High-dose but Not Low-dose Corticosteroids Potentially Delay Viral Shedding of Patients With COVID-19

To the Editor—Considering the cytokine storm secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, some patients with coronavirus disease 2019 (COVID-19), especially severe and critical patients, have received treatment with systemic corticosteroids. In China, systemic corticosteroid administration (methylprednisolone, <1–2 mg/kg, 3–5 days) is recommended as adjuvant therapy for COVID-19 [1]. We read with interest the recent study by Xu et al [2] who determined risk factor associated with prolonged viral shedding in patients with COVID-19. They reported that use of corticosteroids was associated with higher probability of late viral RNA clearance (≥15 days after illness onset) in univariate logistic regression analysis (P = .025), but not in multivariate logistic regression analysis (odds ratio, 1.38 [95% confidence interval {CI}, .53–3.65]; P = .519).

Systemic corticosteroids have always been controversial in treating viral pneumonia. A newly published meta-analysis demonstrated that corticosteroid treatment was associated with longer length of stay, higher probability of bacterial infection, and mortality among patients with coronavirus pneumonia [3]. In addition, whether systemic corticosteroids delay viral clearance is another topic of priority. The first randomized controlled trial about corticosteroids and viral clearance observed that patients with early use of hydrocortisone harbored higher plasma SARS-CoV viral load and longer time of viral shedding than those without hydrocortisone [4]. During the outbreak of Middle East respiratory syndrome (MERS), 48.9% of critical patients received corticosteroid treatment in Saudi Arabia; early use (<7 days after hospital) of high-dose corticosteroids (methylprednisolone equivalent dose >60 mg/day; adjusted hazard ratio [aHR], 0.26 [95% CI, .09–.77]; P = .015) and lose-dose corticosteroids (≤60 mg/day [aHR, 0.41 [95% CI, .19–.88]; P = .022) also delayed viral shedding compared with no use of corticosteroids [5]. High-dose corticosteroids seemingly were more likely to prolong viral clearance of MERS. Ogimi and colleagues [6] further suggested that high-dose steroids (>1 mg/kg) were associated with prolonged shedding of human coronavirus compared with low-dose steroids (≤1 mg/kg). A dose-response manner of corticosteroid and viral shedding also was shown in influenza viral pneumonia. Studies from Cao et al [7] and Boudreault et al [8] also observed that prolonged shedding of influenza virus was found in high-dose corticosteroids, but not shown in low-dose corticosteroids.

We collected >60 variables from 206 patients with COVID-19 to assess risk factors of long-term (>30 days) positive SARS-CoV-2 and viral shedding. Least absolute shrinkage and selection operator (LASSO) analysis effectively resolved the colinearity of high-dimensional data and performed tuning parameter selection using 10-fold cross-validation [9]. LASSO analysis with logistic regression model indicated no impact of corticosteroids on long-term positive SARS-CoV-2. However, LASSO analysis with Cox regression model and restricted mean survival time analysis demonstrated that high-dose (80 mg/day; aHR, 0.67 [95% CI, .46–.96]; P = .031) but not low-dose corticosteroids (40 mg/day; aHR, 0.72 [95% CI, .48–1.08]; P = .11) potentially delayed viral shedding of patients with COVID-19.

Our study suggests that the effect of corticosteroids on viral shedding may be a dose-response manner in Cox regression analysis. In addition, high-dose but not low-dose corticosteroids were found to potentially increase the mortality of patients with severe COVID-19 [10]. Therefore, high-dose corticosteroids should be used with extreme caution in treating COVID-19.

Notes

Author contributions. All authors contributed to data analysis, drafting, or revision of the article; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Acknowledgments. All patients gave written informed consent and the study was approved by the ethics committee of Yichang Central People's Hospital.

Financial support. This work was supported by the Natural Science Foundation of Hubei province (grant number 2018CFB643).

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Sijia Li[1,2] Zhigang Hu,[1,2,a] and Xinyu Song[1,2,a]

[1]Department of Respiratory and Critical Care Medicine, First College of Clinical Medicine Science, China Three Gorges University, Yichang, People's Republic of China, and [2]Department of Respiratory and Critical Care Medicine, Yichang Central People's Hospital, Yichang, People's Republic of China

References

1. National Health Commission of the People's Republic of China. The notice of launching guideline on diagnosis and treatment of the novel coronavirus pneumonia (NCP). 5th edition revised [in Chinese]. Available at: http://www.nhc.gov.cn/xcs/zhengcwj/ 202002/d4b895337e19445f8d728fcaf1e3e13a.shtml. Accessed 8 February 8 2020.
2. Xu K, Chen Y, Yuan J, et al. Factors associated with prolonged viral RNA shedding in patients with COVID-19 [manuscript published online ahead of print 9 April 2020]. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa351.
3. Yang Z, Liu J, Zhou Y, et al. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect **2020**; 81:e13–20.
4. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. J Clin Virol **2004**; 31:304–9.
5. Arabi YM, Mandourah Y, Al-Hameed F, et al; Saudi Critical Care Trial Group. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med **2018**; 197:757–67.
6. Ogimi C, Greninger AL, Waghmare AA, et al. Prolonged shedding of human coronavirus in

hematopoietic cell transplant recipients: risk factors and viral genome evolution. J Infect Dis **2017**; 216:203–9.
7. Cao B, Gao H, Zhou B, et al. Adjuvant corticosteroid treatment in adults with influenza a (H7N9) viral pneumonia. Crit Care Med **2016**; 44:e318–28.
8. Boudreault AA, Xie H, Leisenring W, Englund J, Corey L, Boeckh M. Impact of corticosteroid treatment and antiviral therapy on clinical outcomes in hematopoietic cell transplant patients infected with influenza virus. Biol Blood Marrow Transplant **2011**; 17:979–86.
9. Avalos M, Adroher ND, Lagarde E, et al; CESIR Research Group. Prescription-drug-related risk in driving: comparing conventional and lasso shrinkage logistic regressions. Epidemiology **2012**; 23:706–12.
10. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan [manuscript published online ahead of print 12 April 2020]. J Allergy Clin Immunol **2020**. doi:10.1016/j.jaci.2020.04.006.

[a]Z. H. and X. S. contributed equally to this work.

Correspondence: X. Song, Department of Respiratory Medicine, First College of Clinical Medicine Science, Three Gorges University, No. 183 Yiling Road, Yichang 443003, People's Republic of China (songxinyu@ctgu.edu.cn).

Clinical Infectious Diseases® 2020

DOI: 10.1093/cid/ciaa829