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## Letter to the Editor

**Re: Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19** 

Dear Editor

We have read the article by Fang X, et al.<sup>1</sup> with great interest. The authors reported that low dose steroid therapy did not associated with delaying viral clearance in 55 and 23 patients with general and severe coronavirus disease 2019 (COVID-19). We report a case of viral shedding more than 6 weeks in the nasopharyngeal swab in a critically ill patient with COVID-19 who received low-dose corticosteroid therapy and extracorporeal membrane oxygenation (ECMO). A 73-year-old woman was diagnosed with COVID-19 on February 20, 2020. She was transferred to Asan Medical Center (Seoul, Korea) on February 27 due to pneumonia requiring supplemental oxygen. Real-time reverse transcription (RT)-PCR using Allplex 2019-nCoV (Seegene, Seoul, Korea) showed positive results from the nasopharyngeal swab, throat swab, and sputum specimen (cycle threshold value for the *E* gene: 22.6, 27.6, and 17.8, respectively).

As the patient became more hypoxemic despite oxygen supplementation through high-flow nasal prong, she began to receive mechanical ventilation in the prone position on hospital day (HD) 2 and subsequently switched to veno-venous extracorporeal membrane oxygenation (VV-ECMO) on HD 4. Hydrocortisone (200 mg/day) was administered for 26 days due to hypotension; lopinavir-ritonavir was administered for 2 days, followed by hydroxychloroquine (400 mg/day) for 11 days.

Upon daily follow-up, SARS-CoV-2 PCR from sputum produced negative results after HD 18. Nevertheless, chest x-ray showed progression of multifocal consolidation and air-bronchogram. Unlike sputum, nasopharyngeal swab samples intermittently showed positive results after showing the first negative PCR result on HD 9 (Fig. 1), even showing reversion to a positive result after 4 consecutive negative results. On HD 35 (42 days after symptom onset), the patient remained on mechanical ventilation and VV-ECMO, and SARS-CoV-2 PCR from nasopharyngeal swab samples continued to produce positive results.

Fang X and colleagues reported that low dose steroid therapy (median hydrocortisone- equivalent dose of 237.5 mg/day and 250 mg/day was administered in general and severe group) did not delay viral clearance both in general and severe COVID-19 group.<sup>1</sup> However, median durations of steroid therapy were 7 and 4.5 days in general and severe COVID-19 group. In this case, critically ill patient with COVID-19 received hydrocortisone 200 mg/day for 26 days, and PCR results from nasopharyngeal swab samples contin-

ued to be intermittently positive even until 42 days after symptom onset. Interestingly, those from the lower respiratory tract have been negative following 25 days after symptom onset. It is not certain whether the positive PCR results from the nasopharyngeal swabs are due to non-viable remnant RNA fragments or viable virus due to inadequate clearance caused by immunosuppressive therapy (i.e., hydrocortisone). Further study using cell culture is needed to examine the duration of viable virus shedding in the presence of corticosteroid therapy.

Studies showed that the median duration of viral shedding in patients with COVID-19 after symptom onset is approximately 3 weeks.<sup>1–3</sup> In this context, our patient exhibited a relatively prolonged viral shedding duration, especially from the upper respiratory tract. Corticosteroid therapy is a double-edged sword that can suppress inflammation while hindering pathogen clearance. In cases with MERS-CoV infection, corticosteroid therapy was not associated with decreased mortality but was associated with delayed viral clearance.<sup>4</sup> In SARS, corticosteroid therapy was also associated with delayed clearance of viral RNA from the blood.<sup>5</sup> Therefore, the exceptionally long duration of viral shedding in our patient may be due to long-term use of corticosteroid therapy, and further targeted study is needed to elucidate this issue.

In South Korea, the criteria for the release of patients with COVID-19 from isolation is clinical improvement with two consecutive negative PCR results from specimens collected at least 24 hours apart.<sup>6</sup> As for the CDC, the criteria for discontinuation of transmission-based precaution is the resolution of fever without the use of anti-pyretic, improvement of respiratory symptoms, and negative results for SARS-CoV-2 RNA from at least two consecutive nasopharyngeal swab specimens collected at least 24 hours apart.<sup>7</sup> We observed that even after 4 consecutive negative results, nasopharyngeal swabs may revert back to producing positive results; therefore, two consecutive negative PCR results may not be sufficient to guarantee persistent negative results. This is in line with the recent study about 15% of patients with COVID-19 who discharged had positive PCR results during the follow-up.<sup>8</sup> Several news media also reported on recurrent SARS-CoV-2 positive results due to relapse, remnant RNA detection, or reinfection.<sup>9,10</sup> Sharing the details of various experiences with persistent intermittent positive PCR results such as our current case would be valuable in tackling the issue of patients with recurrence of SARS-CoV-2.

In conclusion, a critically ill patient with COVID-19 continued to show positive PCR results for SARS-CoV-2 from her nasopharynx for at least 6 weeks after symptom onset. Further well-designed studies about the effect of low dose steroid use on the viral shedding kinetics are needed.

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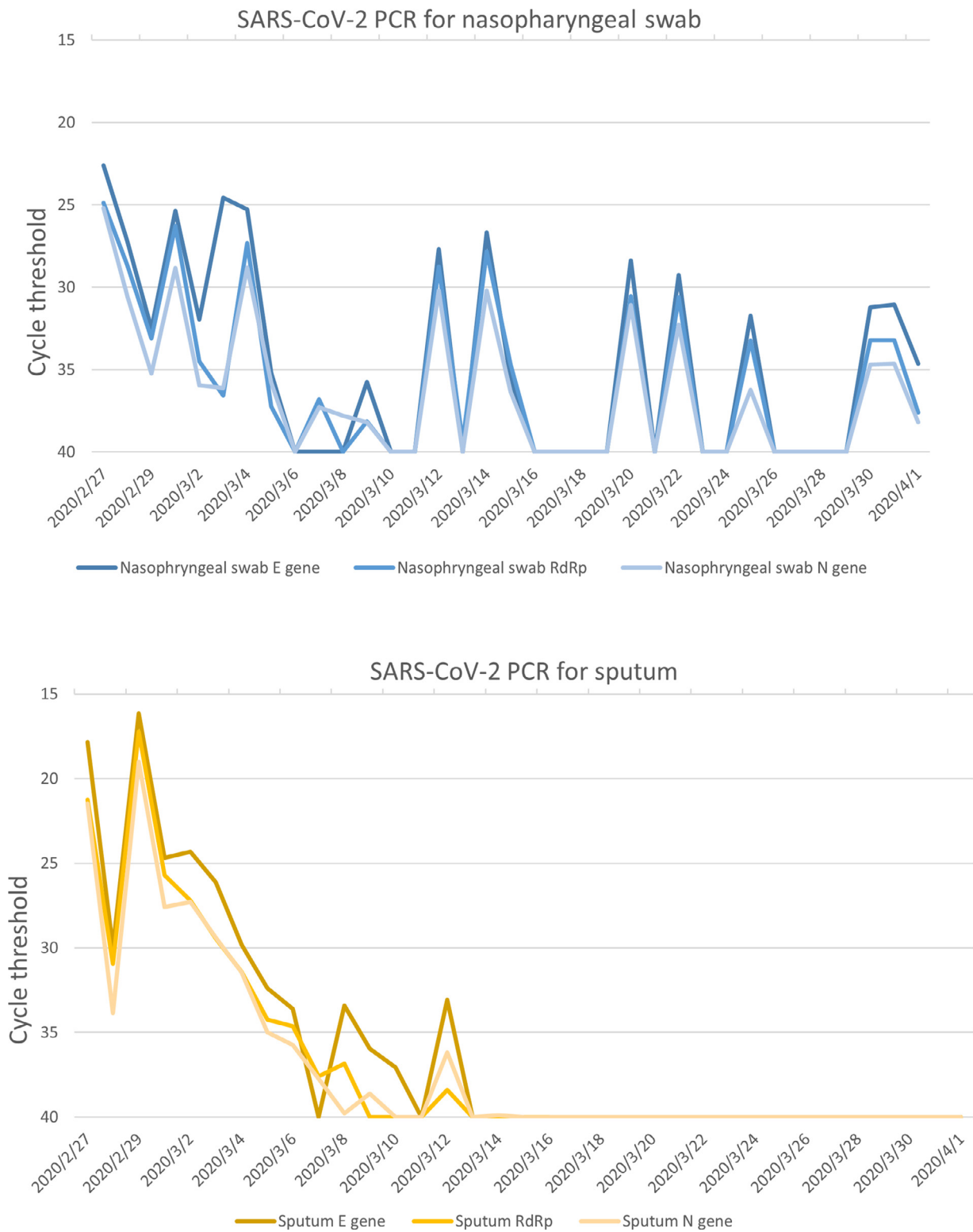


Fig. 1. Serial results of cycle threshold values of SARS-CoV-2 real-time PCR. CT value of 40 indicates undetectable viral load.

**Declaration of Competing Interest**

There are no potential conflicts of interest for any authors.

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