IN VIVO *39*: 844-850 (2025)
doi: 10.21873/invivo.13887

Prolonged Viral Shedding of SARS-CoV-2 in Patients With Underlying Haemato-oncological Disease

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Abstract

Background/Aim: Case reports describe prolonged COVID19 shedding in patients with malignant hematological disease. Similarly, we observed extended viral shedding in hemato-oncological patients (HP) at our SARS-CoV-2 unit. This raises the question of whether HP are more susceptible to prolonged SARS-CoV-2 shedding and which aspects of immunosuppression contribute to this phenomenon.

Patients and Methods: Data from HP treated at a single center between 02/2022 and 02/2023 were retrospectively analyzed. Overall, 47 HP with a positive SARS-CoV-2 PCR test were included. Additional data on 16 HP were retrieved from literature. The duration of SARS-CoV-2 positivity (t[SARS+]) was compared between subgroups with different diagnoses, immune status, and HP with and without medical treatment of SARS-CoV-2.

Results: t[SARS+] of HP was 47 days [interquartile range (IR)=25-95] and 12 HP (19%) were still positive by the end of the follow-up. In our cohort, four HP died while still shedding SARS-CoV-2 [t[SARS+]=47 days (IR=33.5-86)]. Different oncological diagnoses did not influence t[SARS+]. HP under steroids had a significantly longer average t[SARS+] (108 days *vs.* 45 days; p=0.016). HP with B cell depletion/T cell depletion and leukopenia were found to require more time to test negative for SARS-CoV-2 (p_{Logrank} <0.05). Vaccinated HP had a significantly shorter duration of viral shedding (vaccinated 35.5 days *vs.* not vaccinated 86 days; p_{Logrank} <0.01).

Conclusion: Prolonged viral shedding is a common occurrence in HP. Our data illustrate that HP under immune suppression show a significantly longer t[SARS+]. Furthermore, we demonstrate that vaccination influences the length of viral shedding.

Keywords: SARS-CoV-2, viral-shedding, immunosuppression, hemato-oncology, COVID-19.

Introduction

Patients with hematological malignancies (HM) are more susceptible to developing severe symptoms of COVID19 and infection-associated death (1). Recently, a large retrospective study in Spain reported a twice higher risk of HM patients for severe COVID-19 compared to the general population. This risk was even more pronounced in patients with newly

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Received November 28, 2024 | Revised December 12, 2024 | Accepted December 13, 2024

diagnosed HM [<1 year, (2)]. Overall, patients with acute myeloid leukemia, multiple myeloma, or non-Hodgkin's lymphoma showed the highest risk for death (3-8). This vulnerability to COVID-19 is often due to immune deficiencies associated either with patients' HM or with cancer therapy (1). Further, patients with HM show an impaired humoral or cellular immune response after vaccination against SARS-CoV-2 (9). Healthy individuals are estimated to have an average SARS-CoV-2 shedding duration of ten days (10). Patients with HM, however, show longer timespans of SARS-CoV-2 secretion (11). In fact, there is a heterogeneity of data regarding the duration of SARS-CoV-2 excretion in HM with a range from 20 days (11) up to 335 days (12). So far, early antiviral treatment of SARS-CoV-2 does not seem to influence the length of viral shedding (13).

We therefore aimed to investigate the relationship between immunosuppression and the duration of SARS-CoV-2 viral shedding. We observed significantly longer elimination phases in oncological patients and describe how the vaccination status of cancer patients influences SARS-CoV-2 elimination. Furthermore, we present a retrospective study including 63 patients with cancer analysing the impact of immune deficiencies, vaccination status, and the effect of different antiviral drugs on the length of viral shedding.

Patients and Methods

The study was approved by the Göttingen Ethics Committee (approval date 22/03/2023, approval number: 22/3/23). For this single-center study we retrospectively analyzed data from hemato-oncological patients (HP) admitted due to a COVID-19 infection between 02/2022 and 02/2023. Information on tumor entity, blood count at baseline (C-reactive protein, albumin), medication and survival were retrieved from patient records. Follow-up was until being tested negative for COVID-19 by at least one negative PCR or death. For patients who were still positive at the end of the study, the time period between diagnosis and the last positive test was documented. Overall, 47 HP with a positive SARS-CoV-2 PCR were included. Further, we added 16 HP from published case reports after screening the literature. The published case reports were selected using the search commands 'prolonged viral shedding' and 'SARS-CoV-2'. Only case reports of cancer patients with data on duration of illness and HP positive for SARS-CoV-2 were included (Figure 1). The time period from first documented PCR positive for SARS-CoV-2 until the last documented PCR available was defined as t[SARS+].

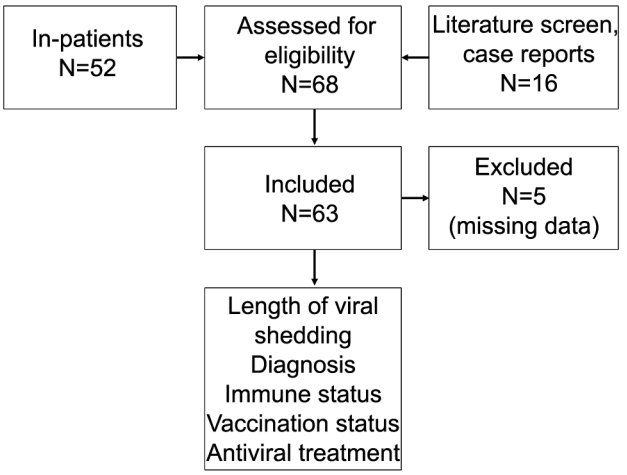

Figure 1. *Flowchart of data acquisition.*

Statistical analysis. IBM SPSS Statistics (IBM, Version 27.0, Armonk, NY, USA) was used for statistical analysis. Graphics were built with GraphPad Prism (Graphpad Software Inc., Version 9.0, La Jolla, CA, USA). Parametric *t*-test, bivariate correlation analysis, linear regression, and Kaplan–Meier function with log-rank test were applied when appropriate. A p-value <0.05 was considered significant.

Results

Clinical characteristics. Sixty-three patients were included in the present study. Among them, 37/63 (58.73%) were women and 26/63 (41.27%) were men. The mean age was 60 years (±12 years, Table I). The mean duration of viral shedding was 47 days [interquartile range (IR)=25-95 days]. Among them, the minimum duration of viral shedding was

Table I. *Clinical characteristics.*

Characteristics	
Sex	
Male	26 (41%)
Female	37 (59%)
Age±SD	60 (±14) years
Diagnosis	
Acute leukemia	15 (24%)
Lymphoma	40 (63%)
Multiple myeloma	5 (8%)
Solid cancer	3 (5%)
After autologous stem cell transplantation	9 (14%)
After allogeneic stem cell transplantation	15 (24%)
Immune status	
Corticosteroids >7 days	19 (30%)
Other immunosuppressive drugs (*e.g.*, tacrolimus, cyclosporine A)	23 (37%)
Treatment with anti-CD20-antibodies (rituximab, obinutuzumab)	16 (25%)
Antibody deficiency	17 (27%)
B cell depletion	13 (21%)
T cell depletion	17 (27%)
NK cell depletion	4 (6%)
Leukopenia (leukocytes <1,000 g/l)	7 (11%)
Clinical chemistry	
Albumin	18.30 mg/dl (9-59 mg/dl)
C-reactive protein	3.3 g/dl (±0.66 g/dl)
SARS-CoV-2	
Symptomatic infection	37 (59%)
SARS-CoV-2 positive at discharge	12 (19%)
SARS-CoV-2 related death	4/47 (Goettingen cohort)
Vaccinated	22 (35%)
Duration of viral shedding	47 (25-95) days
Duration of viral shedding until SARS-CoV-2 negativity	45 (23-82) days
Antiviral treatment	
Casirivimab/Imdevimab	1 (2%)
Ciclesonide	1 (2%)
Convalescent plasma	4 (6%)
Favipiravir	2 (3%)
Interferon	2 (3%)
Ivermectin	2 (3%)
Nirmatrelvir/Ritonavir	10 (16%)
Remdesivir	8 (13%)
Sotrovimab	32 (51%)
Tixagevimab/Cilgavimab	3 (5%)

five days, and the longest duration was 335 days. 12/63 HP (19.05%) were still positive for SARS-COV-2 at the end of follow-up. 4/63 HP (6.35%) died with SARS-CoV-2. The average t[SARS+] in the deceased HP was 47 days (IR=33.5-86.0 days). A total of 37 HP (58.73%) reported symptomatic COVID-19 infection. Furthermore, 22 HP (34.92%) had been vaccinated against SARS-CoV-2, and nine HP (14.29%) had already recovered at least once from SARS-CoV-2. Most included HP suffered from lymphoma or acute leukemia and 23/63 HP (36.51%) underwent either allogeneic or autologous stem cell transplantation (Table I). Immunosuppression caused by medication was common in HP as well as antibody deficiency (17/63 HP, 26.98%), leukopenia, B-cell or T-cell depletion (Table I). At the time point of the first positive SARS-CoV- 2 test, CRP showed an average of 18.30 mg/dl (IR=8.9-59.1 mg/dl), and the mean

Table II. *SARS-CoV-2 - Duration depending on entities, immune status, and therapy.*

	Duration [d]	*t*-test, *p*-value	Kaplan-Meier, *p*-value
Acute leukemia *vs.* others	49.00 *vs.* 75.67	0.057	0.243
Lymphomas *vs.* others	78.15 *vs.* 53.96	0.111	0.120
Solid cancer *vs.* others	66.00 *vs.* 69.48	0.932	0.604
Patients after autologous stem cell transplantation *vs.* others	65.43 *vs.* 70.51	0.856	0.739
Patients after allogeneic stem cell transplantation	60.13 *vs.* 72.19	0.388	0.762
Patients autologous or allogeneic stem cell transplantation *vs.* others	61.86 *vs.* 73.32	0.451	0.873
Corticosteroids >7d *vs.* others	107.89 *vs.* 45.37	0.016	0.010
Other immunosuppressive drugs (*e.g.* tacrolimus, cyclosporine A) *vs.* others	57.74 *vs.* 56.07	0.91	0.032
B cell depletion and/or treatment with anti-CD20-antibodies (rituximab, obinutuzumab) *vs.* others	90.05 *vs.* 54.79	0.064	0.039
T cell depletion *vs.* others	103.00 *vs.* 40.00	0.082	0.156
antibody deficiency *vs.* others	65.39 *vs.* 60.79	0.824	0.518
Leukopenia (leukocytes <1,000 g/l) *vs.* others	58.43 *vs.* 50.51	0.673	0.001
Nirmatrelvir/Ritonavir *vs.* others	43.50 *vs.* 74.25	0.025	0.261
Casirivimab/Imdevimab and Tixagevimab/Cilgavimab *vs.* others	59.12 *vs.* 80.54	0.236	0.029
Remdesivir *vs.* others	170.38 *vs.* 52.75	0.014	0.004

albumin count was 3.3 mg/dl (±0.66 mg/dl). Patients were treated for SARS-CoV-2 with sotrovimab (32/63 HP, 50.79%), followed by nirmatrelvir/ritonavir (10/63 HP, 15.87%) and remdesivir (8/63 HP, 12.70%).

Factors influencing length of viral shedding. The type of oncological disease did not influence t[SARS+] (Table II). Patients who had undergone either allogeneic or autologous stem cell transplantation did not show prolonged SARS-CoV-2 positivity. Significant differences concerning t[SARS+] were observed if HP were immunocompromised: HP who received during their treatment corticosteroids had a significantly longer average t[SARS+] than HP without extended corticosteroid intake ($t[SARS+]_{corticosteroids}$ 108 days *vs.* $t[SARS+]_{no\ corticosteroids}$ 45 days; $p<0.05$, Figure 2). HP under treatment with non-corticosteroid immunosuppressive drugs, as well as those with B cell depletion, T cell depletion, or leukopenia showed longer viral shedding (other immunosuppressive drugs $p_{Logrank}<0.01$; B cell depletion $p_{Logrank}<0.05$ and leukopenia $p_{Logrank}<0.01$; Table II). HP who were vaccinated had a significantly shorter duration of viral shedding SARS-CoV-2 ($p<0.01$, Figure 3). HP treated with Nirmatrelvir/Ritonavir had a significantly shorter t[SARS+] than HP treated with the other options (44 d *vs.* 74 days, $p<0.05$).

Discussion

HP are a particular group of patients characterized by different types of immune decencies, making HP more susceptible to respiratory infections such as SARS-CoV-2 (1). With an average of t[SARS+] 45 days until patients tested negative, we observe a longer virus shedding than in previously published data sets (11, 14). In contrast to the data of Aiello *et al.* who describe a prolonged viral shedding in only 10% of patients after six weeks, most of our patients showed viral shedding in a similar timespan.

Previous data already described prolonged viral shedding in both immunocompetent and immunocompromised individuals. However, while data from Mendes-Correa *et al.* describes viral shedding up to 50 days in immunocompetent individuals, immunocompromised individuals were reported to show viral shedding up to 212 days (15). Similarly, we observed, that especially HP with B cell depletion or non-vaccinated HP had longer SARS-CoV-2 excretion. We also observed a longer t[SARS+] in patients under prolonged exposure to corticosteroids. Just recently Li *et al.* reported that methylprednisolone did not prolong viral shedding in patients with severe COVID-19 disease. Yet, as the dataset of Li *et al.* is missing information on patients' underlying

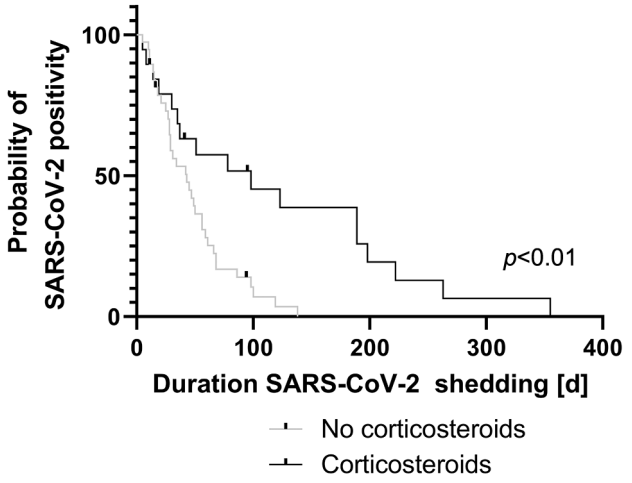

Figure 2. *Duration of SARS-CoV-2 shedding is dependent on corticosteroid treatment. Patients who received corticosteroids for >7 days exhibited significantly prolonged SARS-CoV-2 shedding, as demonstrated by the Kaplan–Meier curve (p<0.01).*

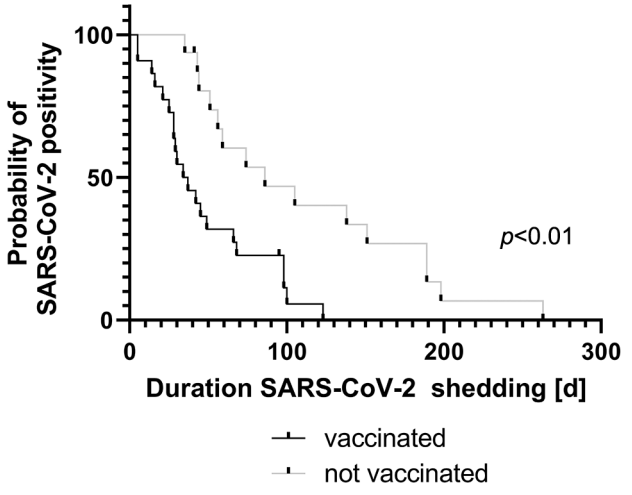

Figure 3. *Duration of SARS-CoV-2 shedding is dependent on the vaccination status of patients. Vaccinated patients exhibited significantly prolonged SARS-CoV-2 shedding, as demonstrated by the Kaplan–Meier curve (p<0.01).*

malignant hematological disease – differences in patient population might explain the differences (16).

Steiner *et al.* described that patients with primary antibody deficiency were also lacking a specific humoral response towards SARS-CoV-2. This group suffered from more severe or fatal infections and a prolonged mucosal shedding of a median of 67 days (17). Similarly, our patients who showed a secondary antibody deficiency after B cell depletion had a longer viral shedding than patients with a non-impaired B cell response. Concerning lowered T cell count our data agrees with previous observations: patients with decreased CD3+ T cells or NK cells also show longer viral shedding (18). Overall, our observations are in line with similar studies, supporting that patients with malignant hematological disease and impairment of either humoral or cytotoxic immune response regularly show a longer virus secretion than immunocompetent individuals.

Analyzing vaccination status and comparing shedding of vaccinated and non-vaccinated patients, we observed shorter viral shedding in vaccinated patients in the inpatient setting. This finding further supports the importance of vaccinating patients, especially while taking into account that an enhanced T cell immunity was observed in B cell-depleted individuals after vaccination or SARS-CoV-2 infection (19).

Study limitations. In our study, we observed relatively long timespans of viral shedding, which differed from previous reports (11, 14). This might be due to 1) the definition of SARS-CoV-2 negativity that patients had to show at least one PCR without any copy number of SARS-CoV-2 and 2) longer mucosal secretion times described for SARS-CoV-2 samples from the upper respiratory tract as opposed to the lower respiratory tract (14). All our samples were obtained by oropharyngeal swabs.

Of course, our cohort was retrospectively analyzed and only comprises data of a single center. While we tried to increase the sample size by adding case reports, the latter is also a limitation of this study as we must consider selection bias – cases with a particular course of disease like an extended viral shedding are more prone to be published. We also have to consider, that data from patients in our cohort spans over twelve months (and the case reports even over years), not considering viral variants, that might explain differences in viral elimination.

Conclusion

Our study shows that prolonged viral shedding is a common occurrence in HP. Our data illustrates that HP under immune suppression show a significantly longer t[SARS+]. We are the first to show in a larger sample that patients with B-cell-, T-cell depletion, and leukopenia require significantly more time to test as SARS-CoV-2 negative. We also showed that this patient group benefits greatly from vaccination.

Conflicts of Interest

The Authors have no conflicts of interest in relation to this study.

Authors' Contributions

AA and BJ curated and annotated data, prepared figures. All Authors were responsible for data analysis and writing the manuscript as well as revising it. BJ was responsible for the organization and coordination of the project.

Acknowledgements

The Authors thank Jennifer Labisch for reading and correcting the manuscript.

Funding

The Authors acknowledge support by the Open Access Publication Funds/transformative agreements of the Göttingen University.

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