Time and risk factors of viral clearance in COVID-19 patients

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To the Editor: Coronavirus disease 2019 (COVID-19) has become a global pandemic. To minimize the risk of viral transmission in the community, some countries require two negative results of reverse transcription polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA on nasopharyngeal swabs collected ≥24 h apart for hospital discharge and discontinuation of isolation. Thus, understanding the time of viral clearance is essential. However, there are limited data reporting the viral clearance time and its risk factors in COVID-19 patients.[1,2] Moreover, the numbers of patients were limited and the risk factors of viral clearance were inconsistent in these studies. Therefore, we aim to determine the time and risk factors of viral clearance in throat swabs in COVID-19 patients.

Patients admitted to Zhongnan Hospital of Wuhan University between January 1, 2020 and March 16, 2020 who met the World Health Organization definition of COVID-19 and had negative tests of SARS-CoV-2 nucleic acid for two consecutive times after treatments were retrospectively observed. This study was approved by the institutional ethics board of Zhongnan Hospital of Wuhan University (No. 2020013). Informed consent from patients was exempted.

The demographic data, comorbidities, symptoms, laboratory, and imaging findings on admission, number of patients who developed respiratory failure, treatments, time of nucleic acid negative conversion (days from the date of symptoms onset to the day when SARS-CoV-2 viral RNA was first undetectable in throat swabs for two consecutive tests), number of patients whose nucleic acid was converted to negative 7 days after, and 14 days after temperature recovery, hospital length-of-stay, and outcome were collected. Medians (Q_1, Q_3) were used for the description of non-normally distributed continuous variables. Number (*n*) and percentage (%) were used to describe categorical variables. Potential risk factors affecting the time of nucleic acid negative conversion were analyzed by the Kaplan-Meier method and log-rank test, and then multivariate Cox regression. Hazard ratio (HR) with 95% confidence interval (CI) was calculated. A two-tailed P value < 0.05 was considered statistically significant. All the statistical analyses were performed using the Statistical Package for the Social Sciences, version 25.0 (SPSS, Inc., Chicago, IL, USA).

In total, 397 patients with COVID-19 were included in this study. The median age was 54 (41, 64) years, and 181 (45.6%) were men. Hypertension (88/397, 22.2%) was the most common comorbidity. Fever (312/397, 78.6%), cough (220/397, 55.4%), and fatigue (141/397, 35.5%) were the most common symptoms on hospital admission. The median time from symptoms onset to SARS-CoV-2 nucleic acid negative conversion was 23.5 (15.8, 32.3) days. In 248 (79.5%) of 312 febrile patients, RT-PCR remained positive after temperature recovery. In 41.0% (128/312) and 17.9% (56/312) of patients, RT-PCR was still positive at 7 and 14 days after temperature recovery. Of 397 patients, 395 (99.5%) were discharged and two (0.5%) were dead at the end of follow-up. The median hospital stay was 14 (10, 22) days. Identifying by log-rank test, age of 55 years or older ($P = 0.034$), development of respiratory failure ($P = 0.003$), lymphopenia ($P < 0.001$), corticoid therapy ($P < 0.001$), oseltamivir ($P < 0.001$), and interferon-α ($P = 0.004$) treatment were associated with the time of SARS-CoV-2 nucleic acid negative conversion. Multivariate Cox regression showed age of 55 years or older (HR: 0.791, 95% CI: 0.643–0.973, $P = 0.026$) and development of respiratory failure (HR: 0.640, 95% CI:

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Table 1: Multivariate Cox regression analysis of factors associated with viral clearance in COVID-19 patients.

Variables	HR	95% CI	*P* values
Age (≥55 *vs*. <55 years)	0.791	0.643–0.973	0.026
Development of respiratory failure (yes *vs*. no)	0.640	0.518–0.791	<0.001
Lymphopenia (yes *vs*. no)	1.543	1.212–1.965	<0.001
Oseltamivir (yes *vs*. no)	1.240	0.978–1.574	0.076
Interferon-α (yes *vs*. no)	1.189	0.960–1.473	0.113
Corticosteroid therapy (yes *vs*. no)	1.742	1.310–2.316	<0.001

CI: Confidence interval; COVID-19: Coronavirus disease 2019; HR: Hazard ratio.

0.518–0.791, $P < 0.001$) were associated with delayed nucleic acid negative conversion; lymphopenia (HR: 1.543, 95% CI: 1.212–1.965, $P < 0.001$) and corticosteroid therapy (HR: 1.742, 95% CI: 1.310–2.316, $P < 0.001$) were associated with rapid nucleic acid negative conversion as shown in Table 1.

The median time of viral clearance in our study was 23.5 days, which was longer than that in Chang *et al*'s report (10.5 days).[2] That study was performed outside of Wuhan, where there was no shortage of medical resource and patients could receive therapy immediately. Our results were similar to Fu *et al*'s study,[1] which was also performed in Wuhan. Furthermore, our results showed that in a significant proportion of COVID-19 patients, nucleic acid tests were still positive after temperature recovery.

Our results revealed that older age was associated with delayed SARS-CoV-2 nucleic acid negative conversion. T cell functions and proliferation were diminished with aging, leading to less control of viral replication. The ability to clear virus might be declined in old patients. The development of respiratory failure was associated with delayed SARS-CoV-2 nucleic acid negative conversion in our study, which was consistent with the report that patients with persistent viral presence have more severe disease outcomes.[3] Lymphopenia was observed in COVID-19 patients. Lymphopenia on admission was associated with rapid SARS-CoV-2 nucleic acid negative conversion in our study. Viral infections could lead to the activation of the hypothalamic-pituitary-adrenal axis, which results in cortisol secretion. Glucocorticoids could induce lymphopenia by driving them out of the peripheral circulation to the infected site to clear virus. In fact, Tan *et al*[4] revealed that lymphopenia could happen to moderately, severely, and critically ill COVID-19 patients in the initial stage of disease. Lymphocytes increased later in recovery patients, whereas, continued to decrease in dead patients. Thus, it is the lymphocyte-time curve that is important for prognosis prediction. Huang *et al*[5] reported that corticosteroid therapy is associated with delayed SARS-CoV-2 clearance in COVID-19 patients. However, other studies demonstrated that corticosteroid therapy did not delay viral clearance in COVID-19 patients.[6] Whereas, our results showed that corticosteroid therapy shortened the time of viral clearance. In our study, the indications for initiating corticosteroid therapy are development from low-grade fever to high-grade fever, appearance of dyspnea, SpO_2 becoming less than 93%, or aggravation of pulmonary imaging in a short time. It is possible that the time to initiate the corticosteroid therapy determines the outcome. Therefore, further researches are needed to clear the effects of corticosteroid therapy in COVID-19 patients.

This study has several limitations. First, the time of nucleic acid negative conversion of blood, stool, and urine was not observed in our study. Second, viral loads (Ct values) were not recorded in our study. The correlations between viral loads and time of viral clearance merits further investigation. Third, the virus was detected by RT-PCR but not by viral culture. As RT-PCR could detect viable and non-viable virus, our results could not distinguish whether the patients with RT-PCR positivity had infectibility or not.

In conclusion, viral clearance occurred after temperature recovery in a significant proportion of COVID-19 patients. Older age and development of respiratory failure were associated with delayed viral clearance, whereas, lymphopenia on admission and corticosteroid therapy were associated with rapid viral clearance in COVID-19 patients.

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Conflicts of interest

None.

References

1. Fu Y, Han P, Zhu R, Bai T, Yi J, Zhao X, *et al*. Risk factors for viral RNA shedding in COVID-19 patients. Eur Respir J 2020;56:2001190. doi: 10.1183/13993003.01190-2020.
2. Chang D, Mo G, Yuan X, Tao Y, Peng X, Wang FS, *et al*. Time kinetics of viral clearance and resolution of symptoms in novel coronavirus infection. Am J Respir Crit Care Med 2020;201:1150–1152. doi: 10.1164/rccm.202003-0524LE.
3. Chang D, Zhao P, Zhang D, Dong JH, Xu Z, Yang G, *et al*. Persistent viral presence determines the clinical course of the disease in COVID-19. J Allergy Clin Immunol Pract 2020;8:2585–2591.e1. doi: 10.1016/j.jaip.2020.06.015.

4. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, *et al*. Correction: lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020;5:61. doi: 10.1038/s41392-020-0159-1.
5. Huang R, Zhu C, Wang J, Xue L, Li C, Yan X, *et al*. Corticosteroid therapy is associated with the delay of SARS-CoV-2 clearance in COVID-19 patients. Eur J Pharmacol 2020;889:173556. doi: 10.1016/j.ejphar.2020.173556.
6. Ji J, Zhang J, Shao Z, Xie Q, Zhong L, Liu Z. Glucocorticoid therapy does not delay viral clearance in COVID-19 patients. Crit Care 2020;24:565. doi: 10.1186/s13054-020-03287-6.

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