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Letter to the Editor

LETTER TO THE EDITOR

Prolonged detection of SARS-CoV-2 RNA in chronic haemodialysis patients

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Patients on maintenance haemodialysis exhibit a high risk of an adverse outcome after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and reported case fatality rates vary from 16% to 32% [1]. Moreover, patients receiving in-centre haemodialysis are particularly vulnerable to SARS-CoV-2 infection due to the impossibility of self-isolating. This situation is further exacerbated by recent reports revealing a diminished immune response after both recovery from coronavirus disease 2019 (COVID-19) and vaccination against SARS-CoV-2 in the dialysis population [2, 3].

In this regard, we want to add another aspect to be considered by presenting two cases of exceptional long detectability of SARS-CoV-2 RNA in chronic haemodialysis patients.

PATIENT 1

The first patient is a 61-year-old woman who was admitted to hospital for evaluation of gastrointestinal discomfort and elevated C-reactive protein (CRP) levels. She was on peritoneal dialysis for 2 years and 3 months; the reason for her end-stage renal disease is unknown. A first routinely collected nasopharyngeal sample tested negative for SARS-CoV-2 RNA by real-time PCR using the *in vitro* diagnostics/Conformité Européenne-labelled cobas® SARS-CoV-2 Test (Roche Diagnostics, Mannheim, Germany) for use on the cobas® 6800/8800 Systems (Roche Molecular Diagnostics) [4]. This assay uses ORF1a/b non-structural region and a conserved region in the structural protein envelope E-gene for detection of SARS-CoV-2 RNA. Cycle threshold (Ct) values of SARS-CoV-2 RNA testing are shown in Table 1. Real-time PCR Ct values represent the number of amplification cycles required for the fluorescence of a PCR product (i.e. target gene) to be detected crossing a threshold that is above the background signal. Ct levels are inversely proportional to the amount of target nucleic acid in the sample (i.e. the lower the Ct level, the greater the amount of target nucleic acid in the sample). Five days after admission, she developed fever. A chest X-ray showed bilateral consolidations. Eleven days after admission, she was admitted to the intensive care unit (ICU) due to progressive respiratory failure. In the ICU, she received continuous positive airway pressure face-mask ventilation and was switched to continuous renal replacement therapy. Remdesivir was given for 5 days. After 13 days in the ICU, she was transferred to the general ward. She still exhibited increased CRP levels that required multiple changes of the antibiotic therapy. Finally, CRP levels decreased and repeated nasopharyngeal SARS-CoV-2 PCR tests resulted negative. After 16 days on the general ward, she developed subfebrile temperature and the CRP levels increased again. On chest X-ray, the bilateral consolidations had improved and no other focus of inflammation could be identified. An antibiotic therapy was re-introduced; the SARS-CoV-2 PCR tested positive again. In the further course, her general condition improved continuously along with decreasing CRP levels. After 37 days on the general ward, SARS-CoV-2 PCR tested negative and the patient was discharged home. At that time, anti-SARS-CoV-2 immunoglobulin G (IgG) titre was 266 U/mL (LIAISON® SARS-CoV-2 S1/S2 IgG, DiaSorin, Saluggia, Italy). She is still on intermittent haemodialysis in our dialysis unit where all patients are frequently screened for SARS-CoV-2 RNA by nasopharyngeal PCR. She tested positive again 4 weeks after discharge without a clinical correlate. No viral variant of concern was found based on melting curve analysis (VirSNIP SARS del69,70 + 484K + 501Y, TIB MOLBIOL®, Berlin, Germany). Repeated SARS-CoV-2 RNA testing performed during the intermittent dialysis sessions resulted

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Table 1. Clinical course and detectability of SARS-CoV-2 RNA of patient 1

Date of sampling	Day	Ct value 1 (ORF1a/b)	Ct value 2 (E-gene)	Additional information
1 December 2020	0	TND	TND	Admission to hospital
7 December 2020	6	14	16	Developed fever
11 December 2020	10	31.27	31.88	Admission to ICU
17 December 2020	16	25.73	26.54	
24 December 2020	23	33.09	34.43	General ward
30 December 2020	29	TND	TND	
7 January 2021	37	TND	TND	Subfebrile temperature, antibiotic therapy
19 January 2021	49	TND	35.78	
21 January 2021	51	33.08	35.78	
26 January 2021	56	21.61	21.18	
28 January 2021	58	TND	TND	Discharged home
26 February 2021	87	33.76	36.60	
2 March 2021	91	30.74	32.20	
9 March 2021	98	31.31	32.21	
16 March 2021	105	TND	TND	
20 March 2021	109	32.99	34.45	
23 March 2021	112	36.31	TND	
25 March 2021	114	TND	TND	

TND, target not detected; Ct, cycle threshold; ORF1a/b, E-gene: target regions of RT–PCR for the detection of SARS-CoV-2 RNA.

Table 2. Clinical course and detectability of SARS-CoV-2 RNA of patient 2

Date of sampling	Day	Ct value 1 (ORF 1a/b)	Ct value 2 (E-gene)	Additional information
28 November 2020	0	17	18	Admission to emergency room/hospital
30 November 2020	2	20.5	20.80	
1 December 2020	3	TND	TND	Transfer to ICU
5 December 2020	7	30.74	31.43	
10 December 2020	12	31.00	31.17	
15 December 2020	17	28.64	28.64	
20 December 2020	22	TND	TND	
22 December 2020	24	31.80	34.71	
25 December 2020	27	TND	TND	
8 January 2021	41	nd	nd	Transfer to general ward
12 January 2021	45	35.21	34.37	
14 January 2021	47	TND	TND	
16 January 2021	49	27.56	27.70	
21 January 2021	54	TND	TND	
23 January 2021	55	35.67	34.52	
29 January 2021	61	TND	TND	
5 February 2021	68	nd	nd	Discharged home

TND, target not detected; nd, not done; Ct, cycle threshold; ORF1a/b, E-gene: target regions of RT–PCR for the detection of SARS-CoV-2 RNA.

positive until 8 weeks after discharge. During this period, she remained completely asymptomatic for COVID-19. Finally, SARS-CoV-2 PCR results turned negative (Table 1).

PATIENT 2

A 55-year-old male patient on maintenance haemodialysis due to diabetic nephropathy (diabetes mellitus type 1) was admitted to the emergency room suffering from chills and faintness. Nasopharyngeal SARS-CoV-2 PCR resulted positive; chest computed tomography revealed bilateral pneumonia. Ampicillin/sulbactam and dexamethasone were started and nasal oxygen was administered. Within 3 days, his respiratory situation critically deteriorated and he was transferred to the ICU where he was intubated and mechanically ventilated. He received three infusions of convalescent plasma; multiple changes of the antibiotic regimen were necessary. The SARS-CoV-2 PCR tested negative for the first time after 22 days but tested positive again 2 days later. Thereafter, SARS-CoV-2 PCR showed alternating (positive and negative) results. After 38 days at the ICU, he was transferred to the general ward. The further stay was complicated by a delirium and ketoacidosis requiring a further transmission to the ICU for 5 days. He tested positive for SARS-CoV-2 RNA until day 55 after the first positive result. At this time, his anti-SARS-CoV-2 IgG titre was 69 U/mL. After an extended convalescent period, he was finally discharged on day 63 and since then remains SARS-CoV-2 negative (Table 2).

The two cases presented here demonstrate a prolonged detectability of SARS-CoV-2 by nasopharyngeal PCR in maintenance haemodialysis after recovery from COVID-19. In a study of immunocompromised patients with haematological malignancies, shedding of viable virus was evidenced up to 63 days after onset of symptoms. Most of these patients received active immunosuppressive treatment or chemotherapy [5]. Our patients did not receive any immunosuppressive treatment. In patient 1, SARS-CoV-2 PCR tested negative for the first time 23 days after

the first positive test and thereafter showed alternating (positive and negative) results for another 83 days. After severe illness, her anti-SARS-CoV-2 IgG titre was 266 AU/mL. Patient 2 tested negative for SARS-CoV-2 for the first time 22 days after his first positive test. Thereafter, SARS-CoV-2 RNA remained repeatedly detectable with short SARS-CoV-2 RNA-negative intervals for further 32 days. After experiencing critical illness, his SARS-CoV-2 IgG titre was only 69 U/mL, revealing a poor immunological response. Although a Ct value of ≥30 indicates a low concentration of viral RNA load indicating decreased transmissibility, quantitation and precision associated with differences in Ct values have not been determined yet [6]. A further unanswered question is whether PCR testing is just detecting lingering viral particles but not live virus, and nobody knows whether patients on dialysis with altered immune systems harbour live virus longer than other populations. The long detectability of SARS-CoV-2 RNA in dialysis patients therefore raises questions about the adequate duration of isolation required in haemodialysis patients who have recovered from COVID-19 and further underlines the fact that our dialysis population is very vulnerable to COVID-19 infections due to their immunocompromised status. Furthermore, our cases demonstrate that a single negative SARS-CoV-2 PCR test is not enough to decide whether a patient has to be isolated or not.

PATIENT CONSENT

The patients gave informed consent to publish their case.

CONFLICT OF INTEREST STATEMENT

None declared.

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