



8 Viral Dynamics of SARS-CoV-2 in Critically Ill Allogeneic Hematopoietic Stem Cell Transplant Recipients and Immunocompetent Patients with COVID-19

To the Editor:

Hematopoietic stem cell transplant (HSCT) recipients and patients receiving chimeric antigen receptor T-cell therapy represent a delicate subgroup within the ICU. Amid the ongoing coronavirus disease (COVID-19) pandemic, the clinical course of the disease in these patients who are at high risk and have elevated mortality rates is still poorly understood. Here, we provide comprehensive data on viral dynamics and outcomes in 6 consecutive patients with a history of HSCT or chimeric antigen receptor T-cell therapy (Tx) requiring ICU treatment for COVID-19 compared with 18 patients with COVID-19 without a history of malignant disease as control patients (individual patient characteristics of patients with Tx are presented in Table 1).

BAL samples and plasma samples were assessed. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was detected and quantified by using real-time RT-PCR, as previously described (1, 2). Antibody titers were determined with the Elecsys Anti-SARS-CoV-2 Ig assay (N-protein) (Elecsys Corp.). Viral isolation was performed using native bronchoalveolar samples as described previously (3). After 48–72 hours, infected Vero cells (CCL81; American Type Culture Collection) were monitored for cytopathic effect, and viral replication was confirmed via RT-PCR (1). For statistical analysis, chi-square analysis, the Fisher exact and Mann-Whitney *U* tests (SPSS 24.0 [IBM Corp.]), and Kaplan-Maier analysis were used (GraphPad Prism 8.4.1 [GraphPad Software]).

Results

On admission, the Sequential Organ Failure Assessment Score and Simplified Acute Physiology Score II did not differ significantly in either study group (see Table 1 for basic patient characteristics). Within the course at the ICU, the need for mechanical ventilation, vasopressor therapy, and renal replacement therapy was high in both study groups (88%, 96%, and 58%, respectively), but mortality was significantly higher for patients with Tx (83% vs. 28%; $P < 0.05$). SARS-CoV-2 RNA could be detected in respiratory samples of all 24 patients without significant differences between the two study groups (100%; mean virus load, 6.25×10^3 copies/ml; range, 4.05×10^2 to 4.55×10^9), whereas viremia was present in 16

of 21 patients with ethylenediaminetetraacetic acid–plasma samples available on admission to the ICU (6 of 6 patients with Tx and 10 of 15 control patients; 76.19% viremia; mean, 2.21×10^3 copies/ml; range, 0 to 1.30×10^5). Notably, viral RNA loads in plasma were not significantly different between patients with Tx and control patients on admission (mean, 2.04×10^4 vs. 2.01×10^4 copies/ml; $P = 0.9875$). Over the course of the ICU treatment, viral loads remained constantly high in respiratory samples (mean, 4.21×10^9 , 5.58×10^7 , and 6.49×10^8 copies SARS-CoV-2 RNA/ml at Days 14, 21, and 28, respectively), and viral RNA counts in plasma increased in five of six patients with Tx (mean, 1.92×10^3 , 3.55×10^3 , and 1.0×10^6 copies SARS-CoV-2 RNA/ml at Days 14, 21, and 28 respectively). In contrast, 18 of 18 patients without hematologic disease could effectively control the infection, which was reflected by decreasing viral RNA loads in both compartments (Figures 1A and 1B). SARS-CoV-2 RNA was below the limit of detection after 21 and 11 days in respiratory and plasma samples, with a median time to 50% clearance of 7 and 11 days ($P = 0.0006$ and $P = 0.006$) (Figures 1C and 1D). Seroconversion with detection of high titers of antibodies against spike and nucleocapsid was detected in only one of the patients with Tx (patient 6) but was detected in all 18 patients in the control group (median antispikes IgG at 4 wk, 290 AU/ml). To analyze infectivity of respiratory samples, viral isolation in cell culture was attempted from bronchoalveolar fluids. Five samples from four patients with Tx (range of RNA load, 3.62×10^5 to 5.14×10^9 copies/ml, 4 to 28 d after admission to the ICU) and four control patients (range of RNA load, 1.02×10^4 to 1.56×10^7 copies/ml; < 7 d after admission to the ICU) were used. Although time after admission to the ICU was higher in the group with Tx, infectious virus was successfully rescued from five of five samples from patients with Tx, whereas isolation failed in four of four control patients.

Discussion

Overall, our data show that in patients with Tx, a high mortality rate (83%) correlated with failure to control SARS-CoV-2 replication. High mortality (36.8%) in patients with hematologic disease and COVID-19 was also observed in other cohorts analyzing SARS-CoV-2 infection in this special patient cohort (4). All 24 patients had significant levels of SARS-CoV-2 RNA detectable in respiratory samples, but in contrast to previous studies (5, 6), we could not find a correlation between the viral load in the respiratory tract at admission and mortality. Interestingly, the majority (16 of 21) of critically ill patients developed SARS-CoV-2 RNA viremia, indicating systemic spreading of the viral disease. This is in line with postmortem data demonstrating viral RNA in plasma and diverse organs, such as the kidney and heart (7, 8). In four of six of the patients with Tx, constantly high viral RNA loads, or even further increases in viral loads, were observed both in the lung and in the plasma, suggesting an inability to control viral infection. In line with this, in these patients, no virus-specific antibodies could be detected. This is particularly evident in the example of patient 6, an outlier in the group with Tx (HSCT more than 10 yr ago with stable cell counts and mild immunosuppressive therapy with steroids), and 18 of 18 control patients were able to control the infection and to mount a significant and potentially neutralizing antibody response against viral spike domains. To compare the infectivity of viruses detected by using RT-PCR, we performed viral cultures.

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Table 1. Overall and Special Demographic Characteristics of ICU Patients with COVID-19 without Underlying Hematologic Diseases and after Stem Cell Therapy

Parameter	Patients with Tx (n = 6)	No Hematologic Disease (n = 18)	OR	95% CI	P Value
Overall demographic characteristics of the cohort					
Age, yr	66.5 (58.3–73.3)	64 (55–73)	1.019	0.421–1.101	0.646
Sex, M	4 (67)	16 (89)	8.000	0.911–70.275	0.061
BMI, kg/m ²	23 (20–27)	27.5 (27.5–32.8)	0.735	0.540–1.001	0.051
Severity of COVID-19 and ARDS					
COVID-19	—	—	0.228	0.021–1.021	0.829
Mild/moderate	1 (17)	2 (11)	—	—	—
Severe	—	—	—	—	—
Critical	5 (83)	16 (89)	—	—	—
ARDS	—	—	0.625	0.046–8.432	0.723
No ARDS	1 (17)	2 (11)	—	—	—
Mild	—	—	—	—	—
Moderate	2 (33)	5 (28)	—	—	—
Severe	3 (50)	11 (61)	—	—	—
Disease severity					
SAPS II, pts.	46 (40.5–50)	39.5 (33.3–50.8)	1.034	0.949–1.126	0.445
SOFA at admission, pts.	5.5 (4.3–7.5)	7.5 (3.3–11.8)	0.898	0.719–1.121	0.341
SOFA, max. at 72 h, pts.	10.5 (4.8–14)	11 (10.3–14.5)	0.891	0.713–1.114	0.312
Procedures during ICU stay					
Ventilation					
Mechanical ventilation	5 (83)	16 (89)	0.723	0.046–8.432	0.723
ECMO	—	5 (28)	—	—	—
Other respiratory support					
High-flow nasal cannula	4 (67)	—	5.200	0.714–37.895	0.104
Noninvasive ventilation	1 (17)	1 (6)	3.400	0.179–64.682	0.415
Low/no respiratory support	1 (17)	—	—	—	—
Tracheostomy	—	6 (33)	—	—	—
ARDS management					
Prone positioning	5 (83)	12 (67)	2.500	0.236–26.480	0.447
Neuromuscular blockade	1 (17)	7 (39)	0.393	0.036–4.276	0.443
Inhaled vasodilatory treatment	3 (50)	7 (39)	1.571	0.245–10.093	0.634
Glucocorticoid th.	4 (67)	7 (39)	3.143	0.450–21.958	0.248
Other ICU th.					
Vasopressor th.	5 (83)	18 (100)	0.250	0.024–2.594	0.246
Renal replacement th.	3 (50)	11 (61)	0.636	0.099–4.087	0.634
Red blood cell transfusion	12 (10–18)	3.5 (1.5–5)	3.200	0.296–34.588	0.338
Thrombocyte transfusion	13 (13–14)	—	—	—	—
Outcome					
Overall mortality	5 (83)	5 (28)	13.00	1.201–140.34	0.035

Special Tx Patient Demographic Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex*	F	M	M	F	M	M
Hematologic disease	PMF [†]	sAML [‡]	HD [‡]	tAML [§]	DLBCL [§]	CML [‡]
Reason for hospital admission	HSCT (first)	HSCT (second)	GVHD	Second salvage th.	CAR-T th. LD th.	DM2
Prior hematologic th.	Ruxo	Salvage th.	HSCT	HSCT, refract. salvage th.	Mult. Cth., aSCT twice	HSCT
Comorbidities	DM2	AHT, DM2, TAA	AHT, CKD, OSAS, obesity	AHT, Parkinson's disease, breast CA (hist.)	RLS, PNP	AHT, prostate CA
Last hematologic th. to VD, d	18	45	358	23	14	4,279
VD to ICU admission	18	8	18	9	21	7
VD to death	25	37	33	41	44	—

(Continued)

Table 1. (Continued)

Special Tx Patient Demographic Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Immunosuppression At SARS-CoV-2 detection	CSA, MMF	CSA	MMF, Ruxo.	None	None	Steroids
Before death	CSA, steroids	CSA, steroids	TAC, steroids	None	Steroids	—
COVID-19 symptoms (at diagnosis)	Subfebrile temperature	Subfebrile temperature, weakness, cough	None (screening result)	None	Fever	Fever, cough, weakness
COVID-19 th. (specific)	Igs	TOCI	Igs, TOCI	None	Igs	None

Definition of abbreviations: AHT = arterial hypertension; ARDS = acute respiratory distress syndrome; aSCT = autologous stem cell transplantation; BMI = body mass index; CA = cancer; CAR-T = chimeric antigen receptor T cell; CI = confidence interval; CKD = chronic kidney disease; CML = chronic myelogenous leukemia; COVID-19 = coronavirus disease; CSA = cyclosporine A; DLBCL = diffuse large B-cell lymphoma; DM2 = diabetes mellitus type 2; ECMO = extracorporeal membrane oxygenation; GVHD = graft-versus-host disease; HD = Hodgkin's disease; hist. = history; Igs = immunoglobulins; HSCT = hematopoietic stem cell transplant; LD = lymphocyte-depleting; max. = maximum; MMF = mycophenolate mofetil; Mult. Cth = multiple chemotherapies; OR = odds ratio; OSAS = obstructive sleep apnea syndrome; PMF = primary myelofibrosis; PNP = polyneuropathy; pts. = points; refract. = refractory; RLS = restless leg syndrome; Ruxo = ruxolitinib; sAML = secondary acute myeloid leukemia; SAPS = Simplified Acute Physiology Score; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOFA = Sequential Organ Failure Assessment; TAA = tachyarrhythmia absoluta; TAC = tacrolimus; tAML = th.-associated acute myeloid leukemia; th. = therapy; TOCI = tocilizumab; Tx = hist. of HSCT or CAR-T th.; VD = viral diagnosis of SARS-CoV-2.

Data are expressed as n (%) or median (interquartile range). Statistically significant values are bold.

*Comment: The median age of the patients was 66.5 (interquartile range, 58.3–73.3) years. The exact age is not provided in order to protect confidentiality.

†Active disease.

‡Complete remission.

§Relapse.

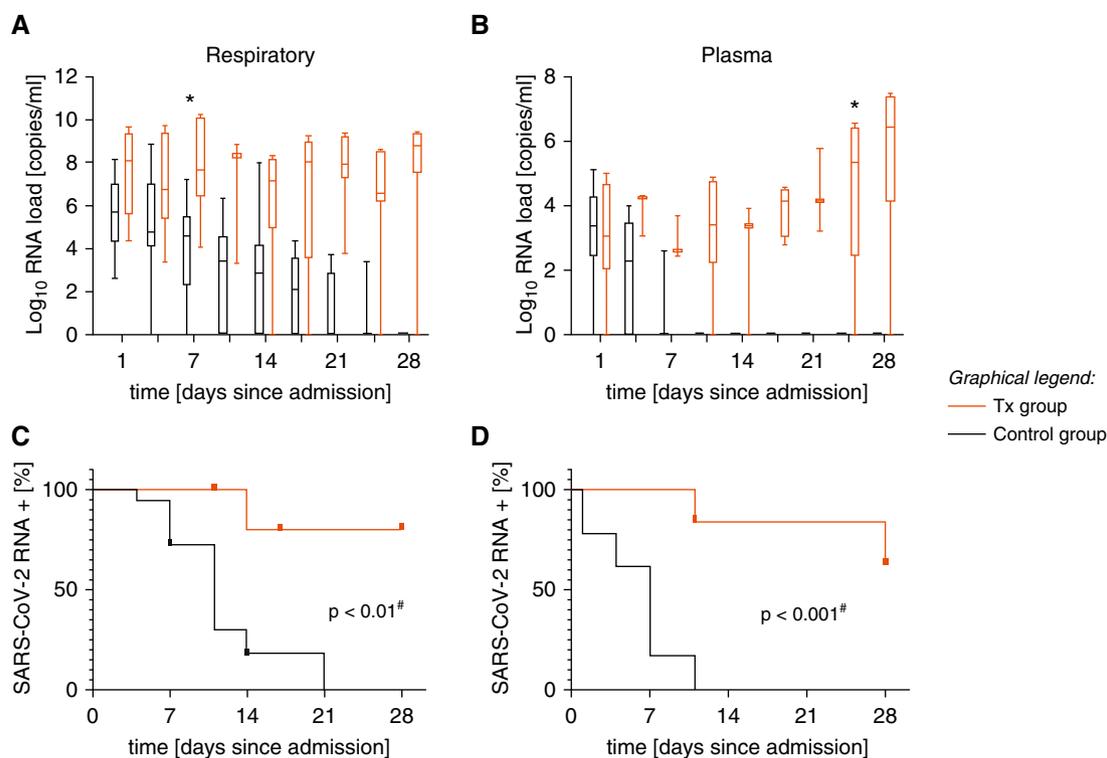


Figure 1. The log_{10} severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA load in (A) respiratory samples and (B) ethylenediaminetetraacetic acid–plasma samples during the observation period of 4 weeks is displayed. Black plots indicate RNA loads in the control group, and red plots show RNA loads in six patients with a history of hematopoietic stem cell transplant or chimeric antigen receptor T-cell therapy (Tx). Kaplan-Meier curves illustrate the time to viral clearance, defined as a PCR result below the limit of detection in (C) respiratory samples and (D) plasma samples. The red lines correspond to patients with Tx, and the black lines correspond to the control group. * $P < 0.001$ (two-sided ANOVA); †log-rank test.

Interestingly, we successfully isolated infectious virus from five of five samples from patients with Tx (obtained 4–28 d after admission to the ICU), but, in line with data from Wölfel and colleagues (9), we were unable to detect infectious virus after Day 7 in immunocompetent control patients (zero of four patients).

Limitations. First, the sample size of our study is limited, but the significant findings with potential major impact on patient management are of great importance. Second, three patients remained under intensive care treatment on the day of data censoring, resulting in an unknown outcome. Third, some cases had incomplete documentation of clinical data, missing laboratory-testing results, or both.

Conclusions. To our knowledge, this is the first comprehensive report on COVID-19 in patients with a history of HSCT that focuses on virological parameters. In these patients, as compared with immunocompetent patients, prolonged shedding of infectious virus, viremia, and high viral loads in respiratory samples highlight the need of the immune system for viral control but also indicate virus-induced mortality and a higher risk for transmission to other patients and medical staff. ■

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Risk Factors for Mortality after COVID-19 in Patients with Preexisting Interstitial Lung Disease

To the Editor:

Patients with preexisting interstitial lung disease (ILD) may be at high risk for severe coronavirus disease (COVID-19) because of impaired lung function, propensity to develop acute exacerbation of pulmonary fibrosis, or immunomodulatory medications that may interact with viral clearance or pathogenesis (1, 2). Previous studies found that patients with ILDs had an increased risk of death compared with control subjects matched for age, sex, comorbidities, and/or race (3, 4). However, whether the type of ILD may influence the outcome of COVID-19 is unknown. Here, we aimed to compare mortality of COVID-19 between patients with fibrotic idiopathic ILD, including idiopathic pulmonary fibrosis (IPF), with those with other types of ILD.

In this multicentric observational survey of specialized centers, we analyzed the survival of COVID-19 in patients with ILDs and compared mortality rates among those with fibrotic idiopathic ILDs, including IPF, with those with other ILDs. Patients were eligible if they had preexisting ILD and if they had COVID-19 during the study period confirmed by RT-PCR or definite clinical manifestations (acute onset of fever, flu-like

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