



## Prolonged shedding of SARS-CoV-2 in COVID-19 infected hemodialysis patients

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Running title: Prolonged shedding of SARS-CoV-2 in HD patients

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Key word: Hemodialysis patients, COVID-19, coronavirus, SARS-CoV-2, end-stage renal disease

Received: July 8, 2020

Revised: July 21, 2020

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/tap.13566

An outbreak of coronavirus disease 2019 (COVID-19), now known to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that began in China in December 2019, has since spread rapidly throughout the world (1). There are several reports of hemodialysis patients with COVID-19 (2, 3, 4). Hemodialysis patients appear to be a population at high risk for severe COVID-19, because factors identified as risk factors for severe COVID-19 are often present in these patients: old age, hypertension, cardiovascular comorbidity, and diabetes mellitus. In addition, these patients also show impaired antiviral immune responses, because of the impaired kidney function. On the other hand, hemodialysis patients may not be at a higher risk for more severe COVID-19 in other respects: They are also aware of their vulnerable condition, they know that they should seek medical advice immediately when they have fever or other complaints, and they have an immunosuppressed state which may attenuate the hyperinflammatory response observed in the stage of severe COVID-19. The usual clinical course of hemodialysis patients with COVID-19 is not yet clear. We examined 5 hemodialysis patients with COVID-19 at our hospital and report, herein, the prolonged persistence of a positive result of the PCR test for SARS-CoV2 in hemodialysis patients.

#### PATIENTS AND METHODS

Five hemodialysis patients transferred to our hospital after treatment of the acute phase of COVID-19 were enrolled in this study. Clinical data were collected from the patients' records. The duration of positive results of the real-time reverse transcriptase–polymerase chain reaction (RT-PCR) test for SARS-CoV-2 was investigated in these patients. The PCR tests were performed on nasopharyngeal swabs. The data are expressed as the means  $\pm$  S.D. This study was conducted in accordance with the principles of the Declaration of Helsinki and with the approval of the research ethics committee of Sangenjaya Hospital (Approved No. R0206).

#### RESULTS

The characteristics of the five patients enrolled in this study are shown in Table 1. The mean age was  $74 \pm 9$  years. Diabetic nephropathy was the cause of the end-stage kidney disease in the majority (60%). The mean dialysis vintage was  $9.4 \pm 10.2$  years. All the 5 patients had a definite history of contact with an infected person. All five received treatment with favipiravir. Two patients also received tocilizumab, ivermectin or a steroid in addition. Ciclesonide was used in one patient. The fever and other subjective symptoms resolved soon after the start of treatment in all the five patients. However, the results of the PCR test for SARS-CoV-2 remained positive for 24 to 37 (mean,  $29 \pm 6$ ) days. The first negative PCR test result was confirmed between 27-42 (mean,  $34 \pm 7$ ) days after the onset of symptoms (Figure 1).

#### DISCUSSION

We report here that in hemodialysis patients with COVID-19, it takes a long time before the PCR test turns negative. The mean length of time over which the PCR test for SARS-CoV-2 remained positive in our patients was 24 to 37 (mean,  $29 \pm 6$ ) days. Prolonged shedding of SARS-CoV-2 in COVID-19 infected hemodialysis patients was observed.

In most general patients with symptomatic COVID-19 infection, viral RNA in the nasopharyngeal swab becomes detectable as early as on day 1 of symptom onset and peaks within the first week of symptom onset, and the positivity rate of the test starts to decline by week 3, with the test result becoming negative soon thereafter in most patients (5). In our study, the PCR test result remained positive for more than 24 days after the onset of disease in all the five hemodialysis patients. Therefore, we report that hemodialysis patients may show prolonged persistence of positive results of the PCR test for SARS-CoV-2.

One of the reasons for the prolonged persistence of a positive test result may be the tendency of hemodialysis patients with COVID-19 to follow a severe clinical course. They frequently have several risk factors for severe COVID-19. The mortality rate of COVID-19 in Japanese population was 4.1% (985/24132) (6), while that of Japanese hemodialysis patients was 17.6% (22/125) (7). In severely ill hospitalized patients with COVID-19, a positive test result of PCR may persist beyond 3 weeks after the onset of illness, whereas the test turns negative by this time in most cases with mild disease (5). Hemodialysis patients with COVID-19 might better to be isolated longer than ordinary infected patients to prevent the environmental contamination in hemodialysis units.

In addition, hemodialysis patients also show impaired antiviral immune responses which could also explain the prolonged persistence of a positive PCR test result. A “positive” PCR test result only reflects the presence of viral RNA, and does not necessarily indicate the presence of viable virus (8). In some cases, viral RNA has been detected by PCR even beyond week 6 after the first positive test. In a few cases, a positive test result has even been reported after 2 consecutive negative results of PCR performed at least 24 hours apart. It remains unclear if the finding in these cases reflects a testing error, reinfection, or reactivation (9). In a study of 9 patients, attempts to isolate the virus in culture were not successful beyond day 8 after the onset of illness, which correlates with the reported decline of infectivity of the patients after the first week of the disease (6). That may be the reason, at least in part, for the changes announced by the Japanese Ministry of Health, Labour and Welfare to the conditions necessary for discharge from the hospital of patients with COVID-19. While the Ministry had once recommended at least two consecutive negative results of the PCR test before patients with COVID-19 could be discharged from the hospital, after reconsidering the evidence, it now recommends that patients may be discharged without a PCR test if they have remained symptom-free for 72 hours and at least 10 days have elapsed after the onset of symptoms. The significance of the prolonged persistence of positive PCR test results in hemodialysis patients remains unclear. The patients in our study showed resolution of their symptoms and signs soon after

the start of treatment and the persistently positive test results may just reflect the trapped RNA of a non-infectious virus in these patients too, as in the general population.

One of the important limitations of our study was that we did not know the detailed clinical courses of the patients from the disease onset, as they were transferred to our hospital after treatment of the acute phase. And we also did not know the characteristics of main hemodialysis population which these patients came from. Accumulation of further cases is necessary.

## CONCLUSION

Prolonged shedding of SARS-CoV-2 in COVID-19 infected hemodialysis patients was observed. Hemodialysis patients with COVID-19 might better to be isolated longer than ordinary infected patients to prevent the environmental contamination in hemodialysis units.

## Conflict of Interest

None.

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Table 1. The characteristics of the 5 hemodialysis patients with COVID-19

Characteristic	Quantity
Age	74 ± 9
Gender (M/F)	3 / 2
Cause of ESKD	
Diabetic Nephropathy	3
Chronic glomerulonephritis	1
unknown	1
Dialysis vintage (Years)	9.4 ± 10.2
Treatment	
Favipiravir	5
Tocilizumab	2
Ivermectin	2
Steroid	2
Ciclesonide	1
Length of time over which the PCR test for SARS-CoV-2 remained positive (days)	29 ± 6

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Mean ± SD

ESKD: end stage kidney disease

Figure legends

Figure 1. Days since onset and nasopharyngeal swabs PCR positive rate

The results of the PCR test for SARS-CoV-2 remained positive for 24 to 37 (mean,  $29 \pm 6$ ) days. The first negative PCR test result was confirmed between 27-42 (mean,  $34 \pm 7$ ) days after the onset of symptoms.

