Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

MAYO CLINIC

Hypoxia in COVID-19: Sign of Severity or Cause for Poor Outcomes

See also page 1138

In December 2019, reports of an outbreak of an unusual viral pneumonia were released from Wuhan, China, which was later found to be due to infection with novel severe acute respiratory syndrome coronavirus 2. In the following months, this viral infection, known as coronavirus disease 2019 (COVID-19), became a pandemic that now is engaging an ever-growing number of individuals across the globe, with a high rate of morbidity and mortality. Coronavirus disease 2019 not only has affected health care systems at the global levels but also has led to a substantial downturn in the world economy, both of which may increase the adverse effects of this infectious disease, particularly in resource-limited areas. Although the COVID-19 pandemic has led to many misfortunate life and livelihood losses, it has also resulted in solidarity at the global level in patient care and instigated innovative approaches to prevent, manage, or treat this disease.[1]

There are several characteristics of COVID-19 which have caused considerable concern. The patterns of transmission of this virus are progressively recognized. It appears that transmission of this virus is mostly via droplets unless infected individuals undergo aerosol-generating procedures that result in the airborne mode of transmission. Indeed, places that implemented social distancing, hand washing, and face masks as a priority have had success in controlling the spread of this virus. The other concern is that asymptomatic individuals could also shed the virus and thus contribute to its rapid spread in communities.[2] Therefore, widespread testing and contact tracking of infected individuals could also result in a slower spread of this disease. Large areas of uncertainty exist regarding COVID-19, and these include the extent of immunity after recovery from COVID-19, inherent and environmental risk factors of more severe illnesses, and a global or local consensus on preventive, management, or therapeutic options for COVID-19.[1]

One of the substantial challenges related to COVID-19 is the high incidence of multiorgan involvement as compared with other viral infections (ie, lungs, heart, kidney, gastrointestinal tract, coagulation system,[3] etc). However, it seems that the respiratory system is one of the most commonly engaged organs. Coronavirus disease 2019–associated pneumonia could lead to acute respiratory distress syndrome (ARDS), and the characteristics of COVID-19–associated ARDS may be similar or differ from those seen in ARDS due to other causes. Specifically, COVID-19–associated ARDS engages older individuals and those with comorbid conditions (eg, hypertension and diabetes mellitus)[4]; it is associated with significant dyspnea[4]; it presents with different phenotypes (ie, L vs H phenotypes that differ by lung elastance, ventilation to perfusion ratio, right-to-left shunt, and lung recruitability[5]); it imposes hypoxia that could be due to high shunt physiology (ie, hypoventilated areas of the lung are hyperemic,[6] particularly in the H phenotype); patients so afflicted require a prolonged period to resolve their ARDS[7]; and it has high mortality rates (51%).[4] These patients frequently require a higher level of care in hospitals or intensive care units, and de-escalation to a lower level of care or discharge may require several days. These factors have led to tremendous pressure on the health care systems, particularly in COVID-19 hot spots. The ability to triage patients who may need care level escalation could not only assist with appropriate bed assignment and prevention of health care overflow but could also potentially improve patients' outcomes by

Mayo Clin Proc. ■ June 2020;95(6):1094-1096 ■ https://doi.org/10.1016/j.mayocp.2020.04.021
www.mayoclinicproceedings.org ■

earlier initiation of preventive and management measures.

In this issue of *Mayo Clinic Proceedings*, Xie et al[8] report the results of a retrospective cohort study of 140 patients with confirmed or presumed COVID-19 who presented with relevant signs and symptoms, with positive COVID-19 real-time reverse transcription–polymerase chain reaction test results present in most patients. These patients received medical attention in hospitals or intensive care units in medical centers in Beijing, China, over 1 month that the study was conducted. The authors reported low peripheral capillary oxygen saturation (Spo_2; with the cutoff of 90%) after receiving oxygen support along with the presence of dyspnea to be a strong predictor of mortality. In addition, they suggested leukocytosis with a left shift along with C-reactive protein levels as a possible predictor of mortality in patients with COVID-19.

This study is commendable for being able to identify clinical and laboratory markers of outcomes in the COVID-19 pandemic. Hypoxia and dyspnea are both signs of lung involvement by severe acute respiratory syndrome coronavirus 2. These results mirror the pathophysiological processes of viral pneumonia, which, in turn, could result in worse outcomes. These markers are readily available at the bedside and could enhance the feasibility of appropriate and quick triage of patients with COVID-19 to a higher level of care; resources are thereby conserved and preventive and management measures more expeditiously initiated. In addition, these markers could be used to potentially enroll appropriate patients in much-needed clinical trials to find the proper treatment of this deadly disease.

Although this article is timely and adds significant value to the current and growing literature on the topic, there remain some unresolved questions that should be addressed in future investigations. The assessment of oxygen saturation in the arterial blood (partial pressure of oxygen, arterial [Pao_2]) when it is estimated by pulse oximetry should be carefully interpreted. Estimated oxygen saturation by CO-oximeters (Spo_2) could be different from measured arterial oxygen saturation by about ±4%.[9] Therefore, validating the results of Xie et al by using measured arterial oxygen saturation could be the next step. Furthermore, to be able to correctly assess the lung capacity for gas exchange, knowing the fraction of inspired oxygen (FIo_2) is a necessity. Achieving this information may be challenging in some clinical scenarios. For example, the estimates of FIo_2 when nasal cannulae or face masks are used may be variable (eg, when 2 L is delivered by a nasal cannula is used, FIo_2 could vary between 24% and 35%, depending on the tidal volume patients demand).[9,10] Therefore, in the next models for the prediction of mortality in patients with COVID-19, using the ratio of Spo_2 or Pao_2 and FIo_2 may be necessary. It is also essential to assess the correlation between lung gas exchange capacity and mortality in light of different phenotypes of ARDS (ie, L vs H phenotypes). When ventilation to perfusion ratio mismatch drives hypoxia, the delivery of higher FIo_2 leads to higher Pao_2 and Spo_2 (L phenotype). In contrast, when shunt drives hypoxia, the effect of FIo_2 on the improvement in oxygen saturation would be less evident.[5,6]

Xie et al also reported dyspnea as a significant predictor of mortality in patients with COVID-19. Dyspnea is defined as a subjective sense of breathlessness, and it is often mistaken for tachypnea, hyperpnea, or hyperventilation. Therefore, it is important in future studies to assess this symptom more objectively. For example, describing its acuity, its presence at rest or exertion or in different positions, and its precipitating or alleviating factors may facilitate triage of these patients into a more appropriate level of care.

As our knowledge and understanding of COVID-19 and its pathophysiology progressively increase, the article by Xie et al represents remarkable progress in the field. In particular, this study links the outcomes of COVID-19–associated pneumonia with straightforward clinical signs and symptoms, a linkage with a clear and plausible pathophysiological basis.

Kianoush B. Kashani, MD, MS
Division of Pulmonary and Critical Care Medicine and
Division of Nephrology and Hypertension
Department of Medicine
Mayo Clinic
Rochester, MN

Potential Competing Interests: The author reports no competing interests.

Correspondence: Address to Kianoush B. Kashani, MD, MS, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905. (kashani.kianoush@mayo.edu; Twitter: @kianoushbk).

ORCID
Kianoush B. Kashani: https://orcid.org/0000-0003-2184-3683

REFERENCES

1. Bhimraj A, Morgan RL, Shumaker AH, et al. *Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19*. Arlington, VA: Infectious Disease Society of America; 2020. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed April 20, 2020.
2. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic population [published online ahead of print April 14, 2020]. *N Engl J Med*, https://doi.org/10.1056/NEJMoa2006100.
3. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med*. 2020;382(17):e38.
4. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China [published online ahead of print March 13, 2020]. *JAMA Intern Med*, https://doi.org/10.1001/jamainternmed.2020.0994.
5. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes [published online ahead of print April 14, 2020]? *Intensive Care Med*, https://doi.org/10.1007/s00134-020-06033-2.
6. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to a "typical" acute respiratory distress syndrome [published online ahead of print March 30, 2020]. *Am J Respir Crit Care Med*, https://doi.org/10.1164/rccm.202003-0817LE.
7. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China [published online ahead of print February 7, 2020]. *JAMA*, https://doi.org/10.1001/jama.2020.1585.
8. Xie J, Covassin N, Fan Z, et al. Association between hypoxemia and mortality in patients with COVID-19. *Mayo Clin Proc*. 2020;95(6):1138-1147.
9. Tobin MJ. Basing respiratory management of coronavirus on physiological principles [published online ahead of print April 13, 2020]. *Am J Respir Crit Care Med*, https://doi.org/10.1164/rccm.202004-1076ED.
10. Chikata Y, Onodera M, Oto J, Nishimura M. FIo_2 in an adult model simulating high-flow nasal cannula therapy. *Respir Care*. 2017;62(2):193-198.