



## Review paper

# Pulmonary complications due to COVID-19 – a literature review

*Anna Maria Romaszko-Wojtowicz* , *Anna Doboszyńska*

*Department of Pulmonology, Faculty of Public Health, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Poland*

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## ABSTRACT

**Introduction:** First cases of a disease called coronavirus disease 2019 (COVID-19), caused by a novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) of the coronavirus family, were detected in December 2019. The disease is manifested by a variety of symptoms and can run a different course: from oligosymptomatic or asymptomatic to the development of acute respiratory failure and even death.

**Aim:** The aim of this paper is to provide critical analysis of the potential pulmonary complications after COVID-19 infection.

**Material and methods:** We have provided the systematic literature review based on which we have discussed the pathophysiology of COVID-19, its outcomes, risk factors and pulmonary complications.

**Results and discussion:** The organs that are most often affected by a SARS-CoV-2 infection are the lungs. An infection with this virus can lead to a severe respiratory tract illness, both in the acute phase and as a complication after a relatively mild case. There are numerous observations of patients convalescing from COVID-19 who suffer from the interstitial pulmonary disease with fibrosis. There are also reported cases of spontaneous pneumothorax after COVID-19.

**Conclusions:** It should be borne in mind that other late complications may appear with time.

## 1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh known virus of the family of coronaviruses.<sup>1</sup> It is a highly virulent, encapsulated virus with single-strand RNA.<sup>2</sup> Genetically, 79% of the RNA sequence is identical to that in the SARS-CoV virus.<sup>3</sup> The disease caused by SARS-CoV-2, called COVID-19, spreads mainly by airborne droplets. The virus was detected in December 2019, in Wuhan, the capital city of the Chinese province Hubei, from where it spread rapidly so that on March 11, 2020 the World Health Organisation (WHO) announced the emergence of a global COVID-19 pandemic. It has been determined that an average incubation period of this virus lasts about 5 days, and its titre peaks just before the symptoms appear. The presence of the virus's genetic material can be detected for at least 8 days, by testing nose, mouth or throat swabs.<sup>4</sup> The course of the disease can be asymptomatic, although the typical symptoms are pyrexia, dry cough and dyspnoea. Using the protein angiotensin-2 (ACE2) converting enzyme as a receptor, SARS-CoV-2 induces interstitial pulmonary damage, which can lead to fibrosis.<sup>5,6</sup> According to WHO, 80% of SARS-CoV-2 infections are mild, 14% of infected persons manifest severe symptoms, and 6% of affected patients are in critical condition. According to the research conducted in Italy and in China, 5% to 12% of patients need care at intensive care units (ICUs).<sup>5,7</sup> It is thought that a more severe course of the illness is predisposed by age, male sex, and presence of comorbidities, such as arterial hypertension, diabetes, and coronary artery disease.<sup>5,6,8,9</sup> The mortality rate due to COVID-19 is quite high. In a study carried out in the UK, Docherty et al. estimated in-hospital mortality at 26% among patients hospitalised in general wards.<sup>10</sup> Furthermore, the mortality rate at ICUs reached 78%.<sup>11</sup> As of February 12, 2021, the disease had developed in 108 353 082 people globally, causing 2 380 469 deaths.<sup>12</sup>

## 2. AIM

The aim of this paper is to systematize the current knowledge of the potential pulmonary complications after COVID-19 infection.

## 3. MATERIAL AND METHODS

A systemic literature review was conducted using the PubMed, Medline and other databases such as: Science Direct. We reviewed 60 articles.

## 4. RESULTS AND DISCUSSION

COVID-19 infection may cause many complications including pulmonary complications such as: acute respiratory distress syndrome (ARDS), pulmonary fibrosis, pulmonary

hypertension (PAH), pulmonary embolism, pneumothorax. All of these complications are described below. However it is also worth to remember that most common pulmonary complication of viral infection is bacterial superinfection.

### 4.1. ARDS – a severe course

ARDS is a life-threatening condition, in which damage to the alveolar capillary barrier occurs.<sup>13</sup> The increased permeability of vascular walls together with decreased pulmonary compliance and pulmonary tissue aeration contribute to impaired gas exchange and hypoxaemia. The diagnosis is made according to overhydration.<sup>14</sup> The following are considered: sudden onset of respiratory tract symptoms, signs of lung oedema in imaging tests (not caused by cardiac diseases or effusion) and hypoxemia. In most cases of COVID-19, there is diffuse injury of pulmonary alveoli. Due to the damage to the endothelial cells of capillaries and epithelial cells of lung alveoli, protein-rich fluid infiltrates into the interstitial and alveolar space, hyaline membrane forms and eventually intracapillary thrombosis develops.<sup>15</sup> It is suggested that the exacerbation of COVID-19 symptoms is associated with a much greater release of inflammatory cytokines, the so-called cytokine storm. This phenomenon consists in the elevated release of inflammatory state mediators, including cytokines and chemokines, such as interleukin (IL) 2, 7, 10, tumour necrosis factor (TNF), granulocyte colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1, also known as CCL2), macrophage inflammatory protein 1 alpha (MIP1 $\alpha$ ; also known as CCL3), chemokine ligand CXCL10 (CXCL10), C-reactive protein, ferritin and D-dimers.<sup>16,17</sup> Activation of a cascade reaction is the consequence of an uncontrollable response of the host's immune system to various activating factors, in this case to the virus SARS-CoV-2. However, clinical and laboratory criteria for recognition of the cytokine storm connected with COVID-19 are still unavailable. Many studies have demonstrated that ICU patients present a much higher level of IL-6.<sup>17,18</sup> Zhang et al., in a study on 901 patients, proved that the IL-6 level correlated with the severity of COVID-19.<sup>19</sup>

Noteworthy is the fact that cases of COVID – ARDS are observed to coincide with abnormal endothelial cell death and distorted angiogenesis.<sup>20</sup> Post-mortem tests have revealed the presence of microvascular thrombi, which may lead to the direct damage of endothelial cells and their death.<sup>21</sup> In response to the vascular injury caused by SARS-CoV-2, there are disorders in endothelial homeostasis, which predispose to the development of organ failure. COVID-19 often occurs with concomitant arterial thrombosis and kidney damage. It is suggested that because of the much frequent incidence of vascular symptoms, COVID-ARDS should be classified as a sub-type of acute respiratory deficiency syndrome concomitant with the dysfunction of pulmonary circulation – the vascular pulmonary phenotype.<sup>22</sup> The evidence to support it is the frequent co-occurrence of pulmonary embolism.<sup>23</sup> Doubtless, vascular dysfunction contributes to progressive fibrosis.<sup>24</sup> What remains unknown is whether the vascular disturbances which occur in the course of COVID-19 will

lead to long-term damage of pulmonary vessels. Van Dongen et al. described a case of a 60-year-old man who developed PAH shortly after recovering from a COVID-19 infection, which was probably connected with residual pulmonary parenchymal abnormalities.<sup>25</sup>

#### 4.2. Pulmonary fibrosis

During the healing phase of chronic pneumonia or proliferative illnesses, cellular elements are being gradually replaced with scar tissue. Some symptoms, such as cough or dyspnoea, are reported by patients for a long time after they recover from COVID-19. These symptoms may be linked to the development of pulmonary fibrosis, or they can be associated with bronchial hyperresponsiveness secondary to viral infection of the upper respiratory tract.<sup>26</sup> A more severe course of COVID-19 plays a considerable role in the development of fibrotic lesions. In the course of ARDS, diffuse injury to pulmonary alveoli occurs, which leads to the growth of type 2 pneumocytes, deposition of collagen and other extracellular matrix components with accompanying damage to and obliteration of the normal architecture of the lungs.<sup>27</sup> Pulmonary fibrosis is more frequent in elderly patients. The average age of patients diagnosed with idiopathic pulmonary fibrosis is 65 years.<sup>28</sup> Moreover, the diagnosis of pulmonary fibrosis correlates with age when the infection co-occurs with acute respiratory failure. In a study completed by Wong et al., elderly patients (over 65 years old) were more often observed to present computed tomography features of pulmonary fibrosis 6 months after recovery from ARDS.<sup>29</sup> In a retrospective study of patients with COVID-19, the observations made by Marvisi et al. 8 weeks after the patients were discharged from hospital showed that about 25% of these patients presented early signs of fibrosis.<sup>30</sup> Huan et al., in a retrospective study on 19 patients completed 30 days after they had been released from hospital showed that ground-glass opacity changes following a COVID-19 infection could resolve without subsequent fibrosis.<sup>31</sup>

The serum LDH level has been used as a marker of the severity of an illness after acute lung injuries. It is an indicator of the extent of damage to lung tissue and is correlated with the risk of death.<sup>29</sup> Das et al. proved that high LDH significantly increases the risk of lung fibrosis after a MERS-CoV infection.<sup>32</sup> Moreover, it has been evidenced that the duration of mechanical ventilation has a significant effect on the development of fibrosis.<sup>33</sup> This relationship may be secondary to inadequately performed mechanical ventilation, for instance incorrect settings of tension and capacity of the lungs.<sup>7</sup>

Smoking is linked to the pathogenesis of many diseases, such as emphysema, chronic bronchitis or lung fibrosis. The published data regarding the influence of smoking on the course of COVID-19 are not so conclusive. Liu et al. noticed that tobacco smoking contributes to the progression of a COVID-19 infection.<sup>34</sup> Smokers around 1.4-fold more often develop a more severe form of COVID-19 and around 2.4-fold more often have to be admitted to ICUs.<sup>5</sup> However, Zhou et al. did not demonstrate any statistically significant

correlation concerning the mortality rate due to COVID-19 among smokers and non-smokers.<sup>8</sup> A large meta-analysis including information from China, the USA and Italy showed that smoking decreased the probability of hospitalisation due to COVID-19.<sup>35</sup> Another meta-analysis (Patanavanich and Glantz) provides evidence that smoking is an independent variable of the risk of developing a severe form of COVID-19, including higher mortality, especially among people less than 45 years of age.<sup>36</sup>

#### 4.3. Thromboembolic complications: pulmonary hypertension and pulmonary embolism

Currently, there are no reliable data confirming the development of PAH in patients after a COVID-19 incident. However, thromboembolic complications are quite common in a more severe course of this illness. Thillai et al. demonstrated in their study on 10 intubated COVID-19 patients that the inferior gas exchange is associated with redistribution caused by microthrombi and/or vasoconstriction of distal pulmonary arteries.<sup>37</sup> Moreover, thromboembolic changes can lead to the remodelling of pulmonary tissue, thereby promoting the development of PAH.<sup>38</sup> It has been demonstrated that the best marker of such complications is D-dimer.<sup>39</sup> In their study on 33 patients with a severe course of COVID-19, Daher et al. showed that 6 weeks after being discharged from hospital, patients presented normal functions of the right and left heart chambers and no signs of PAH were observed.<sup>40</sup> Nevertheless, 4 of those patients were determined to show symptoms of chronic cardiac insufficiency, whilst two other patients showed reduced left ventricular ejection fraction and yet 2 others had reduced left and right ventricular ejection fraction. The latest studies including COVID-19 patients hospitalised at ICUs implicate a more frequent incidence of thromboembolic disorders despite systematic thromboprophylaxis.<sup>23</sup> Poissy J. et al. showed that 20.6% of 107 patients with COVID-19 admitted to the ICU at the University Hospital in Lille (northern France) experienced pulmonary embolism within about 6 days after admission.<sup>41</sup>

The presence of severe PAH is associated with a worse prognosis for patients with ARDS.<sup>42</sup> Development of the haemodynamic instability of the right heart chamber leads to hypoxaemia, and consequently to death.<sup>43</sup> At the moment, it is maintained that the course of a COVID-19 infection itself was no worse in patients with PAH than in the general population. It is also suggested that endothelial dysfunction is not so intensive in patients with PAH because they have pre-existing endothelial dysfunction, which in a certain way protects them from subsequent injury.<sup>44</sup>

#### 4.4. Pneumothorax

Pneumothorax is defined as the presence of air in the thoracic cavity. Considering aetiology, pneumothorax can be spontaneous or traumatic: primary (e.g. during heart pacemaker surgery) or secondary (e.g. in patients with chronic obstructive pulmonary disease). A ruptured emphysema bulla can be a cause of spontaneous pneumothorax.<sup>45</sup> Some

risk factors of pneumothorax are: age, tobacco smoking, low body weight, or chronic cough.<sup>46</sup> First reports have emerged recently about patients with pneumothorax after recovering from COVID-19 infections.<sup>47,48</sup> It is now claimed that spontaneous pneumothorax occurs in fewer than 1% of such patients.<sup>49</sup> Wong et al. described a series of 75 cases of patients with COVID-19 who developed pneumothorax while undergoing mechanical ventilation.<sup>47</sup> Most were men over 60 years of age, with pre-existing illnesses, such as diabetes, hypertension and obesity. It is known that ARDS of any aetiology causes pathophysiological changes (e.g. emphysematous changes) which increase the risk of pneumothorax.<sup>50</sup> The use of positive pressure ventilation itself is a significant factor predisposing to the development of pneumothorax.<sup>51</sup> Yamaya et al. described a case of pneumothorax in a patient with no such risk factors as mechanical ventilation, tobacco smoking or pulmonary comorbidities.<sup>48</sup> These authors suggest that new lesions detected on computed tomography scans of the chest, namely bronchiectasis, and the systemic corticosteroid treatment, by delaying the healing of the pulmonary interstitial tissue, may have had an impact on the development of pneumothorax. Another factor that raises the probability of pneumothorax is pulmonary embolism. Wichmann et al. found deep vein thrombosis in small pulmonary arteries in 58% of cases.<sup>52</sup> Also, Fox et al. described small clots in small peripheral vessels of all the patients included in their study, with 2 of these patients having pulmonary microthrombi and a considerably elevated level of D-dimers.<sup>53</sup> Likewise, Ackermann et al. describe microthrombi 1–2 mm in diameter in pulmonary arteries of COVID-19 patients.<sup>20</sup>

It is believed that the inflammatory response and ischaemic parenchymal damage in COVID-19 infections predispose to the adhesion of cells among type 1 and type 2 pneumocytes, as well as damage to alveoli followed by their rupture.<sup>54</sup> An important finding in this context is that patients convalescing from COVID-19 often complain about chronic, exhausting cough.<sup>55</sup> It is believed that increased respiratory effort during the course of COVID-19 leads to microinjuries of pulmonary parenchyma, which can promote the development of cystic lesions and in consequence can lead to pneumothorax.<sup>56</sup>

The literature also describes cases of spontaneous pneumothorax in patients during or after COVID-19 treatment. Vazzana et al. reported a case of an 80-year-old patient with severe pneumonia, who required assisted respiration with non-invasive mechanical ventilation.<sup>57</sup> Gorospe et al. described a series of 4 cases of patients, with no history of pulmonary illnesses, hospitalised in clinics in Madrid, who were diagnosed with spontaneous pneumomediastinum.<sup>58</sup> Causes of pneumomediastinum are sought in the so-called Makclin effect, that is a sudden increase of pressure in the distal respiratory tract, which results in alveolar ruptures and secondary gas effusion into the pulmonary parenchyma, from which air can eventually reach the mediastinum.<sup>59</sup> One of the symptoms often reported by patients during or after COVID-19 infections are oppressive episodes of dry cough. Pneumomediastinum is associated with a more severe course of COVID-19, although

its pathomechanisms or specific incidence in the course of an infection with the SARS-CoV-2 virus have not been described in greater detail yet. Lung ultrasound seems to be a new highly sensitive diagnostic tool that might help diagnose such complications.<sup>60</sup>

## 5. CONCLUSIONS

- (1) For proper evaluation of later complications, it is essential to carry out long-term, follow-up studies, especially for patients after a severe course of COVID-19.
- (2) There is a need for comparative material for all types of meta-analyses, which will help us to understand the pathomechanism of the disease, factors influencing its course, and to distinguish risk groups as well as to identify possible complications.

## Conflict of interest

None declared.

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None declared.

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