Coronavirus Disease 2019 Pandemic Acute Respiratory Distress Syndrome Survivors: Pain After the Storm?

Alessandro Vittori, MD,* Jerrold Lerman, MD, FRCPC, FANZCA,† Marco Cascella, MD,‡ Andrea D. Gomez-Morad, MD,§ Giuliano Marchetti, MD,* Franco Marinangeli, PhD, MD,‖ and Sergio G. Picardo, MD*

ARDS = acute respiratory distress syndrome; **CoV** = coronavirus; **COVID-19** = coronavirus disease 2019; **ICU** = intensive care unit; **MERS** = Middle East respiratory syndrome; **PTSD** = posttraumatic 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

GLOSSARY

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.[1] 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 (severe acute respiratory syndrome coronavirus [SARS-CoV]), the International Committee on Taxonomy of Viruses termed this new virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated human illness as coronavirus disease 2019 (COVID-19).[1] On March 11, 2020, the WHO declared this global health emergency a pandemic.[2,3]

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).[4]

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%.[5]

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.[6] 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.[7] 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.[7] 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.[7]

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).[8,9] This limited exercise tolerance is related to the use of systemic corticosteroids to treat the disease and multiorgan dysfunction during the

From the *Ospedale Pediatrico Bambino Gesù IRCCS, Department of Anesthesia and Critical Care, ARCO, Rome, Italy; †Department of Anesthesiology, John R. Oishei Children's Hospital, Jacobs School of Medicine and Biomedical Sciences, Buffalo, New York; ‡Istituto Nazionale Tumori-IRCCS-Fondazione Pascale, Naples, Italy; §Department of Anesthesiology Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts; and ‖Department of Anesthesiology, Intensive Care and Pain Treatment, University of L'Aquila, L'Aquila, Italy.

Accepted for publication April 23, 2020.

Funding: None.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

Address correspondence to Alessandro Vittori, MD, Ospedale Pediatrico Bambino Gesù IRCCS, Department of Anesthesia and Critical Care, ARCO, Piazza S Onofrio 4, 00165 Rome, Italy. Address e-mail to alexvittori82@gmail.com.

DOI: 10.1213/ANE.0000000000004914

ICU stay. Chronic pain and weakness will develop in these survivors.[9] 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 posttraumatic 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, and anxiety about serious health conditions and survival.[9] The second relates to the muscle atrophy due to immobility and general inflammation and neurological tropism with CoV.[9,10]

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.[11] Of note, only 16% of ARDS survivors return to work 3 months after ICU discharge, 32% after 6 months, and 49% after 12 months.[9] The probability that the patient will become unemployed is determined by patient's age and the duration of hospitalization.[8] Furthermore, the mean value of the Barthel Index measured in ARDS survivors 6 months after ICU discharge (82.3 ± 22.9) is significantly less than that in non-ARDS patients (89.6 ± 23.2) (P = .007).[8] 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, health care 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.[12]

The first and most immediate strategy is to identify those who are at increased risk for developing PTSD after such a natural disaster (eg, 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.[13]

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.[9] In 1 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.[10] 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.[10] Anticipating the risks posed by a 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.[14] However, this surveillance must also offer therapeutic tools (pharmacological, psychological, and 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 α_2 agonists to prevent opioid dependence after ICU discharge.[15] Other preventive measures include 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.[15] After discharge from hospital, ARDS survivors must be tracked to ensure that 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 health care community worldwide should be prepared.

DISCLOSURES

Name: Alessandro Vittori, MD.
Contribution: This author helped with all sections of the manuscript, writing, editing, and submission.
Name: Jerrold Lerman, MD, FRCPC, FANZCA.
Contribution: This author helped write and revise the manuscript.
Name: Marco Cascella, MD.
Contribution: This author helped write and revise the manuscript.
Name: Andrea D. Gomez-Morad, MD.
Contribution: This author helped write and revise the manuscript.
Name: Giuliano Marchetti, MD.
Contribution: This author helped write and revise the manuscript.
Name: Franco Marinangeli, MD, PhD.
Contribution: This author helped write and revise the manuscript.
Name: Sergio G. Picardo, MD.
Contribution: This author helped write and revise the manuscript.
This manuscript was handled by: Thomas R. Vetter, MD, MPH.

REFERENCES

1. Peng PWH, Ho PL, Hota SS. Outbreak of a new coronavirus: what anaesthetists should know. *Br J Anaesth*. 2020;124:497–501.
2. Novel Coronavirus (2019-nCoV) situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed April 3, 2020.
3. Ludwig S, Zarbock A. Coronaviruses and SARS-CoV-2: a brief overview. *Anesth Analg*. 2020. [Epub ahead of print].
4. Sommer P, Lukovic E, Fagley E, et al. Initial clinical impressions of the critical care of COVID-19 patients in Seattle, New York City, and Chicago. *Anesth Analg*. 2020. [Epub ahead of print].
5. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020.
6. Coronavirus. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed April 16, 2020.
7. Fink S. Worst-case estimates for U.S. coronavirus deaths. *The New York Times*. Available at: https://www.nytimes.com/2020/03/13/us/coronavirus-deaths-estimate.html. Published March 13, 2020. Accessed March 27, 2020.
8. Bein T, Weber-Carstens S, Apfelbacher C. Long-term outcome after the acute respiratory distress syndrome: different from general critical illness? *Curr Opin Crit Care*. 2018;24:35–40.
9. Herridge MS, Cheung AM, Tansey CM, et al; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348:683–693.
10. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. *BMC Neurol*. 2011;11:37.
11. Kamdar BB, Sepulveda KA, Chong A, et al. Return to work and lost earnings after acute respiratory distress syndrome: a 5-year prospective, longitudinal study of long-term survivors. *Thorax*. 2018;73:125–133.
12. Cohen SP, Baber ZB, Buvanendran A, et al. Pain management best practices from multispecialty organizations during the COVID-19 pandemic and public health crises. *Pain Med*. 2020.
13. Heid AR, Christman Z, Pruchno R, Cartwright FP, Wilson-Genderson M. Vulnerable, but why? Post-traumatic stress symptoms in older adults exposed to Hurricane Sandy. *Disaster Med Public Health Prep*. 2016;10:362–370.
14. Coaccioli S, Varrassi G, Sabatini C, Marinangeli F, Giuliani M, Puxeddu A. Fibromyalgia: nosography and therapeutic perspectives. *Pain Pract*. 2008;8:190–201.
15. Stamenkovic DM, Laycock H, Karanikolas M, Ladjevic NG, Neskovic V, Bantel C. Chronic pain and chronic opioid use after intensive care discharge - is it time to change practice? *Front Pharmacol*. 2019;10:23.