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Impact of SARS-CoV-2 in Hematopoietic Stem Cell Transplantation and Chimeric Antigen Receptor T Cell Therapy Recipients

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A B S T R A C T

Coronavirus disease 2019 (COVID-19), a respiratory illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic in March 2020, and has caused more than 600,000 deaths in the United States at the time of this report. Hematopoietic stem cell transplantation (HCT) or chimeric antigen receptor T cell (CAR-T) therapy recipients have a higher risk of mortality with COVID-19 owing to profound immune dysregulation. In this study, we investigated the impact of SARS-CoV-2 in HCT/CAR-T therapy recipients. This single-center prospective study included all (n = 58) adult HCT/CAR-T recipients who were diagnosed with COVID-19 at the University of Kansas Medical Center between March 2020 and May 2021. Baseline and disease-related characteristics were ascertained from medical records. Data were analyzed using SPSS version 21 (IBM, Armonk, NY). Bivariate analyses, using the chi-square and t-test, and logistic regression analyses were conducted. The study included 58 HCT/CAR-T patients who acquired SARS-CoV-2 infection, including recipients of allogeneic HCT (n = 32), autologous HCT (n = 23), and CAR-T therapy (n = 3). The median patient age was 58 years (range, 24 to 77 years), and 64% were males. The median time from HCT/CAR-T therapy to SARS-CoV-2 infection was 17.7 months (range, 0.2 to 201.9 months), and 22% of the patients acquired SARS-CoV-2 within the first 100 days post-HCT/CAR-T therapy. The primary hematologic disorders were plasma cell (36%), myeloid (38%), and lymphoid (26%) malignancies. Myeloablative conditioning was performed in 62% of patients. Donors were autologous (45%), matched sibling (15%), matched unrelated (21%), and haploidentical (19%). Prior history of grade II-IV acute graft-versus-host disease (GVHD), active GVHD, and current immunosuppressive therapy (IST) was noted in 22%, 31%, and 36% of patients, respectively. Concurrent infections were observed in 19%. Lymphopenia (P = .049) and high serum ferritin concentration (P = .020) were associated with mortality. COVID-19 severity was mild in 50% of the patients, moderate in 22%, and severe in 28%. Clinical findings included pneumonia or abnormal chest imaging (in 50%), hypoxia (28%), intensive care unit admission (19%), and mechanical ventilation (10%). Therapies included remdesivir (in 41%), convalescent plasma (35%), dexamethasone (22%), monoclonal antibodies (19%), and tocilizumab (3%). The median duration of viral shedding (positive SARS-CoV-2 PCR) was 7.7 weeks (range, 2 to 18.7 weeks), and 2 patients had a persistent infection for >5 months post-CAR-T therapy. After a median follow-up of 6.1 months (range, 0.5-13.6 months), the mortality rate was 16% in all patients and 28% in allogeneic HCT recipients. Among 9 patients who died, the median survival after SARS-CoV-2 infection was 23 days (range, 14 to 140 days). In survivors with moderate-severe COVID-19, the median time to recovery was 4.2 weeks (range, 1.1 to 24.7 weeks). Among allogeneic HCT recipients, 5 (16%) developed subsequent pulmonary chronic GVHD necessitating systemic steroids and additional IST. Significant predictors of COVID-19 severity included allogeneic HCT (odds ratio [OR], 3.6, 95% confidence interval [CI], 1.2 to 10.8; P = .020), history of grade II-IV acute GVHD (OR, 4.6; 95% CI, 1.10 to 18.86; P = .036) and concurrent IST (OR, 5.9; 95% CI, 1.8 to 19.8; P = .004). HCT and CAR-T cell therapy recipients are at an increased risk of moderate-severe COVID-19 pneumonia and higher mortality with SARS-CoV-2 infection. Our findings confirm the need for continuing vigilance with social distancing and masks, vaccination prioritization, close monitoring, and aggressive treatment of HCT/CAR-T therapy recipients.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), a severe respiratory illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1,2]. As of May 2021, 175 million cases of SARS-CoV-2 have been reported worldwide, including >30 million in the United States [3]. So far, the COVID-19 pandemic has claimed nearly 3.8 million lives worldwide, including >600,000 from the United States alone, and thus has had a significant impact on the healthcare systems across the globe [3]. Cancer patients, especially those with hematologic malignancies, are at a high risk of developing complications and adverse outcomes related to SARS-CoV-2 infection owing to their immunocompromised state [4-8].

Cellular therapeutics, including autologous (auto) and allogeneic (allo) hematopoietic cell transplantation (HCT) and chimeric antigen receptor T cell (CAR-T) therapy, is often the optimal and only potentially curative therapy in several high-risk hematologic malignancies [9]. Cellular therapies cause profound immune dysregulation that leads to increased susceptibility to infections and associated infectious clinical complications and significant morbidity and mortality [9-11]. Transplant and cellular therapy centers worldwide have been challenged with the pandemic because of the high susceptibility to opportunistic and community-acquired infections and their complications in this unique subset of patients [12-14]. Nonetheless, in certain clinical scenarios, postponing transplantation or cellular therapy can negatively affect the prognosis of the malignancy [15,16]. Therefore, even though health systems are overwhelmed with COVID-19 patients and despite the increased risk of complications with cellular therapies, HCT and CAR-T therapy have continued to be performed around the globe [17,18]. Patients undergoing HCT/CAR-T are required to be asymptomatic and to test negative for SARS-CoV-2 before conditioning chemotherapy [19]. Vaccination, preventive practices, and therapeutic strategies for SARS-CoV-2 vary among the transplant centers and follow a pragmatic approach.

Current literature regarding the disease trajectory and outcomes of COVID-19 in HCT and CAR-T recipients is scarce. Very few studies have explored the clinical characteristics and severity of SARS-CoV-2 infections in the context of transplantation and cellular therapy, and only 3 reports have been published reporting outcomes exclusively in such patients [13,20-22]. In the present study, we aimed to investigate the impact of SARS-CoV-2 in HCT/CAR-T recipients.

METHODS

Design, Setting, and Patients

We conducted a single-center prospective study including all adult HCT/CAR-T patients (n = 58) diagnosed with COVID-19 at the University of Kansas Medical Center from March 2020 to May 2021. The number of patients at risk was estimated from the number of cellular therapies provided from January 2019 to May 2021, given the median time from HCT/CAR-T to SARS-CoV-2 infection of 17.7 months. A total of 756 patients received cellular therapies during this period, including 286 allo-HCTs, 373 auto-HCTs, and 97 CAR-T cell therapies. The study was approved by the center's Institutional Review Board.

Inclusion criteria for the study were patients age ≥18 years who had undergone allo-HCT, auto-HCT, or CAR-T cell therapy and had tested positive for SARS-CoV-2 infection.

Data Collection

Data were collected by electronic medical record review. Demographic, clinical, and pathologic factors were ascertained at the time of COVID-19 diagnosis. A COVID-19 case was defined as qualitative detection of nucleic acid from SARS-CoV-2 in upper and/or lower respiratory specimens by RT-PCR [23]. COVID-19 severity was defined according to World Health Organization and National Institutes of Health guidelines as mild (tested positive for SARS-CoV-2 with or without COVID-19 symptoms and absence of dyspnea or abnormal chest imaging), moderate (evidence of lower respiratory disease/pneumonia on clinical assessment or imaging with oxygen saturation ≥94% on room air), severe (oxygen saturation <94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen <300 mm Hg, respiratory rate >30 breaths/minute, or lung infiltrates >50%), or critical (respiratory failure, septic shock, multiple organ dysfunction, and/or death) [24]. For this analysis, COVID-19 severity was stratified into mild disease, moderate-severe disease (including moderate, severe, and critical cases and excluding deaths), and fatal. Immunosuppressive therapy (IST) included prednisone, tacrolimus, and ruxolitinib. Immunotherapeutic agents included immunomodulatory agents (lenalidomide, pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib), Bruton tyrosine kinase inhibitors (ibrutinib), monoclonal antibodies (daratumumab, pembrolizumab), and antibody-drug conjugates (belantamab). A standardized HCT comorbidity index (HCT-CI) was used to report comorbidities [25]. Duration of disease was defined as the time from diagnosis of SARS-Cov-2 infection to documented infection resolution or death. Infection status was defined as persistent if there were no signs of clinically significant improvement and as recovered if all signs and symptoms were resolved and the patient completed the planned course of treatment for the infection.

Statistical Analysis

Descriptive statistics were used to compare baseline demographic characteristics. Categorical variables were compared using the chi-square test, and continuous variables were compared using ANOVA or the *t* test. Univariate logistic regression analyses were performed to compare baseline characteristics with disease severity, and odds ratio (OR) with 95% confidence interval (CI) were obtained. Univariate analysis was conducted for significant factors associated with COVID severity identified in the descriptive bivariate analysis using the chi-square test and ANOVA, including age, sex, type of cell therapy, hematologic malignancy, prior grade II-IV acute graft-versus-host disease (GVHD), active GVHD, current IST, concurrent infections, lymphopenia, ferritin, neutrophil:lymphocyte ratio, and platelet:lymphocyte ratio. Donor type and GVHD prophylaxis was not included, given the same information presented by type of cell therapy, and no statistically significant difference was noted among the allo-HCT recipients. Data were analyzed using SPSS version 21 (IBM, Armonk, NY). $P < .05$ was considered to indicate statistical significance.

RESULTS

Baseline Characteristics

The study included 58 HCT/CAR-T recipients who acquired SARS-CoV-2 infection, including 32 allo-HCT recipients, 23 auto-HCT recipients, and 3 CAR-T therapy recipients. The majority of COVID-19 cases (78%) were diagnosed during the second wave of the pandemic (October 2020 to May 2021). The median patient age was 58 years (range, 24 to 77 years) and 64% were male. The majority of patients were Caucasian (69%), followed by Hispanics (16%), African Americans (12%), and others (3%). Primary hematologic disorders were plasma cell (36%), myeloid (38%), or lymphoid (26%) malignancies. Myeloablative conditioning was provided to 62% of the patients. Donor types included autologous (45%), matched sibling (15%), matched unrelated (21%), and haploidentical (19%). Among the 32 allo-HCT recipients, GVHD prophylaxis regimens included tacrolimus and methotrexate in 21 (66%) and post-transplantation cyclophosphamide, tacrolimus, and mycophenolate mofetil in the other 11 (34%). The HCT-CI was 0-1 in 38%, 2-3 in 33%, and >3 in 29%. Prior history of grade II-IV acute GVHD was noted in 22% of the patients, and 26% of the patients had a history of steroid-requiring chronic GVHD after allo-HCT. Patients with underlying myeloid disease ($P = .042$), allo-HCT recipients ($P = .027$), and those with a prior history of acute GVHD ($P = .017$) had a higher likelihood of severe COVID-19 and mortality (Table 1).

Clinical Characteristics

The median interval from HCT/CAR-T to SARS-CoV-2 infection was 17.7 months (range, 0.2 to 201.9 months). The median time from cellular therapy was shorter in patients who died (3.5 months; range, 1.5 to 118.4 months) or

Table 1
Baseline Characteristics of HCT and CAR-T Cell Therapy Recipients Diagnosed with COVID-19

Characteristic	Total (N = 58)	COVID-19 Severity			*P* value
		Mild (N = 29)	Moderate-Severe (N = 20)	Fatal (N = 9)	
Age, yr, median (range)	58 (24-77)	58 (24-75)	57 (24-77)	62 (25-73)	.974
Male sex, n (%)	37 (64)	20 (69)	12 (60)	5 (56)	.696
Ethnicity, n (%)					
Caucasian	40 (69)	21 (72)	13 (65)	6 (67)	.235
Hispanic	9 (16)	3 (10)	3 (15)	3 (33)	
African American	7 (12)	5 (17)	1 (5.5)	0	
Others	3 (3)	0	2 (10.5)	0	
Time of COVID-19 diagnosis, n (%)					
March 2020-September 2020	13 (22)	8 (28)	4 (20)	1 (11)	.556
October 2020-May 2021	45 (78)	21 (72)	16 (80)	8 (89)	
Hematologic malignancy, n (%)					
Plasma cell disorders	21 (36)	14 (48)	7 (35)	0	.042
Lymphoid disorders	15 (26)	6 (21)	7 (35)	2 (22)	
Myeloid disorders	22 (38)	9 (31)	6 (30)	7 (78)	
Type of cellular therapy, n (%)					
Allogeneic HCT	32 (55)	11 (38)	12 (60)	9 (100)	.027
Autologous HCT	23 (40)	16 (55)	7 (35)	0	
CAR-T	3 (5)	2 (7)	1 (5)	0	
Donor type, n (%)					
Self	26 (45)	18 (62)	8 (40)	0	.054
Matched sibling	9 (15)	3 (10)	3 (15)	3 (33)	
Matched unrelated	12 (21)	4 (14)	4 (20)	4 (45)	
Haploidentical	11 (19)	4 (14)	5 (25)	2 (22)	
Conditioning, n (%)					
Myeloablative	36 (62)	18 (62)	14 (70)	4 (44)	.423
Reduced intensity and nonmyeloablative	22 (38)	11 (38)	6 (30)	3 (56)	
GVHD prophylaxis, n (%)					
Tacrolimus/methotrexate	21 (36)	7 (24)	7 (35)	7 (78)	.015
Post-transplantation cyclophosphamide, tacrolimus, mycophenolate	11 (19)	4 (14)	5 (25)	2 (22)	
None	26 (45)	18 (62)	8 (40)	0	
HCT Comorbidity Index, n (%)					
0-1	22 (38)	13 (44)	5 (25)	4 (45)	.577
2-3	19 (33)	8 (28)	9 (45)	2 (22)	
>3	17 (29)	8 (28)	6 (30)	3 (33)	
Prior acute GVHD grade II-IV, n (%)	13 (22)	3 (10)	5 (25)	5 (56)	.017
Prior chronic GVHD requiring systemic steroids, n (%)	15 (26)	5 (17)	5 (25)	5 (56)	.072

Abbreviations: COVID-19, coronavirus disease 2019; HCT, hematopoietic stem cell transplant; CAR-T, chimeric antigen receptor-T cell therapy; GVHD, graft-versus-host disease.

developed moderate-severe COVID-19 (11.3 months; range, 0.2 to 81.6 months) compared with patients with mild disease (26.5 months; range, 1 to 201.9 months); however, the difference was not statistically significant. Twenty-two percent of patients acquired SARS-CoV-2 within the first 100 days post-HCT/CAR-T. Active GVHD was present in 18 patients (31%) at the time of SARS-CoV-2 infection; of these, 6 patients developed severe disease and died of COVID-19 ($P = .033$). Twenty-one patients (36%) were receiving IST at the time of SARS-CoV-2 infection, and these patients were more likely to have severe COVID-19 ($P < .001$). Patients on IST accounted for 40% of moderate-severe COVID-19 cases (n = 8) and 89% of the deaths (n = 8). IST included prednisone (n = 14; ≥20 mg/day, n = 5; <20 mg/day, n = 9), tacrolimus (n = 12), and/or ruxolitinib (n = 5). Current immunotherapy for hematologic malignancy was reported in 29% of patients. Concurrent infections were observed in 19% of the patients and included cytomegalovirus viremia (n = 3), bacterial pneumonia (n = 3), BK viremia (n = 1), adenovirus respiratory and gastrointestinal infection without viremia (n = 1), aspergillus pneumonia (n = 1), staphylococcal skin/soft tissue infection (n = 1), staphylococcal septic arthritis (n = 1), staphylococcal bacteremia/discitis (n = 1), enterococcal urinary tract infection (n = 1), and *Clostridium difficile* colitis (n = 1). Lymphopenia ($P = .049$), high serum ferritin level ($P = .020$), high neutrophil:lymphocyte ratio ($P = .040$), and high platelet:lymphocyte ratio ($P = .008$) were associated with greater COVID-19 severity and death (Table 2).

COVID-19 Severity, Management, and Outcomes

The estimated number of patients at risk included 756 patients who received HCT/CAR-T at our institution from January 2019 to May 2021, including 286 allo-HCT recipients, 373 auto-HCT recipients, and 97 CAR-T cell therapy recipients. The incidence of SARS-CoV-2 infection was 8% in all patients and was higher in allo-HCT recipients (11%) compared with auto-HCT (6%) and CAR-T therapy (3%) recipients. COVID-19 severity was mild in 50% of the patients, moderate in 22%, and severe/critical in 28%. Allo-HCT recipients were more likely to have

Table 2
Clinical Characteristics of HCT and CAR-T Cell Therapy Recipients Diagnosed with COVID-19

Characteristic	Total (N = 58)	COVID-19 Severity			*P* Value
		Mild (N = 29)	Moderate-Severe (N = 20)	Fatal (N = 9)	
Time since HCT/CAR-T, mo, median (range)	17.7 (0.2-201.9)	26.5 (1-201.9)	11.3 (0.2-81.6)	3.5 (1.5-118.4)	.404
COVID-19 diagnosis in first 100 d post-HCT/CAR-T, n (%)	10 (20)	2 (8)	6 (32)	2 (33)	.105
Active GVHD, n (%)	18 (31)	6 (21)	6 (30)	6 (67)	.033
Current IST, n (%)	21 (36)	5 (17)	8 (40)	8 (89)	<.001
Prednisone ≥20 mg/d	5 (9)	2 (7)	0	3 (33)	
Prednisone <20 mg/d	9 (16)	1 (3)	5 (25)	3 (33)	
Tacrolimus ± prednisone	12 (21)	2 (7)	6 (30)	4 (44)	
Ruxolitinib ± prednisone	5 (9)	1 (3)	1 (5)	3 (33)	
Current immunotherapy, n (%)	17 (29)	13 (45)	4 (20)	0	.019
Concurrent infections, n (%)	11 (19)	5 (17)	4 (20)	2 (22)	.936
Lab indices at COVID diagnosis, median					
Hemoglobin, g/dL	11	11.1	11.2	9.2	.585
Platelets, K/μL	122	146	102	75	.705
Neutrophils, K/μL	3.8	4.3	3.2	4.0	.252
Lymphocytes, K/μL	0.8	1.3	1.0	0.3	.049
C-reactive protein, mg/dL	2.5	0.4	3.1	2.5	.765
D-dimer	1075	1658	1502	1062	.547
Ferritin, ng/dL	637	93	735	2543	.020
Neutrophil:lymphocyte ratio	6.2	3.4	6.2	12.3	.040
Platelet:lymphocyte ratio	147	133	147	537	.008
Follow-up after COVID-19, mo, median (range)	6.1 (0.5-13.6)	6.1 (1.9-13.6)	6.6 (0.9-13.1)	0.8 (0.5-4.6)	<.001

Abbreviations: COVID-19, coronavirus disease 2019; HCT, hematopoietic stem cell transplant; CAR-T, chimeric antigen receptor-T cell therapy; GVHD, graft-versus-host disease; IST, immunosuppressive therapy.

severe COVID-19 compared with auto-HCT or CAR-T therapy recipients (34% vs 17%; *P* = .013). Of 3 CAR-T therapy recipients with COVID-19, the first patient had mild disease and recovered completely, the second patient had severe COVID-19 with recurrent pneumonia (no infectious organism identified except COVID), and the third patient had mild COVID-19 with recurrent pneumonia (*Pseudomonas, Aspergillus*). Clinical findings included pneumonia or abnormal chest imaging in 50% of patients, hypoxia in 28%, intensive care unit (ICU) admission in 19%, and mechanical ventilation in 10%. Therapies for COVID-19 included remdesivir in 41% of patients, convalescent plasma in 35%, dexamethasone in 22%, monoclonal antibodies in 19%, and tocilizumab in 3%. In 38 patients with available data, the median duration of viral shedding (ie, time from first positive SARS-CoV-2 PCR to negative PCR test) was 7.7 weeks (range, 2 to 18.7 weeks), and there was no statistically significant difference between the allo-HCT and auto-HCT recipients. In 2 of the 3 CAR-T therapy recipients with available data, B cell aplasia and persistent SARS-CoV-2 infection were noted for >5 months (first positive on December 8, 2020, and January 16, 2021, respectively; remained positive as of May 31, 2021). We did not observe reactivation with clinical disease in any asymptomatic patients. In survivors with moderate-severe COVID-19 (n = 20), the median time to recovery (ie, no longer meeting the criteria for moderate-severe COVID-19) was 4.2 weeks (range, 1.1 to 24.7 weeks). A trend toward longer symptomatic COVID-19 was noted in allo-HCT recipients compared with auto-HCT recipients (median 5 weeks versus 4 weeks), but the difference was not statistically significant. After a median follow-up of 6.1 months (range, 0.5 to 13.6 months), the mortality rate was 16% (n = 9) in all patients and 28% (n = 9) in allo-HCT recipients. Among 11 patients admitted to the ICU, the mortality rate was 73% (n = 8). Among the 9 patients who died, the median survival after SARS-CoV-2 infection was 23 days (range, 14 to 140 days) (Table 3). Five allo-HCT recipients (16%) developed subsequent pulmonary chronic GVHD necessitating systemic steroids and additional IST. Significant predictors of COVID-19 severity in the univariate logistic regression model (mild versus moderate-severe COVID-19) included allo-HCT (OR, 3.6; 95% CI, 1.2 to 10.8; *P* = .020), history of grade II-IV acute GVHD (OR, 4.6; 95% CI, 1.10 to 18.86; *P* = .036), and concurrent IST (OR, 5.9; 95% CI, 1.8 to 19.8; *P* = .004) (Table 4).

DISCUSSION

In this prospective study, we report our real-world experience of the impact of SARS-CoV-2 in HCT/CAR-T therapy recipients. The estimated incidence of SARS-CoV-2 infection in our cohort was 8%, with a higher rate in allo-HCT recipients compared with auto-HCT/CAR-T therapy recipients (11% versus 5.5%). We report a significantly higher mortality of 16% with COVID-19 in HCT/CAR-T therapy recipients compared with the observed case fatality ratio of 1.8% in the general US population [26]. Previous studies have reported a COVID-19-related mortality rate of approximately 20% in HCT/CAR-T therapy recipients [13,20-22,27-30]. In a US cohort of 34 HCT recipients, Verma et al. [13] reported 21% mortality from COVID-19, with most of the deaths in the allo-HCT group (25%), which is comparable to the 28% mortality rate of allo-HCT recipients in our cohort. Similar findings were reported in a Center for International Blood and Marrow Transplant Research (CIBMTR) analysis by Sharma et al. [20] and a retrospective report from New York by Shah et al. [22], with allo-HCT mortality of 22%. Severe COVID-19 and the need for mechanical ventilation were higher in allo-HCT recipients compared with auto-HCT recipients, similar to the findings of Verma et al. [13]. The mortality rate in 11 patients admitted to the ICU was 73%, consistent with a previous report of 83% mortality in 6 HCT recipients admitted to the ICU [30].

Table 3
Disease Severity, Treatments, and Outcomes of COVID-19 in HCT and CAR-T Cell Therapy Recipients

Characteristic	Total	Type of Cellular Therapy			*P* value
		Allo-HCT	Auto-HCT	CAR-T	
Number at risk (HCT/CAR-T performed 01/2019-05/2021), n	756	286	373	97	
Incidence of SARS-CoV-2 infection, n (%)	58 (8)	32 (11)	23 (6)	3 (3)	
Age, yr, median (range)	58 (24-77)	56 (24-73)	65 (24-77)	60 (51-75)	.188
Time since HCT/CAR-T, mo, median (range)	17.7 (0.2-201.9)	17.3 (1-201.9)	23.9 (0.2-118.7)	2.6 (2.3-4.8)	.407
COVID-19 diagnosis in first 100 d post-HCT/CAR-T, n (%)	13 (22)	8 (25)	3 (13)	2 (67)	.097
COVID-19 severity, n (%)					
Mild	29 (50)	11 (34)	16 (70)	2 (67)	.013
Moderate	13 (22)	10 (31)	3 (13)	0	
Severe	7 (12)	2 (6)	4 (17)	1 (33)	
Critical/fatal	9 (16)	9 (28)	0	0	
Abnormal chest imaging, n (%)	29 (50)	21 (67)	7 (30)	1 (33)	.030
Hypoxia, n (%)	16 (28)	11 (34)	4 (17)	1 (33)	.371
ICU admission, n (%)	11 (19)	9 (28)	2 (9)	0	.133
Mechanical ventilation, n (%)	6 (10)	5 (16)	1 (4)	0	.333
COVID-19 therapy, n (%)					
Remdesivir	24 (41)	20 (63)	3 (13)	1 (33)	.001
Convalescent plasma	20 (35)	16 (50)	3 (13)	1 (33)	.017
Dexamethasone	13 (22)	10 (31)	2 (9)	1 (33)	.127
Monoclonal antibodies	11 (19)	8 (25)	2 (9)	1 (33)	.254
Tocilizumab	2 (3)	2 (6)	0	0	.431
Time to clear SARS-CoV-2 infection, wk, median (range)*	7.7 (2.0-18.7)	7.6 (2.0-18.7)	7.8 (2.6-16.9)	NA	.480
Follow-up after COVID-19, mo, median (range)	6.1 (0.5-13.6)	5.5 (0.5-12.4)	6.4 (3.4-13.6)	5.7 (4.4-8.9)	.025
Outcomes, n (%)					
Recovered	47 (81)	23 (72)	23 (100)	1 (33)	<.001
Persistent	2 (3)	0	0	2 (67)	
Dead	9 (16)	9 (28)	0	0	

NA indicates Not available.
Abbreviations: COVID-19, coronavirus disease 2019; HCT, hematopoietic stem cell transplant; Allo, allogeneic; Auto, autologous; CAR-T, chimeric antigen receptor-T cell therapy; ICU, intensive care unit.
* Data available for 38 patients.†Data available for 2 of 3 patients, both of whom had B cell aplasia and persistent SARS-CoV-2 PCR positive (first positive, 12/8/2020 and 1/16/2021, respectively).

In the present study, significant predictors of COVID-19 severity included allo-HCT, history of grade II-IV acute GVHD, and concurrent IST. The increased mortality with COVID-19 in cellular therapy patients is likely multifactorial and principally due to profound immune dysregulation, prolonged immunosuppression, GVHD, and cytopenias. T cell recovery and functional immune reconstitution after chemotherapy and HCT/CAR-T therapy may take 6 months to 2 years, which has important clinical implications, including a prolonged immunosuppressive state, poor immunogenicity, and increased risk of infections [10,31].

SARS-CoV-2 infection early post-HCT/CAR-T therapy may have adverse outcomes and higher mortality given the profound immune dysregulation. We observed increased COVID-19 severity in patients who had SARS-CoV-2 infection within 1 year of transplantation, similar to previous studies [13,20]. However, the time from HCT/CAR-T therapy was not a statistically significant factor for COVID-19 severity and mortality in our study population, consistent with previous literature [20,22]. Only 22% of the SARS-CoV-2 infections occurred in patients within 100 days post-HCT/CAR-T therapy. Indeed, rigorous infection control practices and patient education are the likely reasons why so few patients have acquired SARS-COV-2 and developed COVID-19 in the early post-HCT/CAR-T period. Therefore, it is no surprise that the median time to COVID-19 after HCT/CAR-T therapy is 17 months in our dataset and others, including the Center for International Blood and Marrow Transplant Research analysis [20].

Table 4
Logistic Regression Analysis of Factors Associated with Disease Severity in HCT and CAR-T Cell Therapy Recipients Diagnosed with COVID-19

Characteristic	COVID-19 Severity (Mild vs Moderate-Severe)	
	OR (95% CI)	P Value
Type of cell therapy (allo-HCT vs auto-HCT/CAR-T)	3.64 (1.23-10.78)	.020
Current IST	5.91 (1.76-19.81)	.004
Prior grade II-IV acute GVHD	4.56 (1.10-18.86)	.036

Not significant: age (P = .849), sex (P = .414), hematologic malignancy (P = .169), active GVHD (P = .094), concurrent infections (P = .518), lymphopenia (P = .055), ferritin (P = .147), neutrophil:lymphocyte ratio (P = .168), platelet:lymphocyte ratio (P = .159).
Abbreviations: COVID-19, coronavirus disease 2019; HCT, hematopoietic stem cell transplant; CAR-T, chimeric antigen receptor-T cell therapy.

Three CAR-T therapy recipients acquired SARS-CoV-2 infection. The first patient had mild COVID-19 and recovered completely, whereas the subsequent 2 patients had persistent SARS-CoV-2 infection with recurrent pneumonia for >5 months. A previous study by Shah et al. [22] that included the largest reported subset of CAR-T patients (n = 5) reported 40% mortality from COVID-19 in those patients.

Age >60 years has been associated with higher mortality in HCT recipients as well as in non-HCT patients [13,28,29,32]. Sharma et al. [20] reported higher mortality in male HCT recipients age >50 years; however, we did not find any significant association of age or sex with COVID-19 severity or mortality in our cohort. Underlying myeloid malignancy was associated

with worse survival, consistent with a previous study [32]. The number of comorbidities has been reported to be associated with COVID-19 severity and mortality [23,32]; however, we did not find any significant relationship between HCT-CI and survival, a finding similar to that of Sharma et al. [20].

In our cohort, 16% of the allo-HCT recipients developed subsequent pulmonary chronic GVHD necessitating systemic steroids and additional immunosuppression. COVID pneumonia results in an inflamed microenvironment in lung parenchyma and T cell infiltration, possibly increasing the risk of lung GVHD and progressive organizing pneumonia. In our study, we found significant effects of history of grade II-IV GVHD and concurrent immunosuppression on COVID-19 severity and mortality. Eight of 9 patients (89%) who died in our cohort were on IST. This finding differs from previous studies in which IST did not have any significant effect on COVID-19 severity or mortality [13,20]. However, 6 of these patients were receiving IST for active GVHD, making it difficult to discern the roles of GVHD, immunosuppression, or both in our cohort.

Lymphopenia and high serum ferritin level were associated with COVID-19 severity and death, as reported in previous studies [13,22,33,34]. We did not find any association of C-reactive protein level with disease severity and mortality, in contrast to previous studies [28,29]. High neutrophil:lymphocyte ratio and high platelet:lymphocyte ratio are poor prognostic markers in cancer patients, reflecting an inflamed microenvironment [35,36], and were associated with greater COVID-19 severity and mortality.

Remdesivir, the first antiviral agent to receive Food and Drug Administration approval for hospitalized COVID-19 patients [37], was the most commonly used treatment in our cohort, followed by convalescent plasma, steroids, and monoclonal antibodies. A recent randomized trial did not show any significant beneficial effect of convalescent plasma on clinical status or overall mortality in immunocompetent hospitalized COVID-19 patients [38]; however, convalescent plasma might have a beneficial role for HCT/CAR-T patients due to B cell aplasia and the resultant inability to mount an antibody response in many such patients. Corticosteroids, most commonly dexamethasone, are now standard of care for patients with hypoxia in COVID-19 pneumonia [39]. Monoclonal antibodies (casirivimab with imdevimab, bamlanivimab) were approved under Emergency Use Authorization by the Food and Drug Administration for mild-moderate COVID-19 in an outpatient setting [40].

The median duration of viral shedding was 7.7 weeks, and 2 patients (post-CAR-T) with B cell aplasia had a persistent infection for >5 months. In our cohort, SARS-CoV-2 PCR served as a surrogate measure of viral shedding. This technique may detect RNA when the intact infective virus is no longer present. In contrast, viral culture is a definitive test. Prolonged viral shedding and low circulating B cell counts have been observed in HCT recipients [29,41]. HCT/CAR-T therapy recipients have profound immune dysregulation and may shed viable SARS-CoV-2 for at least 2 months after symptom onset, consistent with persistent infection [42]. SARS-CoV-2-specific immunologic memory, T cell immunity, memory B cells, and associated antibody production have been noted in healthy individuals and form the basis of vaccination efforts [43-45]. Coronavirus-specific T cells can be expanded from convalescent individuals for future use in HCT/CAR-T therapy recipients with impaired T cell function [46].

Current National Comprehensive Cancer Network guidelines suggest administering COVID-19 vaccination at 3 months after HCT/CAR-T [47]. A Blood and Marrow Transplant Clinical Trials Network study investigating SARS-CoV-2 vaccine immunogenicity in HCT/CAR-T therapy is in its very early phase [48]. Many patients will have a suboptimal response to the vaccine, particularly those early post-cellular therapy and those on prolonged IST for GVHD. Prior experience with influenza vaccination in HCT recipients has shown better seroconversion with vaccination at 6 months post-transplantation compared with 3 to 6 months post-transplantation; however, fewer cases of lower respiratory infections and severe disease have been noted with vaccination after 3 months [49,50].

Our findings suggest that continued vigilance with aggressive infection prevention and control measures is of critical importance in HCT/CAR-T therapy recipients regardless of time since therapy. The use of masks and hand hygiene should be continued in cellular therapy clinics and inpatient units regardless of COVID vaccination status. Patients undergoing allo-HCT, those with a history of GVHD, and those on current IST should be monitored closely in the event of a COVID-19 diagnosis. Early interventions including monoclonal antibodies and convalescent plasma, especially in patients with hypogammaglobulinemia, are suggested. HCT/CAR-T therapy recipients may have prolonged viral shedding and are at elevated risk of mortality and clinical complications from COVID-19.

Our institutional practice is to test for SARS-CoV-2 infection at 48 to 72 hours before providing chemotherapy and cellular therapy. If COVID-19 is detected, therapy is usually deferred for at least 14 days until the patient is asymptomatic and has 2 consecutive negative SARS-CoV-2 PCR tests. Transplantation is not deferred for asymptomatic COVID-19 patients with negative SARS-CoV-2 PCR results. We use the combination of casirivimab and imdevimab to treat mild to moderate COVID-19 in ambulatory patients within 10 days of symptom onset. Two units of convalescent plasma and remdesivir 200 mg i.v., followed by 100 mg i.v. daily for 5 total doses, are used for hospitalized patients with COVID-19. Dexamethasone 6 mg/day for 10 days is used for hospitalized COVID-19 patients with hypoxia.

Our analysis of the characteristics and outcomes of a prospective cohort of HCT/CAR-T patients who acquired SARS-CoV-2 has several limitations, including the small cohort size. Nonetheless, this is one of the largest cohorts of HCT/CAR-T therapy recipients contracting SARS-CoV-2 infection, with the longest follow-up reported to date. However, this is a single-center US population-based study, and findings can differ depending on ethnicity, geography, and institutional practices. Our study spanned more than 1 year, and management strategies have evolved during the duration of the pandemic.

CONCLUSIONS

SARS-CoV-2 infection and resultant COVID-19 cause significant mortality in patients undergoing HCT and CAR-T cell therapy, especially among allo-HCT recipients. Our findings confirm the need for continued vigilance with social distancing and masks, close surveillance, vaccination prioritization, novel treatment modalities such as viral-specific T cells, and aggressive management strategies in HCT/CAR-T therapy recipients. Future prospective studies are needed to investigate the short- and long-term impacts of SARS-CoV-2, the immunogenicity of the SARS-CoV-2 vaccine, and viral-specific cellular therapeutics in HCT/CAR-T therapy recipients.

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