



Predictors of Worsening Oxygenation in COVID-19

Jee Youn Oh, M.D., Ph.D. 

Division of Pulmonary Allergy and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, Seoul, Republic of Korea

The spread of coronavirus disease 2019 (COVID-19) has resulted in a pandemic, leading to a sudden and substantial increase in the use of medical resources worldwide¹. Although the key characteristic of COVID-19 is that most patients have a mild clinical course, some patients demonstrate rapid deterioration to respiratory failure². Thus, it is important to triage and stratify the risk of COVID-19 patients in order to optimize the distribution of medical resources and prevent progression³. Worsening oxygenation is the key finding that forecasts severe cases⁴, but investigating biomarkers for worsening oxygenation is still an unmet medical need in COVID-19 patients.

Hahm et al.⁵ retrospectively evaluated the factors associated with worsening oxygenation in patients with non-severe COVID-19 pneumonia. Quantitative analysis of computed tomography (CT) using artificial intelligence (AI) tools as well as laboratory findings such as C-reactive protein (CRP), ferritin, lactic dehydrogenase (LDH), and lower lymphocyte counts were predictors of worsening oxygenation. Although this was a retrospective, single-center study involving a small number of patients with non-severe pneumonia, it synthetically analyzed the factors known to be associated with deterioration including comorbidities, pro-inflammatory cytokines, and CT findings using AI tools, and provided an automatic and objective estimation of the disease burden.

Previous studies have reported that age and underlying

diseases may be risk factors for COVID-19 patients requiring oxygenation, which is a well-known risk factor for other pneumonia⁶. Particularly for COVID-19, some patients progress to hypoxemia rapidly at approximately 1–2 weeks after onset, likely not due to the cytopathic activity of the virus, but due to the cytokine storm, as evidenced by increased proinflammatory cytokines⁷. Thus, inflammatory markers such as CRP, procalcitonin levels, neutrophil-lymphocyte ratio, and the rate of change of CRP have been reported to predict the progression of COVID-19⁸. Subsequently, more critical COVID-19 patients release procoagulant autoantibodies and markers associated with cytokine-mediated tissue damage and organ failure, and these are reported markers predicting severe COVID-19 or poor outcomes of COVID-19⁹. Elevated D-dimer levels, LDH, troponin I, and thrombocytopenia in patients with severe COVID-19 have also been reported, suggesting that a hypercoagulable state may contribute to the severity of illness and mortality¹⁰.

In non-severe cases, chest CT is pivotal in predicting prognosis^{11,12}. Chest quantitative CT has a promising role in the early diagnosis of COVID-19 and provides new metrics for predicting clinical outcomes¹³. The binding of coronavirus spike protein to angiotensin-converting enzyme II receptor increases pulmonary capillary permeability and causes diffuse opacities in CT¹⁴. CT could reflect the early pathogenesis of COVID-19 inflammation, even though chest radiography could not detect the abnormalities¹⁵. In fact, CT severity score is associated with inflammatory levels, and CT severity score on admission is an independent risk factor for early deterioration¹⁶. Moreover, the rapid improvement of AI has enabled the automatic quantification of lesions and the prediction of outcomes more precisely.

There have been thousands of reports on biomarkers for predicting outcomes of COVID-19 with various parameters, diverse clinical severities, and outcomes. In particular, many studies have dealt with mortality predictors for severe COVID-19 cases^{4,10,17}. However, rather than predicting mortality for initially critical patients, Hahm et al.⁵ investigated the scoring of non-severe patients on potential rapidly worsening oxygenation, which would be a more useful tool in regions where non-severe cases are more prevalent due to mass surveillance

Address for correspondence: Jee Youn Oh, M.D., Ph.D.

Division of Pulmonary Allergy and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 08308, Republic of Korea

Phone: 82-2-2626-3192, Fax: 82-2-2626-1166

E-mail: happymaria0101@hanmail.net

Received: Feb. 26, 2021

Revised: Mar. 1, 2021

Accepted: Mar. 10, 2021

Published online: Mar. 10, 2021

© It is identical to the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>).



Copyright © 2021
The Korean Academy of Tuberculosis and Respiratory Diseases.

screening¹⁸. More accurate, simple, and easily applicable tools for predicting worsening oxygenation in COVID-19 for initial risk stratification and medical resource arrangement are needed.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Gates B. Responding to COVID-19: a once-in-a-century pandemic? *N Engl J Med* 2020;382:1677-9.
2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020;324:782-93.
3. Truog RD, Mitchell C, Daley GQ. The toughest triage: allocating ventilators in a pandemic. *N Engl J Med* 2020;382:1973-5.
4. Choi KJ, Hong HL, Kim EJ. The association between mortality and the oxygen saturation and fraction of inhaled oxygen in patients requiring oxygen therapy due to COVID-19-associated pneumonia. *Tuberc Respir Dis* 2021;84:125-33.
5. Hahm CR, Lee YK, Oh DH, Ahn MY, Choi JP, Kang NR, et al. Factors associated with worsening oxygenation in patient with non-severe COVID-19 pneumonia. *Tuberc Respir Dis* 2021;84:115-24.
6. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. *BMJ* 2020;370:m3339.
7. Sinha P, Matthay MA, Calfee CS. Is a "cytokine storm" relevant to COVID-19? *JAMA Intern Med* 2020;180:1152-4.
8. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of COVID-19 infection: systematic review and critical appraisal. *BMJ* 2020;369:m1328.
9. Gu SX, Tyagi T, Jain K, Gu VW, Lee SH, Hwa JM, et al. Thrombocytopeny and endotheliopathy: crucial contributors to COVID-19 thromboinflammation. *Nat Rev Cardiol* 2021;18:194-209.
10. Cortes-Telles A, Lopez-Romero S, Mancilla-Ceballos R, Ortiz-Farias DL, Nunez-Caamal N, Figueroa-Hurtado E. Risk factors for mortality in hospitalized patients with COVID-19: an overview in a Mexican population. *Tuberc Respir Dis* 2020;83(Suppl 1):S46-54.
11. Lassau N, Ammari S, Chouzenoux E, Gortais H, Herent P, Devilder M, et al. Integrating deep learning CT-scan model, biological and clinical variables to predict severity of COVID-19 patients. *Nat Commun* 2021;12:634.
12. Zhang K, Liu X, Shen J, Li Z, Sang Y, Wu X, et al. Clinically applicable AI system for accurate diagnosis, quantitative measurements, and prognosis of COVID-19 pneumonia using computed tomography. *Cell* 2020;181:1423-33.
13. Wang M, Xia C, Huang L, Xu S, Qin C, Liu J, et al. Deep learning-based triage and analysis of lesion burden for COVID-19: a retrospective study with external validation. *Lancet Digit Health* 2020;2:e506-15.
14. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th Anniversary of the Discovery of ACE2. *Circ Res* 2020;126:1456-74.
15. McInnes MD, Leeflang MM, Salameh JP, McGrath TA, van der Pol CB, Frank RA, et al. Imaging tests for the diagnosis of COVID-19. *Cochrane Database Syst Rev* 2020 Jun 2 [Epub]. <https://doi.org/10.1002/14651858.CD013639>.
16. Feng Z, Yu Q, Yao S, Luo L, Zhou W, Mao X, et al. Early prediction of disease progression in COVID-19 pneumonia patients with chest CT and clinical characteristics. *Nat Commun* 2020;11:4968.
17. Mesas AE, Cavero-Redondo I, Alvarez-Bueno C, Sarria Cabrera MA, Maffei de Andrade S, Sequi-Dominguez I, et al. Predictors of in-hospital COVID-19 mortality: a comprehensive systematic review and meta-analysis exploring differences by age, sex and health conditions. *PLoS One* 2020;15:e0241742.
18. Yang Y, Kim H, Hwang J. Quarantine facility for patients with COVID-19 with mild symptoms in Korea: experience from eighteen residential treatment centers. *J Korean Med Sci* 2020;35:e429.