Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Characteristics and risk factors of prolonged viable virus shedding in immunocompromised patients with COVID-19: a prospective cohort study

Dear Editor,

The previous study reported that patients with immunocompromised conditions were infectious for > 10 days.[1] In addition, the recent study demonstrated that patients receiving chemotherapy had a reduced serological response to COVID-19 vaccine[2] that might affect viable viral shedding.[3] However, there are limited data about the detailed viral shedding kinetics in immunocompromised patients with SARS-CoV-2. Thus, we evaluated the viral kinetics and viable virus shedding time in immunocompromised patients with COVID-19.

From February 1, 2022 to April 1, 2022, we prospectively enrolled immunocompromised patients with COVID-19 who had hematologic malignancies or underwent transplantation and were admitted to the Asan Medical Center, a 2700-bed tertiary teaching hospital located in Seoul, South Korea. All enrolled patients were instructed to submit weekly saliva samples until 12 weeks after diagnosis or discharge. Genomic and subgenomic RNA PCRs were performed and samples positive for genomic RNA were cultured to isolate live virus. Real-time RT-PCR was then performed to identify SARS-CoV-2 variants. Written informed consent was obtained from patients, and the institutional review board of Asan Medical Center approved the study design (IRB-2022-1054). Detailed methods of genomic and subgenomic RNA detection, identification of sublineage of SARS-CoV-2, and virus culture were described in supplement material.

A total of 41 patients were enrolled during the study period (Table 1). Of these, 29 had hematologic malignancies, and the remaining 12 underwent solid organ transplantation. Of the 41 patients, 14 (34%) had received at least 3 doses of vaccine against COVID-19, and the remainder had received less than 3 doses. None of the patients had received a booster dose (4th dose). Realtime RT-PCR revealed that 33 (80%) patients were infected with Omicron BA.2, and 7 with Omicron BA.1. Baseline characteristics between patients with and without B-cell depletion were similar, except for proportion of patients with non-Hodgkin's lymphoma (Supplemental Table 1).

Of 142 saliva samples from the 41 patients, 102 (72%) gave positive culture results (Table 1 and Supplemental Figure 1). Genomic and subgenomic viral copy numbers, and culture positivity according to days from diagnosis, are shown in Supplemental Figure 1. Survival analysis revealed median 4 weeks of viable virus shedding (IQR 3–6 weeks), and median 5 weeks of subgenomic RNA shedding, in these immunocompromised patients with COVID-19 (Fig. 1). Genomic RNA shedding had not reached its median value by the end of the study period. Comparison of the viable virus shedding periods of the B-cell depleted patients and the comparator group revealed a statistically significant prolongation of viable virus shedding in the former (median 4 weeks [IQR 3–5] vs. median not reached [IQR 5 – not reached], $p = 0.01$ by log-rank test; Supplemental Figure 2). A Cox's proportional hazard model was constructed with previously known variables affecting viable virus shedding time, including disease severity and vaccination status.[4] In the model, B-cell depletion was consistently associated with prolonged viable virus shedding (hazard ratio [HR] 12.50, 95% confidence interval [CI] 2.44 – 100.00, $p = 0.003$: Supplemental Table 2), while 3 or more vaccine doses shortened viable virus shedding in the multivariable model (HR 0.28, 95% CI 0.12 – 0.93, $p = 0.04$). Use of COVID-19-specific therapies, regardless of type, was not associated with duration of viable virus shedding.

To date, three studies with small numbers of patients or case series have estimated the duration of virus shedding in immunocompromised patients with COVID-19 by longitudinal sampling.[5–7] These studies consistently reported that immunocompromised patients with COVID-19 had prolonged viral shedding periods that could last for several months. The current CDC guidelines recommend an isolation period of at least 20 days for moderately or severely immunocompromised patients with COVID-19, and ending isolation in conjunction with serial testing and consultation with an infectious disease specialist. Given that our data revealed a median viable viral shedding period of 4 weeks in immunocompromised patients, a cautious approach to de-isolation of immunocompromised patients is needed.

We found that B-cell depleted immunocompromised patients had longer viable virus shedding periods (Supplemental Figure 2 and Supplemental Table 2). Both humoral immunity and cellular immunity play roles in viral clearance of COVID-19.[8] However, B-cell depleted patients or those with B-cell lineage hematologic malignancies have especially protracted courses of COVID-19.[9] These findings suggest that the humoral response has an essential role in viral clearance of SARS-CoV-2.[8,9] In addition, in our study, the duration of viable viral shedding in the patients with B-cell depletion did not reach the median (Supplemental Figure 2). So, a more prolonged period of follow-up samplings will be needed in this patient group.

The impact of COVID-19-specific therapeutics on the course and duration of viral shedding in immunocompromised patients remains controversial.[10] In the present study, COVID-19-specific therapies, regardless of class, did not appear to affect the duration of viral shedding (Supplemental Table 2). However, none of the patients received monoclonal antibody treatment. As an impaired humoral response appears to strongly affect clearance of SARS-CoV-2[8], further studies are required to evaluate the effect of monoclonal antibody therapeutics on the duration of viral shedding in patients with impaired immunity.

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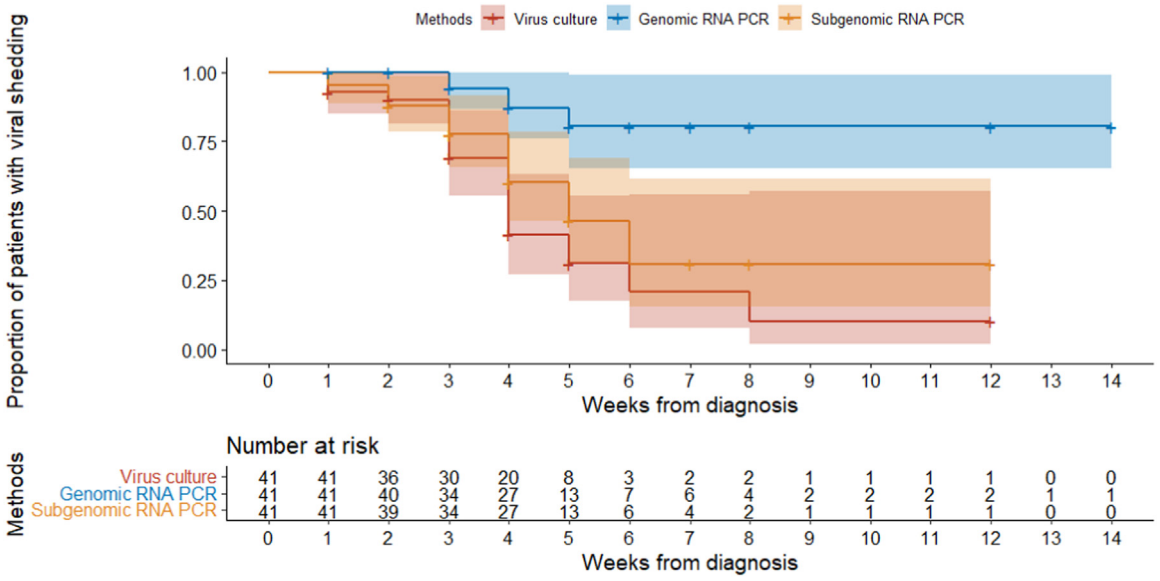

Fig. 1. Kaplan-Meier curves for viral clearance in immunocompromised patients. Red line indicates culturable virus (median 4 weeks, IQR [3 – 6]), blue line indicates detection of genomic RNA (median weeks not reached), and orange line indicates detection of subgenomic RNA (median 5 weeks, IQR [4 – not reached]).

Table 1
Baseline Characteristics of the enrolled patients.

Variable	Total (n = 41)
Age, median years (IQR)	61 (47–65)
Male	27 (66)
Charlson's comorbidity index, median (IQR)	4 (2–5)
Hypertension	9 (22)
Diabetes mellitus	8 (20)
Solid cancer	3 (7)
Chronic kidney diseases	9 (22)
Chronic lung disease	1 (2)
Hematologic malignancy	29 (70)
Acute myeloid leukemia	8 (20)
Acute lymphoblastic leukemia	4 (10)
Myelodysplastic syndrome	3 (7)
Hodgkin's lymphoma	1 (2)
Non-Hodgkin's lymphoma	15 (37)
Solid organ transplantation	12 (30)
Kidney transplantation	9 (22)
Liver transplantation	2 (5)
Lung transplantation	1 (2)
Bone marrow transplantation	14 (34)
Allogenic	9 (22)
Autologous	5 (12)
Days since transplantation, median (IQR)	481 (181–4252)
B-cell depleting therapy[a]	10 (24)
Before COVID-19	4 (10)
After COVID-19	4 (10)
Before and after COVID-19	2 (5)
T-cell depleting therapy[b]	4 (10)
Initial Severity	
Asymptomatic	23 (56)
Mild	8 (20)
Moderate	6 (15)
Severe	4 (10)
Vaccination status	
None	12 (30)
Partial (1- or 2-dose)	15 (38)
Completion of primary series (3-dose)	14[c] (34)
Subvariants	
Omicron BA.1.	7 (17)
Omicron BA.2.	33 (80)
Undetermined	1 (2)

(*continued on next page*)

Table 1 (*continued*)

Variable	Total (n = 41)
COVID-19-specific treatment	39 (95)
Remdesivir	37 (90)
Ritonavir/nirmatrelvir	2 (5)
Dexamethasone	11 (27)
Tocilizumab	4 (10)
Baricitinib	5 (12)
Culture positivity	102/142 (72)
Numbers of sample, median (IQR)	3 (3–4)
Days of first sample after diagnosis, median (IQR)	3 (1–12)
Days from last vaccination to infection, median (IQR)[d]	99 (66.5–176)

NOTE. Data are presented as number of patients (%) unless otherwise indicated.
[a] 9 patients received rituximab, and 1 patient received epocoritamab. 2 patients received rituximab to treat antibody-mediated rejection, while remaining 8 patients received B-cell depleting therapy to treat non-Hodgkin's lymphoma.
[b] 2 patients received anti-thymoglobulin therapy after diagnosis of COVID-19 to treat T-cell- mediated rejection and 1 patient received anti-thymoglobulin therapy as premedication for bone marrow transplantation after diagnosis of COVID-19. These 3 patients also received rituximab. One patient received basiliximab as premedication for lung transplantation before COVID-19.
[c] None of the patients received a booster dose of COVID-19 vaccine.
[d] One patient (partially vaccinated) did not remember the exact date of vaccination.

It is worth noting that the prolonged viable viral shedding in immunocompromised patients may affect the decision on whether intensive chemotherapy or transplantation should be performed after a diagnosis of COVID-19[8], as well as infection control policy in terms of multi-patient room use. A clinical scoring system in immunocompromised patients based on symptom duration and clinical risk factors as used in our previous study[4], which was modelled on immunocompetent patients with COVID-19, might help in making objective decisions on these various clinical issues. Our ongoing studies, with additional immunocompromised patients and longer periods of follow-up, should help to build such a clinical model.

In conclusion, immunocompromised patients with hematologic malignancies or transplant recipients shed viable virus for median 4 weeks. Vaccination against SARS-CoV-2 appears to reduce the period of viable virus shedding in immunocompromised patients, and B-cell depletion therapy may have the opposite effect.

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Conflict of interests

There are no conflicts of interests to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2023.01.024.

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