

Transmissibility and viral replication of SARS-CoV-2 in immunocompromised patients

To the Editor,

It is known that reverse-transcriptase polymerase chain reaction (RT-PCR) can remain positive for a longer duration in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as it cannot differentiate between dead and viable virus.¹ The current guidelines from the Centers for Disease Control and Prevention (CDC) suggest that positive RT-PCR beyond 2 weeks is of unclear significance and recommends isolation for 10 days from symptom onset in coronavirus disease 2019 (COVID-19) and up to 20 days in severe cases.² Most of the available data are for the immunocompetent population, and the duration of live-virus shedding and transmissibility is well-understood in this population.³ However, the data regarding infectiousness and shedding of SARS-CoV-2 in the immunocompromised patients is scarce, with no specific guidelines regarding the isolation precautions of these patients. This review aims to summarize the findings of all the available studies in the English language published until now regarding transmissibility and replication of SARS-CoV-2 in immunosuppressed patients.

We conducted a comprehensive search of electronic databases through January 05, 2021, for all studies that evaluated viral shedding and replication from respiratory samples (oropharynx or nasopharynx) in immunosuppressed adults with COVID-19. Descriptive statistics were performed to analyze the included studies.

A total of 21 studies, including 69 patients (mean age, 52.2 years; 62.3% males), were included (Table 1). Hematological malignancies were the most prevalent etiology of immunosuppression (66.7%), followed by organ transplants (27.5%). All patients were followed with subsequent RT-PCR tests.

All patients had persistently positive RT-PCR for > 3 weeks, with a median duration of 50.5 days (interquartile range [IQR] 35–74 days). Five studies^{3–7} (including nine patients) reported positive viral cultures with a median time of 26 days (IQR 19–94.5). Two studies^{7,8} (including eight patients) reported detecting subgenomic RNA (sg-RNA) with a median duration of 59 days (IQR, 29–78). Eleven studies (involving 13 patients) reported detailed serology results. Of which, nine studies (involving 11 patients) reported seroconversion with a median duration of 41 days (IQR, 35–54.5). Detailed data regarding viral cultures and sg-RNA results for each patient are shown in Table 2.

Our findings emphasize the prolonged persistence of RT-PCR positivity in the immunosuppressed population. This is consistent with a study by Zhu et al.,⁹ which showed longer RT-PCR positivity in immunosuppressed patients (mean, 28.4 days) than the controls (12.2). Duration of RT-PCR positivity in immunocompetent patients is usually <20 days.¹ A recent study by Li et al.¹⁰ showed a median duration of RT-PCR positivity of 11 days in the immunocompetent population. Time to seroconversion was also longer in these patients (median, 41 days) than immunocompetent patients (median of nearly 12 days).¹¹

However, positive RT-PCR reflects only the detection of viral RNA and does not necessarily indicate the presence of active viral replication or infectivity, which is best confirmed with the viral culture.^{1,12} There was no viable virus cultured beyond Day 9 in immunocompetent patients with COVID-19.¹ Our review showed that actively replicating virus was detected for up to 143 days from symptom onset in immunosuppressed patients. This can be explained by impairment of viral clearance by weakened innate and adaptive immune responses in immunocompromised patients.⁹

Detection of sg-RNA is an alternative non-culture-based method for inferring the presence of actively replicating viruses because only actively replicating SARS-CoV-2 initiates RNA synthesis leading to replication and transcription of sgRNAs.^{7,8,12} Unlike genomic RNA, sgRNA does not remain in the upper respiratory tract in the absence of viral replication.⁷ Although sg-RNA was rarely detected beyond Day 8 in immunocompetent patients,¹² sg-RNAs were detected for up to 105 days in immunosuppressed patients.

Our review has certain limitations. The included studies were case reports or small series, and the only limited number of studies isolated viral culture or sg-RNA to confirm active viral replication. Finally, our data were limited to upper respiratory tract swabs, and shedding from other sources, such as feces was not evaluated.

Our review highlights the importance of close follow-up and prolonged isolation precautions in immunosuppressed patients with persistently positive SARS-CoV-2 RT-PCR as the current isolation strategy might not be long enough for this select cohort. The current isolation guidelines for COVID-19 may need to be reassessed for immunosuppressed patients. Since viral culture may not be readily available, it may be reasonable to employ sg-RNA as an additional tool for detecting the infectious virus. Further studies with larger

TABLE 1 Patient characteristics of the included studies

Study, year	Country	Study design	Patients, <i>n</i>	Mean age (SD)	Gender, M/F	Duration of RT-PCR positivity, days, mean (SD)	Viral culture	sg-RNA	Serology (<i>n</i>)	Severe patients ^a (<i>n</i>)	Outcome (<i>n</i>)
Avanzato et al., 2020 ⁷	USA	Case report	1	71	F	105	Positive (Day 70)	Positive (Day 105)	NR	0	Recovered
Aydillo et al., 2020 ³	USA	Retrospective	20	58.5 (10.5)	11/9	49 (20.2)	Positive (mean, 27.4 days, 5 patients)	NR	Positive (7), negative (8)	11	Recovered (16), died (4)
Baang, 2021 ¹³	USA	Case report	1	60	M	131	Positive (Days 7, 12, 22, 29, 33, 38, 93, 106, and 119)	NR	Positive (Day 60 and 88)	1	Recovered
Choi, 2020 ¹⁴	USA	Case report	1	45	M	151	Positive (Days 75 and 143)	NR	Positive (IgG and IgM) at Days 81 and 87	1	Died
Clark, 2020	France	Case report	1	76	F	57	NR	NR	Negative	1	Recovered
Daniel, 2020	Lebanon	Case report	1	55	M	76	NR	NR	Negative	0	Recovered
Decker, 2020 ¹⁵	Germany	Case report	1	62	M	35	Positive (Days 18 and 21)	NR	NR	0	Recovered
Desmazes-Dufeu, 2020	France	Case series	2	37 (4.2)	1/1	25 (21.2)	NR	NR	NR	1	Recovered (2)
Italiano, 2020	USA	Case report	1	20	F	42	NR	NR	Positive (IgG) at Day 35	0	Recovered
Karatas, 2020	Turkey	Case report	1	61	M	74	NR	NR	NR	0	Recovered
Menghua, 2020	China	Case report	1	45	F	35	NR	NR	Positive (IgM) at Day 35	0	Recovered
Mingyao Ma, 2020	Hong Kong	Case report	1	31	F	38	NR	NR	Negative	0	Recovered

(Continues)

TABLE 1 (Continued)

Study, year	Country	Study design	Patients, <i>n</i>	Mean age (SD)	Gender, M/F	Duration of RT-PCR positivity, days, mean (SD)	Viral culture	sg-RNA	Serology (n)	Severe patients ^a (n)	Outcome (n)
Moore, 2020	USA	Case report	1	63	F	74	NR	NR	Negative (Day 90)	1	Recovered
Nakajima, 2020	Japan	Case report	1	47	M	65	NR	NR	Negative (Day 82)	1	Recovered
Niess, 2020	Germany	Case report	1	56	M	31	Negative (Day 49)	NR	Positive (IgG) at Day 21	0	Recovered
Rodriguez-Grande et al., 2020 ^b	Spain	Retrospective	7	56.3 (12.9)	4/3	64.1 (19.5)	NR	Positive (mean, 51.1 days, 7 patients)	Positive (3), negative (2)	4	Recovered (5), Died (2)
Wei, 2020	China	Case report	1	61	M	52	NR	NR	Positive (IgG) at Day 41	0	Recovered
Wu, 2020	China	Retrospective	14	36.5	9/5	26.2 (6.7)	NR	NR	Positive (IgG) (3) with median 36 days, negative (3)	13	Recovered (8), died (6)
Zhang Man, 2020	China	Case report	1	49	M	65	NR	NR	Positive (IgG) at day 47	0	Recovered
Zhu, 2020 (1)	China	Case report	1	55	M	49	NR	NR	Positive (IgG) at day 49	1	Recovered
Zhu et al., 2020 (2) ^c	China	Case series	10	45	8/2	28.4 (9.3)	NR	NR	NR	8	Recovered (9), died (1)

Abbreviations: F, female; M, male; ICU, intensive care unit; *n*, sample size; NR, not reported; RT-PCR, reverse-transcriptase polymerase chain reaction; sg-RNA, subgenomic RNA.

^aRespiratory distress (rate \geq 30/min, oxygen saturation \leq 93% at rest and/or PaO₂/FIO₂ \leq 300 mmHg), ICU admission, and/or death.

TABLE 2 Detailed data regarding positivity of viral culture and subgenomic RNA for each patient in the included studies

Patient number	Study, year	Duration of active viral replication	
		Culture	Subgenomic RNA
1	Avanzato et al., 2020 ⁷	Positive (Day 70)	Positive (Day 105)
2	Aydillo et al., 2020	Positive (Day 8)	NR
3	Aydillo et al., 2020	Positive (Day 17)	NR
4	Aydillo et al., 2020	Positive (Day 25)	NR
5	Aydillo et al., 2020	Positive (Day 26)	NR
6	Aydillo et al., 2020	Positive (Day 61)	NR
7	Decker, 2020	Positive (Days 18 and 21)	NR
8	Rodríguez-Grande et al., 2020 ⁸	NR	Positive (Days 60, 66, 75)
9	Rodríguez-Grande et al., 2020 ⁸	NR	Positive (Day 33)
10	Rodríguez-Grande et al., 2020 ⁸	NR	Positive (Day 63)
11	Rodríguez-Grande et al., 2020 ⁸	NR	Positive (Day 55)
12	Rodríguez-Grande et al., 2020 ⁸	NR	Positive (Day 79)
13	Rodríguez-Grande et al., 2020 ⁸	NR	Positive (Day 29)
14	Rodríguez-Grande et al., 2020 ⁸	NR	Positive (Day 44)
15	Baang, 2021	Positive (Days 7, 12, 22, 29, 33, 38, 93, 106, and 119)	NR
16	Choi, 2020	Positive (Days 75 and 143)	NR

Abbreviation: NR, not reported.

sample sizes are needed to evaluate the SARS-CoV-2 shedding and sg-RNA correlation to viral cultures in immunocompromised patients.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

AUTHOR CONTRIBUTIONS

Azizullah Beran: Study design; data acquisition and interpretation, statistical analysis; manuscript drafting. **Evan Zink, Mohammed Mhanna, and Aya Abugharbyeh:** Data acquisition and interpretation; manuscript drafting. **Jennifer Hanrahan, Joan Duggan, and Ragheb Assaly:** Study supervision; critical revision for intellectual content.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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