Received: 30 January 2021 | Revised: 1 April 2021 | Accepted: 18 April 2021

DOI: 10.1111/tid.13625

ORIGINAL ARTICLE

WILEY

Clinical presentation and outcomes of COVID-19 following hematopoietic cell transplantation and cellular therapy

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Abstract

Background: One year into the pandemic, published data on hematopoietic cell transplantation (HCT) recipients with coronavirus disease 2019 (COVID-19) remain limited.

Methods: Single-center retrospective cohort study of adult HCT recipients with polymerase chain reaction (PCR)-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Results: Twenty-eight consecutive transplantation and cellular therapy patients (autologous, n = 12; allogeneic, n = 15; chimeric antigen receptor T-cell therapy [CAR-T], n = 1) with COVID-19 were identified. The median age was 57 years. The median time from HCT to COVID-19 diagnosis was 656 days (interquartile range [IQR], 33-1274). Patients were followed for a median of 59 days (IQR, 40-88). Among assessable patients (n = 19), 10 (53%) had documented virological clearance; median time to clearance was 34 days (range, 21-56). Out of 28, 12 (43%), 6 (21%), and 10 (36%) patients had mild, moderate, and severe/critical disease, respectively. Overall mortality was 25%, nearly identical for autologous and allogeneic HCT, and exclusively seen in hospitalized patients, older than 50 years of age with severe COVID-19. None of the patients with mild (n = 12) or moderate (n = 6) COVID-19 died whereas 7/10 patients (70%) with severe/critical COVID-19 died ($P = .0001$). Patients diagnosed with COVID-19 within 12 months of HCT exhibited higher mortality (57% vs 14%; $P = .04$). All-cause 30-day mortality (n = 4) was 14%. A higher proportion of patients who died within 30 days of COVID-19 diagnosis (3/4) were receiving ≥2 immunosuppressants, compared with patients who survived beyond 30 days after COVID-19 diagnosis (2/24; 75% vs. 8%; $P = .01$).

Conclusions: Mortality in COVID-19 HCT patients is higher than that of the age-comparable general population and largely dependent on age, disease severity, timing from HCT, and intensity of immunosuppression.

KEYWORDS

COVID-19, hematopoietic cell transplantation, SARS-CoV-2

Jose F. Camargo and Maria A. Mendoza have equal contribution.

1 | INTRODUCTION

As of late March 2021, the World Health Organization (WHO) had reported more than 126 million people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 2.7 million cumulative deaths due to coronavirus disease 2019 (COVID-19).[1] There are many established risk factors for severe COVID-19 disease and mortality, such as older age, diabetes, hypertension, obesity, or heart disease.[2] Additionally, immunosuppressed patients, such as those with malignancies[3] and solid organ transplant patients,[4] are at increased risk; likewise, hematopoietic cell transplantation (HCT) recipients might be at higher risk for severe illness from SARS-CoV-2 according to the Centers for Disease Control and Prevention (CDC).[5] This is likely a result of the effect of immunosuppressive therapy as well as the damped immune reconstitution that occurs following an HCT.[6]

One year into the pandemic, published data on transplantation and cellular therapy (TCT) patients with COVID-19 are limited. As of December 22, 2020, 800 patients have been reported from 24 countries to the European Society for Blood and Marrow Transplantation (EBMT) registry[7]; and as of March 2021, more than 2000 HCT recipients with COVID-19 have been reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) (https://www.cibmtr.org/Covid19/Pages/default.aspx-#repdata, accessed on March 31, 2021). Yet there is still a relative paucity of published data of COVID-19 regarding many aspects of the disease in the HCT population. Here, we report clinical presentation and outcomes of HCT patients with COVID-19 at our center.

2 | METHODS

2.1 | Study subjects

We performed a single-center retrospective cohort study of adult TCT recipients with reverse transcription (RT) polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection, diagnosed from March 2020 to December 2020. The cohort included both hospitalized patients and those managed as outpatient. The study was approved by our institutional review board (IRB # 20080899) and conducted consistent with principles in the Declaration of Helsinki.

2.2 | SARS-CoV-2 PCR

During the study period, multiple PCR platforms were used for SARS-CoV-2 detection: QIAstat-Dx COVID-19 assay, BD MAX RT-PCR, SARS-CoV-2 DiaSorin Simplexa, and Accula SARS-CoV-2. PCR was used for the qualitative detection of SARS-CoV-2 nucleic acid in nasopharyngeal (NP) swabs or bronchoalveolar lavage (BAL). Routine swabbing until negativity was not done.

2.3 | Endpoints and definitions

Symptoms, laboratory and radiological findings on presentation, and treatments administered were recorded for all patients. The primary endpoints were maximum COVID-19 severity and all-cause mortality. COVID-19 severity was defined as mild (COVID-19 symptoms, without shortness of breath [SOB], dyspnea, or abnormal imaging), moderate (pneumonia on imaging), severe (hypoxia requiring fraction of inspired oxygen [FiO_2] > 40%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] < 300 mm Hg, or lung infiltrates > 50%), and critical (acute respiratory distress syndrome [ARDS], mechanical ventilation, or shock). Time to virological clearance was defined as time from initial positive SARS-CoV-2 PCR to first negative PCR (without subsequent tests) or two consecutive negative PCRs. Time of viral shedding was defined as the duration of PCR positivity and calculated from the time from initial positive SARS-CoV-2 PCR until the last positive SARS-CoV-2 PCR available (among patients with at least two consecutive positive tests). Superimposed infections were defined as laboratory-confirmed infections other than SARS-CoV-2 diagnosed by the treating physician during admission for COVID-19. Shock was defined as refractory hypotension requiring the use of vasopressors. Cardiac injury was defined by the presence of abnormally elevated troponin and/or new arrhythmias.

2.4 | Statistical analyses

Demographic, medical, and treatment characteristics were summarized using descriptive statistics. For categorical variables, we conducted Fisher's exact test due to sample size. For continuous variables, we conducted Mann–Whitney test. For time to event analysis, we performed log-rank test. All tests were two-sided, and $P < .05$ was considered of statistical significance. Statistical analyses were performed using SAS Enterprise Guide, Version 7.15, Copyright© [2017] SAS Institute Inc.

3 | RESULTS

3.1 | Demographics

Between March 2020 and December 2020, 28 TCT patients (autologous, n = 12; allogeneic, n = 15; chimeric antigen receptor T-cell therapy [CAR-T], n = 1) met criteria for diagnosis of COVID-19. The median age at the time of COVID-19 diagnosis was 57 years (interquartile range [IQR], 50-67); 16 patients (57%) were male. Underlying diagnosis and transplant specifics are presented in Table 1. The median time from HCT to infection was 656 days (IQR, 33-1274), and not different for autologous versus allogeneic HCT (716 vs 640 days, respectively; $P = .98$). Patients were followed for a median of 59 days (IQR, 40-88). Out of 28 patients, 39% of patients had hypertension, 11% had diabetes mellitus, and 21% had

TABLE 1 Characteristics of study subjects

Characteristic	All (n = 28)	Survivors (n = 21)	Non-survivors (n = 7)	*P*-value
Age, median (IQR), y	57 (50-67)	57 (44-65)	66 (54.5-67.5)	.25
Male sex	16 (57)	13 (62)	3 (43)	.42
Type of transplant				
Autologous	12 (42.8)	9 (42.8)	3 (42.8)	>.99
Allogeneic	15 (53.6)	11 (52.4)	4 (57.1)	>.99
CAR-T	1 (3.6)	1 (4.7)	0	>.99
Follow-up, days from COVID-19 diagnosis	57 (44-79)	63.5 (49.25-94.5)	28 (21.5-46.75)	.02
Days from transplant to infection, median (IQR), post-transplant days[a]	656 (333-1274)	663 (425-1340)	330 (200-886)	.17
Underlying diagnosis				
Leukemia	6 (21.4)	5 (23.8)	1 (14.3)	>.99
Lymphoma	8 (28.6)	6 (28.6)	2 (28.6)	>.99
MDS/MPN	4 (14.3)	2 (9.5)	2 (28.6)	.25
Multiple myeloma/plasma cell disorder	9 (32.1)	7 (33.3)	2 (28.6)	>.99
Other	1 (3.6)	1 (4.8)	0	>.99
Conditioning regimen[b]				
Myeloablative	14 (50)	11 (52.4)	3 (42.3)	>.99
Reduced intensity	12 (43)	8 (38.1)	4 (57.1)	.42
ATG[c]	5 (18)	4 (19)	1 (14.3)	>.99
Stem cell source[b]				
Peripheral blood	25 (89)	18 (86)	7 (100)	.55
Bone marrow	1 (4)	1 (5)	0	>.99
Type of donor[b]				
HLA-mismatched unrelated	2 (13)	1 (9)	1 (25)	.44
HLA-matched unrelated	4 (27)	3 (27)	1 (25)	>.99
HLA-haploidentical	2 (13)	2 (18)	0	>.99
HLA-identical sibling	6 (40)	4 (36)	2 (50)	.62
Immunosuppression at time of COVID-19	11 (39)	6 (29)	5 (71)	.08
Tacrolimus	3 (11)	2 (10)	1 (14)	>.99
Tacrolimus plus prednisone	2 (7)	1 (5)	1 (14)	.44
Tacrolimus plus dasatinib	1 (4)	0	1 (14)	.25
Corticosteroids (prednisone >20 mg/daily)	3 (11)	2 (10)	1 (14)	>.99
Ruxolitinib plus prednisone	1 (4)	0	1 (14)	.25
Mycophenolate mofetil plus sirolimus	1 (4)	1 (5)	0	>.99
Charlson Comorbidity Score, median (IQR)	2 (0-3)	2 (0-3)	2 (0.5-4)	.56
Comorbidities				
Hypertension	11 (39)	6 (29)	5 (71)	.08
Diabetes mellitus	3 (11)	1 (5)	2 (29)	.15
Obesity (BMI > 30)	6 (21)	6 (29)	0	.29
Active GVHD on IS	7 (47)	4 (36)	3 (75)	.28
Hypogammaglobulinemia[d]	6 (35)	5 (38)	1 (25)	>.99

Note: Data are presented as absolute number (percentage), unless specified otherwise.

Abbreviations: ATG, antithymocyte globulin; BMI, body mass index; CAR-T, chimeric antigen receptor T-cell therapy; COVID-19, coronavirus disease 2019; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; IQR, interquartile range; IS, immunosuppression; MDS/MPN, myelodysplastic syndrome/myeloproliferative neoplasm.

[a]Data missing for one patient diagnosed at outside hospital.

[b]One patient with allogeneic transplant missing details.

[c]Typical dose of ATG at our center is 4 mg/kg total.

[d]Hypogammaglobulinemia was defined as IgG levels of <500 mg/dL within 6 mo of diagnosis, assessable in 17 patients.

obesity, defined by a body mass index (BMI) > 30. Eleven patients (39%) were receiving immunosuppression at the time of COVID-19 diagnosis. Among allogeneic HCT recipients, seven patients (47%) had active grade 2-4 graft-versus-host disease (GVHD); hypogammaglobulinemia, defined as IgG < 500 mg/dL, was present in six of 17 assessable patients (Table 1). In this small cohort, there were no differences in demographics or transplant characteristics between survivors and nonsurvivors (Table 1).

3.2 | Diagnosis and clinical presentation

All but one of the 28 patients were diagnosed with COVID-19 through NP swab for SARS-CoV-2 RNA, including one patient tested at an outside hospital; one patient presented with diffuse alveolar hemorrhage and had positive PCR in BAL. Out of the 28 patients, 16 (57%) patients were managed as inpatient. Outpatients (n = 12) were primarily managed with supportive care. Four patients were asymptomatic and were tested due to other reasons (ie, routine screening prior to a procedure and COVID-19 exposure). Among symptomatic patients (n = 24), the most common symptoms at presentation included fever (n = 17 [71%]), cough (n = 13 [54%]), and SOB (n = 8 [33%]). Other symptoms included fatigue (n = 7 [29%]), chills (n = 7 [29%]), myalgia (n = 4 [17%]), headache (n = 4 [17%]), nausea/vomiting (n = 4 [17%]), anosmia (n = 4 [17%]), diarrhea (n = 2 [8%]), abdominal pain (n = 1 [4%]), sore throat (n = 1 [4%]), and nasal congestion (n = 1 [4%]; Table 2). During the peak of illness, most common symptoms, similar to the initial presentation, were fever, cough, and SOB.

3.3 | Laboratory data

Laboratory tests were collected in 19 patients at the time of diagnosis. The median white blood cell count was 3.9 cells × 10^9/L (IQR, 3.45-6.1). Median absolute lymphocyte count was 0.79 cells × 10^9/L (IQR, 0.55-1.08), and lymphopenia defined as lymphocyte count <1000/μL was present in 60% of the patients. The median neutrophil/lymphocyte ratio (NLR; normal range is 0.78-3.53)[8] was 3.3 (IQR, 1.9-3.3). Liver function was largely unaffected with aspartate transaminase (AST) median of 32 U/L and alanine transaminase (ALT) median of 29 U/L. Creatinine median level was 0.99 mg/dL (IQR, 0.81-1.24). Regarding inflammatory markers, elevated C-reactive protein (CRP; n = 14) was present in 100% of the cases with a median 10.5 mg/dL (IQR, 3.3-18.9); procalcitonin (n = 15) was elevated in 60% with a median of 0.16 ng/mL (IQR, 0.08-0.42); lactate dehydrogenase (LDH; n = 14) was elevated in 85% of cases with a median value of 270 U/L (239-406); 83% of patients had increased ferritin (n = 13) with a median of 1736 μg/L (495-7669); and interleukin (IL)-6 (n = 7) was elevated in 86% of cases with a median level of 147.4 pg/mL (70.8-247). The median peak level of inflammatory markers was as follows: CRP, 17.9 mg/dL; IL-6, 147.4 pg/mL; ferritin, 2860 μg/L; and procalcitonin, 0.17 ng/mL. Interestingly, the median serum procalcitonin in patients with a co-infection was 1.79 versus 0.11 ng/mL in patients without superimposed infection ($P = .0004$).

Among 24 symptomatic patients, nine (38%) patients had more than one negative test prior to diagnosis (range, 1-6). Among assessable patients (n = 19), 10 (53%) had documented virological clearance; median time to clearance was 34 days (range, 21-56). One patient had possible reinfection 2 months after initial diagnosis, but whole genome sequencing was not available. Median shedding time, among patients with at least two consecutive positive tests (n = 14), was 26 days (range, 7-64).

3.4 | Imaging

Among the 17 patients who had chest X-ray (CXR) done on admission, 14 (82%) patients had an abnormal CXR. Follow-up CXR was performed in 11 patients after a week, nine of them (82%) had abnormal findings. Computed tomography (CT) of the chest was done in nine patients; seven (78%) patients had findings compatible with organizing pneumonia and two had a normal CT.

3.5 | Management

Among the 11 patients receiving immunosuppressive therapy at time of COVID-19 diagnosis, five (45%) patients had their immunosuppression reduced or discontinued. Among 16 hospitalized patients, data regarding COVID-19-directed treatment were missing in one patient that was admitted to another hospital. Among the remainder 15 patients, corticosteroids were given to 10 patients (67%), with a median duration of 7 days, most patients receiving dexamethasone 6 mg daily. Remdesivir was administered to nine patients (60%) with a median duration of 5 days (range, 5-10 days). Other therapies included azithromycin (n = 6; 40%), hydroxychloroquine (n = 4; 27%), convalescent plasma (n = 4; 27%), and intravenous immunoglobulins (IVIG; n = 2; 13%). Of note, four patients received IL-6-directed therapy with tocilizumab. Among them, three patients received one dose (two patients 400 mg and one patient 600 mg), whereas one patient received two doses of 400 mg each. Among hospitalized patients, 12 (80%) received empiric antibiotics, 11 (73%) patients received prophylactic dose anticoagulation, one (7%) patient received full dose systemic anticoagulation empirically due to suspicion of pulmonary embolism.

3.6 | Clinical outcomes

Out of 28, 12 (43%), 6 (21%), and 10 (36%) patients had mild, moderate, and severe/critical disease (severe n = 3; critical n = 7), respectively. Among the 16 patients who were admitted, seven patients (44%) were admitted to intensive care unit (ICU; Table 2).

At presentation, oxygen saturation was documented in 21 patients, 18/21 (86%) were tolerating room air (RA); two patients needed nasal cannula (NC) between 4 and 5 L/min, and one patient needed high flow NC. At the maximum point of illness, among assessable admitted patients (n = 15), three (20%) were on RA; the remainder required oxygen supplementation as follows: 2 L/min of oxygen via NC (n = 2 [13%]) and 5 L/min of oxygen via NC (n = 2 [13%]); one patient (6.7%) high flow NC; seven patients required mechanical ventilation with one patient (6.7%) on bilevel positive airway pressure (BiPAP) and six (40%) undergoing invasive mechanical ventilation. Of the intubated patients, after nearly 2 months of median follow-up time, only one patient was extubated after 26 days; however, he died subsequently; the other five patients remained on mechanical ventilation until the time of death (Table 2).

Seven (25%) patients had shock. Five patients developed cardiac injury. Renal replacement therapy was required in four (14%) patients. No confirmed thromboembolic events were seen. Of the 16 patients admitted to the hospital, eight were discharged, seven (44%) died, and one patient was still admitted at the end of follow-up.

Laboratory-confirmed superimposed infections occurred following COVID-19 diagnosis in seven (25%) cases. Bacterial infections were confirmed in six patients (21%) and included respiratory cultures positive for extended spectrum beta-lactamase (ESBL) *Escherichia coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Stenotrophomonas maltophilia*, multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Enterococcus faecalis*, and a *Burkholderia cepacia* sinus infection. Bloodstream infections were present in six patients including infections with *Actinomyces neuii*, methicillin-resistant *Staphylococcus epidermidis*, MRSA, and vancomycin-resistant *Enterococcus* (VRE). Two patients had suspected mold infections, and one patient had proven COVID-19-associated pulmonary aspergillosis (CAPA) according to the definitions of the 2020 European Confederation of Medical Mycology/International Society of Human and Animal Mycology (ECMM/ISHAM) consensus criteria.[9] One patient had *Candida auris* fungemia. Regarding viral infections, two patients developed Epstein–Barr virus (EBV) viremia (peak values of 1400 and 1000 IU/mL) and one of them also had cytomegalovirus (CMV) viremia with a peak viral load of 590 IU/mL. All seven patients with superimposed infections had mixed infections.

Among hospitalized patients who survived (n = 9), five patients had documented full recovery after discharge, two continued to have oxygen dependency, and data were missing for two patients. Regarding neurological sequelae, one patient had cognitive dysfunction and another patient developed aseptic meningitis with status migrainosus after SARS-CoV-2 infection. At the end of follow-up, one patient continued to have anosmia.

3.7 | Mortality

Overall mortality during follow-up period was 25% and exclusively seen in hospitalized patients, older than 50 years of age with severe COVID-19. None of the patients with mild (n = 12) or moderate (n = 6) COVID-19 died whereas 7/10 patients (70%) with severe/critical COVID-19 died ($P = .0001$). Hospitalized patients (n = 16) had a higher mortality (n = 7; 44%) compared with patients who did not require admission (n = 12) all of whom survived ($P = .01$). Patients diagnosed with COVID-19 within 12 months of TCT exhibited higher mortality than those transplanted more than 12 months prior (4/7 [57%] vs. 3/21 [14%]; $P = .04$). All-cause 30-day mortality (n = 4) was 14%. A significantly higher proportion of patients who died within 30 days of COVID-19 diagnosis were receiving two or more immunosuppressants at the time of presentation, compared with patients who survived beyond 30 days after COVID-19 diagnosis (3/4 [75%] vs 2/24; [8%]; $P = .01$). The fourth patient who died within 30 days was receiving high-dose steroids (>2 mg/kg/day of prednisone). Causes of death included subarachnoid hemorrhage (n = 1), invasive fungal infection (n = 1), respiratory failure (n = 2), and shock with multisystem organ failure (n = 1); medical care was withdrawn in two cases.

Mortality was not significantly higher in allogeneic versus autologous HCT. Overall mortality was 27% versus 25% ($P > .99$) for allogeneic versus autologous, respectively; and 30-day mortality was 20% versus 8% ($P = .61$) for allogeneic versus autologous, respectively, and did not seem to be affected by any COVID-19 therapy. Severe/critical COVID-19 was not significantly influenced by transplant type (33% for both autologous and allogeneic, $P > .99$) but was exclusively seen in patients 50 and older (48% vs. 0%, $P = .03$).

4 | DISCUSSION

Here, we present a cohort of 28 TCT patients with COVID-19 infection with a near 2-month follow-up. Patients presented mostly with fever, cough, and SOB similar to other cohorts of general population,[2] solid organ transplant,[4,10] and HCT.[11,12] Extrapulmonary manifestations and atypical presentations (eg, without fever or respiratory complaints) were also present, so it is important for transplant providers to have high index of clinical suspicion, particularly in areas of high COVID-19 activity.

Our patients were treated mainly with steroids (64%), remdesivir (50%), tocilizumab (29%), convalescent plasma (21%), and IVIG (7%). Remdesivir had an effect in the reduction of clinical recovery time with no change in mortality according to the ACTT trial[13]; however, it is currently recommended in the setting of severe disease, and the difference on efficacy, if any, between 5 and 10 days of therapy has not been established[14]; these recommendations have not been extrapolated into the HCT population where optimal indication and duration of therapy are not known.[15] Similarly, the use of immunomodulatory therapies for COVID-19 such as tocilizumab has not been evaluated in HCT recipients. In cohort studies, tocilizumab did not improve outcomes in hospitalized patients with COVID-19 but resulted in increased frequency of subsequent infections, transaminitis, and cytopenias.[16] Therefore, it should be carefully used in patients with fungal or severe bacterial infections, which HCT recipients are at higher risk for. With regard to corticosteroids, the

TABLE 2 Severe acute respiratory syndrome coronavirus 2 viral kinetics and disease course among 28 transplantation and cellular therapy patients with coronavirus disease 2019

Patient	Age/ gender	T-cell therapy	Symptoms at presentation	Initial Ct value[a]	Viral shedding[b] (d)	Clearance (d)	Severity[c]	Oxygen requirement[c]	Hospital admission	ICU admission	Shock	Outcome
1	32/F	Allogeneic	Fever, cough, SOB, myalgia, fatigue, HA, N/V, chills	NA	20	34	Mild	0	No	No	No	Alive
2	68/M	Allogeneic	Fever, cough, SOB, fatigue, chills	NA	14	NA	Critical	MV	Yes	Yes	Yes	Death (28 d after diagnosis)
3	54/M	Allogeneic	Fever, myalgia, fatigue, diarrhea, N/V, chills, abdominal pain	NA	NA	NA	Critical	BiPAP	Yes	Yes	Yes	Death (116 d after diagnosis)
4[d]	62/F	Allogeneic	HA	NA	NA	NA	Mild	NA	Yes	No	No	Alive
5	40/F	Allogeneic	Fever, cough, SOB, myalgia, HA, N/V, chills, anosmia, nasal congestion	11.6	25	NA	Mild	0	Yes	No	No	Alive
6	65/M	Allogeneic	Fever, cough, SOB, HA	NA	37	44	Severe	HFNC	Yes	No	No	Alive
7	57/F	Allogeneic	Asymptomatic	NA	NA	NA	Mild	0	No	No	No	Alive
8	40/F	Allogeneic	Anosmia	NA	NA	NA	Mild	0	No	No	No	Alive
9	55/M	Allogeneic	Cough, N/V, anosmia	NA	NA	NA	Mild	0	No	No	No	Alive
10	72/M	Allogeneic	Cough	NA	28	49	Moderate	NC, 2 L	Yes	No	No	Alive
11	75/M	Allogeneic	Fever, cough, sore throat	NA	21	NA	Mild	0	No	No	No	Alive
12	52/F	Allogeneic	Fever, cough, chills	19.2	7	NA	Critical	MV	Yes	Yes	Yes	Death (22 d after diagnosis)
13	55/M	Allogeneic	Fever, cough, SOB, myalgia, fatigue, diarrhea, chills	NA	NA	NA	Critical	MV	Yes	Yes	Yes	Death (16 d after diagnosis)
14	49/M	Allogeneic	Fever, cough, SOB	NA	NA	24	Moderate	NC, 2 L	Yes	No	No	Alive
15	50/F	Allogeneic	Asymptomatic	NA	NA	NA	Mild	0	No	No	No	Alive
16	32/M	Autologous	Asymptomatic at presentation—then developed anosmia	NA	12	NA	Mild	0	No	No	No	Alive
17	72/F	Autologous	Fever	NA	64	36	Moderate	0	Yes	No	No	Alive
18	63/M	Autologous	Fever, SOB	NA	NA	34	Severe	NC, 5 L	Yes	No	No	Alive
19	67/F	Autologous	Fever, chills	31.4	35	NA	Critical	MV	Yes	Yes	Yes	Death (38 d after diagnosis)
20	44/M	Autologous	Fever, cough, fatigue	NA	NA	NA	Moderate	0	No	No	No	Alive

(Continues)

TABLE 2 (Continued)

Patient	Age/ gender	T-cell therapy	Symptoms at presentation	Initial Ct value[a]	Viral shedding[b] (d)	Clearance (d)	Severity[c]	Oxygen requirement[c]	Hospital admission	ICU admission	Shock	Outcome
21	71/F	Autologous	SOB	23.6	37	56	Critical	MV	Yes	Yes	Yes	Death (81 d after diagnosis)
22	68/M	Autologous	Asymptomatic	34.5	NA	21	Mild	0	No	No	No	Alive
23	66/F	Autologous	Fever, fatigue	14	NA	NA	Critical	MV	Yes	Yes	Yes	Death (21 d after diagnosis)
24	57/M	Autologous	Fever, cough	24.1	20	NA	Mild	0	No	No	No	Alive
25	51/M	Autologous	Fever	NA	NA	31	Moderate	0	No	No	No	Alive
26	43/M	Autologous	Asymptomatic	NA	26	NA	Mild	0	No	No	No	Alive
27	64/F	Autologous	Fever	24.4	NA	NA	Moderate	0	Yes	No	No	Alive
28	67/M	CAR-T	Cough, fatigue, anosmia	22	26	NA	Severe	NC, 5 L	Yes	No	No	Alive

Abbreviations: BiPAP, bilevel positive airway pressure; CAR-T, chimeric antigen receptor T-cell therapy; Ct, cycle threshold; HA, headache; HFNC, high flow nasal cannula; ICU, intensive care unit; MV, mechanical ventilation; N/V, nausea/vomit; NA, not available; NC, nasal cannula; SOB, shortness of breath.

[a]Ct values for S (encoding the structural spike glycoprotein) gene target using Simplexa® (DiaSorin molecular) polymerase chain reaction platform.

[b]Refer to Section 2 in main text for definition.

[c]At maximum point of illness.

[d]Diagnosed at outside hospital.

RECOVERY trial showed decreased mortality in patients with severe disease (ie, mechanical ventilation),[17] but once again data in HCT are lacking, and our cohort size did not allow us to draw any conclusions about COVID-19-directed therapies.

Invasive mechanical ventilation was required in six patients (21%) in our cohort. Shah et al reported a mechanical ventilation rate of 12%. Haroon et al reported 11 patients (seven allogeneic and four autologous), and none of them requiring mechanical ventilation.[18] Malard et al reported a cohort of patients with hematological malignancies, of those seven had a history of HCT; 52% developed ARDS, and six received mechanical ventilation.[11] Severe disease requiring mechanical ventilation occurred in 45 (14%) of 318 patients reported by CIBMTR.[19]

In our cohort, the all-cause 30-day mortality was 14%, seen exclusively in hospitalized patients. However, mortality has not been consistent between studies. Shah et al reported a 30-day mortality of 22% for patients undergoing T-cell therapies,[12] whereas Malard et al estimated a 30-day mortality of 40%.[11] Kanellopoulus et al reported a mortality rate of 43%.[20] Altunas et al reported a fatality rate of 16%[21] whereas Sultan et al reported survival of 100% in a small cohort (n = 7) that included some patients with severe disease.[22] Perhaps the most reliable data regarding 30-day mortality in HCT patients with COVID-19, due to large sample size (>300 patients) and multicenter design, are the recent publication by CIBMTR with reported 30-day mortality of 32% and 33% for allogeneic and autologous HCT recipients, respectively.[19]

Mortality in COVID-19 HCT patients depends on several factors. For example, in our cohort, mortality was highest among those with severe/critical COVID-19 (70%) and those within 12 months of HCT (57%). Varma et al reported 34 HCT patients with COVID-19, with overall mortality of 5% among those with mild/moderate COVID-19 and 43% for those with severe disease.[23] The number of comorbidities (hazard ratio [HR] 5.4, $P = .004$), infiltrates on chest imaging (HR 3.08, $P = .03$), and neutropenia (HR 1.2, $P = .04$) have been associated with high oxygen requirements and death.[12] We observed a significantly higher proportion of patients receiving ≥2 immunosuppressants in the group of patients who died within 30 days of COVID-19 diagnosis. In the report by Varma et al, older age, being on steroids at diagnosis of COVID-19, and COVID-19 infection within 12 months of HCT were associated with poor outcomes.[23] In the report from CIBMTR, age 50 years or older, male sex, and development of COVID-19 within 12 months of transplantation were associated with a higher risk of mortality among allogeneic HCT recipients; and disease indication of lymphoma was associated with a higher risk of mortality compared with plasma cell disorders or myeloma in autologous HCT recipients.[19] Our 30-day mortality (14%) and that reported by Shah et al (22%) are somewhat lower to the >30% mortality among COVID-19 patients with known outcome reported to CIBMTR.[19]

The type of transplant does not seem to influence outcomes in COVID-19 patients. Shah et al observed higher mortality among allogeneic HCT and CAR-T compared with autologous HCT recipients, although this difference was not statistically significant.[12] The 30-day mortality for autologous, allogeneic, and CAR-T of 13%, 27%, and 40%, respectively, in their study,[12] could be related to the fact that allogeneic HCT and CAR-T therapy patients experience more prolonged shedding of viable SARS-CoV-2 than autologous HCT recipients.[24] We observed nearly identical mortality for autologous and allogeneic recipients, despite similar timing of SARS-CoV-2 infection relative to transplantation. Likewise, there was no difference in 30-day mortality rates for allogeneic and autologous HCT recipients in the CIBMTR study.[19] The EBMT registry shows that the 6-week mortality is approximately 19% in autologous and 24% in allogeneic HCT recipient.[7] Altogether, these reports indicate that type of transplant is not a key determinant of mortality in HCT recipients with COVID-19.

Viral RNA of SARS-CoV-2 can be detected in HCT recipients for up to 78 days after the onset of symptoms (IQR, 24-64).[24] This is important from an infection control perspective because it raises the question whether immunocompromised patients require longer periods of isolation.[24] In our study, we report a median shedding time of 26 days and a median time to clearance of 34 days; however, it is unclear to what extent prolonged PCR positivity translates into active infection with viable virus.[15] Recent elegant data by Aydillo et al indicate that some HCT patients can have evidence of viable virus by in vitro culture for more than 20 days.[24]

In our study, 43% of the patients received systemic antibiotic therapy whereas superimposed bacterial infections were documented in only 21%. Thus, antibiotic use could have been unjustified in nearly half of the cases. Secondary infections occurred in only 10 (13%) COVID-19 HCT patients reported by Shah et al. A large multicenter study with more than 1700 patients with COVID-19 showed that 57% patients were prescribed early empiric antibiotics whereas only 3.5% had a confirmed bacterial infection.[25] This highlights the importance of evaluating patients individually for their antibiotic need[26]; for example, in the TCT population, the presence of neutropenia might warrant empiric antibiotic therapy if fevers develop in the setting of COVID-19 until culture results are available. Inappropriate antibiotic use can lead to antibiotic resistance, as evidenced by high incidence of MDR organisms seen in our cases; adverse side effects; and unnecessary impact in gut microbiome in COVID-19 patients, especially those infected early post-transplant, as there is a link between early antibiotic (particularly anaerobic coverage) use, disturbed microbiota, and increased risk of CMV reactivation, GVHD, and mortality in HCT recipients.[27-31]

Limitations of our study include those inherent to a retrospective design. Furthermore, we did not have access to serial cycle threshold (Ct) data on SARS-CoV-2 PCR, precluding more detailed assessment of viral kinetics. We also do not have data on SARS-CoV-2 IgG and therefore were unable to comment on rates of seroconversion, which others have reported can occur in two thirds of HCT patients with COVID-19 despite profound lymphopenia.[12] Advantages of our study include the comprehensive report of data that includes not only clinical presentation and mortality but also important data on co-infections, shedding, and COVID-19-associated sequela, which has not been widely published in HCT population. To our knowledge,

to the date, this is one of the largest single-center cohorts of HCT patients with COVID-19.

In conclusion, our study reveals that COVID-19 HCT patients had higher mortality than age-comparable general US population[32] but similar to other HCT cohorts, especially among hospitalized patients.[12,19,23,33] Mortality varied by age, time from HCT, intensity of immunosuppression, and COVID-19 severity but was not influenced by transplant type. Lack of fever on presentation can occur; therefore, a high index of clinical suspicion is needed. Prolonged SARS-CoV-2 shedding is common, and antibiotics, although commonly prescribed, are only justified only in a minority of COVID-19 patients. Until public health efforts and massive vaccination against SARS-CoV-2 mitigate the impact of COVID-19 in transplant centers worldwide, further studies on this vulnerable TCT population, particularly aimed to understand immunological determinants of disease severity, are urgently needed.

ACKNOWLEDGEMENTS

The authors thank all the patients who participated in the study and Humberto Elejalde for assistance with data collection.

CONFLICT OF INTEREST

The authors declare no competing financial interests relevant to this manuscript.

AUTHOR CONTRIBUTIONS

JFC conceived the study; JFC, MAM, RL, IVM, ADA, MIM, MR, LL, AB, AJ, MG, TW, KVK, and DP acquired the data; JFC, MAM, YN, and AN analyzed the data; JFC and MAM prepared the first draft of the manuscript; and all authors were involved in the revision of the draft manuscript and have agreed to the final content.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. World Health Organization. *Weekly epidemiological update - 19 January 2021*. 2021; https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---31-march-2021. Accessed March 30, 2021
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
3. Lian J, Jin X, Hao S, et al. Epidemiological, clinical, and virological characteristics of 465 hospitalized cases of coronavirus disease 2019 (COVID-19) from Zhejiang province in China. *Influenza Other Respir Viruses*. 2020;14(5):564-574.
4. Raja MA, Mendoza MA, Villavicencio A, et al. COVID-19 in solid organ transplant recipients: a systematic review and meta-analysis of current literature. *Transplant Rev (Orlando)*. 2020;35(1):100588.
5. Coronavirus Disease 2019 - People of Any Age with Underlying Medical Conditions [press release]. Centers for Disease Control and Prevention.
6. Ogonek J, Kralj Juric M, Ghimire S, et al. Immune reconstitution after allogeneic hematopoietic stem cell transplantation. *Front Immunol*. 2016;7:507.
7. European Society for Blood and Marrow Transplantation. *Coronavirus disease COVID-19: EBMT recommendations*. 2020; Version 13. Accessed March 30, 2021.
8. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? *BMC Res Notes*. 2017;10(1):12.
9. Koehler P, Bassetti M, Chakrabarti A, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis*. 2020. https://doi.org/10.1016/S1473-3099(20)30847-1.
10. Kates OS, Haydel BM, Florman SS, et al. COVID-19 in solid organ transplant: A multi-center cohort study. *Clin Infect Dis*. 2020;ciaa1097. https://doi.org/10.1093/cid/ciaa1097.
11. Malard F, Genthon A, Brissot E, et al. COVID-19 outcomes in patients with hematologic disease. *Bone Marrow Transplant*. 2020;55(11):2180-2184.
12. Shah GL, DeWolf S, Lee YJ, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. *J Clin Invest*. 2020;130(12):6656-6667.
13. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020;383(19):1813-1826.
14. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med*. 2020;383(19):1827-1837.
15. Waghmare A, Abidi MZ, Boeckh M, et al. Guidelines for COVID-19 management in hematopoietic cell transplantation and cellular therapy recipients. *Biol Blood Marrow Transplant*. 2020;26(11):1983-1994.
16. Hill JA, Menon MP, Dhanireddy S, et al. Tocilizumab in hospitalized patients with COVID-19: clinical outcomes, inflammatory marker kinetics, and safety. *J Med Virol*. 2020;93(4):2270-2280.
17. Group Recovery, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med*. 2020;384(8):693-704.
18. Haroon A, Alnassani M, Aljurf M, et al. COVID - 19 post hematopoietic cell transplant, a report of 11 cases from a single center. *Mediterr J Hematol Infect Dis*. 2020;12(1):e2020070.
19. Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. *Lancet Haematol*. 2021;8(3):e185-e193.
20. Kanellopoulos A, Ahmed MZ, Kishore B, et al. COVID-19 in bone marrow transplant recipients: reflecting on a single centre experience. *Br J Haematol*. 2020;190(2):e67-e70.
21. Altuntas F, Ata N, Yigenoglu TN, et al. COVID-19 in hematopoietic cell transplant recipients. *Bone Marrow Transplant*. 2020;56(4):952-955.
22. Sultan AM, Mahmoud HK, Fathy GM, Abdelfattah NM. The outcome of hematopoietic stem cell transplantation patients with COVID-19 infection. *Bone Marrow Transplant*. 2020;56(4):971-973.
23. Varma A, Kosuri S, Ustun C, et al. COVID-19 infection in hematopoietic cell transplantation: age, time from transplant and steroids matter. *Leukemia*. 2020;34(10):2809-2812.
24. Aydillo T, Gonzalez-Reiche AS, Aslam S, et al. Shedding of viable SARS-CoV-2 after immunosuppressive therapy for cancer. *N Engl J Med*. 2020;383(26):2586-2588.
25. Vaughn VM, Gandhi T, Petty LA, et al. Empiric antibacterial therapy and community-onset bacterial co-infection in patients hospitalized

with COVID-19: a multi-hospital cohort study. *Clin Infect Dis*. 2020;ciaa1239. https://doi.org/10.1093/cid/ciaa1239.
26. Ginsburg AS, Klugman KP. COVID-19 pneumonia and the appropriate use of antibiotics. *Lancet Glob Health*. 2020;8(12):e1453-e1454.
27. Peled JU, Gomes ALC, Devlin SM, et al. Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2020;382(9):822-834.
28. Tanaka JS, Young RR, Heston SM, et al. Anaerobic antibiotics and the risk of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2020;26(11):2053-2060.
29. Shono Y, Docampo MD, Peled JU, et al. Increased GVHD-related mortality with broad-spectrum antibiotic use after allogeneic hematopoietic stem cell transplantation in human patients and mice. *Sci Transl Med*. 2016;8(339):339ra71.
30. Taur Y, Jenq RR, Perales MA, et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic stem cell transplantation. *Blood*. 2014;124(7):1174-1182.
31. Camargo JF, Anderson AD, Natori Y, et al. Early antibiotic use is associated with CMV risk and outcomes following allogeneic hematopoietic cell transplantation. *Blood Adv*. 2020;4(24):6364-6367.
32. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States. 2020;*69*. https://doi.org/10.15585/mmwr.mm6912e2
33. Center for International Blood and Marrow Transplant Research (CIBMTR). *COVID-19 Reported Data as of 1/22/21*. 2021; https://www.cibmtr.org/Covid19/Pages/default.aspx#repdata. Accessed March 12, 2021

How to cite this article: Camargo JF, Mendoza MA, Lin R, et al. Clinical presentation and outcomes of COVID-19 following hematopoietic cell transplantation and cellular therapy. *Transpl Infect Dis*. 2021;23:e13625. https://doi.org/10.1111/tid.13625