

**COVID-19 Pandemic ARDS Survivors: Pain after the Storm?**

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### **Glossary**

ARDS acute respiratory distress syndrome

CoV coronavirus

COVID-19 Coronavirus Disease 2019

ICU intensive care unit

MERS Middle East respiratory syndrome

PTSD post-traumatic stress disorder

SARS severe acute respiratory syndrome

SARS-CoV severe acute respiratory syndrome Coronavirus

SARS-CoV-2 severe acute respiratory syndrome Coronavirus 2

WHO World Health Organization

## Key points

- Setting up a multidisciplinary commission of experts to issue recommendations in order to identify risks for chronic pain and other physical and psychological sequelae during the emergency phase of the COVID-19 pandemic and to recommend adequate therapeutic strategies.
- Creating an international registry of COVID-19 ARDS survivors and COVID-19 survivors with mild or moderate initial disease with a digital platform to share the data.
- Designing multicenter studies to assess the prevalence of chronic pain and other physical and psychological sequelae in COVID-19 survivors, and therapeutic strategies to ameliorate their adverse effects. Secondly, these studies will monitor if and when these patients returned to work, or if not, to implement a timely rehabilitation plan to ensure their ability to return to work.
- Creating an international registry of health care workers caring for COVID-19 pandemic patients to monitor their psychological and physical well-being, with a longitudinal follow-up for up to 5 years after the initial stressful occupational exposure.

At the end of 2019, the Health Committee of Wuhan alerted the World Health Organization (WHO) about a cluster of patients with pneumonia of unknown etiology<sup>1</sup>. The etiology turned out to be a novel variant of the *Coronaviridae* family of viruses, which includes the viruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Because this new coronavirus (CoV) genetically approximates the virus responsible for the SARS outbreak (SARS-CoV), the International Committee on Taxonomy of Viruses termed this new virus as SARS-CoV-2, and its associated human illness as coronavirus disease 2019 (COVID-19)<sup>1</sup>. On March 11, 2020, the WHO declared this global health emergency a pandemic<sup>2,3</sup>.

Until now, clinical and research attention has focused primarily on the etiology, accurate diagnosis, and effective acute treatment of COVID-19, with few acknowledging, let alone addressing the inevitable long-term consequences of surviving the most severe manifestation of the disease, acute respiratory distress syndrome (ARDS)<sup>4</sup>.

ARDS is characterized by hypoxemic respiratory failure with bilateral lung infiltrates often necessitating tracheal intubation and mechanical ventilation. Approximately 5% of patients who test positive for COVID-19 develop a severe form of the disease that requires intensive care unit (ICU) admission, of which, two-thirds develop ARDS. The survival rate for COVID-19 patients with ARDS and ICU admission is approximately 25%<sup>5</sup>.

As of April 15, 2020, there are 1,918,1138 confirmed cases of COVID-19 in 213 countries or areas, and 123,126 associate deaths (6.41%) worldwide<sup>6</sup>. In the worst-case scenario, as many as 29% of the US population (96 million people) will become infected, and about 1 million will require ICU support<sup>7</sup>. If these data are extrapolated, COVID-19 could infect 2.3 billion people worldwide, with 23 million requiring ICU, and about 15 million patients with ARDS<sup>7</sup>. If the same 25% of patients with ARDS and ICU admission survive, approximately 3.7 million patients will survive the acute disease. These survivors will experience the chronic complications that result from the prolonged hospital stay, immobility, long-term mechanical ventilation, and mental health sequelae<sup>7</sup>.

Survivors of ARDS can develop a disorder that is characterized by persistent fatigue, weakness, and limited exercise tolerance (defined as the distance walked in 6 minutes)<sup>8,9</sup>. This limited exercise tolerance is related to the use of systemic corticosteroids to treat the disease and multiorgan dysfunction during the ICU stay. Chronic pain and weakness will develop in these survivors<sup>9</sup>. To date, resources have been concentrated on efforts to prevent the spread of and to treat COVID-19. Concomitant efforts need to be ramped up to study the epidemiology and treatment of post-traumatic stress disorder (PTSD), chronic pain, sleep disorders, fibromyalgia, and fatigue in COVID-19 survivors.

Two mechanisms appear responsible for the post-SARS syndrome. The first relates to the psychological effects of a prolonged ICU admission on sleep and mood/affect. The ICU admission may lead to exacerbation of patient mental health issues, including a feeling of emptiness due to separation and isolation from family and friends, prolonged sedation, a breakdown of one's social

network, as well as anxiety about serious health conditions and survival<sup>9</sup>. The second relates to the muscle atrophy due to immobility and general inflammation, and neurological tropism with CoV<sup>9,10</sup>.

Like SARS, COVID-19 will result in a large proportion of patients being admitted to the hospital and developing ARDS. Chronic disorders emerge throughout the first year after acute recovery from ARDS. Chronic pain after recovery from the acute illness makes returning to work difficult in some patients, necessitating a need to change their profession or even to withdraw completely from any work<sup>11</sup>. Of note, only 16% of ARDS survivors return to work 3 months after ICU discharge, 32% after six months, and 49% after 12 months<sup>9</sup>. The probability that the patient will become unemployed is determined by patient's age and the duration of hospitalization<sup>8</sup>. Furthermore, the mean value of the Barthel Index measured in ARDS survivors 6 months after ICU discharge ( $82.3 \pm 22.9$ ) is significantly less than that in non-ARDS-patients ( $89.6 \pm 23.2$ ) ( $P=0.007$ )<sup>8</sup>. Loss of self-sufficiency and of self-esteem compound the mental health sequelae.

The challenge of reintegrating ARDS survivors from COVID-19 into workplace is vital for the recovery of the local, regional and national economies. Currently, healthcare systems and governments are understandably focused on managing the acute phase of the disease, improving the survival rate and decreasing the rate of disease transmission. However, clinicians and health policymakers must begin to formulate strategies to address and improve the long-term mental health sequelae of COVID-19<sup>12</sup>.

The first and most immediate strategy is to identify those who are at increased risk for developing PTSD after such a natural disaster (e.g., those with chronic health conditions and emotional stress) before the disaster occurs and to target support and resource programs to mitigate the PTSD and other mental health issues, should they develop after the natural disaster like a pandemic<sup>13</sup>.

Previous experience suggested that up to 30% of survivors of ARDS develop PTSD, with elderly patients with preexisting depression and low socioeconomic groups being the most severely affected<sup>9</sup>. In one report from Canada, PTSD was greater in health care workers associated with the

SARS quarantine orders. This is not surprising considering the enormous stress frontline workers endured during the care of SARS patients, which was compounded by the stress from remaining in strict quarantine between hospital shifts<sup>10</sup>. In those who developed these mental health sequelae, symptoms persisted for at least 4 years after the SARS outbreak and other natural disasters— a likely similar pattern will be seen after the COVID-19 pandemic<sup>10</sup>. Anticipating the risks posed by a the COVID-19 pandemic to both patients and health care workers should prompt authorities to mobilize resources for these purposes and to convene multidisciplinary teams as the pandemic surges and begins to dissipate; to identify the most vulnerable patients and providers; and to longitudinally manage their mental health challenges.

The second strategy is to monitor survivors of ARDS from COVID-19 to identify risk factors for the development of PTSD, chronic pain, and a fibromyalgia-like syndrome<sup>14</sup>. However, this surveillance must also offer therapeutic tools (pharmacological, psychological, occupational) aimed at attenuating the risk of developing a pain syndrome and its sequelae. During initial ICU stay, basic opioid sparing is necessary, for example using  $\alpha_2$  agonists to prevent opioid dependence after ICU discharge<sup>15</sup>. Other preventive measures includes early physical rehabilitation to maintain full range of motion of joints and to mitigate against muscle atrophy; virtual reality to distract patients from pain; and music therapy to improve the endogenous opioid system<sup>15</sup>. After discharge from hospital, ARDS survivors must be tracked to ensure an integrated cognitive therapy plan is instituted for PTSD with medications for depression and sleep disturbances.

The third and final strategy must focus on planning multidisciplinary, multicenter studies to identify the prevalence and natural history (clinical trajectory) of physical and psychological disability, including chronic pain and other long-term sequelae, in survivors of ARDS from COVID-19 to assess treatment effectiveness.

COVID-19 patients who survive ARDS are more likely to be severely affected by chronic pain compared with those who only experience mild to moderate infections, but the possible onset of chronic pain should not be underestimated even in those afflicted with the milder forms of the disease.

The survivors of the COVID-19 will find themselves facing a completely different world, with likely distorted human relationships and social fabric, along with a totally changed political and economic context. This requires that clinicians globally share their experiences, data, and treatment successes and failures for each of these sequelae.

Fortunately, intensivists and pain medicine specialists have many interests in common, in many cases they are superimposable. The risk is that after the acute infectious storm with COVID-19 passes, an opioid and disability storm will begin and present another set of challenges for which the healthcare community worldwide should be prepared.



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