient with limited disease extension and an additional contrast-enhanced CT acquisition may be indicated\(^8\).

There is increased evidence of thrombosis of the pulmonary vessels\(^3\). Post mortem histology of pulmonary vessels in patients with COVID-19 has widespread thrombosis with microangiopathy. Alveolar capillary microthrombi were 9 times as prevalent in patients with COVID-19 than in patients with influenza\(^26\).

**Other presentations**

Patients with coexisting lung diseases like asthma, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung diseases and other chronic lung diseases, may present with features of an exacerbation of their lung condition secondary to an infection with COVID-19.
Even though many extra pulmonary manifestations have been described in COVID-19, severe disease, need for ICU care and mortality are almost always related to the respiratory involvement. More research is clearly needed into the pulmonary pathophysiology, and a better understanding of this will go a long way in saving lives.

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